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Contents

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He has graduated from the Faculty of Pharmacy, The Tamil Nadu Dr. M.G.R. Medical University, Chennai. He is a dedicated educationist cum innovative researcher with PhD in Pharmacy (Pharmacology). He has more than a decade of experience in providing professional teaching and imparting quality education cum research to a wide range of Medical and Pharmacy students, He is specialized in Clinical Pharmacy and Pharmacology and expert in handling Advanced Therapeutics and Pharmacy Practice. His research area of interest includes Pharmaceutical Care, Experimental & Clinical Pharmacology, Cardiovascular Pharmacology & Therapeutics, Clinical Research, Drug Interactions Studies, and Phytomedicines. He has guided more than 67 Research projects in the field of pharmacy and received best teacher award many times. He has published several research articles in international journals of repute and presented numerous research papers in various international conferences and received the best research paper award a few times, also he has given numerous invited talks and seminars in his field. He is an Academic editor for the Journal of Advances in Medicine and Medical Research and served as a peer reviewer for Cardiology and Angiology: An International Journal, Asian Journal of Research in Cardiovascular Diseases, and many other journals in the Medical and Pharmacy field. He is a Life Member in Pharmacy Council of India, The Association of Pharmaceutical Teachers of India and other international bodies. He is presently working in the Department of Pharmacy Practice, Faculty of Pharmacy, University of Tabuk, Kingdom of Saudi Arabia with various capacities.

PREFACE

This book covers key areas of medicine and medical research. The contributions by the authors include human papillomavirus, carcinogenesis, cervical ıntraepithelial neoplasia, cervical cancer, HPV prevalence, intraoperative durotomies, pseudomeningocele, epidural blood patch, stem cell leukemia gene, diabetic cystopathy, DCP-related alterations, local flap technique, compound leg injuries, fasciocutaneous flap, extrapulmonary tuberculosis, cartridge-based nucleic acid amplification test, Harden's ladder, competency-based medical education, CBME curriculum, body imaging techniques, biomedical research, duel-energy X-Ray absorptiometry, magnetic resonance spectroscopy, computed axial tomography, bioelectric impedance analysis, colorenal fistula, renal tumour cryotherapy, thoracoabdominal computed tomography, total colectomy, ileorectal anastomosis, terminal ileum perforation, cardiopulmonary auscultation, inguinal hernia repair, sutured hernia repair, prolene hernia system, desarda repair, pulmonary hypertension, congestive heart failure, particularly atrial fibrillation, anesthesia management. This book contains various materials suitable for students, researchers, and academicians in the fields of medicine and medical research.

Chapter 1
Print ISBN: 978-93-48119-61-2, eBook ISBN: 978-93-48119-12-4

Future Applications of Intravesical Stem Cell Leukemia (SCL) Gene Transfer for the Treatment of Diabetic Cystopathy

Yan Chen [a*] and Jin Sheng Li [b]

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ABSTRACT

Diabetic cystopathy, a complication of diabetes affecting the bladder, is mainly characterized by reduced contractility of the detrusor and increased post-voiding residual volume, which is induced by the reduction of the interstitial cells of Cajal. Previous studies have shown that interstitial cells of Cajal (ICCs) in the detrusor have pace-making ability, which is responsible for the contraction of the detrusor. Taken together, increased SCL expression in DCP patients may initiate a cascade of events, resulting in increased c-KIT activity, thus leading to the rescue of bladder function. The *c-KIT* protein is a specific marker of the interstitial cells of Cajal and the product of a *c-KIT* proto-oncogene. The interstitial cells of Cajal in a high glucose medium express less *c-KIT* mRNA and protein. *SCL* gene serves to assemble *SCL* complexes on the *c-KIT* promoter, sustaining *c-KIT* transcription. Proper transduction of exogenous *SCL* genetic material, increases *c-KIT* expression and leads to synthesis of the functional *SCL* protein. Intravesical, lentiviral vector-mediated gene transfer has been shown efficacious and safe. Therefore, proper intravesical transfer of RNA encoding *SCL* to the interstitial cells of Cajal may enhance *c-KIT* transcription and activity in the interstitial cells of Cajal of diabetic bladders, which may improve bladder activity. Therefore, further studies may explore this treatment strategy in detail, not only for diabetic cystopathy but also for other clinical problems, which can ameliorate the quality of life of the patients, and seems therefore valuable.

Keywords: Intravesical; SCL gene; treatment; diabetic cystopathy; c-KIT transcription.

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1. INTRODUCTION

The International Diabetes Federation estimates that 425 million people worldwide have diabetes, making it the largest global epidemic of the 21st century. 115 million people in China, 73 million in India and 30 million in the United States have diabetes [1]. Diabetic cystopathy (DCP) is one of the most common complications in diabetes mellitus, affecting over 25% of diabetic patients [2,3]. The main symptoms of DCP are under-activity of the detrusor mu*scl*e and increased post-voiding residual volume, which would induce severe urinary tract infection, vesico-ureter reflux, hydronephrosis, and even uremia and renal failure [4,5]. Diabetic neuropathy was considered the most common cause of DCP. Diabetic neuropathy is a loss of sensory function beginning distally in the lower extremities that is also characterized by pain and substantial morbidity [6,7]. Previous studies have shown that interstitial cells of Cajal (ICCs) in the detrusor have pace-making ability, which is responsible for the contraction of the detrusor [8,9]. ICCs are involved in signal transmission between smooth muscle bundles, from efferent nerves to smooth muscles, and from the urothelium to afferent nerves [10,11,12]. The underactivity of DCP has the disturbance of spontaneous contractility, caused by reduced suburothelial ICCs in DCP patients [13,14]. ICCs in cultured bladder tissue with high glucose medium were found to exhibit poorly self-excited, reduced connections with detrusor cells and nerve terminals, and expressed less *c-KIT* mRNA and protein than control cells [15]. The *c-KIT* protein is a specific marker on the cell membrane of ICCs, which is encoded by the *c-KIT* proto-oncogene [16,17]. Activation of the *c-KIT* gene can modulate cell growth, differentiation, and phenotype, while mutation of *c-KIT* leads to ICCs absent [18,19,12]. The stem cell leukemia gene (*SCL*) is a tissue-specific transcription factor of the basic helix-loop-helix family, functions in hematopoietic development are normally expressed in pluripotent hematopoietic precursors and are downregulated in maturing cells [20,21]. *SCL* induces *c-KIT* expression in chromatin. For example, ectopic *SCL* expression in transgenic mice sustains *c-KIT* transcription in developing B-lymphocytes, in which both genes are normally downregulated [22]. Increased *SCL* expression upregulates *c-KIT* gene expression in normal bone marrow cells. This *c-KIT* regulation involves the proper activation of the *c-KIT* promoter by the *SCL* protein, which coordinates *SCL* complex binding on the promoter sequence to activate *c-KIT* transcription [23]. Elefanty et al. successfully introduced *SCL* into mutant mice (*SCL* lacZ/w) and demonstrated that functional *SCL* protein was synthesized [24,12]. For the transfer of genetic material to the target tissue, the use of intravesical lentiviral vector-mediated gene delivery to bladder cells has been shown to be efficacious and safe for the treatment of bladder cancers [25]. Taken together, increased *SCL* expression in DCP patients may initiate a cascade of events, resulting in increased *c-KIT* activity, thus leading to the rescue of bladder function.

2. THE HYPOTHESES

Given the results of previous studies, we hypothesize that intravesical *SCL* gene transfer by viral vectors, such as the lentiviral vector, has a high potential to

promote *c-KIT* gene expression in ICCs and relieve bladder under-activity in DCP patients. During infection of ICCs, the viral vector carrying the *SCL* RNA is transduced into the ICCs, reverse-transcribed into double-stranded DNA (dsDNA) in the cytoplasm, and transported into the nucleus to stably integrate into the ICC genome. In DCP patients, the exogenous *SCL* may be expressed, and *SCL* protein may be synthesized in ICCs. Because DCP causes downregulation of the *c-KIT* gene, newly produced *SCL* may activate and sustain *c-KIT* transcription by binding to the promoter. These reactions may enhance/sustain *c-KIT* gene transcription and protein synthesis in DCP patients; therefore, bladder under-activity may be relieved.

3. DISCUSSION

DCP-related alterations of the detrusor are attributed to several mechanisms: changes in cellular excitability or intercellular communication; changes in receptor density, distribution, and function; alterations to intracellular signal transduction; and molecular or genetic changes [10,11]. All of these mechanisms are induced by abnormalities in ICCs in the bladder [26,27,12]. At the molecular level, c-KIT, which is a transmembrane receptor on the ICC cell membrane, is responsible for these abnormalities. Under normal conditions, the stem cell factor (SCF) activates its receptor (c-KIT), and this triggers the activation of MAP kinase and conducts the signal to the cell nucleus to modulate cell growth, differentiation, and phenotype [28]. ICCs and detrusor smooth muscle cells originate from the same cell type, which are embryonic, c-KIT- positive, mesenchymal precursor cells. At the late embryo stage, the mesenchymal precursor cells receiving the *c-KIT* signal differentiate into ICCs, while precursor cells receiving no *c-KIT* signal become smooth muscle cells [19,12]. Mutation of the *dominant white spotting (W)* locus in chromatin, where *c-KIT* has been mapped in embryonic precursor cells, leads to ICCs absent in the mouse [29]. In fact, the *c-KIT* protein is a detection marker, and it plays a crucial role in the control of bladder function. The inhibition of *c-KIT* receptor induces ATP-K+ channel opening and cell membrane hyper-polarization in ICCs; concomitantly, decreased excitability and contractility of the bladder have been detected, which implies that *c-KIT* protein inhibition in ICCs decreases bladder activity [30,31].

SCL is a crucial regulator of diverse developmental processes, such as hematopoiesis, neurogenesis, and myogenesis [32]. *SCL* is required for *c-KIT* expression and function in the hemopoietic cell line and has been shown to induce *c-KIT* transcription in chromatin. In a functional screen of TF-1 cells expressing antisense *SCL* 20, *c-KIT* receptor function and expression were defective [12]. However, co-delivery of *SCL* in the sense orientation rescued *c-KIT* gene expression, which suggests that the latter is a potential downstream target of *SCL* [23]. Ectopic *SCL* expression in transgenic mice induces sustained *c-KIT* transcription in developing B cells. *SCL* levels determine *c-KIT* gene expression in hematopoietic cells, and *c-KIT* expression is directly controlled by *SCL*. In fact, *SCL* serves to nucleate the assembly of a multi-protein complex (*SCL* complex) formed on the *c-KIT* promoter, which contains *SCL*, Lim-only 2, GATA-1/GATA-2, E2A, LIM domain binding protein 1, and specificity protein 1

(Sp1) zinc finger protein. The *SCL* complex activates the *c-KIT* promoter; specifically, *SCL*, E2A, and Sp1 have been shown to occupy the *c-KIT* promoter *in vivo* in TF-1 cells [20-22,12]. Therefore, *c-KIT* is a direct target of the transcription factor *SCL* and its partners, and activation of the *c-KIT* promoter depends on *SCL*. Therefore, exogenously introduced *SCL* genetic material may help cells sustain or enhance *c-KIT* function.

Kurita et al. showed that transduction of exogenous TAL1/*SCL* cDNA into embryonic stem cells using lentiviral vectors is efficient and safe [33]. The viral vectors can deliver significant amounts of genetic information into host cells and integrate the newly synthesized dsDNA into the cellular genome successfully and safely [34,35]. Accordingly, genetically engineered viral vectors, such as lentivirus from the retrovirus family, are currently the most efficient tools for gene delivery [12]. Viral vectors contain a viral promoter, which is used to control the expression of the transgene and virulence genes are removed. Viral vectors are safe to use in the laboratory with security modifications to eliminate pathogenicity [36]. Viral vectors, e.g., the lentiviral vector, can transduce a wide range of dividing and non-dividing mammalian cell types [37,38]. Thus, it is possible that a lentiviral vector harboring *SCL* RNA can transduce ICCs into the mammalian bladder. Upon infection, the single-stranded RNA is transduced into the ICCs and reverse-transcribed to dsDNA in the cytoplasm; then the resulting dsDNA would integrate into the genome of the ICCs (Fig. 1A) [12]. In DCP patients, exogenously introduced *SCL* may be expressed, *SCL* protein may be synthesized, and the *SCL* complex would assemble in the ICCs. In DCP patients with downregulated *c-KIT* transcription, the assembled *SCL* complex may bind the promoter to enhance or sustain *c-KIT* transcription. Thus, ICC function may be restored, and bladder under-activity may be relieved (Fig. 1B) [12].

In fact, intravesical viral gene transfer has been applied to treat bladder cancer, and the procedure was well tolerated; the bladder urothelium appears to prevent systemic dissemination of the viral particles [25]. Lentivirus is the commonly used vector for these procedures. Lu et al. successfully applied lentivirus-mediated RNA interference to knockdown clusterin in bladder cancer cells at the RNA and protein levels [39].

Some urologists may suspect the intravesical application of lentiviral particles might cause some concern for local/systemic immunogenic responses, and there is a possibility of poor viral vector permeability through the watertight barrier formed by the urothelium [12]. A previous study in Taiwan developed an intravesical instillation of an *in situ* biodegradable hydrogel system (15% hydrogel) containing a lentiviral vector harboring *WWOX*, a rat bladder tumor suppressor gene, to treat bladder cancer. The hydrogel system showed promise for *in situ* delivery of lentiviral vectors to bladders and demonstrated gene expression for bladder disease therapy without local/systemic immunogenic responses [40,12]. Another research using lentiviral vector-mediated antisense oligonucleotides targeting heat shock protein-27 with the tubulin inhibitor, taltobulin (HTI-286), discovered that strong preclinical proof-of-principle for intravesical administration of oligonucleotides in combination with HTI-286 for the treatment of high-grade bladder cancer [41].

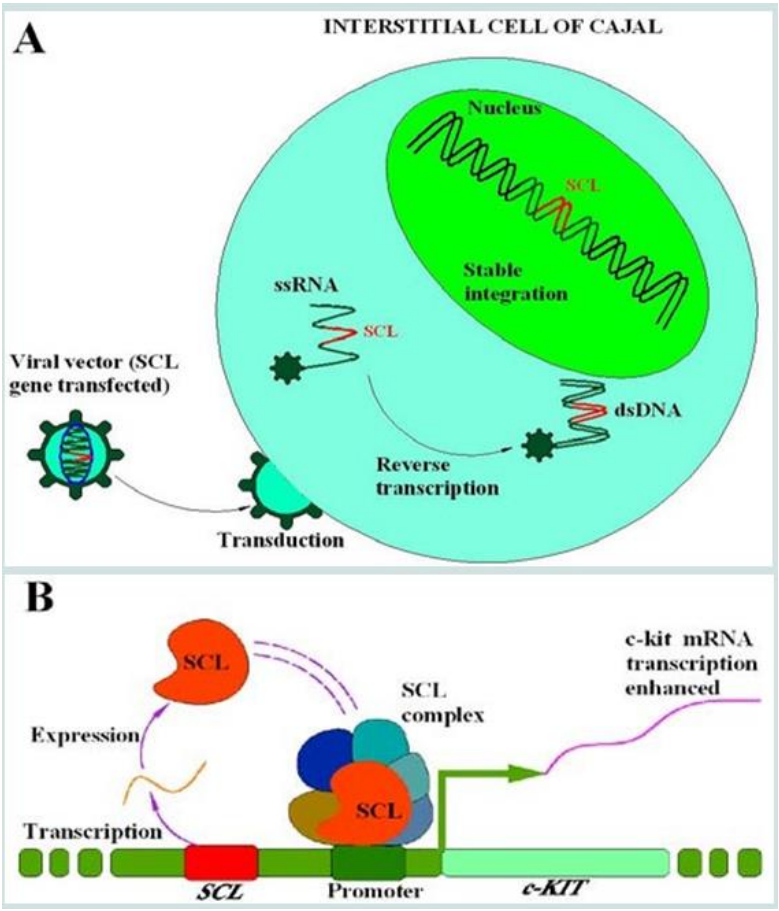

Fig. 1. *SCL* transfer by the lentiviral vector into an interstitial cell of Cajal (ICC). (A) Lentiviral vector carrying *SCL* RNA enters an ICC, and the *SCL* gene is integrated into the host DNA in the nucleus. (B) The *SCL* gene specifically enhances *c-KIT* promoter activity and *c-KIT* gene transcription increases

4. CONCLUSION

Taken together, lentivirus-mediated gene delivery to bladder cells is a safe and promising way to treat the underactivity of DCP by *SCL* gene enhancing *c-KIT* gene expression to rescue the bladder function, so transfection of DNA via an intravesical route using a viral vector is a new strategy of transgene expression for bladder disease therapy [12]. Therefore, we proposed other researchers explore this treatment strategy in detail, not only for diabetic cystopathy but also

for other clinical problems, which can ameliorate the quality of life of our patients, and seem therefore valuable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Feldman EL, Callaghan BC, Pop-Busui R, Zochodne DW, Wright DE, Bennett DL, Bril V, Russell JW, Viswanathan V. Diabetic neuropathy. Nature reviews Disease primers. 2019 Jun 13;5(1):1-8.
2. Daneshgari F, Moore C. Diabetic uropathy. Semin Nephrol. 2006;26:182-185.
3. Goldstraw MA, Kirby MG, Bhardwa J, Kirby RS. Diabetes and the urologist: a growing problem. BJU Int. 2007;99:513-517.
4. Bansal R, Agarwal MM, Modi M, Mandal AK, Singh SK. Urodynamic profile of diabetic patients with lower urinary tract symptoms: Association of diabetic cystopathy with autonomic and peripheral neuropathy. Urology. 2011;77:699-705.
5. Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. Physiol Rev. 2004;84:935-986.
6. Huang Y, Ding L, Shao Y, Chen Z, Shen B, Ma Y, Zhu L, Wei Z. Integrin-linked kinase improves functional recovery of diabetic cystopathy and mesenchymal stem cell survival and engraftment in rats. Canadian Journal of Diabetes. 2017 Jun 1;41(3):312-21.
7. Panigrahy R, Singh B, Das SK. Diabetic uropathy and bladder dysfunctions. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2017 Jan 1;11(1):81-2.
8. Shafik A, El-Sibai O, Shafik AA, Shafik I. Identification of interstitial cells of Cajal in human urinary bladder: Concept of vesical pacemaker. Urology. 2004;64:809-813.
9. Piaseczna-Piotrowska AM, Dzieniecka M, Kulig A, Danilewicz M, Chilarski A. Different distribution of c-kit positive interstitial cells of Cajal-like in children's urinary bladders. Folia Histochem Cytobiol. 2011;49:431-435.
10. Davidson RA, McCloskey KD. Morphology and localization of interstitial cells in the guinea pig bladder: Structural relationships with smooth muscle and neurons. J Urol. 2005;173:1385-1390.
11. Johnston L, Carson C, Lyons AD, Davidson RA, McCloskey KD. Cholinergic- induced Ca2+ signaling in interstitial cells of Cajal from the guinea pig bladder. Am J Physiol Renal Physiol. 2008;294:F645-55.

12. Chen Y, Li JS, Wen JG. Future Applications of Intravesical SCL Gene Transfer for the Treatment of Diabetic Neurogenic Bladder. J Urol Nephrol. 2015;2(1):4.
13. Li YF, Wang QZ, Ding GF. Changes and significances of urodynamics and cajal-like cells in diabetic cystopathy of the early stage. J Clin Urol. 2009;24:694-697.
14. Wang Y, Fang Q, Lu Y, Song B, Li W, et al. Effects of mechanical stretch on interstitial cells of Cajal in guinea pig bladder. J Surg Res. 2010;164: e213-e219.
15. Wang QZ, Ji SQ, Zhu GD, Li YF, Cai ZQ, et al. The morphologic changes and significance of interstitial cells of Cajal-like cells in the bladder of diabetic guinea pig. J Clin Exp Pathol. 2009;25:631-634.
16. Liu YG, Wang QZ, Ding GF, Liu XJ, Zhou JM, et al. Effects of SCF on the expressions of c-kit mRNA and protein of interstitial cells of Cajal- like cells in the bladder of guinea pig in the high glucose environment. J Clin Exp Pathol. 2011;27:282-285.
17. Rasmussen H, Rumessen JJ, Hansen A, Smedts F, Horn T. Ultrastructure of Cajal-like interstitial cells in the human detrusor. Cell Tissue Res. 2009;335:517-527.
18. Chen W, Jiang C, Jin X, Shen W, Song B, et al. Roles of stem cell factor on loss of interstitial cells of Cajal in bladder of diabetic rats. Urology. 2011;78:1443 e1-e6.
19. Torihashi S, Nishi K, Tokutomi Y, Nishi T, Ward S, et al. Blockade of kit signaling induces transdifferentiation of interstitial cells of cajal to a smooth muscle phenotype. Gastroenterology. 1999;117:140-148.
20. Lacombe J, Krosl G, Tremblay M, Gerby B, Martin R, et al. Genetic interaction between Kit and Scl. Blood. 2013;122:1150-1161.
21. Curtis DJ, Salmon JM, Pimanda JE. Concise review: Blood relatives: formation and regulation of hematopoietic stem cells by the basic helix-loop- helix transcription factors stem cell leukemia and lymphoblastic leukemia- derived sequence 1. Stem Cells. 2012;30:1053-1058.
22. Lécuyer E, Herblot S, Saint-Denis M, Martin R, Begley CG, et al. The SCL complex regulates c-kit expression in hematopoietic cells through functional interaction with Sp1. Blood. 2002;100: 2430-2440.
23. Krosl G, He G, Lefrancois M, Charron F, Roméo PH, et al. Transcription factor SCL is required for c-kit expression and c-Kit function in hemopoietic cells. J Exp Med. 1998;188:439-450.
24. Elefanty AG, Begley CG, Metcalf D, Barnett L, Köntgen F, et al. Characterization of hematopoietic progenitor cells that express the transcription factor SCL, using a lacZ “knock-in” strategy. Proc Natl Acad Sci U S A. 1998;95:11897-11902.
25. Perrotte P, Wood M, Slaton JW, Wilson DR, Pagliaro L, et al. Biosafety of *in vivo* adenovirus-p53 intravesical administration in mice. Urology. 2000;56:155-159.
26. Yoshimura N, Chancellor MB, Andersson KE, Christ GJ. Recent advances in understanding the biology of diabetes-associated bladder complications and novel therapy. BJU Int. 2005;95:733-738.

27. McCloskey KD. Bladder interstitial cells: An updated review of current knowledge. Acta Physiol (Oxf). 2013;207:7-15.
28. Kimura S, Kawakami T, Kawa Y, Soma Y, Kushimoto T, et al. Bcl-2 reduced and fas activated by the inhibition of stem cell factor/KIT signaling in murine melanocyte precursors. J Invest Dermatol. 2005;124:229-234.
29. Iino S, Horiguchi S, Horiguchi K. Interstitial cells of Cajal in the gastrointestinal musculature of W (jic) c-kit mutant mice. J Smooth Muscle Res. 2011;47:111-121.
30. Kojima Y, Shibata Y, Imura M, Sasaki S, Kohri K. Role of KIT-positive interstitial cells of cajal in the urinary bladder and possible therapeutic target for overactive bladder. Adv Urol. 2011;2011:816342.
31. Kim BJ, Chae H, Kwon YK, Choi S, Jun JY, et al. Effects of imatinib mesylate in interstitial cells of Cajal from murine small intestine. Biol Pharm Bull. 2010;33:993-997.
32. Begley CG, Green AR. The SCL gene: from case report to critical hematopoietic regulator. Blood. 1999;93:2760-2770.
33. Kurita R, Sasaki E, Yokoo T, Hiroyama T, Takasugi K, et al. Tal1/ Scl gene transduction using a lentiviral vector stimulates highly efficient hematopoietic cell differentiation from common marmoset (*Callithrix jacchus)* embryonic stem cells. Stem Cells. 2006;24:2014-2022.
34. Ni S, Zhao J, Fu Z, Liu H. Lentivirus vector-mediated Rho guanine nucleotide dissociation inhibitor 2 overexpression induces beta-2 adrenergic receptor desensitization in airway smooth muscle cells. J Thorac Dis. 2014;6:118-125.
35. Cribbs AP, Kennedy A, Gregory B, Brennan FM. Simplified production and concentration of lentiviral vectors to achieve high transduction in primary human T cells. BMC Biotechnol. 2013;13:98.
36. Dismuke DJ, Tenenbaum L, Samulski RJ. Biosafety of recombinant adeno-associated virus vectors. Curr Gene Ther. 2013;13:434-452.
37. D'Costa J, Mansfield SG, Humeau LM. Lentiviral vectors in clinical trials: Current status. Curr Opin Mol Ther. 2009;11:554-564.
38. Schambach A, Baum C. Clinical application of lentiviral vectors - concepts and practice. Curr Gene Ther. 200;88:474-482.
39. Lu J, Luo JH, Pang J, Cao JZ, Wu RH, et al. Lentivirus-mediated RNA interference of clusterin enhances the chemosensitivity of EJ bladder cancer cells to epirubicin *in vitro*. Mol Med Rep. 2012;6:1133-1139.
40. Liu C, Tsai T, Fan S, Nien C, Chang L. Hydrogel for enhanced intravesical delivery of lentiviral vector expressing WWOX *in vivo*. The 39th Annual Meeting & Exposition of the Controlled Release Society, Québec, Canada; 2013.
41. Matsui Y, Hadaschik BA, Fazli L, Andersen RJ, Gleave ME, et al. Intravesical combination treatment with antisense oligonucleotides targeting heat shock protein-27 and HTI-286 as a novel strategy for high-grade bladder cancer. Mol Cancer Ther. 2011;8:2402-2011.

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As the first or corresponding author, she has published 10 SCI papers. As the editor-in-chief, she has published 2 medical books, and as the editor, published 3 medical books. As the first prize winner, she won the Henan Provincial Medical Science Progress Award twice. She specialized in Benign diseases of the bladder and urethra, mainly Clinical and Basic Research on Bladder Urethral Injury, Repair, and Inflammation Diseases. She conducted research on Foskolin (targeting immune cells) and H3 receptors (targeting muscle cells) that regulate the NLRP3 inflammasome/IL-1 β pathway, which can alleviate bladder and urinary tract inflammation Cystitis glandular (CG) and seriously affects human health. NLRP3 inflammasome is the core of chronic inflammation and a processing factory for the maturation and secretion of various pro-inflammatory cytokines. Our previous research and preliminary experiments found urine bacterial composition and NLRP3 inflammasome are associated with CG which disclosed NLRP3 inflammasome origin, downstream classical NLRP3/Caspase-1/IL-1β and non-classical NLRP3/Caspase-11/4/5-N-GSDMD pathway, as well as upstream PI3K/AKT/NF- κ B regulatory pathway in bladder epithelial cells, ICC (Interstitial cells of Cajal) cells and macrophages, bladder infusion of probiotics and NLRP3 protein inhibitor may restore natural microecology in diseased bladders.

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Number of Published papers: As the first author and co-author, he has published 6 articles in reputed journals.

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Chapter 2
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Review of Intraoperative Durotomies in Spinal Surgery and Its Management Strategies with Current Advances in Treatment

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ABSTRACT

Intraoperative durotomies in spinal surgeries can have potentially serious consequences if not appropriately addressed. They result from an opening in the dural-arachnoid membrane around the spinal cord, cauda equina or nerve root sleeve. Most causes are iatrogenic, and if not properly addressed or go unnoticed, patients may present with complications such as postural headache, wound breakdown, meningitis, and even death. Magnetic resonance imaging is the diagnostic study of choice, with treatment options ranging from observation, bed rest, and/or epidural blood patch to lumbar subarachnoid drainage, and surgical repair.

Keywords: Intraoperative durotomy; management; treatment.

ABBREVIATIONS

CSF : Cerebrospinal Fluid Leak
MRI : Magnetic Resonance Imaging
CT : Computed Tomography
VM : Valsalva Maneuver
PEG : Polyethylene Glycol
EBP : Epidural Blood Patch

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1. INTRODUCTION

Intraoperative durotomies, whether incidental or intentional, can result in potentially significant complications. Recent advancements in technology and research have given spine surgeons numerous options for both intraoperative dural repair and managing postoperative cerebrospinal fluid (CSF) leaks. Intraoperative durotomies are normally considered on a spectrum, ranging from spinal pseudomeningocele to CSF fistula with CSF leak (which will be referred to as CSF leak in this paper). Most investigators agree a pseudomeningocele is an extravasated collection of extradural CSF. It can be contained within a fibrous capsule with or without an arachnoid-lined membrane [1,2]. If the extradural fluid communicates with another cavity, such as the pleura, or if direct communication to the outside exists, this is when it is considered a CSF fistula. A dural opening needing to be present is believed to be the foundational reason for the existence of this condition. By far, the most common cause is iatrogenic, resulting from a dural tear during spinal surgery. Intraoperative treatment of intentional and incidental durotomies through a variety of synthetic or autologous materials as well as postoperative CSF leak management strategies including conservative measures, epidural blood patches, CSF diversion therapies, and definitive surgical repair will be discussed in the present review.

1.1 Epidemiology

Iatrogenic intraoperative durotomy can be encountered incidentally or intentionally. For example, when accessing intradural tumors, the dura is intentionally opened, in a planned manner and primary repair via suturing is typically intended. If not properly addressed, this can increase the risk of postoperative CSF leaks. Incidental durotomies are more challenging to treat since they result in more complicated tears. Intraoperative incidental durotomies are common, especially during lumbar laminectomy [3–6]. Rates of incidental durotomy in lumbar durotomy have been reported in the literature to occur from 0.5% (in lumbar discectomy) to 35% in a single retrospective study [7,8]. Understandably, durotomy rates vary with the surgical technique employed, for example, open versus a minimally invasive surgical approach. In one meta-analysis it was found that a durotomy rate ranged from 2%-20% in open surgical technique for lumbar degenerative conditions, and approximately ~7% in minimally invasive techniques [9,108]. The incidence of intraoperative incidental durotomy in cervical spine surgery is considerably lower compared to thoracic or lumbosacral surgeries [10,11]. Presumably, this is due to the fact that surgeons are more likely to manipulate the dura around the cauda equina and that there is probably a higher number of laminectomies performed in the lumbar region [12,13]. The incidence of CSF leak in elective anterior cervical spine surgery ranges from 0.3%-21.4% [14,15]. This is appreciated to be higher with patients suffering from ossified posterior longitudinal ligament (4.5%-32%) [16–18]. Cervical laminectomy and corpectomy have also been associated with the development of postoperative pseudomeningocele [19–21]. In one study of 286 patients with ossification of the ligamentum flavum, one-third were reported to have durotomies, but the literature on this is sparse [11,15]. It is more likely that

the real incidence is unknown as many cases are self-limited and asymptomatic [4].

1.2 Pathophysiology

Iatrogenic intraoperative durotomy may or may not be associated with an arachnoid tear, but a dural tear is necessary to have a durotomy. If the arachnoid is not violated, the herniation of CSF and arachnoid membrane tends to resemble a sac with some arguing that this condition should be a “true meningocele” [22]. If the CSF extravasates through a dural-arachnoid tear into the surrounding soft tissue, eventually leading to a fibrous capsule, it is termed a pseudomeningocele [1,2]. In both conditions, there is no communication with another cavity or the outside world.

The debate also exists when it comes to factors contributing to persistent communication. Items that have been evaluated are the amount of CSF leak and/or whether the arachnoid layer is violated or intact but with herniation. In order to discuss the aforementioned fact, it is important to further delineate the continuum with another term known as the pseudocyst. If the arachnoid mater is intact then this is coined the pseudocyst and results in the accumulation of CSF via a ball-valve mechanism [12,23]. Arachnoid mater violations where CSF can directly flow into the extradural tissue forms the false cyst or pseudomeningocele. CSF extravasations, if small, are believed to be self-limited as reabsorption is more likely [24]. This is why the true incidence of intraoperative durotomy is unknown since many cases are likely asymptomatic [4]. With a pseudomeningocele this is less likely, as in some cases, the extravasated CSF causes reactive changes in the postoperative bed of the paraspinal musculature, leading to non-resorption of the fluid [20,25,26]. The vast majority of intraoperative durotomies that lead to pseudomeningocele occur in the lumbar spine because this part of the spine is under higher pressure compared to cervical or thoracic areas [27].

1.3 Clinical Manifestations

Intraoperative durotomy may present in a variety of ways. As previously stated, in the case of a small unnoticed durotomy, most are asymptomatic and self-limited [4,24]. When symptoms do occur they can include, pseudomeningocele, leaking from wound, dizziness, nausea, postural headaches, vertigo, neck pain, diplopia, photophobia, tinnitus, and blurred vision [28]. Other more serious complications, especially when CSF communicates with the outside world, include wound breakdown, meningitis, hydrocephalus, arachnoiditis, and most grave, *death* [29].

The time interval for symptom onset ranges from immediate post-operatively to years after surgery [1]. Pseudomeningoceles typically appear as a fluctuant mass that can enlarge with Valsalva-causing maneuvers [30]. Sometimes pain can be elicited from palpation of the pseudomeningocele [31]. An actual CSF leak can be identified by clear, colorless fluid from an opening in the wound [32]. A cloudier, red or xanthochromic appearance can occur suggesting an infection,

presence of blood, or seroma which can complicate identification [32]. At times, patients may report the return of their preoperative symptoms which can range from radiculopathy to myelopathy or spinal cord injury believed to be caused by the herniation of nerve tissue [5,19–21,31,33–39]. Patients may also present with intracranial hypotension symptoms including photophobia, cranial nerve palsies, and tinnitus [40,41].

2. DIAGNOSTICS

Diagnosis is confirmed via magnetic resonance imaging (MRI) with history and physical examination narrowing down one's differential.

2.1 MRI

Imaging the spine is the initial step, with the signal following that of CSF on all sequences. A region of hypointensity on T1-weighted images and hyperintensity on T2-weighted images is seen [37,42]. MRI is particularly helpful as it can delineate the location of the issue, sometimes showing the level of communication with the dura and can characterize any internal components of the sac. If the cranium is incidentally imaged, findings of intracranial hypotension can be seen which include a subdural fluid collection, intracranial meningeal enhancement, and caudal displacement of cerebellar tonsils [7] further narrowing down one differential.

2.2 Computed Tomography (CT) and CT Myelogram

CT scanning can help better delineate bone than MRI, allowing for improved visualization of a pseudomeningocele/cyst or fistula/leak relative to a surgical site. The introduction of a myelogram, which involves performing a CT scan of the spine after intradural administration of contrast, can identify the presence of a pseudomeningocele or pseudocyst by showing it filling with the administered contrast or by demonstrating active extravasation at the dural defect [43].

2.3 Beta 2-Transferrin

If a fistula/leak is present and direct visualization of clear fluid is noted from a defect in the wound, analysis can be done by looking for Beta 2-Transferrin within a sample of the leaking fluid. Beta 2-Trasnferrin is a protein found only in CSF [44]. Less than 1 mL is needed to test for Beta 2-Trasferrin. Via electrophoresis, one can appreciate 2 bands where one is for Beta 1-Transferrin and the other for the Beta 2-Transferrin isoform which arises from Beta 1-Transferrin. This is relative to serum or another body fluid which would only have a Beta 1-Transferrin band.

Caution must be taken with results interpretation as false positives can occur. In certain patients with specific genetic variations [45] and/or certain medical conditions like alcoholism, cirrhosis, rectal cancer, or rare glycoprotein metabolism disorders [45]. Non-CSF fluid can be mistaken for CSF. To combat

this, false interpretation can be avoided by simultaneously testing other body fluids obtained in the same patient for Beta 2-Trasnferrin to ensure they are different in comparison. Careful attention to clinical history and comparison patterns of CSF with other body fluids will aid in making an accurate interpretation in unusual cases.

3. INTRAOPERATIVE MANAGEMENT

When a dural violation is appreciated, the first and foremost effort should be primary closure to prevent future complications. The goal, though debatable, is to achieve a “watertight” closure of the dura [46]. This is often difficult, especially for incidental intraoperative durotomies due to the unique biomechanical properties of dura mater which can be fragile or if the tear occurred at an inaccessible location. It is, for this reason, that the ultimate goal should be to contain neural elements and prevent pseudomeningoceles/cysts or CSF fistulas/leaks.

If a tear is easily accessible, primary repair is generally recommended. If it is not accessible, then observation, sealants, or CSF diversion maneuvers are used [47,48]. Since several items exist to bring dura together, ranging from sutures to synthetic patches/grafts, it is helpful to organize primary repair strategies into 3 categories: sutures, sealants, and patches/grafts [7,49–53]. Currently, no official consensus exists between which is the most ideal.

3.1 Sutures

Spine surgeons almost universally rely on non-absorbable sutures. The 4 main suture materials include Nurolon, Prolene, Gore-Text, and Silk.

Nurolon is braided and comprised of long-chain aliphatic polymer of Nylon 6 or 6.6. It has been reported to elicit minimal acute inflammation, maintaining 81% tensile strength at 1 year and decreasing to 66% at 11 years [54].

Prolene is a monofilament comprised of an isotactic crystalline stereoisomer of polypropylene, a synthetic linear polyolefin. It does not adhere to tissues and does not cause an inflammatory reaction. Tensile strength is reportedly maintained for up to 2 years [55].

Gore-Tex is a microporous monofilament made of expanded polytetrafluoroethylene (cPTFE). It has a beneficial structure that allows it to have a needle attached which is the diameter of the thread, thus reducing CSF leak at suture sites [56,57].

Lastly, silk was routinely used in earlier neurosurgical literature but has been mentioned less in the past several decades. It is technically non-absorbable but becomes proteolyzed with time and can be undetectable at a 2-year mark [58].

The literature around suturing techniques is sparse though some do exist. The conclusions are mixed and make it challenging for one to make a definitive

statement about what technique is best. One article found that in a small linear incision, simple interrupted silk suturing was superior to running, running locked, or interrupted vertical mattress techniques [59]. To that end another paper studied Prolene and compared simple running to interrupted and found no change in the difference between CSF leaks [60].

A similar statement can be made about suture type when it comes to selecting one of the 4 aforementioned non-absorbable sutures. Biomechanical studies with Gore-Tex found that up to a mean CSF peak pressure of 34 cm H2O can be observed prior to CSF leakage recognition with its use when compared to Nurolon which had a mean CSF peak pressure of only 21 cm H2O. This same study found also that it still remained superior when examined across suturing techniques (running, locked continuously, and interrupted) [61]. In regards to Prolene, another study showed that in cadaveric specimens it too had a higher mean pressure threshold when compared to Nurolon [62]. No studies currently exist giving a direct comparison between Gore-Tex and Prolene.

Ultimately a decision around the best suture or suture technique remains a challenging one and we advocate for using the material one is most comfortable, familiar, and has had the most success with in the past as surgeon experience has been shown to impact outcomes [63].

After completing a primary closure one should test for a persistent CSF leak via a Valsalva maneuver (VM) where the anesthesiologist increases the intrathoracic pressure. The VM can be performed simply by switching the ventilator to manual ventilation, fully closing the adjustable pressure-limiting valve, increasing the fresh gas flow, and squeezing the breathing circuit bag for 15-20 seconds to generate the needed VM pressure which is around 40 mmHg intrathoracic pressure [64]. Its usefulness is more convincing during intraoperative durotomy repair but one should be mindful that rare complications have been reported, ranging from stroke and retinopathy to pneumothorax [64]. Clinical judgment should prevail when deciding to perform a VM.

3.2 Grafts/Patches

If an intraoperative durotomy is not ideal for a primary closure, for example, such as a far lateral one, or when neural elements become compressed, dural grafts or patches are useful options. Numerous materials can act as dural substitutes. Ideally, the goal is to restore the continuity of dura mater to minimize CSF leaks by mimicking the compliance of dura while being biologically inert [65]. Currently, the options fall into 4 categories, with those being: autograft, allograft (i.e. cadaveric dura), xenograft (animal-derived), and synthetic materials. Surgicel is sometimes used to augment some dural repairs as well.

In the autologous family, the options during spinal surgery typically include fascia lata, fat tissue, and muscle.

Some commonly used xenografts or synthetic materials include the following: Durasis, DuraGaurd/Matrix, Durepair, Alloderm, Preclude, and Neuro-Patch. The xenografts: DuraGen, DuraMatrix, and Derepair are all type I Collagen matrixes made from bovine Achilles tendon.

DuraGen has been shown to have 20% more conformability than DuraMatrix while DuraMatrix has a 50 times lower liquid permeability [66,67]. DuraGen has the most published data [68] and is widely utilized for dural repair. An interesting property of DuraGen is its secondary hemostatic capabilities: its porosity allows platelets and fibroblasts to infiltrate, forming fibrin clots and laying down natural collagen fibers, which help prevent CSF leakage and initiate dural repair [69]. DuraGen has also been show to completely resorb within 1 year [69]. It is reported to have no inflammatory response, a 1.9% infection rate, and a 2.1% leakage rate [70,108].

Durepair is made up of type I and III collagen and is produced by bovine skin [71]. Biomechanical studies show it has up to 4 times more tensile strength than cranial dura mater [72].

Durasis is made from porcine small intestinal submucosa. It manages to keep the cells' extracellular membrane intact as it is harvested by removing the cells between the mucosal and muscular layers. Because of this notion, it contains collagen, bioactive proteins, and cytokines that guide host-tissue remodeling [73]. In 2007 it was demonstrated to have comparable rates of infection, CSF leak, and meningitis with that of other comparable dural substitutes of that time [73,108].

DuraGuard is made from bovine pericardium that is cross-linked with glutaraldehyde. It has been reported to have superior tear resistance and tensile strength making suturing to it more feasible.

Alloderm is made from human donor skin which contains no cellular tissue but retains its biochemical and structural components [74]. It has been shown to become vascularized and integrated with native dura [74]. One study showed a reoperation rate for CSF leak in Chiari decompression surgery of 2.2% when compared to DuraGaurd, DuraGen, and Durepair which had a 17.1% rate.

Lastly, Preclude is made of inert polytetrafluoroethylene and elastomeric fluoropolymer in a 3-layer construct [75] and Neuro-Patch is made of microporous fleece from polyester urethane that also supports fibroblastic proliferation [76]. Interestingly in a study looking at postoperative adhesions and fibrosis-induced spinal cord tethering between Surgicel, Durasis, DuraGen, and Preclude, it was appreciated that DuraGen caused the least amount of local inflammation in the subarachnoid and Preclude generated the most [69].

3.3 Sealants

If a VM maneuver reveals a persistent CSF leak after a primary closure and after a graft/patch is attempted, a sealant can be placed over the area of the leak. Despite animal studies suggesting sealant alone can withstand high hydrostatic

pressures [16,77,78], some remain in situ for only up to 10-14 days [79], thus it must be supplemental to a patch or graft.
Two types of sealants are commercially available which fall into the category of either absorbable: synthetic consisting of polyethylene glycol (PEG)-based polymers or fibrin-based (from allogenic or autogenic fibrinogen in combination with thrombin and other hemostatic factors) categories. Both can be found in liquid or patch form.

Subtypes of fibrin-based sealants and liquid glue formulations include Tisseel or Tissucol, Evicel, and dry patch products, called Tachosil and Tachocomb. Literature around fibrin-based sealants has been mixed [80]. Their ability to augment sutures or aid in achieving “watertight” dural closure was found not to significantly decrease CSF leak when compared to sutures alone [80]. Although this was a retrospective study with inherent limitations, it is relevant as no randomized controlled trials exist looking at intraoperative durotomies during spinal surgery and the use of fibrin-based sealants. An interesting fact about the make of these agents is that they are technically useful as hemostatic agents as well.

Tisseel has 2 components: human fibrinogen and aprotinin, and human thrombin and calcium chloride dihydrate [81]. When mixed via the application tip during use, a fibrin clot is formed that adheres and provides hemostasis to tissues.

Evicel is made from human plasma and also has 2 components: Biological Active Component 2 (largely cryoprecipitate) and thrombin.

Subtypes of synthetic PEG-based sealants include DuraSeal Exact and Adherus. Both work in the form of hydrogels to minimize mass on the spine. DuraSeal, the predecessor to DuraSeal Exact, was reported to swell once applied [82,83]. In regards to efficacy, a randomized controlled trial looking at incidental and intentional spinal durotomies showed no significant difference in CSF leakage or superficial skin infection rates between the standard of care and DuralSeal Exact [84]. FDA-approved secondary agent for dural closure in the spine is currently only applicable for DuralSeal Exact [85]. Regardless of the use of dural sealant, effective primary closure of the defect is critical to prevent further CSF extravasation.

If after use of these items proves there to be a residual CSF leak, some authors describe keeping a subfascial drain that would normally be placed intraoperatively for a longer period of time but keeping it “off suction” for several more days until drainage slowed [86].

4. POSTOPERATIVE PSEUDOCYST/PSEUDOMENINGOCELE/CSF FISTULA/LEAK TREATMENT

4.1 Conservative Therapy

If an intraoperative spinal durotomy could not be closed “watertight” or went unnoticed and the patient exhibited any of the before-mentioned symptoms, preventing pseudomeningocele formation/controlling CSF leak relies on

manipulating differences in subarachnoid and epidural pressure to impede flow [87]. The literature is mixed on bed rest/Trendelenburg positioning if primary closure was attempted for a lumbar durotomy. Bed rest is traditionally prescribed as a standard approach for the management of dural tears [88]. The rationale behind this approach is that the orthostatic position increases the hydrostatic pressure of the CSF and consequently may worsen the leakage [89]. Multiple survey-based studies conducted over the last decade indeed confirm this preference in the spine surgery community, with up to 89% of surgeons in favor of prolonged bed rest in this patient population [90–93]. The data supporting this approach, however, is composed of case series describing patients successfully treated with prolonged bed rest, without a control group of alternative options [94]. A recent meta-analysis from 2023 found in patients with incidental durotomies during spine surgery, who underwent primary closure, early mobilization may reduce pulmonary complications compared to prolonged bed rest, without a significant difference between groups in the incidence of CSF leak or the need for additional surgical durotomy repair [95]. Although prolonged bed rest is traditionally prescribed following a dural tear, it is not without risks. Surgeons should use this strategy with caution, given the risk of the aforementioned postoperative complications [96]. This result was also confirmed by the one randomized control trial to date that looked at this question in lumbar surgical patients who had primarily repaired intraoperative durotomies and was included in the meta-analysis [95].

If a primary closure was not performed because the durotomy was unnoticed, and the patient is exhibiting symptoms, it is reasonable to try Trendelenburg positioning/bedrest for a short course of 1 to 3 days in someone with a suspected lumbar durotomy. Direct pressure at the site of durotomy with a pressure dressing or brace may counteract egress through the area of least resistance as well [52]. Interestingly in the cervical spine, Kim et al published a report where a polycarbonate face mask was able to apply pressure on the cervical wound and resolve a refractory pesudomeningocele [52]. If the durotomy occurred in the cervical or thoracic spine, primary closure was not attempted, and the patient is symptomatic, the elevation of the head of the bed is reasonable for 1 to 3 days.

Inhibiting CSF formation with acetazolamide has been described in a randomized control trial to stop CSF leak in cranial patients [97] but the literature is limited regarding its use in spinal patients.

4.2 Non-conservative Therapy

If a CSF leak persists, the patient has a pseudomeningocele/cyst with subjective symptoms, non-conservative therapies should be discussed which include epidural blood patch, CSF diversion measures, and re-operation for residual or previously unnoticed intraoperative durotomy identification and primary closure attempt/reattempt.

4.3 Epidural Blood Patch

Epidural blood patch (EBP) is a procedure in which the patient’s blood is injected into the epidural space. It is thought that the blood forms a clot over the dural

tear, allowing the healing of the dura, as well as raising extradural pressure relative to the subarachnoid pressure in turn decreasing the efflux CSF gradient [98]. Limited cases are described stating the efficacy of EBP in resolving pseudoemingoceles [99]. Skepticism, however, exists among spine surgeons as no robust large studies have been done [98,100,101].

4.4 CSF Diversion

There is a paucity of literature describing CSF diversion therapy via a subarachnoid drain, normally placed in the lumbar region, after intraoperative spinal durotomy, but the benefits and timing are not as clear. In the cases of a large pseudomeningocele, it has been shown that they are best treated by a combination of primary closure and implantation of a subarachnoid drain [12]. If placed, it has shown efficacy at an output rate of 5-10 mL/hr for 3-5 days as a primary tool or supplement to other measures [102]. Lumbar subarachnoid drainage has been reported to have a complication rate of up to 44% with symptoms ranging from headache and nerve root pain to subdural hematoma, pneumocephalus, and meningitis [103]. These are important to consider when choosing to use a lumbar subarachnoid drain.

Lastly, there have been reports of a lumbo-peritoneal shunt being used to successfully treat a pseudomeningocele and CSF fistula/leak [104–108]. However, this should only be a consideration after an attempt at a primary closure has failed.

5. CONCLUSION

There are many options for the repair of intraoperative durotomies that can be utilized. Iatrogenic causes are common, and the goal when identified is to achieve “watertight” closure of the dura with sutures whenever possible. Dural sealants and patches/grafts may be used as adjuncts. MRI is the neurodiagnostic modality of choice for diagnosis. If a durotomy goes unnoticed or a “watertight” closure cannot be achieved, and the patient becomes symptomatic, several conservative therapies are available. These include bed rest and head-of-bed elevation (depending on whether the durotomy is in the cervicothoracic or lumbar region), pressure dressing, epidural blood patch, and lumbar subarachnoid drain placement. If these measures fail, re-operation to obtain a primary closure should be attempted/reattempted. In rare cases, the placement of a ventriculo-peritoneal or lumbo-peritoneal shunt may be considered.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Miller PR, Elder FW. Meningeal pseudocysts (meningocele spurius) following laminectomy. Report of ten cases. J Bone Joint Surg Am. 1968;50(2):268-276.
   DOI: 10.2106/00004623-196850020-00005
2. Pagni CA, Cassinari V, Bernasconi V. Meningocele spurius following hemilaminectomy in a case of lumbar discal hernia. J Neurosurg. 1961;18:709-710.
   DOI: 10.3171/jns.1961.18.5.0709
3. Jones AA, Stambough JL, Balderston RA, Rothman RH, Booth RE. Long-term results of lumbar spine surgery complicated by unintended incidental durotomy. Spine (Phila Pa 1976). 1989;14(4):443-446.
   DOI: 10.1097/00007632-198904000-00021
4. Lee KS, Hardy IM. Postlaminectomy lumbar pseudomeningocele: report of four cases. Neurosurgery. 1992;30(1):111-114.
   DOI: 10.1227/00006123-199201000-00020
5. O'Connor D, Maskery N, Griffiths WE. Pseudomeningocele nerve root entrapment after lumbar discectomy. Spine (Phila Pa 1976). 1998;23(13):1501-1502.
   DOI: 10.1097/00007632-199807010-00014
6. Oppel F, Schramm J, Schirmer M, Zeitner M. Results and Complicated Course after Surgery for Lumbar Disc Herniation. In: Wüllenweber R, Brock M, Hamer J, Klinger M, Spoerri O, eds. Lumbar Disc Adult Hydrocephalus. Advances in Neurosurgery. Springer Berlin Heidelberg. 1977;4:36-51.
   DOI: 10.1007/978-3-642-66578-3_9
7. Mayfield FH, Kurokawa K. Watertight closure of spinal dura mater. Technical note. J Neurosurg. 1975;43(5):639-640.
   DOI: 10.3171/jns.1975.43.5.0639
8. Rodriguez-Olaverri JC, Zimick NC, Merola A, et al. Comparing the clinical and radiological outcomes of pedicular transvertebral screw fixation of the lumbosacral spine in spondylolisthesis versus unilateral transforaminal lumbar interbody fusion (TLIF) with posterior fixation using anterior cages. Spine (Phila Pa 1976). 2008;33(18):1977-1981.
   DOI: 10.1097/BRS.0b013e31817ecc01
9. Ghobrial GM, Theofanis T, Darden BV, Arnold P, Fehlings MG, Harrop JS. Unintended durotomy in lumbar degenerative spinal surgery: A 10-year systematic review of the literature. Neurosurg Focus. 2015;39(4):E8.
   DOI: 10.3171/2015.7.FOCUS15266
10. McMahon P, Dididze M, Levi AD. Incidental durotomy after spinal surgery: a prospective study in an academic institution. J Neurosurg Spine. 2012;17(1):30-36.
    DOI: 10.3171/2012.3.SPINE11939
11. Williams BJ, Sansur CA, Smith JS, et al. Incidence of unintended durotomy in spine surgery based on 108,478 cases. Neurosurgery. 2011;68(1):117-123; discussion 123-124.
    DOI: 10.1227/NEU.0b013e3181fcf14e

12. Weng YJ, Cheng CC, Li YY, Huang TJ, Hsu RWW. Management of giant pseudomeningoceles after spinal surgery. BMC Musculoskelet Disord. 2010;11:53.
DOI: 10.1186/1471-2474-11-53
13. Hawk MW, Kim KD. Review of spinal pseudomeningoceles and cerebrospinal fluid fistulas. Neurosurg Focus. 2000;9(1):e5.
DOI: 10.3171/foc.2000.9.1.5
14. Cammisa FP, Girardi FP, Sangani PK, Parvataneni HK, Cadag S, Sandhu HS. Incidental Durotomy in Spine Surgery: Spine. 2000;25(20):2663-2667.
DOI: 10.1097/00007632-200010150-00019
15. Tani T, Ushida T, Ishida K, Iai H, Noguchi T, Yamamoto H. Relative safety of anterior microsurgical decompression versus laminoplasty for cervical myelopathy with a massive ossified posterior longitudinal ligament. Spine (Phila Pa 1976). 2002;27(22):2491-2498.
DOI: 10.1097/00007632-200211150-00013
16. Epstein NE, Hollingsworth R. Anterior cervical micro-dural repair of cerebrospinal fluid fistula after surgery for ossification of the posterior longitudinal ligament. Technical note. Surg Neurol. 1999;52(5):511-514.
DOI: 10.1016/s0090-3019(99)00135-4
17. Macdonald RL, Fehlings MG, Tator CH, et al. Multilevel anterior cervical corpectomy and fibular allograft fusion for cervical myelopathy. J Neurosurg. 1997;86(6):990-997.
DOI: 10.3171/jns.1997.86.6.0990
18. Smith MD, Bolesta MJ, Leventhal M, Bohlman HH. Postoperative cerebrospinal-fluid fistula associated with erosion of the dura. Findings after anterior resection of ossification of the posterior longitudinal ligament in the cervical spine. J Bone Joint Surg Am. 1992;74(2):270-277.
19. Cobb C, Ehni G. Herniation of the spinal cord into an iatrogenic meningocele. Case report. J Neurosurg. 1973;39(4):533-536.
DOI: 10.3171/jns.1973.39.4.0533
20. Goodman SJ, Gregorius FK. Cervical pseudomeningocele after laminectomy as a cause of progressive myelopathy. Bull Los Angeles Neurol Soc. 1974;39(3):121-127.
21. Maiuri F, Corriero G, Giamundo A, Donati P, Gambardella A. Postoperative cervical pseudomeningocele. Neurochirurgia (Stuttg). 1988;31(1):29-31.
DOI: 10.1055/s-2008-1053895
22. Rinaldi I, Peach WF. Postoperative lumbar meningocele. Report of two cases. J Neurosurg. 1969;30(4):504-507.
DOI: 10.3171/jns.1969.30.4.0504
23. Hyndman OR, Gerber WF. Spinal extradural cysts, congenital and acquired; report of cases. J Neurosurg. 1946;3(6):474-486. DOI: 10.3171/jns.1946.3.6.0474
24. Tsuji H, Handa N, Handa O, Tajima G, Mori K. Postlaminectomy ossified extradural pseudocyst. Case report. J Neurosurg. 1990;73(5):785-787.
DOI: 10.3171/jns.1990.73.5.0785
25. Bhatoe HS. Postoperative lumbar pseudomeningocele. J Indian Med Assoc. 1995;93(7):280, 282.

26. Pau A. Postoperative “meningocele spurius”. Report of two cases. J Neurosurg Sci. 1974;18(2):150-152.
27. Cervical cerebral spinal fluid pressure. The Spine Journal. 2002;2(2):34-35.
DOI: 10.1016/S1529-9430(01)00257-1
28. Deyo RA, Cherkin DC, Loeser JD, Bigos SJ, Ciol MA. Morbidity and mortality in association with operations on the lumbar spine. The influence of age, diagnosis, and procedure. J Bone Joint Surg Am. 1992;74(4):536-543.
29. Couture D, Branch CL. Spinal pseudomeningoceles and cerebrospinal fluid fistulas. Neurosurg Focus. 2003;15(6):E6.
DOI: 10.3171/foc.2003.15.6.6
30. Rocca A, Turtas S, Pirisi A, Agnetti V. Iatrogenic lumbar pseudomeningocele. Zentralbl Neurochir. 1986;47(4):311-315.
31. Aldrete JA, Ghaly R. Postlaminectomy pseudomeningocele. An unsuspected cause of low back pain. Reg Anesth. 1995;20(1):75-79.
32. Huff T, Tadi P, Weisbrod LJ, Varacallo M. Neuroanatomy, Cerebrospinal Fluid. In: StatPearls. StatPearls Publishing; 2024.
Accessed July 20, 2024.
Available:http://www.ncbi.nlm.nih.gov/books/NBK470578/
33. Burres KP, Conley FK. Progressive neurological dysfunction secondary to postoperative cervical pseudomeningocele in a C-4 quadriplegic. Case report. J Neurosurg. 1978;48(2):289-291.
DOI: 10.3171/jns.1978.48.2.0289
34. Hadani M, Findler G, Knoler N, Tadmor R, Sahar A, Shacked I. Entrapped lumbar nerve root in pseudomeningocele after laminectomy: Report of three cases. Neurosurgery. 1986;19(3):405-407.
DOI: 10.1227/00006123-198609000-00011
35. Helle T, Conley FK. Postoperative Cervical Pseudomeningocele as a Cause of Delayed Myelopathy. Neurosurgery. 1981;9(3):314-316.
36. Horowitz SW, Azar-Kia B, Fine M. Postoperative cervical pseudomeningocele. AJNR Am J Neuroradiol. 1990;11(4):784.
37. Hosono N, Yonenobu K, Ono K. Postoperative cervical pseudomeningocele with herniation of the spinal cord. Spine (Phila Pa 1976). 1995;20(19):2147-2150.
DOI: 10.1097/00007632-199510000-00014
38. Rinaldi I, Hodges TO. Iatrogenic lumbar meningocoele: report of three cases. J Neurol Neurosurg Psychiatry. 1970;33(4):484-492.
DOI: 10.1136/jnnp.33.4.484
39. Wilkinson HA. Nerve-root entrapment in “traumatic” extradural arachnoid cyst. J Bone Joint Surg Am. 1971;53(1):163-166.
40. Bell WE, Joynt RJ, Sahs AL. Low spinal fluid pressure syndromes. Neurology. 1960;10:512-521.
DOI: 10.1212/wnl.10.5.512
41. Hochman MS, Naidich TP, Kobetz SA, Fernandez-Maitin A. Spontaneous intracranial hypotension with pachymeningeal enhancement on MRI. Neurology. 1992;42(8):1628-1630.
DOI: 10.1212/wnl.42.8.1628

42. Schumacher HW, Wassmann H, Podlinski C. Pseudomeningocele of the lumbar spine. Surg Neurol. 1988;29(1):77-78. DOI: 10.1016/0090-3019(88)90127-9
43. Lauer KK, Haddox JD. Epidural blood patch as treatment for a surgical durocutaneous fistula. J Clin Anesth. 1992;4(1):45-47. DOI: 10.1016/0952-8180(92)90120-p
44. Ryall RG, Peacock MK, Simpson DA. Usefulness of beta 2-transferrin assay in the detection of cerebrospinal fluid leaks following head injury. J Neurosurg. 1992;77(5):737-739. DOI: 10.3171/jns.1992.77.5.0737
45. Sloman AJ, Kelly RH. Transferrin allelic variants may cause false positives in the detection of cerebrospinal fluid fistulae. Clin Chem. 1993;39(7): 1444-1445.
46. Barth M, Tuettenberg J, Thomé C, Weiss C, Vajkoczy P, Schmiedek P. Watertight dural closure: is it necessary? A prospective randomized trial in patients with supratentorial craniotomies. Neurosurgery. 2008;63(4 Suppl 2):352-358; discussion 358. DOI: 10.1227/01.NEU.0000310696.52302.99
47. Hannallah D, Lee J, Khan M, Donaldson WF, Kang JD. Cerebrospinal fluid leaks following cervical spine surgery. J Bone Joint Surg Am. 2008;90(5):1101-1105. DOI: 10.2106/JBJS.F.01114
48. Kitchel SH, Eismont FJ, Green BA. Closed subarachnoid drainage for management of cerebrospinal fluid leakage after an operation on the spine. J Bone Joint Surg Am. 1989;71(7):984-987.
49. Eismont FJ, Wiesel SW, Rothman RH. Treatment of dural tears associated with spinal surgery. J Bone Joint Surg Am. 1981;63(7):1132-1136.
50. Foyt D, Johnson JP, Kirsch AJ, Bruce JN, Wazen JJ. Dural closure with laser tissue welding. Otolaryngol Head Neck Surg. 1996;115(6):513-518. DOI: 10.1016/S0194-59989670005-0
51. Levy DI, Sonntag VK. Titanium dural clip testing. Technical note. J Neurosurg. 1994;81(6):947-949. DOI: 10.3171/jns.1994.81.6.0947
52. Kerr E, Ripul P, Kim KD. Refractory Cervical Spinal Pseudomeningocele Successfully Treated with a Polycarbonate Face Mask: Technical Note. JSM Neurosurgery and Spine.
53. Shimada Y, Hongo M, Miyakoshi N, et al. Dural substitute with polyglycolic acid mesh and fibrin glue for dural repair: Technical note and preliminary results. J Orthop Sci. 2006;11(5):454-458. DOI: 10.1007/s00776-006-1044-7
54. Dafford EE, Anderson PA. Comparison of dural repair techniques. Spine J. 2015;15(5):1099-1105. DOI: 10.1016/j.spinee.2013.06.044
55. Chu CC, Pratt L, Zhang L, Hsu A, Chu A. A comparison of a new polypropylene suture with Prolene. J Appl Biomater. 1993;4(2):169-181. DOI: 10.1002/jab.770040209

56. Miller CM, Sangiolo P, Jacobson JH. Reduced anastomotic bleeding using new sutures with a needle-suture diameter ratio of one. Surgery. 1987;101(2):156-160.
57. Dang MC, Thacker JG, Hwang JC, Rodeheaver GT, Melton SM, Edlich RF. Some biomechanical considerations of polytetrafluoroethylene sutures. Arch Surg. 1990;125(5):647-650.
DOI: 10.1001/archsurg.1990.01410170095020
58. Gallini G, Pasqualini M. [Sutures in oral surgery]. Attual Dent. 1988;4(20): 14-18.
59. Megyesi JF, Ranger A, MacDonald W, Del Maestro RF. Suturing technique and the integrity of dural closures: An *in vitro* study. Neurosurgery. 2004;55(4):950-954; discussion 954-955.
DOI: 10.1227/01.neu.0000138441.07112.1b
60. Ebel F, Wanderer S, Beck J, Raabe A, Ulrich CT. The optimal dura closure technique and material – An *In-Vitro* Evaluation. J Neurol Surg A Cent Eur Neurosurg. 2017;78(S 01):S1-S22.
DOI: 10.1055/s-0037-1603847
61. Ghobrial GM, Maulucci CM, Viereck MJ, et al. Suture Choice in lumbar dural closure contributes to variation in leak pressures: Experimental Model. Clin Spine Surg. 2017;30(6):272-275.
DOI: 10.1097/BSD.0000000000000169
62. Bakhsheshian J, Strickland BA, Patel NN, et al. The use of a novel perfusion-based cadaveric simulation model with cerebrospinal fluid reconstitution comparing dural repair techniques: A pilot study. Spine J. 2017;17(9):1335-1341.
DOI: 10.1016/j.spinee.2017.04.007
63. Kelz RR, Sellers MM, Niknam BA, et al. A national comparison of operative outcomes of new and experienced surgeons. Ann Surg. 2021;273(2):280-288.
DOI: 10.1097/SLA.0000000000003388
64. Kumar CM, Van Zundert AAJ. Intraoperative Valsalva maneuver: A narrative review. Can J Anaesth. 2018;65(5):578-585.
DOI: 10.1007/s12630-018-1074-6
65. MacEwan MR, Kovacs T, Osbun J, Ray WZ. Comparative analysis of a fully-synthetic nanofabricated dura substitute and bovine collagen dura substitute in a large animal model of dural repair. Interdisciplinary Neurosurgery. 2018;13:145-150.
DOI: 10.1016/j.inat.2018.05.001
66. Integra. Stryker Promotional Material #9410-400-152 Rev. A.
Available:https://products.integralife.com/file/general/1453796534.pdf
67. Danish SF, Samdani A, Hanna A, Storm P, Sutton L. Experience with acellular human dura and bovine collagen matrix for duraplasty after posterior fossa decompression for Chiari malformations. J Neurosurg. 2006;104(1 Suppl):16-20.
DOI: 10.3171/ped.2006.104.1.16
68. Integra. Integra Promotional Material#0179531-2.
69. Haq I, Cruz-Almeida Y, Siqueira EB, Norenberg M, Green BA, Levi AD. Postoperative fibrosis after surgical treatment of the porcine spinal cord: a

comparison of dural substitutes. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004. J Neurosurg Spine. 2005;2(1):50-54.
DOI: 10.3171/spi.2005.2.1.0050

70. Integra. Integra Promotional Material #0069447- 3-EN.
Available:https://products.integralife.com/file/general/1518550095.pdf
71. McCall TD, Fults DW, Schmidt RH. Use of resorbable collagen dural substitutes in the presence of cranial and spinal infections-report of 3 cases. Surg Neurol. 2008;70(1):92-96; discussion 96-97.
DOI: 10.1016/j.surneu.2007.04.007
72. Kizmazoglu C, Aydin HE, Kaya I, et al. Comparison of Biomechanical Properties of Dura Mater Substitutes and Cranial Human Dura Mater: An In Vitro Study. J Korean Neurosurg Soc. 2019;62(6):635-642.
DOI: 10.3340/jkns.2019.0122
73. Hodde JP, Badylak SF, Brightman AO, Voytik-Harbin SL. Glycosaminoglycan content of small intestinal submucosa: a bioscaffold for tissue replacement. Tissue Eng. 1996;2(3):209-217.
DOI: 10.1089/ten.1996.2.209
74. Bowers CA, Brimley C, Cole C, Gluf W, Schmidt RH. AlloDerm for duraplasty in Chiari malformation: Superior outcomes. Acta Neurochir (Wien). 2015;157(3):507-511.
DOI: 10.1007/s00701-014-2263-x
75. Chappell ET, Pare L, Salehpour M, Mathews M, Middlehof C. GORE PRECLUDE MVP dura substitute applied as a nonwatertight “underlay” graft for craniotomies: product and technique evaluation. Surg Neurol. 2009;71(1):126-128; discussion 128-129.
DOI: 10.1016/j.surneu.2007.08.041
76. Raul JS, Godard J, Arbez-Gindre F, Czorny A. [Use of polyester urethane (Neuro-Patch) as a dural substitute. Prospective study of 70 cases]. Neurochirurgie. 2003;49(2-3 Pt 1):83-89.
77. Cain JE, Rosenthal HG, Broom MJ, Jauch EC, Borek DA, Jacobs RR. Quantification of leakage pressures after durotomy repairs in the canine. Spine (Phila Pa 1976). 1990;15(9):969-970.
DOI: 10.1097/00007632-199009000-00024
78. Pomeranz S, Constantini S, Umansky F. The use of fibrin sealant in cerebrospinal fluid leakage. Neurochirurgia (Stuttg). 1991;34(6):166-169.
DOI: 10.1055/s-2008-1052082
79. Tisseel. Baxter Advanced Surgery.
Available:https://advancedsurgery.baxter.com/tisseel
80. Jankowitz BT, Atteberry DS, Gerszten PC, et al. Effect of fibrin glue on the prevention of persistent cerebral spinal fluid leakage after incidental durotomy during lumbar spinal surgery. Eur Spine J. 2009;18(8):1169-1174.
DOI: 10.1007/s00586-009-0928-6
81. Baxter. Highlights of Prescribing Information.
Available:https://baxterpi.com/pi-pdf/Tisseel_PI.pdf

82. Mulder M, Crosier J, Dunn R. Cauda equina compression by hydrogel dural sealant after a laminotomy and discectomy: Case report. Spine (Phila Pa 1976). 2009;34(4):E144-148.
DOI: 10.1097/BRS.0b013e31818d5427
83. Tseng WL, Xiao F. Duraseal thecal sac compression after lumbar discectomy causing radiculopathy. Spine J. 2015;15(8):1892-1893.
DOI: 10.1016/j.spinee.2015.03.048
84. Kim KD, Wright NM. Polyethylene glycol hydrogel spinal sealant (DuraSeal Spinal Sealant) as an adjunct to sutured dural repair in the spine: results of a prospective, multicenter, randomized controlled study. Spine (Phila Pa 1976). 2011;36(23):1906-1912.
DOI: 10.1097/BRS.0b013e3181fdb4db
85. FDA. Premarket Approval (PMA). US Food & Drug Administration.
Available:https://www.accessdata.fda.gov/scripts/cdrh/
86. Sellin JN, Kolcun JPG, Levi AD. Cerebrospinal fluid leak and symptomatic pseudomeningocele after intradural spine surgery. World Neurosurg. 2018;120:e497-e502.
DOI: 10.1016/j.wneu.2018.08.112
87. Fang Z, Tian R, Jia YT, Xu TT, Liu Y. Treatment of cerebrospinal fluid leak after spine surgery. Chin J Traumatol. 2017;20(2):81-83.
DOI: 10.1016/j.cjtee.2016.12.002
88. Hodges SD, Humphreys SC, Eck JC, Covington LA. Management of incidental durotomy without mandatory bed rest. A retrospective review of 20 cases. Spine (Phila Pa 1976). 1999;24(19):2062-2064.
DOI: 10.1097/00007632-199910010-00017
89. Khan MH, Rihn J, Steele G, et al. Postoperative management protocol for incidental dural tears during degenerative lumbar spine surgery: A review of 3,183 consecutive degenerative lumbar cases. Spine (Phila Pa 1976). 2006;31(22):2609-2613.
DOI: 10.1097/01.brs.0000241066.55849.41
90. Oitment C, Aref M, Almenawar S, Reddy K. Spinal dural repair: A canadian questionnaire. Global Spine Journal. 2018;8(4):359-364.
91. Clajus C, Stockhammer F, Rohde V. The intra- and postoperative management of accidental durotomy in lumbar spine surgery: results of a German survey. Acta Neurochir (Wien). 2015;157(3):525-530.
DOI: 10.1007/s00701-014-2325-0
92. Lewandrowski KU, Hellinger S, De Carvalho PST, et al. Dural tears during lumbar spinal endoscopy: Surgeon Skill, Training, Incidence, Risk Factors, and Management. Int J Spine Surg. 2021;15(2):280-294.
DOI: 10.14444/8038
93. Gautschi OP, Stienen MN, Smoll NR, Corniola MV, Tessitore E, Schaller K. Incidental durotomy in lumbar spine surgery--a three-nation survey to evaluate its management. Acta Neurochir (Wien). 2014;156(9):1813-1820.
DOI: 10.1007/s00701-014-2177-7
94. Winter F, Hasslinger S, Frueh A, et al. Incidence, risk factors, and treatment of incidental durotomy during decompression in degenerative lumbar spine conditions. J Neurosurg Sci. 2023;67(4):507-511.
DOI: 10.23736/S0390-5616.21.05404-7

95. Farshad M, Aichmair A, Wanivenhaus F, Betz M, Spirig J, Bauer DE. No benefit of early versus late ambulation after incidental durotomy in lumbar spine surgery: A randomized controlled trial. Eur Spine J. 2020;29(1):141-146.
DOI: 10.1007/s00586-019-06144-5
96. Gomes FC, Larcipretti ALL, Elvir FAR, et al. Early ambulation versus prolonged bed rest for incidental durotomies in spine procedures: A systematic review and meta-analysis. Neurosurg Rev. 2023;46(1):310.
DOI: 10.1007/s10143-023-02201-2
97. Abrishamkar S, Khalighinejad N, Moeim P. Analysing the effect of early acetazolamide administration on patients with a high risk of permanent Cerebrospinal Fluid Leakage. Acta Medica Iranica. 2013;51(No 7).
98. McCormack BM, Taylor SL, Heath S, Scanlon J. Pseudomeningocele/CSF fistula in a patient with lumbar spinal implants treated with epidural blood patch and a brief course of closed subarachnoid drainage. A case report. Spine (Phila Pa 1976). 1996;21(19):2273-2276.
DOI: 10.1097/00007632-199610010-00019
99. Sandwell S, Walter K, Westesson PL. Pseudomeningocele Aspiration and Blood Patch Effectively Treats Positional Headache Associated With Postoperative Lumbosacral Pseudomeningocele. Spine (Phila Pa 1976). 2017;42(15):1139-1144.
DOI: 10.1097/BRS.0000000000002003
100. Maycock NF, van Essen J, Pfitzner J. Post-laminectomy cerebrospinal fluid fistula treated with epidural blood patch. Spine (Phila Pa 1976). 1994;19(19):2223-2225.
DOI: 10.1097/00007632-199410000-00018
101. Fridley JS, Jea A, Glover CD, Nguyen KP. Symptomatic postsurgical cerebrospinal fluid leak treated by aspiration and epidural blood patch under ultrasound guidance in 2 adolescents. J Neurosurg Pediatr. 2013;11(1):87-90.
DOI: 10.3171/2012.9.PEDS12314
102. Shapiro SA, Scully T. Closed continuous drainage of cerebrospinal fluid via a lumbar subarachnoid catheter for treatment or prevention of cranial/spinal cerebrospinal fluid fistula. Neurosurgery. 1992;30(2):241-245.
DOI: 10.1227/00006123-199202000-00015
103. Açikbaş SC, Akyüz M, Kazan S, Tuncer R. Complications of closed continuous lumbar drainage of cerebrospinal fluid. Acta Neurochir (Wien). 2002;144(5):475-480.
DOI: 10.1007/s007010200068
104. Duthel R, Nuti C, Motuo-Fotso MJ, Beauchesne P, Brunon J. [Complications of lumboperitoneal shunts. A retrospective study of a series of 195 patients (214 procedures)]. Neurochirurgie. 1996;42(2):83-89; discussion 89-90.
105. James HE, Tibbs PA. Diverse clinical applications of percutaneous lumboperitoneal shunts. Neurosurgery. 1981;8(1):39-42.
DOI: 10.1227/00006123-198101000-00008

106. Katz SS, Savitz MH, Osei C, Harris L. Successful treatment by lumboperitoneal shunting of a spinal subclavicular fistula following thoracotomy. Neurosurgery. 1982;11(6):795-796. DOI: 10.1227/00006123-198212000-00014
107. Kitchen N, Bradford R, Platts A. Occult spinal pseudomeningocele following a trivial injury successfully treated with a lumboperitoneal shunt: a case report. Surg Neurol. 1992;38(1):46-49. DOI: 10.1016/0090-3019(92)90211-5
108. Karnati T, Kulubya ES, Kim KD. Advances in the management of spinal durotomy. Medical Research Archives. 2020 Sep 28;8(9).

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Integration in Medical Education through Harden's Ladder

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ABSTRACT

The new curriculum of Medical Education prescribed by NMC in India differs from the older one, which was used for many years, by being more learner and patient-centric, outcome-based, aligned and integrated with an emphasis on skill development. Ethics, communication and affective domains shall be addressed explicitly here. Newer additions like foundation courses, early clinical exposure and self-directed learning are being made [1]. Emphasis is made on making the curriculum aligned and integrated to provide a holistic approach to the learners. The curriculum implementation support programme is making tremendous efforts to inculcate the new curriculum into day-to-day teaching. Hence, a thorough understanding of alignment and integration by these members is very essential.

Keywords: Integration; CBME; Harden's ladder.

1. INTRODUCTION

Integration in the context of Competency-Based Medical Education (CBME), the new curriculum of medical education introduced in India according to Graduate Medical Regulations 2019, refers to the alignment of competencies of various subjects across different domains and their incorporation into educational programs. It is one of the vital components of the CBME curriculum. Integration involves ensuring that the essential knowledge, skills, and attitudes required for effective clinical practice are interconnected and complementary within the curriculum.

Integration means aligning competencies with educational activities, assessments, and learning outcomes to ensure that Indian Medical Graduates develop a

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comprehensive set of skills necessary for their future roles as physicians of first contact. It involves connecting various components of education to create a cohesive learning experience that promotes the acquisition of core competencies to achieve a holistic approach to patient care which reflects the real world [1].

Professor Ronald M Harden was a renowned medical educationist with an immense contribution to the field. He was the pioneer of objective structured clinical examination, spiral curriculum and SPICES model for curriculum planning. He has also developed new approaches to curriculum planning, teaching and assessment [2]. He has described the 11 steps in integration, which is called Harden's ladder. Each step of the ladder describes one level of integration. The lower four levels of the ladder refer to individual discipline (subject) based teaching and moving up the ladder, the emphasis is on integration across various disciplines. In the last step of the ladder, the student is expected to take the responsibility to integrate the components learnt in different disciplines in a given situation [3,4].

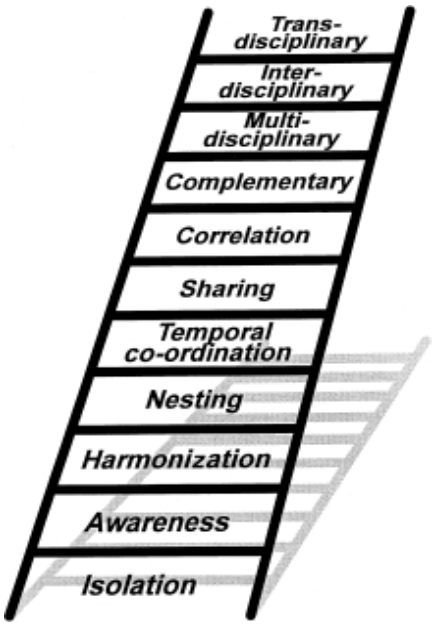

Fig. 1. Harden's ladder [5]

Step 1: Isolation

The subjects are taught in isolation without considering what is being taught in other subjects.

Example:

1st year disciplines: the topics scheduled-
Department of Anatomy: Cardiovascular system
Department of Physiology: Endocrine system
Department of Biochemistry: Metabolic diseases.

Here, there is no alignment of any topics and no attention is paid to topics covered in related subjects [1]. The major disadvantage is that the students don't develop any relationship between subjects when taught in isolation [5].

Step 2: Awareness

The teaching is again subject-based, but the teacher is aware of what is taught or being taught in other subjects (6).

Example:

Dept. of Physiology: Physiology of thyroid glands - synthesis, secretion, transport, physiological actions, regulation and effect of altered (hypo and hyper) secretion of thyroid hormones. Dept. of Biochemistry - The functions of the thyroid, the tests that are commonly done in clinical practice to assess the functions thyroid gland, and abnormalities of thyroid glands.

These topics will be dealt with at different time frames and there is no concurrence. Here, an overlap of functions and abnormalities of the thyroid gland is obvious. In awareness, the teacher in one subject is made aware of what is covered in other subjects in the curriculum. The teacher can take account of what colleagues cover in other parts of the course when planning teaching, avoiding redundancy and cross-referring. However, there is no explicit attempt to provide an integrated view of the subject to the student. Awareness may be through documentation/lecture notes/handouts that are made available to the teacher. So, during planning, the teacher **may** plan to avoid repetitions and stress on other aspects [3,4,5].

Step 3: Harmonization

The faculty from concerned departments consult through informal discussions between teachers or through curriculum planning committees. This encourages teachers to adapt their programs so that each course makes an appropriate contribution to the curriculum and the overall curriculum objectives are more likely to be achieved [5].

Example:

Dept of Microbiology: Discuss the clinical evolution, etiopathogenesis and the laboratory diagnosis of malaria.

Dept of Pathology: Define and describe the pathogenesis and pathophysiology of malaria. Both these topics are taught at different time frames. The staff in the Department of Pathology make reference to malaria in brief and refresh the

memory of what is learnt in microbiology during their topic on infections & infestations. Thus, an explicit connection with topics already learnt in other subjects is made [4,5].

Step 4: Nesting

The teacher tries to bring in concepts from other subjects within a subject-based course. It could be the clinical skills/concepts brought into pre and para-clinical subjects or a basic skill introduced in clinical subjects [1,3,4,5,6].

This concept enriches the teaching in one particular subject.

Example 1:

Dept of Biochemistry: Tests that are commonly done in clinical practice to assess the functions of the liver.

In the above class, relevance to clinical practice is introduced through - A case of alcoholic liver disease may be discussed during this class to bring in relevance of Liver function tests.

Example 2:

Dept of Obstetrics &gynaecology: changes in the genital tract, cardiovascular system, respiratory, haematology, renal and gastrointestinal system in pregnancy.

In the above class, relevance to basic knowledge/skill is introduced through - A discussion on normal physiology of the above systems before proceeding to changes in pregnancy.

Step 5: Temporal Coordination:

The related organ systems or topics/diseases in subjects are scheduled around the same time. This is done in consultation with other disciplines. Though the concepts in each subject are learnt separately, the students have a high scope to relate the concepts and learn [1,3,4,5,6].

Example based on Organ Systems:

Dept of Anatomy: Anatomy of the heart.

Dept of Physiology: Properties of cardiac muscle including its morphology, electrical, mechanical and metabolic functions.

Dept of Biochemistry: Basis and rationale of biochemical tests in cardiovascular diseases.

Example based on Topics/ Diseases:

Dept of Pathology: Etiopathogenesis and pathology of myocardial infarction.
Dept of Pharmacology: Anti-angina drugs.

The topics related to the Cardiovascular system are scheduled at the same time by different departments in the timetable so that the students can correlate better.

Step 6: Sharing:

Two disciplines come together and share a class so as to avoid repetitions. Such sharing of classes is effective and efficient in imparting knowledge/skills to the students [5].

Example:

Dept. of Physiology: Physiology of liver function.
Dept. of Biochemistry: Metabolism of bilirubin.

Since these two topics have many overlapping specific learning objectives (SLOs), they may be clubbed together and a common consensus arrived at. The SLOs may be divided among the staff of respective departments depending on the importance of their subjects. Then the staff in each discipline may come together and teach in the same class [1,3,4,5].

Step 7: Correlation:

The topics dealt with are subject or discipline-based and they take up most part of the curriculum time. In a separate session on correlation, only areas of common interest are brought together [5, 6, 7].

Example:

Dept. of Anatomy: Anatomy of Pancreas (1 hr)
Dept. of Physiology: Physiology of pancreas (1hr)
Dept. of Biochemistry: Biochemical changes by pancreatic hormones (1hr)

Following the above classes, there shall be a separate INTEGRATION CLASS:
Case of Diabetes/diabetic coma/complications – is used as a linker for the integration class (2 Hrs.) with contributions from all the 3 departments.

In a single session, all three disciplines should come together and stress the importance of the above topics with regard to diabetes. The facilitators shall avoid teaching again the topics on the pancreas but stress the role of the pancreas only in diabetes.

During assessment, questions are more focused on topics covered in individual subject classes rather than on integration classes [1,4,5].

Step 8: Complementary

This type of integration is both subject-based as well as integrated. The focus of teaching is a theme or topic to which the disciplines will contribute [5]. The teaching is subject-based and in individual classes, the focus is on the theme (not on the subject as in correlation). Running parallel to these individual classes is an integrated class where each subject teacher shall emphasize the theme so that the student has a holistic approach to the theme. Individual subjects are given less importance in terms of time, resources and assessment [1,3,4,5].

Example:

Theme: Diabetes in pregnancy

Subject-based classes are conducted individually in different departments: Dept. of Obstetrics & gynaecology – incidence, management and complications of DM in pregnancy (1 hr)

Dept. of Paediatrics: management of neonates born to diabetic mothers (1 hr)
Dept. of Community Medicine: burden of DM in the community. (2 hr)
Dept. of Medicine: recent advances in the treatment of DM (1hr)

Complementary teaching session on the Theme 'Diabetes in Pregnancy' (8 hours)**:** A case of Gestational diabetes is used and various departments discuss the theme in detail. During assessment, questions are based on integrated sessions rather than on individual sessions. In contrast to correlation which is subject-based and each topic is dealt with in detail and a common session brings in the relevance with a linker, the complementary integration places importance on the theme.

Step 9: Multidisciplinary:

The topic is not dealt subject-based and it transcends subject boundaries. In one session the staffs from various departments imparts knowledge as much necessary for the theme. Courses are developed around systems. The scenarios a professional may have to deal with in real-time may be considered for such integrations [1,3,4,5,8]**.**

For example: In the thyroid module of the endocrine system block, the contributions from different departments may be as follows:

Dept. of Physiology: to thyroid hormone synthesis and its regulation,
Dept. of Pathology: to the underlying pathophysiology of the processes,
Dept. of Pharmacology: to the action of anti-thyroid drugs,
Dept. of Surgery: to the management of goitre
Dept. of Medicine: to the clinical manifestations and investigations of thyroid disease.
With this kind of approach, a student has a good idea of what to expect and how to go about when cases of thyroid land on his table.

CMEs where talks are arranged around a particular theme are examples of such multidisciplinary integration [5].

Example:

Topic of CME: Diabetes.
Dept. of Biochemistry: Regulation of blood glucose
Dept. of Pathology: Pathophysiology of Diabetes
Dept. of Medicine: Management of Diabetes and complications
Dept. of Surgery: Diabetic Foot management
Dept. of OBG: Gestational diabetes
Dept. of Paediatrics: Diabetes in children

Step 10: Interdisciplinary:

It is a study of a phenomenon that involves the use of two or more academic disciplines simultaneously. This is a higher level of integration where the content of all or most subjects is combined into a new course. There is no subject demarcation at this level [3,4,5,6,9].

Example:

Approach to acute abdomen: A case of acute abdomen in middle-aged women is used as a linker. Departments of Medicine, Surgery and OBG will discuss their approach towards diagnosis and management of that particular case without any subject demarcation.

Emergency medicine (initially started as a course, only in the recent past was started as a degree) where there is no demarcation between the two subjects of medicine and anaesthesia and is an amalgamation of the above two mentioned disciplines.

Other examples are courses like geriatric medicine, laboratory medicine etc.

Step 11: Transdisciplinary:

This is the highest level of integration. The emphasis is here on knowledge as exemplified in the real world. It is the responsibility of the student to integrate all that is learnt in different disciplines in a comprehensive way when a real-life situation arises [3,4,5,9,10].

Example:

When an intern sees a case of MI in an emergency, he integrates his knowledge of various disciplines:

Dept of Anatomy: anatomy of the heart.
Dept of Biochemistry: Biochemical markers for diagnosis of MI
Dept of Pathology: pathophysiology and investigations in a case of myocardial infarction

Dept of Pharmacology: drugs used in MI
Dept of Medicine: management of a case of MI.

With this understanding during the various phases, the student should be able to manage a case of MI during the internship [5].

Finally, as we climb up Harden's integration ladder, there is less emphasis given to individual subjects and more emphasis on achieving the goal of the holistic approach to medical education.

2. CONCLUSION

Alignment and Integration being an integral part CBME curriculum require a thorough understanding of different levels of integration for effective implementation of the new curriculum. Harden's ladder provides a valuable framework for understanding the stages of integration in medical education and the progression of learners from novice to expert. The ladder can serve as a guide for designing curricula and assessment methods that align with the principles of competency-based learning. It needs more training and clarity in this aspect for all medical educators, as it requires faculty from across phases to work in coordination to make it effective and relevant [5]. The curriculum committee has a huge task to train the faculty in their respective institutes for a smooth implementation of the program.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Medical Council of India. Alignment and Integration Module for Undergraduate Medical Education Program. 2019;1- 34.
2. Available:http://edo.med.miami.edu/grand-rounds/schedule-2017-2018.
3. Atwa HS, Gouda EM. Curriculum integration in medical education: theoretical review. Intel Prop Rights. 2014;2:113. DOI:10.4172/ipr.1000113.
4. Harden RM. The integration ladder: a tool for curriculum planning and evaluation. Med Edu. 2000; 34:551.
5. Hamsaveena, Rashmi MV. An Attempt to Understand the Different Levels of Harden's Ladder. JMSH. 2022;8(1):88-92.

6. Husain M, Khan S, Badyal D. Integration in medical education. Indian Pediatr 2020;57:842-847.
7. Klement BJ, Paulsen DF, Wineski LE. Clinical Correlations as a Tool in Basic Science Medical Education. J Med Educ Curric Dev. 2016 Jan 1;3
8. Youm J, Christner J, Hittle K, Ko P, Stone C, Blood AD, Ginzburg S. The 6 degrees of curriculum integration in medical education in the United States. J Educ Eval Health Prof. 2024;21.15.
9. Heck AJ, Chase AJ. A Tool for Evaluating Session-Level Integration in Medical Education. Med Sci Educ. 2021 Apr 2;31(2):647-654.
10. Shrivastava, Saurabh RamBihariLal, Shrivastava, Prateek Saurabh. Understanding Transdisciplinary Level of Integration in Medical Education. Medical Journal of Dr. D.Y. Patil Vidyapeeth. 2020;13(1): 3-4

Biography of author(s)

Dr. Hamsaveena (Professor & HOD)
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She has been in this noble profession for the past 21yrs besides working as a Clinical Biochemist. She is a passionate teacher as well excellent mentor for students. To achieve excellence, she has completed the highest degree in medical education, and advanced course in medical education and heads the medical education unit in the college. She is the first rank holder in her postgraduate degree for the year 2006 from RGUHS. She has been on the board of studies, and curriculum committees of various colleges and has been valuable in implementing various changes in medical education. Her passion for teaching is reflected in the achievements of her students as well as the number of students who approach her for mentoring.

As a clinical biochemist, she has established and headed the departments in various medical colleges for the past 10 years and is acclaimed as one of the youngest & successful HODs in Karnataka. She has a keen interest in research and ethics and has served and continues to do so in the above-mentioned committees. She is also the executive member of the Association of Medical Biochemists, Karnataka Chapter with a commendable contribution to the association.

Dr. Rashmi. M.V (Professor & HOD)
Department of Pathology, Siddaganga Medical College and Research Institute, Tumkur, India.

She is currently working as a Professor & Head, of Dept. of Pathology at Siddaganga Medical College & Research Institute, Tumkur, Karnataka, India. She has 22 years of experience in Pathology and Medical education. She is a very passionate pathologist and an educationist. She has had the privilege to be the founder of HOD in two medical colleges giving her remarkable experience in setting up of department. She is very passionate about her job as a pathologist doing her best to every slide or specimen that comes to her table.

She took up the job as a teacher because of her love to teach and to be amongst the younger generation of students which has been a life changer. To build on her teaching capabilities, she has completed courses like advanced courses in medical education. She has been on the board of studies and curriculum committee and made a few suggestions that have been implemented to improve the quality of education. She is interested in research and has taken up the responsibility of the research committee as member secretary. She has many publications in various national & international journals to her credit. She is associated with various organizations like the Karnataka Association for Pathologists and Microbiologists where she has served as the executive member, the local pathologists association as secretary, and various other organizations.

DISCLAIMER
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Chapter 4
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Local Flap Technique for Soft Tissue Defect in Compound Leg Injuries: A Reliable Single Stage Coverage

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ABSTRACT

Objective: The aim of this study is to evaluate the feasibility of local flaps, Fasciocutaneous, Muscle & Musculocutaneous flaps, in the management of soft tissue defects with exposed fracture bone fragments in compound injuries of the lower extremity as a single-stage procedure (particularly the leg). To lay down clear and concise guidelines, merits and demerits of this technique for Orthopaedic surgeons in trauma wards.
Methods: In traumatised lower extremity having a soft tissue defect & an exposed bone with or without associated fractures. Local flaps provide a reliable single-stage procedure for coverage of lower extremity soft tissue defects. The traumatised limb selected in which the wound was found to be preferably in the upper 1/3rd, middle 1/3rd& uppermost part of the lower 1/3rd leg due to easy accessibility & placement of the local flap to these areas. All flaps i.e. Fasciocutaneous, Musculocutaneous & local muscle flaps were undertaken as a delayed procedure after careful evaluation of traumatised limb by repeated dressings, debridement & control of infection. Daily assessment of the wound for infection, and motor & sensory & vascular status was made.
Definitive wound coverage was done by using a selected technique in a routine operation at the same time a split-thickness skin graft was applied on muscle pedicle flap or the defective area created by the transposition of Fasciocutaneous, Musculocutaneous flap.
Fixation of bone was done before applying the technique.

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Results: Stable wound coverage was achieved in all patients. The excellent result was obtained in Muscle & Musculocutaneous flaps while the good result was obtained in 10% of cases of Fasciocutaneous flaps. In a study longest duration follow-up was 14 months & shortest was 3 months. 20 cases of traumatised lower extremities (particularly the leg) which required local flap coverage for soft tissue defects with exposed bone fragments.
Conclusion: Stable coverage can be achieved by flap techniques using Fasciocutaneous, Muscle or Musculocutaneous flaps. Coverage of exposed cortical bones, tendons & major vessels & adequate control of infection can be achieved by Muscle & Musculocutaneous flap in post traumatised limb.
Fasciocutaneous flap (Ponten super flap) is very useful in the repair of soft tissue defects as it is a much simpler, easy to design & construct large flaps are safe due to good circulations, require less time without any functional loss, post-operative management is simple for both patient & staff.

Keywords: Fasciocutaneous flap; muscle flap and musculocutaneous flap; S.S.G. split skin graft.

1. INTRODUCTION

Rapid industrialization and urbanisation have led to a tremendous increase in the density of vehicular traffic, which makes automobile accidents an inevitable event. The majority of patients with polytrauma admitted to Orthopaedic wards, all over the world, are mainly due to vehicular accidents. Severely polytraumatised patients of vehicular accidents, almost always have an injured lower extremity (particularly the leg) which possesses a challenging problem of management (with regard to morbidity). The problems include large soft tissue defects along with exposed fractured bone fragments.

Repairing for the soft tissue defects of the hand has been a major challenge of hand or reconstructive surgery [1,2]. In polytraumatized patients, compound injuries to the leg constitute a challenging problem. Inadequate soft tissue coverage of the injured limb is of prime importance otherwise may lead to necrosis of tendons, exposed bone ends and subsequent infection. Coverage of soft tissue defects is considered to be the stepping stone towards the reconstruction of deeper tissue, primarily the bone. Fig. 1. The primary coverage (direct closure) of the wound of the leg may not be possible as The cylindrical shape of the extremity limits the amount of tissue for adequate closure and the circumference of the extremity increases with oedema of trauma, tension increases in Direct closure and leads to ischaemia of tissue within closed compartments. The edema limits the elasticity of the skin, primary wound closure without tension and primary skin coverage of large soft tissue defects of exposed bones is the essence of treatment [3]. These are the two basic objectives of wound treatment in the compound injury of the leg. Infection of deeper tissues and bones is a dreadful complication which prolongs the hospital stay and thereby increases the cost of treatment [4].

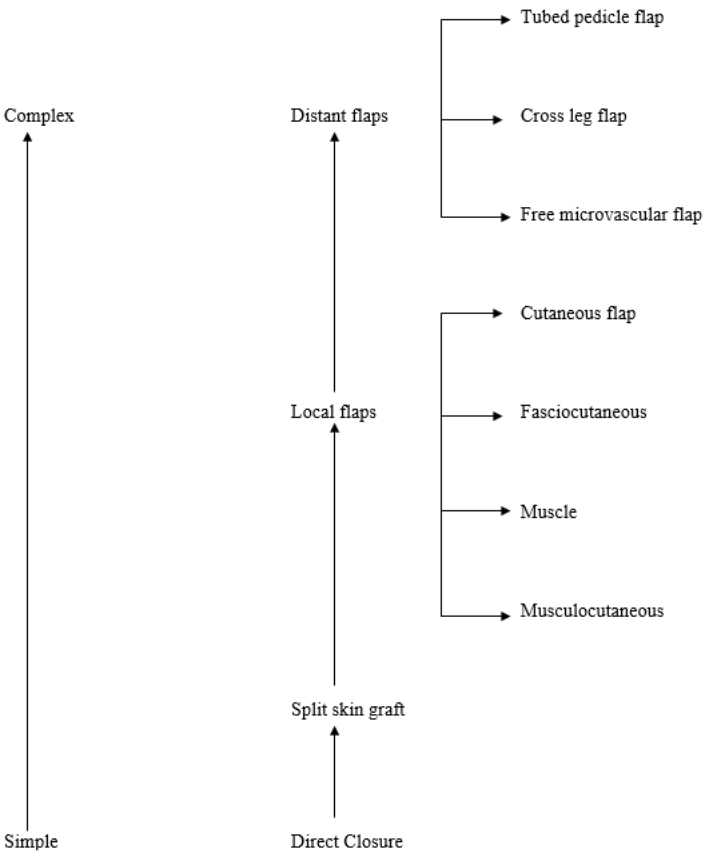

Fig. 1. Reconstructive ladder

In such conditions, appropriate and adequate stable skin cover is provided at the earliest to minimise the period of recovery and hospital stay. A few techniques of primary wound closure are available:

1. Split thickness graft (SSG) will not be accepted at the avascular exposed surface, i.e. bare bones tendons, across open joints.
2. Prolonged and protracted plastic reconstructive surgery in the form of a distant full-thickness flap is not a procedure of choice.

The local flaps in the form of Muscle, Musculocutaneous and Fasciocutaneous flaps are valuable techniques that have profoundly changed the contemporary practice of reconstructive surgery as major advancement by providing excellent single-stage coverage of soft tissue defect, with exposed bones and neurovascular structure [3]. The donor area is grafted with S.S.G. With more

familiarity with the anatomy of extremity Orthopaedic surgeon is in a better position to reconstruct the soft tissue defect, hence decreasing the dependency on plastic surgeons.

Table 1. Asthetic and functional consideration of Muscle flap and Musculocutaneous flap[5]

TYPE		
Consideration	Muscle flap and skin graft	Musculocutaneous flap
Asthetic		
Flap	Good to fair	Excellent to fair
Donar defect	Excellent	Excellent to poor
Flap atrophy	Muscle will atrophy	Subcutaneous fat will not Atrophy
Functional		
Sensibility	No	Yes
Pliability	Fair	Excellent
Size	Limited to size of muscle	May be extended beyond muscle

2. MATERIALS AND METHODS

The present study included 20 cases of traumatised lower extremity having a soft tissue defect and an exposed bone with or without associated fractures. The study was conducted from January 1989 to August 1990.

Most of the cases having a compound fracture of the leg with soft tissue defects in the upper 1/3rd, and middle 1/3rd leg and the uppermost part of the lower 1/3rd of the leg were included in this study [3]. Evaluation of the traumatised limb for the presence of neurovascular complications and associated fractures was done.

Debridement of the wound and stabilization of fracture was done before. Assessment of the wound for infection, motor sensory and vascular status was done till the wound became healthy. The study was conducted with admitted patients, in the Department of Orthopaedics Hamidia Hospital Bhopal, proper consents were taken before the surgery.

Definitive wound coverage was done as the delayed procedure by using a selected technique and at the same time split-thickness skin graft was applied on the muscle pedicle flap or on the raw area created by the transposition of the flap [3].

2.1 Procedure

The ideal flap for wound coverage was selected on the basis of the anatomical location of the traumatised zone and the availability of expendable Muscle, Musculocutaneous or Fasciocutaneous flap of suitable vascular anatomy in the adjacent healthy zone.

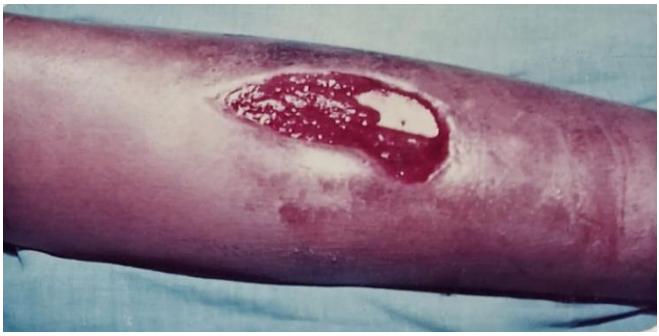

Fig. 2. Case 1 (i)- Preoperative – Soft tissue defect with Exposed bone of the leg (Tibia)

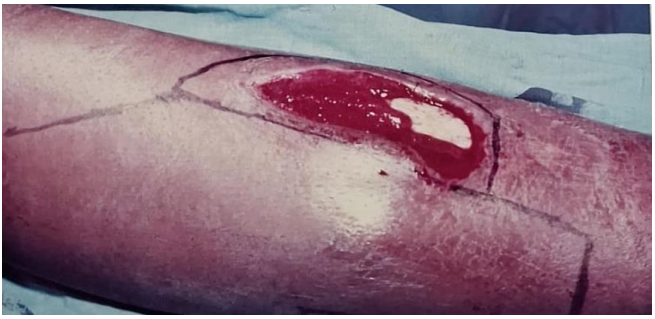

Fig. 3. Case 1 (ii) – Soft tissue defect with Exposed bone of the leg (Tibia)- Preoperative Planning (Marking)

With all aseptic precautions under the tourniquet, the wound was prepared by excising all dead tissue and scarred margins. Fixation of bone was done before applying the technique either by external/Internal fixation or by pin traction and plaster cast application [3].

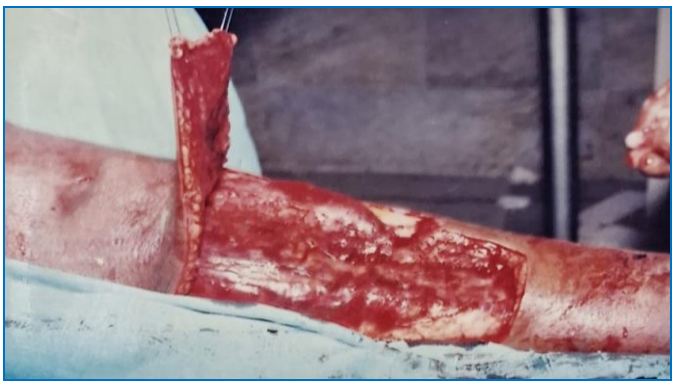

Fig. 4. Case 1 (iii) – Flap raised with Facia, Subcutaneous tissue, and Skin

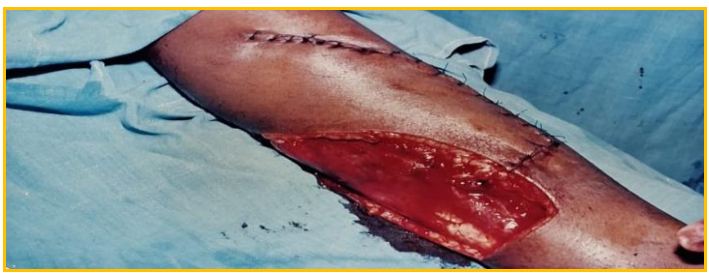

Fig. 5. Case 1 (iv) –Raised facio- cutaneous flap transposed to the defect raw donor area is visible.

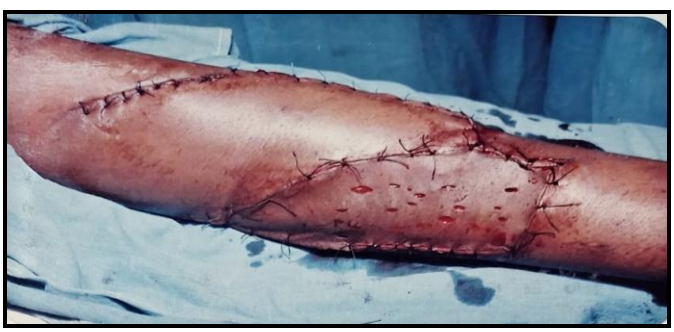

Fig. 6. Case 1 (v) Donar area grafted with split-thickness skin graft

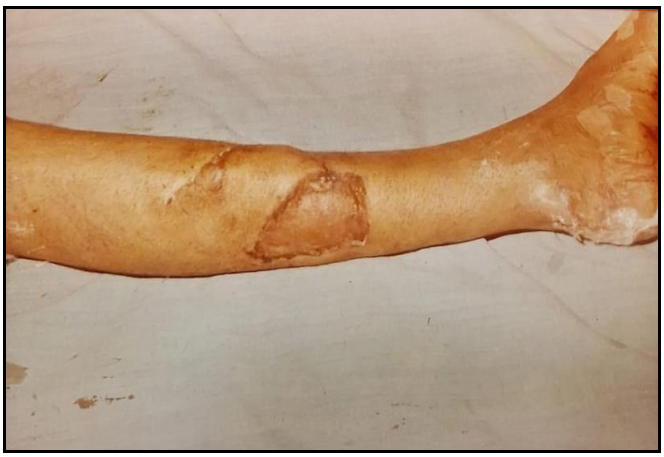

Fig. 7. Case 1 (vi)- Fascio-cutaneous flap taken up appearance after six months

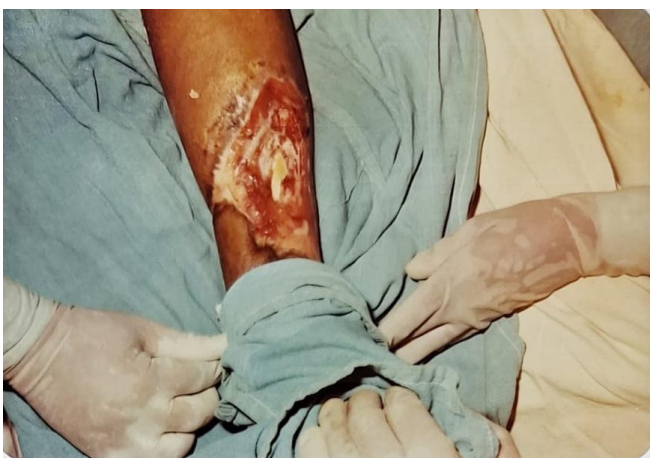

Fig. 8. Case 2 (i) – Soft tissue defect with exposed bone ends

2.2 Fasciocutaneous Flap

The Fasciocutaneous flaps (‘Ponten Super Flap’). The Fasciocutaneous flap was dissected along with skin subcutaneous tissue and deep fascia. The flap was transposed over the wound and stitched with the margin of the wound without tension. The width of the distal portion of the flap should be more than the width of the wound and the base of the flap should be widened at least 3 times that of the distal end. The donor area is grafted with SSG (Figs. 1 to 6) [3].

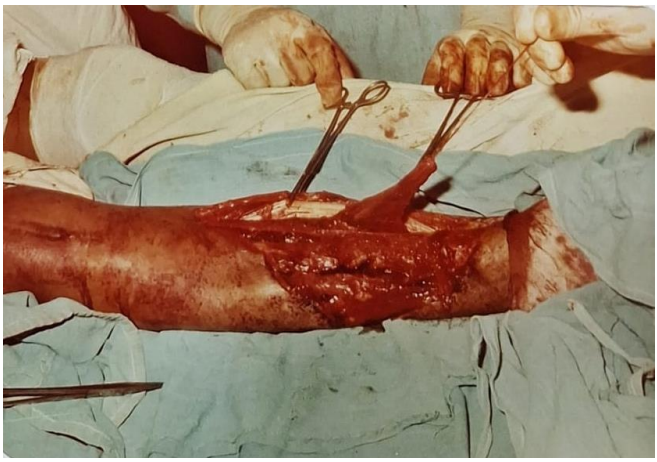

Fig. 9. Case 2 (ii) Soleus muscle flap raised

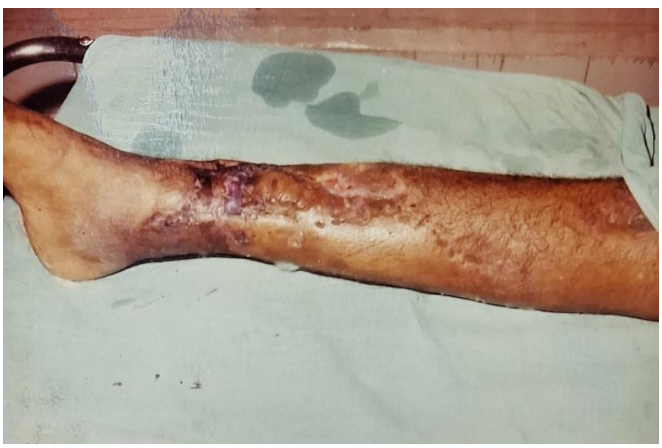

Fig. 10. Case 2 (iii)- Muscle graft taken up after six weeks.

2.3 Muscle Flap

In this series transposition of soleus muscle was done as described by Ger R.

In this study, the Soleus muscle was used as a muscle flap. The dissection was dependent and cleavage was always made between the Soleus and Gastrocnemius (the muscle which is easily identified by the Plantaris tendon). The Soleus muscle was cut from its lower end where its tendinous portion merged with the Gastrocnemeus tendon sheath. The tendinous portion was removed and the Soleus portion was fanned out so that the whole of the bony

and soft tissue raw area was covered by Soleus. The muscle margins were stitched. The raw surface of the muscle was skin-grafted (SSG) immediately (Figs. 7 to 10).

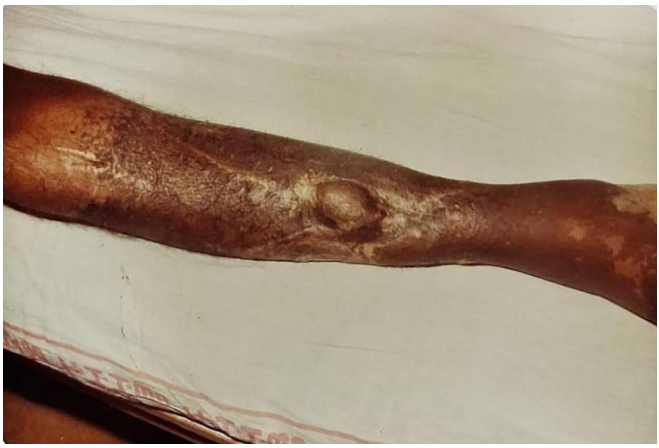

Fig. 11. Case 3 Soleus Muscle transposed with thiersch graft coverage, after nine-month

2.4 Musculocutaneous Flap

In the case of musculocutaneous flaps, one head of Gastrocnemeous was used. Skin incision deepened in all directions except proximally near the base and one head of Gastrocnemeous was separated along with fascia, deep fascia subcutaneous tissue as well as skin and whole unit transposed to the prepared wound area. Donor area grafted with SSG. 9 Fasciocutaneous flaps, 7 Muscle flaps (4 Soleus & 1 Tibiatis anterior) and 4 Musculocutaneous flaps (medial head of Gastrocnemeous) were used.

In all cases along with antibiotics, anti-inflammatory and vasodilates were given for 5 days post-operatively.

The first post-operative inspection was done after 48 hrs for colour discharge from stitches and position of grafted skin and the wound was inspected every 5^{th} day till the stitches were removed [3].

3. RESULTS

The present study includes 20 cases. Most of the patients were in the age group of 18 to 42 years. There were only 2 females [3].

The study includes twenty cases of traumatised lower extremities (particularly the leg) which required local flap coverage for soft tissue defects with exposed fractured bone fragments.

Most of the patients were male in the age group of 18 to 42 years. There were only two females Maximum number of flap coverage was done in the middle 1/3rd of leg [3].

The excellent result was obtained in Muscle & Myocutaneous & Fasciocutaneous flaps, while the good result was obtained in 10% of cases.

3.1 Fasciocutaneous Flap

Fasciocutaneous flap was done in 45% of cases in this series.

The result was found to be excellent in 77% of FCF while good in 22%. Minor infection was noted in 2 cases out of which one had inadequate flap cover which was successfully healed by granulation tissue.

3.3 Muscle Flap

An excellent result was found in the Muscle flap. Soleus muscle was used in six cases and Ant. The tibial muscle is used in one phase. The functional loss due to muscle transposition was found in one case and loss of skin graft was noted in one case which was regrafted.

3.3 Musculocutaneous Flap

An excellent result was found in the Myocutaneous flap, 4 Gastrocnemius muscle medial head was used. Mild marginal infection was noted which was healed by regular dressing.

4. DISCUSSION

Appropriate management of compound injuries of the lower extremity leads to the vicious cycle described by Converc (Fig.1). The proper approach should be to get a well-vascularised soft tissue cover in place as soon as possible. This concept demands an aggressive initial debridement followed by aggressive wound care (Biological dressings). The timing of bone coverage must be carefully determined and must be based on sound clinical judgement. One cannot make a general statement that all compound wounds should or should not have immediate coverage with flaps [3]. Each case must be carefully assessed in terms of the specific tissue needed and the amount of wound contamination present. Within this framework, the appropriate timing of the coverage can be best determined 3 [6].

Local flaps provide a reliable single-stage procedure for the coverage of lower extremity soft tissue defects. Distant flaps provide good coverage but these procedures are long drawn out and tedious [3].

Most of the patients 55% belong to the age group of 21-30 years, of these 90% were male (Table 2). A. Yadav et al. [7] described 61% in the 21-30 years age group and 92% were male. G.Patrix Maxwell et al. [6] reported all 100% male in 77% 21-30 age groups. B.Ponten male predominance in 90% of cases of average age of 42 years [8].

These injuries are more common in the younger age group, which was perhaps due to a more vigorous lifestyle, particularly in males [3].

In all cases site of injury was the crural region (Table 3) shows the different anatomical sites of injury in this series. 30% of cases reported in upper 1/3rd, 40% in middle 1/3rd and 30% cases in lower 1/3rd of leg. While in A.Yadav et al showed 30% in the upper 1/3rd, 46% in the middle 1/3rd and 23% in the lower 1/3rd of the leg.

In this series, transposition of all flaps was undertaken as a delayed procedure after repeated dressings, debridement and controlling of infection. A.Yadav et al [7] also delayed the procedure till the wound became healthy. G.Patrix Maxwell [6] delayed the procedure till the control of infection, Mathes and Vasconez, [5] delayed the procedure for 5 to 7 days. Ger R. suggested the use of Muscle flaps for the immediate repair of traumatic defects [9,3].

The muscle used for achieving soft tissue coverage depends on the anatomical site of the lesion [4]. The Gastrocnemius muscle flap is the flap of choice in the proximal 1/3rd of the leg and was used as myocutaneous flap in 4 cases [10] (Table 4). Ger. R [9] and G.Patrix Maxwell et al.[6] use the medial head of the Gastrocnemeous myocutaneous flap in compound fracture 1/3rd upper successfully in 3 cases [6].

Fitzgerald et al. [11] used and Gastrocnemeous Muscle flap in the treatment of chronic osteomyelitis. The result was satisfactory. A.Yadav used 3 Gastrocnemeous Muscles for the upper 1/3rd leg and 3 soleus Muscle flaps for the middle 1/3rd [3].

The Soleus muscle is the most useful for covering soft tissue defects in the middle 1/3rd of the leg as suggested [12] by Mathes & Nahal [5], (1982), Swertz & Jones [12]. The second choice for coverage of soft tissue defect in the middle 1/3rd of the leg is the medial head of Gastrocnemius. In this series, 5 flaps of Soleus Muscle were used in the middle 1/3rd. A total of 6 soleus muscle flaps were used (Table 6) [3]. Fitzgerald et al. 1985 used 18 soleus muscles in the treatment of osteomyelitis with excellent results [11].

The tibialis anterior muscle can be used with functional preservation [13,14] to cover the upper 2/3rd of the outer surface of the tibia. It was used in one case in

the middle1/3rd of the leg in this series (Table 6). A.Yadav [7] successfully applied the tibialis anterior muscle in one case [7].

The Fasciocutaneous super flap [15] described that this flap can be used from the level of the knee down to the foot. He successfully used these flaps in the proximal middle, a lower 1/3rd of the leg [3]. He describes soft tissue defect of the lower 1/3rd of the leg as a difficult area for coverage by muscle and usually it was covered by distant flaps but the disadvantage of this is well known. Ponten [15], described Fasciocutaneous flap as very useful for soft tissue defects of the lower leg. The Soleus muscle can be used to cover the distal tibia [15], Mathes & Nahal [5] and it was used in one case in this series for lower 1/3rd defect.

The lower 1/3rd of the leg is a difficult area for coverage by Muscle flap and usually requires coverage by the distant flap.

In this series, 5 cases of lower 1/3rd soft tissue defect were covered by Fasciocutaneous flaps (Table 5) [3]. There is no problem in designing a flap measuring 18 x 8 cm. It is very easy to design and construct large flaps that are safe because of good circulation. Operation time is short for an experienced surgeon. Post-operative treatment is simple for both the patient and staff [15]. Barclay confirmed the reliability of Ponten's Fasciocutaneous or 'super flap' in the management of lower leg injury. The result of the super flap was very satisfactory. In this series, 16 cases healed primarily and in two cases, there was marginal distal skin loss. He described the damage as superficial [16] [3].

In the present series, two cases of distal marginal necrosis of the terminal 2 cm of Fasciocutaneous flap were noted, probably due to excessive tension in the terminal part of the flap. This portion was re-grafted with SSG after 5 to 7 days while in another case gap was filled up by granulation tissue. Vascones et al. (1974) showed that excessive tension on the flap was found to be one of the causes of flap failure. In this series, results were found to be very satisfactory as in all cases the flaps healed. The advantage of Fasciocutaneous flap is obvious.

The Fasciocutaneous manoeuvre should always be considered when one is faced with the problem of covering a soft tissue defect on the lower leg [3].

In the presence of infection use of a Muscle or Musculocutaneous flap has certain advantages over Fasciocutaneous and random cutaneous flaps [17,18]. Post-traumatic infection results were satisfactory as in all cases infections were controlled. The role of Muscle flap in the treatment of chronic Osteomyelitis has been emphasised by Stark (1946), Chang & Mathes [17], Fitzgerald et al.[11] indifferent series. They demonstrated that muscle provided greater oxygen delivery in cellular and non-cellular environments at the site of infection and increase of concentration of antibiotics in a fibrotic cavity in an experimental animal [18], Russell & Graham [3].

In almost all cases fracture was present. These fractures were stabilised i.e. by nail, external fixator or Pin traction and plaster application. A. Yadav [7] used an

external fixator and plaster application. G.Patrix and Maxwell et al. used Hoffman's double frame external fixation system. He showed that Hydrotherapy, biological dressing's skin grafting and flap coverage have been made easier by its use [6].

In 8 cases there was flaring of the infection (Table 8) necessitating prolonged use of a suction drain system & daily dressing till complete healing was achieved [3]. Delayed loss in split skin graft was noted and a second skin grafting procedure was done.

Table 2. Age and sex distribution of patients

Sl. No.	Age in years	Male	Female
1.	11 - 20	1	--
2.	21 - 30	10	1
3.	31 - 40	5	1
4.	41 & above	2	--
Total		**18**	**2**

Table 3. Anatomical area in the leg where flap was used

Sl. No.	Site	No. of cases	Flaps used
1.	Upper 1/3rd of leg	6	Musculocutaneous flap Fasciocutaneous flap
2.	Middle 1/3rd of leg	8	Muscle flap Fasciocutaneous flap
3.	Lower 1/3rd of leg	6	Fasciocutaneous flap
Total		20	

Table 4. Flaps used for coverage of soft tissue defects with exposed bone fragments

Sl. No.	Flap Used	No. Of Cases
1.	Musculocutaneous flap	**4**
2.	Muscle flap with a split skin graft	**7**
3.	Fasciocutaneous flap	**9**
Total		**20**

Table 5. Fasciocutaneous flaps are used in anatomical areas of the leg

Sl. No.	Anatomical Area	No. of cases
1.	Upper 1/3rd of leg	2
2.	Middle 1/3rd of leg	2
3.	Lower 1/3rd of leg (upper part)	5
Total		**9**

Kojima, Kohno et al. [19] pointed out the disadvantage of primary grafting that oozing from the Muscle flap interferes with grafted skin leading to necrosis & may require regrafting. Fitzgerald et al. [20] used SSG after 48 hrs.

Functional loss due to muscle transposition was reported in one case of the Soleus muscle. Tobin used a Hemi soleus flap either proximately based or distally (reversed) transfer. It prevents plantar flexion power by Hemi soleus belly left in situ. In this series functional loss was little & Gastrocnemius muscle overcame the function of Soleus [21] [3].

Table 6. Muscle used in local flap

Sl. No.	Muscle Used	No. of cases
1.	Gastrocnemius Medial Head	4
2.	Soleus	6
3.	Anterior Tibial	1
Total		**11**

Table 7. Technique used for stabilization of fractures

Sl. No.	Methods	No. of cases
1.	Pin Traction & Plaster Application	13
2.	Internal Fixation	6
3.	External Fixation	1
Total		**20**

Table 8. Post-operative complications

Sl. No.	Type of Complications	No. of Cases
1.	Infection	8
2.	Necrosis of Fasciocutaneous flap at the distal edge	2
3.	Inadequate flap coverage	1
4.	Functional loss due to muscle-transposed	1
5.	Loss of split skin graft	1
Total		**13**

Table 9. Results obtained in flap study

Sl. No.	Flap Used	No. of Cases	Results
1.	Fasciocutaneous	9 (7 cases) (2 cases)	Excellent Good
2.	Muscle Flap	7	Excellent
3.	Musculocutaneous	4	Excellent
Total		**20**	

In this study, stable wound coverage was achieved in all patients, the longest duration of follow-up was 14 months and the shortest 4 months. A. Yadav [7] showed longest follow-up of 10 months and the shortest 4 months [3].

1. High rate of success (98%) was due to:

- Proper selection of cases
- Proper selection of extendable muscle &
- Proper planning of flaps, better knowledge of the vascular pattern of muscle and skin and meticulous aseptic technique used.

Early physiotherapy is of immense help in preventing functional loss by strengthening synergistic muscles. Adequate aggressive debridement, fixation of the fracture, and proper positioning of limbs to prevent pressure on the flap or pedicle were of profound importance for the success of flaps in this study [3].

Although the present study comprises only a small number of patients, the Fasciocutameous, Muscle and Musculocutaneous flaps provided a single-stage procedure for coverage of the soft tissue defects of the traumatised leg. Stable wound coverage was possible with control of infection and soft tissue coverage was possible in those cases where bone, tendon or major neurovascular structure were exposed. The results found in this study are in agreement with several other studies [8,16,6], Bent Barford et al., (1970) [22] and Stephen S. Orrapin S, Rekasem K.[23] and A. Yadav et al. [7].

5. CONCLUSION

1. The most common site of soft tissue defect in the lower extremity is the leg. Single-stage stable wound coverage to exposed cortical bone, tendons and major vessels could be achieved by using the Fasciocutaneous, Muscle or Musculocutaneous flaps technique.
2. Fasciocutaneous flap manoeuvre should always be considered when facing difficulty in covering the soft tissue defect on the lower leg. This flap is simpler, easy to design and can construct large flaps, that are safe because of good circulation. These flaps (Fasciocutaneous) require less time and involve less risk to the patient without any functional loss. Ponten called them “Super Flap” and can be used from knee to leg. Post-operative management is simple for both the patient and the staff.
3. Adequate control of infection was achieved by using Muscle and Musculocutaneous flaps [3].
4. Fixation of bony fragments provided easy access to the wound by providing stability.
5. No functional deficit was noted in cases where complete reconstructions of limbs were possible during the study period. The total period of hospital stay of the patient was reduced [3].
6. Local flap technique was found to be the best procedure for single-stage stable coverage of soft tissue defect in compound injuries of the leg by Orthopaedic surgeons in trauma ward as:-

a) It reduces the hospital stay and expenses.
b) Cumbersome time-consuming plastic and micro-surgical procedure can be avoided. Hence increasing the dependency on plastic and reconstructive micro-surgeon.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of this manuscript.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration between both authors. Author RS was the principal investigator of the study, and was involved in the design, conduct, and analysis and author VP contributed in applying anatomical concepts, report wrote, reviewed and edited the manuscript. Both authors read and approved the final manuscript.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Zhao F. Flap repair technique for soft tissue defects of the hand. Annals of Plastic Surgery. 2021 Mar 1;86(3S):S319-21.
2. De SD, Sebastin SJ. Considerations in flap selection for soft tissue defects of the hand. Clinics in Plastic Surgery. 2019 Jul 1;46(3):393-406.
3. Sadh R, Pal V. Roll of local flap technique in the management of compound injuries of Leg. Asian J Pharm Clin Res.2024;17(5):114-118.
4. Arnald PG, Irons GB. Lower extremity muscle flaps.The Orthop. Clinc. Nor. Amer. 1984;15:3:441-449.
5. Mathes SJ, Nahai F. 1. Selection of muscle & musculotaneous flap in reconstructive surgery.2. Vascular anatomy of muscle:Classification & application. 3. Musculocutaneous perforators. 4. An analysis of cause of flap failure. In clinical application for muscle.St. Louis, C.V. Mosby Co; 1982.
6. Maxwell GP, Hoppes JE. Management of compound injuries of the lower extremity. Plast. Reconstr. Surg. 1979;63:176–185.
7. Yadav A. Role of local muscle flaps in traumatised lower extremity. Thesis, submitted for the degree of M.S.(Ortho.), University, Delhi; 1988.

8. Ponten B. The Fasciocutaneous flap: Its use in soft tissue defects of the lower leg. Br. J. of plast Surg.1981;34215-220.
9. Ger R. The management of open fracture of Tibia with skin loss.J. Trauma.1970;10:112-121.
10. Ger R, McCrawJB. Closure of defects of the lower extremity by muscle and myocutaneous flaps in Reconstructive Surgery of lower extremity (Ch.86) in Reconstructive plastic surg.: Principles & Procedures in correction reconstruction and transplantation. Converse J.M.(Ed), W.B. Saunders Company. 1977;7.
11. Fitzgerald P, Tolhurst DE. The use of muscle flaps to covery exposed bone.Br. J. Plast. Surg. 1985;33:99–114.
12. Swertz & Jones; 1985.
13. Moller Larson F, Peterson NC. Longitudinal split anterior tibial muscle flaps with preserved function. Plast. Reconstr. Surg.1984;74:398–401.
14. Robbins TH. Use of Fascio-muscle flaps to repair defects in the lower leg.Plast, Reconstr. Surg.1976;57:460.
15. Wright JK, Watkins RF. Use of the soleus muscle flap to cover part of the distal tibia. Plast. Reconstr. Surg.1981;68:957.
16. Barclay TL, Cardoso E, Sharpe DT, Crockett DJ. Repair of lower leg injuries with Fasciocutaneous flaps. Br.J. of Plastic Surg.1982;35:127-132.
17. Chang N, Mathes ST. Comparison of the effect of bacterial Inoculation in musculocutaneous and random pattern flaps. Plastic & Reco. Surgery.July 1982;70(1): P 1-9.
18. Russell RC, Grahm DR, Feller AM, Zook EG, Mathur A. Experimenatl evaluation of the antibiotic carrying capacity of a muscle flap into a fibrotic cavity plast. and Reconstr Surg.1988;81:162–170.
19. Kojima T, Kohno T, Ito T. Muscle flap with simultaneous mash skin graft for skin defects of the lower leg. J. Trauma.1979;19:724.
20. Fitzgerald P, Tolhurst DE. The use of muscle flaps to covery exposed bone. Br. J. Plast. Surg. 1985;33:99–114.
21. Tobin G R Soleus flaps, Ch 396, page 1706 – 1711, Encyclopedia of flaps, 1st edition, by Grabbs. Hemisoleus & reversed hemisoleus flaps, Plastic Reconstructive Surgery. 1985;3(76):87-96.
22. Barford T, Pers M. Gastrocnemius plasty for primary closure of compound injuries of knees. J. Bone Joint Surg.1970;52(B):124.
23. Orrapin S, Rekasem K. Role of topical biological therapies and dressings in healing ischemic wounds. The International Journal of Lower Extremity Wounds. 2018;17(4):236-246.

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He is an active member of the Progressive Anatomical Education Society and the MPCG chapter of the Anatomical Society of India, underscoring his dedication to enhancing anatomical education and research in India.

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Chapter 5
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Anogenital System and HPV-Related Lesions in Women: Anatomy, Pathophysiology, and Screening

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ABSTRACT

Aims: This chapter aims to provide a comprehensive overview of the anatomy, physiology, and histology of the cervix and anal canal in women. It further explores the role of the Human Papilloma Virus (HPV) in the pathogenesis of cervical and anal carcinogenesis, emphasizing the epidemiology, oncogenic mechanisms, and associated lesions.
Study Design: The chapter is structured as a detailed review of current literature, integrating anatomical, physiological, and pathological aspects with epidemiological data on HPV-related cancers. Key areas include the anatomy and histology of the cervix and anal canal, HPV virology, the epidemiology of HPV-related cancers, and the mechanisms of HPV-induced oncogenesis.
Place and Duration of Study: The literature review covers studies published globally, focusing on research from the last two decades, with particular attention to studies from 2000 to 2024.
Results: The findings highlight the significant impact of HPV on cervical and anal cancer development. The chapter outlines the progression from HPV infection to carcinogenesis, identifying the critical role of specific HPV strains. It also discusses the screening and vaccination strategies currently in place to prevent HPV-related lesions and their effectiveness in reducing cancer incidence.
Conclusion: HPV plays a central role in the development of cervical and anal cancers in women. Understanding the anatomical and physiological aspects of the cervix and anal canal, along with the pathophysiology of HPV, is crucial for developing effective prevention and treatment strategies. The chapter concludes with recommendations for improving screening and vaccination programs to reduce the burden of HPV-related cancers.

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Keywords: Anogenital system; cervix; anal canal; human papilloma virus (HPV); cervical cancer; anal cancer.

DEFINITIONS, ACRONYMS, ABBREVIATIONS

Definitions:

- ***Human Papillomavirus (HPV):*** *A group of more than 200 related viruses, some of which cause genital warts or cancer.*
- ***Cervical Intraepithelial Neoplasia (CIN):*** *A term used to describe abnormal changes in the cells on the surface of the cervix that could potentially lead to cervical cancer.*
- ***Pap Smear (Papanicolaou Test):*** *A screening procedure for cervical cancer that tests for the presence of precancerous or cancerous cells on the cervix.*
- ***Colposcopy:*** *A procedure to closely examine the cervix, vagina, and vulva for signs of disease.*
- ***Ablation:*** *A medical procedure that involves removing or destroying tissue.*

Acronyms:

- ***HPV:*** *Human Papillomavirus*
- ***CIN:*** *Cervical Intraepithelial Neoplasia*
- ***AIS:*** *Adenocarcinoma In Situ*
- ***LSIL:*** *Low-Grade Squamous Intraepithelial Lesion*
- ***HSIL:*** *High-Grade Squamous Intraepithelial Lesion*
- ***ACOG:*** *American College of Obstetricians and Gynecologists*
- ***ASCCP:*** *American Society for Colposcopy and Cervical Pathology*
- ***WHO:*** *World Health Organization*
- ***FDA:*** *Food and Drug Administration*
- ***HGAIN:*** *High-Grade Anal Intraepithelial Neoplasia*
- ***AIN:*** *Anal Intraepithelial Neoplasia*

Abbreviations:

- ***Ca:*** *Cancer*
- ***DNA:*** *Deoxyribonucleic Acid*
- ***HIV:*** *Human Immunodeficiency Virus*
- ***VIA:*** *Visual Inspection with Acetic Acid*
- ***pRB:*** *Retinoblastoma Protein*
- ***p53:*** *Tumor Protein 53 (a tumor suppressor protein)*
- ***MHC:*** *Major Histocompatibility Complex*
- ***E6/E7:*** *Oncogenes from HPV involved in the progression to cancer*
- ***nAbs:*** *Neutralizing Antibodies*

1. INTRODUCTION

Human Papillomavirus (HPV) is a pervasive DNA virus recognized for its crucial role in the development of various anogenital cancers, particularly cervical and anal cancers in women. Comprising over 400 distinct tissue-specific types, HPV exhibits unique genomic structures that facilitate its ability to infect diverse epithelial tissues [1]. The virus's capacity for persistent infection, especially with high-risk oncogenic types, is a primary factor in the progression from benign lesions to malignant transformations [2].

The cervix and anal canal are anatomically and histologically distinct yet share similarities in their epithelial structures, making them susceptible to HPV infections. The cervix, a vital component of the female reproductive system, consists of the ectocervix and endocervix, each with distinct histological characteristics [3]. The anal canal, part of the lower gastrointestinal tract, is lined with stratified squamous epithelium, similar to the ectocervix, which contributes to its susceptibility to HPV-related lesions [4].

HPV's role in the pathogenesis of cervical and anal cancers involves several mechanisms. Upon infection, the viral DNA can integrate into the host genome, leading to the expression of oncoproteins E6 and E7, which interfere with tumor suppressor proteins p53 and Rb, respectively. This interference disrupts cell cycle regulation, promoting uncontrolled cellular proliferation and ultimately carcinogenesis [5]. Among the numerous HPV types, HPV16 and HPV18 are the most oncogenic, responsible for approximately 70% of cervical cancers and a significant proportion of anal cancers [6].

Epidemiologically, HPV is implicated in approximately 5% of all cancers globally, with over 700,000 new HPV-related cancer cases diagnosed annually and around 400,000 resulting in mortality [7]. The prevalence and impact of HPV-related cancers are influenced by factors such as socioeconomic status, access to healthcare, and the implementation of preventive measures like vaccination and screening programs [8]. In regions with robust screening and vaccination initiatives, the incidence of cervical cancer has declined, highlighting the effectiveness of these public health strategies [9]. However, the burden of anal cancer remains a concern, necessitating similar preventive approaches [10].

Screening and vaccination are pivotal in reducing the incidence and mortality associated with HPV-related cancers. Cervical cancer screening through Pap smears and HPV testing has been instrumental in early detection and prevention [11]. Vaccination against high-risk HPV types has shown significant efficacy in preventing infections and subsequent malignancies [12]. Extending screening programs to include anal cancer, particularly in high-risk populations, could further mitigate the burden of HPV-related diseases [13].

In conclusion, HPV plays a central role in the development of cervical and anal cancers in women. A comprehensive understanding of the anatomy, physiology, and histology of the cervix and anal canal, combined with insights into the

pathophysiology of HPV, is essential for developing effective prevention and treatment strategies. Enhancing screening and vaccination programs globally is critical to reducing the incidence and mortality of HPV-related cancers.

This chapter aims to provide a comprehensive overview of the anatomy, physiology, and histology of the cervix and anal canal in women, as well as explore the critical role of HPV in the pathogenesis of cervical and anal carcinogenesis. By integrating current literature on anatomical, physiological, and pathological aspects with epidemiological data on HPV-related cancers, this chapter seeks to enhance the understanding of these cancers' development and progression.

Understanding the intricate relationship between HPV infection and the anogenital system is crucial for developing targeted prevention and treatment strategies. With the increasing burden of HPV-related cancers worldwide, especially in regions with limited access to healthcare resources, this chapter underscores the importance of expanding and improving screening and vaccination programs. By highlighting the significant impact of HPV on women's health, this chapter advocates for stronger public health measures to reduce the global incidence and mortality associated with these cancers.

2. ANOGENITAL SYSTEM IN WOMEN

2.1 Anatomy, Physiology, and Histology of the Cervix

The cervix is the fibromuscular lower part of the uterus. It acts as a canal between the endometrial cavity proximally and the vagina distally. It is 3-4 cm in length and 2.5 cm in diameter. The part of the cervix that remains in the vagina is called the ectocervix. It has a convex, smooth surface and a round or horizontally slit-shaped entry point called the external os. The external os is observed during speculum examination. This entry point continues as the endocervical canal. The endocervical canal is 2-3 cm long and proximally opens into the endometrial cavity through the internal os [7]. The anatomy of the cervix is shown in Fig. 1. The junction where the vaginal wall meets the cervix is called the portio vaginalis (the portion remaining within the vagina), while the upper two-thirds of the cervix is referred to as the portio supravaginalis. The portio supravaginalis has two surfaces, anterior and posterior, and two lateral borders. The anterior surface is adjacent to the posterior surface of the bladder, with fibrous connective tissue between them. The posterior surface contains muscle fibers that extend toward the sacrum and rectum. The portio supravaginalis is adjacent to the ureters at a distance of 1.5 cm from the lateral borders. It is supported laterally by the cardinal ligament and posteriorly by the uterosacral ligament [8].

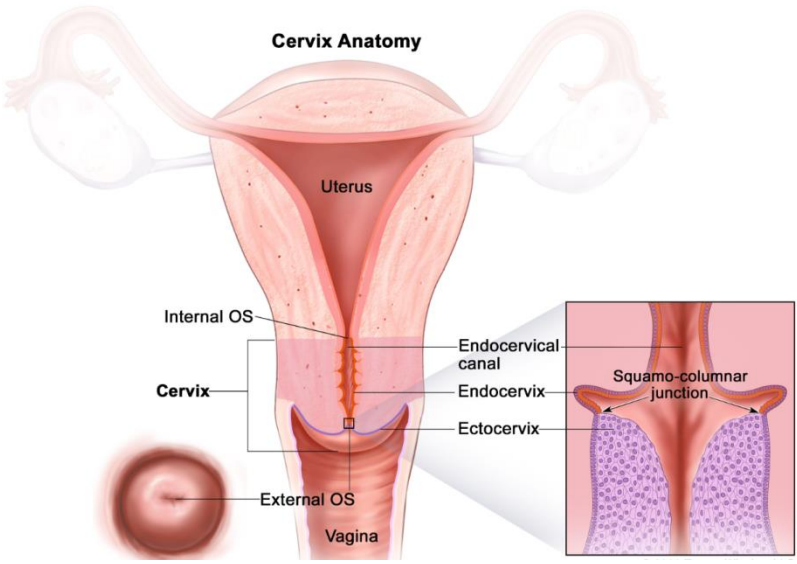

Fig. 1. Anatomy of the cervix [9]

The size and shape of the cervix vary depending on factors such as age, parity, and hormonal status. In women who have given birth, the cervix appears larger, and the external os is wide and transversely slit. In nulliparous women, it is typically circular. The vascular network, lymphatics, and nerves converge within the cervical stroma. The cervix receives its blood supply from the cervical and vaginal branches of the uterine artery, which originates from the internal iliac artery. These branches descend from the lateral sides of the cervix at the 3 and 9 o'clock positions. The uterine artery crosses the ureter within the parametrium and extends approximately 2 cm anterior to the cervix. Veins accompany the arteries and drain into the hypogastric plexus. Lymphatic drainage flows to the common iliac, internal iliac, external iliac, parametrial, and obturator lymph nodes. The cervix is innervated by the hypogastric nerve. While the endocervix has a dense network of nerve endings, the ectocervix does not, making procedures like biopsies, coagulation, and cryotherapy in the ectocervix relatively well-tolerated in terms of pain. Due to potential trauma during childbirth, the endocervical canal may exhibit reduced responsiveness in women who have given birth. The presence of abundant sympathetic and parasympathetic nerve fibers in the endocervical canal can lead to vasovagal reactions during procedures such as dilation and curettage.

The cervix functions as the connection between the vagina and the endometrium. During fertilization, sperm passes through the cervix, facilitated by clear cervical mucus that enhances sperm motility. Cervical mucus undergoes hormone-dependent changes, with estrogen levels rising from the 8th day of the menstrual cycle until ovulation. This increase in estrogen leads to an increase in cervical

mucus production and a decrease in its viscosity, facilitating sperm passage through the cervix. After ovulation, the fluidity of cervical mucus decreases. The external os, where the cervix connects with the vagina, slightly opens to allow menstrual blood to flow.

The lower genital tract develops embryologically from the fusion of the Müllerian ducts during intrauterine weeks 6-7, eventually merging with the urogenital sinus via invagination. The cervix and vagina, which originate from the Müllerian ducts, are lined with columnar epithelium. Around intrauterine week 16, the columnar epithelium of the vagina and cervix begins to undergo squamous metaplasia, transitioning into squamous epithelium. The squamocolumnar junction formed during this process is referred to as the original squamocolumnar junction. After puberty and during the reproductive years, under the influence of estrogen, the cervix swells, enlarges, and extends into the endocervical canal, a condition known as ectropion. Squamous metaplasia occurs in response to external stimuli such as trauma, hormonal changes, pH alterations, and vaginal infections. The newly formed boundary is referred to as the physiological squamocolumnar junction. The majority of the cervix and the entirety of the vagina are lined with stratified squamous epithelium. This tissue stains with Lugol's iodine due to its glycogen content and appears smooth and slightly pink to the naked eye. During pregnancy, increased vascularization causes the epithelium to take on a bluish hue. The basal layer of the squamous epithelium contains large, dark-staining nuclei, with minimal cytoplasm, and is attached to the basement membrane. The stratified squamous epithelium consists of four layers: superficial, intermediate, parabasal, and basal. HPV can infect cells within these layers as it progresses through the infection cycle:

- **Basal Layer:** The lowest layer, responsible for active mitosis and epithelial regeneration. The other layers form as the basal layer differentiates. This is the entry point for HPV infection. The cells in this layer are characterized by large nuclei and minimal cytoplasm, arranged in a single columnar pattern.
- **Parabasal Layer:** Cells in this layer have large nuclei and are arranged in multiple layers of polyhedral cells. This layer contains keratin filaments.
- **Intermediate Layer:** Composed of cells with smaller nuclei and abundant cytoplasm, in contrast to the basal layer.
- **Superficial Layer:** This layer contains cells with a large glycogen-filled cytoplasm and small nuclei, arranged in 7-8 layers of squamous cells. These cells are observed during the evaluation of Pap smears.

The endocervical canal is lined with columnar epithelium, characterized by a single layer of tall cells with dark-staining nuclei near the basement membrane. Due to its single-layer structure, the columnar epithelium has a lower height compared to the stratified squamous epithelium of the cervix. During visual examination, it may appear thin and reddish. The columnar epithelium does not form a flat surface in the endocervical canal but rather creates folds and projections into the canal lumen, forming invaginations into the cervical stroma that give rise to endocervical glands. Localized overgrowth of these structures

can result in the formation of cervical polyps. The area where the stratified squamous epithelium meets the single-layer columnar epithelium is known as the squamocolumnar junction. The location of this junction can change in response to external stimuli [11].

2.2 Anatomy, Physiology, and Histology of the Anal Canal

The anal canal is 2.5-3.5 cm in length and constitutes the terminal portion of the bowel. It begins at the point where the rectal ampulla narrows and ends at the anus. The canal is surrounded by the internal and external anal sphincters. The internal anal sphincter surrounds the upper two-thirds of the anal canal and remains contracted to prevent incontinence. It temporarily relaxes when the rectal ampulla expands due to feces or gas. For the discharge of gas or feces, the voluntary contraction of the external anal sphincter and the puborectalis muscle is required. The anal canal is encircled by a ring of thickened circular muscle fibers, which are a continuation of the rectum's circular smooth muscle layer, forming the internal anal sphincter. The lower end is surrounded by bundles of striated muscle, forming the external anal sphincter. The external anal sphincter terminates below the internal anal sphincter. The palpable space between them is called the intersphincteric groove, which indicates the distal part of the anal canal.

In the anal canal, the squamocolumnar junction is located at the proximal part of the canal, where the columnar epithelium of the rectum transitions into the squamous epithelium of the anus. Anal intraepithelial neoplasias and HPV infections occur in the anal transformation zone, which is the junction between the rectal columnar epithelium and the anal squamous epithelium. This transition zone shows similarities to the cervix in this respect [12]. The anal transformation zone extends from the squamocolumnar junction proximally to the level of the pectinate line distally.

The upper boundary of the anal valves is embryologically derived from the hindgut, while the lower boundary is derived from the proctodeum. At the junction of these two areas, the anorectal junction's mucosa transforms into stratified squamous epithelium, referred to as the pectinate line. The pectinate line appears as an irregular line within the internal portion of the anal canal, formed by the anal valves, and it divides the anal canal into proximal and distal sections. The proximal and distal parts differ in arterial supply, neural innervation, and lymphatic drainage. The areas above the pectinate line are supplied by the superior and middle rectal arteries, while the area below the pectinate line is supplied by two inferior rectal arteries. Venous drainage is provided by a venous plexus located in the submucosa. This plexus can become dilated in conditions with increased intra-abdominal pressure (e.g., pregnancy, pelvic masses, chronic constipation, ascites), leading to symptomatic presentations such as rectal bleeding or painful hemorrhoids. Above the pectinate line, visceral innervation is supplied by the inferior hypogastric plexus.

Sympathetic fibers are responsible for maintaining the tone of the internal anal sphincter. Parasympathetic fibers inhibit the tone of the internal anal sphincter and trigger the peristaltic contractions necessary for fecal discharge. The anal canal above the pectinate line is only sensitive to stretching. Below the pectinate line, somatic innervation is provided by the inferior rectal nerves, branches of the pudendal nerve. This part of the anal canal is sensitive to pain, touch, and temperature. Fecal continence is primarily maintained by the puborectalis muscle and the internal-external sphincters. The puborectalis muscle surrounds the anal hiatus within the pelvic diaphragm and forms a hammock-like structure behind the rectum. The external anal sphincter encircles the terminal anal canal below the level of the levator ani. Increasing evidence today supports the importance of both the external sphincter and the levator ani muscle in fecal continence and demonstrates that various traumas can lead to pelvic floor dysfunction.

An MRI study reported that levator ani injury was observed in 19.1% of women who had vaginal delivery with external sphincter injury and in 3.5% of women without sphincter injury. In women who delivered by cesarean section without undergoing labor, no levator ani injury was observed. Among women with external sphincter injury, those with major levator ani injury were more frequently observed to have fecal incontinence. Other studies have shown that internal anal sphincter thickening increases with age, and thinning of the external anal sphincter, leading to decreased squeeze pressure, has been correlated with fecal incontinence. However, in this study, age alone was not found to be a determining factor for fecal incontinence.

3. HPV AND CERVICAL CARCINOGENESIS

3.1 Papillomaviruses and Human Papilloma Virus (HPV)

Papillomaviruses are a group of DNA viruses that infect the skin and mucous membranes of animals. These viruses are primarily transmitted through physical contact and typically do not cause significant disease. To date, more than 200 types of HPV have been identified, and categorized into alpha, beta, gamma, mu, and nu genera. The specific sites of infection in the human body are determined by the type and characteristics of the HPV strain. Low-risk HPV types [6,11,14-19] are associated with genital warts [20]. HPV types in the beta and gamma genera are commonly associated with skin infections during childhood, usually with low viral loads. Mu genus HPVs are characterized by their tendency to cause deep warts on the hands and soles of the feet [21].

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide, with persistent HPV infection strongly associated with the risk of cervical cancer and genital warts [22]. Globally, HPV is responsible for approximately 4.5% of all cancers [2]. Tumors associated with HPV include those of the cervix, anal canal, vagina, penis, oropharynx, vulva, oral cavity, and larynx [23].

HPV is a double-stranded DNA virus that belongs to the Papillomaviruses (PVs) group [24]. Papillomaviruses have an affinity for the epithelial cells of vertebrates, where they can induce neoplasias (tumor formations) following infection [25]. However, not all infections lead to cancer. For example, it has been shown that approximately 80% of women will have acquired an HPV infection by the age of 50, but only a small percentage of these cases will develop into cancer [26].

Based on current data, HPV is considered one of the most significant human carcinogens [27]. Of the 448 documented HPV types, only 12 are classified as carcinogenic. Most HPV types do not cause cancer [1]. The HPV types that cause diseases and premalignant/malignant lesions in the cervix belong to the alpha genus. Group 1 Carcinogens (High-Risk [HR] HPV) include HPV16, HPV31, HPV33, HPV35, HPV52, and HPV58 in Alpha-9; HPV18, HPV39, HPV45, and HPV59 in Alpha-7; HPV51 in Alpha-5; and HPV56 in Alpha-6. HPV68, classified as a probable carcinogen, is also part of the Alpha-7 group. Other HPV types rarely exhibit carcinogenic properties [28]. These high-risk HPV types are sexually transmitted and are generally cleared by the immune system within three years in 80% of cases. Only about 3% of infections progress to premalignant/malignant lesions of the cervix within seven years [29]. The progression to cancer is primarily due to the persistence of the HPV infection [30].

HPV16 and HPV18 are responsible for 70% of cervical cancers. Among these, HPV16 is the most oncogenic, accounting for 60% of cervical cancers, making it the most prominent type [31]. Identifying the genetic variants of HPV that contribute to carcinogenesis is challenging, primarily due to the lack of comprehensive HPV genome sequences; even when sequences are available, data interpretation can be complex [32]. There is a weak correlation between the carcinogenicity of HPV types and their genetic similarity. Although HPV18 and HPV16 are highly carcinogenic, their genomes are significantly different, and HPV18 typically leads to basal lesions. Similarly, while HPV31 and HPV35 are genetically similar to HPV16, their carcinogenic potential is much lower.

3.2 HPV and Cancer Epidemiology

HPV can lead to cancer development in various tissues, with cervical cancer being the most prevalent among them [33]. Cervical cancers are most commonly diagnosed in women aged 50-59 years. The association between HPV and cervical cancer is even stronger than the association between smoking and lung cancer [34]. Cervical cancer is the fourth most common and fatal cancer among women worldwide. A study conducted in 2012 revealed that HPV caused approximately 600,000 invasive cancers, with over 500,000 cases being invasive cervical cancer, leading to 250,000 deaths. In men, this rate is significantly lower (<1%). The cervix is highly susceptible to HPV, and the virus readily exhibits its carcinogenic properties in this tissue [35].

HPV is transmitted through direct contact. Although vaginal and anal intercourse are the most common modes of transmission, infections have also been observed in individuals who identify as virgins [36]. Most infections occur within

the first few years of becoming sexually active. A study involving 603 university students found that approximately 40% of HPV infections occurred within the first two years [37]. The primary factor that increases the risk of HPV infection is having multiple sexual partners. Numerous studies support this, showing a higher rate of HPV infection among individuals with an increased number of sexual partners.

Early age at first intercourse and young age at marriage significantly increase the risk of developing cervical cancer following HPV infection. A study found that women who married before the age of 16 had approximately a 50% higher rate of developing cervical cancer compared to those who married after the age of 20 [38]. Condoms can reduce the risk of transmission but are not 100% effective in preventing HPV infection.

In addition to the number of sexual partners and early age at first intercourse, other risk factors for HPV infection include being over 30 years old, having given birth (multiparity), early age at first sexual activity, conditions leading to immunosuppression, smoking, and the use of oral contraceptives [39]. Furthermore, the presence of HPV alongside Herpes Simplex Virus (HSV-2) and Chlamydia trachomatis infections increases the risk of developing cervical cancer compared to those without these infections [40].

3.3 Mechanisms of Oral Contraceptives and Smoking in Cervical Cancer Development

The exact mechanism by which oral contraceptives (OCs) increase the risk of cervical cancer is not yet fully understood. However, it is believed that women who are HPV-positive and use OCs may have twice the risk of their infection progressing to cervical cancer. This elevated risk is thought to return to normal approximately 10 years after discontinuing OCs [41].

Smoking is directly associated with the development of squamous cell carcinoma. The stress induced by smoking, the increase in reactive oxygen species (ROS), and the polymorphism in the GST genotype—which is responsible for encoding the enzyme involved in detoxification—contribute to the increase in oncogenic HPV infections and the immune system's inability to respond effectively to the infection. A study investigating the relationship between HPV positivity and smoking found that exposure of cervical cells to benzopyrene, a compound found in cigarette smoke, increases the synthesis of HPV in these cells [42].

Some studies have also found similarities in the dietary habits and medication use among patients with HPV infections and cervical cancer. For instance, patients with low folate levels have been found to have a higher likelihood of developing HPV16 infections [43]. Additionally, women with lower levels of Vitamin A (retinol) have been observed to have a higher progression rate of cervical cancer compared to those with higher levels [44]. The use of diethylstilbestrol (DES) has been associated with an increased incidence of vaginal and cervical cancers in affected individuals [45].

3.4 Geographic and Socioeconomic Factors in HPV-Related Cervical Cancer

The development of HPV-related cervical cancer is significantly influenced by the economic status of countries and their geographic regions. The prevalence of HPV in a given area and the effectiveness of cancer screening programs play a crucial role in these differences [14]. In developing and underdeveloped countries, the rates of cervical cancer are significantly higher, accounting for approximately 84% of cases (about 445,000 women per year). In these countries, cervical cancer is the second most common cancer after breast cancer [15]. The high incidence rates in these regions are attributed to factors such as low socioeconomic status, lack of knowledge about and access to preventive healthcare services, inadequate or poor-quality screening, and less healthy dietary habits [16]. In developed countries, cervical cancer accounts for less than 1% of all cancers, thanks to higher public awareness, easier access to healthcare, and well-functioning vaccination programs.

Globally, when examining age-standardized data for every 100,000 women, the incidence of cervical cancer is 14, with a mortality rate of 6.8. Regionally, the incidence rate of cervical cancer is 42.7 in East Africa compared to 4.4 in Western Asia. The mortality rate is 27.6 in East Africa, while it is only 1.5 in Australia [17,18].

3.5 HPV-Related Anogenital Cancers

When considering anogenital cancers, these cancers are less common than cervical cancer, and data is reliably reported only from high-income countries. Nearly all cervical cancers and about 90% of squamous anal cancers are caused by HPV. In contrast, the rates for vulvar and penile cancers are much lower (approximately <50%). This discrepancy is likely due to the presence of other more common causes of carcinogenesis in vulvar and penile cancers, such as chronic inflammation [46].

Approximately 80% of HPV infections are suppressed by the immune system within 2-3 years. Not everyone exposed to HPV will develop an infection, and the inability to suppress the infection plays a crucial role in its persistence and progression to chronicity. Upon entering the body, HPV induces minimal inflammation in the immune system, which is important in preventing persistent infection [47]. As with other risk factors, conditions that cause immunosuppression in an individual can alter the course of the infection. For example, organ transplant recipients and women with HIV infection who have low CD4 counts are at higher risk for persistent cervical HPV infection.

3.6 Oropharyngeal Cancers and HPV

Oropharyngeal cancers are classified into two subtypes based on their etiology: those associated with smoking and alcohol use, and those associated with HPV. The prevalence of HPV-related oropharyngeal cancers parallels the economic development of countries. This trend is attributed to the decline in smoking rates

and the increase in HPV infection rates in high-income countries over the past 20 years [48].

As with other regions, the prevalence of oral HPV in oropharyngeal cancers and lesions varies according to the population studied, and it is more common in men. Two different meta-analyses involving 4,581 and 3,762 healthy individuals were conducted. The first meta-analysis reported an oral HPV prevalence of 4.5%, while the second reported 7.5%. It is known that the samples in these studies varied [49,50]. In a study conducted in the United States, the overall prevalence of HPV in the general population was found to be 6.9%, with a significant difference between men and women. The prevalence was 10.1% in men and 3.6% in women [51]. The prevalence of oral HPV16 (1.3%) is much lower compared to that in the cervical and anogenital systems.

The distinction between latent HPV infections and complete clearance from the body is not clearly defined. The current tests available are insufficient to make this distinction. When a previously HPV DNA-negative patient's result turns positive again, it could indicate either a new HPV infection or the reactivation of a latent infection. It is estimated that the likelihood of reactivation of a latent infection increases with age. This hypothesis is supported by the observation that, as age increases, the number of new sexual partners tends to decrease, and the immune system may become weaker. These factors may help explain the second peak in HPV prevalence observed in older populations. However, the reactivation of latent infections is thought to have a weak association with the development of cervical cancer.

Prevalence, by definition, refers to the proportion of individuals within a specific population who have a particular disease within a defined time period. It is a measure of how widespread a disease is within a community. Prevalence is determined by dividing the number of existing cases of a disease in a population by the number of people at risk in that population. Incidence, in contrast to prevalence, refers to the number of new cases of a disease that develop in a specific population during a particular time period.

HPV prevalence, like that of any disease, varies regionally and nationally. Understanding these differences is critical for assessing and managing the risk among individuals in different areas. A higher prevalence in a specific region implies a greater spread of HPV among individuals, which in turn directly increases the risk of transmission.

It is well established that HPV is associated with cervical cytology abnormalities, cervical premalignant and malignant lesions, anogenital lesions and cancers, and oropharyngeal lesions and cancers. The degree of association between HPV and each organ or lesion varies. Understanding these relationships is crucial for assessing a patient’s risk profile. The most current data on this topic are based on systematic reviews and meta-analyses conducted by the Institut Catala d’Oncologia (ICO)/ Information Centre on HPV and Cancer (IARC) [4].

Globally, the prevalence of HPV infection among individuals with normal cervical cytology is estimated to be 11.7%. Regions where prevalence is particularly high include Africa and Oceania. In these patients, 70-90% of infections are asymptomatic and tend to regress spontaneously within 1-2 years.

HPV infections are most commonly observed in young women, peaking in those under 25 years of age. As age progresses, particularly in Europe and America, the prevalence of HPV is known to decline. However, this decrease is not as pronounced in regions like Africa and Asia. In some parts of West Africa and South America, a second peak of HPV prevalence is observed in older women, which is thought to be due to the reactivation of latent infections [52]. When evaluating HPV types on a global scale, HPV16 is the most frequently observed high-risk HPV type among women with normal cervical cytology, with a prevalence of 3.2%, making it the most oncogenic type. This is followed by HPV18 (1.4%), HPV52 (0.9%), HPV31 (0.8%), and HPV58 (0.7%).

The relationship between HPV and cervical precancerous lesions is even stronger and supported by data. HPV has been detected in 52.5% of ASCUS lesions, 74.8% of low-grade cervical lesions (low-grade squamous intraepithelial lesion [LG-SIL] and cervical intraepithelial neoplasia [CIN1]), and 88.9% of high-grade cervical lesions (high-grade squamous intraepithelial lesion [HGSIL] and CIN2/CIN3]). HPV16 is the most frequently detected type, present in 19.3% of low-grade cervical lesions and 45.1% of high-grade cervical lesions. Compared to normal cervical cytology, the significantly increased prevalence of HPV16, HPV18, and HPV45 in cervical precancerous lesions highlights the carcinogenic potential and impact of HPV [53].

HPV infections are known not only to cause cervical lesions but also to lead to anogenital and oral lesions. Although the association between these lesions and HPV is not as strong as with cervical lesions, and there are fewer studies on this topic, understanding the prevalence of HPV in the anogenital and oral regions is useful for assessing potential risks associated with HPV infections.

The prevalence of HPV infections is higher in men than in women, but the persistence of the infection is much less likely in men. While HPV prevalence varies more significantly with age in women, this variation is minimal in men. Due to differences in sampling techniques, the anatomical sites sampled, and the populations studied, obtaining consistent data can be challenging [54]. Anatomically, HPV is most commonly found in the penile region in men, with the lowest prevalence in the urethra.

When considering anal HPV infections, they are frequently detected in both sexes, with prevalence varying according to gender and sexual orientation. The highest prevalence of anal HPV is found in HIV-positive individuals and men who have sex with men (MSM). The prevalence of anal HPV in MSM is 58.8%, which is nearly twice that of the anal HPV prevalence in women (30.7%). In men who have sex with women, the prevalence is 14.2%, approximately half of that in women. Studies examining concurrent cervical and anal HPV levels in women

have shown a correlation between the prevalences, and like cervical HPV, these rates decline with age [12,19].

A study conducted in 2012 found that 4.5% of newly developed cancer cases were associated with HPV, accounting for 29.5% of all infection-related cancers that year, with more than 80% of these cases being cervical cancer [33]. Meta-analyses updated in 2015 by the ICO/IARC HPV and Cancer Information Center indicated that HPV16 remains the most prevalent genotype in cervical cancers globally, with a prevalence of 60.6%. This rate is 49% in Africa and 58.8% in Europe. HPV16 is most commonly detected in squamous cell carcinoma (SCC) at a rate of 61.7% and in adenocarcinomas at a rate of 50%. HPV18 is found in 8.3% of SCCs and 32.3% of adenocarcinomas. For HPV45, the rate is 5.4% in SCCs and 11.9% in adenocarcinomas [19].

HPV infections are also known to cause cancers in the anogenital region (vulva, vagina, penis, anus) apart from cervical cancer. The incidence of cancers in these areas is much lower compared to cervical cancer. A study identified 115,000 cases of anogenital cancer worldwide, of which 68,500 were associated with HPV infection. Among males, 17,000 cases were diagnosed in the anal canal and 13,000 in the penis, totaling 30,000 cancer cases. Among females, 18,000 cases were diagnosed in the anal canal, 8,500 in the vulva, and 12,000 in the vagina, making a total of 38,500 cases [2,33]. Anogenital cancers are generally squamous cell carcinomas.

There has been an observed increase in the incidence of anal canal cancers within the anogenital cancers. This increase is attributed to risk factors such as sexual behavior variations that heighten exposure to HPV [55]. When examining the connection between these cancers and HPV, it is found that 88% of anal canal cancer cases, 51% of penile cancer cases, 78% of vaginal cancer cases, and between 15% and 48% of vulvar cancer cases are associated with HPV infection [33].

Similar to cervical cancer, HPV16 shows a significant predominance in anogenital cancers. In some regions, such as the anal canal, its prevalence is even higher than that associated with cervical cancer. The prevalence of HPV16 is 60.6% in cervical cancers, whereas it is detected in 71.4% of anal canal cancers. In vaginal cancers, the prevalence is 43.6%; in vulvar cancers, 19.4%; and in penile cancers, 22.8% [4].

In light of all these findings, the presence, detection, and management of HPV infection have become increasingly critical. As the frequency of HPV infections rises, the impact on human health becomes more evident. The increase in the number of HPV-related cancers in recent years underscores the need for systematic detection and monitoring of HPV infections. The rising incidence of HPV-related infections and associated cancers clearly indicates the global importance of addressing this issue.

4. HPV ONCOGENICITY AND PATHOPHYSIOLOGY

Papillomaviruses, regardless of type, share a common genomic organization. Their life cycle and subsequent infection processes rely on infecting a differentiating epithelial cell. The virus particles consist of an icosahedral capsid, which contains a double-stranded circular DNA of approximately 8,000 base pairs and is composed of 360 copies of the L1 gene product. This capsid is non-enveloped [56]. The L2 proteins also bind the capsid to the DNA content; however, they are fewer in number and variable [57]. The genomes of papillomaviruses contain eight or nine open reading frames (ORFs). The post-infection life cycle is controlled through a complex cycle of mRNA activation, involving specific coders. These can be categorized into early ORFs and late ORFs. Early ORFs primarily play a role in the replication of the virus and the initial stages of infection.

Typically, early ORFs are responsible for the proliferation of the virus within the cell. In contrast, late ORFs are associated with proteins involved in the formation of virus particles and are active in the later stages of infection. These are responsible for the replication of the virus within the cell and the formation of new viral particles.

Both sets of open reading frames (ORFs) are activated by different promoters. In HPV, the early open reading frames include the E1, E2, E4, E5, E6, and E7 proteins, with the "E" standing for "early." The late open reading frames include the L1 and L2 proteins, with the "L" standing for "late." These proteins can also be classified as essential and auxiliary proteins. E1, E2, L1, and L2 are considered essential proteins. E1 and E2 are primarily involved in the replication of the virus, while the other essential proteins, L1 and L2, play a role in the formation of the virus. These essential proteins are termed "essential" because they are highly conserved across different papillomavirus types and show little variation [58]. In contrast, the auxiliary proteins (E4, E5, E6, E7) vary in their functional properties depending on the HPV type. The processing and differential coding of these proteins contributes to the distinct pathogenic outcomes associated with different HPV types, leading to their classification into low-risk and high-risk groups. Notably, significant differences exist between the high-risk and low-risk HPV groups in the coding and genetic expression of E6 and E7 [59]. Each protein plays a unique role in HPV's infection process and its life cycle continuation. To summarize the functions of these proteins in the cell cycle:

- **E6 and E7**: These are the primary oncogenic proteins. E6 exerts its oncogenicity by inactivating the tumor suppressor gene p53, while E7 inactivates another tumor suppressor gene, pRB (Retinoblastoma protein) [60]. They also function through various mechanisms to delay cellular differentiation, promote DNA replication, and evade the host immune system [61]. These proteins play crucial roles in the development of cervical cancer.
- **E5**: This protein is an auxiliary oncoprotein that supports the oncogenic properties of the virus. It reduces the expression of Major

Histocompatibility Complex (MHC) and disrupts the presentation of proteins to cytotoxic (CD8+) T cells, aiding in immune evasion [62]. E5 is divided into four groups: E5α, E5β, E5γ, and E5δ, with E5α being predominantly found in highly oncogenic HPV types.

- **E1 and E2**: These are essential viral proteins. E1 is primarily involved in viral replication, while E2 plays a role in binding the virus to host chromosomes and regulates the expression of E6 and E7 at specific points in the viral life cycle [63]. E2 also has a role in immune evasion.
- **E4**: This protein assists in viral synthesis and release by disrupting the cellular keratin in the host's upper epithelium. It is one of the most abundant proteins in HPV-infected cells [64]. E4 does not have a protective protein and functions in conjunction with E1.
- **L1 and L2**: L1 is the major capsid protein, present in 360 copies per viral particle, and is responsible for binding the virus to the host cell and facilitating its entry. L1 is the most conserved protein among HPV types and is used to identify HPV types. Vaccines generate immunity by targeting the L1 protein. L2 is the minor capsid protein, and after the virus infects the tissue, it helps deliver viral genomes to the nucleus.

All proteins within the structure of HPV play crucial roles in its life cycle. However, the primary factors that we need to examine and scrutinize for their involvement in the virus's oncogenic properties are the E6 and E7 proteins. These proteins enable the virus to exhibit its oncogenic characteristics within tissues through different mechanisms. It is well known that E6 inhibits the tumor suppressor protein p53, while E7 inhibits the retinoblastoma protein (RB). The E6/E7 complex, through these activities, leads to multiple oncogenic effects, including chromosomal instability, inhibition of apoptotic signaling pathways, and increased telomerase activity [65].

Under normal conditions, p53 acts via p21 to regulate the cell cycle's checkpoints, preventing abnormal cell growth. By inactivating p53, E6 promotes the mitotic cycle of the cell and inhibits apoptosis. This suppression of p53 by E6 disrupts the cell’s ability to halt the cell cycle in response to DNA damage, allowing for unchecked cellular proliferation.

E7 binds to RB and induces its degradation. The degradation of RB results in the activation of E2F transcription factors [66]. The activation of E2F causes the failure of the G1/S checkpoint in the cell cycle, allowing the cell to progress into the S phase, where DNA synthesis occurs. This uncontrolled cell proliferation and subsequent viral replication are thus initiated. The virus drives the host cell into the S phase to access host replication factors, which are essential for viral replication.

Additionally, the degradation of RB leads to an increase in p16 expression. p16, in turn, further inactivates RB, thereby promoting uncontrolled cell division [67]. This disruption in cell cycle regulation is a key mechanism by which HPV, particularly its high-risk types, contributes to the development of cancer, particularly in the cervix and anogenital regions.

Understanding how HPV infection enters the host cell, establishes the infection, and progresses to cancer is crucial [68]. This knowledge is fundamental not only for developing preventive healthcare measures like vaccines but also for guiding medical or surgical treatment processes. These mechanisms must be understood for these reasons.

HPV infection progresses intraepithelial, meaning that the virus does not initially cause viremia within the host body. Consequently, there is no cell death observed at the early stages. This lack of cellular destruction means that the viral replication process does not trigger inflammation, allowing the virus to evade the host's immune system. The antigen-presenting cells of the squamous epithelium are known as Langerhans cells. Since no significant inflammation occurs during most of the infection cycle, cytokine release is not initiated, which means that Langerhans cells remain inactive. As a result, antigen-specific responses do not begin, and effector cells are not recruited to the site of infection [15].

Regardless of whether HPV is a high-risk or low-risk type, for the virus to replicate, it must access a damaged basal layer of the epithelium [69]. For the infection to persist, the initially infected cell must be a long-lived epithelial stem cell or stem cell-like, capable of division [64]. In the basal layer of the cell, HPV binds to heparan sulfate proteoglycans and/or Laminin 5, a process primarily mediated by the L1 capsid protein [70,71]. This binding induces conformational changes in the viral capsid, leading to further attachment facilitated by L2.

This process is critical because it determines the virus's ability to establish a persistent infection, which is necessary for the progression to cancer. The initial attachment and entry of HPV into basal epithelial cells set the stage for the virus to evade immune detection and establish a long-term presence within the host, ultimately leading to the potential development of malignancy.

Once the virion enters the cell nucleus, it begins its replication process. Initially, HPV maintains a specific copy number within the set of infected reserve cells, typically around 50-200 copies. This replication is mediated by the E1 and E2 proteins. The low level of gene expression in the basal layer allows the virus to remain undetected by the immune system [63]. Until a high copy number is reached, the E6 and E7 proteins continuously stimulate the E1 and E2 proteins to drive replication. As keratinocytes differentiate, the viral genome progresses toward the upper epithelial layers, with new gene expressions occurring at each stage. Thus, the virus initially infects cells at the site of basal layer damage and, as the tissue continues to divide, it moves up into the upper epithelial layers.

As the infected basal cells divide and their numbers increase, they begin to move into the parabasal layer. Viral genome amplification occurs in the middle epithelial layers, and viral release takes place in the upper layers of the epithelium [72,73]. When sister cells reach the epithelial surface and complete their gene expressions, the genome copy numbers exceed 10^3, leading to the formation of viral particles [71,74,75]. The E4 protein is then activated to package these high-copy genomes and facilitate their release in conjunction with the L1

and L2 proteins. E4 disrupts the cytokeratin filaments, allowing the virions to be released [56].

During this intraepithelial process of viremia, the absence of cell death and inflammation renders the virus invisible to the host immune system, facilitating the persistence of the infection. The movement of the virus is directed from the lower to the upper layers of the epithelium. As a result, although the viral genome may be present in adjacent basal cells, viral particles themselves are not found there [75].

This mechanism underscores how HPV can establish persistent infections by evading immune detection, primarily due to its intraepithelial replication strategy that avoids triggering an inflammatory response. The virus's ability to maintain a low profile during the early stages of infection is critical for its long-term persistence and eventual progression to oncogenesis in some cases.

There are some significant differences in the viral replication processes between high-risk (HR) and low-risk HPV types. High-risk HPV types can significantly increase cell proliferation in the basal and parabasal cell layers. The activity of E6 and E7 proteins has been found to be higher in these types. This elevated activity results in cellular proliferation extending into the middle layers of the epithelium, leading to an increase in cell division. Additionally, in high-risk types, infected basal cells exhibit reduced sensitivity to contact inhibition with normal cells, and cellular differentiation is inhibited [76]. The molecular differences between high-risk and low-risk HPV types are summarized in Table 1.

Table 1. Molecular differences between high-risk and low-risk HPV types

Function	High-Risk HPVs	Low-Risk HPVs
E6 Protein		
Gene Expression	Fully encoded and present	Absent or minimally encoded
Binding and Degradation	Strongly binds to p53	Weakly binds to p53
Ubiquitin Ligase Binding	Interacts via E6AP	Interacts via E6AP
p53 Transactivation and Acetylation	Inhibits	Inhibits
Apoptosis	Inhibits	Unknown
Growth Arrest	Inhibits with DNA damage	Continues normally
Keratinocyte Differentiation	Inhibits	Unknown
Interferon Response	Inhibits	Weak inhibition
Signal Pathway Modulation	AKT, WNT, Notch, and mTORC1	Unknown
Telomerase Activation	Activates	Does not activate
MYC Activation	Activates	Does not activate
E7 Protein		
Binding and Degradation	pRB, p107, p130	No degradation

Function	**High-Risk HPVs**	**Low-Risk HPVs**
Binding (without degradation)	Strongly binds E2F	Weakly binds pRB and E2F
Entry into Cell Cycle and DNA Synthesis	Triggers	Triggers
Genomic Instability	Triggers	Does not trigger
STAT1 Function	Suppresses	Does not suppress
Cellular Immortality and Transformation	Plays a role	Does not play a role
Signal Pathway Modulation	AKT	Unknown
Viral Genome Amplification	Yes	Yes

Hanahan and colleagues, in 2022, based their understanding of cancer markers on 14 fundamental mechanisms. They suggested that the development of a tumor in tissue could result from the presence of one or more of these mechanisms. These 14 mechanisms include:

- Cellular senescence
- Genomic instability
- Resistance to cell death
- Deregulation of cellular metabolism
- Loss of phenotypic plasticity
- Sustained proliferative signaling
- Resistance to growth-suppressing genes
- Epigenetic reprogramming
- Immune evasion
- Replicative immortality
- Tumor-promoting inflammation
- Polymorphic microbiomes
- Activation of metastasis and invasion
- Ability to access vascular structures.

Understanding these mechanisms is crucial for grasping the complexity of HPV's role in oncogenesis, particularly in how the virus hijacks cellular processes to drive malignancy, with the high-risk HPV types demonstrating a more aggressive pattern of disruption compared to low-risk types.

The study conducted by Roden and colleagues in 2018 explored the relationship between HPV and established cancer markers, highlighting that HPV influences nearly all of these markers. At that time, ten cancer hallmarks were recognized, and the study focused on how HPV, particularly through its E6, E7, and E5 proteins, contributes to carcinogenesis. The following outlines HPV's role in cancer development based on the mentioned hallmarks:

- **Sustained Proliferative Signaling:** E5 activates the epidermal growth factor receptor (EGFR), and E7 inhibits the retinoblastoma protein (RB), promoting continuous proliferative signals.
- **Resistance to Growth Suppressors:** E7 activates RB, while E6 inhibits p53, both contributing to resistance against growth-suppressing genes.
- **Immune Evasion:** E5 inhibits major histocompatibility complexes (MHCs) and TAP, E6 inhibits interferon regulatory factor 3 (IRF3), and E7 inhibits CXCL14 and IRF1, allowing the virus to evade the immune response.
- **Tumor-Promoting Inflammation:** E6 and E7 inhibit the release of CCL20 and local antigen-presenting cells (APCs) and promote the production of interleukin-6 (IL-6), CCL2, and matrix metalloproteinase-9 (MMP9) in conjunction with monocytes, contributing to a tumor-supportive inflammatory environment.
- **Activation of Invasion and Metastasis:** E6 facilitates invasion and metastasis by inhibiting PDZ domain-containing proteins.
- **Inducing Angiogenesis:** E6 promotes angiogenesis through vascular endothelial growth factor (VEGF) and IL-8, while E7 activates hypoxia-inducible factor 1 (HIF1).
- **Genomic Instability and Mutation:** E7 contributes to genomic instability by causing double-stranded DNA breaks.
- **Deregulation of Cellular Metabolism**: E6 activates mTOR and MYC, leading to deregulated cellular metabolism.
- **Resisting Cell Death:** E6 inhibits p53 and BAK while activating Bcl-2, thereby promoting resistance to apoptosis.
- **Enabling Replicative Immortality:** E6 contributes to replicative immortality by activating telomerase.

Although HPV's oncogenic features, replication processes, and the differences among its types suggest a strong potential for persistent infection and carcinogenesis, the host immune system often mounts a robust response to these infections. In fact, most HPV infections regress within the first two years, demonstrating the effectiveness of the immune response. Natural Immune Response to HPV Infection:

- **Damage Detection**: Local antigen-presenting cells (APCs) are activated, initiating damage detection.
- **Cytokine and Chemokine Release**: Pro-inflammatory cytokines and chemokines are released, facilitating the migration of viral antigens to the lymph nodes.
- **Activation of T Cells**: Once APCs reach the lymph nodes, they stimulate antigen-specific CD4+ T cells, which in turn activate CD8+ T cells or promote the production of neutralizing antibodies (nAbs) by B cells.

- **Innate Immune Activation**: Concurrently, the innate immune response, including the activation of natural killer (NK) cells, occurs, leading to the release of interferons and further recruitment of APCs.
- **Inflammation and CD8+ T Cell Recruitment**: The inflammatory environment and infected cells attract CD8+ T cells to the site, targeting the infected tissue.
- **Antibody Production**: Plasma cells produce nAbs, which target viral particles but not infected cells. While nAbs cannot cure the infection, they can prevent its spread. However, it may take months for these antibody responses to fully develop. Moreover, the antibody levels detected might not be sufficient to prevent reinfection with the same virus. For long-term immunity, cell-mediated immunity is necessary, as the effects of nAbs are more limited [71].

This comprehensive understanding of the immune response and the role of HPV proteins in carcinogenesis underscores the complexity of HPV's interactions with the host and the importance of both preventive and therapeutic strategies in managing HPV-related diseases.

4.1 HPV-Related Cervical Lesions

In 1842, Rigoni-Stern observed that cervical cancers predominantly occurred in married women and were virtually nonexistent among nuns, likely due to their celibacy. This observation led to the early theory that cervical cancer was linked to sexual activity. Over time, it became evident that other risk factors also contributed to the development of cancer.

In the early 1940s, cellular changes in cervical pathology detected through PAP smear tests were termed "koilocytosis." Following this, research into cervical diseases and cancers intensified. In 1980, de zur Hausen identified HPV as the etiological agent in cervical oncogenesis, a discovery that earned him the Nobel Prize in 2008. Once the relationship between HPV and cervical lesions was clearly established, research efforts focused on understanding HPV's role in oncogenesis, its connection to cervical cancers, and refining screening techniques.

In 1941, the combination of the cervical cytology technique developed by George Papanicolaou and Herbert Trout in the United States and the colposcopy method developed by Hans Hinselmann in Germany in 1927 enabled the early detection and intervention of precancerous cervical lesions before they could progress to invasive cancer. These advancements allowed for the identification of at-risk women through cervical cytology, followed by colposcopy to pinpoint lesions. As a result, cervical cancer mortality rates in the United States have decreased by 70% over the past 50 years.

In 1956, Reagan and Hamonic introduced the term "dysplasia," used to describe cervical epithelial abnormalities such as cytological atypia, increased mitotic activity, and loss of polarization. Dysplastic changes were graded as mild,

moderate, or severe. Due to the inadequacy in distinguishing between carcinoma in situ (CIS) and severe dysplasia, and recognizing that severe dysplasia was actually a premalignant lesion, Ralph Richart introduced the concept of cervical intraepithelial neoplasia (CIN) in 1969. CIN was categorized into CIN I, CIN II, and CIN III based on the extent of undifferentiated cell replacement in the epithelium, indicating the spread of basaloid changes in the lower, middle, and upper segments of the cervical epithelium.

The Bethesda System was first introduced in 1988, updated in 1991, and revised in 2001. In 2012, Darragh and colleagues proposed changes related to cytological and histological staging. In the United States, the Lower Anogenital Squamous Terminology (LAST) system is used. According to this terminology, CIN I and other changes caused by HPV are classified as low-grade squamous intraepithelial lesions (LSIL), while CIN III-related changes are classified as high-grade squamous intraepithelial lesions (HSIL) [77]. Due to the sometimes spontaneous regression of CIN II lesions and their occasional behavior as premalignant lesions, an additional molecular test is often needed, with p16 being commonly used. However, because p16 can be stained without being a cancer marker in many HPV infections, it is not entirely specific. No definitive biomarker has been identified for reliably distinguishing between LSIL and HSIL, although p16 is considered a predictor of HSIL. Histologically, LAST classifies CIN I as LSIL, and CIN II and CIN III as HGSIL. These systems and concepts have been developed to estimate the future cancer risk of lesions.

For cytological screenings, the Papanicolaou (Pap) classification is used, ranging from I to V, based on increasing degrees of cervical cytological abnormalities. When assessing these differences, factors such as the degree of lost cytoplasmic maturation and changes in nuclear shape and size are considered. LSIL lesions, which show cellular changes detected by Pap smear tests but are insufficient for diagnosis, are categorized as atypical squamous cells of undetermined significance (ASC-US) or atypical squamous cells where a high-grade lesion cannot be excluded (ASC-H). Non-cancerous glandular abnormalities are classified as atypical glandular cells (AGC) and adenocarcinoma in situ (AIS). A summary of the histological, molecular, and cytological classifications of lesions is presented in Table 2.

Table 2. Relationship between lesion classifications

Histology	LAST	Pap	WHO	Bethesda	Classification
Normal	Normal	I	Negative	NILM	Normal Cervix
CIN 1	LSIL	II	Squamous Atypia	ASC-US	HPV Infection
CIN 2	LSIL/HSIL	III	Mild	LSIL	Pre-cancerous Lesion
CIN 3	HSIL	IV	Severe	HSIL	Pre-cancerous Lesion
Cancer	Cancer	V	Cancer	Cancer	Cancer

Cervical intraepithelial neoplasias (CIN) can either regress spontaneously or progress to invasive cancer. The rates of regression and progression of lesions are shown in Table 3. The goal of optimized management is to prevent overtreatment, which can lead to morbidity while ensuring that high-risk lesions receive appropriate treatment and monitoring. Applying the correct treatment or follow-up protocol to the right patient is crucial in this context.

Table 3. Regression and Progression Rates of Cervical Intraepithelial Lesions [78]

Histologic Lesion	Regression Rate	Rate of Persistence Without Change	Progression to CIN III	Progression to Squamous Carcinoma
CIN I	60%	20-30%	5-10%	1%
CIN II	40%	40%	15-20%	5%
CIN III	33%	-	10-12%	-

The likelihood that a CIN lesion will progress to invasive cancer depends largely on the patient's age and the grade of the CIN lesion. The rate of cancer progression is notably low in individuals under the age of 25, leading to a preference for monitoring the lesion and HPV infection over immediate intervention. A 2012 study in the United States examined the incidence of cervical cancer in women under 40, finding that 78% of cervical cancers occurred in women aged 30-39, 21% in women aged 20-29, and only 1% in women under 20 [79]. These data support the approach of age-specific management.

For patients with CIN 1 lesions, follow-up is often preferred, especially considering the patient's obstetric history, age, and family planning status. This follow-up approach can also be applied to patients with CIN 2 lesions, although treatment is generally recommended for those with CIN 3 lesions.

The average age at which CIN 1 is diagnosed is 29.2 years. A follow-up examination conducted six months later showed a regression rate of 49% in these patients. Approximately 35% of the lesions remained as CIN 1, and only 7% progressed to high-grade lesions [80]. Among patients with regressed lesions, 80% showed no lesions at the 12-month follow-up. In those whose CIN 1 lesions persisted at the six-month mark, 50% showed regression at the 12-month follow-up, while 46% had ongoing low-grade lesions, and 4% developed high-grade lesions.

Even without treatment, about half of patients with CIN 2 lesions will experience regression. A meta-analysis of 36 studies involving 3,160 patients found that after 24 months, 50% of the lesions had regressed, 50% persisted, and 18% progressed to CIN 3 [81]. Another retrospective study of 27,500 patients with CIN 2 who were either monitored or underwent excision found that, over 20 years, 104 developed invasive cervical cancer. The cancer risk was 2.75% in those who

were monitored, compared to 0.89% in those who underwent excision procedures [82].

Spontaneous regression rates for CIN 3 lesions range from 32% to 47%, while the risk of progression to invasive cancer ranges from 12% to 40% if left untreated. In a study of 736 patients with CIN 3, 143 were closely monitored without treatment, while 593 received the necessary treatment. Over ten years, cancer developed in 20% of untreated patients compared to 0.3% of treated patients. After 30 years, the rate was 31% in untreated patients and 0.7% in treated patients [83].

HPV infections lead to cellular changes detectable through cytological and histological examinations. As the lesion progresses, changes such as nuclear enlargement, multinucleation, hyperchromasia, and perinuclear cytoplasmic halos occur. In CIN 1 lesions, the upper two-thirds of the stratified squamous epithelium shows normal maturation, with mild nuclear atypia and a low number of mitoses observed in the basal third. In CIN 2 lesions, the upper half of the stratified squamous epithelium is mature, with the upper third unaffected. Nuclear atypia may be present, with mitoses observed in the basal two-thirds. In CIN 3 lesions, the entire stratified squamous epithelium is typically affected, or only the upper third shows normal maturation. Numerous mitoses are observed throughout the epithelium.

For HPV to progress from a precancerous lesion to cancer, it must induce the necessary cellular changes, a process that can take years. If an HPV infection persists for more than four years, the likelihood of regression is very low [84]. Women with persistent infections are at risk of developing cervical intraepithelial neoplasia (CIN).

Approaches to CIN lesions have evolved significantly since the 1960s. Due to potential complications from procedures, particularly in women desiring future fertility, management strategies have become increasingly minimally invasive. This shift has been driven by long-term research and the ability to monitor HPV infections. In the 1970s and 1980s, cryotherapy and laser ablation were commonly used, but these methods often failed to distinguish between different levels of dysplasia, particularly in patients with advanced lesions. As the importance of distinguishing between dysplastic lesions became clear in the 1990s, treatments like LEEP (loop electrosurgical excision procedure) replaced cryotherapy and laser ablation, providing better differentiation and management of lesions. As screening and vaccination programs became more effective, interventional procedures began to give way to observation [10]. In 2019, the American Society for Colposcopy and Cervical Pathology (ASCCP) released guidelines to optimize approaches to cervical lesions. These guidelines differentiate between patients under and over the age of 25. According to these guidelines:

- Patients with CIN 1 lesions, LSIL, ASC-US, or negative cytology for intraepithelial lesions or malignancy (NILM) but positive for HPV are

considered low-risk for cervical cancer. Annual HPV monitoring and observation are recommended [85]. A cohort study of over 100,000 patients found that those with CIN 1 detected by colposcopic biopsy had a 10-year risk of progression to CIN 3 of 0.7% after one year and 2.3% after five years. For patients with ASC-US and HPV positivity, the risk of progression to CIN 3 was 0.5% after one year and 2.6% after five years. In patients with NILM, the risk of progression to CIN 3 was 0.7% after one year and 2.8% after five years [86].

- Patients with CIN 1 lesions who develop ASC-H or HSIL raise concerns about missed high-grade lesions during colposcopic biopsy. In the same cohort study, the progression rate to CIN 3 for ASC-H lesions was 1.4% after one year and 5.6% after five years. For HSIL, the progression rate was 3.9% after one year and 6.5% after five years [86]. These data support a more aggressive management approach for patients with HSIL, recommending excisional procedures or continued observation depending on patient adherence to follow-up and birth planning. Annual HPV testing and colposcopy are recommended during observation, with continued monitoring if results are negative.
- If CIN 1 persists for two years, the risk of progression to CIN 3 is low. In the same cohort study, HPV positivity persisted in 48% of patients, and more than 90% of these patients had follow-up cytology showing LSIL or lower-grade lesions [86]. In another study of 126 patients with two consecutive CIN 1 biopsies, LEEP was performed, revealing CIN 1 or no intraepithelial lesions in 87% of cases. CIN 2 was found in only 13% [87]. These findings further support the option of observation with annual colposcopy and HPV testing.
- Patients with CIN 2 and CIN 3 lesions are at higher risk for progression, warranting treatment. Decisions regarding treatment modalities should consider the patient's age, birth planning, pregnancy status, and adherence to follow-up. For women over 25 who are not pregnant, treatment is recommended. Patients who opt for observation should be informed of the risks, and follow-up with colposcopy and HPV assessment every six months is advised. When treatment is planned, excisional procedures (LEEP, cold knife conization) are preferred. Ablation (cryotherapy, laser ablation) is an alternative but is less preferred for differentiating lesions. Hysterectomy is not recommended as a first-line treatment [85]. A study published in 2023 provided updates to the 2019 ASCCP guidelines, including new recommendations for managing CIN 2. For patients who are concerned about treatment and have reproductive plans, observation or treatment is acceptable if the squamocolumnar junction is fully visible and the endocervical sampling shows CIN 2 or lower [88]. While treatment was mandatory for HSIL lesions in 2019, the 2023 update allows for observation in certain cases, with increased monitoring frequency, including biannual follow-ups for two years.

The 2019 ASCCP guidelines introduced several changes from previous approaches. These guidelines emphasized considering the impact of a patient's

previous results and other risk factors in management decisions. This led to more frequent follow-up, colposcopy, and treatment recommendations for higher-risk patients, while lower-risk patients could be managed with delayed colposcopy and extended follow-up intervals. The guidelines also incorporated data from a prospective study involving 1.5 million patients at Kaiser Permanente Northern California (KPNC), which included current test results and screening history in risk estimation tables. Based on these tables, the patient's risk of CIN 3 progression could be calculated using an online program available on the ASCCP website. This program, which automates the risk calculation, can guide treatment planning, including options like delayed colposcopy and expedited treatment (without colposcopy), depending on the patient's risk level [86].

4.2 HPV-Associated Anal Canal Lesions

While the exact pathogenesis of anal cancer and lesions has not been as clearly defined as cervical cancers, HPV infections are strongly associated with anal canal cancers and lesions. The risk factors for these infections are similar. Additionally, the diversity in sexual orientations among men and the increase in HPV and HIV infections have led to a recent rise in anal canal lesions. These increasing rates highlight the need for the development of screening programs for the anal canal. The highest rates of anal HPV infection are observed in HIV-positive men who have sex with men (MSM), with over 90% of these patients having anal HPV infections and multiple HPV-type positivity [89]. In contrast, these rates are significantly lower in heterosexual men without HIV. Data on the prevalence of anal HPV in women are limited, but unexpectedly high rates of anal HPV infection have been found across all age groups [90]. Studies comparing women with a high risk of HIV infection, both HIV-positive and HIV-negative, have found that anal HPV infection is more common in these populations than cervical HPV infection [91]. In HIV-positive individuals, the presence of high-risk HPV in the anal canal is significantly higher than in those without HIV, likely due to the higher incidence of infection in this patient population and the decreased immune response to the infection [12].

Anal cancers are less common than cervical cancers and occur more frequently in women than in men when considering the general population. The incidence rate of anal squamous cell carcinoma (ASCC) is approximately 1 per 100,000 people per year [92,93]. The incidence has increased by about 2% per year since the 1970s [94], with a peak incidence in individuals in their 60s. Approximately 80% of ASCC cases are attributed to HPV. According to the International Agency for Research on Cancer (IARC), HPV16 accounts for 66% of HPV-associated ASCC cases, while HPV18 is responsible for 6% [95].

It has been suggested that HPV infections in women primarily spread through receptive anal intercourse [96]. However, subsequent studies have shown that the transmission of the infection can occur with or without anal intercourse. Therefore, it is more appropriate to screen all women at risk for HPV infection, not just those who engage in anal intercourse, for anal canal HPV infections [5]. In a study conducted on healthy women in Hawaii, the rate of cervical HPV

infection was found to be 29%, while the rate of anal canal HPV infection was 27%, showing a close correlation. The HPV types involved were found to be similar, suggesting that there may be transmission between the cervix and anal canal, supporting the hypothesis of a shared source of infection [97]. Limiting anal canal HPV infection to those engaging in anal intercourse may not be accurate. Another study that followed patients with anal canal HPV infections found that the infection regressed in 58% of patients within one year [90].

Two primary mechanisms of HPV transmission in the anal canal have been proposed: direct transmission and auto-inoculation. Of four studies evaluating sexual transmission routes, all but one found that the transmission rate of cervical or anal HPV infection from men to women was significantly higher than the transmission rate from women to men [98]. HPV-positive samples taken immediately after vaginal intercourse are not considered to represent active HPV infections but rather should be considered as accumulation or contamination from the partner [99]. Various studies have shown higher HPV rates following sexual intercourse within 24 hours, which can be misleading. Similarly, high HPV infection rates have been observed in samples taken after sexual intercourse, but this does not indicate active infection. High levels of male DNA were detected in vaginal swabs taken within 48 hours of intercourse. By the third day, the amount of male DNA decreased, and subsequent tests more accurately reflected true HPV infections. In the context of direct sexual transmission, the viral load of the transmitting partner is important, as individuals with a higher viral load are more likely to transmit the infection [100].

While proving the transmission of infection between the cervix and anal canal is challenging, evidence suggests that both regions can serve as sources of infection for each other. The transfer of infection between these regions is believed to occur through auto-inoculation, where the virus spreads to adjacent areas of the skin. Today, it is not possible to differentiate between this type of transmission and contamination or latent infection in the area. Women who engage in anal intercourse are at higher risk for anal canal HPV infection. Despite this increased risk, anal intercourse is not considered an absolute risk factor for developing high-risk HPV infections. Many women who do not engage in anal intercourse also test positive for high-risk HPV infections, indicating that transmission likely occurs through auto-inoculation [101]. A study by Goodman and colleagues found that sequential development of anal and cervical HPV infections is common. The relative risk of developing an anal canal infection after a cervical infection with the same HPV genotype was 20.5, while the relative risk of developing a cervical infection after an anal canal infection was 8 [102]. In addition to this mode of transmission, non-penetrative sexual contact and transmission through fingers have also been identified. Several studies have found that HPV types present on the hands or fingers of both men and women are the same as those in the genital area [103]. Although hand or finger infections are more likely due to DNA accumulation from genital infections rather than active infection, they should not be ignored as a potential route of auto-inoculation. In addition to the hands and fingers, a study conducted in San Francisco demonstrated that the scrotum could play a role in transmission during

heterosexual intercourse through passive contact with the genital area, without penetration. The scrotum may serve as a reservoir or source of penile infections, which can then be transmitted through contact between partners [104].

In a 2013 study by Güler and colleagues conducted on Turkish women, 106 women with cervical HPV infection were examined, and 51.9% of these patients also tested positive for anal HPV. The most common HPV types in cervical infections were HPV16, HPV6, and HPV39, while in anal samples, HPV16, HPV6, and HPV44 were most frequently observed. When analyzing the risk factors in patients who tested positive for anal HPV, it was found that women over 30, those who had their first sexual intercourse before the age of 18, those with more than three-lifetime sexual partners, those who used oral contraceptives, smokers, those with genital warts, and those who engaged in anal intercourse were at higher risk [5].

Persistent HPV infections in the transformation zone of the anal canal lead to dysplasia in the region. These dysplastic changes are categorized as low-grade intraepithelial lesions (LSIL) and high-grade intraepithelial lesions (HSIL). LSIL cytology is typically characterized by abnormal nuclei in basal cells, an increased nucleus-to-cytoplasm ratio, and changes that occur in less than one-third of the epithelium. Many studies have found that the sensitivity and specificity of anal cytology are much lower compared to cervical cytology [105]. The transformation zone of the anal canal can be observed with anoscopy, and biopsies can be taken from suspicious areas. Histologically, these lesions are termed anal intraepithelial neoplasia (AIN) and are classified as AIN 1, 2, or 3. AIN 1 is referred to as low-grade anal intraepithelial neoplasia (LGAIN), while AIN 2 and AIN 3 are considered high-grade anal intraepithelial neoplasia (HGAIN). HGAIN is recognized as a precursor to anal squamous cell carcinoma (ASCC).

Histologically similar to CIN, the natural progression of anorectal intraepithelial neoplasia (AIN) in HIV-negative individuals is not well documented. The presence of high-grade AIN (HGAIN) correlates with the presence of anal HPV in various populations, with the highest prevalence observed among HIV-positive men who have sex with men (MSM), followed by HIV-negative MSM. In a study conducted in San Francisco, the prevalence of AIN in HIV-positive MSM was found to be 57%, with HGAIN prevalence at 43% [106]. Among HIV-negative MSM, the prevalence of AIN was 35%, and HGAIN was 25%. In these patients, anal HPV infection is considered a significant risk factor. HPV shows its oncogenic effects predominantly in the transformation zone of the cervix, and similarly, it affects the transformation zone in the anal canal, where epithelial changes occur. The active metaplasia in both regions allows the virus to enter the basal epithelial cells and continue its replication. However, the data regarding the oncogenic processes in the anal canal are not as robust as those for the cervix.

Given the strong link between HPV infection in the anal canal and the progression to anal cancer, screening and appropriate treatments are crucial for preventive measures. There are limited studies on the prevalence of AIN in

women, and these studies typically focus on HIV-positive women. In women without immunodeficiency, who have CIN or vulvar intraepithelial neoplasia (VIN) or vaginal intraepithelial neoplasia (VAIN) lesions, AIN was detected in 12% of cases, with HGAIN present in 8%. When considering only the association with CIN, AIN was found in 17.4% of these women, and HGAIN in 4% [107]. HGAIN is observed at very high rates in HIV-positive MSM. However, the progression rate of HGAIN to anal squamous cell carcinoma (ASCC) is believed to be much lower than the progression rate of CIN3 to cervical cancer. If the rate were as high as in cervical lesions, we would expect to see a much higher incidence of ASCC [12]. This suggests that spontaneous regression of HGAIN lesions is common.

5. SCREENING AND VACCINATION FOR HPV-RELATED LESIONS

For an effective screening program to be implemented, the disease or type of cancer being screened must have a high incidence in the population. Conducting screening in groups with low incidence is not cost-effective for the general population. A screening program must be appropriately targeted at the right population, with an acceptable detection rate. There must also be an effective intervention method available for individuals who test positive during screening, to ensure that the benefits of early detection translate into improved public health outcomes. The intervention should be accessible, minimally harmful, tolerable by the patient, and informative regarding pre-cancerous lesions. Cervical cancer meets all these criteria, making screening programs highly effective in preventing the disease. One of the best preventive measures is the implementation of a robust screening and vaccination program. When considering the relationship between HPV and anal canal cancer, it is predicted that vaccination would also be beneficial in preventing anal canal cancers. Especially for high-risk populations concerning anal canal cancer, expanding screening programs and taking preventive measures could reduce the increasing mortality and morbidity rates associated with this type of cancer. In countries with a high incidence of cervical cancer, vaccination programs are often not effectively implemented. In countries where vaccination programs are effective, the generations that missed vaccination are more heavily affected by cervical cancer.

The primary goal of screening programs is to detect treatable pre-cancerous lesions before they progress to invasive cancer and to establish an appropriate management strategy. In managing these lesions, while reducing cancer-related mortality and morbidity, it is also important to avoid over-treatment, which can lead to unnecessary complications. Screening involves identifying patients in high-risk groups and directing them to necessary examinations, such as colposcopy and biopsy for cervical cancer.

Preventive approaches for cervical cancer can be categorized into primary and secondary prevention. Primary prevention involves preventing the development of pre-cancerous lesions through HPV vaccination, while secondary prevention involves detecting pre-cancerous lesions through screening and treating them before they progress to cancer. In developed countries, the application of these two methods has significantly reduced the incidence of cervical cancer [108,109].

Three different methods are considered in cervical cancer screening programs, each covering countries with different socio-economic levels. These include visual inspection with acetic acid (VIA), cytology/Pap smear test, and HPV DNA test. The VIA method involves inspecting the cervix under magnification or without magnification after applying acetic acid. However, the sensitivity and specificity of this method are not high enough to make it suitable for screening [110]. In developed countries, screening programs primarily utilize the Pap smear test and HPV DNA testing. The Pap smear test is cytology-based and involves microscopic examination of cells taken from the cervix. Although cytological examination is still the most widely used test worldwide, HPV DNA testing has been found to have higher sensitivity compared to VIA and Pap smear tests [111,112]. Additionally, the cost-effectiveness ratio of HPV DNA testing is higher than other tests. A good cervical cancer screening program should include HPV DNA testing. It can also be included in screening programs as a co-test along with the Pap smear. The Pap smear test is gradually being replaced by HPV DNA testing in screening programs [110]. For patients who test positive in the screening, especially those who test positive for HPV DNA, additional triage should be performed to assess their risk. Based on this triage assessment, patients can be referred for colposcopic biopsy or treatment. Triage can be conducted visually under acetic acid, through cytological examination, or molecular tests. Visual examination under acetic acid without biopsy is not effective in distinguishing pre-cancerous lesions from acute HPV infections [113]. In developed countries, cytological examinations are used to make this distinction. In molecular triage, p16 and Ki67 are used. Many studies suggest that women who test positive for p16 and Ki67 should be referred for colposcopy, while those who test negative should be monitored at specific intervals [113]. Cervical cancer screening strategies in high-income and low-income regions are summarized in Table 4.

Table 4. Cervical cancer screening strategies in high-ıncome and low-ıncome regions

High-Resource Regions	Low-Resource Regions
Cytology HPV Test Co-Test	VIA (Visual Inspection with Acetic Acid) HPV Test Direct Visual Inspection
Sensitivity to Pre-Cancerous Lesions	Low
Follow-Up Interval After Negative Screen	Short
Triage Necessity Definitive Diagnosis Treatment	In suspicious cytology Colposcopic Biopsy Excision

The frequency and method of cervical cancer screening were recommended in 2023 by the American College of Obstetricians and Gynecologists (ACOG), the American Society for Colposcopy and Cervical Pathology (ASCCP), and the U.S. Preventive Services Task Force (USPSTF). According to these

recommendations, Pap smear testing should be repeated every 3 years, HPV DNA testing every 5 years, and co-testing every 5 years. No screening is recommended for individuals under 21 years of age. For those aged 21-29, Pap smear screening is recommended, while for those aged 30-65, screening with Pap smear, HPV DNA testing, or co-testing is recommended at the intervals specified. For individuals over 65, if three Pap smear tests two HPV DNA tests or two co-tests have been negative within the past 10 years, and there is no history of CIN 2-3, screening should be discontinued. In hysterectomized patients, if there is no history of CIN 2-3, screening should also be discontinued [114]. Additionally, in 2020, the American Cancer Society (ACS) suggested that HPV DNA screening could also be performed for individuals over 25 years of age [115]. However, this recommendation has not yet been incorporated into current guidelines. Screening intervals and management strategies vary for patients with immunodeficiencies, such as those with HIV, systemic lupus erythematosus (SLE), rheumatoid arthritis, or those who have undergone organ transplantation.

After the co-test, which includes both the Pap smear and HPV DNA test, patients identified as high-risk are directed to colposcopic examination. Colposcopy plays a crucial role in evaluating cervical lesions, obtaining biopsies, and conducting histological examinations. This method became widely used in the 1960s for identifying pre-cancerous cervical lesions. During the procedure, after the patient is positioned in the lithotomy position, a speculum is inserted to visualize the external os, and the transformation zone is observed. Acetic acid is applied and allowed to sit for 60-90 seconds, after which suspicious areas appear white, and biopsies are taken from these areas. Subsequently, Schiller's solution, which is rich in glycogen, is applied. Dark-stained cells indicate non-infected cells, while lightly stained cells, poor in glycogen, indicate abnormal epithelial cells.

HPV vaccines are a primary preventive measure in the development of anogenital cancer and in reducing HPV infections. Vaccines play a critical role in preventing the transmission of high-risk HPV types. Regardless of gender, administering vaccines disrupts the chain of HPV transmission and helps reduce the endemic spread of HPV. Even a single dose of the vaccine has a significant impact on preventing cancer development and reducing the incidence of warts. HPV vaccines have been developed chronologically as Bivalent (2-valent) for types 16 and 18, Quadrivalent (4-valent) for types 6-11-16-18, and Nonavalent (9-valent) for types 6-11-16-18-31-33-45-52-58.

6. CONCLUSION

The World Health Organization (WHO) has published an HPV elimination program aiming for 2030. This program targets a 30% reduction in cervical cancer mortality by 2030. The program aims to vaccinate 90% of girls by age 15, include women aged 35-45 in a robust screening program, and treat 90% of pre-invasive cancers detected in screening programs. With the anticipated progress of these targets, the hope is to eliminate HPV-related cancers worldwide by 2090 [116]. According to the recommendations published by the American College of Obstetricians and Gynecologists (ACOG) in 2020 [117].

- Two doses of the vaccine are sufficient for individuals under 15 years of age. For this age group, the second dose should be administered 6-12 months after the first dose, with the first dose being considered as "month 0."
- The target vaccination group includes all children, both boys and girls, aged 11-12 years, although vaccination can start as early as 9 years old.
- For those over 15 years of age, three doses of the vaccine are required. In this age group, the second dose should be given in the 2nd month, and the third dose in the 6th month, with the first dose considered as "month 0."
- Individuals with immunodeficiency should receive three doses regardless of age.
- Healthcare workers must be vaccinated.
- In the "catch-up" period, which refers to individuals aged 13-26, vaccination is recommended regardless of sexual activity status, prior HPV exposure, or sexual orientation.
- For those aged 27-45, vaccination decisions should be made on an individual basis, considering the person's situation. While vaccination is safe in this age group, its benefits are less pronounced compared to younger age groups. It is especially recommended for individuals who are not in monogamous relationships or those who have sexually transmitted infections.
- The FDA does not license the vaccine for individuals over 45 years old.
- Individuals who have already received the quadrivalent (4-valent) vaccine are not recommended to be re-vaccinated with the nonavalent (9-valent) vaccine.
- Routine HPV DNA testing before vaccination is not recommended.
- The HPV vaccine is not recommended during pregnancy, nor is it necessary to conduct a pregnancy test before vaccination. It is recommended, however, to vaccinate women under 26 years of age who are breastfeeding and have not been previously vaccinated.
- Children with a history of sexual abuse or assault should be vaccinated at the earliest possible age (9 years old).

To determine the relationship between the quadrivalent (4-valent) vaccine and cervical cancer, a study conducted in Sweden between 2006 and 2017 evaluated the HPV vaccination and the risk of developing invasive cervical cancer among 1,672,983 individuals aged 10-30. The study found that 19 women who received the 4-valent vaccine developed invasive cervical cancer, compared to 538 women who were not vaccinated. The cumulative incidence of cervical cancer was 47 per 100,000 individuals for those vaccinated, compared to 94 per 100,000 for those not vaccinated [118].

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Van Doorslaer K, Li Z, Xirasagar S, Maes P, Kaminsky D, Liou D, et al. The Papillomavirus Episteme: a major update to the papillomavirus sequence database. Nucleic Acids Research. 2017;45(D1):D499-D506.
2. De Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. International Journal of Cancer. 2017;141(4):664-70.
3. Gultekin M, Dundar S, Keskinkilic B, Turkyilmaz M, Ozgul N, Yuce K, et al. How to triage HPV positive cases: Results of four million females. Gynecologic Oncology. 2020;158(1):105-11.
4. Bruni L, Albero G, Serrano B, Mena M, Collado J, Gómez D, et al. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and related diseases in the world. Summary Report 10 March 2023, Available:https://hpvcentre.net/statistics/reports/XWX.pdf,
5. Guler T, Uygur D, Uncu M, Yayci E, Atacag T, Bas K, et al. Coexisting anal human papilloma virus infection in heterosexual women with cervical HPV infection. Archives of Gynecology and Obstetrics. 2013;288:667-72.
6. Valari O, Koliopoulos G, Karakitsos P, Valasoulis G, Founta C, Godevenos D, et al. Human papillomavirus DNA and mRNA positivity of the anal canal in women with lower genital tract HPV lesions: predictors and clinical implications. Gynecologic Oncology. 2011;122(3):505-8.
7. Berek JS. Berek & Novak's gynecology. Lippincott Williams & Wilkins; 2019.
8. Hoffman BL. Hoffman BL, Schorge JO, Schaffer JI, Halvorson LM, Bradshaw KD, Cunningham F, Calver LE. Chapter 10. Endometriosis. Williams Gynecology. New York: McGraw-Hill; 2012.
9. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/cervix
10. Crum CP, Meserve EE, Peters III WA. Cervical squamous neoplasia. Diagnostic gynecologic and obstetric pathology. Elsevier; 2018. p. 298-374.
11. Prendiville W, Sankaranarayanan R. Colposcopy and treatment of cervical precancer: International Agency for Research on Cancer, World Health Organization; 2017.

12. Schim van der Loeff MF, Mooij SH, Richel O, de Vries HJ, Prins JM. HPV and anal cancer in HIV-infected individuals: a review. Current HIV/AIDS Reports. 2014;11:250-62.
13. Palefsky JM, Brickman C. Anal squamous intraepithelial lesions: Epidemiology, clinical presentation, diagnosis, screening, prevention, and treatment. 2022.
Available:https://medilib.ir/uptodate/show/8032
14. Vaccarella S, Franceschi S, Engholm G, Lönnberg S, Khan S, Bray F. 50 years of screening in the Nordic countries: quantifying the effects on cervical cancer incidence. British Journal of Cancer. 2014;111(5):965-9.
15. Ervik M, Lam F, Ferlay J, Mery L, Soerjomataram I, Bray F. Cancer Today. Lyon, France: International agency for research on cancer. Cancer Today. 2016;3:235-48.
16. dos Santos Silva I, Beral V. Socioeconomic differences in reproductive behaviour. IARC Scientific Publications. 1997(138):285-308.
17. Forman D, Bray F, Brewster D, Gombe Mbalawa C, Kohler B, Piñeros M, et al. Cancer Incidence in Five Continents, Vol. X (electronic version) Lyon, IARC. 2013.
18. Vaccarella S, Lortet-Tieulent J, Plummer M, Franceschi S, Bray F. Worldwide trends in cervical cancer incidence: impact of screening against changes in disease risk factors. European Journal of Cancer. 2013;49(15):3262-73.
19. De Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. The Lancet Oncology. 2010; 11(11): 1048-56.
20. Muñoz N, Bosch FX, De Sanjosé S, Herrero R, Castellsagué X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. New England Journal of Medicine. 2003;348(6):518-27.
21. Schiffman M, Doorbar J, Wentzensen N, De Sanjosé S, Fakhry C, Monk BJ, et al. Carcinogenic human papillomavirus infection. Nature Reviews Disease Primers. 2016;2(1):1-20.
22. Braaten KP, Laufer MR. Human papillomavirus (HPV), HPV-related disease, and the HPV vaccine. Reviews in Obstetrics and Gynecology. 2008;1(1):2.
23. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. The Lancet Global Health. 2020;8(2):e180-e90.
24. Bernard H-U, Burk RD, Chen Z, Van Doorslaer K, Zur Hausen H, de Villiers E-M. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology. 2010;401(1):70-9.
25. van Regenmortel MH, Fauquet CM, Bishop DH, Carstens E, Estes M, Lemon S, et al. Virus taxonomy: classification and nomenclature of viruses. Seventh report of the International Committee on Taxonomy of Viruses: Academic Press; 2000.

26. Centers for Disease Control and Prevention. Genital HPV infection Fact Sheet. Rockville, Md: CDC National Prevention Information Network; 2004.
27. IARC Working Group. A Review of Human Carcinogens. F. Chemical Agents and Related Occupations: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 2012.
28. Schiffman M, Clifford G, Buonaguro FM. Classification of weakly carcinogenic human papillomavirus types: addressing the limits of epidemiology at the borderline. Infectious Agents and Cancer. 2009;4(1):1-8.
29. Demarco M, Hyun N, Carter-Pokras O, Raine-Bennett TR, Cheung L, Chen X, et al. A study of type-specific HPV natural history and implications for contemporary cervical cancer screening programs. EClinical Medicine. 2020;22.
30. Rodríguez AC, Schiffman M, Herrero R, Wacholder S, Hildesheim A, Castle PE, et al. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. Journal of the National Cancer Institute. 2008;100(7):513-7.
31. Clifford G, Smith J, Aguado T, Franceschi S. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. British Journal of Cancer. 2003;89(1):101-5.
32. Burk RD, Chen Z, Van Doorslaer K. Human papillomaviruses: genetic basis of carcinogenicity. Public Health Genomics. 2009;12(5-6):281-90.
33. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: A synthetic analysis. The Lancet Global Health. 2016;4(9):e609-e16.
34. Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. Journal of Clinical Virology. 2005;32:16-24.
35. Arsenide G, Phosphide I, Pentoxide V. IARC monographs on the evaluation of carcinogenic risks to humans. IARC, Lyon, France.
36. Kjaer, SK. High-risk human papillomavirus is sexually transmitted: evidence from a follow-up study of virgins starting sexual activity (intercourse). Cancer Epidemiol Biomarkers Prev. 2001;10:101-6.
37. Winer RL, Lee S-K, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. American Journal of Epidemiology. 2003;157(3):218-26.
38. Hatch KD. Handbook of colposcopy: diagnosis and treatment of lower genital tract neoplasia and HPV infections: Little, Brown Medical Division; 1989.
39. Castellsagué X, Munoz N. Chapter 3: Cofactors in human papillomavirus carcinogenesis—role of parity, oral contraceptives, and tobacco smoking. JNCI Monographs. 2003;2003(31):20-8.
40. Smith JS, Herrero R, Bosetti C, Munoz N, Bosch FX, Eluf-Neto J, et al. Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. Journal of the National Cancer Institute. 2002;94(21):1604-13.

41. Sasieni P. Cervical cancer prevention and hormonal contraception. The Lancet. 2007;370(9599):1591-2.
42. Alam S, Conway MJ, Chen H-S, Meyers C. The cigarette smoke carcinogen benzo [a] pyrene enhances human papillomavirus synthesis. Journal of Virology. 2008;82(2):1053-8.
43. Liu T, Soong S, Alvarez RD, Butterworth Jr CE. A longitudinal analysis of human papillomavirus 16 infection, nutritional status, and cervical dysplasia progression. Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology. 1995;4(4):373-80.
44. DiSaia PJ, Creasman WT, Mannel RS, McMeekin DS, Mutch DG. Clinical gynecologic oncology e-book: Elsevier Health Sciences; 2017.
45. Attar E, Ata B. Gomel'in Jinekolojisi. Nobel Tıp Kitabevi İstanbul. 2007.
46. De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. International Journal of Cancer. 2009;124(7):1626-36.
47. Rock JA, Jones HW, Te Linde RW. Te Linde's Operative Gynecology. Lippincott Williams & Wilkins, 2008.
48. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. Journal of Clinical Oncology. 2013;31(36):4550.
49. Kreimer AR, Bhatia RK, Messeguer AL, González P, Herrero R, Giuliano AR. Oral human papillomavirus in healthy individuals: a systematic review of the literature. Sexually Transmitted Diseases. 2010; 37(6):386-91.
50. Wood ZC, Bain CJ, Smith DD, Whiteman DC, Antonsson A. Oral human papillomavirus infection incidence and clearance: a systematic review of the literature. Journal of General Virology. 2017;98(4):519-26.
51. Gillison ML, Broutian T, Pickard RK, Tong Z-y, Xiao W, Kahle L, et al. Prevalence of oral HPV infection in the United States, 2009-2010. JAMA. 2012;307(7):693-703.
52. Bruni L, Diaz M, Castellsagué M, Ferrer E, Bosch FX, de Sanjosé S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. Journal of Infectious Diseases. 2010;202(12):1789-99.
53. Guan P, Howell-Jones R, Li N, Bruni L, De Sanjosé S, Franceschi S, et al. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. International Journal of Cancer. 2012;131(10):2349-59.
54. Giuliano AR, Nyitray AG, Kreimer AR, Pierce Campbell CM, Goodman MT, Sudenga SL, et al. E UROGIN 2014 roadmap: Differences in human papillomavirus infection natural history, transmission and human papillomavirus-related cancer incidence by gender and anatomic site of infection. International Journal of Cancer. 2015;136(12):2752-60.
55. Islami F, Ferlay J, Lortet-Tieulent J, Bray F, Jemal A. International trends in anal cancer incidence rates. International Journal of Epidemiology. 2017;46(3):924-38.

56. Doorbar J, Quint W, Banks L, Bravo IG, Stoler M, Broker TR, et al. The biology and life-cycle of human papillomaviruses. Vaccine. 2012;30:F55-F70.
57. Capsid P. Arrangement of L2 within the. J Virol. 2008;82(11):5190.
58. Nelson CW, Mirabello L. Human papillomavirus genomics: Understanding carcinogenicity. Tumour Virus Research. 2023:200258.
59. Wise-Draper TM, Wells SI. Papillomavirus E6 and E7 proteins and their cellular targets. Frontiers in Bioscience-Landmark. 2008;13(3):1003-17.
60. Vats A, Trejo-Cerro O, Thomas M, Banks L. Human papillomavirus E6 and E7: What remains? Tumour Virus Research. 2021;11:200213.
61. Krump NA, You J. Molecular mechanisms of viral oncogenesis in humans. Nature Reviews Microbiology. 2018;16(11):684-98.
62. Bravo IG, Alonso A. Mucosal human papillomaviruses encode four different E5 proteins whose chemistry and phylogeny correlate with malignant or benign growth. Journal of Virology. 2004;78(24):13613-26.
63. Sakakibara N, Chen D, McBride AA. Papillomaviruses use recombination-dependent replication to vegetatively amplify their genomes in differentiated cells. PLoS Pathogens. 2013;9(7):e1003321.
64. Doorbar J. The E4 protein; structure, function and patterns of expression. Virology. 2013;445(1-2):80-98.
65. Klingelhutz AJ, Foster SA, McDougall JK. Telomerase activation by the E6 gene product of human papillomavirus type 16. Nature. 1996;380(6569):79-82.
66. Dyson N, Howley PM, Münger K, Harlow E. The human papilloma virus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. Science. 1989;243(4893):934-7.
67. McLaughlin-Drubin ME, Park D, Munger K. Tumor suppressor p16INK4A is necessary for survival of cervical carcinoma cell lines. Proceedings of the National Academy of Sciences. 2013;110(40):16175-80.
68. Taberna M, Mena M, Pavón M, Alemany L, Gillison M, Mesía R. Human papillomavirus-related oropharyngeal cancer. Annals of Oncology. 2017; 28(10): 2386-98.
69. Pyeon D, Pearce SM, Lank SM, Ahlquist P, Lambert PF. Establishment of human papillomavirus infection requires cell cycle progression. PLoS Pathogens. 2009; 5(2):e1000318.
70. Guan J, Bywaters SM, Brendle SA, Ashley RE, Makhov AM, Conway JF, et al. Cryoelectron microscopy maps of human papillomavirus 16 reveal L2 densities and heparin binding site. Structure. 2017;25(2):253-63.
71. Roden R, Stern PL. Opportunities and challenges for human papillomavirus vaccination in cancer. Nature Reviews Cancer. 2018;18(4):240-54.
72. Doorbar J. Molecular biology of human papillomavirus infection and cervical cancer. Clinical Science. 2006;110(5):525-41.
73. Doorbar J. The papillomavirus life cycle. Journal of Clinical Virology. 2005;32:7- 15.
74. Maglennon GA, McIntosh P, Doorbar J. Persistence of viral DNA in the epithelial basal layer suggests a model for papillomavirus latency following immune regression. Virology. 2011;414(2):153-63.

75. Stanley MA. Epithelial cell responses to infection with human papillomavirus. Clinical Microbiology Reviews. 2012;25(2):215-22.
76. Isaacson Wechsler E, Wang Q, Roberts I, Pagliarulo E, Jackson D, Untersperger C, et al. Reconstruction of human papillomavirus type 16-mediated early-stage neoplasia implicates E6/E7 deregulation and the loss of contact inhibition in neoplastic progression. Journal of Virology. 2012;86(11):6358-64.
77. Hanahan D. Hallmarks of cancer: new dimensions. Cancer Discovery. 2022; 12(1): 31-46.
78. Sudenga SL, Shrestha S. Key considerations and current perspectives of epidemiological studies on human papillomavirus persistence, the intermediate phenotype to cervical cancer. International Journal of Infectious Diseases. 2013; 17(4):e216-e20.
79. Benard VB, Watson M, Castle PE, Saraiya M. Cervical carcinoma rates among young females in the United States. Obstetrics and Gynecology. 2012;120(5):1117.
80. Bansal N, Wright JD, Cohen CJ, Herzog TJ. Natural history of established low grade cervical intraepithelial (CIN 1) lesions. Anticancer Research. 2008;28(3B):1763-6.
81. Tainio K, Athanasiou A, Tikkinen KA, Aaltonen R, Cárdenas J, Glazer-Livson S, et al. Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis. BMJ. 2018;360.
82. Lycke KD, Kahlert J, Petersen LK, Damgaard RK, Cheung LC, Gravitt PE, et al. Untreated cervical intraepithelial neoplasia grade 2 and subsequent risk of cervical cancer: population based cohort study. BMJ. 2023;383.
83. McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. The Lancet Oncology. 2008; 9(5):425-34.
84. Kotloff KL, Wasserman SS, Russ K, Shapiro S, Daniel R, Brown W, et al. Detection of genital human papillomavirus and associated cytological abnormalities among college women. Sexually Transmitted Diseases. 1998:243-50.
85. Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, et al. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. Journal of Lower Genital Tract Disease. 2020; 24(2):102.
86. Egemen D, Cheung LC, Chen X, Demarco M, Perkins RB, Kinney W, et al. Risk estimates supporting the 2019 ASCCP risk-based management consensus guidelines. Journal of Lower Genital Tract Disease. 2020;24(2):132.
87. Leung SOA, Vitonis A, Feldman S. Yield of loop electrosurgical excision procedure (LEEP) among patients with and without known high-grade cervical dysplasia. Gynecologic Oncology. 2020;159:194.
88. Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines:

Updates Through 2023. Journal of Lower Genital Tract Disease. 2024;28(1):3-6.
89. Denny LA, Franceschi S, de Sanjosé S, Heard I, Moscicki AB, Palefsky J. Human papillomavirus, human immunodeficiency virus and immunosuppression. Vaccine. 2012;30:F168-F74.
90. Shvetsov YB, Hernandez BY, McDuffie K, Wilkens LR, Zhu X, Ning L, et al. Duration and clearance of anal human papillomavirus (HPV) infection among women: the Hawaii HPV cohort study. Clinical Infectious Diseases. 2009;48(5):536- 46.
91. Moscicki A-B, Ellenberg JH, Farhat S, Xu J. Persistence of human papillomavirus infection in HIV-infected and-uninfected adolescent girls: risk factors and differences, by phylogenetic type. The Journal of Infectious Diseases. 2004; 190(1): 37-45.
92. Hartwig S, Syrjänen S, Dominiak-Felden G, Brotons M, Castellsagué X. Estimation of the epidemiological burden of human papillomavirus-related cancers and non- malignant diseases in men in Europe: a review. BMC Cancer. 2012;12(1):1-18.
93. Wu X, Watson M, Wilson R, Saraiya M, Cleveland JL, Markowitz L. Human papillomavirus-associated cancers-United States, 2004-2008. 2012.
94. Johnson LG, Madeleine MM, Newcomer LM, Schwartz SM, Daling JR. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973–2000. Cancer. 2004;101(2):281-8.
95. Hoots BE, Palefsky JM, Pimenta JM, Smith JS. Human papillomavirus type distribution in anal cancer and anal intraepithelial lesions. International Journal of Cancer. 2009;124(10):2375-83.
96. Holly EA, Ralston ML, Darragh TM, Greenblatt RM, Jay N, Palefsky JM. Prevalence and risk factors for anal squamous intraepithelial lesions in women. Journal of the National Cancer Institute. 2001;93(11):843-9.
97. Hernandez BY, McDuffie K, Zhu X, Wilkens LR, Killeen J, Kessel B, et al. Anal human papillomavirus infection in women and its relationship with cervical infection. Cancer Epidemiology Biomarkers & Prevention. 2005;14(11):2550-6.
98. Burchell AN, Coutlée F, Tellier P-P, Hanley J, Franco EL. Genital transmission of human papillomavirus in recently formed heterosexual couples. Journal of Infectious Diseases. 2011;204(11):1723-9.
99. Moscicki A-B, Schiffman M, Burchell A, Albero G, Giuliano AR, Goodman MT, et al. Updating the natural history of human papillomavirus and anogenital cancers. Vaccine. 2012;30:F24-F33.
100. Bleeker MC, Hogewoning CJ, Berkhof J, Voorhorst FJ, Hesselink AT, van Diemen PM, et al. Concordance of specific human papillomavirus types in sex partners is more prevalent than would be expected by chance and is associated with increased viral loads. Clinical Infectious Diseases. 2005;41(5):612-20.
101. Goodman MT, Shvetsov YB, McDuffie K, Wilkens LR, Zhu X, Ning L, et al. Acquisition of anal human papillomavirus (HPV) infection in women: the Hawaii HPV Cohort study. The Journal of Infectious Diseases. 2008;197(7):957-66.

102. Goodman MT, Shvetsov YB, McDuffie K, Wilkens LR, Zhu X, Thompson PJ, et al. Sequential acquisition of human papillomavirus (HPV) infection of the anus and cervix: the Hawaii HPV Cohort Study. The Journal of Infectious Diseases. 2010; 201(9):1331-9.
103. Partridge JM, Hughes JP, Feng Q, Winer RL, Weaver BA, Xi L-F, et al. Genital human papillomavirus infection in men: incidence and risk factors in a cohort of university students. The Journal of Infectious Diseases. 2007;196(8):1128-36.
104. Widdice LE, Breland DJ, Jonte J, Farhat S, Ma Y, Leonard AC, et al. Human papillomavirus concordance in heterosexual couples. Journal of Adolescent Health. 2010;47(2):151-9.
105. Cachay ER, Agmas W, Mathews WC. Relative accuracy of cervical and anal cytology for detection of high grade lesions by colposcope guided biopsy: A cut- point meta-analytic comparison. PloS One. 2012;7(7):e38956.
106. Chin-Hong PV, Berry JM, Cheng S-C, Catania JA, Costa MD, Darragh TM, et al. Comparison of patient-and clinician-collected anal cytology samples to screen for human papillomavirus–associated anal intraepithelial neoplasia in men who have sex with men. Annals of Internal Medicine. 2008;149(5):300-6.
107. Santoso JT, Long M, Crigger M, Wan JY, Haefner HK. Anal intraepithelial neoplasia in women with genital intraepithelial neoplasia. Obstetrics & Gynecology. 2010; 116(3):578-82.
108. Katz IT, Wright AA. Preventing cervical cancer in the developing world. New England Journal of Medicine. 2006;354(11):1110-.
109. Sankaranarayanan R. Screening for cancer in low-and middle-income countries. Annals of Global Health. 2014;80(5):412-7.
110. Sharma J, Yennapu M, Priyanka Y. Screening Guidelines and Programs for Cervical Cancer Control in Countries of Different Economic Groups: A Narrative Review. Cureus. 2023;15(6).
111. Mayrand M-H, Duarte-Franco E, Rodrigues I, Walter SD, Hanley J, Ferenczy A, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. New England Journal of Medicine. 2007;357(16):1579-88.
112. Gravitt PE, Paul P, Katki HA, Vendantham H, Ramakrishna G, Sudula M, et al. Effectiveness of VIA, Pap, and HPV DNA testing in a cervical cancer screening program in a peri-urban community in Andhra Pradesh, India. PloS One. 2010; 5(10): e13711.
113. Massad LS, Jeronimo J, Schiffman M, Health NIo. Interobserver agreement in the assessment of components of colposcopic grading. Obstetrics & Gynecology. 2008; 111(6):1279-84.
114. Marcus JZ, Cason P, Downs Jr LS, Einstein MH, Flowers L. The ASCCP Cervical Cancer Screening Task Force endorsement and opinion on the American Cancer Society updated cervical cancer screening guidelines. Journal of Lower Genital Tract Disease. 2021;25(3):187-91.
115. Auguste P. Cervical cancer screening: updated guidelines from the American Cancer Society. American Family Physician. 2021;104(2):314-5.

116. Organization WH. Global strategy to accelerate the elimination of cervical cancer as a public health problem: World Health Organization; 2020.
117. Eckert LON. Human papillomavirus vaccination ACOG committee opinion, number 809. Obstetrics and Gynecology. 2020;136(2):E15-E21.
118. Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, et al. HPV vaccination and the risk of invasive cervical cancer. New England Journal of Medicine. 2020; 383(14):1340-8.

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Chapter 6
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Patterns of Extrapulmonary Tuberculosis Using CBNAAT: A Retrospective Study

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ABSTRACT

Background: Extra-pulmonary tuberculosis is a milder form of the disease in terms of infectivity as compared to pulmonary tuberculosis. Diagnosis of Extra-pulmonary TB (EPTB) is a challenge.
Aim: The study seeks to assess the sites of extra-pulmonary involvement during 2013-2017 in a tertiary care hospital cum medical college. The study also wanted to evaluate the role of the Cartridge Based Nucleic Acid Amplification Test (CBNAAT) in the diagnosis of EPTB and compare its efficacy with AFB Culture.
Methods: A total of 470 EPTB cases were diagnosed between 2013 and 2017 from 840 TB treatment records maintained in designated microscopy centre. Specific samples from appropriate sites were taken up for smear for AFB, CBNAAT and AFB culture. The sensitivity and specificity of CB NAAT were also computed. All the analysis was carried out using standard statistically significant STATA 15.1.
Results: There was incremental detection and registration in both TB and EPTB cases from 96 and 50 cases in 2013 to 246 and 150 cases in 2017 respectively. Among the total 470 EPTB cases in 2013-2017 (55.9%), lymph nodes followed by pleura and abdomen were the organs having maximum involvement. Bone involvement was more witnessed in adult males than children ($p < 0.05$). There was male preponderance. CBNAAT results were 100 % sensitive and 87.5% specific. Lymph node samples and pus elsewhere in the body had much better diagnostic yield than serous effusions. The number of patients diagnosed from 2013 revealed a steady increase in numbers till 2017; this is due to improved awareness among the clinicians and availability of new diagnostic modalities in

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the extrapulmonary presentations and awareness to register in RNTCP services for availing the services.
Conclusions: EPTB needs a high index of suspicion and judicious invasive diagnostic tests. Awareness and availability of diagnostic services in tertiary care institutions have led to increased reporting of EPTB under RNTCP services. CBNAAT can also be utilized as a point of care testing for lymph node aspirate and pus specimens.

Keywords: CBNAAT; EPTB; RNTCP; extrapulmonary tuberculosis.

1. INTRODUCTION

Extra-pulmonary TB (EPTB) is defined as a disease involving any other organs and includes pleural and isolated intrathoracic lymph node TB. This differs from the terminology for reporting in Canada, which classifies TB as either respiratory (lungs and the conducting airways, pleural, fibrosis of the lung, bronchiectasis, pneumonia, pneumothorax, primary, intrathoracic and mediastinal lymph nodes, isolated tracheal or bronchial, laryngitis, nasopharynx, nose and sinus TB) or non-respiratory (all other disease sites not listed) [1]. Extrapulmonary Tuberculosis is a protean disease affecting virtually all the organs. It is common in the low socioeconomic section of the population [2]. The impact of TB is higher with greater involvement of extra-pulmonary organs in this vulnerable population [3,4]. TB infections affect the lungs in the majority of patients, namely pulmonary tuberculosis (PTB), and also frequently occur in extrapulmonary sites, such as the intestine, meninges, bones, joints and lymph nodes, resulting in extrapulmonary tuberculosis (EPTB) [5].

Globally around 10.4 million people contract tuberculosis [6]. Of these in India, there were an estimated 2.8 million new cases and 0.48 million deaths due to TB in 2015 [7]. The incidence rate of TB is 167(156-179)/1 lakh/year. In 2014-number clinical diagnoses of new PTB and EPTB were 3,43,032 and 1,12,066, respectively. It is a cause for concern in India [8,9].

Extra-pulmonary tuberculosis is a milder form of disease in terms of infectivity as compared to pulmonary tuberculosis. It is common in people living with HIV and AIDS and also witnessed in malnutrition victims.

Prevalence is also higher in the paediatric age group [10]. Better diagnostic availability has led to increased reporting of the disease. Following the haematogenous spread of bacilli during primary pulmonary infection, EPTB may develop later in any anatomic location [11]. Once the diagnosis has been considered, confirmation can be difficult, with sample collection from deep-seated tissues being challenging and the disease typically being pauci-bacillary [9].

In April 2017, Indian EPTB guidelines were developed as an evidence-based practice for suspecting, diagnosing and managing EPTB in medical care services. CBNAAT (Xpert MTB/RIF) is a commercially available test for M. tuberculosis complex (MTB) which uses polymerase chain reaction (PCR) to test

specimen for genetic material specific to MTB and simultaneously detects a gene (rpoB) which confers resistance to rifampicin [12,13].

This diagnostic facility is available at the Regional Medical Research Centre (ICMR), Bhubaneswar. Both respiratory and non-respiratory specimens are accepted for the CBNAAT study [9]. Kalinga Institute of Medical Sciences (KIMS), a tertiary care centre caters to the health needs of the local population residing in its vicinity. It has a designated microscopy centre.

The authors, in this study, wanted to evaluate the site predilection, and demographics of EPTB involvement. The diagnostic utility of CBNAAT in extra-pulmonary specimens was also evaluated, which is the first of its kind in Odisha after its clinical utility in TB Control Programme in 2017 [9].

1.1 Primary Objective

To study the pattern of extra-pulmonary TB diagnosed in the clinical suspects who attended KIMS, Bhubaneswar for evaluation.

1.2 Secondary Objective

To evaluate the diagnostic utility of CBNAAT in extra-pulmonary specimens in selected cases in 2017.

2. METHODS

Extra pulmonary tuberculosis refers to any bacteriologically confirmed or clinically diagnosed case of tuberculosis involving organs other than the lungs e.g. pleura, lymph node, abdomen, genito-urinary tract, skin, joint and bones, meninges etc. The study period was EPTB cases diagnosed during 2013-2017 [9]. Retrospective study from the medical records of diagnosed cases in our institute during above mentioned period. Considering the incidence rate of TB in India 167 (156-179) per one lakh population per year with a proportion of EPTB TB cases around 15%-20%, the sample size would be around 175 cases over 5 year period. However initial scrutiny of records during 2013-2017 revealed around 470 EPTB cases were diagnosed and registered for treatment.

2.1 Inclusion Criteria

RNTCP registered eligible EPTB cases residing around the vicinity of KIMS (designated microscopic centre).

2.2 Exclusion Criteria

- Cases with pulmonary involvement
- Cases with HIV co-infection.

The cases satisfying the inclusion criteria only were considered in the study. These cases were mainly diagnosed by imaging techniques such as Chest X-ray, Ultrasound, CT and MRI scans, FNAC and smear for AFB and histopathological study of biopsy material from the involved organs [9].

All the cases were diagnosed by concerned consultants as per the investigations mentioned above and referred to the DOTS center for registration. All the cohorts were followed for full completion of the chemotherapy under supervision and the outcome was recorded.

The five-year data of the cases were collected from inpatient and outpatient department records and the DOTS centre at KIMS including demographics, clinical presentation, and treatment outcome. The cases for which CBNAAT was performed for diagnosis were considered as a subgroup in the study [9].

2.3 Statistical Analysis

Summary statistics for all the categorical clinical parameters were presented as frequency and percentage. As the subgroup sample size is very small, categorical characteristics were compared between the two groups using Fisher's exact test. The sensitivity and specificity of CB NAAT were also computed [9]. A p value of <0.05 was considered statistically significant. All the analysis was carried out using standard statistically significant STATA 15.1.

3. RESULTS

The number of cases of tuberculosis and EPTB cases registered in 2013 were 96 and 50 respectively, which has increased to 246 and 150 in the year 2017 (Table 1) [9].

Among 840 cases registered for treatment, 470 (55.90%) had EPTB. Among the EPTB cases, males constituted 54.6% (257 cases) compared to 45.6% females (213 cases) (Table 3). The major site predilection was in the following sequence: lymph node (249, 52.9%) followed by pleura (122, 24.9%), abdomen (40, 8.5%), spine (24,5.2%), bone (18, 3.9%), eye (9, 1.9%), disseminated (5,1%) and CNS (3, 0.7%) (Table 2) [9].

The lymph node and pleura were the most commonly affected extra-pulmonary organs in both age groups. Tuberculosis of the spine, bone, and abdomen was more commonly encountered in more than 15 yrs age group (21,13 and 25 cases respectively) than 4-14 yrs age group. Tuberculosis of the Eye was more witnessed in the age range of more than 15 years (6 cases) than in 4-14 years of age (3 cases) (Table 4) [9].

Pleural fluid was the most common sample for which CBNAAT was performed (38.1%) followed by lymph node aspirate (23.8%) [9].

Lymph node aspirates and pus provided the highest CBNAAT-positive cases (Table 5) [9]. All the samples were put for mycobacterial culture. The sensitivity and specificity of CBNAAT against culture were detected to be 100% and 87.5% respectively (Table 6) [9].

Table 1. Year-wise distribution of cases in the percentage of involvement of extrapulmonary sites

Year	No. of TB cases registered	No. of EPTB cases registered	%	LN %	Pleura %	Spine %	Bone and joint %	Abdomen n%	Disseminated %	Eye %	CNS %
2013	96	50	52	42	32	4	2	6	4	8	2
2014	109	76	69	60	21	0	1.3	13	1.3	-	2.6
2015	176	80	46	80	10	-	1	3.7	2.4	-	-
2016	213	114	53	39	30	8.7	4.3	14	-	2.6	-
2017	246	150	60	48	30	8	6.6	5	2	-	-

Table 2. Site of Involvement of extra-pulmonary TB (2013-2017)

Site	No. of ex-pulmonary TB case registered	Frequency	Percentage (%)
Lymphnode	470	249	52.9
Pleura	470	122	25.9
Spine	470	24	5.2
Bone	470	18	3.9
Abdomen	470	40	8.5
Disseminated	470	5	1
Eye	470	9	1.9
CNS	470	3	0.7

Table 3. Site of involvement in EPTB sites in relation to gender (2013-2017)

Site	Male	Female	Total
Lymphnode	134 (53.8%)	115 (46.2%)	249
Pleura	66 (54%)	56 (46%)	122
Spine	14 (58.3%)	10 (41.7%)	24
Bone	11 (61%)	7 (39%)	18
Abdomen	22 (55%)	18 (45%)	40
Disseminated	3 (60%)	2 (40%)	5
Eye	5 (55.5%)	4 (44.5%)	9
CNS	2 (66.6%)	1 (33.4%)	3

Table 4. Site predilection in relation to age and gender (n=470)

Pattern		LN	Pleura	Spine	Bone	Abdomen	Disseminated	Eye	CNS	Total
	Total	42	42	3	5	15	3	3	1	114
4-14yrs	Male	24(36.9%)	22(33.8%)	2(3.1%)	3(4.6%)	9(13.8%)	2(3.1%)	2(3.1%)	1(1.54%)	65
	Female	18 (36.7%)	20(40.8%)	1(2.0%)	2(4.1%)	6(12.2%)	1(2.0%)	1(2.0%)	0(0.0%)	49
	p-value	0.984	0.445	1.00	1.00	0.802	1.00	1.00	1.00	
	Total	207	80	21	13	25	2	6	2	356
	Male	110(56.4%)	44(22.6%)	12(6.1%)	11(5.6%)	13(6.7%)	1(0.5%)	3(1.5%)	1(0.5%)	195
≥15yrs	Female	97(60.2%)	36(22.4%)	9(5.6%)	2(1.2%)	12(7.4%)	1(0.6%)	3(1.9%)	1(0.6%)	161
	p-value	0.465	0.963	0.822	0.043	0.772	1.00	1.00	1.00	
Grand total		249	122	24	18	40	5	9	3	470

** p<0.05 is significant*

Table 5. CBNAAT results from extra-pulmonary samples

Site		Smear for AFB		CB NAAT		AFB culture	
	Total	POS	NEG	POS	NEG	POS	NEG
Lymph node aspirate	15	8	7	7	8	4	11
lymph node pus	8	2	6	3	5	1	7
Tissue from lymph node	3	0	3	1	2	0	3
Tissue from skin	3	0	3	1	2	0	3
Pus from bone	3	1	2	2	1	2	1
Pus from breast	1	0	1	0	1	0	1
Pleural fluid	24	0	24	0	24	0	24
CSF	5	0	5	0	5	0	5
Peritoneal fluid	1	0	1	0	1	0	1
Total	63	11	52	14	49	7	56

Table 6. Diagnostic indices of CB NAAT compared with the AFB culture

	AFB culture (positive)	AFB culture (negative)	Total	
CB NAAT Positive	7	7	14	Sensitivity=100%
CB NAAT Negative	0	49	49	Specificity= 87.5%
Total	7	56	63	

Of 470 cases registered for DOTS, CAT I regimen was advised for 422 cases while the CAT II regimen was prescribed for 48 cases respectively. Among the CAT I regimen prescribed for 422 cases, 415 (98.3%) were declared treatment completed while 7 (1.7%) defaulted. In the case of the CATII regimen prescribed for 48 cases, 37(77%) were declared treatment completed, 8 (16.7%) defaulted and 3 (6.3%) died (Table 7) [9].

Table 7. Treatment outcome 2013-2017

	Total	Completed treatment	Default	Death
CAT I	422	415	7	
CAT II	48	37	8	3

4. DISCUSSION

The study was done to evaluate the pattern of extrapulmonary TB over a 5 years period. The number of patients diagnosed from 2013 revealed a steady increase in numbers till 2017; this is due to improved awareness among the clinicians and availability of new diagnostic modalities in the extrapulmonary presentations and awareness to register in RNTCP services for availing the services. Similar results were reported by Pandit S et al. [14]. The role models played by medical colleges cannot be over-emphasized as they are pioneers in the RNTCP framework [9]. Involvement of extra-pulmonary sites as a percentage of total TB cases registered was much higher than the RNTCP National data of 15-20 percent. Similar observations were reported by Gonzalez et al, (538 EPTB cases out of a total of 1878 tuberculosis cases), Aysel Sunnectcioglu et al, (49.4% EPTB cases), Tahir et al, (722 EPTB cases out of 1490 TB cases) [15-17].

Among the total EPTB cases lymph node involvement was highest at about 52.9% followed by pleura (25.9%); this raises the possibility that higher transmission of infection during early years of life compounded with malnutrition and overcrowding had been responsible for these outcomes [9]. Similar observations were reported from the study by Maltezou HC et al, in their assessment of 102 children with extra-pulmonary tuberculosis where they found not only a 50% increase in admission for EPTB cases over the past decade but also that the majority had superficial lymphadenitis (n=48) and pleural effusion (n=27) [18].

EPTB was more witnessed in males (54.6%) than females (45.4%). Similar observations were made in the study by Ramaprakash et al, who documented 51.52% of males and Mavila R et al, who reported 112 (59.9%) males as sufferers of extra-pulmonary TB [19,20,9]

In the present series, lymph node involvement was the most common site (52.9%) followed by pleura (25.9%). Similar results were reported by Ilgazli et al, who witnessed 56.3% lymph node involvement followed by 31.1% pleural involvement out of 636 cases with EPTB [21].

CBNAAT results of the EPTB specimen revealed higher diagnostic yield from lymph node aspirate and pus compared to no detection from pleural fluid, CSF and peritoneal fluids [9]. This could be explained by the hypersensitivity phenomenon; because few organisms are present in the pleural space, this is a Cell-Mediated Immunity phenomenon. In such cases, pleural fluid culture results are positive in 20-40% of patients with proven tubercular pleuritis [22,23]. However, in our series, the overall CBNAAT sensitivity was 100% and specificity was 87.5%.

Denkinger et al, in a meta-analysis identified 18 studies involving 4461 samples, where they found Xpert sensitivity differed substantially between sample types. In lymph node tissues or aspirates Xpert pooled sensitivity was 83.1% (95% CI 71.4-90.7%) versus culture and 81.2% (95%CI 72.4-87.7%) versus composite reference standards (CRS). In pleural fluid sensitivity was 46.4% (95% CI, 26.3-67.8%) against culture and 21.4% (95% CI 8.8-33.9%) against CRS. CSF sensitivity was 80.5% (95% CI 59.0-92.2%) against culture and 62.8% (95% CI 47.7-75.8%) against CRS [9]. Xpert pooled sensitivity was consistently 98.7% against CRS across different sample types [24].

Similarly, a study by Lawn SD et al, revealed sensitivity of CBNAAT exceeded 75% for tissue biopsies and fine needle aspirate (88.3%; 95% CI: 82-95) gastric aspirate (78.7%; 95% CI: 68-89), pus samples (87.3%; 95% CI:67-100), CSF (85.7%;95% CI: 67-100) and urine (87.5%;95% CI :71-100). The lowest sensitivity was observed in pleural fluid samples (44.4%; 95% CI: 21-67), and other body fluids including pericardial, peritoneal and synovial fluids (50%; 95% CI: 19-81) [25,9]

The limitation of the study was a greater number of cases to undergo the CBNAAT test for better diagnostic predictability.

5. CONCLUSION

EPTB needs a high index of suspicion and judicious invasive diagnostic tests. There was a high detection rate of EPTB cases over a five-year period. Lymph nodes followed by pleura, abdomen and bone were the most common sites of involvement. Male preponderance was noticed. CBNAAT had a high diagnostic yield in cases of lymph node aspirates and pus [9]. Thus, CBNAAT can be utilized as a point of care testing in these samples.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of this manuscript.

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DEDICATION

To my parents and my wife to whom I owe and without whose blessings this academic journey could not been possible.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Barss L, Connors WJ, Fisher D. Chapter 7: Extra-pulmonary tuberculosis. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine. 2022;6(sup1):87-108.
2. Olson NA, Davidow AL, Winston CA, Chen MP, Gazmararian JA, Katz DJ. A national study of socioeconomic status and tuberculosis rates by country of birth, United States, 1996-2005. BMC Public Health. 2012; 12(1):365.
3. Government of India. The National Tribal Policy (Draft). A Policy for the Scheduled Tribes of India; 2006.
   Available: http://www.legalpundits.com?content folder/tribalpolicy.pdf.
4. Basu SK. A health profile of tribal India. Health Millions. 1994;2(2): 12-4.
5. Fang Y, Zhou Q, Li L, Zhou Y, Sha W. Epidemiological characteristics of extrapulmonary tuberculosis patients with or without pulmonary tuberculosis. Epidemiology & Infection. 2022;150:e158.
6. WHO global tuberculosis report; 2016.
   Available:http://www.who.int/tb/publications/global_report/en/.
7. TB India 2017. RNTCP status Report. Central TB division, Directorate General of Health Services, Ministry of Health and Family Welfare, Nirman Bawan, New Delhi; 2017.
8. WHO. Tuberculosis Control in South East Asia Region, Regional Report; 2016.
9. Rao CM, Thakur B, Thakur S, Dash DP. Pattern of extra pulmonary tuberculosis among urban population with special reference to CBNAAT as a diagnostic tool: a retrospective study at a tertiary care hospital of Odisha, India. Int J Res Med Sci. 2018;6:3375-80.
10. Arora VK, Gupta R. Directly observed treatment for tuberculosis. Indian J Paedtr. 2003;70:885-9.
11. Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. Am Fam Physician. 2005;72(9):1761-8.
12. Lawn SD, Mwaba P, Bates M, Piatek A, Alexander H, Marais BJ, et al. Advances in tuberculosis diagnostics: the Xpert MTB/RIF assay and future prospects for a point-of-care test. Lancet Infectious Dis. 2013;13(4):349-61.
13. Sharma SK, Ryan H, Khaparde S, Sachdeva KS, Singh AD, Mohan A, et al. Index-TB Guidelines: Guidelines on extrapulmonary tuberculosis for India. Indian J Med Res. 2017;145(4):448.

14. Pandit S, Dey A, Chaudhuri AD, Saha M, Sengupta A, Kundu S, et al. Five-years experiences of the revised national tuberculosis control programme in northern part of Kolkata, India. Lung India: official organ of Indian Chest Society. 2009;26(4):109.
15. Gonzalez OY, Adams G, Teeter LD, Bui TT, Musser JM, Graviss EA. Extra-pulmonary manifestations in a large metropolitan area with a low incidence of tuberculosis. Int J Tuberculosis Lung Dis. 2003;7(12):1178-85.
16. Sunnetcioglu A, Sunnetcioglu M, Binici I, Baran AI, Karahocagil MK, Saydan MR. Comparative analysis of pulmonary and extrapulmonary tuberculosis of 411 cases. Ann Clin Microbiol Antimicrob. 2015;14(1):34.
17. Tahir M, Sharma SK, Rohrberg DS, Gupta D, Singh UB, Sinha PK. DOTS at a tertiary care center in northern India: successes, challenges and the next steps in tuberculosis control. Indian J Med Res. 2006;123(5):702.
18. Maltezou HC, Spyridis P, Kafetzis DA. Extrapulmonary tuberculosis in children. Arch Dis Child. 2000;83:342-6.
19. Prakasha SR, Suresh G, D'sa IP, Shetty SS, Kumar SG. Mapping the pattern and trends of extrapulmonary tuberculosis. J Global Infect Dis. 2013;5(2):54.
20. Mavila R, Kottarath M, Nair S, Thaha MM. Site predilection of extrapulmonary tuberculosis: study from a tertiary care centre. Int J Res Med Sci. 2017;3(11):3386-90.
21. Ilgazli A, Boyaci H, Basyigit İ, Yildiz F. Extrapulmonary tuberculosis: clinical and epidemiologic spectrum of 636 cases. Arch Med Res. 2004;35(5):435-41.
22. Berger HW, Mejia E. Tuberculosis Pleurisy. Chest. 1973;63(1):88-92.
23. Scharer L, McClement JH. Isolation of tubercle bacilli from needle biopsy specimens of parietal pleura. Am Rev Respir Dis. 1968;97(3):466-8.
24. Detjen AK, DiNardo AR, Leyden J, Steingart KR, Menzies D, Schiller I, et al. Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: a systematic review and meta-analysis. Lancet Resp Med. 2015;3(6):451-61.
25. Lawn SD, Zumla AI. Diagnosis of extrapulmonary tuberculosis using the Xpert® MTB/RIF assay. Expert Rev Anti Infect Ther. 2012;10(6):631-5.

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Research and academic experience: I have 35 years of experience and I have worked as a guide DNB faculty from 2007 to 2015. I have also worked as a Guide for MD as a faculty since the 2017 till date. I am a dedicated doctor and researcher who has made an immense contribution to the scientific community through his publications. My most notable publication is “Role of Cartridge-based Nuclear Amplification Test (CB NAAT) Polymerase Chain Reaction Technique in the Diagnosis of Extra Pulmonary Tuberculosis.” This publication in 2018 was a remarkable one. This study had 410 reads and 5 citations that made a positive impact on the new molecular diagnosis that made new vistas in the diagnosis of Extra Pulmonary Tuberculosis easier. It has contributed to the positive impact of the elimination of TB through early diagnosis and reduction of disability and death. We are envisaging in 2025, a National Tuberculosis Elimination Program in our Odisha state which is ranked second in Tuberculosis diagnosis and management in the National ranking. As the scientific community is getting

wiser further refinement of the knowledge will make it useful to manage tuberculosis. I have publications related to healthcare-associated pneumonia that are a guiding force for antibiotic stewardship this has been helpful for creating antibiotic policies for any big medical institutions. I have also authored publications on COVID-19 that have opened interesting observations in National and International scientific communities. I have about 1500 reads and 24 citations in different publications to date to his credit.

Research specialization: My areas of specialization mainly include airway disease, tuberculosis, cancer of the lungs, and COVID-19.

Number of published papers: I have published more than 30 papers in reputed journals.

Special award: I received the Best Research Faculty Award. I am also the Recipient of Bharat Gourav Puraskar and the Lifetime Achievement Award from the Odisha Chest Society.

Any other remarkable point: I am also a Peer reviewer of the Cureus group of publication, a British medical journal group of publication. My research articles have achieved more than 1500 reads and 24 citations.

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Chapter 7
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A Review of Currently Available Body Imaging Techniques and their Applications in Clinical Practice and Biomedical Research

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ABSTRACT

Background: Imaging modalities have advanced both clinical practice and research by providing a systematic method for differentiating phenotypes of human BC that diverge from what is considered normal, that is, having low bone mass (osteopaenia/osteoporosis), low muscle mass (sarcopenia high-fat mass, obesity), or high-fat with low muscle mass (sarcopenic obesity). Applications of imaging technology modalities have accumulated evidence that individual components of body composition (BC) have significant influences on chronic disease onset, disease progression, treatment responses, and health outcomes.
Objective: This study analyzed the currently available body imaging techniques and their applications in clinical practice and medical research.
Methods: To review the various body imaging techniques and their applications in clinical practice and medical research, Medline, PubMed, Google Scholar, Research Gate, and other databases were searched. Furthermore, references to selected studies and documents available in different libraries were also searched. Many comprehensive reviews have been published on assessing BC using various imaging methods.
Findings: Imaging modalities have provided a systematic method for differentiating phenotypes of BC that diverge from normal, i.e. having low bone mass (osteopenia/osteoporosis), low muscle mass (sarcopenia), high-fat mass (obesity), or high fat with low muscle mass (sarcopenic obesity). Tremendous

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advances have been made over the past decades in the sensitivity and quality of imaging techniques such as Duel-Energy X-Ray Absorptiometry (DXA), Computed Axial Tomography (CT), Ultrasound (US), Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopy (MRS), Positron Emission Tomography (PET), Bioelectrical Impedance Analysis (BIA) etc. Advances in DXA, CT, and US techniques have increased their applications in assessing adipose and lean tissue in various body deposits. US has become one of the most convenient imaging methods that have emerged for quantifying tissue amounts and types, due to widespread availability in clinical practice. These imaging techniques have been useful in differentiating layers or depots within tissues and cells enhancing our understanding of distinct mechanistic, metabolic, and functional roles of BC within human phenotypes.

Conclusion: In the present overview, focus was given on the DXA, CT, and US for use in clinical practice and biomedical research relevant to future investigation of human BC and how they may be applied to remedy the pandemic of obesity, diabetes, and metabolic syndrome.

Keywords: Imaging techniques; bioelectric impedance analysis; computed axial tomography; ultrasonogram.

1. INTRODUCTION

Medical imaging is the process of visual representation of the structure and function of different tissues and organs of the human body for clinical purposes and medical science for the detailed study of normal and abnormal anatomy and physiology of the body. Medical imaging techniques are used to show internal structures under the skin and bones, as well as to diagnose abnormalities and treat diseases [1].

The human body comprises more than thirty measurable components. A direct in vivo measurement of body components is currently not possible; consequently, indirect methods and models have been developed to do that [2]. The importance of understanding body composition (BC) in clinical practice and research has been increasingly recognised over the past decades, along with substantial progress in measuring body composition using sophisticated imaging methodologies. These advances have been partly driven by the increasing evidence that individual components of BC have a significant influence on chronic disease onset, disease progression, treatment response, and health outcomes. Moving toward individualized medicine, specific measures of body composition could greatly advance our understanding of obesity, metabolic health, aging, and chronic diseases [3]. It has been revealed that, even within a disease state, there is wide variability with regard to the role of BC [3,4]. Further, the BC response to treatment, whether dietary, pharmaceutical, or surgical, may vary owing to individual phenotype characteristics, including genetic traits, gender, and race [5]. Unfortunately, anthropometric methods, i.e. body mass index (BMI), waist circumference, or waist-hip ratio, and available clinical tools to assess body composition, i.e. girth tape measures, skin fold callipers, or bioelectric impedance machines, are unable to precisely specify components of

BC (e.g. visceral versus subcutaneous adipose tissue (SAT) or ectopic fat in tissues and organs) and thus, are limited in providing the information necessary to target preventative or treatment strategies to improve health or reduce the risk that is phenotype specific [6-9,10].

Imaging modalities have advanced both clinical practice and research by providing a systematic method for differentiating phenotypes of human BC that diverge from what is considered normal, that is, having low bone mass (osteopaenia/osteoporosis), low muscle mass (sarcopenia high-fat mass, obesity), or high-fat with low muscle mass (sarcopenic obesity) [8]. Within the body, imaging methods can provide information about the spatial distribution of tissues and organs based on differences in their tissue and molecular properties that may be acquired as two-dimensional (2D) projections using a dual-energy X-ray absorptiometry (DXA) scanner or 2D or three- dimensional (3D) image volumes using computed axial tomography (CT) or magnetic resonance imaging (MRI) or positron emission tomographic (PET) scanners or bioelectric impedance analysis (BIA) or ultrasound (US). Magnetic resonance spectroscopy (MRS) provides detailed information about the actual composition of signals from metabolites within a volume of tissue. The accuracy for distinguishing tissue type and amount depends on the sensitivity of a particular imaging method with regard to contrasting tissues and the spatial resolution of the employed modality, as well as the speed and stability with which images are acquired [11-14,8]

Many comprehensive reviews have been published on assessing BC using various imaging methods [7,14,15]. A detailed review of the principles of each method, as well as their respective, strength and limitations, is beyond the scope of the present article. Here, we present an overview of advancements occurring in imaging technologies such as DXA, CT, and US that show strong promise for future applications in the investigation of obesity and metabolic syndrome that impair health and nutritional status [8].

2. DUAL-ENERGY X-RAY ABSORPTIOMETRY (DXA)

In organizing research on BC, it has been suggested that the human body comprises more than thirty measurable components. As in vivo measurement of body components directly is not possible currently, indirect methods and models have been developed for this purpose [16,17]. Although originally designed for determining bone mineral density and diagnosing osteoporosis and other bone diseases, DXA is also used to assess fat and fat-free soft tissue. DXA measures the absorption (attenuation) of two X-ray photon energies, typically near 40 and 70 KeV which allows for the distinguishing of bone from soft tissue (high attenuation for bone and low attenuation for fat).

After excluding pixels that represent bone tissue, DXA estimates fat from the proportion of fat to lean soft tissue in each pixel of a whole body image based on X-ray attenuation [8]. It is assumed that when estimating fat and lean soft tissue, the percentage of pixels that are excluded as bone does not differ from one area of the body to another. Additionally, DXA estimation of fat tissue may be

influenced by conditions where the ratio of extracellular to intracellular water varies (e.g. due to oedema, infancy, or aging), as it is assumed that the hydration of lean soft tissue remains constant. However, in normal, healthy conditions, a change in hydration of 5% influenced fat estimation by only 11.5%. An additional consideration in obese persons is that body thickness (>25 cm) can result in an underestimation of fat mass [18,19,8]

DXA is used in people of all ages owing to its relatively low ionizing radiation exposure (-1 mSv per scan), although it is recommended that DXA not be performed during pregnancy. Comparison to the in vivo gold standard four-compartment model has demonstrated the accuracy of DXA for assessing the percent of fat within the body (±5%) as well as changes in body fat over time. Within-individual test coefficients of variation of <3% for fat and lean mass have demonstrated the reliability of DXA measures in obese children and adults. Hence, DXA has been utilized extensively, including for the development of body composition reference values from National Health and Nutrition Examination Survey data. In contrast to anthropometric measures (i.e. waist circumference or waist-hip ratio, which correlate well with the progression of atherosclerosis and cardiometabolic risk), the use of regional distribution of fat mass by DXA in obese individuals first provided recognition of the differential risk from excess fat accumulated in the android versus the ganoid regions of the body [8]. Even in children and adolescents, greater android fat was shown to be significantly and independently associated with elevated serum triglycerides, reduced HDL cholesterol levels, and higher systolic blood pressure. Another contribution from DXA has been identifying differences in body fat patterns by race and ethnicity [20-24].

In considering the importance of measuring visceral adipose tissue (VAT) volume or mass, it is remarkable that over half of US non-Hispanic males, 63% of US non-Hispanic females, and 75% of Hispanic adults have a level of abdominal obesity that is associated a fivefold increased risk for coronary heart disease. Several studies have demonstrated that ethnicity influences susceptibility to the adverse cardiometabolic effects of VAT. Although the prevalence of diabetes is 50% greater and coronary heart disease is 20% greater when comparing African Americans to non-Hispanic whites, African Americans seem to be more prone to accumulating SAT than VAT [8]. In contrast, Asians-even those with BMI in the range of normal weight-accumulate larger amounts of VAT than whites who have similar waist circumference [25-27].

DXA measurement is becoming increasingly important due to its advantages in terms of accuracy, simplicity, availability, relatively low expense, and low radiation exposure. DXA systems are practical, require no active subject involvement, and impose minimal risk [28-31,8] Therefore, DXA is gaining international acceptance and emerging as the current reference method for the assessment of BC, mainly because it provides accurate estimates of bone mineral, fat and lean soft tissue, the so-called three-component model. In addition, DXA is capable of supplying estimates of visceral fat using validated predictive algorithms and provides a measure of truncal fat mass, which was

found to be predictive of disease risk [13,28-31]. Although there are no contraindications reported to the use of DXA in clinical practice except pregnancy, it should not be performed more than twice a year [13,32-34]. However, uncertainty regarding the accuracy of DXA body composition measures, particularly in individuals at the lower and upper ranges of BMI, indicates that other imaging modalities may be more suitable choices depending on the research/clinical question or population group being addressed [17,25-27,8]

3. COMPUTED AXIAL TOMOGRAPHY (CT)

Computed axial tomography (CT) maps X-ray attenuation characteristics of tissue, which are determined by the elemental composition (electron density) of the tissue through which X-rays pass. Using X-ray measurements from a large number of projection view angles, cross-sectional images (tomograms) are reconstructed, providing a 2D or 3D map of pixels that are given a numerical value (Hounsfield unit) where 0 is assigned to water and -1000 is assigned to air; lower numbers represent lower electron density. Thus, values of adipose tissue density typically fall in the range of 30 to -190 Hounsfield units [8]. However, since whole body composition can be estimated from a single cross-sectional image or slice, where the radiation dose is closer to 2.7 mSv for quantifying liver fat and as low I mSv for quantifying abdominal fat, there is renewed interest in using CT scans for body composition research. In addition, advances in CT scanner technology and reconstruction algorithms, particularly with diagnostic cardiac CT, are not only improving image quality but also reducing radiation exposure in people of all body sizes by constraining image reconstruction to avoid artifacts and using sophisticated techniques that reduce radiation exposure throughout the scan [32-34,8]

An important contribution of CT imaging has been elucidating relationships between VAT, insulin resistance, and cardiometabolic risk, both in persons who are obese and those who are normal weight but “metabolically obese.” Indeed, anthropometric measures such as waist circumference, waist-hip ratio, or even percent body fat are not as robust in predicting cardiometabolic dysfunction when BMI falls within the range of normal or underweight [8]. The use of CT to measure adipose tissue distribution among individuals with obesity has also identified sex and race/ethnicity differences. Not only is the proportional amount of VAT to SAT different with regard to sex and race/ethnicity, but it appears that accumulation of VAT is more robustly associated with insulin resistance in individuals of European and Asian descent, while insulin sensitivity in persons of African descent may be more greatly influenced by accumulation of excess SAT. Application of CT has also expanded our understanding of the strength of the relationship between the largest component of total body fat, SAT, and insulin resistance [35-37,8]. A major contribution of body composition research has been advancing our understanding of whether changes in adipose tissue depots from weight loss interventions have differential effects on components of cardiometabolic disease. It is understood that weight loss in overweight or obese persons, including those with metabolic syndrome, diabetes, or cardiovascular

disease, can improve various risk factors including blood pressure, dyslipidemia, and insulin sensitivity. Improved insulin sensitivity after weight loss from consumption of very low-calorie diets and from gastric surgery has been strongly associated with reduced VAT measured by CT [8]. Moreover, when considering macronutrient composition (e.g. low fat versus high fat) of very-low-calorie diets, CT measures show no difference by diet type for the amount of VAT loss, suggesting that the relative amount of a particular macronutrient may not be the driving factor in achieving weight loss [38,39].

In addition to differentiating layers of adipose tissue depots; determining the quantity of fat deposition in the liver and skeletal muscle (ie ectopic lipid) has become of great interest, primarily due to its relationship with insulin resistance. Moreover, accumulation of hepatic lipids leads to inflammation, cirrhosis, and, ultimately, liver failure as seen in the most common liver disease in the United States, nonalcoholic fatty liver disease (NAFLD) [8]. Being a noninvasive method, compared to liver biopsy, CT attenuation is used to evaluate the degree of hepatic steatosis. CT data from Framingham Heart Study subjects showed reproducibility of single-slice abdominal scans (r= 0.98) for quantifying fatty liver. Greater awareness of the importance of maintaining muscle mass in health and disease has stimulated the use of scans that have been acquired in patient populations, typically as part of standard medical diagnosing and assessment of treatment response, to investigate the role of body composition in disease and treatment outcomes. Indeed, CT measurement of skeletal muscle attenuation, which reflects intramuscular adipose tissue (IMAT) accumulation, may be as robustly associated with insulin resistance as VAT [8]. CT measurement of IMAT provides information on the effectiveness of interventions (diet, exercise, surgery) in various muscle groups, offering insight into the potential of such interventions for altering the physical and physiologic effects of obesity, disease and aging [40-42].

Moreover, CT images acquired as part of routine clinical practice are being used to determine the relationships between loss of skeletal muscle mass (sarcopenia) and efficacy or toxicity of pharmacologic therapy, as well as the outcomes of surgical treatments. Skeletal muscle content from slices acquired at the anatomical region of the third lumbar (L3) vertebra rightly correlated with whole-body muscle volume (r = 0.71-0,92100) [8]. Further advancing the potential of exploiting single-slice CT images, both manual and automated software programs have been developed for the segmentation of muscle, VAT and SAT Cross-sectional area of VAT and SAT, quantified from a single CT slice, are strongly correlated with whole-body measures in persons of various ages, race/ ethnicities, and BMI (r= 0.84-0.96 for whole- body adipose tissue volume). This information is highly useful, as sarcopenic obesity (i.e. having the double burden of low skeletal muscle mass and high-fat mass) is increasing in the general population. Currently, the contribution of sarcopenic obesity to cardiometabolic disease risk is unclear, particularly due to the limitation of having no established criteria or cut points to classify individuals [8]. Although some epidemiological investigations have not detected an association between sarcopenic obesity and cardiovascular risk, a low skeletal muscle-to-VAT ratio has been associated with

metabolic syndrome and arterial stiffness (via pulse-wave velocity) in otherwise healthy adults [43-45].

Recent advances in imaging modalities have been useful in early detection of severity and complications of metabolic syndrome thus reducing morbidity and mortality from it [36,8] This early detection has been helpful in monitoring target organ injury and in turn developing novel therapeutic targets to alleviate and avert them. In particular, using CT to assess metabolic syndrome reported that accumulation of VAT is the best predictor of metabolic syndrome in women and a good predictor of metabolic syndrome in men [45-47].

4. ULTRASOUND (US)

Ultrasound (US) is likely the most convenient imaging method that has emerged for quantifying tissue amounts and types, due to its widespread availability in clinical practice (where it is used for purposes of diagnosis and treatment response), portability, and relatively low cost. The US transducer produces sound waves that reflect off tissues, making echoes that are converted into signals for processing [8]. The amount of sound reflected is determined by the acoustic impedance between tissues; while air has relatively no impedance, bone has a relatively high impedance (0.78 g/cm/s) and adipose and lean tissue have impedances of 0.138 and 0.170 g/c/s, respectively. Measurement of mesenteric fat thickness by the US is strongly associated with cardiovascular risk factors in healthy young adults, but a comparison of US measures for adipose tissue (VAT and SAT) to those acquired by CT suggests that, while there is a strong correlation with VAT, there may be less accuracy and reliability with measurement of SAT [8]. However, US-detected changes in total body fat after weight loss were comparable to DXA measures in obese adolescents [48,49].

Dysregulation of the human's energy balance, mediated by non-performing endocrine organs (liver, skeletal muscle, adipose tissue, etc. can be related to human metabolic disorders characterized by an impaired BC such as obesity and sarcopenia [8,50,51]. The US, a fast, non-invasive, low-cost, and widely available imaging technique, holds great potential in the study of BC. The US can directly measure muscles, organs, and visceral and subcutaneous fat tissue in different sections of the abdomen and body, overcoming some limits of anthropometric evaluation and other imaging techniques [52,53]. US examination has the potential role in the context of BC characterization, investigating four pivotal topics i.e. abdominal fat compartments, SAT, skeletal muscle, and liver [49,54,8,55,56].

5. CONCLUSION

Advances in DXA, CT, and US techniques have increased their applications in assessing adipose and lean tissue in various body deposits. DXA is gaining international acceptance and emerging as the current reference method for the assessment of BC. CT measurement of IMTA provides information on the effectiveness of interventions (diet, exercise, surgery) offering insight into the

potential of such interventions for altering the physical and physiological effects of obesity, disease, and aging [8]. US has become one of the most convenient imaging methods that has emerged for quantifying tissue amounts and types, due to widespread availability in clinical practice. Measurement of mesenteric fat thickness by the US is associated with cardiovascular risk factors in healthy young adults and there may be less accuracy and reliability with the measurement of SAT compared to VAT. However, US-detected changes in total body fat after weight loss were comparable to DXA measures in obese adolescents. Thus, biomedical imaging modalities have improved the ability to assess adipose and lean tissue in various body depots, have increased the availability of imaging modalities in clinical and research settings, have reduced scanning time and subject burden, and have lowered some of the cost of imaging [8]. These advances have enhanced our understanding of the multifactorial and complex nature of obesity, metabolic syndrome, and the development of diabetes and cardiovascular disease. However, applications of other imaging modalities may be considered also depending on the research clinical question or population group addressed.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Hussain S, Mubeen I, Ullah N, Shah SS, Khan BA, Zahoor M, Ullah R, Khan FA, Sultan MA. Modern diagnostic imaging technique applications and risk factors in the medical field: a review. BioMed Res Int 2022; 2022(1): 5164970.
   Available:https://doi.org/10.115/2022/5164970.
2. Marra M, Sammarco R, De Lorenzo A, Iellamo F, Siervo M, Pietrobelli A, Donini LM, Santarpia L, Cataldi M, Pasanisi F, Contaldo F. Assessment of body composition in health and disease using bioelectrical impedance analysis (BIA) and dual energy X-ray absorptiometry (DXA): A critical overview. Contrast Media & Molecular Imaging. 2019; 2019(1):3548284.
3. Linge J, Borga M, West J, Tuthill T, Miller MR, Dumitriu A, Thomas EL, Romu T, Tunón P, Bell JD, Dahlqvist Leinhard O. Body composition profiling in the UK Biobank Imaging Study. Obesity. 2018;26(11):1785-17-95.
4. Camhi SM, Katzmarzyk PT. Differences in body composition between metabolically healthy obese and metabolically abnormal obese adults. Int J Obes (Lond.). 2014;38(1):142-145.

5. Muller MI, Lagerpusch M, Enderle J, et al. Beyond the body mass index: Tracking body composition in the pathogenesis of obesity and the metabolic syndrome. Obes Res. 2012;13(Suppl. 2):6-13.
6. Moller JB, Pedersen M, Tanaka H, et al. Body composition is the main determinant for the difference in type 2 diabetes pathophysiology between Japanese and Caucasians. Diabetes Care. 2014;37:796-804.
7. Andreoli F, Garaci F, Cafarelli P, Guglielmi G. Body composition in clinical practice. Eur J Radiol. 2016;85:1461-1468.
8. Giasuddin ASM, Jhuma KA, Nabi S. Applications of Body Imaging Techniques in Clinical Practice and Biomedical Research: A review. Bangladesh Med Res Counc Bull. 2021;47(2):103-109.
9. Franks PW, Christophi CA, Jablonski KA, et al. Common variation at PPARGC1A/B and change in body composition and metabolic traits following preventive interventions: The Diabetes Prevention Program. Diabetologia. 2014:57:485-490.
10. Hwang YC, Hayashi T, Fujimoto WY, et al. Visceral abdominal fat accumulation predicts the conversion of metabolically healthy obese subjects to an unhealthy phenotype. Int J Obes (Lond.); 2014. DOI:10.1038/ijo.lijo.2015.75
11. Prado CM, Heymsfield SB. Lean tissue imaging: A new era for nutritional assessment and intervention. J Parenter Enteral Nutr. 2014;38:940-953.
12. Widen EM, Gallagher D. Body composition changes in pregnancy: Measurement, predictors and outcomes. Eur J Clin Nutr 2014; 68: 643-652.
Available:https://doi.org/10.1038/ejcn.2014.40. PMID: 24667754.
13. Pourhassan M, Schautz B, Braun W, et al. lmpact of body composition methodology on the composition of weight loss and weight gain. Eur J Clin Nutr. 2013;67:446-454.
14. Rubiano F, Nunez C, Heymsfield SB. A comparison of body composition techniques. Ann N Y Acad Sci. 2000;904:335-338.
15. Basu STC. Kwee TC, Surti S et al. Fundamentals of PET and PET/CT imaging. Ann N Y Acad Sci. 2011;1228:1-18.
16. Wang Z, Pierson RN, Heymsfield SB. The five level model: A new approach to organizing body composition research. Am J Clin Nutr. 1992;56:19-28.
17. Marra M, Sammarco R, Lorenzo Ade, Lellamo F, Siervo M, Pietrobelli A, et al. Assessment of body composition in health and disease using bioelectrical impedance analysis (BIA) and dual energy x-ray absorptiometry (DXA): A critical overview. Hindawi Contrast Media & Molecular Imaging; 2019. Article ID: 3548284.
DOI: 10.1155/2019/ 3548284
18. Wang Z, Heymsfield SB, Chen Z, et al. Estimation of percentage body fat by dual-energy x-ray absorptiometry: evaluation by in vivo human elemental composition. Phys Med Biol. 2010;55:2619-2635,
19. Genton L, Hans D, Kyle UG, Pichard C. Dualenergy X-ray absorptiometry and body composition: Differences between devices and comparison with reference methods. Nutrition. 2002;18:66-70.

20. Toombs RJ, Ducher G, Shepherd JA, De Souza MJ. The impact of recent technological advances on the trueness and precision of DXA to assess body composition. Obesity (Silver Spring). 2012;20:30-39.
21. Silver Hi, Niswender KD, Kullberg j, et al. Comparison of gross body fat-water magnetic resonance imaging at 3 Tesla to dual-energy X-ray absorptiometry in obese women. Obesity (Silver Spring). 2013;21:765-774.
22. Stults-Kolehmainen MA, Stanforth PR, Bartholomew JB, et al, DXA estimates of fat in abdominal, trunk and hip regions varies by ethnicity in men. Nutr Diabetes. 2013; 3: e64.
23. Micklesfield LK, Evans J, Norris SA, et al. Dual energy X- ray absorptiometry and anthropometric estimates of visceral fat in Black and White South African women. Obesity (Silver Spring). 2010;18: 619-624.
24. Taylor AE, Kuper H, Varma RD, et al. Validation of dual energy X-ray absorptiometry measures of abdominal fat by comparison with magnetic resonance imaging in an Indian population. PLoS One. 2012;7:e51042.
25. Ghandehari H, Kamal-Bahl VLeS, et al. Abdominal obesity and the spectrum of global cardiometabolic risks in US adults. Int J Obes (Lond.) 2009;33:239-248.
26. Katzmarzyk PT, Greenway FL, Heymsfield SB, BouchardC. Clinical utility and reproducibility of visceral adipose tissue measurements derived from dual energy X-ray absorptiometry in white and African American adults. Obesity (Silver Spring). 2013;21:2221-2224.
27. Bi X, Seabolt L, Shibao C, et al. 20t5. DXA-measured visceral adipose tissue predicts impaired glucose tolerance and metabolic syndrome in obese Caucasian and African American women. Eur J Clin Nutr. 2015;69:329-336.
28. Hemsfield SB, Gonzalez MC, Lu J, Jia G, Zheng J. Skeletal muscle mass and quality: evolution of modern measurement concepts in the context of sarcoma. Proc Nutr Soc. 2015;74:355-366.
29. Lee SY, Ghallagher D. Assessment methods in human body composition. Curr Opin Clin Nutr Metab Care. 2008;11:556-572.
30. Pietrobelli A, Formica C, Wang Z, Heymsfield SB. Duel- energy X-ray absorptiometry body composition model: review of physical concepts. Am J Physiol Endocrinol Metab. 1996;271:E941-E951.
31. Pietrobelli A, Wang C, Formica C, Heymsfield SB. Duel- energy X-ray absorptiometry fat estimation errors due to variation in soft tissue hydration. Am J Physiol Endocrinol Metab. 1998;274:E808-E816.
32. Kullberg J, Brandberg J, Angelhed JE, et al.Whole body adipose tissue analysis: Comparison of MRI, CT and dual energy X-ray absorptiometry. Br J Radiol. 2009;82:123-130.
33. Chen MY, Shanbhag SM, Arai AE. Submillisievert median radiation dose for coronary angiography with a second- generation 320-detector row CT scanner in 107 consecutive patients. Radiology. 2013;267:76-85.
34. Meyer MH, Haubenreisser H, Schoepf UJ, et al. Closing in on the K edge: Coronary CT angiography at 100, 80 and 70 kV - initial comparison of a second-versus a third-generation dual-source CT system. Radiology. 2014;273:373-382.

35. Brooks Y, Black DR, Coster DC, et al. Body mass index and percentage body fat as health indicators for young adults. Am J Heath Behav. 2007;31:687-700.
36. Nazare JA, Smith JD, Borel AL, et al. Ethnic influences on the relations between abdominal subcutaneous and visceral adiposity, liver fat, and cardiometabolic risk profile: the international study of prediction of intra-abdominal adiposity and its relationship with cardiometabolic risk/intra-abdominal adiposity. Am J Clin Nutr. 2012;96:714-726.
37. Hiuge-Shimizu A, Kishida K, Funahashi T, et al. Absolute value of visceral fat area measured on computed tomography scans and obesity-related cardiovascular risk factors in large-scale Japanese general population (the VACATION-J study). Ann Med. 2012;44:82-92.
38. Carroll JF, Franks SF, Smith AB, Phelps DR. Visceral adipose tissue loss and insulin resistance 6 months after laparoscopic gastric banding surgery: a preliminary study. Obes Surg. 2009;19:47-55.
39. de Souza RI, Bray GA, Carey Vi, et al. Effects of 4 weight- loss diets differing in fat, protein, and carbohydrate on fat mass, lean mass, visceral adipose tissue, and hepatic fat: results from the POUNDS LOST trial. Am J Clin Nutr. 2012;95:614-625.
40. Mellinger JL, Pencina KM, Massaro JM, et al. Hepatic steatosis and cardiovascular disease outcomes: an analysis of the Framingham Heart Study. J Hepatol. 2015; ii: S0168-8278(15):00167-1.
41. Dube MC, Lemieux S, Piche ME, et al. The contribution of visceral adiposity and mid-thigh fat-rich muscle to the metabolic profile in postmenopausal women. Obesity (Silver Spring). 2011;19:953-959.
42. Ryan AS, Harduarsingh-Permaul AS. Effects of weight loss and exercise on trunk muscle composition in older women. Clin Interv Aging. 2014;9:395-402.
43. Cousin S, Hollebecque A, Koscielny S, et al. Low skeletal muscle is associated with toxicity in patients included in phase I trials. Invest New Drugs. 2014;32(1):382-387.
44. Montano-Loza AJ, Meza-Junco J, Baracos VE, et al. Severe muscle depletion predicts postoperative length of stay but is not associated with survival after liver transplantation. Liver Transpl. 2014;20:640-448.
45. Kim TN, Park MS, Lim Ki, et al. Skeletal muscle mass to visceral fat area ratio is associated with metabolic syndrome and arterial stiffness: The Korean Sarcopenic Obesity Study (KSOS). Diabetes Res Clin Pract. 2011;93:285- 291.
46. Knibbe CA, Brill MJ, van Rongen A, et al. Drug disposition in obesity: Toward evidence-based dosing. Annu Rev Pharmacol Toxicol. 2015;55:149-167.
47. Kim SR, Lerman LO. Diagnostic imaging in the management of patients with metabolic syndrome. Transl Res. 2018;194:1-18.
DOI: https://doi.org/10.1016/j.trsl.2017.10.009.
48. Wagner DR. Ultrasound as a tool to assess body fat. J Obes. 2013;280713.
Available:https//doi.org/10.1155/2013/280713. PM ID: 24062944.

49. Pineau JC, L. Lalys L, Bocquet M, et al. Ultrasound measurement of total body fat in obese adolescents. Ann Nutr Metab. 2010;56:36-44.
50. Mazess RB, Barden HS, Bisek JP, Hanson J. Duel-energy X-ray absorptiometry for total-body and regional bone- mineral and soft-tissue composition. Am J Clin Nutr. 1990;51:1106-1112.
51. Kaul M, Rotheny P, Peters DM, et al. Duel-energy x-ray absorptiometry for quantification of visceral fat. Obesity. 2012;20:1313-1318.
52. Snijder MB, Dekker JM, Visser M, et al. Trunk fat and leg fat have independent and opposite associations with fasting and post load glucose levels. Diabetes Care. 2004;27(2):372-77.
53. Williams JE, Wells JC, Wilson CM, et al. Evaluation of lunar prodigy duel-energy X-ray absorptiometry for assessing body composition in healthy persons and patients by composition with the criterion 4-components model. Am J Clin Nutr. 2006;83:1047-1054.
54. Ponti F, Cingue Ade, Fazio N, Napoli A, Guglielmi G, Bazzocchi A. Ultrasound imaging, a stethoscope for body composition assessment. Quantitative Imaging Med Surg. 2020;10:1699-1722.
55. McCollough CH, Schueler BA, Atwell TD, et al. Radiation exposure and pregnancy: When should we be concerned? Radiographics. 2007;27:909-918.
56. Kendler DL, Borges JLC, Fielding RA, et al. The official positions of the international society for clinical densitometry: indications of use and reporting of DXA for body composition. J Clin Densitom. 2013;16: 496-507.

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Chapter 8
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Colorenal Fistula after Renal Tumour Cryotherapy: A Case Report

Andoni Alaba Sorabilla [a], Julia Pelayo Rodríguez [a], Oihan Loidi Lázaro-Carrasco [a], Rubén Gonzalo González [a*], Ruben Caiña Ruiz [a], Berta Martín Rivas [a] and José Manuel Gutiérrez Cabezas [a]

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ABSTRACT

Introduction: The incidence of renal cell carcinoma has been increasing in recent years. The primary techniques for the treatment of these tumours are cryoablation, radiofrequency ablation, percutaneous ethanol injection, and microwave ablation. Computed tomography (CT)-guided percutaneous cryoablation is increasingly utilized for renal cell carcinoma. Bowel injury is a known complication but is extremely rare. This study presents a rare case of colorenal fistula after cryoablation of a left renal tumour.
Presentation of Case: A 58-year-old man with no significant history was diagnosed with left renal carcinoma A left renal tumour was incidentally found on an abdominal CT examination performed for a slight increase in transaminases. Abdominal ultrasonography revealed a 31 × 32-mm solid, well-defined, cortical tumour at the lower pole of his left kidney. The patient was asymptomatic and had no distant metastasis. The decision was made to treat the tumour with percutaneous cryoablation, with a good response to the technique. Two months later, the patient had recurrent urinary tract infections and pneumaturia. In the absence of improvement with antibiotic treatment, CT was performed and revealed a fistula connecting the descending colon and renal parenchyma. The decision was made to perform surgery to repair the defect caused by percutaneous cryotherapy. The patient recovered from surgery and was discharged with no complications.
Discussion: To reduce the adverse effects of radical or partial nephrectomy and preserve renal function, percutaneous ablation techniques have been developed. Internal injury is a known complication and it is particularly common in cases of

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renal tumours located in the upper and anterior kidney. The diagnosis is based on symptoms and imaging. Most colorenal fistulas have been treated conservatively with good results.
Conclusion: Cryoablation of renal tumours is a safe, low-risk procedure, but recurrent urinary tract infections and pneumaturia may indicate a colorenal fistula, with conservative treatment preferred and surgery reserved for persistent cases. If possible, conservative medical treatment should be used,
reserving surgery for complicated or persistent colorenal fistulas.

Keywords: Colorenal fistula; cryoablation; renal tumour; urinary tract infection; pneumaturia; fistulectomy.

1. INTRODUCTION

In the past two decades, there has been an increase in the number of diagnosed renal cell carcinomas (RCC) due to incidental detection of small renal tumours resulting from increased use of computed tomography (CT) scanning. Though renal cell carcinoma (RCC) accounts for 2% of global cancer diagnoses and deaths, it has more than doubled in incidence in the developed world over the past half-century, and today is the ninth most common neoplasm in the United States [1,2]. This work has been reported in line with the SCARE criteria [3]. This study presents a rare case of colorenal fistula after cryoablation of a left renal tumour. The Surgical Case Report (SCARE) guidelines were introduced in 2016 as a standardised method for reporting surgical cases in the medical literature [4]. Percutaneous ablation techniques are now used to treat some solid visceral neoplasms [5]. These techniques include radiofrequency, cryoablation, and microwave ablation. A variety of different imaging modalities have been used for guidance for ablation, including ultrasound (both percutaneous and intraoperative), computed tomography (CT), CT fluoroscopy, magnetic resonance imaging (MRI), and, occasionally, plain films/fluoroscopy. The modality used for guidance is heavily influenced by both the location of the tumour and the local availability of equipment [6]. For small renal tumours, cryoablation offers promising results with a low complication rate [7,8]. Complications are a potential risk with any invasive procedure and although bowel injury is a known complication of the technique, it is extremely rare [9,10].

2. PRESENTATION OF CASE

A 58-year-old man with no significant history was diagnosed with left renal carcinoma. Although asymptomatic, he underwent abdominal ultrasonography due to a slight increase in transaminases, which revealed a 31 × 32-mm solid, well-defined, cortical tumour at the lower pole of his left kidney [6]. Thoracoabdominal computed tomography (CT) confirmed the presence of a 35-mm, well-defined, heterogeneous, anterior mesorenal mass with increased uptake and malignant appearance in the left kidney, but no extracapsular extension, fat infiltration, or perirenal adenopathy. The study was completed with urinary cytology, which proved negative for urothelial tumour cells. The decision was made to treat the tumour with percutaneous cryoablation (Fig. 1) [6]. During

the cryoablation technique, there was suspicion of a possible intestinal perforation seen on CT. Therefore, abdominal ultrasonography was performed, but no changes were identified. Two months later, he developed recurrent urinary tract infections, with pneumaturia and urine culture positive for *Escherichia coli*, which did not improve despite antibiotic therapy. An abdominal CT with intravenous contrast was performed, which revealed a segment of the descending colon in contact with the anterior face of the left kidney, with air bubbles in the renal parenchyma, left renal calyces, and bladder (Fig. 2) [6]. He was diagnosed with a colorenal fistula after cryoablation. The possibility of performing a CT urography was considered to complete the study, but the patient rejected the test. In view of the failure of medical treatment (antibiotics), surgery was performed with laparoscopy. The colorenal fistula was located in the descending colon, as revealed on CT (Fig. 3) [6]. The colon was released from the renal parenchyma with scissors and monopolar coagulation. Both the renal and colonic orifices were sutured with absorbable monofilament stitches and omental transposition was performed. Intestinal resection was not necessary because of the good condition of the colon and a double J stent was not placed. The patient was discharged with no complications. He remains asymptomatic and has negative urine cultures.

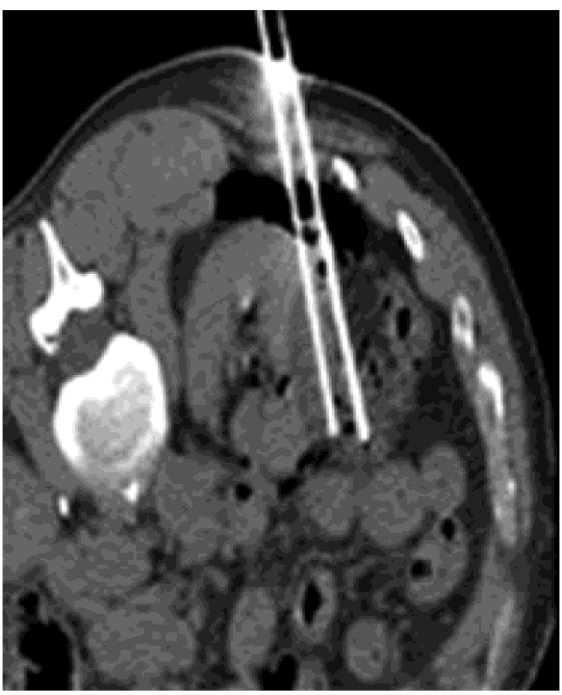

Fig. 1. Percutaneous cryoablation monitoring of the cortical tumour at the lower pole of the left kidney using computed tomography

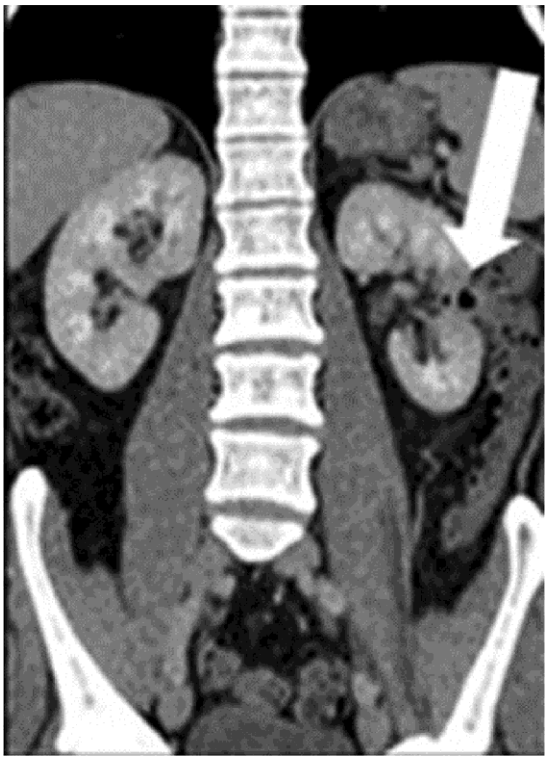

Fig. 2. Abdominal CT with intravenous contrast. Left colorenal fistula after renal tumour cryotherapy

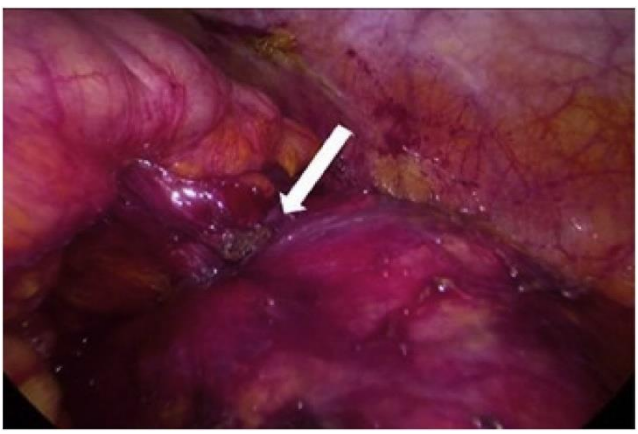

Fig. 3. Left colorenal fistula viewed on laparoscopy

3. DISCUSSION

The incidence of renal cell carcinoma has been increasing in recent years. The preferred treatment has been radical or partial nephrectomy. To reduce the adverse effects of the procedure and preserve renal function, percutaneous ablation techniques have been developed for the treatment of these tumours with excellent results [5,6]. The primary techniques are cryoablation, radiofrequency ablation, percutaneous ethanol injection, and microwave ablation. Improvement in technique has led to an increase in their use for small renal tumours. Cryoablation has shown that low temperatures can be applied for tissue destruction and can be used with an open, laparoscopic, or percutaneous approach. During cryoablation, a cryogenic probe is inserted in the target tissue, and liquid gas (argon) is used to cool it rapidly, forming an ice ball around the probe that thickens as the procedure progresses (cell death depends on the time and temperature) [11,6]. The low temperatures reached in the kidney can be transferred to adjacent organs such as the colon, duodenum, or ureter, which leads to serious complications. Due to the close proximity of the cryoablation site to the kidney, there is a risk of injuring nearby intestinal tissue, especially when the tumour is located in the upper or front part of the kidney.

Intestinal injury is a rare complication, accounting for only 0–1% of injuries at this level [12,13,14,6]. If not enough fat is present between the tumour and the intestine (minimum of 5 mm), different manoeuvres have been described to separate the kidney from the colon, including postural displacement, hydro dissection with 5% dextrose, injection of carbon dioxide, or balloon interposition [15].

Imaging methods are used to determine the extent to which freezing is appropriate. Better monitoring of the procedure is obtained with CT or MRI than with ultrasonography. CT allows for easy, fast, and accurate visualization of the ablation area by decreasing the attenuation of frozen tissue. MRI allows for manual displacement of the lesion without the operator being exposed to radiation. However, artifacts will appear in the image because of air, movement, and the metal cryoprobe [6]. Although the advantages of this technique are greater than those of CT, it is not available at our center [11].

The diagnosis of bowel lesions after cryoablation is based on symptoms and imaging. There may be an interval of days or weeks between cryoablation and the onset of symptoms. Urinary symptoms and pneumaturia were the characteristic symptoms that made us suspect the possibility of a colorenal fistula in our patient. Although the follow-up ultrasonography after the procedure showed no immediate complications, the symptoms, and abdominal CT proved diagnostic [6].

No data are available to identify optimal treatment. Different options include both conservative treatment (antibiotic therapy, percutaneous abscess drainage, and therapeutic colonoscopy) and surgical treatment (laparoscopy or laparotomy with or without nephrectomy and/or colectomy). Most colon lesions have been treated

conservatively with good results [10,16,6]. Emergency surgery should be considered when damage to the colon causes obstruction, perforation, or severe sepsis [10]. In our case, antibiotic treatment was tried, but owing to its failure, the decision was made to perform surgery. Given the good condition of the patient, fistulectomy and epiploic repair were performed, reserving the most aggressive techniques for use in the event of failure or complication. The patient progressed without complications and was discharged. He is currently asymptomatic.

4. CONCLUSION

Cryoablation of renal tumours is a safe, low-risk technique with few complications. We should suspect a colorenal fistula in the presence of repeated urinary tract infections and pneumaturia in patients undergoing renal cryoablation [6]. The treatment is controversial. If possible, conservative medical treatment should be used, reserving surgery for complicated or persistent colorenal fistulas.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. Author AAS and JPR acquired the data and wrote the article. Authors OLLC, RGG, RCR, BMR and JMG coordinated and critically revised the study. All authors read and approved the final manuscript.

ETHICS APPROVAL

The study is exempt from ethics approval by our institution, as the case was managed as per standard guidelines and no modification or experimental intervention was employed.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Pedersen M, Andersen MB, Christiansen H, Azawi NH. Classification of renal tumour using convolutional neural networks to detect oncocytoma. European Journal of Radiology. 2020 Dec 1;133:109343.
2. Padala SA, Barsouk A, Thandra KC, Saginala K, Mohammed A, Vakiti A, Rawla P, Barsouk A. Epidemiology of renal cell carcinoma. World journal of oncology. 2020 Jun;11(3):79.
3. Agha RA, Fowler AJ, Saetta A, Barai I, Rajmohan S, Orgill DP. For the SCARE Group, The SCARE statement: Consensus-based surgical case report guidelines, Int. J. Surg. 2016;34:180–186.
4. Sohrabi C, Mathew G, Maria N, Kerwan A, Franchi T, Agha RA. The SCARE 2023 guideline: Updating consensus Surgical CAse REport (SCARE) guidelines. International Journal of Surgery. 2023 May 1;109(5):1136-40.
5. Cornelis F, Balageas P, Le Bras Y, Rigou G, Boutault JR, Bouzgarrou M, et al. Radiologically-guided thermal ablation of renal tumors, Diagn. Interv. Imaging. 2012;93:246–261.
6. Mozo M, Gonzálo R, Gutiérrez JM, Gutiérrez LE, Cotruta L, Roca A, García R. Colorenal fistula after renal tumour cryotherapy. International Journal of Surgery Case Reports. 2018 Jan 1;53:441-3.
7. Georgiades CS, Rodriguez R. Efficacy and safety of percutaneous cryoblation for stage 1A/B renal cell carcinoma: Results of a prospective, single-arm, 5 year study, Cardiovasc. Intervent. Radiol. 2014;37:1494–1499.
8. Blue ML, Okhunov Z, Moreira DM, George AK, Sunday S, Lobko II, et al. Image-guided percutaneous renal cryoablation: Preoperative risk factors for recurrence and complications, BJU Int. 2013;11:E181–E185.
9. Shimizu K, Mogami T, Michimoto K, Kameoka Y, Tokashiki T, Kurata N, et al. Digestive tract complications of renal cryoablation, Cardiovasc. Intervent. Radiol. 2016;39:122–126.
10. Morgan AI, Doble A, Davies RJ. Successful conservative management of a colorenal fistula complicating percutaneous cryoablation of renal tumors: a case report, J. Med. Case Rep. 2012;6:365.
11. Quiroz CO, De la torre CK. Crioterapia en tumores renales, Acta Médica Grupo Angeles. 2013;14:S62–S67.
12. Kim KR, Thomas S. Complications of image-guided thermal ablation of liver and kidney neoplasms, Semin. Intervent. Radiol. 2014;31(2):138–148.
13. Parakh A, Kortman P, NB, Teisch L. Colorectal cancer presenting as acute abdomen in the emergency department: A case report, Radiology Case Reports. 2020;15:689–692.
14. Stacul F, Sachs C, Giudici F, et al. Cryoablation of renal tumors: Long-term follow-up from a multicenter experience. Abdom Radiol. 2021;46: 4476–4488.

15. Gervais DA, Arellano RS, McGovern FJ, McDougal WS, Mueller PR. Radiofrequency ablation of renal cell carcinoma: Part 2, lessons learned with ablation of 100 tumors, AJR Am. J. Roentgenol. 2005;185:72–80.
16. Vanderbink BA, Rastinehad A, Caplin D, Ost MC, Lobko I, Lee BR, Successful conservative management of colorenal fistula after percutaneous cryoablation of renal-cell carcinoma, J. Endourol. 2007;21: 726–729.

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I am a General Surgery resident at Sierrallana Hospital. I completed my medical studies at Universidad Francisco de Vitoria.

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I studied Medicine at the Complutense University of Madrid for 6 years. During my studies, I completed clinical rotations at the Hospital General Universitario Gregorio Marañón, including a 2-year internship in the Hepatopancreatobiliary Department, where I was part of a research team focused on hepatocellular carcinoma. We developed a predictive model for hepatic decompensation in patients with hepatocellular carcinoma undergoing surgical resection, which became the subject of my final thesis.

Since May 2023, I have been working at Hospital Sierrallana as a resident in the General Surgery and Digestive System Department and I am currently collaborating on the compilation of a colorectal surgery database.

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Research and academic experience: I completed my studies at the University of Oviedo (Spain), graduating in 2019. In 2020, I began my residency in General Surgery and Digestive System Surgery at Sierrallana Hospital. Throughout my training, I made valuable contributions to the academic field, participating as an author of several posters and oral presentations at national Surgery congresses, as well as at prominent international events, such as the annual NATA symposium. Additionally, I have published an article in the International Journal of Clinical Studies & Medical Case Reports. Currently, in my 5th year of residency, I am focused on mastering the fundamentals of my speciality while continuing to collaborate on clinical research projects. My aim is to acquire a solid technical and theoretical foundation with the goal of contributing to the advancement of my field. I balance my practical training

with a strong interest in research, seeking new ways to improve surgical outcomes and optimize patient treatments.

Research specialization: My areas of specialization mainly include general surgery and the digestive system.

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I completed my studies at the University of Salamanca (Spain), graduating in 2007 (2001-2007). I specialized in General and Digestive Surgery at the Hospital Universitario Central de Asturias. During the 5 years of residency (2008-2013), I acquired comprehensive training with a special emphasis on minimally invasive surgery. After completing my training, I worked at various hospitals, before moving to Sierrallana Hospital (2016), where I have established my reputation as an expert in minimally invasive surgery. Currently, I practice at the JM Gutierrez Cabezas Clinic, where I continue to focus on abdominal surgery and obesity treatment through bariatric surgery. I am a member of the Spanish Association of Surgeons (AEC) and the Spanish Society of Obesity Surgery and Metabolic Diseases (SECO), actively contributing to research and the development of new surgical techniques, particularly in digestive surgery.

Research and Academic Experience: I completed a PhD from the University of Cantabria. I have a Doctorate in Health Sciences with the distinction of CUM LAUDE. “Analysis of the factors predicting remission of type 2 diabetes mellitus in morbidly obese patients after Roux-en-Y gastric bypass." 2016.

I also completed an international visiting scholar research fellowship program in trauma surgery, surgical critical care, and acute care surgery from the Jackson Memorial Hospital, “Ryder Trauma Center, Miami, USA. Tutor: Juan A. Asensio, M.D., F.A.C.S., F.C.C.M. (2011) and presented "IV Master's Degree in Coloproctology: colorectal and pelvic floor surgery, organized by the University of Zaragoza, Spain (2014).

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After completing my medical studies at the Francisco de Vitoria University (2011-2017), I specialized in General and Digestive Surgery at the Marqués de Valdecilla University Hospital. I chose this center for its outstanding development in all branches of the specialty, including colorectal surgery,

esophagogastric surgery, hepatobiliopancreatic surgery, endocrine surgery (bariatric, adrenal, thyroid, and parathyroid), general surgery, and liver and pancreatic transplantation. During the 5 years of residency (2018-2023), I acquired comprehensive training with a special emphasis on minimally invasive and robotic surgery. This focus was strengthened by the laparoscopic and robotic skills training program at the Valdecilla Virtual Hospital.

In 2022, I obtained a scholarship from the Spanish Association of Surgeons to undertake a training stay at the Liver Institute of King's College London, delving into liver transplantation at a center that manages the largest transplant program in Europe and is a pioneer in pancreatic islet cell transplantation.

I completed my training by attending various theoretical and practical courses, as well as a Master's degree in Abdominal Wall Surgery.

Within my research career, notable international publications include the analysis of the safety of laparoscopic cholecystectomy beyond the seventh day, published in Updates in Surgery; the development of the Chole-Risk Score to predict postoperative complications, in the Journal of Gastrointestinal Surgery; the impact of bridging therapy on the survival of patients with hepatocellular carcinoma after liver transplantation, in Transplantation Proceedings; and two articles in Colorectal Disease on surgery in Crohn's disease and colon cancer.

After completing my training, I have served as a Specialist Physician at Sierrallana Hospital, where I am currently part of the supramesocolic surgery unit, performing procedures in hepatobiliopancreatic surgery, esophagogastric surgery, bariatric surgery, and peritoneal carcinomatosis. I am also a member of the Spanish Association of Surgeons and the Spanish Society of Obesity Surgery.

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I am the Head of the Department of General and Digestive Surgery at Sierrallana Hospital. I completed my residency at the Marqués de Valdecilla University Hospital, where I trained in general and digestive surgery, as well as in advanced laparoscopic techniques. After completing my training, I worked at various hospitals, including the Pontevedra Hospital, before moving to Sierrallana Hospital, where I established my reputation as an expert in minimally invasive surgery.

Currently, I also practice at the JM Gutierrez Cabezas Clinic, where I continue to focus on abdominal surgery and obesity treatment through bariatric surgery. I am a member of the Spanish Association of Surgeons (AEC) and the Spanish Society of Obesity Surgery and Metabolic Diseases (SECO), actively contributing to research and the development of new surgical techniques, particularly in digestive surgery.

I have been involved in numerous medical projects, both nationally and internationally, focusing on optimizing surgical procedures and implementing advanced technologies in bariatric surgery and hernia treatment. My dedication to continuous learning and my pursuit of innovation positioned me as a leader in my field. Among my most notable works is the analysis of postoperative complications, particularly those associated with gastric bypass and other restrictive techniques. My research focuses on identifying and managing complications such as stomal stenosis, anastomotic ulcers, and metabolic disorders resulting from these interventions. My work has contributed to optimizing clinical and surgical approaches to improve long-term patient safety.

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Chapter 9
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Complications of Total Colectomy with Ileorectal Anastomosis: Case Study of Terminal Ileum Perforation

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ABSTRACT

Total colectomy followed by ileorectal anastomosis is an established operation that may be employed as a surgical solution for a variety of colonic diseases. Postoperative morbidity and mortality rates are generally considered low, with most patients rating the functional outcomes as good to excellent. The ileorectal anastomosis is usually latero-terminal and is constructed with staples. If the segment of the terminal ileum extending beyond the anastomosis site is too long, it may remain as an appendage, which can fold or twist upon itself, causing intermittent closed-loop obstruction at its tip. This can lead to localized perforation, sepsis, and eventually the formation of a fistula. In conclusion, total colectomy with ileorectal anastomosis is a safe procedure with good functional outcomes, though there is a high risk of postoperative intestinal obstruction, and distal ileum perforation is a rare but possible complication. A case is reported of a patient who developed significant complications from this portion of the bowel.

Keywords: Total colectomy; ileorectal anastomosis; intestinal perforation; mechanical suture.

1. INTRODUCTION

Total colectomy (TC) with ileorectal (IRA) is frequently performed for colorectal cancer, familial adenomatous polyposis, unidentified bleeding from the lower GI

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tract, inflammatory bowel disease, and sometimes for extended diverticulosis or colonic inertia [1]. Total colectomy (TC) with ileorectal anastomosis (IRA) is a relatively common procedure today. Its indications are clearly established, the functional outcomes allow a nearly normal quality of life, and postoperative morbidity and mortality rates are low [2-6]. Since its first use in 1908, total colectomy with ileorectal anastomosis (TC-IRA) has become the most widely adopted procedure for the treatment of Colonics low-transit constipation [7]. TC can be performed via laparotomy or laparoscopy, and IRA can be either manual or mechanical, in an end-to-end or side-to-end configuration. When performing a side-to-end mechanical IRA, the circular stapler head is first introduced through the end of the ileum, leaving 5 cm of terminal ileum distal to the anastomosis, and the circular stapler is inserted through the anus. The stapler is then assembled, and the anastomosis is completed. If this remaining section of the distal ileum is too long, it may function like an appendix or blind loop. We describe a case where a patient developed a serious complication arising from this portion of the distal ileum.

2. CASE REPORT

This 64-year-old male patient had no significant prior medical history. His previous surgeries included a laparoscopic total colectomy (TC) with mechanical side-to-end ileorectal anastomosis (IRA) performed 10 years earlier to treat synchronous colonic adenocarcinoma located in the sigmoid and transverse colon (T3N0M0). Currently, he is undergoing periodic follow-up visits and annual rectal endoscopy conducted by the Digestive Department, with no significant findings [8].

He presented to the emergency department with abdominal pain in the left hemiabdomen. The pain had been present for the past 15 days and had sharply increased in the last 12 hours. He also reported nausea without vomiting. His last bowel movement, 24 hours prior, was normal. He had a fever of 38°C, was conscious, oriented, and well hydrated, with normal skin color [8].

Cardiopulmonary auscultation was unremarkable. The abdomen was distended and tympanic. Palpation of the left hemiabdomen elicited pain, but there was no guarding. No palpable masses or hernias were detected. A hemogram revealed leukocytosis (14,000 leukocytes with 75% neutrophils) and elevated C-reactive protein (10.70 mg/dL). Renal function, pancreatic enzymes, and hepatic profile were normal. A simple chest X-ray demonstrated significant pneumoperitoneum (Fig. 1) [8]. An urgent abdominal CT scan showed the presence of a large pneumoperitoneum and a thickened, inflammatory small bowel loop on the left side with significant stranding of peripheral fat and a minimal amount of adjacent fluid (corresponding to the terminal ileum segment distal to the IRA). The possibility that this process was the source of the pneumoperitoneum could not be ruled out [8].

At the pelvic level, the IRA appeared without complications (Figs. 2-4) [8]. A decision was made to perform a median laparotomy, which revealed purulent

peritonitis secondary to a perforation on the border of the terminal ileum distal to the IRA. This approximately 15 cm-long segment of the small bowel (acting as an appendix or blind loop) was hypertrophic, thickened, and dilated. No additional pathological findings were observed at the IRA or in the rest of the abdominal cavity [8].

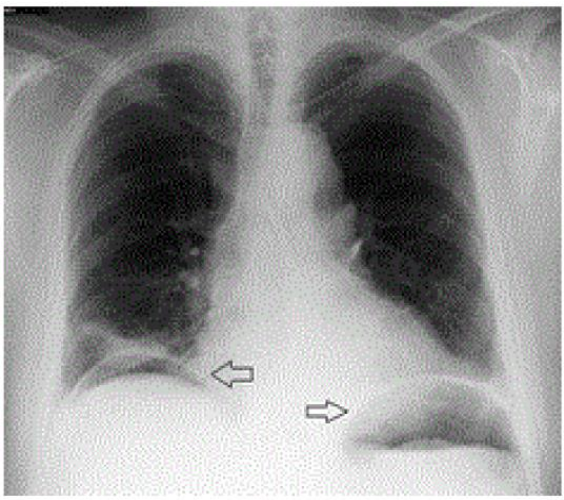

Fig. 1. Thoracic X-ray: Arrows point at the pneumoperitoneum

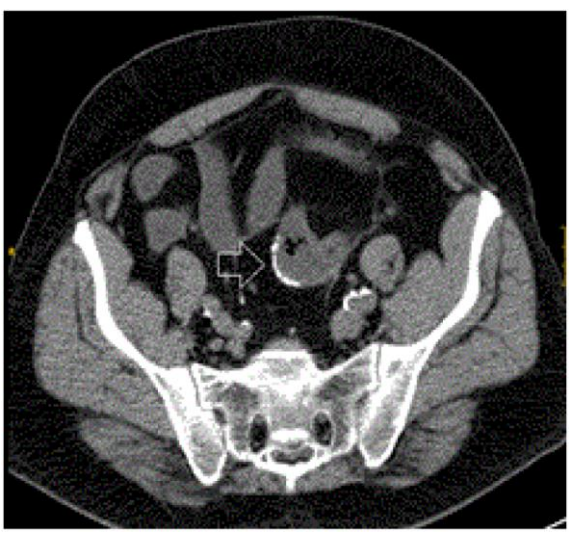

Fig. 2. The arrow points at the IRA. No complications seen

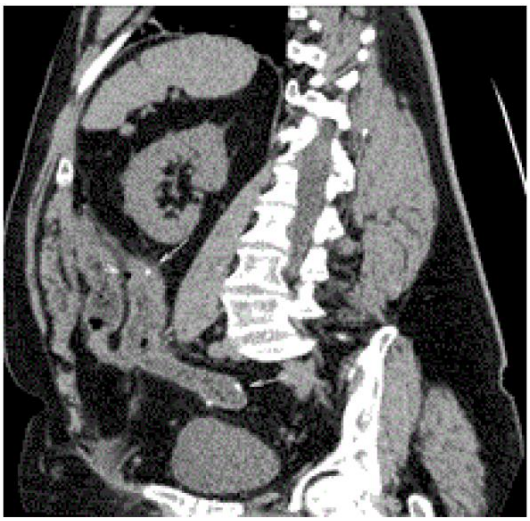

Fig. 3. The lower arrow points at the IRA stapling area. The upper arrow points at the end of the terminal ileum distal to the IRA with an adjacent pneumoperitoneum bubble

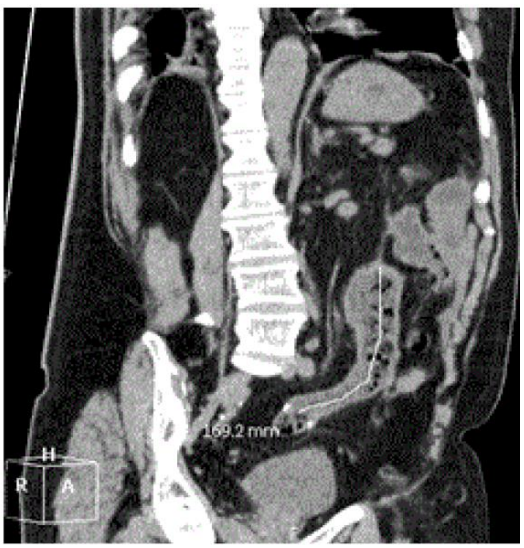

Fig. 4. End of the terminal ileum distal to the IRA (~16 cm long)

Resection was performed using a gastrointestinal anastomosis (GIA) stapler, followed by intussusception of the stapling line, irrigation of the abdominal cavity,

and placement of a drain. Due to persistent hematic drainage, the patient underwent reoperation three days after the initial surgery. A small laceration was identified at the lower pole of the spleen, requiring a splenectomy. Subsequently, percutaneous drainage was performed in both the splenic fossa and the left pleural space due to fluid collection and pleural bleeding, respectively. The patient was discharged 4 weeks after admission and is currently asymptomatic.

3. DISCUSSION

Total colectomy (TC) with ileorectal anastomosis (IRA) is a relatively common procedure in both elective and emergency surgeries today. Indications include colon cancer (familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, synchronous tumors), inflammatory bowel diseases (Crohn's disease and ulcerative colitis), functional disorders (megacolon/megarectum, colonic inertia), and less common conditions such as diverticular disease and ischemic/infectious colitis [5]. Before performing the procedure, it is essential to confirm that the patient has normal sphincter tone without perianal disease and adequate rectal distensibility, with no evidence of dysplasia or cancer. Additionally, the procedure can be performed temporarily in young patients who wish to preserve fertility [6].

Physiological adaptation to TC is generally very satisfactory, with functional outcomes supporting an almost normal quality of life. Indeed, 90% of patients achieve normal continence and have an average of four bowel movements daily [9-11]. Morbidity and mortality rates are approximately 26% and 1% (ranging from 0-6%), respectively, with higher rates in patients with Crohn's disease and functional disorders [5]. The surgical re-intervention rate is about 7.5% [5,10]. The most common postoperative complication reported in the literature is intestinal obstruction, with rates ranging from 2% to 70%, associated with adhesions, abnormal motility in patients with functional disorders, and recurrence of Crohn's disease. However, laparoscopy has reduced the incidence of obstruction to about 20%. Other significant complications include anastomotic dehiscence (6.5%), surgical wound infection (8.8%), rectovaginal fistula (5.5%), and anastomotic stenosis [5]. In our case, the patient presented with an intestinal perforation at the terminal ileum distal to the IRA, an extremely rare complication [8].

The most commonly performed anastomosis is a side-to-end mechanical IRA. This is achieved by introducing the head of the circular stapler through the end of the ileum and perforating the anti-mesenteric border, leaving 5 cm of ileum distal to the anastomosis. The circular stapler is then introduced through the anus and assembled with its head to perform the anastomosis at the level of the promontory. This technique helps bring a better-irrigated ileal border to the rectum, whichis advantageous.

The end of the ileum is then closed using a mechanical stapler or manual suture. We have found no evidence defining the optimal length or ideal type of closure for the distal ileum in side-to-end IRA [12]. Perforation of this portion of the

terminal ileum is rare, and in the immediate postoperative period, it usually results from an ischemic issue. During surgery, the vascularisation of the distal segment may be compromised, either by tissue manipulation or by insufficient irrigation due to the distance between the ileal border and the point of anastomosis. This can lead to mucosal necrosis and subsequent perforation of the affected segment.

However, if this segment is left too long, we believe that over time, as seen in our case, it can act as an appendix or blind loop, leading to bacterial overgrowth, which may predispose the segment to torsion and/or perforation (Fig. 5) [8]. In addition, a segment of the ileum that is too long can become mobile within the abdominal cavity, facilitating its torsion around its mesentery. Twisting of the ileum compromises blood flow, leading to acute ischaemia and subsequent perforation [13,14]. Perforation may also occur due to accumulation of digestive secretions in the distal terminal ileum. The terminal ileum is essential for the reabsorption of bile salts. If an ileal segment becomes redundant, these digestive secretions may accumulate, irritating the local mucosa and predisposing to chronic inflammation, and even ulceration or perforation.

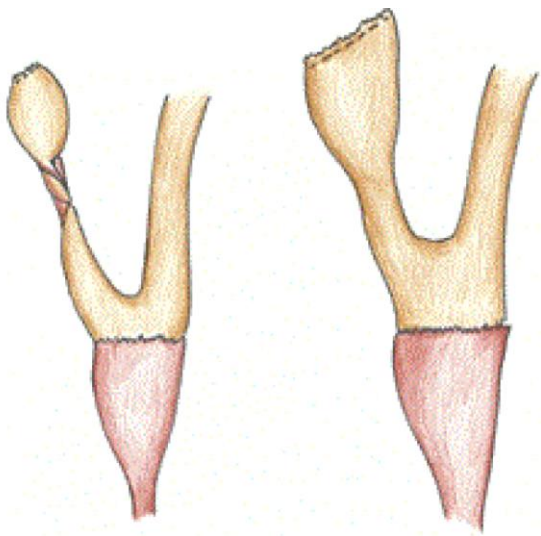

Fig. 5. Terminal ileum distal to the IRA. If it is too long, it acts as an appendix or blind loop which can fold or spin around and therefore become perforated

These complications can be easily avoided by resecting the terminal ileum as close to the anastomosis as possible during the procedure.

In patients undergoing total colectomy (TC) with ileorectal anastomosis (IRA) who present to the emergency department with an acute abdomen, intestinal

obstruction should be considered as a possible cause. It is also important to recognize that the terminal ileum distal to the IRA may be the source of the issue if it was left excessively long. In the literature, we found only two cases similar to the one described, where leaving an overly long terminal ileum resulted in complications during a restorative proctocolectomy with an ileoanal J-pouch [15,16].

4. CONCLUSION

TC with IRA is a safe procedure, offering excellent functional outcomes in selected patients, with low morbidity and mortality rates [8]. While there is a high incidence of intestinal obstruction post-surgery, a significant number of patients may require surgical re-intervention. Intestinal perforation of the terminal ileum distal to the anastomosis is a rare complication. If this segment is too long, it can act as an appendix or blind loop, which may fold or twist, leading to intermittent obstruction at its tip and potentially causing perforation.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been usedduring the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Shen MY, Leow YC, Chen WT. Laparoscopic left hemicolectomy. In Mastering Endo-Laparoscopic and Thoracoscopic Surgery: ELSA Manual. Singapore: Springer Nature Singapore. 2022 Nov 17;505-513.
2. Aylett SO. Three hundred cases of diffuse ulcerative colitis treated by total colectomy and ileo-rectal anastomosis. Br Med J. 1966;1:1001-1005.
3. Iacconi P, Aldi R, Bucceri R, Bendinelli C, Barsotti F, et al. [Total colectomy with ileorectal anastomosis (IRA): our experience in 57 patients]. G Chir. 1996;17:231-234.
4. Eu KW, Lim SL, Seow-Choen F, Leong AF, Ho YH. Clinical outcome and bowel function following total abdominal colectomy and ileorectal anastomosis in the Oriental population. Dis Colon Rectum. 1998;41:215-218.
5. da Luz Moreira A, Kiran RP, Lavery I. Clinical outcomes of ileorectal anastomosis for ulcerative colitis. Br J Surg. 2010;97:65-69.
6. Elton C, Makin G, Hitos K, Cohen CR. Mortality, morbidity and functional outcome after ileorectal anastomosis. Br J Surg. 2003;90:59-65.
7. Xie XY, Sun KL, Chen WH, Zhou Y, Chen BX, Ding Z, Yu XQ, Wu YH, Qian Q, Jiang CQ, Liu WC. Surgical outcomes of subtotal colectomy with antiperistaltic caecorectal anastomosis vs total colectomy with ileorectal

anastomosis for intractable slow-transit constipation. Gastroenterology report. 2019 Dec;7(6):449-54.
8. González RG, Diez SR, de Andrés Fuertes MA, Conty SJ, Tapia AD. Total Colectomy with an Ileorectal Anastomosis: Perforation of Distal Portion of the Terminal Ileum. J Gastrointest Dig Syst. 2015;5(323):2.
9. Pastore RL, Wolff BG, Hodge D. Total abdominal colectomy and ileorectal anastomosis for inflammatory bowel disease. Dis Colon Rectum. 1997;40:1455-1464.
10. Soravia C, Klein L, Berk T, O'Connor BI, Cohen Z, et al. Comparison of ileal pouch-anal anastomosis and ileorectal anastomosis in patients with familial adenomatous polyposis. Dis Colon Rectum. 1999;42:1028-1034.
11. Günther K, Braunrieder G, Bittorf BR, Hohenberger W, Matzel KE. Patients with familial adenomatous polyposis experience better bowel function and quality of life after ileorectal anastomosis than after ileoanal pouch. Colorectal Dis. 2003;5:38-44.
12. Scoglio D, Ahmed Ali U, Fichera A. Surgical treatment of ulcerative colitis: Ileorectal vs ileal pouch-anal anastomosis. World J Gastroenterol. 2014;20:13211-13218.
13. Shen MMY, Chen WT-L. Laparoscopic total colectomy. In Lomanto D, Chen WT-L, Fuentes MB. Mastering Endo-Laparoscopic and Thoracoscopic Surgery. 2022;1:537–44.
14. Cologne KG, Asgeirsson T, Kaiser AM. (Sub-)total colectomy with ileostomy or ileo-rectal anastomosis (open, laparoscopic). In: Chassin's Operative Strategy in General Surgery. 2022;5:497–504.
15. Bannura BG, Barrera EA, Contreras PJ, Melo LC, Soto CD, et al. Colectomía total e ileorrectoanastomosis mecánica: Análisis de 45 pacientes consecutivos. Rev Chil Cir. 2005;57:213-219.
16. Pezim ME, Taylor BA, Davis CJ, Beart RW Jr. Perforation of terminal ileal appendage of J-pelvic ileal reservoir. Dis Colon Rectum. 1987;30:161-163.

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In 2022, I obtained a scholarship from the Spanish Association of Surgeons to undertake a training stay at the Liver Institute of King's College London, delving into liver transplantation at a center that manages the largest transplant program in Europe and is a pioneer in pancreatic islet cell transplantation.

I completed my training by attending various theoretical and practical courses, as well as a Master's degree in Abdominal Wall Surgery.

Within my research career, notable international publications include the analysis of the safety of laparoscopic cholecystectomy beyond the seventh day, published in Updates in Surgery; the development of the Chole-Risk Score to predict postoperative complications, in the Journal of Gastrointestinal Surgery; the impact of bridging therapy on the survival of patients with hepatocellular carcinoma after liver transplantation, in Transplantation Proceedings; and two articles in Colorectal Disease on surgery in Crohn's disease and colon cancer.

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DISCLAIMER
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Chapter 10
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Open Inguinal Hernia Repair in Adults: An Update

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ABSTRACT

In this study, we look at the various types of open inguinal hernia repair that include tension-free and suture-based repairs. We also look at chronic pain after open inguinal hernia repairs. The open inguinal hernia repairs can be divided into tissue repair and mesh repair. Among the tissue repairs, the Shouldice repair is the most common repair that is performed, with the Bassini repair and Darning method being rarely performed. Mesh-based repairs are the most popular open inguinal hernia repair with the Lichtenstein repair the most common procedure that is performed. Several technical modifications have been done for the Lichtenstein repair which include using a larger mesh size, using interrupted sutures to anchor the mesh to the aponeurosis of the internal oblique muscle and greater overlap of the mesh over the pubic symphysis. The sutured-based repairs are not commonly performed with the Shouldice repair being the most performed, but the Desarda repair is slowly emerging as a viable sutured-based repair. We have conducted this review article to look at the current state of the various types of repairs for open inguinal hernia repair including their complications and recurrence rate. We also looked at the effect of chronic pain in open inguinal hernia repair. Open inguinal hernia repairs will continue to be one of the most common operations that are performed worldwide, and it will retain its place in the surgical treatment of inguinal hernias despite the introduction of laparoscopic inguinal hernia repair.

Keywords: *Mesh repair; open hernia repair; tension-free repair; sutured hernia repair; chronic pain.*

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1. INTRODUCTION

Inguinal hernia repair is probably the most common procedure in general surgery. It is also one of the earliest operations in a junior surgical resident's postgraduate training period. Numerous repair techniques have been described to date, however tension-free mesh repairs are widely used methods today because of their low recurrence rates [1]. Open inguinal hernia repairs are still the most common hernia repair that is performed worldwide despite the introduction of laparoscopic repair. The initial open inguinal hernia repairs were done under tension with sutures to strengthen the posterior wall of the inguinal canal. The introduction of the Lichtenstein repair which uses synthetic mesh, was sutured to the posterior wall of the inguinal canal under no tension. This method has revolutionized the management of inguinal hernias, and it has become the most performed procedure in the world [2,3,4,5]. The risk factors for an inguinal hernia include a family history of groin hernia, chronic obstructive pulmonary disease, smoking, low body-mass index, increased intraabdominal pressure, collagen diseases, patent processus vaginalis, history of appendectomy, and peritoneal dialysis [6].

The open inguinal hernia repairs can be divided into tissue repair and mesh repair. Among the tissue repairs, the Shouldice repair is the most common repair that is performed, with the Bassini repair and Darning method rarely performed [5]. For the mesh repair, the Lichtenstein repair is the most common procedure that is performed, with the plug and patch method by Rudkow and Robbins and the Prolene hernia system being the other variants of the mesh repair [7]. The surgical treatment of open inguinal hernia can also be divided into mesh and non-mesh-based repair with the addition of the Desarda repair being the latest tension-free tissue-based repair [8,9,5].

The advantages of performing open inguinal hernia repairs are that they can be performed under local or regional anesthesia, the learning curve for these procedures is short they are associated with very low complications. All open inguinal hernia procedures are also cost-effective and can be performed as a daycare procedure, and they do not require any additional and costly operative material [10,5].

The European Hernia Society guidelines on the treatment of inguinal hernia in adults have recommended the Lichtenstein repair as the best open inguinal hernia surgery as it has a short learning curve, and it has a low recurrence rate of less than 2 %. For patients who opt out of performing a mesh repair, the Shouldice repair is the best non-mesh open inguinal hernia operation that can be performed [11-13,5].

The Hernia Surge guidelines for the management of groin hernias have recommended that mesh and non-mesh-based repairs are the best and most effective surgical approaches [5]. The mesh-based approaches are associated with the least risk of recurrence. Shouldice repair is considered the best non-mesh-based inguinal hernia repair for patients who do not want a mesh or where a mesh is contraindicated. Shouldice repair is associated with the lowest recurrence among the non-mesh-based or tissue repairs. The Desarda technique though is associated with a shorter learning curve but is not recommended due to its limited data on recurrence and chronic pain [14,5].

In this chapter, we will look at the various types of open inguinal hernia repair including tension-free and suture-based repairs. We also look at chronic pain after open inguinal hernia repairs.

2. MESH-BASED OPEN INGUINAL HERNIA REPAIRS

2.1 Lichtenstein Repair

This is the most popular open mesh-based repair that was introduced by Irving Lichtenstein in 1984 and is also known as the tension-free inguinal hernia repair. This procedure was originally performed under local anesthesia and after ligation of the hernia sac and identification of the ilioinguinal and iliohypogastric nerves, the posterior wall of the inguinal canal is reinforced with a synthetic mesh [5]. The mesh is anchored with non-absorbable sutures to the inguinal ligament and conjoint tendon. This procedure is not done under tension, and it is associated with reduced morbidity and recurrence [15,5]. The Lichtenstein repair has been retrospectively reviewed and the risk of surgical site infection was low, the incidence of seroma formation and scrotal hematoma were low. The recurrence rate was around 1% for this type of inguinal hernia repair [16]. The learning curve for performing this operation among surgical residents and junior surgeons is relatively short and 40 cases are usually sufficient before performing it independently [17,5].

Several technical modifications have been done for the Lichtenstein repair which include using a larger mesh size, using interrupted sutures to anchor the mesh to the aponeurosis of the internal oblique muscle and greater overlap of the mesh over the pubic symphysis. Further recommendations include identification and preservation of the ilioinguinal and iliohypogastric nerve, protecting the cremasteric fascia, management of the hernia sac, proper fixation of the mesh to the rectus abdominus sheath, and using a mesh size of 7.5 cm by 15 cm [18-20,5].

The identification of the ilioinguinal and iliohypogastric nerve during the hernia repair is important to reduce the risk of injury during dissection and fixation of the mesh. A systemic review and meta-analysis by Moseholm et al on nerve identification during inguinal hernia repair concluded that the rate of identification of the ilioinguinal nerve was 82% and the iliohypogastric nerve was 62% [21,22,5].

The mesh repair was compared against the non-mesh repair of inguinal hernias by Smith et al, and they concluded that mesh repair was associated with a reduced

recurrence rate and the risk factors for recurrence include obesity, history of smoking, and direct hernias [23]. Bisgaard et al and Butters et al followed up on patients who underwent the Lichtenstein repair for 5 years and concluded that the recurrence rate was 0 when compared to those who underwent sutured hernia repair [24,25,5].

The Lichtenstein repair was compared to the Shouldice repair in a randomized trial by Danielsson et al, and the recurrence rate was significantly higher in the Shouldice group, and the number of sick leave taken was also higher in this group [26]. A similar randomized control trial comparing the Lichtenstein repair and the Shouldice repair by Ahmadinejad et al. also concluded that the recurrence rate was lower in the Lichtenstein repair group [27,5].

The method of fixation of the mesh has been evaluated with sutured fixation being compared with glue fixation. There have been several systemic reviews and meta-analyses that have been conducted, with the use of fibrin or butyl-2-cyabiacrylate being used as the glue to fix the mesh. These studies concluded that glue fixation is associated with reduced operative time and comparable post-operative pain, chronic pain and length of hospital stay [5]. However, the duration of follow-up in all of the studies was not consistent, hence further randomized trials will be needed to evaluate the true recurrence rate and efficacy of glue fixation [28-32]. A systemic review and meta-analysis comparing the use of self-gripping mesh against sutured mesh fixation was conducted by Sajid et al., and this study concluded that self-gripping mesh failed to demonstrate any advantage over sutured mesh fixation with the incidence of postoperative pain, chronic pain and recurrence rates being the same [33,5]. Table 1 shows the comparison of the recurrence rates of the Lichtenstein repair, Shouldice repair and Desarda repair.

2.2 The Plug and Patch and the Prolene Hernia System

The plug and patch repair involves the use of a mesh that is inserted in the pre-peritoneal space and anchored to the tissues at the internal ring with sutures, followed by a flat mesh that is then inserted and anchored to the inguinal ligament and conjoint tendon [5]. The operative time and post-operative complications were reduced, and it was introduced as an alternative to the Lichtenstein repair [34-36]. The Plug and Patch repair was compared to the Lichtenstein repair and the duration of operation, post-operative complications and recurrence rate were comparable [37]. A randomized control trial comparing the Plug and Patch repair with the Lichtenstein repair concluded that though the operative time was reduced in the Plug and Patch repair, there was no difference with regard to the post-operative complication, chronic pain and recurrence rate [38,5].

Table 1. Table comparing the recurrence rate of the Lichtenstein repair, Desarda repair and Shouldice repair for inguinal hernias

Study	Study Type	Year	N=numbers	Lichtenstein repair recurrence rate (%)	Desarda repair recurrence rate (%)	Shouldice repair recurrence rate (%)
Emile et al.	Systemic Review/Meta-analysis	2017	2159	0.98%	0.91%	
Jain et al.	Randomized control trial	2021	87	0	0	
Mohamedahmed et al.	Meta-analysis	2022	3177	0.9%	0.65%	
Butters et al.	Randomized study	2006	150	1.3%		10.12%
Danielsson et al.	Randomized study	1999	178	0		10.11%

The Prolene hernia system is a three-dimensional bilayer mesh that reinforces the posterior wall of the inguinal canal and pre-peritoneal space during an open inguinal hernia repair. Blunt dissection is done in the preperitoneal space, and it is inserted via the deep ring, and it requires minimal sutures to anchor the mesh [39,5]. A retrospective evaluation of this procedure showed that the operative time was comparable to the other mesh repairs the most common complication was hematoma formation, and wound infection and the recurrence rate was 1.6% [40,5]. A prospective randomized control trial by Pierides et al, comparing the Prolene hernia system with the Lichtenstein repair concluded that both procedures were associated with comparable post-operative complications, chronic pain and recurrence rate [41]. A meta-analysis by Decker et al comparing the Prolene hernia system versus the Lichtenstein repair. This study included 1377 hernia repairs, and they concluded that there was no difference with regard to recurrence rate and chronic pain [42,5].

A meta-analysis of randomized control trials of open mesh techniques for inguinal hernia repair was conducted by Zhao et al.2708 patients were included in this study and they concluded that the Lichtenstein, Plug and Patch and Prolene hernia Systems were associated with similar post-operative complications, chronic pain and mid-term recurrence rates [43,5]. A prospective randomized controlled trial comparing the three-year outcome of the Prolene hernia system, Lichtenstein mesh and the Plug and Patch for primary inguinal hernia repair was conducted by Dalenback et al. A total of 472 patients had undergone hernia repair and they were follow-up to three years. This study concluded that there was no difference with regard to postoperative complications, recurrence rates and chronic pain [44,5].

3. NON-MESH-BASED OPEN INGUINAL HERNIA REPAIR

3.1 Shouldice Repair

Shouldice repair is the most common non-mesh-based open inguinal hernia repair. The important components of this operation include resection of the cremaster muscle, division of the posterior wall of the inguinal canal, and reconstruction of the posterior wall that is conducted with stainless steel wires [45,5]. Hay et al. conducted a multi-center trial on 1578 patients who underwent the Shouldice repair and Bassini repair and the recurrence rates were 6.1% for the Shouldice repair and 8.6% for the Bassini repair [46]. The recurrence rate of the Shouldice repair is around 4.7% to 10.1% with the number of operations being performed decreased due to the introduction of the-mesh-based repairs [47]. Certain centers have performed the Shouldice repair and followed up with the patients after five years have obtained a recurrence rate of 2.88% [48,5].

A Cochrane review was conducted by Amato et al comparing Shouldice repair versus other open inguinal hernia techniques. A total of 2566 patients underwent Shouldice repair,1121 mesh repair and 1608 non-mesh repair. The recurrence rate of the Shouldice repair was higher than the mesh repair but it was the lowest among the sutured repairs [5]. This study concluded that the Shouldice repair was the best non-mesh hernia repair with reference to recurrence, but it requires a

higher learning curve and operative time [49]. Kockerling et al. compared the Shouldice repair with the Lichtenstein and laparoscopic inguinal hernia repair and they concluded that in certain patients with small hernias, the Shouldice repair is indicated due to its low chronic pain rate [50].

3.2 Desarda Repair

This inguinal hernia repair technique was introduced by Desarda where after excision of the hernia sac, an incision is made on the external oblique aponeurosis and a strip of the external oblique aponeurosis is incised and sutured to the posterior wall to reinforce it. This repair is under no tension, and it functions to strengthen the posterior wall. Desarda operated on 400 patients and there was one patient who developed recurrence [51,5]. Several other studies were done on the Desarda repair, and the operative time and postoperative morbidity and mortality were low. The recurrence rates were low, and the cost of the procedure was also low [52-54,5].

The Desarda technique was compared with the Lichtenstein repair in several studies and these studies concluded that there was no difference regarding post-operative morbidity, mortality, length of hospital stays, recurrence rate and chronic pain [55-59]. A systemic review and meta-analysis of randomized control trials comparing the Desarda technique versus the Lichtenstein repair in primary inguinal hernias. 2159 patients from 6 randomized control trials were included in the study [5]. This study concluded that both procedures were associated with reduced complications and recurrence rates, with the Lichtenstein repair being associated with a slight increase in seroma formation [60]. A systemic review by Ge et al also compares the Desarda technique and Lichtenstein repair for the treatment of primary inguinal hernias.1014 patients were included in this study and this study also concluded that there were no differences with regard to postoperative complications, recurrence rate, chronic pain and hospital stay [61,5]. A similar systemic review and meta-analysis by Pereira et al comparing the Desarda technique with the Lichtenstein repair also came out with the same conclusions [62].

A randomized control trial comparing the Desarda technique versus the Lichtenstein repair was performed by Szopinski et al. 208 patients were randomized to 105 who underwent the Desarda repair and 103 the Lichtenstein repair [5]. This study concluded that the incidence of chronic pain and recurrence rates were equal among both groups [63]. A systemic review and meta-analysis was conducted by Ndong et al to look at the suitability of the Desarda repair in the emergency inguinal hernia repair. 199 patients were included in this study and the postoperative complication, recurrence rates and seroma rates were similar, hence it has been suggested that the Desarda repair can be used in emergency inguinal hernia repair [64,5].

3.3 Bassini Repair and Other Open Repairs

This inguinal hernia repair was introduced by Eduardo Bassini and it involves suturing the transversalis fascia and conjoint tendon to the inguinal ligament behind the spermatic cord and employing a Tanner slide to prevent tension. This procedure was popular before the introduction of the mesh-based repair and the major downside of this repair was that it was done under tension and the recurrence rates were around 6% to 8%. This repair is commonly done in countries where mesh is not available or is too costly [65,5]. The Bassini repair was compared to other repair methods like the Lichtenstein repair, Darning Method and Shouldice repair and although there were no major post-operative complications, the recurrence rate was high with the Bassini repair and hence it is rarely used [66-68,5].

The Darning technique involves the approximation of the conjoint tendon to the inguinal ligament with non-absorbable sutures thereby forming a weave in the posterior wall. This method is done in cases where a mesh repair cannot be performed, and it has a higher recurrence rate when compared to mesh-based repairs [69,70,5]. McVay's repair involves the approximation of the transversalis fascia to Cooper's ligament, but this repair was under tension and associated with post-operative pain and a high recurrence rate [71-73].

3.4 Chronic Pain After Inguinal Hernia Repair

This is defined as pain arising from the surgical site that persists for more than 3 months after the inguinal hernia repair. As the recurrence rates decreased after the introduction of mesh-based repairs, chronic pain has become a problem. The risk factors for developing chronic pain include young patients, female sex and developing pain during the immediate post-operative period [5]. The cause of chronic pain is still unknown, but several theories include the inflammatory reaction from the mesh, nerve entrapment, type of mesh and fixation of the mesh [74-76]. A systemic review and Meta-analysis by Oberg et al compared chronic pain after mesh versus non-mesh repair for inguinal hernia and this study concluded that there was no difference with regard to the type of hernia repair regarding chronic pain [77,5]. The incidence of chronic pain is also not affected by the prophylactic division of the ilioinguinal nerve and also by the type and characteristics of the mesh that is used [78-80].

4. CONCLUSION

Open inguinal hernia repair has seen a change in trend with the introduction of mesh-based repairs. The Lichtenstein repair is the most popular repair that is practiced worldwide. It is simple to perform, requires a short learning curve, can be done under local anesthesia and is associated with the lowest recurrence rate among all the open inguinal hernia repairs. The other mesh-based repairs like the Plug and Patch and the Prolene hernia system are not as commonly used [5].

The Shouldice repair is the most popular sutured-based repair, but it has a longer learning curve, and although it can be performed under local anesthesia, the recurrence rate is still higher when compared to the Lichtenstein repair. The Desarda technique is a good tissue-based repair that can be easily learned and since it is a tension-free procedure, it can be an alternative to the Lichtenstein repair [5]. The only drawback of the Desarda technique is the long-term recurrence rate which has not been established yet. Chronic pain now is an emerging post-operative complication that occurs especially after the mesh-based repair, and there is no consensus on its management [5]. Open inguinal hernia repairs will continue to be one of the most common operations that are performed worldwide, and it will retain its place in the surgical treatment of inguinal hernias despite the introduction of laparoscopic inguinal hernia repair.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Kulacoglu H. Current options in inguinal hernia repair in adult patients. Hippokratia. 2011;15(3):223.
2. Awad SS, Fagan SP. Current approaches to inguinal hernia repair. Am J Surg. 2004;188(6A Suppl):9S-16S.
   DOI: 10.1016/j.amjsurg.2004.09.007
   PMID: 15610887.
3. Amid PK. Groin hernia repair: Open techniques. World J Surg. 2005;29(8):1046-51.
   DOI: 10.1007/s00268-005-7967-x
   PMID: 15983714.
4. Rajah KH, Somanathan M. Open hernia repair. In Hernia Updates and Approaches; 2023 Dec 13. Intech Open.
5. Kumar HR. The current status of open inguinal hernia repair in adults: A narrative review. Asian Journal of Medicine and Health. 2024;22(9):142-52.
6. Gudigopuram SV, Raguthu CC, Gajjela H, Kela I, Kakarala CL, Hassan M, Belavadi R, Sange I. Inguinal hernia mesh repair: The factors to consider when deciding between open versus laparoscopic repair. Cureus. 2021;13(11).
7. Antoniou SA, Pointner R, Granderath FA. Current treatment concepts for groin hernia. Langenbecks Arch Surg. 2014;399(5):553-8.
   DOI: 10.1007/s00423-014-1212-8
   Epub 2014 May 14. PMID: 24824799.

8. Sapiyeva ST, Abatov NT, Aliyakparov MT, Badyrov RM, Yoshihiro N, Brizitskaya LV, et al. Non-mesh inguinal hernia repair: Review. Asian J Surg. 2024;S1015-9584(24)01272-7.
DOI: 10.1016/j.asjsur.2024.06.055
Epub ahead of print. PMID: 38960759.
9. Faylona JM. Open anterior groin hernia repair. Ann Laparosc Endosc Surg. 2017;2:96–96.
DOI: 10.21037/ales.2017.05.06
10. Morrison, John. A case for open inguinal hernia repair. International Journal of Abdominal Wall and Hernia Surgery. 2018;1(3):69-73.
DOI: 10.4103/ijawhs.ijawhs_17_18
11. Miserez M, Peeters E, Aufenacker T, Bouillot JL, Campanelli G, Conze J, et al. Update with level 1 studies of the European Hernia Society guidelines on the treatment of inguinal hernia in adult patients. Hernia. 2014;18(2):151-63.
DOI: 10.1007/s10029-014-1236-6
Epub 2014 Mar 20.
Erratum in: Hernia. 2014 Jun;18(3):443-4.
PMID: 24647885.
12. Simons MP, Aufenacker T, Bay-Nielsen M, Bouillot JL, Campanelli G, Conze J, et al. European Hernia Society guidelines on the treatment of inguinal hernia in adult patients. Hernia. 2009;13(4):343-403.
DOI: 10.1007/s10029-009-0529-7
Epub 2009 Jul 28. PMID: 19636493; PMCID: PMC2719730.
13. Köckerling F, Schug-Pass C. Tailored approach in inguinal hernia repair - decision tree based on the guidelines. Front Surg. 2014;1:20.
DOI: 10.3389/fsurg.2014.00020
PMID: 25593944; PMCID: PMC4286983.
14. Stabilini C, van Veenendaal N, Aasvang E, Agresta F, Aufenacker T, Berrevoet F, et al. Update of the international HerniaSurge guidelines for groin hernia management. BJS Open. 2023 Sep 5;7(5):zrad080.
DOI: 10.1093/bjsopen/zrad080
Erratum in: BJS Open. 2024;8(2):zrae034.
DOI: 10.1093/bjsopen/zrae034
PMID: 37862616; PMCID: PMC10588975.
15. Amid PK, Shulman AG, Lichtenstein IL. The Lichtenstein open tension-free mesh repair of inguinal Hernias. Surg Today. 1995;25:619–625.
Available:https://doi.org/10.1007/BF00311436
16. Sakorafas GH, Halikias I, Nissotakis C, Kotsifopoulos N, Stavrou A, Antonopoulos C, Kassaras GA. Open tension free repair of inguinal hernias; the Lichtenstein technique. BMC Surg. 2001;1:3.
DOI: 10.1186/1471-2482-1-3
Epub 2001 Oct 15. PMID: 11696246; PMCID: PMC59657.
17. Merola G, Cavallaro G, Iorio O, Frascio M, Pontecorvi E, Corcione F, et al. Learning curve in open inguinal hernia repair: A quality improvement multicentre study about Lichtenstein technique. Hernia. 2020;24(3):651-659.
DOI: 10.1007/s10029-019-02064-x

Epub 2019 Nov 22. PMID: 31758277.

18. Messias BA, Nicastro RG, Mocchetti ER, Waisberg J, Roll S, Junior MAFR. Lichtenstein technique for inguinal hernia repair: Ten recommendations to optimize surgical outcomes. Hernia. 2024;28(4):1467-1476.
DOI: 10.1007/s10029-024-03094-w
Epub 2024 Jun 20. PMID: 38900355; PMCID: PMC11297121.
19. Messias BA, Almeida PL, Ichinose TMS, Mocchetti ÉR, Barbosa CA, Waisberg J, et al. The Lichtenstein technique is being used adequately in inguinal hernia repair: National analysis and review of the surgical technique. Rev Col Bras Cir. 2023;50:e20233655.
DOI: 10.1590/0100-6991e-20233655-en
PMID: 38088634; PMCID: PMC10668585.
20. Kulacoglu, Hakan. Some more time with an old friend: Small details for better outcomes with Lichtenstein repair for inguinal hernias. International Journal of Abdominal Wall and Hernia Surgery.2022;5(4):221-228.
DOI: 10.4103/ijawhs.ijawhs_40_22
21. Moseholm VB, Baker JJ, Rosenberg J. Nerve identification during open inguinal hernia repair: A systematic review and meta-analyses. Langenbecks Arch Surg. 2023;408(1):417.
DOI: 10.1007/s00423-023-03154-2
Erratum in: Langenbecks Arch Surg. 2023 Nov 18;408(1):439.
DOI: 10.1007/s00423-023-03180-0
PMID: 37874414; PMCID: PMC10598160.
22. Moseholm VB, Baker JJ, Rosenberg J. Identification of the ilioinguinal and iliohypogastric nerves during open inguinal hernia repair: A nationwide register-based study. Hernia. 2024;28(4):1181-1186.
DOI: 10.1007/s10029-024-03002-2
Epub 2024 Mar 19. PMID: 38502369; PMCID: PMC11297051.
23. Smith SM, Khoja AA, Jacobsen JHW, Kovoor JG, Tivey DR, Babidge WJ, et al. Mesh versus non-mesh repair of groin hernias: A rapid review. ANZ J Surg. 2022;92(10):2492-2499.
DOI: 10.1111/ans.17721
Epub 2022 Apr 21. PMID: 35451174; PMCID: PMC9790697.
24. Bisgaard T, Bay-Nielsen M, Christensen IJ, Kehlet H. Risk of recurrence 5 years or more after primary Lichtenstein mesh and sutured inguinal hernia repair. Br J Surg. 2007 Aug;94(8):1038-40.
DOI: 10.1002/bjs.5756
PMID: 17607708.
25. Butters M, Redecke J, Köninger J. Long-term results of a randomized clinical trial of Shouldice, Lichtenstein and transabdominal preperitoneal hernia repairs. Br J Surg. 2007 May;94(5):562-5.
DOI: 10.1002/bjs.5733
PMID: 17443855.
26. Danielsson P, Isacson S, Hansen MV. Randomised study of Lichtenstein compared with Shouldice inguinal hernia repair by surgeons in training. Eur J Surg. 1999;165(1):49-53.
DOI: 10.1080/110241599750007504
PMID: 10069634.

27. Ahmadinejad I, Jalali A, Ahmadinejad M, Soltanian A, Ahamdinejad Y, Shirzadi A, Chaghamirzayi P. Inguinal hernia: Lichtenstein VS Shouldice technique repair: A randomized controlled trial. Surg Open Sci. 2024 Jan 15;17:70-74.
DOI: 10.1016/j.sopen.2024.01.001
PMID: 38298435; PMCID: PMC10828570.
28. Ladwa N, Sajid MS, Sains P, Baig MK. Suture mesh fixation versus glue mesh fixation in open inguinal hernia repair: A systematic review and meta-analysis. Int J Surg. 2013;11(2):128-35.
DOI: 10.1016/j.ijsu.2012.12.013
Epub 2012 Dec 25. PMID: 23270616.
29. Liu H, Zheng X, Gu Y, Guo S. A meta-analysis examining the use of fibrin glue mesh fixation versus suture mesh fixation in open inguinal hernia repair. Dig Surg. 2014;31(6):444-51.
DOI: 10.1159/000370249
Epub 2015 Jan 14. PMID: 25592242.
30. Sun P, Cheng X, Deng S, Hu Q, Sun Y, Zheng Q. Mesh fixation with glue versus suture for chronic pain and recurrence in Lichtenstein inguinal hernioplasty. Cochrane Database Syst Rev. 2017;2(2):CD010814.
DOI: 10.1002/14651858.CD010814.pub2
PMID: 28170080; PMCID: PMC6464532.
31. Lin H, Zhuang Z, Ma T, Sun X, Huang X, Li Y. A meta-analysis of randomized control trials assessing mesh fixation with glue versus suture in Lichtenstein inguinal hernia repair. Medicine (Baltimore). 2018;97(14):e0227.
DOI: 10.1097/MD.0000000000010227
PMID: 29620633; PMCID: PMC5902270.
32. Trisca R, Oprea V, Toma M, Bucuri CE, Stancu B, Grad O, Gherman C. The Effectiveness of Cyanoacrylates versus Sutures for Mesh Fixation after Lichtenstein Repair (SCyMeLi STUDY) A Systematic Review and Meta-Analyze of Randomized Controlled Trials. Chirurgia (Bucur). 2024;119(1):87-101
DOI: 10.21614/chirurgia.2024.v.119.i.1.p.87
PMID: 38465719.
33. Sajid MS, Farag S, Singh KK, Miles WF. Systematic review and meta-analysis of published randomized controlled trials comparing the role of self-gripping mesh against suture mesh fixation in patients undergoing open inguinal hernia repair. Updates Surg. 2014;66(3):189-96.
DOI: 10.1007/s13304-013-0237-9
Epub 2013 Oct 22. PMID: 24146297.
34. Sven Bringman, Stig Ramel, Björn Nyberg, Bo Anderberg. Introduction of herniorraphy with mesh plug and patch, European Journal of Surgery. May 2000;166(4):310–312.
Available:https://doi.org/10.1080/110241500750009159
35. Rutkow IM. The PerFix plug repair for groin hernias. Surg Clin North Am. 2003 Oct;83(5):1079-98, vi.
DOI: 10.1016/S0039-6109(03)00125-7
Erratum in: Surg Clin North Am. 2003 Dec;83(6):xiii.

PMID: 14533905.

36. Zieren J, Hoksch B, Wenger FA, Opitz I, Müller JM. Inguinal hernia repair in the new millennium: plug and patch repair with local anesthesia. World J Surg. 2001;25(2):138-41.
DOI: 10.1007/s002680020093
PMID: 11338012.
37. Singh R, Gupta A, Shah A, Singh A. A study about inguinal hernia mesh repairs: Plug and patch versus lichtenstein mesh repair technique. International Surgery Journal. 2016;1967–74.
Available:https://doi.org/10.18203/2349-2902.isj20163562
38. Kingsnorth AN, Porter CS, Bennett DH, Walker AJ, Hyland ME, Sodergren S. Lichtenstein patch or Perfix plug-and-patch in inguinal hernia: A prospective double-blind randomized controlled trial of short-term outcome. Surgery. 2000;127(3):276-83.
DOI: 10.1067/msy.2000.104124
PMID: 10715982.
39. Gilbert AI, Graham MF, Voigt WJ. A bilayer patch device for inguinal hernia repair. Hernia. 1999;3:161–166.
Available:https://doi.org/10.1007/BF01195319
40. Berende CA, Ruurda JP, Hazenberg CE, Olsman JG, van Geffen HJ. Inguinal hernia treatment with the Prolene Hernia System in a Dutch regional training hospital. Hernia. 2007;11(4):303-6.
DOI: 10.1007/s10029-007-0218-3
Epub 2007 Apr 4. PMID: 17406785.
41. Pierides G, Vironen J. A prospective randomized clinical trial comparing the Prolene Hernia System® and the Lichtenstein patch technique for inguinal hernia repair in long term: 2- and 5-Year results. Am J Surg. 2011;202(2):188-93.
DOI: 10.1016/j.amjsurg.2010.06.027
PMID: 21810499.
42. Decker E, Currie A, Baig MK. Prolene hernia system versus Lichtenstein repair for inguinal hernia: A meta-analysis. Hernia. 2019;23(3):541-546.
DOI: 10.1007/s10029-019-01897-w
Epub 2019 Feb 15. PMID: 30771031.
43. Zhao G, Gao P, Ma B, Tian J, Yang K. Open mesh techniques for inguinal hernia repair: A meta-analysis of randomized controlled trials. Ann Surg. 2009;250(1):35-42.
DOI: 10.1097/SLA.0b013e3181ad63cc
PMID: 19561484.
44. Dalenbäck J, Andersson C, Anesten B, Björck S, Eklund S, Magnusson O, et al. Prolene Hernia System, Lichtenstein mesh and plug-and-patch for primary inguinal hernia repair: 3-year outcome of a prospective randomised controlled trial. The BOOP study: bi-layer and connector, on-lay, and on-lay with plug for inguinal hernia repair. Hernia. 2009;13(2):121-9; discussion 231.
DOI: 10.1007/s10029-008-0443-4
Epub 2008 Nov 13. PMID: 19015933.

45. Bendavid R. The Shouldice technique: A canon in hernia repair. Can J Surg. 1997 Jun;40(3):199-205, 207.
PMID: 9194781; PMCID: PMC3952996.
46. Hay JM, Boudet MJ, Fingerhut A, Poucher J, Hennet H, Habib E, Veyrières M, Flamant Y. Shouldice inguinal hernia repair in the male adult: the gold standard? A multicenter controlled trial in 1578 patients. Ann Surg. 1995;222(6):719-27.
DOI: 10.1097/00000658-199512000-00005
PMID: 8526578; PMCID: PMC1235020.
47. Lorenz R, Arlt G, Conze J, Fortelny R, Gorjanc J, Koch A, Morrison J, Oprea V, Campanelli G. Shouldice standard 2020: Review of the current literature and results of an international consensus meeting. Hernia. 2021;25(5):1199-1207.
DOI: 10.1007/s10029-020-02365-6
Epub 2021 Jan 27. PMID: 33502639.
48. Martín Duce A, Lozano O, Galván M, Muriel A, Villeta S, Gómez J. Results of Shouldice hernia repair after 18 years of follow-up in all the patients. Hernia. 2021 Oct;25(5):1215-1222.
DOI: 10.1007/s10029-021-02422-8
Epub 2021 May 19. PMID: 34009507.
49. Amato B, Moja L, Panico S, Persico G, Rispoli C, Rocco N, Moschetti I. Shouldice technique versus other open techniques for inguinal hernia repair. Cochrane Database Syst Rev. 2012;2012(4):CD001543.
DOI: 10.1002/14651858.CD001543.pub4
PMID: 22513902; PMCID: PMC6465190.
50. Köckerling F, Koch A, Adolf D, Keller T, Lorenz R, Fortelny RH, Schug-Pass C. Has Shouldice Repair in a Selected Group of Patients with Inguinal Hernia Comparable Results to Lichtenstein, TEP and TAPP Techniques? World J Surg. 2018;42(7):2001-2010.
DOI: 10.1007/s00268-017-4433-5
PMID: 29299648; PMCID: PMC5990577.
51. Desarda MP. Introduction new method of inguinal hernia repair: A new solution. ANZ J. Surg. 2001;71.
Available:https://doi.org/10.1046/j.1440-1622.2001.02092.x
52. Bashir SH, Afzal MO, Rafi YA. Desarda technique for inguinal hernia repair, a multicenter experience. Pak J Med Health Sci. 2015;9(1):311-.
53. Gurgenidze M, Datuashvili G. Desarda technique for inguinal hernia repair. Georgian Med News. 2018;(280-281):7-10.
PMID: 30204086
54. Khairy, Mustafa, Madbouly, Abd El-Wahab, Sharaf, Mohammed. Evaluation of Desarda Technique in Inguinal Herniorrhaphy, Al-Azhar International Medical Journal. 2020;1(2):Article 7.
Available:https://doi.org/10.21608/aimj.2020.23116.1116
55. Moghe D, Prajapati R, Banker A, Khajanchi M. A comparative study of desarda's versus lichtenstein's technique for uncomplicated inguinal hernia repair. Cureus. 2022;14(4):e23998.
DOI: 10.7759/cureus.23998
PMID: 35547436; PMCID: PMC9086529.

56. Ali A, Bukhari SUS, Awan SA, Ahmed U, Ahmed A, Babar MW. Comparison between Desarda's inguinal hernia repair and lichtenstein hernioplasty in terms of complications, Operative time and Cost-effectiveness. Pak Armed Forces Med J. 2022;72(4):1339-42.
Available:https://www.pafmj.org/PAFMJ/article/view/8016
57. Gedam BS, Bansod PY, Kale VB, Shah Y, Akhtar M. A comparative study of Desarda's technique with Lichtenstein mesh repair in treatment of inguinal hernia: A prospective cohort study. Int J Surg. 2017;39:150-155.
DOI: 10.1016/j.ijsu.2017.01.083
Epub 2017 Jan 25. PMID: 28131917.
58. Philipp M, Leuchter M, Lorenz R, Grambow E, Schafmayer C, Wiessner R. Quality of Life after Desarda technique for inguinal hernia repair-A Comparative Retrospective Multicenter Study of 120 Patients. J Clin Med. 2023;12(3):1001.
DOI: 10.3390/jcm12031001
PMID: 36769652; PMCID: PMC9917682.
59. Zulu HG, Mewa Kinoo S, Singh B. Comparison of Lichtenstein inguinal hernia repair with the tension-free Desarda technique: A clinical audit and review of the literature. Trop Doct. 2016;46(3):125-9.
DOI: 10.1177/0049475516655070
Epub 2016 Jun 16. PMID: 27317612.
60. Emile SH, Elfeki H. Desarda's technique versus Lichtenstein technique for the treatment of primary inguinal hernia: A systematic review and meta-analysis of randomized controlled trials. Hernia. 2018;22(3):385-395.
DOI: 10.1007/s10029-017-1666-z
Epub 2017 Sep 9. PMID: 28889330.
61. Ge H, Liang C, Xu Y, Ren S, Wu J. Desarda versus Lichtenstein technique for the treatment of primary inguinal hernia: A systematic review. Int J Surg. 2018;50:22-27.
DOI: 10.1016/j.ijsu.2017.11.055
Epub 2017 Dec 23. PMID: 29277678
62. Pereira C, Varghese B. Desarda non-mesh technique versus lichtenstein technique for the treatment of primary inguinal hernias: A Systematic Review and Meta-Analysis. Cureus. 2022;14(11):e31630.
DOI: 10.7759/cureus.31630
PMID: 36540427; PMCID: PMC9759756.
63. Szopinski J, Dabrowiecki S, Pierscinski S, Jackowski M, Jaworski M, Szuflet Z. Desarda versus Lichtenstein technique for primary inguinal hernia treatment: 3-year results of a randomized clinical trial. World J Surg. 2012;36(5):984-992.
DOI: 10.1007/s00268-012-1508-1
PMID: 22392354; PMCID: PMC3321139.
64. Ndong A, Tendeng JN, Diallo AC, Diao ML, Diop S, Dia DA, Ma Nyemb PM, Konaté I. Is Desarda technique suitable to emergency inguinal hernia surgery? A systematic review and meta-analysis. Ann Med Surg (Lond). 2020;60:664-668.
DOI: 10.1016/j.amsu.2020.11.086
PMID: 33312559; PMCID: PMC7721661

65. Tse W, Johns W, Maher J, Rivers J, Miller T. Bassini inguinal hernia repair: Obsolete or still a viable surgical option? A single center cohort study. International Journal of Surgery Open. 2021;36.
Available:https://doi.org/10.1016/j.ijso.2021.100415
66. N N, R S. A Comparative Study between Modified Bassini's Repair and Lichtenstein Mesh Repair (LMR) of Inguinal Hernias in Rural Population. J Clin Diagn Res. 2014;8(2):88-91.
DOI: 10.7860/JCDR/2014/7431.4016
Epub 2014 Feb 3. PMID: 24701491; PMCID: PMC3972608.
67. Elsebae MM, Nasr M, Said M. Tension-free repair versus Bassini technique for strangulated inguinal hernia: A controlled randomized study. Int J Surg. 2008;6(4):302-5.
DOI: 10.1016/j.ijsu.2008.04.006
Epub 2008 May 2. PMID: 18573702.
68. Horharin P, Wilasrusmee C, Cherudchayaporn K, Pinyaku N, Phanpradi O, Phromsopha N. Comparative study of tailor-made mesh plug herniorrhaphy versus Lichtenstein herniorrhaphy versus Bassini operation: a prospective clinical trial. Asian J Surg. 2006;29(2):74-8.
DOI: 10.1016/S1015-9584(09)60111-1
PMID: 16644506.
69. Essawy A, Ibrahim M, Ashraf Mohamed Thabet E, Erfan M, Fathi Ismail Mohammed I. Outcome of darning method of inguinal hernia repair. Print)Online) Fayoum University Medical Journal Ismail et al. 2019(1):15–23.
Available:http://dx.doi.org/10.21608/fumj.2019.60370
70. Olasehinde OO, Adisa AO, Agbakwuru EA, Etonyeaku AC, Kolawole OA, Mosanya AO. A 5-year Review of Darning Technique of Inguinal Hernia Repair. Niger J Surg. 2015;21(1):52-5.
DOI: 10.4103/1117-6806.152722
PMID: 25838768; PMCID: PMC4382644.
71. Banks SB, Cotlar AM. Classic groin hernia repair...lest we forget. Curr Surg. 2005;62(2):249-52.
DOI: 10.1016/j.cursur.2004.08.018
PMID: 15796951.
72. Ryan JJ. The McVay Operation. In: Bendavid, R, Abrahamson, J, Arregui, M.E, Flament, J.B, Phillips, E.H. (eds) Abdominal Wall Hernias. Springer, New York, NY; 2001.
Available:https://doi.org/10.1007/978-1-4419-8574-3_52
73. Junge K. Lotheissen/McVay Repair; 2019.
Available:https://www.ebsco.com/terms-of-use
74. Nikkolo C, Lepner U. Chronic pain after open inguinal hernia repair. Postgrad Med. 2016;128(1):69-75.
DOI: 10.1080/00325481.2016.1121090
Epub 2015 Dec 4. PMID: 26567717.
75. Reinpold W. Risk factors of chronic pain after inguinal hernia repair: A systematic review. Innov Surg Sci. 2017;2(2):61-68.
DOI: 10.1515/iss-2017-0017
PMID: 31579738; PMCID: PMC6754000.

76. Pierides GA, Paajanen HE, Vironen JH. Factors predicting chronic pain after open mesh based inguinal hernia repair: A prospective cohort study. Int J Surg. 2016;29:165-70.
DOI: 10.1016/j.ijsu.2016.03.061
Epub 2016 Apr 4. PMID: 27058113.
77. Öberg S, Andresen K, Klausen TW, Rosenberg J. Chronic pain after mesh versus nonmesh repair of inguinal hernias: A systematic review and a network meta-analysis of randomized controlled trials. Surgery. 2018;163(5):1151-1159.
DOI: 10.1016/j.surg.2017.12.017
Epub 2018 Mar 13. PMID: 29506882.
78. Charalambous MP, Charalambous CP. Incidence of chronic groin pain following open mesh inguinal hernia repair, and effect of elective division of the ilioinguinal nerve: Meta-analysis of randomized controlled trials. Hernia. 2018;22(3):401-409.
DOI: 10.1007/s10029-018-1753-9
Epub 2018 Mar 17. PMID: 29550948.
79. Rutegård M, Lindqvist M, Svensson J, Nordin P, Haapamäki MM. Chronic pain after open inguinal hernia repair: Expertise-based randomized clinical trial of heavyweight or lightweight mesh. Br J Surg. 2021;108(2):138-144.
DOI: 10.1093/bjs/znaa049
PMID: 33711123; PMCID: PMC10364858.
80. Rutegård M, Gümüsçü R, Stylianidis G, Nordin P, Nilsson E, Haapamäki MM. Chronic pain, discomfort, quality of life and impact on sex life after open inguinal hernia mesh repair: An expertise-based randomized clinical trial comparing lightweight and heavyweight mesh. Hernia. 2018;22(3):411-418.
DOI: 10.1007/s10029-018-1734-z
Epub 2018 Jan 20. PMID: 29353339; PMCID: PMC5960495.

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Chapter 11
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A Comprehensive Review of Anesthesia and Pulmonary Hypertension: Insights into Preoperative Preparation, Monitoring and Treatment

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ABSTRACT

Pulmonary hypertension (PH) is a complex disease of the cardiopulmonary system. The most common causes of postoperative mortality in PH patients are acute RVF, arrhythmias (particularly atrial fibrillation [AF]), ischemia, congestive heart failure (CHF), unstable hemodynamic status, hypoxia, respiratory and renal failure, sepsis, and stroke. Perioperative management of PH is one of the most challenging issues for anesthetists. Morbidity and mortality are significantly high in PH patients undergoing surgery due to right heart failure, arrhythmia, atrial fibrillation, ischemia, hemodynamic instability, hypoxia, respiratory failure, renal failure, sepsis, and stroke. Detailed preoperative evaluation and correct anesthetic management will significantly increase the chances of a successful peri-operative outcome in these patients. In PH patients, it is important that more than one physician, including anesthesiologist, intensivist, pulmonologist, cardiologist, and surgeon, discuss the patient's possible difficulties and complications with a multidisciplinary approach and make a decision. In order to optimize the management of PH patients, it is necessary to comprehensively evaluate the underlying cause, pathophysiology, risk factors, course, and treatment of the disease. Currently, no evidence-based information is available for choosing general, regional, or combined anesthesia as anesthetic techniques for PH patients. A balanced anesthesia technique, including inhalation or intravenous agents, appropriate regional anesthesia (RA), opioids, and α-2-adrenoceptor agonists may provide the most uniform hemodynamic profile in these patients. The basis of anesthesia management should be to prevent and treat triggering factors,

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provide perfusion pressures, and optimize right ventricular functions. Advanced monitoring, pulmonary vasodilator therapies, adequate anesthesia and analgesia, and appropriate ventilator settings should be performed for patients with PH. Patients with PH should be followed in the intensive care unit in the first 48–72 h postoperatively. In PH patients, advanced intraoperative and postoperative follow-up, pulmonary vasodilator treatments, adequate anesthesia, and analgesia should be considered. It is essential to optimize the patient for surgery in a nonemergency situation and to organize treatment and education of the patient for the long-term period of the disease. This book chapter aims to focus on appropriate preoperative preparation, perioperative monitoring, anesthesia and ventilator management, pain control, preventive methods, and treatment in patients with PH in light of the literature.

Keywords: Anesthesia management; comprehensive preoperative evaluation; multidisciplinary approach; pulmonary hypertension.

1. INTRODUCTION

Pulmonary hypertension (PH) remained an unexplained intractable disease with a poor prognosis [1]. PH is a heterogeneous systemic disease that affects the heart, brain, liver, kidneys, gastrointestinal tract, skeletal muscles, endocrine, immune and autonomic systems and it eventually leads to right ventricular failure (RVF) [2,3]. The global burden of PH is substantial. In the last 2 decades, however, the diagnosis and treatment methods for this disease changed markedly [4]. The pathophysiology includes decreased organ perfusion, unbalanced neurohormonal activation, oxidative stress, abnormal immune cell signaling, and various hemodynamic consequences in response to the interaction of these systems. Major advances in pulmonary arterial hypertension, pulmonary hypertension (PH) associated with lung disease, and chronic thromboembolic PH cast new light on the pathogenetic mechanisms, epidemiology, diagnostic approach, and therapeutic armamentarium for pulmonary vascular disease [5]. The most common causes of postoperative mortality in PH patients are acute RVF, arrhythmias (particularly atrial fibrillation [AF]), ischemia, congestive heart failure (CHF), unstable hemodynamic status, hypoxia, respiratory and renal failure, sepsis, and stroke [3,6,7].

PH is seen in 15–50 people per million [8]. Although it usually affects women between the ages of 30 and 60, adverse clinical outcomes are more often pronounced in men. Hereditary and idiopathic causes account for 52.6% of all PH cases. The most common etiological causes are left heart or lung diseases [8,9]. Early diagnosis and treatment in patients with PH are critical in morbidity and mortality [10].

PH is a severe progressive and chronic cardiopulmonary disease affecting patients' clinical course throughout the peri-operative period. Our review aims to focus on how to manage patients with PH properly and effectively as anesthesiologists in the perioperative period.

2. DEFINITION AND CLASSIFICATION

The diagnostic criteria for PH include:

a. Mean pulmonary artery pressure (mPAP) >25 mmHg at rest or
b. mPAP >30 mmHg during exercise
c. Pulmonary vascular resistance (PVR) >240 dyn/s/cm^5 (N: 100–200).

PH is a hemodynamic and physiopathological condition characterized by a progressive course. An mPAP between 20 mmHg and 24 mmHg is defined as borderline PH [3,11,12]. PH is divided into five groups in terms of etiological causes, hemodynamic, and therapeutic modalities [Table 1] [3,9,12,7].

1. Pulmonary arterial hypertension (Group I)
2. PH associated with left heart disease (LHD) (Group II)
3. PH due to chronic lung disease and/or hypoxia (Group III)
4. PH due to pulmonary artery obstructions (Group IV)
5. PH due to unclear and/or multi factorial mechanisms (GroupV).

PH can also be defined according to hemodynamic parameters [Table 1] [12,13,7].

1. Precapillary PH: Groups I, III, IV, and V
   - mPAP ≥25 mmHg
   - Pulmonary artery wedge pressure (PAWP) ≤15 mmHg
   - PVR ≥3 wood units (WUs).
2. Isolated postcapillary PH: Groups II and V
   - mPAP ≥25 mmHg
   - PAWP >15 mmHg
   - PVR ≤3 WU.
3. Combined precapillary and postcapillary PH: Groups II and V [12,13,7]
   - mPAP ≥25 mmHg
   - PAWP >15 mmHg
   - PVR ≥3 WU.

The follow-up and treatment of PH in the perioperative period are one of the most significant challenges for anesthesiologists and intensivists due to high mortality and morbidity [10,14,7]. By understanding the relevant and important risk factors, administering appropriate treatments based on PH classification, and enabling careful planning; we can accurately and appropriately perform any surgery or intervention in these patients. Management of patients with PH requires a comprehensive approach to optimize hemodynamics (right ventricular [RV], preload, afterload, and contractility), minimizing risks and triggers, and carefully handling complications [6,14,15,7].

In noncardiac surgery, mortality and morbidity vary between 1%–18% and 14%–42%, respectively for patients with PH [6]. Therefore, it significantly prolongs the length of both hospital and intensive care unit (ICU) stays. Eventually, it causes an increase in hospital costs and the risk of re-hospitalization [3,6].

3. THE PATHOGENESIS OF PULMONARY HYPERTENSION

Etiological causes that initiate the pathogenesis of PH include inappropriate angiogenesis, DNA damage, genetic mutations, metabolic disorders, and factors that disrupt the vascular structure [16]. The mediators most accused in the pathogenesis of PH are endothelin 1, serotonin, thromboxane A_2 (TXA_2), epinephrine, norepinephrine (NE), nitric oxide (NO), and prostacyclin (PGI_2) [7]. Endothelin 1 is a vasoconstrictor peptide secreted by vascular endothelial cells, leading to pulmonary vasoconstriction and vascular smooth muscle cell proliferation. NO and PGI_2 are endogenous vasodilators produced in pulmonary vascular endothelial cells, and their production is decreased in many types of PH [16-18].

The pathogenesis of PH occurs in three different stages pathologically [Fig. 1]: (1) endothelial dysfunction, (2) vascular remodeling, and (3) decreased apoptosis, neo adventitial excess cell proliferation, and thrombosis in pulmonary arterioles [18,19,7]. Endothelial dysfunction is the primary factor in the pathogenesis of PH, and many molecular pathways have been described. Genetic susceptibility is significant in the development of PH. In particular, the bone morphogenetic protein receptor type II gene is thought to play a role in 75% of familial cases and 20% of sporadic cases [20]. Other mutations associated with the development of PH include GDF2 (codes BMP9), type I receptor (ACVRL1), and SMAD9 (codes Smad8). K+ channel subfamily K member 3 and caveolin-1 mutations have also been described, along with others [18,21]. Therefore, there is a relationship between vasoconstrictive and proliferative mediators (endothelin-1, serotonin, and TXA2), which are normally regulated and balanced according to physiological requirements. This balance is disturbed in PH among mediators with vasodilatory and anti-proliferative effects (NO, PGI2, and K+ channels of smooth muscle cells). PH develops due to increased activity of serotonin, endothelin-1, and TXA2 mediators and decreased activity of NO, PGI2 mediators, and K+ channels of smooth muscle cells [14-17]. Raised PVR caused by progressive vascular remodeling may lead to PH crisis and RVF, which has very high morbidity and mortality [Fig. 1] [22,23].

4. PERIOPERATIVE ANESTHETIC MANAGEMENT

Preoperative evaluation: The management of PH patients can be challenging and complicated. Detailed preoperative evaluation and correct anesthetic management will significantly increase the chances of a successful peri-operative outcome in these patients. Since PH affects many organ systems (heart, lungs, liver, and kidneys), surgical preparations should be guided by a team's comprehensive anesthetic, surgical, pulmonary, and cardiac evaluation. Perioperative planning should be done by a multidisciplinary team in equipped centers [Fig. 2] [2,14,15,24,7].

Detailed history, signs, symptoms, and physical examination are extremely important in the preoperative assessment.

Table 1. Classification of pulmonary hypertension type based on hemodynamics and world health organization clinical groups [7]

Definition	Characteristic	WHO clinical groups
PH	mPAP >25 mmHg	All
Precapillary PH	mPAP ≥25 mmHg PAWP ≤15 mmHg PVR ≥3 WU CO normal/reduced/high	PAH PH due to CLD CTEPH PH with unclear and/or multifactorial mechanisms
Postcapillary PH	mPAP >25 mmHg PAWP ≥15 mmHg CO normal/reduced/high	PH due to LHD
Isolated postcapillary PH	PAWP >15 mmHg	PH due to LHD
Postcapillary PH with precapillary component	DPAP-PAWP <7 mmHg PAWP >15 mmHg DPAP-PAWP ≥7 mmHg	PH due to LHD

WHO=World health organization, mPAP=Mean pulmonary arterial pressure, PAH=Pulmonary arterial hypertension, PAWP=Pulmonary artery wedge pressure, PH=Pulmonary hypertension, PVR=Pulmonary vascular resistance, CTEPH=Chronic thromboembolic PH, CO=Cardiac output, DPAP=Diastolic PAP, CLD=Chronic lung disease, LHD=Left heart disease, WU=Wood units

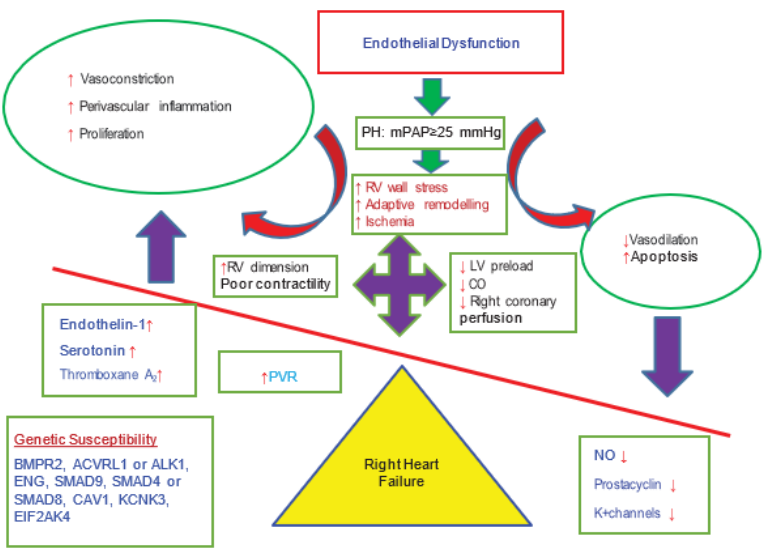

Fig. 1. Pathogenesis and genetic susceptibility of pulmonary hypertension. mPAP=Mean pulmonary arterial pressure, PH=Pulmonary hypertension, RV=Right ventricular, LV=Left ventricular, CO=Cardiac output, PVR=Pulmonary vascular resistance, NO=Nitric oxide [7]

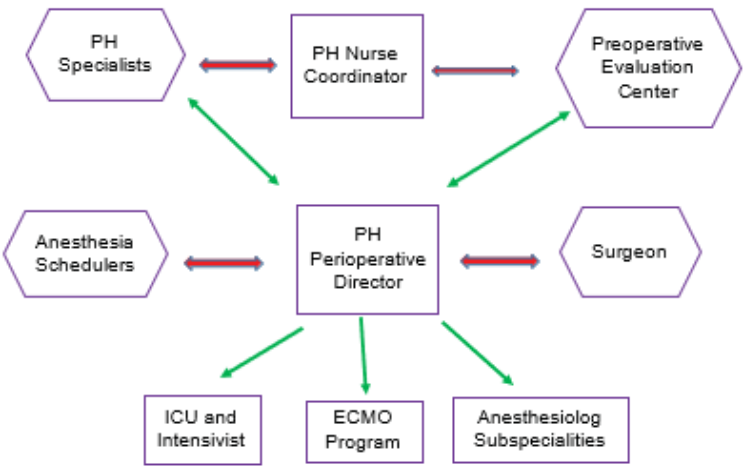

Fig. 2. Management of pulmonary hypertension in the peri-operative period. PH=Pulmonary hypertension, ICU=Intensive care unit, ECMO=Extracorporeal membrane oxygenation [7]

The preoperative evaluation of the patient with PH and the identified risk factors are summarized in Fig. 3 [10,14,15,24,7]. All important factors should be considered in the evaluation, such as the etiology and disease severity, comorbid conditions, type and emergency of the surgery, the patient's functional status, home medication regimen, treatment adherence, preoperative medication optimization and appropriate treatment, and assessment of baseline oxygen requirements [10,24-26]. The presence of RVF findings such as S3 gallop, neck venous distention, peripheral edema, hepatomegaly, and abdominal ascites in the physical examination is important for clinical follow-up [27,28,7].

In general, the primary investigations include a comprehensive metabolic panel, preoperative routine laboratory evaluations (hemoglobin and hematocrit, creatinine, glomerular filtration rate, pro-brain natriuretic peptide [pro-BNP], and liver function tests), pulmonary function tests involving arterial blood gas (ABG) analysis, chest radiography, an electrocardiogram (ECG), transthoracic echocardiogram (TTE), 6-min walk distance (6-MWD) test, should be obtained and reviewed when necessary [10,14,25,26]. There are identified risk factors to determine the prognosis in terms of mortality and morbidity [Table 2] [6,10,14,7].

If the patient has dyspnea at rest, syncope history, functional impairment, presence of hypoxemia, exhibits exacerbated symptoms of RVF, or acid-based changes on the day of surgery, the anesthesiologist and surgical team should consider the risk-benefit ratio if the operation is not urgent and confirm that the anesthetist has the knowledge, attitude, and tools to manage this status well in case of acute RVF

development [14]. Perioperative risk factors include operation-specific and patient-related factors. The most important patient-related factors are the New York Heart Association grade >2, 6-MWD <300 m, estimated history of diagnosis, coronary artery disease, RVF, chronic kidney disease, and pulmonary thromboembolism (PTE) [27,29,28,7]. Surgical factors include emergency surgical procedures that last longer than 3 h, moderate or high-risk surgeries (including thoracic, major abdominal, and orthopedic surgeries), and procedures that may increase the risk of venous insufficiency or embolization, and use of vasopressors [6,14,30]. To predict postoperative cardiac mortality in noncardiac surgery, monitoring of pro-BNP levels is recommended [10,7].

It is common for patients with PH to overlook their disease in the preoperative period, and TTE findings can often be unnoticed in these patients. Therefore, TTE should be evaluated in detail in patients with suspected PH. We should consider that systolic pulmonary artery pressure (sPAP) measurement can be beneficial for risk stratification and optimal guiding for the intraoperative management of these patients. Patients with sPAP above 35 mmHg should be evaluated more thoroughly [27]. Tricuspid annular plane systolic excursion (TAPSE) should be between 17 mm and 20 mm [7]. TAPSE provides a great deal of information about RV function and prognosis in PH. In addition, right atrial enlargement surface (>27 mm^2), TAPSE/sPAP (N: <0.8 – 1 mm/mmHg), tricuspid regurgitation velocity (TRV) (N: <2.8 m/sn) measurements can also give information about the prognosis. The presence of pericardial effusion, decreased TAPSE, increased TAPSE/sPAP, TRV, and right atrial enlargement surface (>27 mm^2) are distinguished prognostic markers [26]. Preoperative determination of prognostic factors by TTE in patients with PH is vital for optimizing anesthetic management, preventing complications, and decreasing mortality and morbidity [Table 3] [27,29,7].

Patients should be reassessed and optimized before operation to decrease PVR and improve RV function if necessary. In addition, transesophageal echocardiography (TEE) and pulmonary artery catheterization (PAC) should be evaluated preoperatively if the patient has comorbidities or symptoms of RVF [14-17,27].

Medications used for treating PH should be taken before the operation. If the patient is not on treatment and the operation will not be postponed, Sildenafil 0.5 mg/kg PO every 6 h, 50–100 mg daily for adults, or 0.2 mg/kg/h intravenous (i.v.) should be started [7].

Fluid restriction and diuretics should be considered in RVF and hypervolemia. Anti-coagulation is needed for thrombosis prophylaxis. Besides, if the risk of venous thrombosis is high and there are clinical signs, heparin should be given as bridge therapy instead of coumadin. Anemia and iron deficiency should be corrected in the preoperative period to prevent worsening PH. ACEI, ARBs, β–blockers, and ivabradine should be avoided in the preoperative period [6,11,14,27]. In our clinic, we start treatment for PH patients according to the etiological reason preoperatively (sildenafil, heparin, diuretic, etc.) and continue with appropriate medication (milrinone, inotropes, and diuretics) in the intraoperative period [7].

Table 2. Prognostic assessment in pulmonary hypertension [7]

Prognostic determinant	**Risk**		
	Low	**Intermediate**	**High**
Clinical signs of RHF	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional	Repeated
Functional class	I, II	III	IV
6- MWD (m)	>440	165- 440	<165
Cardiopulmonary exertion test	VO_2- peak > 15 mL/kg/min (>65%)VE/ VCO_2 <36%	VO_2- peak 11-15 mL/kg/min (35%-65%) VE/ VCO_2 (36%- 44.9%)	VO_2- peak<11 mL/kg/min (<35%) VE/ VCO_2 (≥45%)
BNP or NT-proBNP	BNP <50 ng/L NT- proBNP < 300 ng/L	BNP 50-300ng/L NT- proBNP 300-1400 ng/L	BNP >300ng/L NT- proBNP >1400 ng/L
Imaging techniques	RA area < 18cm^2 No pericardial effusion	RA area 18-26 cm^2 Without or with minimal pericardial effusion	RA area > 26 cm^2 Pericardial effusion
Hemodynamics	RAP < 8 mmHg CI≥ 2.5 L/min/m^2 SvO_2 >65% $ScvO_2$ >70% PaO_2 < 80mmHg	RAP 8-14 mmHg CI 2.0-2.4 L/min/m^2 SvO_2 60%-65% $ScvO_2$ 55%-70% PaO_2 < 50-65 mmHg	RAP >14 mmHg CI <2.0 L/min/m^2 SvO_2 <60% $ScvO_2$ <55% PaO_2 < 50 mmHg

VE/VCO_2 = The ratio between minute ventilation and CO_2 production, VO_2- peak = Peak oxygen uptake, RHF= Right heart failure, 6- MWD= 6-min walk distance test, BNP= Brain natriuretic peptide, CI= Cardiac Index, NT- proBNP = N- terminal prohormone brain natriuretic peptide, RA= Right atrium, RAP= Right atrium pressure, SvO_2 = Oxygen saturation mixed venous blood, $ScvO_2$ = Central venous oxygen saturation

Intraoperative monitoring and management: Anesthesia or sedation is highly risky in PH patients with or without RVF. Operation groups according to risk ratio are given in Table 4 [6,14]. Since PH patients are difficult to manage, hemodynamic instability is quite common. Currently, anesthesiologists are increasingly likely to encounter PH patients who apply for elective operations [14,31]. Understanding the underlying cause, subgroup, and severity of PH allows anesthesiologists to make a comprehensive anesthesia management plan to reduce patient-related risks [7]. With the advent of advanced hemodynamic monitoring techniques and treatments, the successful management of these patients is increasing [31].

Individualized preoperative risk evaluation, treatment optimization, and advanced peri-operative planning can reduce difficulties and complications. To minimize complications, evidence-based, systematic, and disciplined team consensus is required. Anesthetic and surgical stress can exacerbate PH and lead to arrhythmias, CHF, myocardial infarction, postoperative respiratory failure, hemodynamic instability, and delayed extubation [27]. Anesthesiologists need to optimize hemodynamics, ventilation, oxygenation, and perfusion, maintain body temperature, acid-base, and fluid-electrolyte balance, use therapeutic vasodilators or vasopressors when necessary, avoid factors that may trigger PH, and control pain peri-operatively to ensure better outcomes [7].

Anesthetic applications of PH are shown in Table 5 [6,14,27].

In the case of intravascular volume depletion due to insensible losses and excessive blood loss, the CO decreases because of insufficient right-sided filling pressures, and therefore perfusion cannot be achieved [6]. If necessary, volume replacement with appropriate fluids and inotropes should be started immediately. The main goal of anesthetic management in PH patients should be to prevent RVF and PH crises and to provide systemic perfusion [16].

Patients with PH should be appropriately premedicated, but adequate preoxygenation should be ensured, especially in anesthesia induction, and hypotension and respiratory acidosis to be prevented as much as possible. Invasive monitoring should be performed in addition to standard monitoring, based on the risk of the operation, duration, and concomitant diseases [7]. The American Society of Anesthesiologists recommends ECG, noninvasive heart rate, blood pressure (BP) devices, pulse oximetry (SpO2), respiratory rate (RR), end-tidal carbon dioxide ($EtCO_2$), and temperature monitoring for all surgical cases. Cardiac output (CO) monitoring with advanced dynamic parameters may guide hemodynamic management in major surgeries. Neuromuscular monitoring should be performed with bispectral index (BIS) and train-of-four monitoring. While standard monitoring is considered adequate for minor and moderate operations in functional status II, all major operations and procedures in functional status III should be performed with advanced monitoring [7]. Warm fluids are of choice to prevent hypothermia and i.v. liquid heaters, heating blankets, and forced air heaters should be used [6,14,15,27].

Intermittent ABG sampling should also be performed. An arterial line may be placed to provide continuous access to ABG samples and systemic BP monitoring. It allows rapid intervention, appropriate ventilation management, and drug treatment determination [32-34]. Central venous catheterization should be performed carefully to prevent triggering arrhythmias. Central venous pressure (CVP) can be monitored for volume status. CO monitoring includes the following hemodynamic parameters [7]:

- Systemic vascular resistance (SVR)
- Stroke volume
- Pulse pressure variation
- Stroke volume variation
- Extravascular lung water
- Cardiac index (CI)
- Central venous oxygen saturation ($ScvO_2$)
- Mixed venous oxygen saturation (SvO_2).

TEE must be kept in the operating room intraoperatively. PAC can be placed and evaluated preoperatively in severe PH cases when necessary [14,34-36]. The main goal in perioperative targeted therapy should be to ensure the perfusion and oxygenation of vital organs [37]. In addition, its monitoring can show global tissue perfusion [34,7] In our clinic, we perform PAC in PH patients undergoing major surgery and support it with TEE. TEE can give information on cardiac wall motions, anatomy, and valves' functions, and evaluate volume status [14,38-40].

Table 3. Peri-operative risk assessment according to transthoracic echocardiogram (systolic pulmonary artery pressure, tricuspid annular plane systolic excursion/systolic pulmonary artery pressure and tricuspid regurgitation velocity) [7]

RV/PA systolic pressure (sPAP)	TAPSE/sPAP (mm/mmHg)	TRV (m/sn)	Secondary signs of PH	Probability of PH	Severity of PH
<35 mmHg or undetectable	<0.55	≤2.8	No	Low	**Mild**
<35 mmHg or undetectable 35–50 mmHg	0.19–0.32	2.9–3.4	Yes No	Intermediate	**Moderate**
35–50mmHg	>0.19	>3.4	Yes	High	**Severe**
>50 mmHg			Not required	High	

sPAP=Systolic pulmonary artery pressure, TAPSE=Tricuspid annular plane systolic excursion, TRV=Tricuspid regurgitation velocity, PH=Pulmonary hypertension, RV=Right ventricular, PA=Pulmonary artery

Table 4. Types of surgery according to risk status in patients with pulmonary hypertension [7]

Low risk <1%	Intermediate risk 1%-5%	High risk >5%
Superficial surgery	Intraperitoneal splenectomy, hiatal hernia repair cholecystectomy	Aortic and major vascular surgery
Breast	CEA and CAS	Open lower limb revascularisation or amputation
Dental	Peripheral arterial angioplasty	Tromboembolectomy
Endocrine thyroid	Endovascular aneurysm	Duodenal- pancreatic surgery
Eye	Endovascular aneurysm repair	Live resection
Reconstructive	Head and neck surgery	Bile duct surgery
Carotid symptomatic (CEA or CAS)	Neurological or orthopedic major (hip and supine surgery)	Oesophajectomy
Gynaecologic minor	Urological or gynecological major	Adrenal resection
Orthopedic minor (meniscectomy)	Renal transplant	Total repair of a perforated bowel
Urological minor (transurethral resection of the prostate	Intra- thoracic nonmajor	Total cystectomy
		Pneumonectomy
		Pulmonary or liver transplant

CEA= Carotid endarterectomy, CAS= Carotid artery stenting

5. ANESTHETIC TECHNIQUE PREFERENCE AND METHODS

Currently, no evidence-based information is available for choosing general, regional, or combined anesthesia as anesthetic techniques for PH patients. General anesthesia (GA) is frequently used in patients with PH. However, current PH guidelines and experts recommend regional anethesia (RA) in eligible patients for elective surgeries, as positive pressure ventilation (PPV) with high positive end-expiratory pressure (PEEP) and tidal volume may worsen RV afterload. Spinal anesthesia should be avoided as much as possible due to its sympathetic-blocking effects and rapid onset [14]. Many opinions suggest a balanced method with high-dose opioids and low-dose inhaled anesthetics if GA is to be applied [14,15,7]. It is vital to maintain RV function and reduce risk factors that cause pulmonary vasoconstriction (increasing RV afterload) or systemic hypotension (reducing RV perfusion) [40]. Epidural and/or peripheral nerve blocks are useful in peri-operative pain control. Uncontrolled pain may trigger PH. Therefore, it is important to make a personalized plan according to the underlying etiology, pathophysiology, and systemic involvement in a patient with PH [14-16,7].

The advantages of GA include controlled ventilation, safe oxygenation, uncomplicated airway, and a direct route for administering inhaled pulmonary

vasodilators. The disadvantages of GA are due to PPV, PEEP, and the BP changes caused by anesthetics. Severe hypotension may decrease coronary perfusion pressure (CPP), resulting in a vicious circle that may lead to RV ischemia, disruption of RV contractility, cardiogenic shock, and even death [41].

Sufficient depth of anesthesia and analgesia provide reduced catecholamine discharge and PVR. Laryngoscopy and intubation can cause PH crisis, RVF, and death in patients with serious PH; thus, meticulously laryngoscopy and intubation methods are essential. Lidocaine, opioids, Mg^{++}, α-2 agonists, and nonhistamine-releasing nondepolarizing muscle relaxants can reduce the sympathetic response and suppress the stress response to intubation [14,7]. Moreover, i.v. or nebulized treatments with inhaled NO (iNO) or prostanoids may be given to minimize PH responses to intubation. The overall goal should be to prevent changes in preload, SVR, and contraction of RV to maintain CO [42].

Before induction of GA, a patient with PH must be adequately pre oxygenated with 100% fractionated inspired oxygen (FiO_2) to prevent hypercarbia, respiratory acidosis, and hypoxemia, and to increase functional residual capacity. Oxygen is a pulmonary vasodilator and helps prevent hypoxemia. Triggering factors such as hypoxemia, hypercapnia, acidosis, hypotension, and hypothermia should be avoided, and appropriate ventilation, adequate fluid therapy, and low-dose vasopressor should be administered when needed [Table 5] [6,30,43-45,7].

There is no ideal anesthetic agent for PH patients. After premedication with benzodiazepines, balanced anesthesia induction and maintenance can be achieved with concomitant use of opioids, etomidate, propofol, ketamine, α-2 agonists (dexmedetomidine and clonidine), and/or volatile anesthetics (such as isoflurane and sevoflurane), as appropriate [41].

Benzodiazepines, which cause minor respiratory depression and hemodynamic changes, can be used carefully in unstable conditions. Hemodynamic effects of inhalational or i.v. anesthetics are given in Table 6 [7]. Propofol does not increase systemic vasoconstriction with minimal pulmonary vasodilation [31]. Propofol significantly reduces SVR and slightly reduces cardiac contractility [42]. Therefore, propofol may trigger oxygen desaturation in patients with cardiac shunt and high PVR by accelerating the right-to-left shunt. Therefore, care should be taken in induction [42]. Although thiopental has no effect on PVR, it decreases RV contractility and causes myocardial depression and hypotension [27].

Etomidate is a widely recommended induction agent because of its rapid onset and hemodynamic stability with minor effects on myocardial contractility, SVR, and PVR [27,42]. Ketamine-induced catecholamine release may cause pulmonary vasoconstriction, and this effect can be attenuated with pulmonary vasodilators, benzodiazepines, or increasing FiO [41,7]. Ketamine preserves SVR and BP without causing excessive PVR, thereby protecting systemic and pulmonary circulation. In addition, low doses of ketamine as part of the multimodal analgesia may be beneficial for pain control [27,46].

Opioids have a modest impact on PVR and can be used to blunt response to sympathetic stimulation [27,41,46]. Short-acting opioids, including remifentanil, are highly recommended anesthetic drugs in balanced anesthesia [27,46,47]. Neuromuscular agents such as atracurium and mivacurium that can increase PVR by releasing histamine should be avoided in patients with PH. Rocuronium and vecuronium are generally preferred as neuromuscular blockers [27,47,7].

Dexmedetomidine is a centrally acting α-2 agonist that prevents the increase in PVR by reducing the stress and hemodynamic response to intubation and extubation with its sympatholytic effect. Dexmedetomidine is a convenient and effective sedative-anesthetic drug for reducing opioid usage in both GA and RA. It is an important advantage that dexmedetomidine does not interact with diuretics and phosphodiesterase (PDE)-5 inhibitors used in the treatment of PH [48].

Table 5. Anesthetic implications of severe pulmonary hypertension [7]

Period	Anesthetic implication
Preoperative	A comprehensive evaluation of PH severity
	Avoid anxiety, pain and sympathetic stimulation
	Avoid oversedation and hypoventilation
	Continue all PH- specific, long- term therapy perioperatively
Intraoperative	Use suitable invasive monitoring
	Provide adequate anesthesia and analgesia
	PPV parameters
	FiO_2 titrate to 60%-100%
	Low tidal volumes (6mL/kg)
	$PaCO_2$: 30-35 mmHg
	$EtCO_2$:30-35 mmHg
	Low PEEP (5-10 cmH_2O)
	Aggressively treat hypotension
	Maintain sinus rhythm
	Maintain systemic pressures
	Optimize RV function and CO with adequate preload, SVR and contractility
	MAP> 65 mmHg, CI $\geq$ 2.2 L/min/m^2
	Monitor RV and treat dysfunction
	Optimize fluid balance
	Minimize blood loss
	Minimize transfusion
	Avoid trigger factors that worsen PH and increase PVR:
	Hypoxemia
	Hypervolemia
	Increased intrathoracic pressure
	Atelectasis and hyperinflation
	Pain
	Consider pulmonary vasodilators to decrease RV afterload
Postoperative	Avoid pain and shivering
	Advanced monitoring
	Closely follow up first 48-72 h in the ICU

PH= Pulmonary hypertension, PPV= Positive pressure ventilation, FiO_2= Fraction of inspired oxygen, $PaCO_2$= Partial pressure of CO, $EtCO_2$= End- tidal CO2, PEEP= Positive end- expiratory pressure, RV= Right ventricular, MAP= Mean arterial pressure, CO= Cardiac output, CI= Cardiac index, PVR= Pulmonary vascular resistance, SVR= Systemic vascular resistance, ICU= Intensive care unit

Table 6. Effect of anaesthetic agents [7]

Anesthetic agent	RV contractility	PVR	SVR
Isoflurane	↓↓	↑	↓
Desflurane	↓↓	↑	↓
Sevoflurane	↓↓	↔	↓
NO	↓	↑↑	↑↑
Thiopental	↓	↔	↓
Etomidate	-	-	↔
Ketamine	↓	↑**adult, child**↔	**↑**
Propofol	↓↓	↓	↓↓
Opioids	↔	↔	↓
Dexmedetomidine	↔	↔	↑

↓↓: Marked decrease, ↑↑: Marked increase, ↑: Increase, ↓: Decrease, ↔: No change, -: Not known, RV: Right ventricular, PVR: Pulmonary vascular resistance, SVR: Systemic vascular resistance, NO: Nitrous oxide

Volatile anesthetics reduce hypoxic pulmonary vasoconstriction (HPV), thus decreasing ventilation-perfusion (V/Q) matching [49]. Volatile anesthetic agents can be administered without adverse effects on PVR. Minimum alveolar concentration values of below 1.0 are generally recommended to minimize myocardial depression. BIS monitoring can be helpful in evaluating the anesthetic depth.[46] All inhalation anesthetics reduce SVR by blocking ATP-dependent K^+ channels, causing vascular smooth muscle relaxation and eventually hypotension. Nitrous oxide should not be used due to increases in PVR [27,42,46,47,7]. Desflurane increases HPV, while isoflurane reduces the severity of HPV. Isoflurane and desflurane may reduce RV contractility in a dose-dependent manner with a rise in RV afterload [50].

Isoflurane and enflurane cause pulmonary vasodilation and inhibition of endothelium-dependent relaxation without prominent change in pulmonary circulation tonus. Sevoflurane causes a decrease in RV function and has a pulmonary vasodilation effect similar to isoflurane, which does not affect PVR. In PH patients, sevoflurane and isoflurane are generally preferred for induction and maintenance of anesthesia [51].

Extubation should be performed in patients with FiO_2 below 40% and appropriate ventilation parameters. In addition, deep or early extubation should be preferred to prevent sympathetic stimulation in these patients [27,46,47,7].

As a result, balanced anesthesia with opioids and low-dose volatile anesthetic agents is used for maintenance. Maintaining the balance between oxygen delivery and consumption during anesthesia and surgery is important [27,42,46]. In our clinic, etomidate and opioids are mostly used for anesthesia induction. We use remifentanil or dexmedetomidine, volatile agents (sevoflurane), and neuromuscular blockers (rocuronium and vecuronium) for anesthesia maintenance in these patients. We also use dexmedetomidine for anesthesia and sedation in patients who have epidural anesthesia.

RA techniques can help maintain spontaneous breathing and avoid high pulmonary artery pressure (PAP) and intrathoracic pressure caused by PPV [42].

Plexus blockades and peripheral nerve blocks are advantageous as they minimally affect hemodynamics, and have a high success rate and better postoperative pain control. Continuous RA methods are significant utilities for both intraoperative anesthesia and postoperative analgesia. When administering epidural analgesia, the concentration, dose, and volume of drugs should be fractionated and administered carefully, as they cause SVR, CPP reduction, and RVF [42,43]. In thoracic and abdominal surgery, the combined administration of GA and thoracic epidural anesthesia (TEA) is recommended to decrease the utilization of GA anesthetics and peri-operative opioid consumption. TEA has no adverse effect on oxygenation and PVR [43,44]. However, high-level epidural block (T1–T4) may cause a sympathetic blockade that alters cardiac inotropy and chronotropy. Epidural anesthesia and analgesia in patients with PH are associated with reduced arrhythmias, improved CO, better pain control, and reduced postoperative ileus.

Management of pulmonary hypertensive crisis: Factors such as hypotension, hypoxia, hypovolemia, hypervolemia, hypercarbia, respiratory or metabolic acidosis, hypothermia, raised intrathoracic pressure, and pain may cause major cardiopulmonary complications by increasing PVR [6,14,27,42,51]. In a PH crisis (e.g., increased PVR and PAP intraoperatively), the most critical point is to avoid increases in RV afterload and PVR. Maintaining RV contractility is crucial. Since calcium channel blockers reduce SVR, CO, and CPP, they may cause ischemia in the PH crisis. Decompensated RVF, cardiogenic shock, and even death may occur due to PH crisis [51] Hypothermia should be avoided as much as possible since it increases SVR, V/Q mismatch, HPV, shivering, energy consumption, and ultimately PAP to a significant extent. It is essential to maintain ventilation, oxygenation, systemic perfusion, and hemodynamics [Table 5] [14,32,34].

Management of hypotension: Sudden hypotension should be avoided during anesthesia scenarios [2,6,42]. Severe hypotension can worsen RV function in two ways: reducing CPP and ventricular interdependence [51,52]. As a result, perfusion deteriorates gradually and often manifests as cardiogenic shock together with ischemic events [6,14,27,51,52].

TTE or TEE is the gold standard in diagnosing and guiding treatment approaches in PH patients with hypotension because it provides detailed information about cardiac function and volume status [39]. Since these patients have poor tolerance to systemic hypotension, they should be treated with appropriate inotropes and/or vasopressors such as NE, vasopressin, phenylephrine, and dobutamine. Treatment with iNO, a synthetic analog of PGI_2, or inhaled vasodilators such as iloprost may be beneficial to prevent exacerbations. It does restore systemic BP and CPP [52]. The hemodynamic effects of drugs used in PH are given in Table 7 [52-58,7].

Vasopressin is a noncatecholamine agent that effectively restores SVR without increasing PVR, RV afterload, and tachyarrhythmias [53]. Since vasopressin induces coronary vasoconstriction at high doses (>0.08 U/min), the dose should be kept within a narrow range (0.01–0.08 U/min). Many authors recommend

vasopressin as the first agent to increase contractility and SVR, and to prevent hypotension for patients with PH in general and noncardiac surgery [53,54,7].

Pure α-agonists should not be given to prevent hypotension due to their negative effects on the pulmonary circulation. NE is usually preferred to phenylephrine in these patients [55,56]. Dobutamine is a synthetic β1-and β2-agonist with mild peripheral α-agonists activity. It protects SVR at lower and intermediate doses primarily by its chronotropic effect. It improves CO and reduces PVR. Since dobutamine also produces systemic vasodilation, it will potentiate the systemic vasodilation effect of anesthetics. Thus, NE having inotropic and vasopressor properties is more often preferred intraoperatively [57,58]. In our clinic, we use NE or vasopressin as the first choice in case of systemic hypotension.

Table 7. Drug's effects on hemodynamic parameters [7]

	CI	PVR	SVR	PVR/SVR	TSG
Inotropes					
Epinephrine	↑↑	↑	↑↑	↓	↑
Dobutamine	↑↑	↓	↓	↓	↓
Isoproterenol	↑	←	←	←	←
Dopamine*	↑↑	←/↑	↑	↑	←/↑
Inodilators					
Milrinone	↑↑	↓↓	↓↓	↓	↓↓
Levosimendan	↑↑	↓↓	↓↓	←/↓↓	↓↓
Vasopressors					
NE	↑	↑	↑	↑	←
Phenylephrine	↓	↑↑	↑↑	↑	←
Vasopressin	↓		↑↑	↓	←/↑
IV prostanoids					
PGI_2 (epoprostenol/flolan)	←	↓	↓	↓	↓

↑=Increased, ↓=Decreased, ←=No change, CI=Cardiac index, PVR=Pulmonary vascular resistance, SVR=Systemic vascular resistance, TSG=Transeptal gradient, PGI_2=Prostacyclin, NE=Norepinephrine

We use iNO, sildenafil, and milrinone frequently in our clinic in addition to these treatments when necessary. Extracorporeal membrane oxygenation (ECMO) can contribute cardiopulmonary support when acute RVF is refractory to medical therapy in the appropriate indication and clinical condition [41,52,59,7].

6. MANAGEMENT OF ARRHYTHMIAS

Although ventricular arrhythmias are infrequent, atrial flutter and AF are more common and can lead to right heart decompensation. In addition, these rhythm disturbances impair myocardial oxygenation, resulting in decreased RV compliance and diastolic dysfunction. As a result, systemic hypotension and RV ischemia may develop, worsening decompensation. Establishing and maintaining sinus rhythm in patients with Parkinson's disease is extremely important. The aim should be to rapidly provide normal sinus rhythm with cardioversion, ablation, or amiodarone in the preoperative period [59]. In cases where cardioversion or ablation are not suitable; calcium channel blockers, β-blockers, and amiodarone should be considered in the preoperative period [51,7].

We insist on maintaining normal sinus rhythm perioperatively whenever possible. We use amiodarone as the first agent for intraoperative arrhythmias. According to the patient's clinic, we also use β-blockers or calcium channel blockers.

Fluid management: Maintaining an optimal intravascular volume status in PH patients is important and difficult. Relative or true hypovolemia may develop when continuous fluid-blood losses are combined with the inflammatory response and prolonged losses to the third space from major surgery. In such surgeries, replacement should be done with appropriate fluids to ensure effective intravascular volume [51,52,7].

Since RV dysfunction is present in most PH cases, fluid overload and the development of RVF have to be considered. These may be difficult to detect clinically. Since large volumes of fluid infusion can cause RVF due to existing RV dysfunction and, indirectly, left ventricular (LV) dysfunction. Fluids should be given by analyzing dynamic parameters with CO monitoring. Cold liquids should be avoided as much as possible, as they may cause RV oxygen supply-consumption imbalance [6,27,51,59,7]. In major surgeries, patients with RVF poorly tolerate pericardial-pleural effusions due to excessive fluid shifts and blood loss impairing systemic perfusion and pressures. Thus, major surgeries result in increased mortality and morbidity in these populations [26,27].

Drug management: Vasodilator drugs frequently used in PH are iNO, prostanoids, PDE-3–5 inhibitors, and endothelin receptor antagonists (ERA) [51]. The effects and doses of vasodilator drugs are given in Table 8 [51,52,58-61]. The aim of treatment in PH is to reduce RV afterload and PVR. Inhaled pulmonary vasodilators are the most effective, accurate, and safe methods of restoring cardiac functions in PH [7].

- iNO (5–40 ppm continuously)
- Inhaled PGI_2 (nebulized or i.v. 2–20 μg/kg/min)
- Iloprost (5–10 mg, inhaled over 10 min, every 2–4 h or i.v. 1–3 ng/kg/min)
- Milrinone (25–50 μg/kg bolus, 0.5–0.75 μg/kg/min infusion)
- Sildenafil (0.25–0.5 mg/kg, every 4–8 h peroral, or i.v. 1.6 mg/kg/day)
- Nitroglycerine (i.v. 2–10 μg/kg/min)
- Sodium nitroprusside (0.2–0.3 μg/kg/min)
- Epoprostenol (10–50 ng/kg/min continuously) [52,56-61]

However, inhaled pulmonary vasodilator therapies have no effect on the chronic thromboembolic PH subtype [60,61].

In the treatment of PH, iNO is widely used in all periods [41]. iNO dilates pulmonary vascular smooth muscle by activating cyclic guanosine monophosphate (cGMP). Since iNO is rapidly inactivated by hemoglobin, it has no systemic vasodilator effect. iNO causes pulmonary vasodilation, reducing PVR, RV afterload, and PAP without affecting SVR [52]. Since iNO only reaches the alveoli involved in gas exchange, it improves the ventilation/perfusion balance by increasing pulmonary blood flow in these areas [62-64]. In addition, iNO significantly improves $ScvO_2$ and CO in critically ill patients with circulatory shock secondary to RVF [64,65]. However, its effects are short-term as it is rapidly degraded by cGMP-PDE [7]. Prostacyclin causes pulmonary vasodilation by activating cyclic adenosine monophosphate [64]. The effects of inhaled epoprostenol on hemodynamics and V/Q adjustment are similar to those of iNO. Furthermore, prostacyclins inhibit

platelet aggregation with vasodilatory effects. Pulmonary vasodilators should be used with caution in PH subtypes caused by pulmonary venous-occlusive disease, pulmonary vein stenosis, and LHD, as their use before the obstruction is resolved can lead to acute, life-threatening fatal outcomes [63]. Systemic vasodilators cause a significant decrease in RV perfusion pressure by vasodilating the pulmonary and systemic vasculature. ERAs produce vasodilation by antagonizing endothelin. Besides, they have anti-inflammatory effects and they reduce vascular smooth muscle proliferation [62,7] These drugs are effective in improving hemodynamics and exercise capacity. In our clinic, ERAs and PDE-5 inhibitors are prescribed orally by the cardiologists in the preoperative period in these patients. Since inhaled pulmonary vasodilators may cause rebound PH and RVF, dose adjustment and discontinuation should be made carefully [64,65].

Milrinone is a PDE-3 inhibitor with inodilator properties that improve LV and RV contractility, CO and it causes peripheral and pulmonary vasodilation. Co-administration of inotropic and/or vasopressors may be required to provide adequate mean arterial pressure (MAP) [41,52,7]. Drugs used to provide hemodynamic stability during anesthesia for patients with PH are given in Table 8 [7]. Vasopressin has minimal pulmonary vasoconstrictive effects. Concomitant use of milrinone and vasopressin in the intraoperative period is appropriate for preserving RV contractility, SVR, and reducing PVR [52,66]. Dobutamine can be used together with milrinone because it reduces PVR [41].

In our clinic, we continue i.v. pulmonary vasodilator therapy in the intraoperative period. In addition to this treatment, we use iNO and milrinone with NE or vasopressin. Inhaled pulmonary vasodilators may be administered through a high-flow nasal cannula, which may facilitate weaning and extubation [67,68]. Oral sildenafil and tadalafil of PDE-5 inhibitors potentiate the effect of inhaled pulmonary vasodilators [52]. They are effective in all types of PH, including LHD [69]. Unlike other systemic vasodilators, they do not worsen intrapulmonary shunt in chronic respiratory diseases [52,69-71]. PDE-5 inhibitors should be titrated slowly as they may cause systemic hypotension in the peri-operative and oral sildenafil with milrinone infusion postoperatively when necessary. Inotropics are often necessary to restore RV systolic function [52,7].

Despite all interventions, patients with severe PH may not improve their RV dysfunction and cardiogenic shock with severe deterioration of organ perfusion may occur. Maintaining systemic perfusion is the most critical goal. The most effective and fastest way is to initiate veno-arterial (VA)-ECMO [59]. It contributes to the improvement of oxygenation and ventilation, significantly reducing PVR [72]. This may allow time to supplement other therapies with respiratory and cardiac supports [7]. Furthermore, it is used as a bridge to transplantation in more critical situations [73]. We use VA-ECMO to prevent RVF and assist circulation when necessary.

Ventilation and oxygenation strategy: The optimization of ventilation and oxygenation is based on surgery type and anesthesia strategy. PPV worsens CO, [74], especially in the failing RV [75]. For adequate oxygenation, high FiO2 (0.6–1.0) is typically used to prevent hypoxic vasoconstriction. It is appropriate to start

with a tidal volume of 6 mL/kg and not to increase the peak airway pressures above 30 mmHg [14]. Alveolar overstrain should be avoided to prevent the increase in PVR. The RR should be adjusted to target $PaCO_2$ of 30–35 mmHg and $EtCO_2$ of 30–35 mmHg [7]. Since hypercarbia and acidosis can increase pulmonary vasoconstriction and worsen PH, adequate minute ventilation should be provided [14,27]. PEEP is set to 5–10 cmH O, ideally [27]. Adequate PEEP and recruitment maneuvers may contribute to the maintenance of V/Q matching. Higher PEEP levels can reduce preload and cause systemic hypotension. It may be required to increase FiO_2 rather than PEEP to improve oxygenation. In thoracic surgery, one-lung ventilation is avoided as much as possible because blood flow to the nonventilated lung decreases and the ventilation/perfusion ratio deteriorates, resulting in acute exacerbation of HPV-related PH [14,7].

In laparoscopic surgeries, pneumoperitoneum with insufflation reduces lung compliance and venous return due to increased intraabdominal pressure leading to the deterioration of oxygenation and hemodynamics. In addition, increased intraabdominal pressure and hypercarbia may trigger existing PH and lead to significant complications [14]. Therefore, close and careful monitoring is recommended to ensure mPAP <35, PVR/SVR ratio <0.5, MAP >65 mmHg, systolic pressure >90 mmHg, and CI >2.2 L/min/m^2 [6,14,27,52].

7. ANESTHESIA FOR PREGNANTS WITH PULMONARY HYPERTENSION

Changes occur in vital organs due to physiological, mechanical, and hormonal effects during pregnancy. These effects, in turn, are due to: (1) constrict of the nearby organs by enlargement of the uterus, (2) increment of relaxin peptide, which mediate the vasodilatory effects of hormonal changes by estrogen and progesterone and facilitate blood flow to critical organs, (3) increases in the systemic circulation [7]. PH makes significant changes in all systems (cardiovascular, respiratory, and hematologic) of pregnant woman [76] In pregnant with PH, the outcome is not good despite advanced treatments. Avoiding pregnancy as possible for these patients is recommended. Epoprostenol, treprostinil, nebulized iloprost, sildenafil, and iNO can be used in medical treatment. ERAs are contraindicated during pregnancy due to their teratogenic effects [76-78].

In these patients, elective cesarean section is usually recommended under epidural or low-dose combined spinal-epidural anesthesia at 34–36 weeks [77,78]. The target should be to maintain sufficient pain control while minimizing adverse effects. Early neuraxial analgesia (epidural, combined spinal-epidural) is recommended to reduce catecholamine-related cardiovascular stress due to labor pain. Controlled infusion analgesia or programmed intermittent bolus technique is preferred. The goal in normal labor is painless delivery without significant motor block [78,7]. Appropriate volume replacement and, if necessary, a vasopressor infusion can be used to minimize the vasodilator effects of spinal and/or epidural anesthesia. Most anesthesiologists choose a combined spinal-epidural approach. According to the literature, the maternal mortality rate has been reported to be similar in RA and GA (~20%) [77].

Table 8. Drugs used in the treatment of pulmonary hypertension [7]

	Mechanism	Treatment dose	Adverse effects
Prostanoid			
Epoprostenol	Pulmonary vasodilation	IV: 1-2 μg/h increase as tolerated with initial target 6 mL/h after 48-72h	Systemic hypotension, flushing, headache, diarrhea, leg and jaw pain
Iloprost	Pulmonary vasodilation	IV: 1-2 ηg/kg/min increase as tolerated with initial target 10 ηg/kg/min after 48-72 h	Systemic hypotension, flushing, headache, diarrhea, leg and jaw pain
NO pathway			
NO	Pulmonary vasodilation	Nebulized 5-80 ppm continuously	Rebound PH, methemoglobinemia
Inotropes			
Dobutamine	CI↑↑ PVR↓	IV: 2.5-20 μg/kg/min	Tachycardia Hypotension Tachyarrythmias
Dopamine	CI↑↑ PVR↔/↑ SVR↑	IV: 3-10 μg/kg/min	Tachycardia Hypotension Tachyarrythmias
Inodilators			
Milrinone	CI↑↑ PVR↓↓ SVR↓↓	IV: 50 μg/kg over 10 min. then 0.375- 0.75 μg/kg/min. Nebulized: 0.2- 0.3 mL/min.	Hypotension
Levosimendan	CI↑↑ PVR↓↓ SVR↓↓	6-12 μg/kg/min over 10 min. then 0.1 μg/kg/min infusion	Hypotension

	Mechanism	**Treatment dose**	**Adverse effects**
Vasopressors			
NE	CI↑	IV: 0.01-0.4 μg/kg/min	Bradycardia
	PVR↑		
	SVR↑		
Phenylephrine	CI↓	IV: 40-100 μg bolus, 50-300 μg/min	Bradycardia
	PVR↑↑		
	SVR↑↑		
Vasopressin	CI↓	IV: 0.001-0.004 U/min	Bradycardia
	SVR↑↑		

↑: Increased, ↓: Decreased, ↔ : No Change, CI: Cardiac index, PVR: Pulmonary vascular resistance, SVR: Systemic vascular resistance, IV: Intravenous, NO: Nitric oxide, NE: Norepinephrine

Comprehensive knowledge of pathophysiological changes in pregnancy and a multidisciplinary approach with related specialties are needed for better anesthetic management of pregnant with PH. Pregnant women have a higher risk of difficulty with airway and aspiration. Due to these risks and the variable cardiopulmonary balance in patients with PH, RA should be preferred to GA whenever possible. It is suggested that these patients are followed up in the ICU [7].

Both pregnancy and PH predispose to thrombosis [76-78]. The most common cause of mortality is RVF and PTE in the peripartum period. Pregnant women with PH undergoing RA have a high risk of hematoma, and care should be taken in the peripartum period [77,78]. We prefer epidural anesthesia to reduce sympathetic charge and control pain if surgery is not emergent.

8. POSTOPERATIVE CARE IN PULMONARY HYPERTENSION

The most risky period for PH patients undergoing noncardiac surgery is the postoperative period. These patients are followed up in postanesthesia care unit (PACU) and ICU for the first 48–72 h. Many patients with mild PH (mPAP <35 mmHg) undergoing low-risk and minor surgery can be effectively managed in the PACU. Appropriate management of these patients with a multidisciplinary approach perioperatively will reduce mortality and morbidity [79,80]. PACU staff should be given clear instructions regarding early physiological symptoms of deterioration and be thoroughly informed about who should be informed [80,81]. In our clinic, we follow the patients with mild PH in PACU for the first 24 h and those with moderate and severe PH in ICU for the first 48–72 h [7].

Patients with PH are at high risk of sudden increases in PVR, arrhythmias, fluid shifts, PTE, ischemia, respiratory failure, and RVF. The most common causes of mortality are respiratory failure (60%) and RVF (50%) [6,27,51,52,80,81].

As in acute respiratory distress syndrome, a protective ventilator strategy should be used for patients on mechanical ventilation [52]. Hypercarbia and acute respiratory acidosis may develop with a protective ventilation strategy, which may increase PVR. Therefore, the ventilator parameters must be adjusted accordingly. Hypoventilation and alveolar derecruitment may occur during spontaneous breathing trials [14,41,52]. Early mobilization and respiratory therapies are important to prevent atelectasis [52] To prevent hypoxemia, oxygen supplementation must be provided, and SpO_2 must be kept above 92% [52,79,81,82,7].

Post-operative atelectasis may increase RV afterload, impair the V/Q ratio, and increase intrapulmonary shunt. In addition, atelectasis may cause fever and thus increased metabolic rate, oxygen consumption, and eventually hypoxemia. Aggressive pulmonary toileting is important for all PH patients and should be started as early as possible. Spirometry, respiratory therapy, and if necessary, noninvasive PPV with low PEEP should be performed early [52,81,82].

Ensuring diuresis is critical in the postoperative period to prevent RV volume overload. Cardiac biomarkers such as Pro-BNP and troponin may be increased due to RV overload.

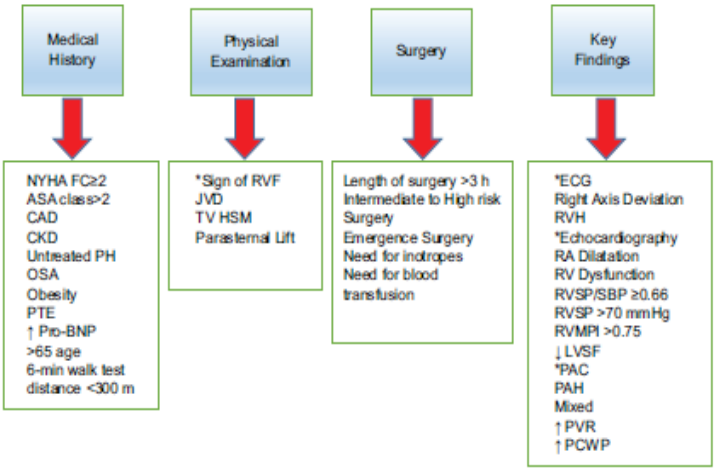

Fig. 3. Preoperative evaluation of the patient with pulmonary hypertension and identified risk factors. ASA=American society of anesthesiologist, CAD=Coronary artery disease, CKD=Chronic kidney disease, PCWP=Pulmonary capillary wedge pressure, JVD=Jugular venous distension, LVSF=Left ventricular systolic function, NYHA FC=New York Heart Association Functional Classification, OSA=Obstructive sleep apnea, PAH=Pulmonary arterial hypertension, PTE=Pulmonary thromboembolism, PH=Pulmonary hypertension, PVR=Pulmonary vascular resistance, RA=Right atrium, RVF=Right ventricular failure, RVH=Right ventricular hypertrophy, RVMPI=Right ventricular myocardial performance index, RVSP=Right ventricular systolic pressure, SBP=Systolic blood pressure, TVHSM=Tricuspid valve holosystolic murmur, ECG=Electrocardiographic, *=Indicates the presence of high risk in patients with PH [7]

These markers, together with perfusion markers such as lactate, $ScvO_2$ and SvO_2 may contribute to the adjustment of diuretic therapy [80,7] In patients with oliguric renal failure who do not respond to diuretic therapy, nephrology consultation is needed for continuous renal replacement therapy, and a decision should be made by common consensus [52,80-83].

Price et al. reviewed 13 clinical studies with adult PH, 8 with PH undergoing endoscopy, 16 reviews, and 5 case reports for patients undergoing GA or sedation for noncardiac and nonobstetric surgery. In these studies, 30-day mortality was 2%–18% and 15%–50% for elective surgeries and emergency surgery, respectively. The most critical complication was RVF. Moreover, they suggest that personalized preoperative risk evaluation, treatment optimization, and advanced perioperative planning may improve outcomes [84].

Finally, the most common causes of early mortality in patients with PH are respiratory failure, arrhythmia, and RVF [30,7] The incidence of surgery for any

reason in patients with previously treated or undiagnosed or diagnosed and incompletely treated PH continues to increase worldwide. Anesthesiologists need to recognize the symptoms and signs correctly in the preoperative evaluation to determine the safest anesthesia method and to manage the patient correctly in the peri-operative period, as it will reduce the risk of complications and death [3,6,14,24,27,30,41,52]. In our clinic, we have created a multidisciplinary team-based approach to evaluating patients with anesthesia. In our study, which is in progress in our clinic, we evaluate the postoperative follow-up, important risk factors, and first 30-day complications in the postoperative period, mortality and morbidity of previously diagnosed patients with PH.

9. CONCLUSION

Management of patients with PH peri-operatively requires knowledge and experience. It is necessary to discuss the patient's short and long-term care goals, potential difficulties, and complications with a multidisciplinary team. The main goals in anesthesia management are understanding the main pathophysiology, optimizing functional status and hemodynamics, managing comorbidities, and avoiding PH crisis and RVF [7]. A balanced anesthesia technique, including inhalation agents, appropriate RA, and opioids may provide these patients steady hemodynamic profile. In PH patients, advanced intraoperative and postoperative follow-up, pulmonary vasodilator treatments, adequate anesthesia, and analgesia should be considered. It is essential to optimize the patient for surgery in a nonemergency situation and to organize treatment and education of the patient for the long-term period of the disease.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

We declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators were used during the writing or editing of this post.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. Author NÇ came up with the concept, designed the study and supervised the manuscript. Authors NC and BNG collected, analyzed and interpreted the data. Both authors participated in the manuscript preparation and have given final approval for the current version to be published. Both authors read and approved the final manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Fukuda K, Date H, Doi S, Fukumoto Y, Fukushima N, Hatano M, Tsutsui H. Guidelines for the treatment of pulmonary hypertension (JCS 2017/JPCPHS 2017). Circulation Journal. 2019;83(4):842-945.

2. Rosenkranz S, Howard LS, Gomberg-Maitland M, Hoeper MM. Systemic consequences of pulmonary hypertension and right-sided heart failure. Circulation. 2020;141:678-93.
3. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37:67-119.
4. Cullivan S, Gaine S, Sitbon O. New trends in pulmonary hypertension. European Respiratory Review. 2023;32(167).
5. Johnson S, Sommer N, Cox-Flaherty K, Weissmann N. Pulmonary hypertension: A contemporary review. American Journal of Respiratory and Critical Care Medicine. 2023;208(5):528-548.
6. Pilkington SA, Taboada D, Martinez G. Pulmonary hypertension and its management in patients undergoing non-cardiac surgery. Anaesthesia. 2015;70:56-70.
7. Çekmen N, Gökdemir BN. Anesthesia and pulmonary hypertension: A Narrative review. Heart and Mind. 2024;8(2):60-73.
8. Lau EM, Giannoulatou E, Celermajer DS, Humbert M. Epidemiology and treatment of pulmonary arterial hypertension. Nat Rev Cardiol. 2017;14:603-14.
9. Hoeper MM, Humbert M, Souza R, Idrees M, Kawut SM, Sliwa-Hahnle K, et al. A global view of pulmonary hypertension. Lancet Respir Med. 2016;4:306-22.
10. Beshay S, Sahay S, Humbert M. Evaluation and management of pulmonary arterial hypertension. Respir Med. 2020;171:106099.
11. Hirani N, Brunner NW, Kapasi A, Chandy G, Rudski L, Paterson I, et al. Canadian Cardiovascular Society/Canadian Thoracic Society position statement on pulmonary hypertension. Can J Cardiol. 2020;36:977-92.
12. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53:1801913.
13. Kovacs G, Dumitrescu D, Barner A, Greiner S, Grünig E, Hager A, et al. Definition, clinical classification and initial diagnosis of pulmonary hypertension: Updated recommendations from the Cologne Consensus Conference 2018. Int J Cardiol. 2018;272S:11-9.
14. Minai OA, Yared JP, Kaw R, Subramaniam K, Hill NS. Perioperative risk and management in patients with pulmonary hypertension. Chest. 2013;144:329-40.
15. Steppan J, Diaz-Rodriguez N, Barodka VM, Nyhan D, Pullins E, Housten T, et al. Focused review of perioperative care of patients with pulmonary hypertension and proposal of a perioperative pathway. Cureus. 2018;10:e2072.

16. Bourgeois A, Omura J, Habbout K, Bonnet S, Boucherat O. Pulmonary arterial hypertension: New pathophysiological insights and emerging therapeutic targets. Int J Biochem Cell Biol. 2018;104:9-13.
17. Humbert M, Guignabert C, Bonnet S, Dorfmüller P, Klinger JR, Nicolls MR, et al. Pathology and pathobiology of pulmonary hypertension: State of the art and research perspectives. Eur Respir J. 2019;53:1801887.
18. Morrell NW, Aldred MA, Chung WK, Elliott CG, Nichols WC, Soubrier F, et al. Genetics and genomics of pulmonary arterial hypertension. Eur Respir J. 2019;53:1801899.
19. Vonk Noordegraaf A, Chin KM, Haddad F, Hassoun PM, Hemnes AR, Hopkins SR, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: An update. Eur Respir J. 2019;53:1801900.
20. Soubrier F, Chung WK, Machado R, Grünig E, Aldred M, Geraci M, et al. Genetics and genomics of pulmonary arterial hypertension. J Am Coll Cardiol. 2013;62:D13-21.
21. Prins KW, Thenappan T. World Health Organization Group I pulmonary hypertension: Epidemiology and pathophysiology. Cardiol Clin. 2016;34:363-74.
22. Strumpher J, Jacobsohn E. Pulmonary hypertension and right ventricular dysfunction: Physiology and perioperative management. J Cardiothorac Vasc Anesth. 2011;25:687-704.
23. Hrymak C, Strumpher J, Jacobsohn E. Acute right ventricle failure in the Intensive Care Unit: Assessment and management. Can J Cardiol. 2017;33:61-71.
24. Rodseth RN, Biccard BM, Chu R, Lurati Buse GA, Thabane L, Bakhai A, et al. Postoperative B-type natriuretic peptide for prediction of major cardiac events in patients undergoing noncardiac surgery: Systematic review and individual patient meta-analysis. Anesthesiology. 2013;119:270-83.
25. Sarkar MS, Desai PM. Pulmonary hypertension and cardiac anesthesia: Anesthesiologist's perspective. Ann Card Anaesth. 2018;21:116-22.
26. Raymond RJ, Hinderliter AL, Willis PW, Ralph D, Caldwell EJ, Williams W, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. J Am Coll Cardiol. 2002;39:1214-9.
27. McGlothlin D, Ivascu N, Heerdt PM. Anesthesia and pulmonary hypertension. Prog Cardiovasc Dis. 2012;55:199-217.
28. Moceri P, Baudouy D, Chiche O, Cerboni P, Bouvier P, Chaussade C, et al. Imaging in pulmonary hypertension: Focus on the role of echocardiography. Arch Cardiovasc Dis. 2014;107:261-71.
29. Hosseinian L. Pulmonary hypertension and noncardiac surgery: Implications for the anesthesiologist. J Cardiothorac Vasc Anesth. 2014;28:1064 74.
30. Ramakrishna G, Sprung J, Ravi BS, Chandrasekaran K, McGoon MD. Impact of pulmonary hypertension on the outcomes of noncardiac surgery: Predictors of perioperative morbidity and mortality. J Am Coll Cardiol. 2005;45:1691-9.

31. Blaise G, Langleben D, Hubert B. Pulmonary arterial hypertension: Pathophysiology and anesthetic approach. Anesthesiology. 2003;99:1415-32.
32. Ortega R, Connor CW. Intraoperative management of patients with pulmonary hypertension. Adv Pulm Hypertens. 2013;12:18-23.
33. Subramaniam K, Yared JP. Management of pulmonary hypertension in the operating room. Semin Cardiothorac Vasc Anesth. 2007;11:119-36.
34. Adler AC, Sharma R, Higgins T, McGee WT. Hemodynamic assessment and monitoring in the İntensive Care Unit: An overview. J Anesth Crit Care Med. 2014;1:010.
35. Eldendy MA, Esmat IM, Kassim DY. The outcome of intraoperative goal-directed therapy using Vigileo/FloTrac in high-risk patients scheduled for major abdominal surgeries: A prospective randomized trial. Egypt J Anesth. 2017;33:263-9.
36. Jeong DM, Ahn HJ, Park HW, Yang M, Kim JA, Park J. Stroke volume variation and pulse pressure variation are not useful for predicting fluid responsiveness in thoracic surgery. Anesth Analg. 2017;125:1158-65.
37. Shin CH, Long DR, McLean D, Grabitz SD, Ladha K, Timm FP, et al. Effects of intraoperative fluid management on postoperative outcomes: A hospital registry study. Ann Surg. 2018;267:1084 92.
38. Evans DC, Doraiswamy VA, Prosciak MP, Silviera M, Seamon MJ, Rodriguez Funes V, et al. Complications associated with pulmonary artery catheters: A comprehensive clinical review. Scand J Surg. 2009;98:199-208.
39. Ashes C, Roscoe A. Transesophageal echocardiography in thoracic anesthesia: Pulmonary hypertension and right ventricular function. Curr Opin Anaesthesiol. 2015;28:38-44.
40. Green JB, Hart B, Cornett EM, Kaye AD, Salehi A, Fox CJ. Pulmonary vasodilators and anesthesia considerations. Anesthesiol Clin. 2017;35:221-32.
41. Gille J, Seyfarth HJ, Gerlach S, Malcharek M, Czeslick E, Sablotzki A. Perioperative anesthesiological management of patients with pulmonary hypertension. Anesthesiol Res Pract. 2012;2012:356982.
42. Pritts CD, Pearl RG. Anesthesia for patients with pulmonary hypertension. Curr Opin Anaesthesiol. 2010;23:411-6.
43. Preckel B, Eberl S, Fräßdorf J, Hollmann MW. Management of patients with pulmonary hypertension. Anaesthesist. 2012;61:574-7, 580-7.
44. Veering BT, Cousins MJ. Cardiovascular and pulmonary effects of epidural anaesthesia. Anaesth Intensive Care. 2000;28:620-35.
45. Yang EI. Perioperative management of patients with pulmonary hypertension for non-cardiac surgery. Curr Rheumatol Rep. 2015;17:15.
46. Rich GF, Roos CM, Anderson SM, Daugherty MO, Uncles DR. Direct effects of intravenous anesthetics on pulmonary vascular resistance in the isolated rat lung. Anesth Analg. 1994;78:961-6.
47. Salehi A. Pulmonary hypertension: A review of pathophysiology and anesthetic management. Am J Ther. 2012;19:377-83.

48. Nathan AT, Marino BS, Hanna B, Nicolson SC. Novel use of dexmedetomidine in a patient with pulmonary hypertension. Paediatr Anaesth. 2008;18:782-4.
49. Kerbaul F, Bellezza M, Mekkaoui C, Feier H, Guidon C, Gouvernet J, et al. Sevoflurane alters right ventricular performance but not pulmonary vascular resistance in acutely instrumented anesthetized pigs. J Cardiothorac Vasc Anesth. 2006;20:209-16.
50. Kerbaul F, Rondelet B, Motte S, Fesler P, Hubloue I, Ewalenko P, et al. Isoflurane and desflurane impair right ventricular-pulmonary arterial coupling in dogs. Anesthesiology. 2004;101:1357-62.
51. Olsson KM, Halank M, Egenlauf B, Fistera D, Gall H, Kaehler C, et al. Decompensated right heart failure, intensive care and perioperative management in patients with pulmonary hypertension: Updated recommendations from the Cologne Consensus Conference 2018. Int J Cardiol. 2018;272S: 46-52.
52. Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ. Pulmonary vascular and right ventricular dysfunction in adult critical care: Current and emerging options for management: A systematic literature review. Crit Care. 2010;14:R169.
53. Tayama E, Ueda T, Shojima T, Akasu K, Oda T, Fukunaga S, et al. Arginine vasopressin is an ideal drug after cardiac surgery for the management of low systemic vascular resistant hypotension concomitant with pulmonary hypertension. Interact Cardiovasc Thorac Surg. 2007;6:715-9.
54. Walker BR, Childs ME, Adams EM. Direct cardiac effects of vasopressin: Role of V1- and V2-vasopressinergic receptors. Am J Physiol. 1988;255:H261-5.
55. Wang M, Shibamoto T, Kuda Y, Tanida M, Kurata Y. Systemic vasoconstriction modulates the responses of pulmonary vasculature and airway to vasoconstrictors in anesthetized rats. Exp Lung Res. 2015;41:324-34.
56. Kwak YL, Lee CS, Park YH, Hong YW. The effect of phenylephrine and norepinephrine in patients with chronic pulmonary hypertension. Anaesthesia. 2002;57:9-14.
57. Kerbaul F, Rondelet B, Motte S, Fesler P, Hubloue I, Ewalenko P, et al. Effects of norepinephrine and dobutamine on pressure load-induced right ventricular failure. Crit Care Med. 2004;32:1035-40.
58. Lahm T, McCaslin CA, Wozniak TC, Ghumman W, Fadl YY, Obeidat OS, et al. Medical and surgical treatment of acute right ventricular failure. J Am Coll Cardiol. 2010;56:1435-46.
59. Hoeper MM, Granton J. Intensive Care Unit management of patients with severe pulmonary hypertension and right heart failure. Am J Respir Crit Care Med. 2011;184:1114-24.
60. Steudel W, Hurford WE, Zapol WM. Inhaled nitric oxide: Basic biology and clinical applications. Anesthesiology. 1999;91:1090-121.
61. Lowson SM, Doctor A, Walsh BK, Doorley PA. Inhaled prostacyclin for the treatment of pulmonary hypertension after cardiac surgery. Crit Care Med. 2002;30:2762-4.

62. Seferian A, Simonneau G. Therapies for pulmonary arterial hypertension: Where are we today, where do we go tomorrow? Eur Respir Rev. 2013;22:217-26.
63. Calcaianu G, Calcaianu M, Canuet M, Enache I, Kessler R. Withdrawal of long-term epoprostenol therapy in pulmonary arterial hypertension (PAH). Pulm Circ. 2017;7:439-47.
64. Thunberg CA, Morozowich ST, Ramakrishna H. Inhaled therapy for the management of perioperative pulmonary hypertension. Ann Card Anaesth. 2015;18:394-402.
65. Augoustides JG, Ochroch EA. Inhaled selective pulmonary vasodilators. Int Anesthesiol Clin. 2005;43:101-14.
66. Currigan DA, Hughes RJ, Wright CE, Angus JA, Soeding PF. Vasoconstrictor responses to vasopressor agents in human pulmonary and radial arteries: An *in vitro* study. Anesthesiology. 2014;121:930-6.
67. Nair J, Orie J, Lakshminrusimha S. Successful treatment of a neonate with idiopathic persistent pulmonary hypertension with inhaled nitric oxide via nasal cannula without mechanical ventilation. AJP Rep. 2012;2:29 32.
68. Miller K, Misselbeck TS, Ebert BA, editors. The utilization of high-flow oxygen to administer inhaled pulmonary vasodilators in post-operative left ventricular assists the patient population in facilitating extubation. Tampa (FL): AARC International Congress; 2015.
69. Jiang R, Wang L, Zhu CT, Yuan P, Pudasaini B, Zhao QH, et al. Comparative effectiveness of sildenafil for pulmonary hypertension due to left heart disease with HFrEF. Hypertens Res 2015;38:829-39.
70. Barnes H, Brown Z, Burns A, Williams T. Phosphodiesterase 5 inhibitors for pulmonary hypertension. Cochrane Database Syst Rev 2019;1:CD012621.
71. Taichman DB, Ornelas J, Chung L, Klinger JR, Lewis S, Mandel J, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. Chest. 2014;146:449-75.
72. Ventetuolo CE, Klinger JR. Management of acute right ventricular failure in the Intensive Care Unit. Ann Am Thorac Soc. 2014;11:811 22.
73. Biscotti M, Vail E, Cook KE, Kachulis B, Rosenzweig EB, Bacchetta M. Extracorporeal membrane oxygenation with subclavian artery cannulation in awake patients with pulmonary hypertension. ASAIO J. 2014;60:748-50.
74. Kyhl K, Ahtarovski KA, Iversen K, Thomsen C, Vejlstrup N, Engstrøm T, et al. The decrease of cardiac chamber volumes and output during positive-pressure ventilation. Am J Physiol Heart Circ Physiol. 2013;305:H1004-9.
75. Morris K, Beghetti M, Petros A, Adatia I, Bohn D. Comparison of hyperventilation and inhaled nitric oxide for pulmonary hypertension after repair of congenital heart disease. Crit Care Med. 2000;28:2974-8.
76. Hemnes AR, Kiely DG, Cockrill BA, Safdar Z, Wilson VJ, Al Hazmi M, et al. Statement on pregnancy in pulmonary hypertension from the Pulmonary Vascular Research Institute. Pulm Circ. 2015;5:435-65.
77. Jaïs X, Olsson KM, Barbera JA, Blanco I, Torbicki A, Peacock A, et al. Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. Eur Respir J. 2012;40:881-5.
78. Leffert L, Butwick A, Carvalho B, Arendt K, Bates SM, Friedman A, et al. The Society for Obstetric Anesthesia and Perinatology Consensus

Statement on the anesthetic management of pregnant and postpartum women receiving thromboprophylaxis or higher dose anticoagulants. Anesth Analg. 2018;126:928-44.
79. Hristovska AM, Duch P, Allingstrup M, Afshari A. The comparative efficacy and safety of sugammadex and neostigmine in reversing neuromuscular blockade in adults. A Cochrane systematic review with meta-analysis and trial sequential analysis. Anaesthesia. 2018;73:631-41.
80. Díaz-Gómez JL, Ripoll JG, Mira-Avendano I, Moss JE, Divertie GD, Frank RD, et al. Multidisciplinary perioperative management of pulmonary arterial hypertension in patients undergoing noncardiac surgery. South Med J. 2018;111:64-73.
81. Galiè N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. Eur Respir J. 2019;53: 1802148.
82. Aguirre MA, Lynch I, Hardman B. Perioperative management of pulmonary hypertension and right ventricular failure during noncardiac surgery. Adv Anesth. 2018;36:201-30.
83. Lai HC, Lai HC, Wang KY, Lee WL, Ting CT, Liu TJ. Severe pulmonary hypertension complicates postoperative outcome of non-cardiac surgery. Br J Anaesth. 2007;99:184-90.
84. Price LC, Martinez G, Brame A, Pickworth T, Samaranayake C, Alexander D, et al. Perioperative management of patients with pulmonary hypertension undergoing non-cardiothoracic, non-obstetric surgery: A systematic review and expert consensus statement. Br J Anaesth. 2021;126:774-90.

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