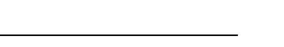

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REVIEW ARTICLE

Big data and RCT's in surgical oncology: Impact on improving hepatopancreatobiliary cancer surgical care on the global stage

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Abstract

Randomized controlled clinical trials (RCTs) are at the heart of "evidence-based" medicine. Conducting well-designed RCTs for surgical procedures is often challenged by inadequate recruitment accrual, blinding, or standardization of the surgical procedure, as well as lack of funding and evolution of the treatment strategy during the many years over which such trials are conducted. In addition, most clinical trials are performed in academic high-volume centers with highly selected patients, which may not necessarily reflect a "real-world" practice setting. Large databases provide easy and inexpensive access to data on a large and diverse patient population at a variety of treatment centers. Furthermore, large database studies provide the opportunity to answer questions that would be impossible or very arduous to answer using RCTs, including questions regarding health policy efficacy, trends in surgical practice, access to health care, the impact of hospital volume, and adherence to practice guidelines, as well as research questions regarding rare disease, infrequent surgical outcomes, and specific subpopulations. Prospective data registries may also allow for quality benchmarking and auditing. There are several high-quality RCTs providing evidence to support current practices in hepatopancreatobiliary (HPB) oncology. Evidence from big data bridges the gap in several instances where RCTs are lacking. In this article, we review the evidence from RCTs and big data in HPB oncology identify the existing lacunae, and discuss the future directions of research in HPB oncology.

KEYWORDS

big data, hepatobiliary surgery, large database studies, randomized clinical trials, surgical oncology

1 | INTRODUCTION

Evidence-based medicine has been the guiding philosophy of modern medicine since the introduction of the concept in the early 1990s.[1,2] It encourages clinicians to make clinical decisions while evaluating the external evidence available and individualizing it to each of their patient's needs and expectations using their clinical experience and judgment. The evidence pyramid describes levels of evidence based on the robustness and reliability of data generated by each type of evidence, with randomized controlled trials (RCTs) and meta-analyses considered to provide evidence of the highest level.[3] However, despite the robust quality of data that stands to be generated, poor patient accrual, difficulties in standardizing surgical interventions, relative lack of accrual to the control arm, underrepresentation of ethnic minorities, escalating costs, industry influence, prolonged study duration, rapidly changing treatment paradigms, diminishing

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relevance of results over time, and multiple sources of bias are only few of the challenges one encounters while conducting RCTs, especially in the context of surgical oncology, which limits the number of RCTs reaching a successful conclusion or publication.[4–8] Consequently, the number of new surgical RCTs conducted has been slowly dwindling over the last few decades.[9,10]

To overcome the pitfalls of surgical RCTs, there has been a growing interest in alternative research methodologies, such as the use of large database studies, or big data analytics.[11,12] Large-scale data obtained from health records, cancer registries, image libraries, wearable technology, patient portals, and multiple other sources has the potential to unlock important insights into surgical treatments of cancer and their outcomes that are difficult to be tested or are incompletely answered by RCTs.[12,13] This "Real world data" enables the assessment of interventions as observed in a real-life environment as opposed to the controlled environment of a trial. Moreover, big data can generate answers to questions much faster contrary to RCTs. However, evidence derived from big data also has its drawbacks; limitations in study design, higher potential for type I error, bias, coding errors, and missing data to name a few.[14,15]

At present, information derived from RCTs and big data is used in a complementary fashion to maximize evidence-based practice not only to improve patient care but also to guide healthcare policy decisions. This article reviews the contributions of RCTs and big data to the existing evidence available for decision-making in hepatopancreatobiliary (HPB) cancer care and identifies any lacunae that remain in a variety of clinical scenarios.

2 | PANCREAS

2.1 | Laparoscopic pancreatoduodenectomy (PD)

The LEOPARD-2 trial was a phase II/III RCT that provided conclusive evidence that laparoscopic PD was associated with higher complication-related deaths with no difference in time to functional recovery.[16] A meta-analysis of three RCTs by Nickel et al. showed no advantage of laparoscopic PD over open PD.[17] A more recent meta-analysis of 10 retrospective studies comprising 11,535 patients by Feng et al. concluded that laparoscopic PD was a safe and feasible alternative to open PD for pancreatic cancer with comparable overall survival (OS).[18]

2.2 | Surgical approaches for resection of pancreatic cancer

2.2.1 | Superior mesenteric artery (SMA)-first approach

The SMA-first approach has a sound theoretical basis with several techniques described in the literature. However, the majority of the evidence regarding the efficacy and safety of the SMA-first approach exists in the form of non-randomized studies, with only a single RCT published in the literature. The safety and feasibility of the uncinate-first approach to the SMA were demonstrated by Shrikhande et al.[19] Six different SMA-first approaches have been described in detail by Sanjay et al. in a comprehensive review of the literature.[20] Sabater et al. found no difference in R-0 resection rates or postoperative complications between a standard and artery-first approach in a multicenter RCT.[21] A systematic review and meta-analysis of 1 RCT and 13 nonrandomized comparative studies comprising a total of 1154 patients by Negoi et al. reported better perioperative outcomes and lower recurrence rate with an artery-first compared to a standard PD.[22] Another meta-analysis of 1 RCT and 16 nonrandomized comparative studies comprising a total of 1472 patients reported that the SMA-first approach may be associated with better perioperative outcomes and better long-term survival.[23] Based on the complementary evidence provided by big data analytics, the SMA-first approach is practiced as the preferred approach in several high-volume centers worldwide.

2.2.2 | Resection of locally advanced pancreatic cancer

Several techniques have been described for the resection of locally advanced pancreatic cancers encasing critical arterial structures. Inoue et al. described the safety and feasibility of systematic mesopancreas dissection with an SMA-first approach.[24] Diener et al. described the feasibility of periadventitial arterial divestment as an alternative to arterial resection in advanced pancreatic cancer.[25] Cai et al. described the technique of subadventitial arterial divestment for arterial preservation in advanced pancreatic cancer.[26] However, the evidence for these procedures is limited and is a potential area where big data analytics can make a valuable contribution in providing the evidence required to justify the propagation of these techniques.

2.3 | Risk mitigation strategies in PD

PD is a procedure associated with high postoperative morbidity, and over the years, several studies have focussed on evaluating mitigation strategies to reduce complications such as postpancreatectomy hemorrhage (PPH), postoperative pancreatic fistula (POPF) and infective complications. The majority of the evidence in this regard is available in the form of well conducted RCTs, along with complementary findings available from big data.

The recently published PANDA trial reported reduced rates of PPH with the "falciform wrap" technique.[27] A recent RCT demonstrated that the use of a polyethylene glycol-coated hemostatic patch reduced the risk of a clinically relevant postoperative pancreatic fistula (CR-POPF) by 90%.[28] A large National Surgical Quality Improvement Program analysis of 7583 patients showed that routine placement of surgical drains decreased postoperative complications but prolonged drainage was associated with increased

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complications.[29] A randomized trial by Ke et al. showed no difference in POPF rates between conventional limb reconstruction and Roux-en-Y reconstruction with an isolated pancreatic limb after a pancreatoduonectomy.[30] A systematic review and meta-analysis of two randomized trials and four nonrandomized studies comprising 712 patients also reported similar results with no difference between a conventional and Roux-en-Y reconstruction.[31] Two recent meta-analyses concluded that immunonutrition reduced infectious complications and length of stay after a PD.[32,33] The PANasta trial represents the most robust analysis comparing two different techniques of pancreato-jejunal anastomosis and reported no difference between the Blumgart and Cattel-Warren techniques.[34] Ellis et al. have recently published the results of a robust RCT demonstrating a significant reduction in rates of CR-POPF and surgical site infections by implementing piperacillin-tazobactam in perioperative antibiotic prophylaxis for patients undergoing a PD.[35]

2.4 | Adjuvant therapy in pancreatic cancer

The PRODIGE-24 trial conclusively demonstrated the superiority of FOLFIRINOX over Gemcitabine and is now the accepted standard for adjuvant chemotherapy in pancreatic cancer.[36] The contribution of big data analytics in this regard was provided by Valle et al. who provided an understanding of real-world data and showed that only 68% of patients in the ESPAC-3 study completed all six cycles of adjuvant chemotherapy and that completion of all six cycles was associated with a survival benefit.[37]

2.5 | Neoadjuvant therapy in pancreatic cancer

Large-scale evidence generated from RCTs is lacking for neoadjuvant chemotherapy (NACT) in borderline resectable pancreatic cancer (BRPC); however, that gap is bridged by ample evidence accumulated from big data analytics. Similarly, the majority of the evidence regarding the addition of radiation to NACT as well as the role of neoadjuvant therapy in resectable pancreatic cancer is provided by big data, with few large RCTs in the literature (Table 1).

Chaudhari et al. published their retrospective analysis of the efficacy of neoadjuvant therapy in BRPC and reported a higher R-0 resection rate as well as superior OS with neoadjuvant therapy compared to upfront resection.[40] A systematic review and meta-analysis of 8 prospective and 16 retrospective studies evaluating the efficacy of neoadjuvant FOLFIRINOX in BRPC reported favorable R-0 resection rates as well as OS.[41]

The results of the ALLIANCE A021501 phase II randomized trial showed no survival benefit of the addition of hypofractionated radiation to neoadjuvant FOLFIRINOX in BRPC.[38] The recently published PREOPANC trial shed light on the role of neoadjuvant chemoradiation in resectable and BRPC and showed improved R-0 resection rates and disease-free survival (DFS); however, no OS benefit was reported.[39]

A large meta-analysis of 39 studies comprising 1458 patients evaluated the role of neoadjuvant therapy in pancreatic cancer and concluded that neoadjuvant therapy was not beneficial in resectable pancreatic cancer, but provides a survival benefit in borderline resectable and locally advanced pancreatic cancer.[42] Mokdad et al. have reported the results of a propensity-matched analysis of the efficacy of neoadjuvant therapy in 15 237 patients of resectable pancreatic cancer from the National Cancer Database (NCDB). This study reported a significant survival benefit in favor of neoadjuvant therapy compared to upfront surgery in resectable pancreatic cancer.[43]

The evidence for neoadjuvant therapy in locally advanced pancreatic cancer is entirely derived from big data, with no phase III RCT reported in the literature. However, due to the high quality of the data, neoadjuvant therapy and total neoadjuvant therapy strategies have come to be adopted as standard-of-care for locally advanced pancreatic cancers.

Murphy et al. reported an R-0 resection rate of 61% with a total neoadjuvant therapy approach with the FOLFIRINOX regimen in locally advanced pancreatic cancer in a single-arm phase II clinical trial.[44] Truty et al. in their analysis of 194 patients of borderline resectable and locally advanced pancreatic cancer demonstrated the efficacy of the total neoadjuvant therapy approach and identified ≥6 chemotherapy cycles, optimal postchemotherapy CA 19–9 response, and a major pathologic response as prognosticators for long-term survival.[45] A large NCDB analysis of 5402 patients of borderline resectable and locally advanced pancreatic cancer by Barrak et al. reported a higher pathologic complete response (pCR) rate with a total neoadjuvant therapy approach compared to other strategies of neoadjuvant therapy. A pCR was also associated with a significantly longer OS in this study.[46]

3 | LIVER

3.1 | Treatment modalities for hepatocellular carcinoma (HCC)

There is no RCT to date to compare outcomes of resection to liver transplantation for HCC, with all the evidence provided by big data. Menahem et al. have published a meta-analysis of nine studies with a total of 570 patients undergoing resection and 861 patients undergoing a liver transplant for HCC. They reported an OS benefit only after 10 years for tumors within the Milan criteria undergoing liver transplantation compared to resection, however, a DFS benefit was seen after 3 years in the liver transplantation group.[47]

There is ample evidence provided by RCTs as well as big data comparing various techniques for the ablation of HCCs. Tan et al. published their results of a meta-analysis including four RCTs and 10 cohort studies comparing the efficacy of radiofrequency ablation (RFA) to microwave ablation (MWA) in HCC. This study demonstrated an equivalent therapeutic effect of MWA compared to RFA, but was unable to demonstrate the superiority of MWA.[48]

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TABLE 1 Evidence from randomized clinical trials and big data in HPB oncology.

Clinical scenario	Evidence from RCTs	Evidence from big data	Comments
Laparoscopic pancreatoduodenectomy	LEOPARD-2 trial[16] Nickel et al.—meta-analysis of RCTs[17]	Feng et al.—meta-analysis[18]	Adequate evidence shows that although safe and feasible in competent hands, laparoscopic resection offers no advantage over open surgery.
SMA-first approach	Sabater et al.[21]	Shrikhande et al.[19] Sanjay et al.[20] Negoi et al.—meta-analysis[22] Ironside et al.—meta-analysis[23]	Adequate evidence from big data to adopt the SMA-first approach as a standard of care.
Locally advanced pancreatic cancer: Surgery	-	Inoue et al.—systemic mesopancreas dissection[24] Diener et al.—periadventitial divestment[25] Cai et al.—subadventitial divestment[26]	Evaluation of complex surgical techniques in an RCT is difficult. More evidence from big data can generate additional evidence regarding these techniques.
Risk mitigating strategies in pancreatic surgery	PANDA trial- falciform wrap[27] Martín et al.—hemostatic patch[28] Ke at al- isolated pancreatic limb[30] Halloran et al.—PJ anastomosis technique[34] Ellis et al.—antibiotic prophylaxis[35]	Addison et al.—drain placement[29] Deng et al.—isolated pancreatic limb[31] Fan et al.—immunonutrition meta-analysis[32] Ricci et al.—meta-analysis[33]	Adequate large-scale data from RCTs and big data supporting various risk-mitigation strategies. Focussed studies on high-risk populations are required.
Adjuvant therapy in pancreatic cancer	PRODIGE-24 trial—mFOLFIRINOX[36]	Valle et al.—duration of chemotherapy[37]	Robust evidence in support of adjuvant FOLFIRINOX. Additional studies focus on the personalization of chemotherapy.
Neoadjuvant therapy in resectable and borderline resectable pancreatic cancer (BRPC)	ALLIANCE 021501 trial—SBRT in BRPC[38] PREOPANC trial—NACT-RT in resectable and BRPC[39]	Chaudhari et al.—NACT in BRPC[40] Janssen et al.—NACT in BRPC- meta-analysis[41] Zhan et al.—NACT in pancreatic cancer[42] Mokadad et al.—NACT in resectable pancreatic cancer[43]	Adequate evidence for NACT in BRPC. The role of NACT in resectable pancreatic cancer is unclear and requires RCT evidence to be adopted as standard-of-care.
Total neoadjuvant therapy (TNT) approach in locally advanced pancreatic cancer	–	Murphy et al.—phase II single-arm trial- TNT approach in LAPC[44] Truty et al.—TNT approach in BRPC and LAPC[45] Barrak et al.—TNT approach and pCR[46]	Adequate evidence from big data to adopt the TNT approach as standard-of-care in LAPC.
HCC: Role of liver transplantation	–	Menahem et al.—meta-analysis[47]	Adequate evidence for liver transplant in well-selected patient population. Expanded indications require a larger RCT.
HCC: MWA vs. RFA		Tan et al.[48]—meta-analysis of 4 RCTs and 10 cohort studies	Adequate evidence from RCTs and big data to show MWA is not superior to RFA.
Liver transplantation in colorectal liver metastases	–	SECA-1 study[49] SECA-II study[50]	Evidence suggests the benefit of transplantation, but restricted to research settings only.

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TABLE 1 (Continued)

Clinical scenario	Evidence from RCTs	Evidence from big data	Comments
		Giannis et al.—meta-analysis[51]	Large RCT is required to establish as standard-of-care.
ALPPS in colorectal liver metastases		Moris et al.—meta-analysis of ALPPS vs. TSH[52]	Conclusive evidence from big data demonstrating higher morbidity with ALPPS and obviating the need for an RCT.
Adjuvant therapy in gallbladder cancer	BILCAP trial- adjuvant capecitabine in biliary tract cancers[53] JCOG 1202, ASCOT trial- adjuvant S1 in biliary tract cancers[54]	Kunte et al.—adjuvant therapy in stage II gallbladder cancer[55]	The majority of evidence for gallbladder cancer extrapolated from biliary tract cancer data. RCT evidence specific to gallbladder cancer is required to support current practice standards.
Neoadjuvant therapy in gallbladder cancer	–	Kunte et al.—multimodality management in gallbladder cancer[56] Chaudhari et al.—NACT in gallbladder cancer[57]	RCT evidence is required to establish the role of NACT in gallbladder cancer.

Abbreviations: ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; ASCOT, Adjuvant S-1 for Cholangiocarcinoma Trial; HCC, hepatocellular carcinoma; HPB, hepatopancreatobiliary; JCOG, Japan Clinical Oncology Group; LAPC, locally advanced unresectable pancreatic cancer; MWA, microwave ablation; NACT, neoadjuvant chemotherapy; pCR, pathologic complete response; PJ, pancreaticojejunostomy; RCT, randomized controlled trial; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; SMA, superior mesenteric artery; TSH, two-stage hepatectomy.

3.2 | Colorectal liver metastases

There has been growing interest in the surgical management of unresectable colorectal liver metastases. Liver transplantation and techniques for staged resection are the current areas of interest in this field for which additional evidence is required.

There are no RCTs in the literature comparing resection to liver transplantation for unresectable colorectal liver metastases. The current evidence, although encouraging is still in its infancy and provides an opportunity for the generation of additional evidence via big data analytics. The SECA-1 study was a prospective pilot study that reported 1, 3, and 5-year OS rates of 95%, 68%, and 60%, respectively, in 21 patients who underwent liver transplantation for unresectable colorectal liver metastases.[49] In the SECA-II study, liver transplantation for unresectable colorectal metastases yielded 1-, 3-, and 5-year OS rates of 100%, 83%, and 80% respectively, with the adoption of better patient selection criteria.[50] A meta-analysis by Giannis et al. included 18 studies of a total of 118 patients with unresectable colorectal liver metastases undergoing liver transplantation and reported pooled 5-year OS rates of 50.5%. They concluded that liver transplantation should be considered in patients with unresectable colorectal liver metastases but under strict selection criteria and only under well-designed research protocols.[51]

A meta-analysis by Moris et al. of nine studies comprising 657 patients compared the outcomes of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) and two-stage hepatectomy in unresectable colorectal liver metastases and found no difference in OS, but reported significantly higher morbidity and mortality with ALPPS.[52] This example highlights how the availability of big data can aid the planning of more pragmatic RCTs and better allocation of resources. The evidence generated by big data, in this case, is sufficient to avoid a randomized trial, which would unnecessarily expose patients to a surgical procedure proven to have a significantly higher morbidity and mortality.

4 | BILIARY TRACT AND GALLBLADDER

4.1 | Adjuvant chemotherapy in biliary cancer

The BILCAP phase III RCT established Capecitabine as the standard of care for adjuvant therapy in resected biliary tract and gallbladder cancers.[53] More recently, the long-term outcomes of the BILCAP trial were published, reaffirming capecitabine as standard-of-care for adjuvant therapy in biliary tract cancers.[54] The recently published results of the JCOG1202, Adjuvant S-1 for Cholangiocarcinoma Trial trial showed a significant survival benefit with adjuvant S-1 in resected biliary tract cancers and can be considered the standard of care in Asian patients.[55]

These studies provide high-quality evidence for adjuvant therapy in biliary tract cancers, however, the applicability of these results to the Indian setting is limited as these studies include a very small proportion of gallbladder cancers, which is the predominant biliary tract malignancy encountered in the Indian population. More recently, a retrospective analysis of 276 patients by Kunte et al. suggested no benefit of additional chemotherapy in stage II gallbladder cancer, thus suggesting that extrapolating the results of studies performed in biliary tract malignancies to gallbladder cancer may not be advisable.[56] Evidence generated from big data for adjuvant therapy in gallbladder cancer in the Western population as

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well seems to contradict the extrapolated results from the existing RCTs. A large NCDB analysis of 6690 patients of gallbladder cancer showed a survival benefit with adjuvant chemoradiation, with no benefit of adjuvant chemotherapy.[57] Further evidence in the form of RCTs specific to gallbladder cancer is required to generate relevant, high-quality evidence for the role of adjuvant therapy in this setting.

4.2 | Neoadjuvant therapy for gallbladder cancer

Evidence for neoadjuvant and multimodality approaches to the management of locally advanced gallbladder cancer are derived entirely from big data, with no RCTs reported in the literature. Patkar et al. published a series of 510 consecutive resections for gallbladder cancer and reported a median DFS of 33.4 months, with 22% of patients receiving perioperative chemotherapy or chemoradiation, thus highlighting the need for multimodality management in gallbladder cancer.[58] Chaudhari et al. published one of the earliest studies on the role of neoadjuvant therapy in locally advanced gallbladder cancer and reported an overall response rate and clinical benefit rate of 52.5% and 70%, respectively, achieving a 49-month median OS in patients undergoing an R0 resection following neoadjuvant therapy.[59] To that effect, a prospective randomized controlled clinical trial (POLCA-GB trial) is currently actively recruiting at the Tata Memorial Centre, Mumbai, to evaluate the role of NACT and chemoradiation in locally advanced gallbladder cancer.[60]

4.3 | Future directions

Randomized clinical trials are the gold standard to establish evidence for surgical practice, but are limited by high costs, complexity, and time requirements. In certain instances, conducting an RCT may pose logistical, methodological, or ethical challenges, thus limiting the quality of evidence generated. On the other hand, big data derived from retrospective data has its own limitations in assessing causality and elimination of potential sources of bias. A novel approach that combines the best of both worlds is the need of the hour to foster research in surgical oncology. Recent studies have evaluated "Registry based RCTs," in which prospective observational registries have been leveraged as platforms for clinical trials, resulting in adequately powered studies with better generalizability, performed at a lower cost and shorter time than conventional RCTs.[61,62]

5 | CONCLUSIONS

Current practice guidelines in HPB surgery rely on existing evidence both from randomized clinical trials as well as big data. There is good evidence from RCTs and big data to support current practices in the management of resectable pancreatic cancer. In some instances, big data does bridge the gap when evidence from RCTs is lacking. The biggest lacunae in evidence in HPB oncology exist with respect to the management of locally advanced pancreatic and gallbladder cancers. The role of radiotherapy and the efficacy of newer, complex surgical techniques is yet to be assessed. Existing evidence from big data should be used generate used to pragmatically plan future clinical trials. Registry-based clinical trials are a promising research methodology for future studies, combining the advantages of RCTs as well as big data.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. Smith R, Rennie D. Evidence-based medicine—an oral history. *JAMA*. 2014;311(4):365-367.
2. Djulbegovic B, Guyatt GH. Progress in evidence-based medicine: a quarter century on. *Lancet*. 2017;390(10092):415-423.
3. Treasure T, Takkenberg JJ. Randomized trials and big data analysis: we need the best of both worlds. *Eur J Cardiothorac Surg*. 2018;53: 910-914.
4. Evrard S, McKelvie-Sebileau P, Van De Velde C, Nordlinger B, Poston G. What can we learn from oncology surgical trials? *Nat Rev Clin Oncol*. 2016;13(1):55-62.
5. Balch CM, Nelson H, Niederhuber JE. Limitations of prospective surgical oncology trials—a US view. *Nat Rev Clin Oncol*. 2016;13(1):6-8.
6. Ahmed Ali U, Reiber BMM, Ten Hove JR, et al. Journal impact factor and methodological quality of surgical randomized controlled trials: an empirical study. *Langenbecks Arch Surg*. 2017;402:1015-1022.
7. Papet E, Moutel G, Pinson J, et al. Methodological and ethical quality of surgical trials from 2016 to 2020. *Langenbecks Arch Surg*. 2022;407(8):3793-3802.
8. Robinson NB, Fremes S, Hameed I, et al. Characteristics of randomized clinical trials in surgery from 2008 to 2020: a systematic review. *JAMA Netw Open*. 2021;4(6):e2114494.
9. McCulloch P. Randomised trials in surgery: problems and possible solutions. *BMJ*. 2002;324(7351):1448-1451.
10. Farrokhyar F, Karanicolas PJ, Thoma A, et al. Randomized controlled trials of surgical interventions. *Ann Surg*. 2010;251(3):409-416.
11. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence—what is it and what can it tell us. *N Engl J Med*. 2016;375(23): 2293-2297.
12. Frieden TR. Evidence for health decision making—beyond randomized, controlled trials. *N Engl J Med*. 2017;377(5):465-475.
13. Tang M, Pearson SA, Simes RJ, Chua BH. Harnessing real-world evidence to advance cancer research. *Curr Oncol*. 2023;30(2): 1844-1859.
14. Karim S, Booth CM. Effectiveness in the absence of efficacy: cautionary tales from real-world evidence. *J Clin Oncol*. 2019;37(13): 1047-1050.

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15. Booth CM, Karim S, Mackillop WJ. Real-world data: towards achieving the achievable in cancer care. *Nat Rev Clin Oncol*. 2019;16(5):312-325.
16. van Hilst J, de Rooij T, Bosscha K, et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomised controlled phase 2/3 trial. *Lancet Gastroenterol Hepatol*. 2019;4(3):199-207.
17. Nickel F, Haney CM, Kowalewski KF, et al. Laparoscopic versus open pancreaticoduodenectomy: a systematic review and meta-analysis of randomized controlled trials. *Ann Surg*. 2020;271(1):54-66.
18. Feng Q, Liao W, Xin Z, et al. Laparoscopic pancreaticoduodenectomy versus conventional open approach for patients with pancreatic duct adenocarcinoma: an up-to-date systematic review and meta-analysis. *Front Oncol*. 2022;11:749140.
19. Shrikhande SV, Barreto SG, Bodhankar YD, et al. Superior mesenteric artery first combined with uncinate process approach versus uncinate process first approach in pancreatoduodenectomy: a comparative study evaluating perioperative outcomes. *Langenbecks Arch Surg*. 2011;396(8):1205-1212.
20. Sanjay P, Takaori K, Govil S, Shrikhande SV, Windsor JA. 'Artery-first' approaches to pancreatoduodenectomy. *Br J Surg*. 2012;99(8):1027-1035.
21. Sabater L, Cugat E, Serrablo A, et al. Does the artery-first approach improve the rate of R0 resection in pancreatoduodenectomy? a multicenter, randomized, controlled trial. *Ann Surg*. 2019;270(5):738-746.
22. Negoi I, Hostiuc S, Runcanu A, Negoi RI, Beuran M. Superior mesenteric artery first approach versus standard pancreaticoduodenectomy: a systematic review and meta-analysis. *Hepatobiliary Pancreatic Dis Int*. 2017;16(2):127-138.
23. Ironside N, Barreto SG, Loveday B, Shrikhande SV, Windsor JA, Pandanaboyana S. Meta-analysis of an artery-first approach versus standard pancreatoduodenectomy on perioperative outcomes and survival. *Br J Surg*. 2018;105(6):628-636.
24. Inoue Y, Saiura A, Yoshioka R, et al. Pancreatoduodenectomy with systematic mesopancreas dissection using a supracolic anterior artery-first approach. *Ann Surg*. 2015;262(6):1092-1101.
25. Diener MK, Mihaljevic AL, Strobel O, et al. Periarterial divestment in pancreatic cancer surgery. *Surgery*. 2021;169(5):1019-1025.
26. Cai B, Lu Z, Neoptolemos JP, et al. Sub-adventitial divestment technique for resecting artery-involved pancreatic cancer: a retrospective cohort study. *Langenbecks Arch Surg*. 2021;406(3):691-701.
27. Welsch T, Müssle B, Korn S, et al. Pancreatoduodenectomy with or without prophylactic falciform ligament wrap around the hepatic artery for prevention of postpancreatectomy haemorrhage: randomized clinical trial (PANDA trial). *Br J Surg*. 2021;109(1):37-45.
28. Martín MS, Palomares Cano A, Cantalejo Díaz M, et al. Use of hemopatch as a sealant at the pancreaticojejunostomy to prevent postoperative pancreatic fistula. A randomized control trial. *HPB*. 2021;23:S305.
29. Addison P, Nauka PC, Fatakhova K, Amodu L, Kohn N, Rodriguez Rilo HL. Impact of drain placement and duration on outcomes after pancreaticoduodenectomy: a National Surgical Quality Improvement Program analysis. *J Surg Res*. 2019;243:100-107.
30. Ke S, Ding X, Gao J, et al. A prospective, randomized trial of Roux-en-Y reconstruction with isolated pancreatic drainage versus conventional loop reconstruction after pancreaticoduodenectomy. *Surgery*. 2013;153(6):743-752.
31. Deng LH, Xiong JJ, Xia Q. Isolated Roux-en-Y pancreaticojejunostomy versus conventional pancreaticojejunostomy after pancreaticoduodenectomy: a systematic review and meta-analysis. *J Evid Based Med*. 2017;10(1):37-45.
32. Fan Y, Li N, Zhang J, Fu Q, Qiu Y, Chen Y. The Effect of immunonutrition in patients undergoing pancreaticoduodenectomy: a systematic review and meta-analysis. *BMC Cancer*. 2023;23(1):351.
33. Ricci C, Serbassi F, Alberici L, et al. Value of immunonutrition in patients undergoing pancreatic resection: a trial sequential meta-analysis. *HPB*. 2023.
34. Halloran CM, Neoptolemos JP, Jackson R, et al. A multicenter, randomized, double-blinded, clinical trial comparing Cattell-Warren and Blumgart anastomoses following partial pancreatoduodenectomy. *Ann Surg Open*. 2022;3(3):e198.
35. Ellis RJ, Brajcich BC, Bertens KA, et al. Association between biliary pathogens, surgical site infection, and pancreatic fistula: results of a randomized trial of perioperative antibiotic prophylaxis in patients undergoing pancreatoduodenectomy. *Ann Surg*. 2023;278(3):310-319.
36. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med*. 2018;379(25):2395-2406.
37. Valle JW, Palmer D, Jackson R, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. *J Clin Oncol*. 2014;32:504-512.
38. Katz MHG, Shi Q, Meyers JP, et al. Alliance A021501: preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy (RT) for borderline resectable (BR) adenocarcinoma of the pancreas. *J Clin Oncol*. 2021;39(3_suppl):377.
39. Versteijne E, Suker M, Groothuis K, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: results of the Dutch randomized phase III PREOPANC trial. *J Clin Oncol*. 2020;38(16):1763-1773.
40. Chaudhari VA, Mitra A, Gupta V, et al. Neoadjuvant therapy in borderline resectable pancreatic cancer: outcomes in the era of changing practices and evolving evidence. *Surgery*. 2022;171(5):1388-1395.
41. Janssen QP, Buettner S, Suker M, et al. Neoadjuvant FOLFIRINOX in patients with borderline resectable pancreatic cancer: a systematic review and patient-level meta-analysis. *J Natl Cancer Inst*. 2019;111(8):782-794.
42. Zhan HX, Xu JW, Wu D, et al. Neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of prospective studies. *Cancer Med*. 2017;6(6):1201-1219.
43. Mokdad AA, Minter RM, Zhu H, et al. Neoadjuvant therapy followed by resection versus upfront resection for resectable pancreatic cancer: a propensity score matched analysis. *J Clin Oncol*. 2017;35(5):515-522.
44. Murphy JE, Wo JY, Ryan DP, et al. Total neoadjuvant therapy with FOLFIRINOX in combination with losartan followed by chemoradiotherapy for locally advanced pancreatic cancer: a phase 2 clinical trial. *JAMA Oncol*. 2019;5(7):1020-1027.
45. Truty MJ, Kendrick ML, Nagorney DM, et al. Factors predicting response, perioperative outcomes, and survival following total neoadjuvant therapy for borderline/locally advanced pancreatic cancer. *Ann Surg*. 2021;273(2):341-349.
46. Barrak D, Villano AM, Villafane-Ferriol N, et al. Total neoadjuvant therapy for pancreatic adenocarcinoma increases probability for a complete pathologic response. *Eur J Surg Oncol*. 2022;48(6):1356-1361.
47. Menahem B, Lubrano J, Duvoux C, et al. Liver transplantation versus liver resection for hepatocellular carcinoma in intention to treat: an attempt to perform an ideal meta-analysis. *Liver Transpl*. 2017;23(6):836-844.
48. Tan W, Deng Q, Lin S, Wang Y, Xu G. Comparison of microwave ablation and radiofrequency ablation for hepatocellular carcinoma: a systematic review and meta-analysis. *Int J Hyperthermia*. 2019;36(1):263-271.
49. Hagness M, Foss A, Line PD, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg*. 2013;257(5):800-806.

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50. Dueland S, Syversveen T, Solheim JM, et al. Survival following liver transplantation for patients with nonresectable liver-only colorectal metastases. *Ann Surg*. 2020;271(2):212-218.
51. Giannis D, Sideris G, Kakos CD, Katsaros I, Ziogas IA. The role of liver transplantation for colorectal liver metastases: a systematic review and pooled analysis. *Transplant Rev*. 2020;34(4):100570.
52. Moris D, Ronnekleiv-Kelly S, Kostakis ID, et al. Operative results and oncologic outcomes of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) versus two-stage hepatectomy (TSH) in patients with unresectable colorectal liver metastases: a systematic review and meta-analysis. *World J Surg*. 2018;42(3):806-815.
53. Primrose JN, Fox RP, Palmer DH, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *Lancet Oncol*. 2019;20(5):663-673.
54. Bridgewater J, Fletcher P, Palmer DH, et al. Long-term outcomes and exploratory analyses of the randomized phase III BILCAP study. *J Clin Oncol*. 2022;40(18):2048-2057.
55. Nakachi K, Ikeda M, Konishi M, et al. Adjuvant S-1 compared with observation in resected biliary tract cancer (JCOG1202, ASCOT): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet*. 2023;401(10372):195-203.
56. Kunte A, Patkar S, Chaudhari V, Goel M. Role of peri-operative chemotherapy in stage II (pT2N0) gallbladder cancers. *J Gastrointest Surg*. 2023;27(1):78-88.
57. Hoehn RS, Wima K, Ertel AE, et al. Adjuvant therapy for gallbladder cancer: an analysis of the National Cancer Data Base. *J Gastrointest Surg*. 2015;19(10):1794-1801.
58. Patkar S, Ostwal V, Ramaswamy A, et al. Emerging role of multimodality treatment in gall bladder cancer: outcomes following 510 consecutive resections in a tertiary referral center. *J Surg Oncol*. 2018;117(3):372-379.
59. Chaudhari VA, Ostwal V, Patkar S, et al. Outcome of neoadjuvant chemotherapy in “locally advanced/borderline resectable” gallbladder cancer: the need to define indications. *HPB*. 2018;20(9):841-847.
60. Engineer R. *Perioperative Therapy Preoperative Chemotherapy Versus Chemoradiotherapy in Locally Advanced Gall Bladder Cancers* [Internet] (Report No.: NCT02867865). 2022. Accessed September 5, 2023. https://clinicaltrials.gov/study/NCT02867865
61. Zolin SJ, Petro CC, Prabhu AS, et al. Registry-based randomized controlled trials: a new paradigm for surgical research. *J Surg Res*. 2020;255:428-435.
62. Mathes T, Buehn S, Prengel P, Pieper D. Registry-based randomized controlled trials merged the strength of randomized controlled trails and observational studies and give rise to more pragmatic trials. *J Clin Epidemiol*. 2018;93:120-127.

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