Restorative surgery after protocolectomy. Studies on functional results, complications, and quality of life after restorative proctocolectomy with Ileo Neo Rectal and with Ileal Pouch Anal Anastomosis

Heikens, J.T.

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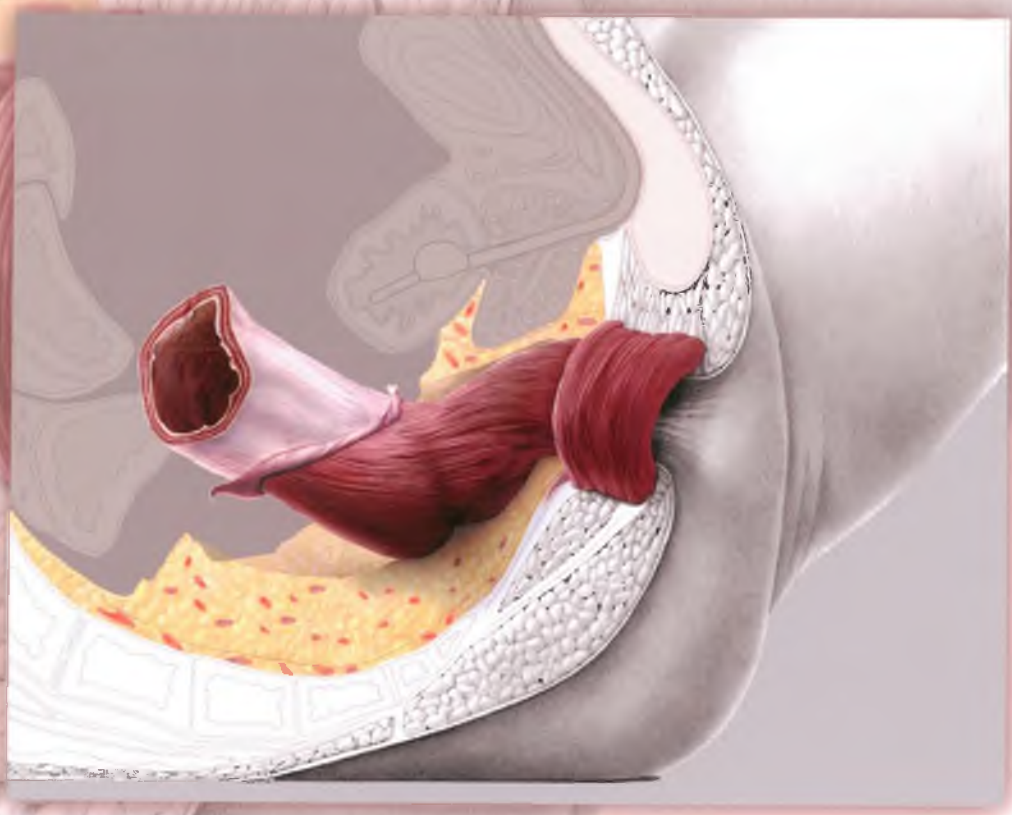

Joost T. Heikens

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Colofon

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Studies on functional results, complications, and quality of life after restorative proctocolectomy with Ileo Neo Rectal and with Ileal Pouch Anal Anastomosis

Thesis, Radboud University Nijmegen, the Netherlands

The work described in this thesis was performed at the departments of Surgery and Gastroenterology of the Utrecht University, St Elisabeth Hospital Tilburg, and Radboud University Nijmegen Medical Centre, the Netherlands.

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Contents

Chapter 1

General introduction and outline of this thesis

Ulcerative Colitis and Familial Adenomatous Polyposis

Ulcerative Colitis (UC) is a chronic inflammatory disease of the rectum and colon. In the past 50 years, the incidence of UC has respectively increased from 9 to 20/100,000.[1] Since its aetiology remains largely unknown, the medical management of UC is mainly empirical and therefore largely symptomatic. Therapies are aimed at reducing the inflammation and the patient's discomfort. Medical treatment is effective in 70%-80% of all patients. The remaining 20%-30% patients become refractory to medical treatment and surgical intervention is deemed necessary.[1;2] As UC is a disease of the rectum and colon, the surgical treatment consists of removal of colon and rectum.[1]

Familial Adenomatous Polyposis (FAP) usually commences in the second decade of life and is characterized by the development of hundreds to thousands of adenomas predominantly in the rectum and colon. One in 8,300 people is born with the potential to develop FAP. If left untreated colorectal cancer will develop in 100% of the cases. A prophylactic removal of the rectum and colon prevents the development of colorectal cancer.[3]

After proctocolectomy (removal of rectum and colon) there are two options: either a lifelong ileostomy or have intestinal continuity restored.

Restorative surgery

Historically, primary attempts to restore intestinal continuity after proctocolectomy with straight ileo-anal anastomosis were virtually abandoned because of the high frequency of watery stools and poor postoperative continence.[4-8] In 1978, Parks introduced a surgical innovation: restorative proctocolectomy with the Ileal Pouch Anal Anastomosis (IPAA).[1;9;10] This technique preserves the natural route for defecation while maintaining faecal continence with an acceptable bowel function (*Illustration 1*). Despite its modifications and experience in many thousands of patients morbidity after IPAA remains substantial.[11;12]

In an attempt to reduce procedure-related complications without compromising function, a new surgical technique was developed: the Ileo Neo Rectal Anastomosis (INRA). This procedure focuses on restoration of intestinal continuity without pelvic dissection in the same patient category as those patients being offered IPAA.[13]

The concept of INRA was physiologically sound and promising. The INRA technique removes only diseased mucosa, leaves healthy anatomic structures intact, and only replaces diseased tissues with completely vascularised and healthy transpositions of autologous material. The technique, however, was demanding and laborious.

INRA is achieved by first denuding the rectal muscle wall through a mucosectomy (*Illustrations 2* and *3*), subsequently a new rectal mucosal lining is prepared through dissection of the distal ileal serosa and muscle layers, leaving the ileal mucosa intact (*Illustration 4*). The procedure is concluded by a transposition of healthy ileal mucosa with vascular pedicles onto the denuded rectum (*Illustrations 5* and *6*). INRA has been developed and described previously by Van Laarhoven. Over the last two decades INRA and its modifications have been reviewed and improved.[13;14]

Aim and method of this series of studies

Aim and rationale

INRA has proven to be a safe technique with acceptable bowel function for patients and has passed the stage of being an experimental technique.[15] The next step, from a technical safe and valuable technique towards a broadly accepted and implemented standard surgical procedure, evaluation of the effectiveness of INRA against the current gold standard (IPAA) was needed. This was the rationale of this thesis.

Different studies in this thesis

To achieve this aim, four main aspects of restorative surgery in patients after UC and FAP have been addressed in this thesis. A summary of the study questions, hypotheses, and methods used to answer these four aspects are listed in *Table 1*.

1. Patient-reported outcome after restorative surgery
2. Evaluation of the process of implementation of INRA as a surgical innovation in restorative surgery
3. Long-term results of INRA
4. Comparison of surgical innovation (INRA) to the gold standard (IPAA)

Study design, setting and groups

Patients in need of restorative surgery after proctocolectomy are operated in tertiary centres. This thesis reports studies on a prospective cohort of 150 patients, which, between 1996 and 2006, underwent restorative surgery in three tertiary centres in the Netherlands. The patients had either undergone INRA (n=79) (University Medical Centre Utrecht or St Elisabeth Hospital Tilburg) or IPAA (n=71) at the Radboud University Nijmegen Medical Centre.

Ethical considerations

Ethical approval was obtained from the ethical review committees from the University Medical Centre Utrecht, the St Elisabeth Hospital Tilburg, and the Radboud University Nijmegen Medical Centre.

Table 1: Summary of study questions, hypotheses, and method used to answer these questions

	Chapter	Study question and hypothesis	Method
Patient-reported outcome after restorative surgery	2.	For patients with Ulcerative Colitis, what is the patient-reported outcome after restorative surgery? **It was hypothesised that patients had good patient-reported outcomes.**	Systematic review
	3.	For patients with Ulcerative Colitis, what is the outcome in terms of Quality of Life and Health Status before and after restorative surgery and how does it relate to the healthy population? **It was hypothesised that Quality of Life and Health Status improve after surgery achieving levels comparable to the healthy population.**	Multicentre prospective cohort study
Evaluation of surgical innovation in restorative surgery	4.	For surgical innovations, is an evidence-based assessment possible warranting a safe and phased introduction into the realm of science? **It was hypothesised that it is possible to introduce and assess a surgical innovation in an evidence-based manner.**	Descriptive study
Long-term results of INRA	5.	For patients who require restorative surgery, INRA has a theoretical potential to be superior to the current technique (IPAA). Does this theoretical potential translate into clinical favourable results? **It was hypothesised that there would be a place for INRA in the armamentarium of a surgeon.**	Prospective case series
		For patients who require restorative surgery, is a vascularised mucosal transposition a safe technique with good long-term results? **It was hypothesised that a vascularised mucosal transposition is a safe technique with good long-term results.**	Prospective case series
	7.	For patients with restorative surgery, what is the outcome in terms of function, complications, and Quality of Life after intra-operative INRA conversions to IPAA compared to patients with IPAA as their procedure of choice? **It was hypothesised that the results of INRA conversions to IPAA were not inferior to the results of patients with IPAA as their procedure of choice.**	Prospective cohort study
Comparison of INRA to IPAA	6.	For patients with restorative surgery, what is the outcome in terms of functional results, complications, and Quality of Life after INRA and IPAA? **It was hypothesised that INRA has at least equal functional results and Quality of Life to IPAA and a lower complication rate.**	Multicentre prospective cohort study

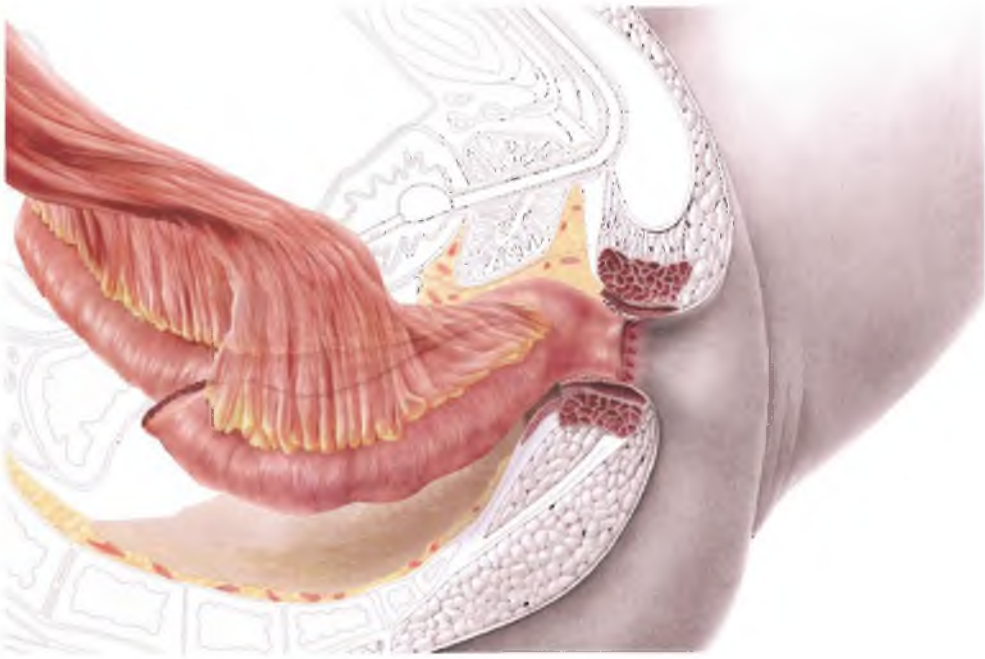

Illustration 1: IPAA

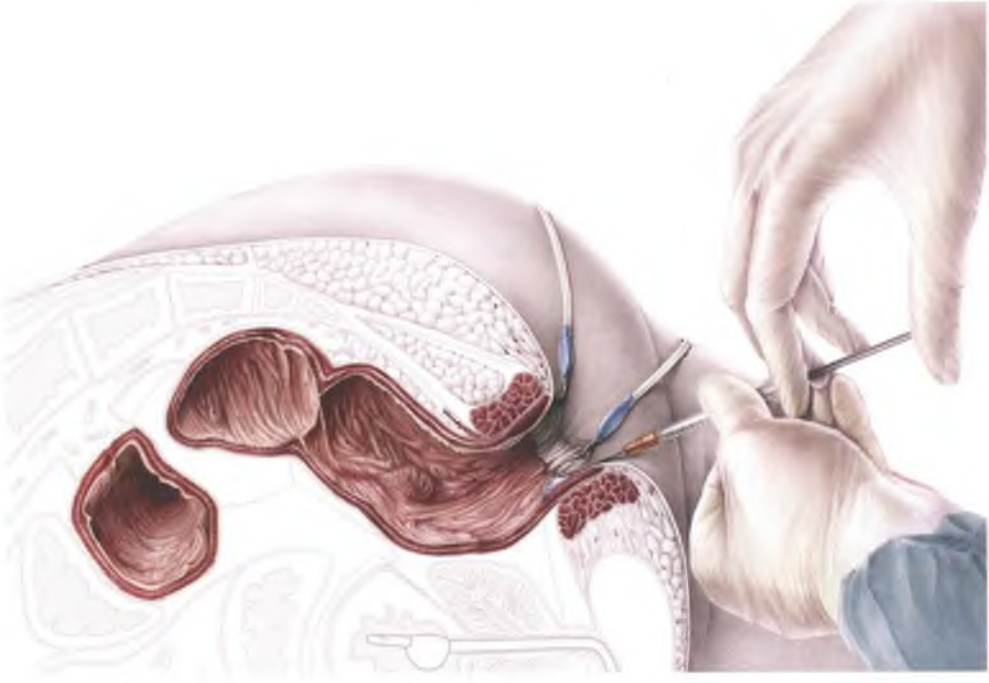

Illustration 2: A saline suspension is injected between the mucosa and rectum muscular lining to facilitate the mucosectomy

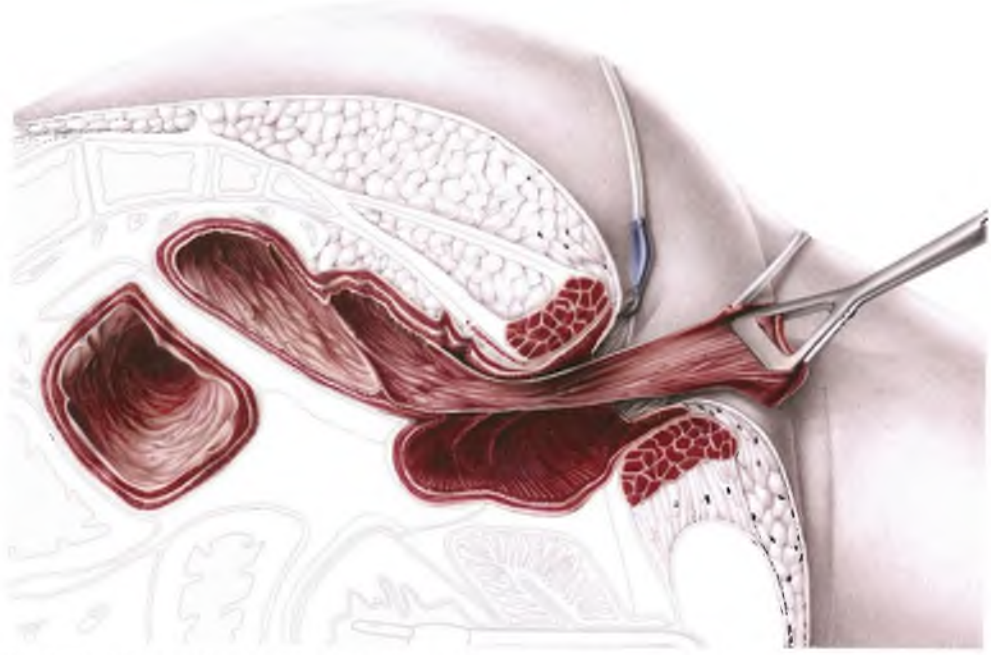

Illustration 3: Denuding the rectal muscle wall through mucosectomy

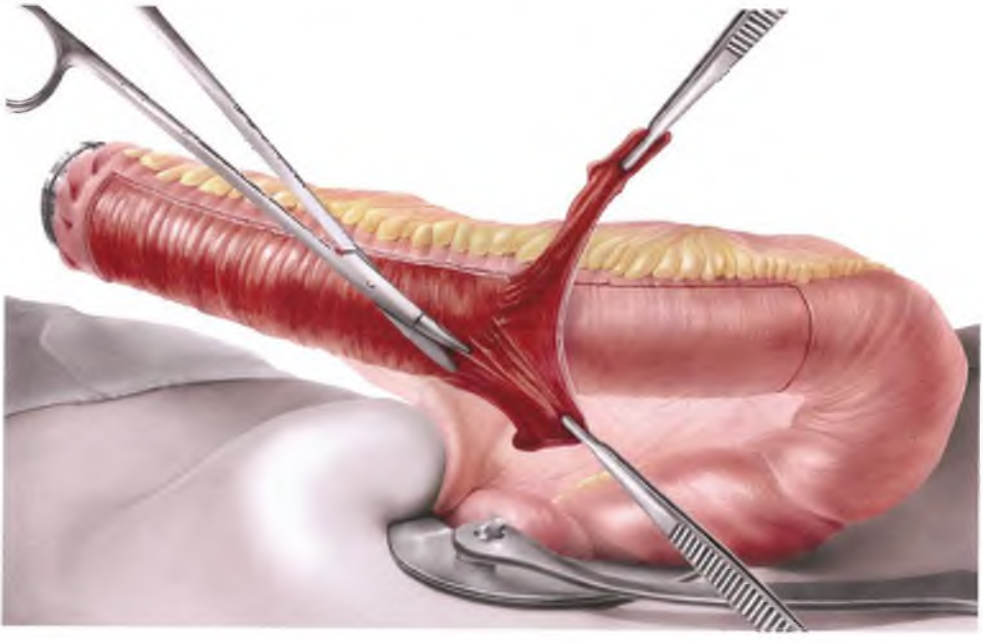

Illustration 4: Preparing a new rectal mucosal lining through dissection of the distal ileal serosa and muscle layers, leaving the ileal mucosa intact

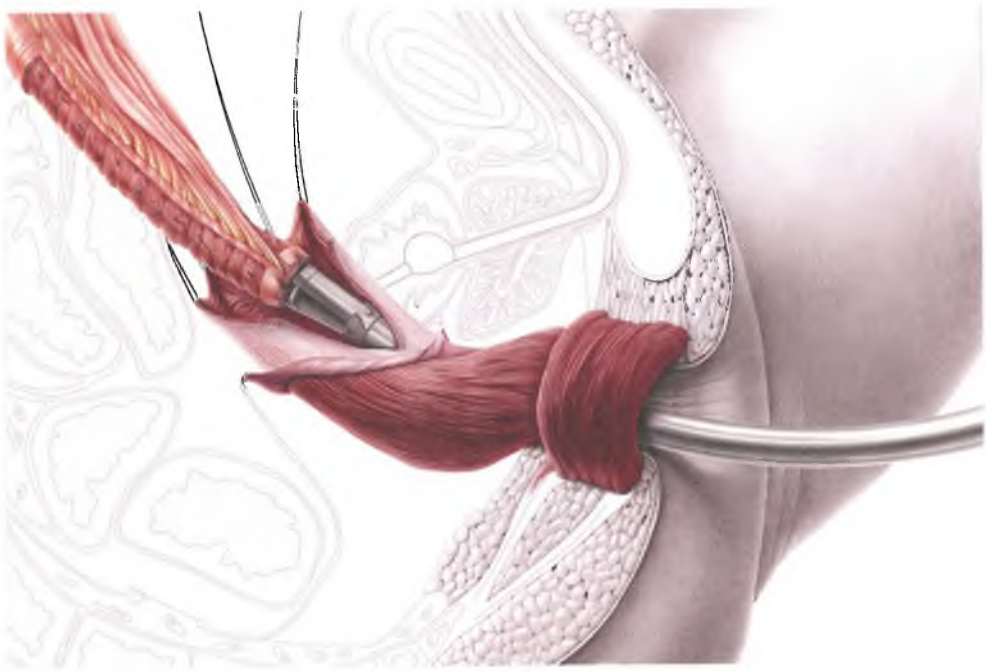

Illustration 5: Transposition of healthy ileal mucosa with vascular pedicles onto the denuded rectum

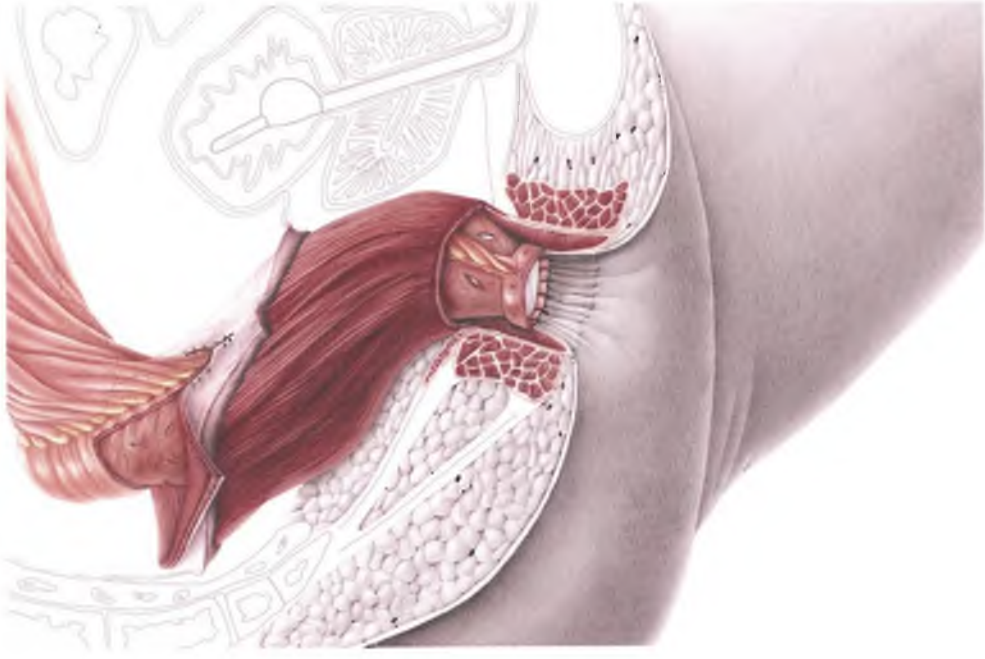

Illustration 6: Completion of INRA

Series of studies

1. Patient-reported outcome after restorative surgery

Endpoints of recovery such as patient-reported outcomes, which comprises Quality of Life (QoL), Health Related Quality of Life (HRQoL), and Health Status (HS), have increasingly been recognised as relevant outcome measures of procedures.

QoL is defined by the World Health Organization (WHO) as 'an individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectations, standards and concerns'.[16]

In other words, QoL is a person's evaluation of his/her functioning in a wide range of areas. This definition implies that QoL is subjective and can, therefore, only be judged by the individuals themselves. In literature often HRQoL is used, which refers to QoL but is restricted to the physical, psychological, and social domains. HRQoL is often confused with HS.

HS refers to 'the defined well-being in terms of physical, mental, and social condition or function'.[17] Thus, HS measures the impact of disease on functioning. Patients are asked solely about their physical possibilities, social activities, and state of mind and not about their feelings concerning their functioning. Therefore, HS indicates whether there are limitations, whereas QoL also reflects to what extent a patient is bothered by these limitations in daily life.[18]

Restoring intestinal continuity is considered 'quality of life surgery'.[19] *Chapter 2* describes a systematic review in which the literature on patient-reported outcomes in patients with IPAA for UC is analysed. Previous studies have, according to the definition of the WHO, not investigated QoL.[20-53] As a consequence a study was initiated to investigate QoL and HS in patients before and after IPAA for UC (*Chapter 3*). It illustrates the effect that IPAA has on QoL and HS, and how these results compare to those of a healthy reference population.

2. Evaluation of the process of implementation of INRA as a surgical innovation in restorative surgery

Historically and in contrast to the formalised approach for drug development, the process of surgical innovation has been unregulated, unstructured and variable. Surgery and other invasive therapies are complex interventions. Their assessment is challenged by factors that depend on the operator, its team and the setting. In the past, surgical advances have been based on the trial and error principle, formal and comparative assessment of procedures had little role. Moreover, traditional health technology assessment is based on a posteriori evaluation of interventions already entered clinical practice; hence it is, therefore, difficult to carry out the kind of evaluation that would be necessary.[54-56]

Nevertheless, surgical innovation seems to proceed in phases and the international Balliol group has proposed the so-called IDEAL recommendations for the assessment of surgical innovation.[57] The IDEAL recommendations comprise of a five-stage paradigm describing each step in the development of innovative surgical procedures: the Idea, its Development, its Evaluation, its Assessment, and the Long-term study of the outcome of the undertaken study and tested hypothesis.[57-59] Reporting these phases of surgical innovation is deemed essential if surgery is to enter the realm of evidence-based medicine. Apart from looking at the true value of the INRA technique itself, evaluation of the past process of development and implementation of INRA as a surgical innovation was considered to be of interest. Therefore, in *Chapter 4* the process of introducing the INRA technique as a surgical innovation was evaluated according to this IDEAL framework.

3. Long-term evaluation of INRA

Chapter 5 aims to evaluate the true value of INRA as a surgical technique by describing the long-term results of all 79 patients with INRA as their restorative procedure of choice. Morbidity, functional outcome, inflammatory responses, anal and neorectal physiology, bladder and sexual dysfunction, endoscopy, and histopathology results are examined and will be discussed. *Chapter 7* describes all patients whose procedure of choice was INRA, however, during surgery were converted to IPAA. Functional results of these conversion-IPAA patients, morbidity, and QoL were evaluated and compared to patients whose procedure of choice was IPAA. Furthermore, this part of the thesis describes the rationale why INRA is no longer being used as a technique for restoring continuity, despite 'acceptable' or even 'good' results.

4. Comparing surgical innovation (INRA) to the gold standard (IPAA)

Evaluation of INRA in this thesis showed that long-term function, complications and patient-reported outcomes were in range with IPAA.[12;60] For reasons explained in *Chapters 4 and 5*, a study was initiated to compare INRA to IPAA. *Chapter 6* describes a multicentre prospective cohort study between INRA and IPAA for UC.

Series of studies

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Chapter 2

Quality of life, health related quality of life and health status in patients with ileal pouch anal anastomosis for ulcerative colitis: a systematic review

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Abstract

Quality of life, health related quality of life and health status in patients with ileal pouch anal anastomosis for ulcerative colitis: a systematic review

Aim

A systematic review of published literature to establish the quality of studies and determine Quality of Life (QoL), Health Related Quality of Life (HRQoL), and Health Status (HS) in patients after ileal pouch anal anastomosis for ulcerative colitis.

Method

All published studies describing QoL, HRQoL, and HS in adult patients in combination with ileal pouch anal anastomosis for ulcerative colitis, were reviewed systematically. No time or language limitations were applied. Independent extraction of articles was performed by two authors using predefined data fields, including study quality indicators. The following data was extracted from each study: author, characteristics of the study population, number of participants, pouch construction, duration of follow-up, time of assessment and the results of QoL, HRQoL, and HS measurements.

Results

The review included 33 studies comprising 4,790 patients. Three studies were graded of high, 23 of moderate, and seven of low quality. All studies reported improved HS and the majority reported improved HRQoL. However, none of the studies reported on QoL.

Conclusions

HRQoL and HS improved in 12 months' time after ileal pouch anal anastomosis and were indistinguishable from normal healthy populations. This can only be proven with high quality studies. A systematic and uniform approach to QoL measurement can improve future patient care.

Introduction

Over the past decades, improved medical and surgical interventions have resulted in improved outcomes in patients treated for ulcerative colitis (UC).[1-6] Since its introduction in 1978, proctocolectomy with an Ileal Pouch Anal Anastomosis (IPAA) has been considered the procedure of choice in patients with medical refractory colitis (*Illustration 1*, page 12).[7] With IPAA, focus of interventions has shifted from merely reducing mortality to efforts in decreasing morbidity and improving quality of life (QoL).[8]

Nowadays, practitioners cannot suffice by only looking at the physical outcome of the intervention. The patient's QoL, health related quality of life (HRQoL), and health status (HS) are increasingly recognised as an important outcome of medical interventions in patient populations and become, therefore, an important qualification of provided health care, especially in patients with a chronic disease.[9] Furthermore, these outcome measures help to inform clinicians how to decide and prioritise interventions, improving patient-practitioner relationship and patient care.[10;11] As restorative surgery after proctocolectomy is considered 'QoL surgery', the surgical intervention determines QoL, HRQoL, and HS.[12]

Quality of life

QoL is a broad evaluation of human function in a variety of domains. The robust and internationally accepted definition of QoL, as defined by the World Health Organization Quality of Life Group (WHOQOL group), is the individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives, and in relation to his/her goals, expectations, standards and concerns.[13]

Health related quality of life

HRQoL is a part of QoL. It is the patients' own evaluation of its functioning in the physical, psychological and social domains.[14] Compared to QoL, HRQoL is measured using less domains. Hence, evaluation of HRQoL is not as extensive compared to QoL assessment.

Health status

HS refers to the impact that a disease has on a patient's physical, psychological and social functioning. HS determines, as outcome variable, the patients' physical (in)abilities, social activities, and state of mind. In contrast to QoL and HRQoL: in studies reporting HS, patients are not asked about their (dis)contentment concerning their functioning.[15] *Figure 1* illustrates the relationship between HS, HRQoL, and QoL.

QoL has been a keyword in the Index Medicus for nearly 20 years. Regretfully, different definitions and multiple interpretations of QoL, HRQoL and HS are currently being used interchangeably in the literature.[12] The increasing amount of articles published on QoL, HRQoL and HS in patients after IPAA for UC, combined with the growing number of IPAA's

due to their good long-term results, challenged us to take a closer look at the existing literature.

The aim of this study was to examine the influence of IPAA on QoL, HRQoL, and HS in patients suffering initially from UC by identifying, appraising, synthesizing and combining the results of the relevant studies. This is the first study which reviewed all available literature in a systematic manner. The definitions used in this review for QoL, HRQoL, and HS are the internationally recognised definitions as mentioned.

Figure 1: HS related to HRQoL and QoL

Method

Search strategy

The following databases were searched to identify studies reporting on QoL, HRQoL, and HS after IPAA for UC: the Cochrane database, MEDLINE using PubMed as the search engine, Embase, ISI Web of Knowledge (Web of Science), CINAHL, and PsychINFO. Our aim was to perform a maximal sensitive search, without time or language limitations. For each database, a specific search strategy was devised and adapted to the syntax and capabilities of the respective databases. National experts in search strategies were consulted to optimize the search for the different databases. All keywords suited for the different databases were used in different order to expose the maximum amount of hits relevant to the subject. All terms used are shown in *Table 1*.

Non-English-language studies were classified according to their English title and abstract. Abstracts of international meetings were reviewed and used to find full text articles. Only full text studies were included for the purpose of retrieving data since abstracts alone do not contain all information necessary to score the quality of a study. Assessment of reference lists of all selected studies was performed for cross-references to retrieve relevant publications that were not identified in our earlier searches. Relevant articles were also identified using the 'related articles' function in PubMed and were appraised in the same order. After completion of the review, the literature search was repeated to detect the latest reported studies; the most recent being January 2009.

Table 1: Keywords used and search strategy for electronic databases

ibd OR inflammatory bowel disease OR ulcerative colitis OR colitis ulcerosa OR "uc" OR colitis OR ulcerative OR morbus crohn OR "mc" OR crohn's disease OR ic OR indeterminate colitis
AND
Randomized Controlled Trial [pt] OR Controlled Clinical Trial [pt] OR Randomized Controlled Trials [mh] OR Random Allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND
(mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR
follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw] NOT animals [mh])
AND
quality of life OR "QoL" OR health-related quality of life OR "HRQoL" OR well-being OR health status OR "HS"
AND
surgery OR surgical OR surgically OR laparoscopy OR laparoscopic OR laparoscopically OR ileal pouch OR ileal pouch OR pouch anal anastomosis OR pelvic pouch OR pouch-anal anastomosis OR "IPAA" OR restorative surgery OR restorative proctocolectomy OR "RPC" OR "RP" OR colorectal surgery OR colonic pouch OR proctocolectomy, restorative

Selection criteria

All studies describing aspects of QoL, HRQoL, and or HS in adult patients in combination with IPAA for UC, were considered. The titles and descriptor terms of all the initial hits from the electronic searches were analysed by one reviewer (JTH). Irrelevant reports were discarded. The remainders were inspected by two reviewers (JTH and JDV) who graded the abstracts independently and in different order.

Relevance was established on the basis of pre-specified selection criteria for grading abstracts: 1) if IPAA was performed for UC, 2) if QoL, HRQoL and/or HS were reported as outcome of the study and 3) if studies reported the postoperative period for maximal benefit post IPAA. Studies have shown that many patients require as long as 9-12 months after surgery to achieve maximal benefit of IPAA.[16-18] Therefore, the minimum follow-up period after surgery had to be 12 months.

Appraisal of the reviewed studies

After identifying relevant abstracts, the quality of the selected studies was appraised (JTH and JDV). Approval was based by reviewing the full texts using a checklist of 19 predefined criteria for assessing the methodological quality of studies (*Table 2*).

Table 2: List of criteria for assessing the methodological quality of studies on QoL, HRQoL and HS in patients with IPAA for UC

Study assessment	
A.	a description is given of QoL, HRQoL, and/or HS by describing the domains
B.	a reason is given for choosing a certain questionnaire
C.	a distinction is made between QoL, HRQoL, and/or HS
Study population	
D.	a description is present of at least two socio-demographic variables (age, sex, economic status, employment, educational status, etc.)
E.	a description is present of clinical variables (operation, complications, permanent ileostomy, etc.)
F.	postoperative diagnosis is given (CD, indeterminate colitis or UC)
G.	a description is made for inclusion and/or exclusion criteria
H.	participation rates for groups were mentioned and were more than 70%
I.	information is given about non-responders versus responders
Study design	
J.	patients have signed an informed consent form before study participation
K.	the study population was at least consisting 50 patients
L.	the collection of data was prospectively gathered
M.	the study design was longitudinal (>1yr)
N.	the loss to follow-up was <20%
O	the process of data collection is described (interview, questionnaires, self-report, etc.)
Outcome measures	
P.	validated data collection instruments were used
Results	
Q.	mean, median, standard deviation, range and/or confidence interval are reported for outcome measures
R.	the results were compared between two groups or more
S.	results are compared with at least two time points
Maximum score: 19	

Our checklist is tailored to suit this study question; it incorporates well-established and validated criteria for assessing the quality of trials and systematic reviews evaluating QoL, HRQoL and HS.[19-22]

For each item in the checklist, studies could be assigned one point. If an item was not mentioned or was incomplete, no point was assigned. The highest possible score was 19. Studies scoring 75% or more of the 19 attainable points (≥14 points) were considered high quality studies. Studies scoring between 50% and 75% were considered medium quality studies and studies scoring lower than 50% (≤8 points) were considered low quality studies. Findings were considered consistent if ≥75% of the studies that investigated a particular domain showed the same direction of the association.[23;24]

Data extraction

Outcome variables included results of QoL, HRQoL, and HS questionnaires, characteristics of the study population, number of participants in the study and in the UC group, pouch construction (J-, S-, or W-pouch), duration of follow-up, and time of assessment.

Data extraction, from the selected full text articles, was conducted independently by JTH and JDV. Scoring characteristics had to be clearly stated in the study, otherwise they were excluded. In the case of incomplete data reporting in studies, the corresponding author was contacted to clarify the data.

From studies reporting an overlap in patient samples from one and the same centre, only the highest quality study was included. If two or more studies described the same patient population, data were combined to extract all information. If, at any stage during the analysis, there was disagreement between the initial reviewers, a third reviewer (CVL) joined the discussion and disagreements were solved by consensus.

Data synthesis

Descriptive data synthesis was performed of the collated evidence to assess the results of the studies included in the review. This was done by tabulation displaying the methodological quality, study characteristics, and conclusions on QoL, HRQoL, and HS measurements in the studies.

Results

Search results

Thirty-three studies evaluating QoL, HRQoL, and HS with approximately 4,790 patients were retrieved from the databases. Search results are displayed in *Figure 2*. Most studies used data from an existing database, a cross-sectional study, a case series, or a cohort design. Weinryb et al. presents in two different studies one and the same population;[25;26]

hence, data of these studies were combined to extract the relevant information. Thirty-three studies, published between 1985 and 2008, were included in this analysis.[16-18;25-55]

Table 3 displays the results of the methodological assessment, based on criteria listed in *Table 2*, as well as the general conclusion of the study, according to the definitions used in this review. Characteristics of each trial are given in *Table 4*.

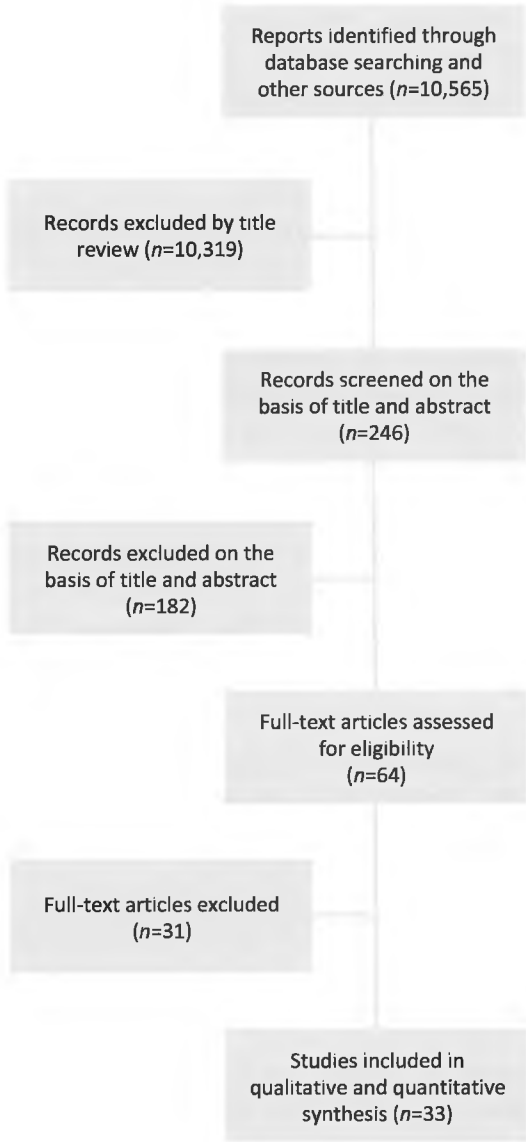

Figure 2: Results of the systematic search of published literature to extract studies determining QoL, HRQoL, and HS in patients after IPAA for UC

Twenty-nine studies indicated to describe QoL and four studies indicated to describe HRQoL in 4,790 patients (2,225 males and 2,063 females).[34;42;49;52] Three studies were graded of high, 23 of moderate, and seven of low quality (*Table 3*). Twenty-one studies (64%) used at least one or more questionnaires to measure Qol, HRQoL, and HS. These studies used a total of 24 different established questionnaires. Eight authors used 'self-made' questionnaires or 'a questionnaire' without providing information on validation and reliability (*Table 5*).

High quality studies

The three high quality studies claimed to describe QoL after IPAA in a total of 117 patients, comprising of 64 males (55%), ages ranging between 35 and 41 years.[16;17;40] QoL, however, was measured in none of the studies. HRQoL was measured in two studies[17;40] and HS was measured in two studies (*Table 5*).[16;17] The general conclusion of these studies was: HRQoL and HS of patients improve after IPAA and are indistinguishable from the general population. All results were considered consistent.

Moderate quality studies

In the studies of moderate quality, 23 studies described 4,423 patients.[18;25;26;28;30-35;37;39;41-44;46-51;54;55] Eighteen studies reported a total of 2,070 males and 1,921 females. Five studies did not report gender. Average age mentioned in 21 studies ranged from 31 to 47 years. Follow-up time ranged from 12 to 130 months (mean 65, *Table 4*). QoL was measured in none of the studies. HRQoL was measured in nine studies and HS was measured in 17 studies. Nine studies used questionnaires that were self-made or not specified, none of them were validated (*Tables 3* and *4*). Nonetheless, the general conclusion of the moderate quality studies was that the HRQoL and HS after IPAA improves and is comparable to general levels in a healthy population. All results were considered consistent.

Low quality studies

Seven studies, describing a total of 226 patients, were graded of low quality.[27;29;36;38;45;52;53] Five studies reported on 91 males and 89 females. Age ranged between 32 and 47 years. Follow-up time ranged from 28 to 96 months with a mean of 45 months (*Table 4*). QoL was measured in none of the studies. HRQoL was measured in one study and HS was measured in two studies. In four studies questionnaires were used which were self-made or not specified, none of them were validated. Overall, some studies showed overlapping enquiries due to the use of multiple questionnaires (*Table 5*). The general conclusion in this population was that HRQoL and HS improves after surgery and ranges between satisfactory to good. All results were considered consistent.

Table 3: Results, based on the criteria in *Table 2*, of methodological assessment of QoL, HRQoL and HS in patients with IPAA for UC

Author	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	Total	Conclusion
McLeod[40]	-	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	16	Surgery is usually successful in improving HRQoL
Polle[17]	+	+	-	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	16	HS and HRQoL improves after IPAA
Thirlby[16]	+	+	-	+	+	-	+	+	-	-	-	+	+	+	+	+	+	+	+	14	HS improves postoperatively comparable to general population
Delaney[32]	-	-	-	+	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	12	Prudent case selection allows acceptable HRQoL in patients of all ages
Hahnloser[33]	-	-	-	+	+	+	+	+	-	-	+	+	+	+	+	-	+	-	+	12	HS is preserved after IPAA
Heuschen[35]	+	-	-	+	+	-	+	+	-	-	+	+	+	-	+	+	+	+	-	12	HS comparable to healthy controls if postoperative complications are avoided
Scarpa[49]	-	+	-	+	+	-	+	+	-	-	+	-	+	+	+	-	+	+	+	12	HS is influenced by drugs, stool frequency, pouchitis, age at diagnosis, and postoperative pelvic complications
Berndtsson[28]	-	-	-	+	+	-	+	+	-	-	-	+	+	+	+	+	+	-	+	11	General HS and HRQoL did not change after IPAA
Carmon[31]	-	+	-	+	+	-	+	+	-	-	+	-	+	-	+	+	+	+	-	11	HS comparable with general population
Muir[42]	-	-	+	+	+	-	-	+	-	-	-	+	+	+	+	+	+	-	+	11	HS improved after IPAA
Robb[47]	-	+	-	+	-	+	+	-	-	+	+	-	+	-	+	+	+	-	+	11	IPAA increases HS significantly and approximates general population
Young[55]	-	-	-	+	+	+	+	+	-	-	+	+	+	+	+	-	+	-	-	11	Majority of patients report poor HRQoL after IPAA
Camilleri[30]	-	-	-	+	+	-	+	+	-	+	-	-	+	-	+	+	+	+	-	10	IPAA and ileostomy comparable high levels of HS
Holubar[37]	-	-	-	+	+	-	+	+	-	-	+	-	-	+	+	+	+	+	-	10	Despite changes in continence HS is extremely well preserved
Martin[39]	-	+	-	+	+	-	+	+	+	-	-	-	-	+	+	-	+	+	-	10	HS after IPAA is comparable to patients in remission or with mild symptoms
Mowschenson[41]	-	-	-	+	+	-	+	+	+	-	+	+	+	+	+	-	-	-	-	10	Majority of patients report normal HS after IPAA
Pace[44]	+	-	-	+	+	-	+	+	-	-	-	+	+	+	+	+	-	-	-	10	HS reported to be generally satisfying

Table 3 (continued): Results, based on the criteria in *Table 2*, of methodological assessment of QoL, HRQoL and HS in patients with IPAA for UC

Author	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	Total	Conclusion
Weinryb[25,26]	-	+	-	+	-	-	-	-	+	-	+	+	+	-	+	+	+	-	+	10	HS is good and comparable in ileostomy and IPAA patients
Coffey[18]	-	-	-	+	+	-	-	+	-	-	+	+	+	+	+	+	-	-	-	9	HRQoL after IPAA is affected by diet, timing of intake, preoperative diagnosis, and pregnancy
Hauser[34]	-	-	-	+	+	-	+	+	-	+	+	-	-	-	+	+	+	-	-	9	HS after IPAA is also determined by anxiety and extra-intestinal manifestations
O'Bichere[43]	-	-	-	+	+	-	+	-	-	+	+	-	-	-	+	+	+	+	-	9	Improved pelvic function reflects in better HS after IPAA
Richards[46]	-	+	-	+	-	-	+	+	-	-	+	-	-	+	+	+	+	-	+	9	HS and HRQoL is normal to general population
Sagar[48]	-	+	-	+	+	-	+	+	-	-	+	-	-	+	+	-	-	+	-	9	HS after IPAA is good
Seidel[50]	-	-	-	+	+	-	+	-	+	-	+	-	+	-	+	-	+	+	-	9	HS is good and in the majority improved
Steens[51]	-	-	-	+	+	-	+	-	+	-	-	-	+	-	+	+	+	+	-	9	HS and HRQoL after IPAA is only slightly decreased
Willis[54]	-	-	-	+	+	-	+	-	+	-	-	-	+	-	+	+	+	-	+	9	Patients with uneventful course have a significantly better HS
Barton[27]	-	+	-	+	+	-	-	-	+	-	-	-	-	-	+	+	+	+	-	8	CU and FAP have similar good HS
Pezim[45]	-	-	-	+	+	-	+	+	+	-	+	-	+	-	+	-	-	-	-	8	HS is satisfactory
Tiainen[52]	-	+	-	+	+	-	+	-	-	-	+	-	-	-	+	+	+	+	-	8	HS comparable with normal population
Besançon[38]	-	-	-	+	+	-	-	+	-	-	-	-	+	+	-	-	+	+	-	7	HRQoL is similar between continent and incontinent patients
Brunel[29]	-	-	-	+	+	+	-	-	-	-	-	+	+	-	+	-	-	-	+	7	Restorative proctocolectomy improves HRQoL
Hildebrandt[36]	-	-	-	+	+	-	-	+	-	-	-	+	-	+	-	-	-	-	-	5	HRQoL was graded nine out of ten
Vendrell[53]	-	-	-	+	+	-	+	-	-	-	-	-	+	-	+	-	-	-	-	5	HS improves after surgery

Legend Table 3:

A-S: criteria according to Table 2
+ : criteria present in study and awarded one point
- : criteria not clearly defined or not present in study and awarded no points
Total: total number of points awarded to study according to criteria Table 2

Table 4: Study characteristics

Author	Age	N	Male	Female	S / J / W - pouch	Follow-up period after IPAA (months)	UC patients in study	Time of assessment
McLeod[40]	36	37	23	14	i.n.a.	12	37	after IPAA
Polle[17]	35	53	19	34	J	12	34	before and after IPAA
Thirlby[16]	41	27	22	5	i.n.a.	12	27	before and after IPAA
Delaney[32]	i.n.a.	1285	773	512	J	55	1285	after IPAA
Hahnloser[33]	34	1885	862	1023	1824 J + 44 S + 17 W	130	1885	before and after IPAA
Heuschen[35]	i.n.a.	243	i.n.a.	i n.a	J	43	185	after IPAA
Scarpa[49]	40	36	27	9	i.n.a.	101	36	after IPAA
Berndtsson[28]	36	32	22	10	J of W	12	32	before and after IPAA
Carmon[31]	38	78	35	43	i.n.a.	51	78	after IPAA
Muir[42]	38	20	10	10	J	12	20	before and after IPAA
Robb[47]	44	138	67	71	S>J + 9 other constructions	45	138	after IPAA
Young[55]	38	48	i.n.a.	i.n.a	J	68	48	before and after IPAA
Camilleri[30]	41	19	12	7	4 S, 1 W, 14 J	41	19	after IPAA
Holubar[37]	42	51	25	26	i.n.a	85	51	after IPAA
Martin[39]	35	29	22	7	J	46	29	after IPAA
Mowschenson[41]	34	111	i.n.a.	i.n.a.	J	75	127	after IPAA
Pace[44]	35	13	8	5	J	24	13	after IPAA

Table 4 (continued): Study characteristics

Author	Age	N	Male	Female	S / J / W - pouch	Follow-up period after IPAA (months)	UC patients in study	Time of assessment
Weinryb[25,26]	44	40	25	15	J	82	14	after IPAA
Coffey[18]	31	54	24	30	J	67	54	after IPAA
Hauser[34]	47	61	32	29	59J + 2 kock pouch	80	61	after IPAA
O'Bichere[43]	43	30	i.n.a.	i.n.a	i.n.a.	13	30	after IPAA
Richards[46]	34	56	32	24	i.n.a.	48	56	after IPAA
Sagar[48]	34	103	50	53	41 S, 50 W, 14 J	12	103	after IPAA
Seidel[50]	31	55	30	25	i n.a.	31	35	after IPAA
Steens[51]	38	36	14	22	18 J, 17 S, 1W	67	31	after IPAA
Willis[54]	43	24	i.n.a.	i.n.a.	J	96	24	after IPAA
Barton[27]	47	37	i.n.a.	i.n.a.	J	33	37	after IPAA
Pezim[45]	34	51	31	24	53 S + 2 W	28	44	after IPAA
Tiainen[52]	40	68	32	36	J	96	68	after IPAA
Besançon[38]	36	13	i.n.a.	i.n.a.	J	31	13	after IPAA
Brunel[29]	45	27	16	11	J	35	27	before and after IPAA
Hildebrandt[36]	17-36	5	2	3	J	i.n.a	5	after IPAA
Vendrell[53]	32	25	10	15	i.n.a.	i n.a.	25	after IPAA

Legend Table 4:
i.n.a.: information not available

Table 5: List of different questionnaires used in studies and what they measure

Questionnaire	QoL	HRQoL	HS	Study	Remark
Short Inflammatory Bowel Disease Questionnaire (SIBDQ)	-	+	-	[27]	
Inflammatory Bowel Disease Questionnaire (IBDQ)	-	-	+	[30,34,39,49]	
RAND SF-36	-	-	+	[16-18,27,30,31,34, 42-44,46,47,51,52]	
General Quality of Life according to Kajandi (GQL)	-	+	-	[28]	
Visual Analogue Scale (VAS) or equivalent scales rating from 1-1-	-	+	-	[28,36,43,55]	often not all the required domains are questioned separately
Modified disease-specific Olbrisch Adjustment Scale (OAS)	-	-	+	[28]	
Functional outcome score according to Öresland (GFO)	-	-	+	[28,35]	questionnaire only includes the physical domain
Mayo Clinic Questionnaire	-	-	+	[35]	
Cleveland Global Quality of Life Score (CGQL)	-	+	-	[18,32]	questionnaire approximates HRQoL
Modified medical questionnaire of the German competence network inflammatory bowel diseases	-	+	-	[34]	questionnaire approximates HRQoL, comparable to a VAS
Giessener Symptom List (GBB24)	-	-	+	[34]	questionnaire approximates HS, does not cover psychological and social domain
Fecal Incontinence Quality of Life (FIQL) questionnaire	-	-	+	[37]	questionnaire approximates HS, questions one domain

Table 5 (continued): List of different questionnaires used in studies and what they measure

Questionnaire	QoL	HRQoL	HS	Study	Remark
Time Trade-Off (TTO)	-	-	-	[40,42]	utility measure
Rating Form of IBD Patient Concerns (RFIPC)	-	-	+	[42,47]	measures impact of disease
EuroQol	-	+	-	[46]	
Psychological Adjustment to Illness Scale (PAIS)	-	-	-	[25]	psychological assessment
Modified Kelly-Hohlschneider-Score	-	-	+	[54]	
EORTC QLQ-C3-	-	-	+	[54]	measure HS in cancer patients
Gastrointestinal Quality of Life Index (GIQLI) / Gastrointestinaler lebensqualitatsindex (GLQI)	-	+	-	[17,35,51]	
Fecal incontinence severity index (FISI)	-	-	-	[37]	questionnaire scores faecal incontinence
Direct Questioning of Objectives (DQO)	-	-	-	[40]	questionnaire often not include requested domains
Well-Being Profile (WBP)	-	-	+	[25]	
Hospital Anxiety and Depression test (HAD)	-	-	-	[34,48]	questionnaire designed for assessment of anxiety and depression, not (HR)QoL or HS
open questions	-	-	-	[28]	domains are not questioned
homemade or name questionnaire not mentioned	?	?	?	[29,33,38,41, 45,48,50,53]	questionnaires most often approximate measuring HS

Discussion

As IPAA surgery is considered 'QoL' surgery, our aim with this systematic review was to explore the QoL, HRQoL, and HS in patients with IPAA for UC. All studies measured HRQoL and/or HS, reporting levels comparable to the general population. This review showed, that despite IPAA is called QoL surgery, this was neither measured nor reported. Furthermore, the quality of studies was examined. We observed that the methodological quality for most of studies was moderate to low.

Only three studies qualified as high quality with low bias risk and could be considered conclusive in this systematic review. These studies supported the observations that HRQoL and HS improved in patients after IPAA for UC and that patients reached levels comparable to that of a healthy population. These findings were consistent with those of moderate and low quality studies.

One has to be cautious interpreting the conclusions of the studies for several reasons. Clinical heterogeneity was present between studies. Key characteristics such as histopathological diagnosis were not identical in all studies. While in patients with UC, IPAA cures the patients from disease, this is in contrast to patients suffering from Crohn's disease (CD). CD is one of the most important risk factors for pouch failure.[5] Five studies reported the postoperative histological diagnosis.[29;32;33;47;55] UC and CD are different diseases which may have different effects on QoL, HRQoL, and HS. In addition, rehabilitation from disease is a process and not a one-off result; hence the patients' perceived QoL might differ over time. If therefore QoL is used as outcome measure in this population, repeated measurements are required.[56]

Furthermore, seven studies reported measuring HRQoL and/or HS before and after IPAA.[16;17;28;29;33;42;55] Observations on HRQoL and HS measured after IPAA can only be drawn in relation to the normal population and not if these qualities improve or diminish after IPAA.

Most studies used different measures to assess QoL, HRQoL, and HS. Because the studies were too heterogeneous on this aspect, pooling data was not possible. Methodological heterogeneity in study design and quality was present. Grading the quality of the different studies made it possible to judge the relative importance of the given results. We recognize that the use of quality scoring is controversial, because scores constructed in an ad hoc fashion may lack demonstrated validity, and results may not be associated with quality.[57] Nevertheless, some particular aspects of study quality have been shown to be associated with effect.[58] Thus, key components of design, rather than aggregate scores themselves, may be important. Because of the substantial heterogeneity present in and between these studies, the necessary data to perform a meta-analysis could not be obtained.

This systematic review has demonstrated that HRQoL and HS reach levels comparable to the general population after IPAA. It also illustrated that a systematic and uniform approach to QoL and its measurement is needed. Often in studies HS or HRQoL instruments were used while titles incorrectly referred to QoL.[12] QoL, HRQoL, and HS are different entities and are not interchangeable. Considering the HRQoL results in the high quality studies and the consistent results observed in the other studies, one might expect that QoL results in patients after IPAA for UC will be comparable to the general population as well. However, studies will have to be performed examining all the domains of QoL to answer this question.

To be able to improve future patient care, QoL evaluation is of importance. QoL is evaluated by assessing many more domains than HRQoL. This makes QoL questionnaires the most sensitive tool to detect subtle changes and flaws in today's patient care with regard to (HR)QoL. During the last decades, great advances have been made reducing mortality and decreasing morbidity which resulted in levels of HRQoL and HS comparable to the general population. Evaluating QoL and the separate domains can make further improvements possible for patients entrusted to us.

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Chapter 3

Quality of life and health status in patients before and after ileal pouch anal anastomosis for ulcerative colitis

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Abstract

Quality of life and health status in patients before and after ileal pouch anal anastomosis for ulcerative colitis

Background
Ileal Pouch Anal Anastomosis (IPAA) is considered the surgical treatment of choice for patients with ulcerative colitis. Quality of life (QoL) and health status (HS) are the most important patient-related outcomes. Studies investigating QoL are often cross-sectional and focus on HS. The purpose of this study was to longitudinally evaluate the QoL and HS of patients who underwent IPAA for ulcerative colitis and to compare these to the reference data of the healthy population.

Method
The study group composed of patients with ulcerative colitis who underwent a pouch operation between 2003 and 2008 and who had completed validated questionnaires for QoL and HS. Questionnaires were completed before pouch surgery and 6, 12, 24, 36 months after surgery. Effect of IPAA on QoL and HS was analysed and compared with the healthy reference population.

Results
Data were obtained for 30 of the 32 patients. Six months after IPAA, QoL was comparable to the reference population in four of the six domains. Twelve months after IPAA, overall QoL improved, supported by three QoL-domains. Six months after IPAA, HS was comparable to the reference population in three of the eight dimensions. After three years, HS was at least comparable in five of the eight dimensions.

Conclusions
QoL and HS increased after IPAA and reached levels comparable to the healthy reference population in a majority of the domains and dimensions. QoL was restored first after IPAA, followed by HS.

Introduction

Over the past decades, improved medical and surgical interventions have resulted in better outcomes for patients with Ulcerative Colitis (UC).[1-6] Proctocolectomy with an Ileal Pouch Anal Anastomosis (IPAA) has played a major role in this improvement and is currently considered the procedure of choice in patients' refractory for medical interventions (*Illustration 1*, page 12). With IPAA, the focus of interventions has shifted over the years from merely reducing mortality to efforts in decreasing morbidity and improving patient-reported outcomes, such as defecation frequency and faecal (in)continence. Nowadays, practitioners cannot suffice by only looking at the physical outcome of the intervention. The patient's quality of life (QoL) and health status (HS) are increasingly recognised as important outcomes of medical interventions in patient populations and become, therefore, an important qualification of provided health care, especially in patients with a chronic disease.[7;8]

In most studies, the term 'QoL' is used to illustrate the patient's perspective. The value attributed to the outcome of QoL assessment can be high and lead to a preference for one intervention over another. The term QoL, however, may be used for related – but very different – concepts.[9] Frequently-used aspects of patient-reported outcomes are QoL and perceived HS, both are multidimensional concepts that incorporate the physical, psychological, and social aspects of life.[10]

There is no single fully agreed definition of QoL, although a working group of the World Health Organization has defined the concept with emphasis on the personal evaluation of functioning in relation to individual and/or cultural standards, values, expectations, and goals.

HS measures assess physical, mental, and social functioning, but bear no relationship to the perception of the individual and his or her values and expectations. Consequently, it does not capture an individual's QoL. The concept of QoL is first and foremost subjective and can only be determined by the individual.

Recognising the difference between these two concepts and being able to break down QoL and HS into separate domains and dimensions, gives valuable information for the counselling of patients with UC who are often reluctant towards surgery.[11;12]

However, most studies regarding QoL in these patients have several drawbacks. For instance, most studies have a cross-sectional design, disregarding the fact that rehabilitation from disease is a process and not a one-off result. If, therefore, QoL is used as an outcome measure in this population, repeated measurements are required.[13] The use of patient-reported outcome questionnaires is considered to be mandatory when assessing treatment outcome. A recent review illustrated that due to the lack of use of uniform definitions and standardised measurements, comparison of QoL and HS across studies is challenging.

Despite the fact that IPAA is considered QoL surgery, QoL has not been examined in relation to IPAA according to definitions as stated by the WHO.[14;15] Prospective studies are needed evaluating patient-related outcomes over a period of time, before and after surgery using internationally accepted definitions and using validated tools. This study examined the course of QoL and HS in patients before and after IPAA for UC according to earlier stated criteria. In addition, in order to evaluate if IPAA restores QoL and HS, the results of patients were compared to data from the healthy population.

Method

Patients were recruited between January 2003 and January 2008 from the abdominal surgery department of two hospitals in The Netherlands: the St Elisabeth Hospital in Tilburg and the Radboud University Nijmegen Medical Centre. Inclusion criteria were: at least 18 years of age, diagnosis of UC based on histopathological findings after subtotal colectomy, willing to undergo IPAA surgery, and fluency in Dutch. Patients who underwent proctocolectomy and IPAA at the same time were excluded from the study for reasons of heterogeneity.

After consultation and giving written informed consent, patients completed the first questionnaires before surgery. The same questionnaires were completed 6, 12, 24, and 36 months after IPAA. QoL and HS data was collected under repeated conditions from the patients in order to eliminate individual differences.

Both centres performed IPAA as described by Nicholls with a temporary deviating ileostomy.[16;17] Data concerning clinical and outpatients' visits were recorded in a prospective electronic database. The effect size analysis for our study, with one group of patients with 5 measurement points showed that, for an effect size of 0.25, a sample of 28 patients would be enough to reach a power of 80% (α=0.05). The study was approved by the local medical ethics committees. (ClinicalTrials.gov Identifier NCT00922103)

Measures

The questionnaires used were a socio-demographic questionnaire (education level, marital status, and parenthood) as well as a QoL and HS measure. QoL was assessed with the World Health Organization Quality of Life assessment instrument (WHOQOL-100), the Dutch version.[18] This instrument covers 24 specific facets belonging to the six domains of QoL (Physical health, Psychological health, Level of independence, Social relationships, Environment, and Spirituality) as well as a generic facet assessing the patients overall QoL scores. The WHOQOL-100 was developed cross-culturally and simultaneously in 15 centres worldwide. Reliability and validity are adequate and sensitivity is high.[19-22] To assess general health status the RAND-36, Dutch version, was used that covers HS in eight dimensions (Physical functioning, Social functioning, Role limitations due to physical health problems, Role limitations due to personal or emotional problems, General mental

health, Vitality (energy & fatigue), Bodily pain, and General health perceptions).[23;24] Additionally, it includes a single item providing an indication of perceived changes in health. A high score indicates a good health status. The RAND-36 has a good reliability and validity.[25]

Generic measurement tools were chosen for the analysis to be able to compare the results from IPAA with reference scores. These reference scores were derived from the manuals of the WHOQOL-100 and RAND-36 and are based on healthy Dutch populations with comparable age.[18;26] All questionnaires were validated for use in this patient population.

Statistical analysis

Descriptive statistics were used to summarise patient demographics and clinical data. Continuous data was tested using ANOVA for repeated measures to analyse differences in QoL and HS before and after IPAA. One-Sample T Tests were used to compare results of QoL and HS to the reference values of the healthy population at each time point. The p values in the figures display these results. Effect size analysis was performed using G*Power. Data analysis was done on basis of intention to treat and performed with the Statistical Package for Social Sciences (SPSS® version 16.0).

Results

The demographic and baseline clinical data for all patients in this study are shown in *Table 1*. Thirty-two consecutive patients underwent IPAA surgery (J-pouch with a stapled anastomosis) for UC during the study period.

Table 1: Patient characteristics and socio-demographic features (range in square brackets)

		n=30
male : female		18 : 12
median age in years		37.8 [22.3-63.7]
highest level of education	primary school	1
	vocational training	18
	secondary school	1
	higher education	10
parenthood (yes)		9
marital status (married/partner)		10

All patients underwent a two-stage procedure with primary subtotal colectomy followed by IPAA at a later stage. IPAA was performed after the patient's health was restored and steroid therapy was no longer needed. This was at a median of 6 months (4-11). The subtotal colectomy and IPAA were all done by an open approach.

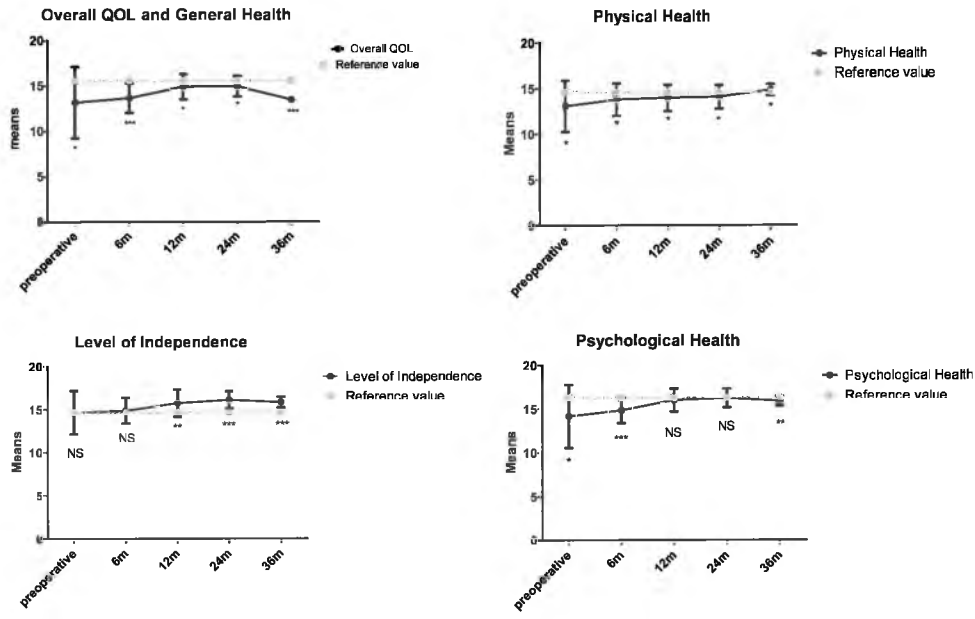

Figure 1: QoL (y-axis) before and after IPAA (x-axis) in UC and compared to the reference population
Note: ***= p<.0001; **= p<.001; *= p<.05; NS= not significant

At a median of 3.2 months (1.7-7.8) after IPAA, intestinal continuity was restored in all patients. Two patients declined participation due to the increased burden of completing multiple questionnaires. Thirty patients enrolled in the study. All patients completed the questionnaires at the required moments during outpatient visits. Two patients had pouch failure: one patient developed a pelvic sepsis, and another had invalidating anal stenosis which, despite dilatations, persevered. Both patients underwent surgery and an ileostomy was constructed.

Influence of surgery on QoL

When comparing QoL scores before and after IPAA surgery, it took 12 months after restorative surgery for the domains of Physical health, Psychological health, Level of independence and the general facet Overall QoL to improve ($p \leq 0.05$). No deterioration in QoL was observed (*Figure 1*).

QoL in patients before and after IPAA compared to the healthy population

Scores on QoL and the separate domains of the WHOQOL-100 of these patients and the reference scores are presented in *Figure 1*. Overall QoL and the domains Physical health, and Psychological health were significantly lower before IPAA surgery. Six months after IPAA, QoL in 4 domains, was comparable to the healthy reference population. During the next years, QoL stayed comparable to the healthy reference population except for Psychological health and Social relationships.

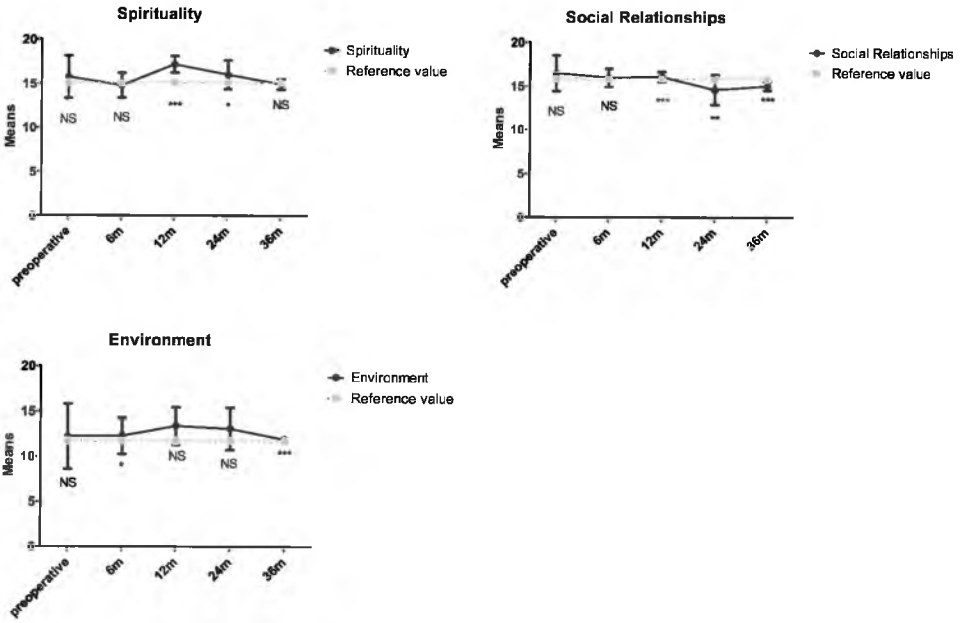

Figure 1 (continued): QoL (y-axis) before and after IPAA (x-axis) in UC and compared to the reference population

Note: ***= $p<.0001$; **= $p<.001$; *= $p<.05$; NS= not significant

Influence of surgery on HS

When comparing scores before and after IPAA surgery, six months after IPAA, HS improved ($p\leq0.05$) in two dimensions (Social functioning and General health perception), the other dimensions were comparable to the pre-IPAA level. As time progressed after IPAA, HS improved and after three years, this was seen in all dimensions except for the dimension Bodily pain. Scores on Bodily pain did not improve over time (*Figure 2*).

HS in patients before and after IPAA compared to the healthy population

Scores of the patients on the dimensions of the RAND-36 and the reference scores, are presented in *Figure 2*. Before IPAA surgery, significant lower levels of HS were observed in the following five dimensions: Social functioning, Role limitations physical and emotional, Vitality, and General health perception. Twelve months after surgery and onwards, patients' HS was comparable to the healthy reference population except for Physical functioning and Health changes. On these dimensions patients scored better than the healthy reference population.

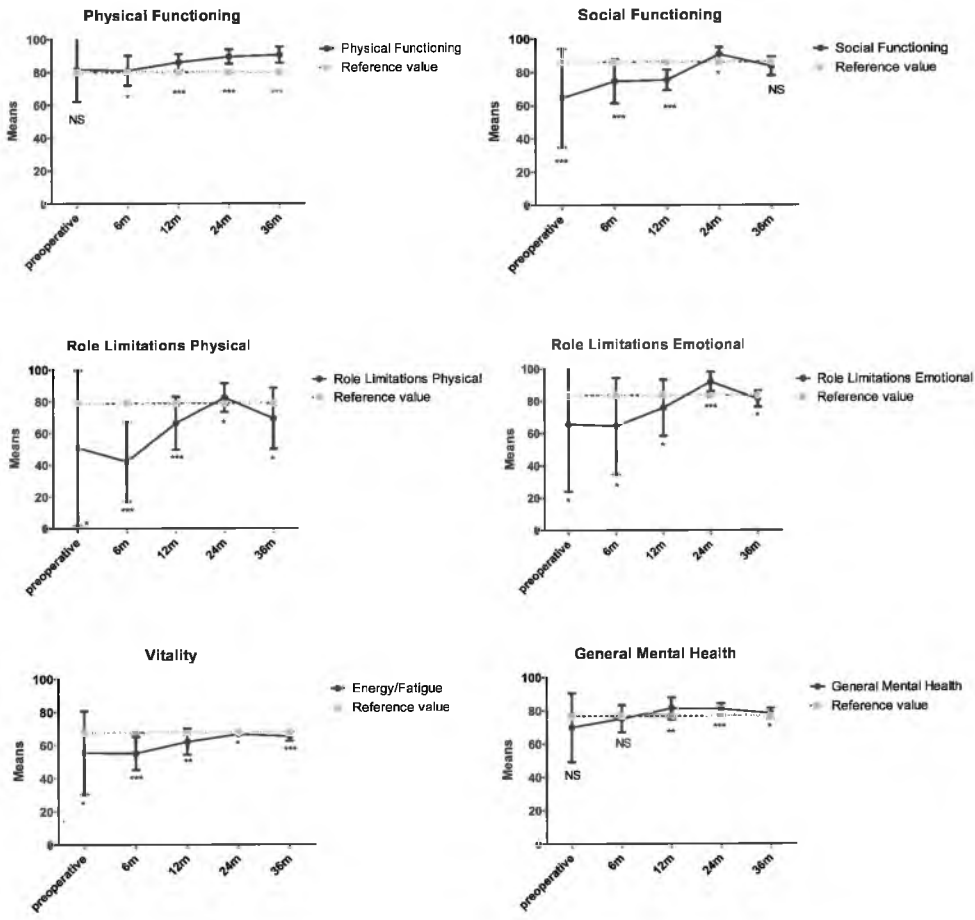

Figure 2: HS (y-axis) in patients before and after IPAA (x-axis) for UC and compared to the reference population

Note: ***= $p<.0001$; **= $p<.001$; *= $p<.05$; NS= not significant

Discussion

The aim of this study was to examine the course of QoL and HS in patients before and after IPAA for UC. This study showed that with the use of adequate, reliable and validated tools measuring QoL and HS, levels were deteriorated in the period after subtotal colectomy with an ileostomy and prior to IPAA, compared to the healthy reference population. A significant improvement was observed after IPAA surgery reaching levels comparable to the healthy reference population. Hence, IPAA improved contentment in patients concerning their functioning as well as an improvement in their functioning.

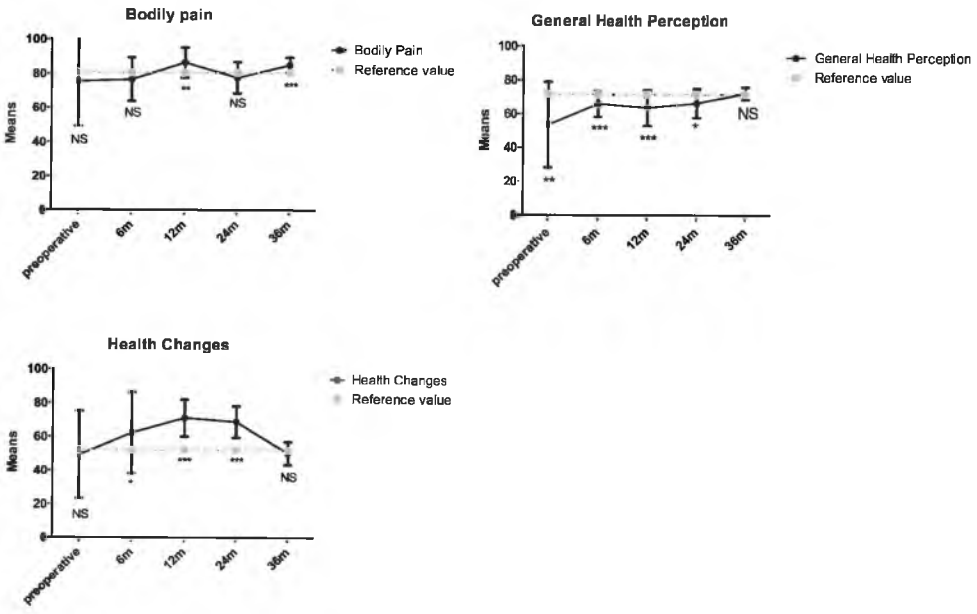

Figure 2 (continued): HS (y-axis) in patients before and after IPAA (x-axis) for UC and compared to the reference population

Note: ***= $p<.0001$; **= $p<.001$; *= $p<.05$; NS= not significant

Based on the outcome of the WHOQOL-100, we concluded that, after colectomy with ileostomy for UC and before IPAA, the patients deteriorated QoL was mainly contributed to deterioration in their Overall QoL and in the domains Physical health and Level of independence. These results may be related to the patients' rehabilitation from the subtotal colectomy for a toxic or medical refractory colitis and due to the fact that they are bothered by the presence of an ileostomy. These patients had to rely on others for some activities of daily life, therefore, compromising their independence.

Based on the outcome of the RAND-36, we concluded that after subtotal colectomy with ileostomy and prior to restorative surgery, deterioration in HS was observed in the dimensions Social functioning, Physical and Emotional limitations, Vitality, and General health perception. Possibly an ileostomy impairs a patient's life not only on a physical but also on a psychological level. This results in a limitation of a patient's social activities. These results showed that patients with IPAA for UC had physical impairments up to one year after restorative surgery. However, despite the fact that it takes one year to reach HS levels comparable to the healthy reference population, already at six months after surgery, QoL was comparable to the healthy reference population. Hence, patients were not bothered by the physical impairments but apparently satisfied with the achieved change.

The significant improvement in both QoL and HS, reaching comparable levels to the healthy population, not only makes IPAA true 'QoL surgery' increasing patients' contentment, but also 'HS surgery' increasing patients' functioning. These results on the course of QoL and HS after restorative surgery as well as the course of the different domains of QoL and dimensions of HS add valuable information for the counselling of future patients.

Our results with regard to HS are in line with the existing literature. High quality studies showed an improvement of HS in the 12 months after IPAA, resulting in levels indistinguishable to the healthy population.[8;15;27;28]

Concerning QoL no previous study exists making it impossible to compare our results with other results.[15] However, since our HS results are in line with previous studies, this provides an indication that our QoL results can be generalised.

The main advantage of using the WHOQOL-100 and the Rand-36 as research questionnaires is that these questionnaires also analyse QoL and HS in subgroups, making it easier to detect (subtle) changes in the different categories. Clinical implications from this study will focus on informing clinicians in which QoL domains and HS dimensions their patients are expected to encounter problems. Subsequently clinicians can chose and prioritise their interventions and inform patients thoroughly. In the future, when discussing these physical limitations with the patient and what to expect in due course of treatment, we expect they will be bothered less by these limitations, hence increasing QoL.

One limitation of this study was the size of the cohort when compared to other studies. However, the patient numbers undergoing this kind of surgery are generally small. The prospective and longitudinal design of this consecutive cohort of patients with high compliance rate and use of validated questionnaires in combination with a medium effect size analysis, should minimize both selection and information bias. We believe the results of this study will be sustained in larger and future cohorts. This study has shown that restorative surgery, in the form of IPAA for patients for UC, not only restored intestinal continuity but also restored QoL and HS.

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Chapter 4

Stages and evaluation of surgical innovation: a clinical example of the ileo neo rectal anastomosis after ulcerative colitis and familial adenomatous polyposis

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Surgical Innovation (accepted October 28th 2012)

Abstract

Stages and evaluation of surgical innovation: a clinical exampie of the ileo neo rectal anastomosis after ulcerative colitis and familial adenomatous polyposis

Aim

So far, not many clinical examples, that follow the IDEAL (Idea, Development, Evaluation, Assessment, and Long term study) – recommendations for evaluating and reporting surgical innovation and adoption, are available.

Method

In this paper, all IDEAL stages will be described for a recent surgical innovation, the Ileo Neo Rectal Anastomosis (INRA), a procedure restoring intestinal continuity after colectomy.

Results

INRA showed that the technique of small bowel transposition with a vascular pedicle is feasible with good long-term results. From the patient's point of view, no distinct advantage for INRA was found, with morbidity and functional results being in range with the gold standard Ileal Pouch Anal Anastomosis (IPAA).

Conclusion

The adoption of the IDEAL-recommendations, i.e. by performing evidence-based surgical studies, will improve surgical science with the consequence that progress in surgical care continues and interventions become safer, more efficient and allow a better quality of life in surgical patients.

Introduction

Innovation is an important part of surgical practice. In medicine, the most widely recognised framework for the thorough investigation of an innovation is that of pharmaceuticals. The assessment of a drug along its phases of development (I-IV) is well characterised and regulated. For drugs, innovation is tightly controlled in a series of developmental processes (phase I-III) which occur before its approval. Therefore, the process of innovation and adoption relate to the phenomena that are separate in time, although assessment still continues thereafter (phase IV).

By contrast with the formalised approach for drug development, the process of surgical innovation has been unregulated, unstructured and variable. Surgery and other invasive therapies are complex interventions, and their assessment is challenged by factors that depend on operator, team, and setting, such as learning curves, quality variations, and perception of equipoise.

In surgery, innovation of a procedure often continues as it is adopted into practice, and it is broadly characterised by the early events related to its adoption. Any opportunity for formal assessment will thus need to be sought during the early period of adoption of a new surgical operation.

Nevertheless, surgical innovation seems to proceed in phases. A model, similar to that of the phases of drug development, was needed to transform the liberal approach of surgical innovation into a structured process based on scientific principles of evidence-based health care. The international Balliol group has therefore proposed Idea, Development, Evaluation, Assessment and Long term study, the so-called IDEAL-recommendations for the assessment of surgery, which comprises of a five-stage description of the surgical development process, encouraging concurrent evolution, evaluation, and reporting of new techniques.

Simulator or animal studies could be regarded as stage 0. Stage 1 of innovation happens when a surgeon or small group of surgeons try out a procedure for the first time. If early reports suggest benefits, some early adopters may take up the innovation (stage 2a). In this phase (development stage), the focus is on the technical development of the procedure. Subsequently, attention is on the investigation of indications for use of the procedure, understanding its potential benefits and harms, and increasing effectiveness to an optimum (stage 2b, exploration phase). Early adopters refine their skills, moving up their learning curve. During stage 3, the key question is posed: is this technique better than established methods in terms of clinical efficacy, subsequent quality of life, and cost-effectiveness (assessment phase)? Definitive studies are needed, but a tipping point may occur once there is an optimised procedure and a sufficiently large group of surgeons skilled in its use. If the opportunity for robust evaluation is not seized, widespread adoption may happen without adequate evidence. Finally (stage 4), when the procedure

has become widely adopted, its effectiveness in routine use should come under scrutiny (long-term study phase). Rare and long-term outcomes might become clear at this stage, and outcome variability can lead to clarification of indications or of important technical details.[1-3]

As far as we are aware, not many clinical examples, that follow all IDEAL-recommendations, are available.[4] We will therefore describe all IDEAL phases using a recent surgical innovation, the Ileo Neo Rectal Anastomosis (INRA), a procedure restoring intestinal continuity after colectomy in patients suffering from Ulcerative Colitis (UC) and Familial Adenomatous Polyposis (FAP).[5]

The clinical example

INRA after UC and FAP

For the past decades, after removal of the colonic mucosa, hereby curing the disease, constructing an Ileal Pouch Anal Anastomosis (IPAA) was the preferred approach in restoring intestinal continuity (*Illustration 1*, page 12).[6] This technique preserves a natural route for defecation while maintaining faecal continence with acceptable bowel function. However, morbidity remained substantial, despite modifications and experience in many thousands of patients.[7-9] In the absence of an alternative, these results are usually referred to as 'acceptable' or even 'good', if compared to life with an ileostomy.

In an attempt to find a new solution to this demanding and frequent clinical problem, reducing procedure-related complications of the pelvic dissection, a new surgical technique was developed: INRA. This procedure focuses on restoration of intestinal continuity in the same patient category as IPAA.[10]

Compared to IPAA, INRA is conceptually a different procedure. INRA and its modifications through time have been related to clinical manoeuvres that applied clear-cut pathophysiological (in terms of potential nerve damage) and anatomical concepts. In contrast to IPAA, the rectal muscle wall is denuded by mucosectomy (*Illustration 2*, page 12 and *Illustration 3*, page 13), new rectal mucosal lining is prepared by performing a dissection of the most distal ileal serosa and muscle layers leaving the mucosa intact (*Illustration 4*, page 13), and a transposition of this healthy ileal mucosa with vascular pedicle is carried out into the denuded rectum (*Illustrations 5* and *6*, page 14).[10;11] In the following paragraphs we will describe all developmental phases according to the IDEAL-recommendations.

Stage 0: early steps in innovation

In 1996 a protocol was made to assess the feasibility of INRA with transposition of healthy ileal mucosa to the rectum. The idea of small bowel mucosa was not new. In the 1960s, Brody and McCorriston[12] performed experimental transposition of small bowel mucosa to

the rectum of dogs. In 1964, Peck and Hallenbeck demonstrated that results of rectal mucosal transposition improved by leaving a vascular pedicle intact.[13] This formed the concept of INRA. The first INRA procedures were performed in an animal laboratory on 12 Yorkshire-Dutch land pigs. After INRA, rectal histopathological and evaluation of function was performed. Six non-operated pigs served as controls.

Approval by the ethics committee of the University Medical Centre Utrecht was obtained prior to the start of the surgery on the pigs. Insurance for this investigational procedure at this stage and all the following stages was organised by the ethics committee. No external funding was required as all expenses were paid by the University Medical Centre Utrecht. The surgical procedure of INRA was technically successful in this animal study.[11] Repeated endoscopy and histology showed complete ileal mucosa grown into the neorectum without severe fibrosis. After one-year follow-up no colonic metaplasia had occurred. Initially, the functional capacity of the neorectum in patients with INRA was significantly decreased. However, a gradual improvement of neorectal capacity and compliance was observed in the course of the experiment. Spontaneous anal reflexes were observed after INRA, indicating the pelvic innervations to be intact. This was in line with the expectations, as INRA keeps the pelvic anatomy intact.

This study illustrated that INRA was a feasible and reproducible technique. The histological proven survival of the vascularised ileal mucosa and development of a compliant neorectal reservoir made INRA an interesting alternative restorative procedure.[11]

Stage 1: innovation

The preliminary success during the pre-human stage made it possible to progress with INRA. At this stage, the assessment of safety and proof of concept in humans were the main goals. After the successful completion of stage 0, approval of ethics committee was received including insurance coverage for a human pilot study. This was performed at the University Medical Centre Utrecht, in 11 selected patients. All patients previously underwent colectomy for UC or FAP and were willing to undergo restorative surgery for intestinal continuity with the experimental INRA technique. The surgical team consisted of three surgeons with extensive experience in the field of restorative surgery, assisted by a dedicated team of theatre and ward personnel. To reduce the risk of harm to patients, in case INRA was not feasible during surgery or INRA results were below expectations in the years after surgery, conversion to IPAA was considered possible in all patients.

In 1998 the first pragmatic trial was carried out during which 11 patients were operated, using INRA leaving them with a temporary diverting ileostomy. Clinical history, repeat endoscopy, histologic examination, and rectal compliance measurements were carried out before and after surgery. INRA was technically successful in all patients. Endoscopy showed that the ileal mucosa had grown into the neorectum, with 100% coverage after 6 weeks. Pelvic sepsis, neorectal-anal or -vaginal fistula, autonomic nerve damage, or faecal incontinence were not reported. Neorectal function improved with time. At follow-up 12

months later, the median 24-hour defecation frequency decreased from 15 (range 9 to 25) to 7 (range 4 to 10) and the median maximum tolerated volume increased to 157ml (range 130 to 225 with reference values of 180-200ml). Anal manometry and electrosensitivity were not affected by surgery. Likewise during follow-up, biopsy samples showed a normal intestinal mucous membrane, without inflammation or fibrosis. The overall results of stage 1 after one year follow-up of these 11 patients and their low complication rate and good neorectal function were considered a justification to extend the clinical application of INRA in patients with UC and FAP.[10]

Stage 2a: development

After completion and evaluation of the prospective human pilot study (*n*=11) a larger group of patients (*n*=26) underwent INRA to reproduce the pilot, after this prospective development was registered and uniform documentation of patient selection, procedure and outcomes were defined.[10] Furthermore, at this stage modification and refinement of technique and equipment, as expected, were made. At this new stage, approval of the ethics committee was received before continuing with the surgical innovation.

During stage 1 and the beginning of stage 2 (*n*=12 patients) all patients were placed in the lithotomy position to allow an abdominal and a perineal approach. The 13th patient of the second cohort (stage 2a) was first placed in prone position to facilitate an optimal circumferential mucosectomy before changing the patient to the lithotomy position. Furthermore, the Andouilette© a special appropriately sized mould was developed to facilitate the creation of the vascularised mucosal sling from the terminal ileum.

The primary results (*n*=38) of mucosal transpositions after a median follow-up period of 2.5 years showed good overall results. Endoscopy showed full mucosal coverage of the reservoir and functional results were encouraging with a median defecation frequency of 7 times per 24 hours, and with preservation of continence. The neorectal compliance volume recovered from 12,5ml/kPa after subtotal colectomy and 11ml/kPa at 6 months after INRA to a neorectal compliance of 24ml/kPa (reference values 35-80ml/kPa) at 2 years' follow-up.

Thirteen patients had episodes of 'pouchitis', which were successfully treated with antibiotics. Pelvic sepsis, sexual and bladder dysfunction were not reported. Preliminary results of INRA were substantiated, showing low complication rates and functional results, the latter in range with IPAA.[5;14]

Stage 2b: early dispersion and exploration

Given the results of stage 2a, it was deemed safe to continue and recruit more patients, testing the procedure more broadly than before. At this stage all patients considered for restorative surgery after UC and FAP were candidate for INRA. INRA became the procedure of choice at the University Medical Centre Utrecht instead of IPAA.

Stage 3: assessment

In 2000, INRA was adopted by a second centre the St Elisabeth Hospital in Tilburg. Its surgical team regarded INRA as a potential innovative and efficient procedure in patients after colectomy for UC and FAP. During this stage neither new adjustments were required nor made to the technique. The local ethics committee of the St Elisabeth Hospital approved the INRA protocol. The surgical community, aware of the new technique, referred patients to these two centres.

At this stage, INRA had reached beyond the phase of being an experimental technique. After five years, INRA had become an accepted and proven technique and before implementation in the daily surgical practice, evaluation of its effectiveness against the current gold standard (IPAA) was needed. Using a prospective database, we were able to monitor and evaluate all late and rare outcomes of INRA.

After 58 successful INRA's with a median follow-up of 6.3 years, functional results were comparable to IPAA.[14;15] Defecation frequency was stable with a median of 6 per 24 hours, including a nocturnal frequency of one. Ninety-two percent of patients with INRA are faecal continent or report minor incontinence.[16]

Neither pelvic sepsis nor autonomic nerve damage, which could result in bladder or sexual dysfunction, have been reported in patients with INRA. However, 33% of the patients had anal stenosis, which could be treated resulting in a sufficient neorectum. Inflammation of the neoreservoir, comparable to pouchitis, was reported in 22% of the patients. Anoreservoir physiology testing displayed a decrease in anal resting pressure. However, anal squeeze pressure, sphincter squeeze time and the maximum tolerated volume of the rectum increased. No difference in compliance of the rectum was observed.

At this point, a critical assessment of INRA was made. The results had proven that the technique of small bowel transposition with a vascular pedicle is feasible and has good long term results.[17] Furthermore, the long term functional results and morbidity after INRA are in the same range as obtained with IPAA.[14;15] *Table 1* displays the major outcomes of an unpublished study. These are the results of a direct comparison by case matched controls. From the patient's point of view, no distinct advantage for INRA over IPAA was found. However, from the surgeon's point of view, INRA has its limitations. It is an arduous and lengthy operation (median operating time 336 minutes) and technically a demanding form of restorative surgery, requiring custom built surgical tools and specialized training for theatre and nursing staff. The decision which procedure to perform will therefore be based on the experience and judgement of the surgical team. Hence, surgeons strongly prefer IPAA and accepting this judgement it was decided not to offer INRA anymore and accept the current results of IPAA as the standard of care in patients requiring intestinal continuity after UC and FAP.

Table 1: Results of a matched comparison of INRA (*n*=71) to IPAA (*n*=71)

	INRA	IPAA	*p*-value
Pouchitis (%)	18	18	1.000
Bowel movements (median/24h)	6	8	0.108
Vaizey incontinence scores	5	5	1.000
Sphincter function			
- anal resting pressure (kPa)	7.0	7.2	0.806
- anal squeeze pressure (kPa)	18.1	19.4	0.330
- anal squeeze duration (s)	24	27	0.688

Discussion

This paper illustrates the stages of surgical innovation using the IDEAL-recommendations alongside a clinical example, INRA, a new surgical technique restoring intestinal continuity after colectomy in patients suffering from UC or FAP. Our description of this new procedure according to the recommendations shows how both innovation and evaluation can and should evolve together in an ordered manner from concept through exploration, to validation. Our example confirms the value of the IDEAL-recommendations and its suitability in the evaluation of surgical innovations.

The major strength of this paper is the illustration that surgical innovation, if following a step-up approach like IDEAL, is feasible in an evidence-based manner. The constant and repetitive evaluation from basic research, animal testing and the implementation in every day care including the long-term evaluation is an approach to reporting surgical innovation that is in accordance with today's manner of practising evidence-based medicine.[5;10;11;18]

This is an important aspect of IDEAL as presently too often data of surgical innovations, especially unsuccessful ones, are simply not recorded. Consequently, it is possible that others will continue or repeat such inefficient, or even unsafe procedures at the detriment of the patient.

Furthermore, history has shown us that many introductions of innovative operative procedures are not integrated in any regulatory framework. Many of these innovations have been published as non-comparative trials without special institutional review board requirement. For example, many laparoscopic procedures have been introduced in this manner. The uptake of laparoscopic surgery into society increased suddenly after its introduction and quickly involved an irrevocably large number of adopters. At this point it was not possible to do a formal assessment any more. By this time, the technology was already, rightly or wrongly, destined for adoption. Consequently, efforts to properly evaluate it will rarely be successful or even feasible. For example, the first laparoscopic

cholecystectomy was performed in 1985. In 1992, the first publication of a small randomised controlled trial was published.[19] The IDEAL-approach facilitates critical assessment and reporting of each step, fulfilling the obligation to report outcomes, successful and unsuccessful, in the public and professional forum.

An important limitation of this case study, although recommended by IDEAL is that no Randomised Controlled Trial (RCT) was performed to establish the safety and efficacy of INRA. While RCTs should be the default option at stage 3 and 4, we believe we had valid arguments to perform a non-randomised prospective study.[2] in the case of INRA, it was difficult to decide when to shift from an early exploratory stage of development to a formal investigation. The procedure during the first years was experimental, time consuming and techniques were to be refined. With INRA and IPAA having comparable benefit-to-harm profiles, a preference for IPAA from a surgeon's point of view is understandable since IPAA is a technique widely available with established results in over thousands of patients. Hence we have refrained from taking this path forward.

In the past, surgical advances have been based on the trial and error principle, formal and comparative assessment of procedures had little role. Traditional health technology assessment is based on a posteriori evaluation of interventions already entered clinical practice, and it is, therefore, difficult to carry out the kind of evaluation that would be necessary.[20-22]

Nowadays, results from surgical innovations should only be accepted if derived through evidence-based principles as suggested in the IDEAL-recommendations. In the IDEAL-approach surgical innovation is broken down into sequential stages characteristically reporting the early events and adoption of the technique; hence, not only accurately describing each stage of this development but also allowing for critical appraisal of these stages.[1] IDEAL will further transform the previous rather liberal approach of surgical innovation into a structured process based on the scientific principles of evidence-based medicine. Subsequently this will result in a better surgical care and improve patient-reported outcomes such as quality and length of life.[23]

Conclusion

Our example shows that rigorous evaluation of surgical interventions, although difficult, is feasible and necessary. Through the adoption of the IDEAL-recommendations, i.e. by performing evidence-based surgical studies, surgical science can be improved with the consequence that progress in surgical care continues and interventions become safer, more efficient and allow a better quality of life in the surgical patients.

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Chapter 5

The ileo neo rectal anastomosis: long-term results of surgical innovation in patients after ulcerative colitis and familial adenomatous polyposis

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Abstract

The ileo neo rectal anastomosis: long-term results of surgical innovation in patients after ulcerative colitis and familial adenomatous polyposis

Purpose
Restorative proctocolectomy with Ileo Neo Rectal Anastomosis (INRA) combines cure of ulcerative colitis (UC) or familial adenomatous polyposis (FAP) with restoration of intestinal continuity. Evaluation of long-term results was needed to determine if there is a place for INRA in the armamentarium of a surgeon besides the Ileal Pouch Anal Anastomosis (IPAA).

Method
All patients with INRA were included in the analysis. Patient demographics, clinical and follow-up data (morbidity, dietary problems, defecation frequency, faecal continence, anal and neorectal physiology, and neorectal mucosa assessment) were registered prospectively.

Results
Seventy-nine patients were enrolled, in 58 patients (50 UC, 8 FAP) INRA was successful. In 21 patients, intra-operative conversion to IPAA was needed. In 49 patients with INRA a functional reservoir was achieved. No pelvic sepsis, bladder or sexual dysfunction occurred. Thirteen patients experienced episodes of reservoir inflammation. Median bowel movements of six (5, 8) with a nocturnal defecation frequency of one were recorded with faecal continence or minor incontinence. Anal manometry and neorectal physiology showed a decrease in resting pressure and an increase in squeeze pressure and maximum tolerated volume. The median follow-up was 8.1 years (6.7, 10.1).

Conclusions
This is an example of a surgical innovation with a theoretical potential to be superior to the current technique. This potential was not confirmed in short- and long-term evaluations. Hence, IPAA is currently the best available alternative to a conventional ileostomy.

Introduction

Innovation is an important part of surgical practice. During the last decades, modern surgical care has greatly improved patients' quality and length of life.[1] An illustrative example of surgical innovation is the technique of restoring intestinal continuity in patients after colectomy for ulcerative colitis (UC) or familial adenomatous polyposis (FAP).

After removal of the colonic mucosa hereby curing the disease, an Ileal Pouch Anal Anastomosis (IPAA) can be constructed.[2] This technique preserves a natural route for defecation while maintaining faecal continence with acceptable bowel function (*Illustration 1*, page 12). However, despite modifications and experience in many thousands of patients, morbidity remains a substantial problem.[3-5]

In an attempt to reduce procedure-related complications of the pelvic dissection, a new surgical technique was developed: the Ileo Neo Rectal Anastomosis (INRA). This procedure focuses on restoration of intestinal continuity in the same patient category as IPAA.[6] The technique of INRA previously has been described in detail.[6;7] The procedure and its modifications through time have been related to surgical manoeuvres that applied clear-cut pathophysiological (in terms of potential nerve damage) and anatomical concepts.

The idea of small bowel mucosa was not new. In the 1960s, Brody and McCorriston, performed experimental transposition of small bowel mucosa to the rectum of dogs.[8] In 1964, Peck and Hallenbeck demonstrated that results of rectal mucosal transposition improved by leaving a vascular pedicle intact.[9] This formed the concept of INRA.

In brief, the technique was performed as follows: after subtotal colectomy, the rectal muscle wall is denuded by mucosectomy. A saline suspension is injected between the rectal mucosal and muscular layer (*Illustration 2*, page 12) to facilitate a mucosectomy (*Illustration 3*, page 13). A new rectal mucosal lining is prepared by performing a dissection of the most distal ileal serosa and muscle layers leaving the mucosa intact (*Illustration 4*, page 13), and a transposition of this healthy ileal mucosa with vascular pedicle is carried out into the denuded rectum (*Illustrations 5* and *6*, page 14).[6;7] This resulted in INRA being a demanding technique, requiring long operating times and a distinct learning curve.

In 1996, the first INRA procedures were performed in an animal laboratory on 12 Yorkshire-Dutch landpigs.[7] The preliminary success during the pre-human stage made it possible to progress with INRA. A pilot study was performed for the assessment of safety and proof of concept in humans.[6] After completion and evaluation of the prospective human pilot study, more patients underwent INRA and it became the procedure of choice for restoring intestinal continuity in two hospitals for a period of time.

In this study, and in sequence with reporting on the short- and medium-term results, we report on the long-term outcome of INRA. All patients who underwent INRA for UC and FAP were evaluated. Long-term analysis of function, morbidity, inflammatory responses, anal and neorectal physiology, bladder and sexual dysfunction, endoscopy, histopathology results, and evaluation of the intra-operative conversions to IPAA, are reported.

Method

Restorative proctocolectomy with INRA procedure was performed between 1998 and 2005 in two hospitals in the Netherlands: The University Medical Centre Utrecht (1998-2000) and the St Elisabeth Hospital Tilburg (2000-2005). In these hospitals, INRA was the procedure of choice for patients who required intestinal continuity and had adequate rectal length (15cm or more) after colectomy. If this was the case, mucosectomy of the rectum and INRA was performed. When mucosectomy was not deemed possible, only at that moment intra-operative conversion to IPAA was performed. Hence, during this period, IPAA was reserved as an alternative to INRA only to be performed when INRA was not deemed possible. No patients underwent IPAA as their primary procedure. Selection criteria for INRA were identical to IPAA: disease refractory to medical therapy, dysplasia found during screening colonoscopy, and an unacceptable incidence of rectal cancer. A contraindication for restorative surgery was an incompetent anal sphincter.

All patients who were candidate for INRA were subject to this study. The ethics committee of the University Medical Centre Utrecht and St Elisabeth Hospital Tilburg approved the study protocol. All patients were informed about the experimental character of the procedure and gave written informed consent. (ClinicalTrials.gov Identifier NCT00922103)

Patients were pre-operatively seen in the outpatients' clinic for detailed history, physical examination, endoscopy and ano-rectal physiology evaluation. Postoperatively, patients were seen in the outpatients' clinic at three and six weeks after the operation, at three months intervals thereafter until the end of the first year and then followed annually. All data was registered prospectively using pre-specified (electronic) case record forms scoring patient demographics, clinical and follow-up data including: morbidity, dietary problems, defecation frequency, faecal continence, bladder and sexual (dys)function, and medication use.

We used the definition of a complication as defined by the Association of Surgeons of The Netherlands to register morbidity: A complication is a condition or event, unfavourable to the patient's health, causing irreversible damage or requiring a change in therapeutic policy, including prolonged hospital stay.[10] Long-term complications related to the neorectal reservoir were analysed.

Function was defined in terms of defecation frequency and faecal (in)continence. A good functional neorectal reservoir was defined as: a functional reservoir with the ability to defer and evacuate, with a defecation frequency ranging from 4-12 times per 24 hours and without severe faecal incontinence. The degree of faecal incontinence was assessed using the Vaizey score.[11] Normal continence, minor, moderate and severe incontinence are set on a Vaizey score of respectively of 0-5, 6-10, 11-15, and 16-24.

Anal and neorectal physiology evaluation was performed preoperatively, at six and twelve months, and annually afterwards. Anal sphincter pressure was measured by a circular 4-channel low compliance water fusion manometry. Volume capacity and compliance of the neorectum were measured by means of balloon distension. All measurements were performed in the left supine position.[12-14]

Endoscopic assessment was done pre-operatively, one week, three, six, and twelve months, and annually afterwards to assess quality of the mucosa of the reservoir and distal ileum. All INRA's were assessed on degree of inflammation, vessel proliferation, granular mucosal structure, and mucosal strictures.

The tissue slides from colon resection samples, which had been processed for routine histopathological evaluation (hematoxylin and eosin staining), were collected. Since the histopathological diagnosis of UC in adults is challenging, especially because mucosal biopsies are often not conclusive, two blinded-independent experienced pathologists reviewed all (transmural) resection specimens of rectum and colon, re-evaluating the histological diagnosis, without knowledge of the initial diagnosis.[15] Non-concurring diagnoses were solved in a microscopical session to reach consensus.

Statistical analysis

Descriptive statistics were used to summarize patient demographics, clinical data, surgical details, histopathology results, morbidity, functional outcome, faecal incontinence, bladder-, and sexual dysfunction. Results are expressed as medians with interquartile range (25th and 75th quartile) unless stated otherwise. Anal and neorectal physiology data were analyzed with the Mann-Whitney Test (2-sided). Statistical significance was considered when $p<0.05$. SPSS® version 16.0 was used for all statistical analysis.

Results

Between January 1998 and September 2005, 79 consecutive patients were eligible for an INRA procedure (*Figure 1*). This was successfully carried out in 58 and 21 underwent intra-operative conversion to IPAA. Median defecation frequency of all 79 patients who underwent restorative surgery was 6 times (5, 8) per 24 hours. Median Vaizey score was 4 (1.5, 7.5). In nine patients the created neoreservoir failed to comply to the terms of a functioning neorectum. Median follow-up was 8.1 years (6.7, 10.1). Demographics of the

population are summarized in *Table 1*, as are the details of the surgical procedure, histological diagnosis and postoperative follow-up period.

In all patients the ileal mesentery had sufficient length to reach the pelvic floor. All patients had complete overgrowth and maturation of the transposed mucosa at endoscopy in the first weeks after surgery. A functional reservoir was achieved in 49 patients (85%). In nine patients there was a failure to achieve a functioning neorectum. Two patients, after INRA construction with deviating ileostomy, never opted to restore intestinal continuity on their own demand. The other seven INRA's failed due to medical reasons and are subject to our analysis when discussing the failures, as summarized in *Table 2*. The median postoperative follow-up period is for all patients after INRA was 8.3 years (6.6, 10.5).

Functional outcome INRA cohort

Median defecation frequency in the 49 patients (UC + FAP) with a functioning INRA, after ileostomy closure (median 3.2 months), was 10 (7, 12) including a median nocturnal frequency of 2 (2, 4). This decreased to a median of 6 (5, 8) per 24 hours, with a nocturnal frequency of 1 (1, 2) at a median follow up of 8.3 years after INRA.

Continence was measured according to the Vaizey scale in all patients (UC and FAP) with INRA: median of 4 points (1, 7). Twenty-nine patients (59%) reported normal continence, 16 patients (33%) minor incontinence, three patients (6%) moderate incontinence and one patient reported severe incontinence. All but one patient were able to defer defecation for more than 15 minutes.

For patients with INRA after UC (n=42), the median defecation frequency after closure of the ileostomy (median 3.7 months) was 10 (7, 12) including a nocturnal frequency of 2 (1, 4). This decreased to a median of 6 (5, 8) including a nocturnal frequency of 1 (1, 2) at a median follow up of 8.0 years (6.6, 10.5) after INRA.

Median continence score was 5 points (1, 9). Twenty-two patients (52%) reported normal continence for faeces, 15 patients (36%) reported minor incontinence, four patients (10%) reported moderate incontinence and one patient reported severe incontinence. All patients were able to defer defecation for 15 minutes.

For patients with INRA for FAP (n=7) the defecation frequency after ileostomy closure (median 3.3 months), was median 6 (5, 12) including night-time frequency of 2 (1, 3). This decreased to a median of 5 (5, 6) including night-time frequency of 1 (0, 1) at a median follow-up of 9.2 years (6.1, 10.5). FAP patients, after 8 years, scored a median of 2 (2, 4), reporting normal continence.

In total, eleven patients (18%) indicated to have altered their diet to avoid higher stool frequencies, the majority missing out of spices. There is no significant difference in defecation frequency between UC and FAP patients.

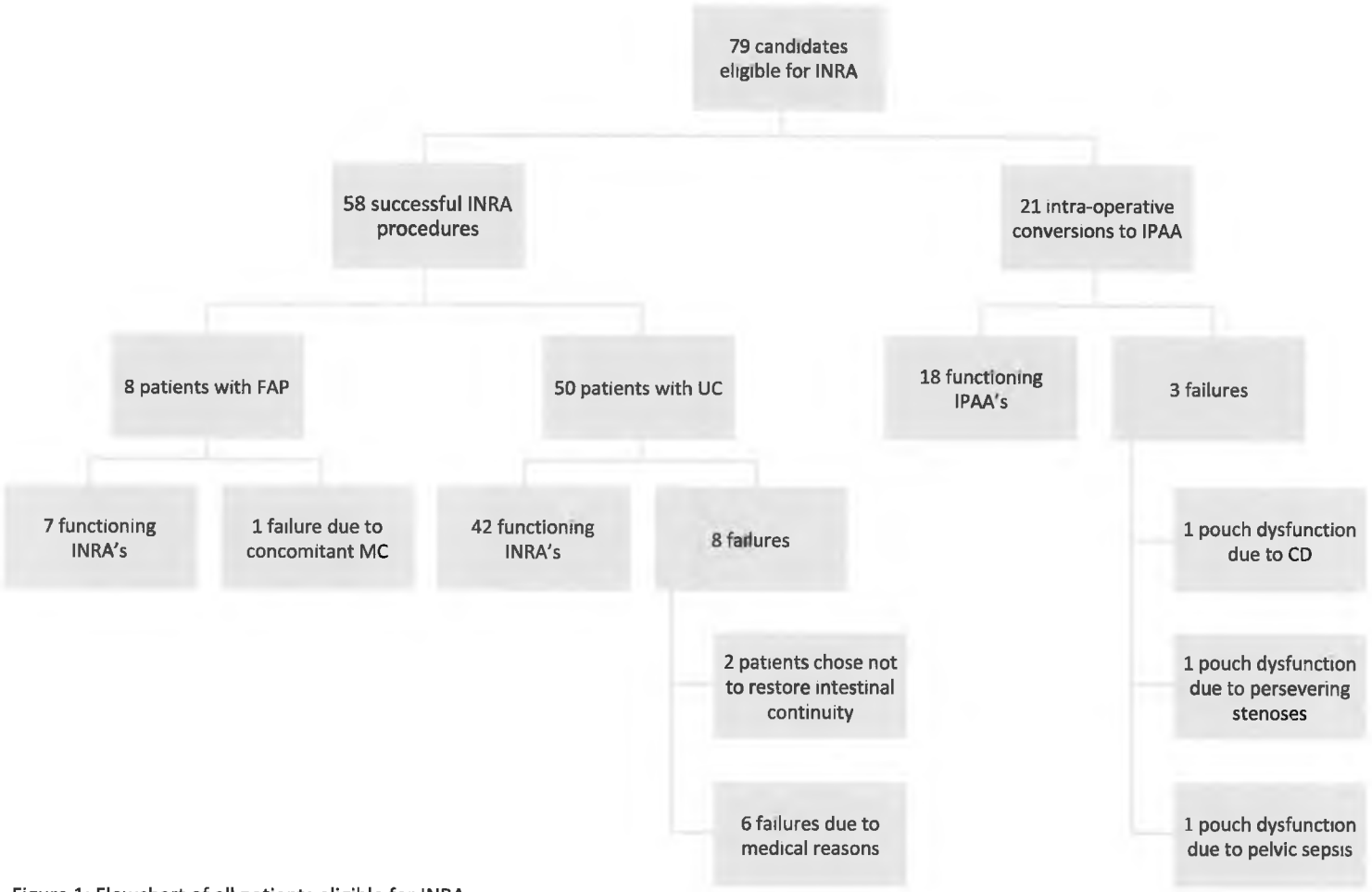

Figure 1: Flowchart of all patients eligible for INRA

Table 1: Demographic and clinical data (quartiles in parentheses, unless indicated otherwise)

	INRA (*n*=58)	**IPAA conversion (*n*=21)**	**INRA + IPAA (*n*=79)**
Sex ratio (M:F)	26:32	12:9	38:41
Median age at INRA / conversion	32.2 (24.3, 41.3)	40.3 (27.8, 44.8)	32.9 (25.6, 42.1)
Histological diagnosis preoperative-, / final diagnosis			
- UC	50 (86.2%) / 38 (65.5%)	20 / 19	70 (89%) /57 (72%)
- Indeterminate Colitis	0 / 2	0 / 0	0 / 2
- CD	0 / 10	0 / 1	0 / 11
- FAP	8 / 8	1 / 1	9 / 9
Surgical details			
- Median operating time (minutes)	336 (290, 390)	286 (213, 337)	330 (286, 360)
- Median blood loss (millilitres)	1350 (788, 2025)	1500 (1238, 2500)	1400 (1100, 1500)
Median length of mucosectomy (cm)	14 (12, 15)	-	-
Median time to ileostomy closure (days)	97 (79, 132)	105 (92, 140)	99 (81, 138)
Median follow-up (years)	8.3 (6.6, 10.5)	5.6 (4.6, 7.8)	6.2 (4.8, 8.3)

Table 2: INRA failures

Patient	**Final diagnosis**	**Reason for failure**
1	FAP + CD	Concomitant manifestation of CD
2	CD	Medical refractory proctitis
3	CD	Medical refractory proctitis
4	CD	Daily soiling day and night, urge <15 minutes
5	CD	Invalidating fistulas to perineum and vagina
6	CD	Incurable anal stenosis with invalidating high defecation
7	CD	Medical refractory proctitis

Complications of the INRA cohort

Neorectal reservoir-related complications

Complications are described of all patients with INRA (n=58). No pelvic sepsis occurred. Autonomic nerve damage with bladder dysfunction, ejaculation or erection disturbance was not reported during the detailed outpatients' history or questionnaire surveys. Nineteen patients (33%) had mucosa-anal stenosis, of which 10 patients were treated successfully by (self-)dilatation (Hegar® dilators) alone. Eight patients were treated successfully with self-dilatation followed by surgical stenoplasty. In one patient, despite repeated dilatation and stenoplasty, the stenosis persevered with invalidating high defecation frequency, resulting in excision of the neorectum and ileostomy.

Inflammatory complications

Seven patients reported fistulas. Three of these seven patients were diagnosed with Crohn's disease (CD) postoperatively of which two patients developed a fulminant Crohn's perineal disease with fistulas with failure of the neorectum and subsequently excision of INRA. All, but the two cases of CD, had functioning INRA's despite the fistula. Thirteen (22%) patients (8 UC, 1 Indeterminate Colitis, and 4 CD) had one or more clinical episodes of inflammation of the reservoir. Three patients (1 UC and 2 CD) had medical refractory pouchitis like inflammation leading to invalidating high defecation frequencies and eventually excision of the neorectum. One patient with INRA for FAP developed persevering inflammation of the neoreservoir after surgery. Histopathologic revision of colonic specimens and eventually of the excised reservoir revealed coincidental CD.

Anal and neorectal physiology

All patients could clearly indicate volume changes in the reservoir during manometry testing. Long-term results show a significant decrease in anal resting pressure (p=0.005). Anal squeeze pressure (p=0.025), maximum anal squeeze time of the sphincter (26 seconds, p=0.033), and the maximum tolerated volume of the neoreservoir (p=0.014) all improve after INRA. Compliance of the neoreservoir is comparable to the rectum before INRA (23 ml/kPa, p=0.251). Results of anorectal reservoir function tests are summarized *Figures 2* and *3*.

Bladder and sexual dysfunction

No bladder dysfunction was reported in total group during the detailed outpatients' history or in the questionnaire survey. In the male patient group, no retrograde ejaculation or erection disorders was reported nor dyspareunia in the female group.

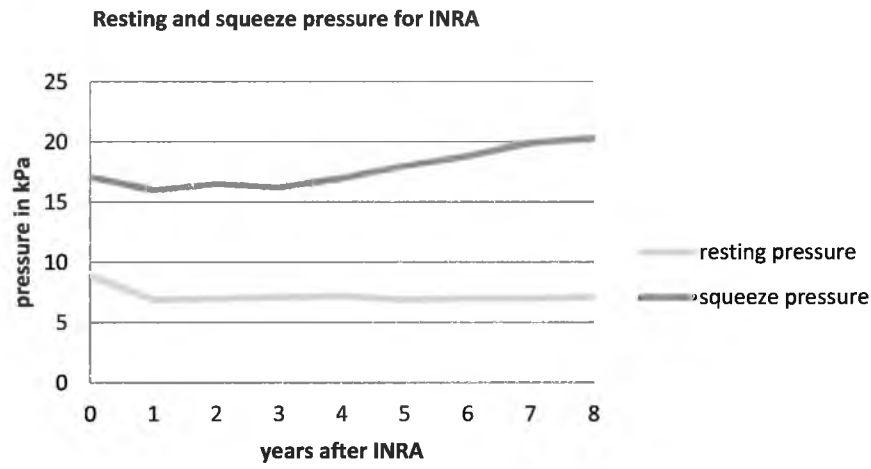

Figure 2: Results of anorectal reservoir function tests (resting and squeeze pressure)

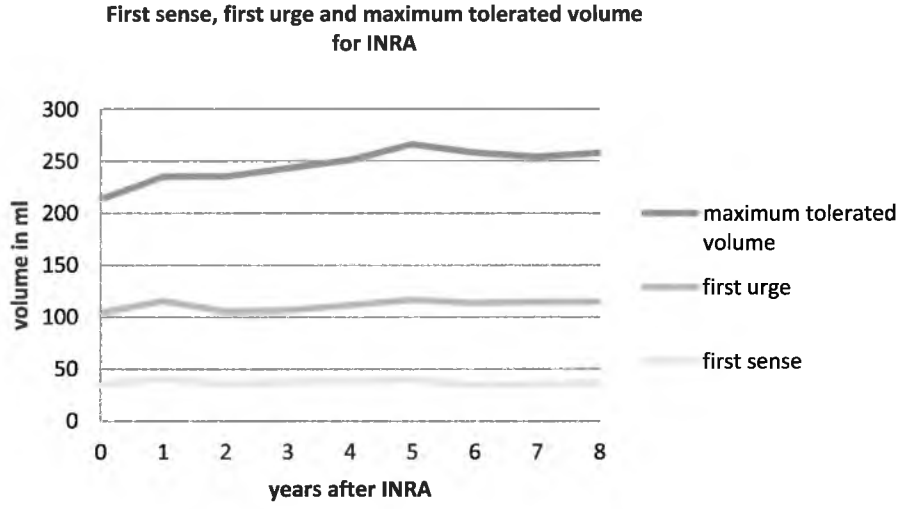

Figure 3: Results of anorectal reservoir function tests (first sense, urge, and maximum tolerated volume)

Endoscopy

Sequential endoscopy reports, complete in 38 (66%) cases, showed 100% mucosal coverage of the neorectum. Ulcers were seen in 2 patients and six patients (15%) had aftoid lesions. Thirteen patients (36%) had mucosal bridges, successfully resolved during endoscopy. Forty-seven (96%) of the 49 patients underwent endoscopy at a median of 5.5 years after INRA. All showed 100% mucosal coverage of the neorectum.

Histopathology

In 54 of the 58 cases the two independent pathologists agreed on the diagnosis. In 4 cases consensus was reached in a microscopical session. Review of all (n=58) resection specimens of rectum and colon in patients with INRA for UC resulted in reclassification of 12 (21%) cases. Ten patients were diagnosed with CD and one patient with indeterminate colitis. In one case no diagnosis related to inflammatory bowel disease was made, instead there was evidence of an ischaemic colitis based on the histological findings. Diagnosis of UC was based on continuous distal inflammation without fissures. The diagnosis of CD was based on the presence of fissures and discontinuous inflammation.

Intra-operative conversion to IPAA

In 21 cases, intra-operative conversion to IPAA was necessary due to difficulty to complete mucosectomy (17), inadequate length of rectal stump (2), too small diameter of the rectum, as a result of which the expected compliance of the neorectum would not be adequate (1), or the presence of intra-abdominal desmoid (1). No mortality was observed.

Eighteen (86%) of the 21 constructed IPAA's were successful and have functioning reservoirs. In three cases this was not accomplished. One patient had a clinical and histopathological course highly suggestive for the diagnosis of CD and in the end invalidating perineal fistula led to pouch failure. Another patient had pelvic sepsis and the third patient had a failure due to anal stenosis, which, despite dilatation and stenoplasty, persisted, resulting in a pouch malfunction with invalidating high defecation frequency. In all three cases IPAA was excised and a permanent ileostomy was created (*Figure 1*). Morbidity, and functional (defecation frequency and faecal (in)continence) in this group of patients was comparable to results of IPAA in literature.[16;17] In one patient late conversion to IPAA was required. After INRA for FAP, neorectal inflammation persevered causing a fibrotic neorectum with invalidating function. The neorectum was excised and an IPAA was constructed. However, as with INRA, ongoing inflammation was the cause for failure of IPAA. The latter was excised, leaving the patient with an ileostomy. Re-evaluation at a later stage of the excised neorectum and pouch revealed a histopathologic course of MC, concomitant to FAP.

Conclusions

This paper focuses on the outcome of an innovating new surgical procedure tested in patients requiring restorative surgery after UC or FAP. We had hypothesized that with this technique, the innervations of the rectum, bladder, vagina, prostate would be left intact, the risk of anastomotic leakage would be in range of ileorectal anastomosis, and the function of the neorectum would be normal to near normal.[6;7;13]

Complications related to a pelvic dissection were avoided with INRA leaving pelvic integrity intact. This study underlines results reported earlier on short- and medium-term complications.[6;13]

Furthermore, INRA with its unique large segment of vascularised small bowel mucosa transposition has added a new chapter in the field of autologous tissue transplantation/transportation in the human body. No anastomotic leakage was reported in patients with INRA, exceeding expectations. Undoubtedly, the manner in which the mucosal pedicle with its mesentery is attached to the denuded rectal wall over a distance of 14cm plays an important role, i.e., eliminating chances of local ischemia end therefore anastomotic leakage.

Hence, this study showed that the technique of small bowel transposition with a vascular pedicle is feasible and has good long-term results with a defecation frequency and the faecal continence in the same range as obtained with IPAA.[16;17] The primary aim of INRA, to achieve good functional results and to avoid complications related to pelvic dissection, has been achieved.

INRA, however, has its limitations. It is an arduous and lengthy operation, technically more demanding than the established form of restorative surgery. Furthermore, the INRA failure rate (7/58) is worrisome. This was mainly contributed to the missed diagnosis of Crohn's disease at a preoperative stage. Preoperative selection of patients eligible for restorative surgery remains challenging.[18]

With functional outcome in the same range of IPAA for a demanding procedure with theoretical physiological advantages as the early results, the most logical next step would have been to design a comparative study, preferentially a randomized control trial (RCT).[6;13] Currently, around 80 IPAA procedures are performed in the Netherlands on a yearly basis and theoretically these patients could be included in such a trial. The design of such a trial can be predicted to be difficult and the numbers needed to be included high, given the reference data that the outcome in function, the most clinically relevant outcome measure, will be similar to IPAA. Furthermore, the difference to be shown between these two techniques will be in complications and costs, for a technique with a distinct learning curve and more than two times as time consuming. It is not difficult to predict that the enthusiasm for such a RCT will be limited and although, the most logical

step, we have refrained from embarking on such a project, accepted the results as they were and have drawn the following conclusions.

INRA has distinct theoretical – in terms of physiology and anatomy – advantages. However, these advantages were not reflected in functional outcome of the procedure if compared with results in the literature for IPAA.

A proper comparison in a RCT is bound to end up with no clinically relevant difference in functional outcome in combination with a difference in cost and investment in terms of learning and operating time in favour of IPAA.

This experience is an example of a properly designed technique with a theoretical potential to be superior to the current technique. This potential was not confirmed in a thorough short and long-term evaluation. As a consequence we decided to stop the new technique and accept the current results of IPAA as the best available alternative to a conventional ileostomy.

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Chapter 6

Evaluation of long-term function, complications, quality of life and health status after restorative proctocolectomy with ileo neo rectal and with ileal pouch anal anastomosis for ulcerative colitis

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Abstract

Evaluation of long-term function, complications, quality of life and health status after restorative proctocolectomy with ileo neo rectal and with ileal pouch anal anastomosis for ulcerative colitis

Aim

Restorative surgery after (procto)colectomy with ileo neo rectal anastomosis (INRA) or restorative proctocolectomy with ileal pouch anal anastomosis (RPC) combines cure of ulcerative colitis (UC) with restoration of intestinal continuity. This study aimed to evaluate these two operations.

Method

Patients having INRA and RPC were matched according to sex, age at onset of UC, age at restorative surgery, and duration of follow-up. Patients were included if they were over 18 years of age, had UC confirmed histopathologically, and had undergone either operation. Long-term function, anal and neorectal physiology, complications, quality of life (QoL), and health status (HS) were determined.

Results

Seventy-one consecutive patients underwent surgery with the intention of performing an INRA procedure. This was successfully carried out in 50, 21 underwent intra-operative conversion to RPC. Median defecation frequency was 6/24 hours. In 11/71 patients, reservoir failure occurred and 13/71 developed pouchitis. QoL and HS were comparable to the healthy population. Median follow-up was 6.2 years.

These patients were matched with 71 patients who underwent restorative proctocolectomy. RPC was successful in all patients. Median defecation frequency was 8/24 hours. Failure occurred in 7/71 patients and 13/71 developed pouchitis. QoL and HS were comparable with the healthy population. Median follow-up was 6.9 years.

Conclusions

Comparison of INRA and RPC on an intention to treat basis was not considered to be realistic due to the high intra-operative conversion rate and the failures in the INRA group. RPC remains the procedure of choice for restoring intestinal continuity after proctocolectomy for ulcerative colitis.

Introduction

Restorative proctocolectomy with ileal pouch anal anastomosis (RPC) is the method of choice to restore continuity in patients with ulcerative colitis (UC) and has been carried out in many thousands of patients (*Illustration 1*, page 12).[1-3] In the absence of an alternative procedure, bowel function following RPC is referred to as 'acceptable'.[4;5] Furthermore, RPC is a technically demanding operation associated with serious complications, which may have a detrimental effect on function, quality of life (QoL) and health status (HS).[4;6]

In the late 1990s, a surgical innovation, the ileo neo rectal anastomosis (INRA) was developed.[7] The INRA technique is based on the transposition of healthy ileal mucosa to the rectum (*Illustrations 2-6*, pages 12-14). This was not a revolutionary idea but it had not yet been performed on a broad scale in humans. In the 1960s, Brody and McCorriston, performed experimental transposition of small bowel mucosa to the rectum of dogs.[8] In 1964, Peck and Hallenbeck demonstrated that results of rectal mucosal transposition improved by leaving a vascular pedicle intact.[9] This formed the concept of INRA, restoring intestinal continuity in the same patient category as RPC.

The technique of INRA previously has been described in detail.[7;10] In brief, the technique was performed as follows: after subtotal colectomy, the rectal muscle wall is denuded by mucosectomy. A new rectal mucosal lining is prepared by performing a dissection of the most distal ileal serosa and muscle layers leaving the mucosa intact, finally a transposition of this healthy ileal mucosa with vascular pedicle is carried out into the denuded rectum. At any stage, if INRA was not deemed possible, intra-operative conversion to RPC is possible. Hence, INRA is conceptually a different procedure in which no pelvic dissection is carried out, keeping the pelvic muscle integrity intact.[11-15] In this study the long-term function and physiology, complications, QoL and HS of INRA to RPC are compared.

Method

Patient population

The INRA procedure was performed between 1998 and 2005 in two hospitals in the Netherlands: The University Medical Centre Utrecht (1998-2000) and the St Elisabeth Hospital Tilburg (2000-2005). In these, INRA was the procedure of choice for patients who required intestinal continuity for UC.

Patients with INRA as their procedure of choice were matched with patients having RPC. The two groups were also matched on the basis of sex, age at onset disease, age at restorative surgery, date of restorative surgery, duration of follow-up, and socio-demographics. Patients were included if they were over 18 years of age, had UC confirmed histopathologically, and had undergone either operation.

The RPC patients had undergone surgery at the Radboud University Nijmegen Medical Centre. These patients were eligible for comparison for several reasons. First, in this centre, the procedure was, routinely performed in two stages with a temporary loop ileostomy, similar to INRA. Secondly, the cohort of RPC patients was large enough and was described extensively to allow adequate matching. If data were missing, patients were contacted and extensive interviews followed to complete the registry. Third, this cohort of patients with RPC underwent surgery during the same period in time, providing matching follow-up times. It was performed by other surgeons than those who performed INRA, avoiding bias. RPC was performed by three surgeons in the Radboud University Nijmegen Medical Centre and INRA was carried out by two dedicated surgeons from the University Medical Centre Utrecht and one from the St Elisabeth Hospital Tilburg. INRA was performed after colectomy as described by Van Laarhoven.[7;10] RPC was performed as described by Nicholls.[16]

Study design

The ethical committee of the University Medical Centre Utrecht, St Elisabeth Hospital Tilburg, and Radboud University Nijmegen Medical Centre approved the study protocol. All patients gave written informed consent. (ClinicalTrials.gov Identifier NCT00922103)

Long-term follow-up data from all patients with INRA as their procedure of choice were compared with the long-term follow-up data of the matched RPC patients. Data extracted included neoreservoir function, anal and neorectal physiology, complications, QoL, and HS.

Function

The frequency of defecation was recorded as evacuations/24 hours. Nocturnal defecation frequency was recorded separately. Faecal continence was assessed using the Vaizey scoring system (0-24).[17] Normal continence, minor, moderate and severe incontinence correspond to scores as follows: 0-5, 6-10, 11-15, and 16-24.

Manometry was performed with the patient in the left lateral position, according to the previously described technique using a standard station pull-through.[18;19] Mean maximum resting and squeeze pressure in the four quadrants of the anal canal was calculated.[20;21] Neorectal compliance was assessed by balloon manometry.[7;10;11]

Long-term complications

Complications were defined according to the criteria of the Dutch Association of Surgeons.[22;23] Pouch failure and sepsis, erectile dysfunction, dyspareunia, bladder dysfunction, fistulae, pouchitis, anal strictures, diet limitations, and the prolonged use of antidiarhoeal medication were all recorded.

QoL and HS

Patients received a questionnaire package containing a socio-demographic questionnaire (education level, marital status, and parenthood), a QoL and HS questionnaire. Socio-demographics influence QoL and HS.[24;25] To be able to contribute differences in QoL or HS to surgery, information on socio-demographics is essential.

QoL was assessed with the World Health Organization Quality of Life assessment instrument (WHOQOL-100), the Dutch version.[26] This covers 24 specific facets belonging to the six domains of QoL (Physical health, Psychological health, Level of independence, Social relationships, Environment, and Spirituality) as well as a generic facet assessing the patients overall QoL scores. The WHOQOL-100 was developed in 15 centres worldwide. Reliability and validity are adequate and sensitivity is high.[27-30]

To assess general health status the RAND-36, Dutch version, was used that covers HS in eight dimensions (Physical functioning, Social functioning, Role limitations due to physical health problems, Role limitations due to personal or emotional problems, General mental health, Vitality (energy & fatigue), Bodily pain, and General health perceptions).[31;32] Additionally, it includes a single item providing an indication of perceived changes in health. A high score indicates a good health status. The RAND-36 has a good reliability and validity.[33]

Generic measurement tools were chosen for the analysis to be able to compare the results of restorative surgery with reference scores. These scores were derived from the manuals of the WHOQOL-100 and RAND-36 and are based on healthy Dutch populations of comparable age.[26;34] All questionnaires were validated for use in this patient population.

Statistical Analysis

Descriptive statistics were used to summarize patient demographics and function. Associations between baseline characteristics of patients with INRA and RPC were analysed using the Chi-Square Test (or Fisher exact tests) for categorical variables and the Independent-Sample t-test for continuous variables. For data with a non-parametric distribution the Mann-Whitney test was used.

A p-value of <0.05 was taken to indicate statistical significance. The results are expressed as median with interquartile range unless otherwise stated. The Statistical Package for Social Sciences (SPSS® version 17.0) was used for analysis.

Results

Between January 1998 and September 2005, 71 consecutive patients underwent surgery with the intention of performing an INRA procedure. This was successfully carried out in 50 (70%) patients. Twenty-one underwent intra-operative conversion to RPC because the

completeness of the mucosectomy was too unreliable owing to inflammation or to an inadequate length or diameter of the rectum.

in the INRA cohort, intestinal continuity was fully restored (median 98 days after restorative surgery) in 69/71 patients. Failure to achieve a functioning reservoir was diagnosed in 11 patients. Two (2/11) patients (after a successful INRA procedure) decided not to undergo closure of the ileostomy. In 9/11 (6 INRA, 3 RPC) failure occurred due to pelvic sepsis (*n*=1), stenosis persisting after dilatation and stenoplasty (*n*=2), reclassification to Crohn's disease (*n*=3), and pouchitis not responding to medical therapy (*n*=3). At the time of this evaluation, 42 of the 50 patients had a functioning INRA.

The matched cohort of 71 patients underwent RPC between January 1996 and November 2006. The operation was successfully carried out in all patients. The ileostomy was closed in all 71 patients at a median of 102 days. Pouch failure occurred in seven (10%) patients due to medical refractory pouchitis (*n*=5) and pelvic sepsis (*n*=2). At the time of evaluation 64 patients had a functioning pouch.

There were no significant differences between INRA and RPC patients regarding demographics, sex, age at onset disease, age at restorative surgery, or at the duration of follow-up (6.2 and 6.9 years; INRA and RPC) (*Table 1*). Due to the high intra-operative conversion rate of the INRA cohort and the INRA failures, it was not possible to compare these two surgical procedures without compromising methodological validity. Owing to this major drawback, results of the full cohort of INRA with intra-operative conversions (*n*=71) and the subgroup of successful INRA patients (*n*=50) are presented separately in relation to the RPC patients.

Table 1: Baseline and socio-demographic characteristics of the INRA and RPC cohort (percentages in parentheses, 25th and 75th quartile in square brackets)

	INRA (*n*=71)	**RCP (*n*=71)**	***p*-value**
Sex ratio (M:F)	29:42	29:42	1.00
Median age onset disease (years)	27.6 [19.3, 36.9]	27.5 [22.2, 31.9]	0.813
Median age at restorative procedure (years)	32.3 [25.6, 41.1]	35.1 [28.3, 40.3]	0.734
Median follow-up (years)	6.2 [4.8, 7.9]	6.9 [3.9, 8.3]	0.655
Highest level of education	3 (4)	2 (3)	0.652
- Primary school	46 (65)	39 (55)	0.234
- Vocational training	1 (1)	3 (4)	0.314
- Secondary school	21 (30)	27 (38)	0.290
- Higher education	26 (37)	20 (28)	0.285
Marital status (married or with partner)	23 (32)	17 (24)	0.266
Parent (yes)	29:42	29:42	1.00

INRA (*n*=71)

Function

INRA and intra-operative conversions (n=71)

The median frequency of defecation was 6 (5, 8)/24h. Fifty-nine (83%) patients in the INRA cohort had nocturnal bowel movements at a median frequency of 1 (1, 2). The median Vaizey incontinence score was 5.

Patients with INRA (n=50)

The median frequency of defecation was 6 (5, 9)/24h with a nocturnal frequency of 1 (1, 2). Median Vaizey incontinence score was 5. Eight patients had an ileostomy due to failure of INRA. These patients were excluded from the analysis.

Physiology

INRA and intra-operative conversions (n=71)

Manometry results were available for 58 (82%) patients. Despite the fact that all patients with an INRA in situ were invited to take part, some refrained from evaluation as the investigations were considered too demanding. Median anal resting pressure was 7.0kPa, anal squeeze pressure 18.1kPa and the duration of squeeze was 26 seconds. Volume thresholds for first sensation, first urge and maximum tolerated volume were 53ml, 128ml and 139ml.

Patients with functioning INRA (n=42)

Forty-two of the original 50 patients having an INRA had continuing anal function. The eight failures were excluded from the analysis. Median anal resting pressure was 7.1kPa, anal squeeze pressure 17.9kPa and the duration of squeeze was 24 seconds. Median volume threshold for first sensation, first urge, and maximum tolerated volume was 30ml, 66ml and 120ml.

Other parameters

Postoperative complications are presented in *Table 2*. Compared with the reference scores, there were no differences in quality of life between patients with INRA and the healthy population (*Table 3*). There was no difference in the health status of INRA patients and the general population (*Table 4*).

RPC (*n*=71)

Function

The median frequency of defecation was 8 (6, 10)/24h. Sixty-two (88%) patients had a median frequency of 2 nocturnal bowel movements at a median frequency of 2 (1, 2). The median Vaizey score was 5. Seven (10%) patients experienced pouch failure, and were excluded from the analysis.

Physiology

Manometry results were available for 52 (73%) of patients in the RPC cohort. All participating patients could clearly indicate volume changes in the reservoir during manometry testing. Anal resting pressure (IPAA 7.2kPa), anal squeeze pressure (IPAA 19.4kPa) and squeeze duration (27s) were calculated. Median volume thresholds for first sense were 51ml, first urge (117ml), and maximum tolerated volume was 185ml. Patients with pouch failure (*n*=7) were excluded from the analysis.

Other parameters

Complications after RPC are shown in *Table 2*. Compared with the reference scores, there were no differences in quality of life between patients with PRC and the general healthy population (*Table 3*). Compared with the reference population, there was no difference in health status of patients having RPC (*Table 4*).

Table 2: Long-term reservoir-related complications of the full INRA cohort including intra-operative conversions (*n*=71), the patients with INRA (*n*=50), and the matched RPC cohort (percentages are presented in parentheses)

Type of complication	**INRA (*n*=50)**	**INRA (*n*=71)**	**RPC (*n*=71)**
Pouch failure	8 (16)	11 (15)	7 (10)
Erectile dysfunction	0	1 (1)	3 (4)
Dyspareunia	0	0	2 (3)
Bladder dysfunction	0	1 (1)	6 (8)
Fistulae	6 (12)	6 (8)	5 (7)
Pelvic sepsis	0	1 (1)	6 (8)
Pouchitis	10 (20)	13 (18)	13 (18)
Anal strictures	15 (30)	18 (25)	13 (18)
Strictures requiring dilatation	15 (30)	18 (25)	13 (18)
Strictures requiring stenoplasty	6 (12)	6 (8)	2 (3)
Diet limitations	9 (18)	12 (17)	21 (30)
Constipating medication	15 (30)	21 (30)	26 (37)

Table 3: Long-term QoL in patients after restorative surgery for UC. Comparison of the reference values to the full INRA cohort including intra-operative conversions (*n*=71), the patients with INRA (*n*=50), and the matched RPC cohort (*p*>0.05 between all values)

WHOQOL-100	***Reference values***	**INRA (*n*=71)**	**INRA (*n*=50)**	**RPC (*n*=71)**
Overall QoL	*15.6*	15.3	15.8	14.6
Physical health	*14.6*	13.7	13.6	14.0
Psychological health	*14.7*	15.5	15.6	15.3
Level of independence	*16.3*	15.0	15.0	15.1
Social relationships	*15.1*	16.6	16.8	15.5
Environment	*15.8*	16.2	16.5	15.2
Spirituality	*13.3*	12.5	12.3	12.8

Table 4: Long-term HS in patients after restorative surgery for UC. Comparison of the reference values to the INRA cohort including intra-operative conversions (n=71), the patients with INRA (n=50), and the matched RPC cohort (p>0.05 between all values)

RAND-36	*Reference values*	INRA (n=71)	INRA (n=50)	RPC (n=71)
Physical functioning	*79.9*	81.1	80.4	81.7
Social functioning	*86.1*	78.9	78.5	80.3
Role limitations physical	*78.9*	73.7	75.1	71.4
Role limitations emotional	*83.6*	82.4	81.2	88.9
General mental health	*76.7*	75.7	73.6	78.7
Energy/fatigue	*67.5*	62.3	65.4	58.3
Bodily pain	*80.5*	80.3	79.1	83.0
General health perception	*71.6*	70.4	73.2	64.1
Health changes	*51.9*	61.7	62.8	50.0

Discussion

This prospective cohort study was initiated to compare two restorative procedures for UC, a surgical innovation (INRA) and the gold standard RPC. The intra-operative conversion rate of 30% in INRA makes analysis on the basis of intention to treat impractical. Comparing only the successful INRAs with RPC excluded 8 patients with a failed INRA of the 50 who ended the operation having had this procedure, thereby introducing a positive selection bias to the INRA cohort. For this reason the results of the two operations have been presented separately.

Of the group of 71 patients eligible for INRA, in only 42 this was successfully accomplished. Of the remaining 29 patients 18 underwent a successful conversion to RPC. Thus it was the case that 60 (85%) of the 71 patients were able to have a restorative procedure whether by INRA or RPC. Conversion from the former to the latter did not seem to prejudice the chance of long-term anal function.

In the patients who had a functioning INRA long-term function was constant over time, being similar to that reported by us in 2004 over a shorter interval from surgery.[35] In addition the present study showed that QoL and HS were comparable to the healthy population.

There were several reasons for intra-operative conversion and postoperative failure. These included a long learning curve for a technically complex procedure, difficulty to complete the mucosectomy, inadequate rectal length or reservoir capacity, and anal stricture due to distal ileal ischaemia. Due to the high rates of intra-operative conversion and the subsequent failure of 16% in those who actually had INRA, we concluded that RPC was the preferred procedure for restoring intestinal continuity in these patients and consequently we stopped performing INRA.[36]

The assessment of an operation is complex since several factors need to be taken into account. These include the operator, the surgical and anaesthetic team, and the setting. The learning curve must be defined and factors that can affect variations in quality should be identified as far as is possible. In surgery, the development of an innovative procedure often continues as it is adopted into practice. For clinicians, researchers, and patients, any opportunity for formal assessment will thus need to be taken to justify whether or not to continue the innovation. Although INRA proved not to be as effective as RPC, the present study is an illustration of how the evaluation of a surgical innovation should proceed with regular assessment over time and, despite promising medium-term results, why it is important to follow patients over the long term.

The challenge to improve and develop the technique of RPC remains and the results have improved in time.[3] Today RPC with close rectal dissection using automated vessel sealing devices may have reduced the trauma of the pelvic dissection. Continued development of RPC in our unit with the introduction of new devices to improve the current technique, may improve the results still further. The preliminary results are promising.[37]

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Chapter 7

Ileo neo rectal anastomosis and ileal pouch anal anastomosis for colorectal mucosal disease: a case series of the intra-operative conversions

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Submitted

Abstract

Ileo neo rectal anastomosis and ileal pouch anal anastomosis for colorectal mucosal disease: a case series of the intra-operative conversions

Purpose
Restorative surgery after colectomy with Ileo Neo Rectal Anastomosis (INRA) combines cure of ulcerative colitis or familial adenomatous polyposis with restoration of intestinal continuity. INRA has a high intra-operative conversion rate (27%) to Ileal Pouch Anal Anastomosis (IPAA). Offering patients INRA, overall results of the intra-operative conversions to IPAA should be comparable to patients with IPAA as their choice of procedure.

Method
All intra-operative conversions to IPAA in patients who underwent INRA were analysed. Long-term function, anal manometry, reservoir physiology, complications, endoscopy results, and quality of life were determined.

Results
All seventy-nine patients undergoing surgery with the intention to perform an INRA procedure were studied. INRA was successfully carried out in 58 of 79 patents; 21 had to undergo an intra-operative conversion to into IPAA. The median follow-up period was 5.6 years since INRA, and one patient was lost to follow-up. The patient group which underwent a conversion after initial INRA procedure showed a median defecation frequency of 7 per 24 hours; anal manometry showed normal resting- and squeeze pressures with lower squeeze times. Pouch failure, stenosis, and pouchitis were observed in 15% of the patients. Scores on the quality of life were comparable to the healthy population.

Conclusions
Patients who undergo INRA with intra-operative conversion to IPAA have long-term function and complication rates comparable to patients with IPAA as procedure of choice. Quality of life scores are comparable to the healthy population.

Introduction

Ulcerative Colitis (UC) and Familial Adenomatous Polyposis (FAP) are mucosal diseases of the colon. Removal of colonic mucosa cures the disease, and reduces the risk of malignant changes in the colonic mucosa. The surgical treatment of both UC and FAP has evolved simultaneously. Nowadays, proctocolectomy is often followed by restoring the natural route for defecation and thus maintaining faecal continence with an acceptable bowel function.

Since its introduction (1978), the Ileal Pouch Anal Anastomosis (IPAA) has become the standard restorative procedure in patients with UC and FAP.[1] However, despite modifications in the procedure and its experience in several thousands of patients, the morbidity after IPAA remains substantial.[2;3]

Twenty years later, with the aim to reduce these procedure-related complications of the pelvic dissection, the Ileo Neo Rectal Anastomosis (INRA) was developed by Van Laarhoven. While offered to the same patient population as IPAA, INRA focuses on restoring the intestinal continuity.[4] Between 1996 and 2005 two centres in the Netherlands subsequently developed INRA, which progressed from a theoretical concept, via animal experiments into a primary surgical intervention for patients suffering from UC and FAP.[5]

If at any point during INRA surgery it was deemed impossible to perform a complete INRA, a conversion to IPAA was always a safe option and definitive form of restorative surgery.[4;6] One of the major drawbacks during INRA surgery became its high conversion rate (27%); hence, an evaluation of this group which had to undergo a conversion is relevant for the eventual position of the INRA in the realms of restorative surgery. If INRA patients which underwent an intra-operative conversion perform inferior to patients with IPAA as their initial procedure, the indication to perform INRA becomes questionable.

In this study, all patients with intra-operative conversions to IPAA during an INRA procedure are presented. The aim of this study is to compare the results of those INRA patients which underwent the conversion with those patients which primarily underwent IPAA, and report and compare their postoperative functional, complications, and quality of life (QoL).

Method

All patients which underwent INRA and which were deemed to an intra-operative conversion are subject of this study. Patients scheduled for INRA were preoperatively screened and a detailed history, a physical examination, an endoscopy and an evaluation of their ano-reservoir physiology were undertaken.

INRA, and therefore the reported intra-operative conversion to IPAA, were carried out by a select group of surgeons in two Dutch hospitals: the University Medical Centre Utrecht and the St Elisabeth Hospital in Tilburg. Their ethics committee approved the study protocol, and all patients gave written informed consent. (ClinicalTrials.gov Identifier NCT00922103)

If during the procedure INRA was deemed impossible, a pouch -not dissimilar from the one commonly performed IPAA procedure- was constructed, and the reason for this intra-operative conversion was recorded.

Postoperatively, all patients were reviewed at three-, six- and twelve months and subsequently at annual intervals. Their data were stored electronically and recorded the patients' demographics, clinical-, and follow-up data, their function, results of ano-reservoir manometry, complications (laparotomy related and long-term complications), and endoscopy results. In addition QoL questionnaires were completed during subsequent similar outpatient clinic visits and stored in the same data-base.

Pouch function was defined in terms of defecation frequency and continence. The degree of faecal incontinence was assessed using the Vaizey score.[7] Normal continence, minor, moderate and severe incontinence are set on a Vaizey score of respectively 0-5, 6-10, 11-15, and 16-24.

During manometry of the ano-reservoir, patients were studied in the left lateral position. A customized ano-rectal motility catheter was inserted via the anal canal. This catheter (Mui scientific, Mississauga, ON, Canada) had a 4.8mm outer diameter and contained four radially oriented recording points (90 degrees apart) and a 12cm latex balloon attached to the distal end. To assess resting and squeeze pressures in the anal canal a, standard station pull-through technique was employed using a water perfused catheter measuring at consecutive levels the four separate quadrants at every centimetre in the distal anal canal.[8;9] The maximum anal resting pressure was defined as the highest resting pressure during a 30s relaxation period, and maximal anal squeeze pressure as the highest increase over a resting pressure during two attempts of maximal anal squeezing.[10] Mean maximum resting and squeeze pressure in the four quadrants of the anal canal were then calculated. Normal values were 5-10kPa for resting pressure, and 20-24kPa for squeeze pressure.[11;12]

Rectal compliance and sensitivity were assessed during distension of a latex balloon tied respectively at 0.5 and 7.5cm from the distal end of the ano-rectal manometry probe. The balloon was positioned 5cm from the anal verge and via a central lumen infused (100ml/min) with water at room temperature. The balloon consisted of a cylindrical polyethylene bag with an infinite compliance up to a maximum volume of 1000ml (maximum diameter 12cm by a length of 10cm). Compliance was defined as the tangent of the straight section of the S-shaped curve after subtracting compliance of the latex balloon. Capacity was defined as the maximum volume in the balloon and determined by reaching the plateau phase of the measured pressure-volume curve. Intra-balloon

pressure was recorded by a separate lumen (0.8mm water perfused) inside the pressure balloon.

The moment of the first sensation/first awareness of 'stool' presence in the neo-rectum was taken as the first 'sense'. The moment of first urge was defined as the moment the patient would indicate the need to go to the toilet. The maximum tolerated volume is the maximum distension of the balloon in millilitres at which the patient experiences an uncontrollable urge or discomfort.

QoL was defined using the World Health Organization Quality of Life Group (WHOQOL group) which defines QoL as the individual's perception of his/her position in life; both in the context of the culture and value systems in which he/she lives, and in relation to his/her goals, expectations, standards and concerns.[13;14] In other words, QoL is a broad evaluation of human satisfaction with functions in different domains, i.e. of physical health, level of independence, psychological health, spirituality, its environment, and social relationships. QoL was measured using an international and cross-culturally validated instrument (World Health Organization Quality of Life-100 items; WHOQOL-100, the Dutch version[15;16]), proven to sensitively measure subtle changes in patients' QoL.[17;18]

Generic measurement tools, derived from the WHOQOL-100 and based on healthy Dutch populations of comparable age, were used to compare the results from IPAA with reference scores.[19] Furthermore, long-term QoL scores of patients with IPAA as their procedure of choice were compared to those of the intra-operative conversions.[20] All questionnaires were validated for use in this patient population.

Statistical Analysis

Descriptive statistics were used to summarize patient demographics, clinical data, surgical details, function, anal manometry and reservoir physiology, complications, and QoL data. Continuous data were tested by paired-T-tests, or otherwise Wilcoxon signed-rank tests as indicated. Statistical significance was considered if $p<0.05$. The SPSS® version 16.0 was used for all statistical analysis.

Results

Between January 1998 and September 2005, 79 patients were selected for INRA surgery and, in 21 of those the surgeon had to resort to an intra-operative conversion to IPAA; all of which were successfully completed. In all patients a J-pouch was constructed followed by a stapled anastomosis. Routinely a temporary diverting ileostomy was performed. Approximately three months after clinical- and radiological assessment of the pouch and the anastomosis, intestinal continuity was realised. Patient characteristics and surgical details of these intra-operative conversions are summarized in *Table 1*.

Table 1: Patient characteristics and surgical details of all patients with an intra-operative conversion to IPAA (25th and 75th quartile in parentheses)

	n=21
Sex ratio (M:F)	12:9
Median age at operation (years)	40.3 (27.8, 44.8)
Surgical details	
- Operating time (median in minutes)	286 (213, 337)
- Blood loss (median in millilitres)	1500 (1238, 2500)
Median follow up (years)	5.6 (4.6, 7.8)

During the operation, the reasons for conversion differed. In 1) 17/21 patients (81%) it was difficult to complete a mucosectomy because of a fulminant proctitis in situ, and in other situations 2) an inadequate length was left to prepare a rectal stump (*n*=2), 3) and in one patient a too small diameter of the rectum – as a result of which the expected compliance of the neo-rectum would be inadequate – was the reason for conversion, further 4) in one patient the presence of intra-abdominal desmoids was the reason (exclusion criterion for INRA). Postoperatively, three patients had a pouch failure; one patient had a clinical and histopathological presentation suspect for the diagnosis of Crohn's disease (CD) in which invalidating peri-anal fistulas, a second patient had a pelvic sepsis and the third patient had a failure due to an anal stenosis, which despite dilatation and stenoplasty, persisted which led to pouch malfunction with invalidating high defecation frequencies. In all three cases IPAA was excised and a permanent ileostomy was created. One patient with a functioning IPAA was lost to follow-up three years after IPAA surgery: its last record noted a functional IPAA and the comment that the patient was satisfied about the procedure and that it did not interfere with its daily life.

Overall, only 17 patients with a functioning pouch were eligible for this study on conversions in the INRA procedure. Analysis on the complications will be performed on all patients with a technical successful conversion to IPAA and who completed follow-up (*n*=20). *Figure 1* displays all patients eligible for INRA and the patients with intra-operative conversions.

Functional outcome

The median defecation frequency, after ileostomy closure, for all 17 patients with a viable IPAA is displayed in *Table 2*. Results are compared to the results of the meta-analysis by Hueting[21]. Faecal (in-)continence scores show 15/17 patients with normal continence, one patient with minor- and one with moderate incontinence. None of the patients had severe incontinence problems after intra-operative conversion to IPAA.

Figure 1: Flowchart of all patients with INRA as procedure of choice

Table 2: Functional outcome of patients with intra-operative conversion to IPAA compared to meta-analysis of patients with IPAA as procedure of choice (95% confidence intervals in square brackets)

Functional results	**Intra-operative conversions** ***n*=17**	**Hueting et al.[21]** ***n*=9317**
Mean defecation frequency/24 hours	7.1 [6.0-8.3]	5.2 [4.4-6.1]
Mean nocturnal defecation	1.0 [0.8-1.8]	1.0 [0.6-1.6]

Ano-reservoir physiology

All patients with a functioning IPAA underwent ano-reservoir manometry at follow-up, the results of which are summarized in *Table 3*. Overall, squeeze time was reduced and first sensation and urge were high, as was the maximum tolerated volume.

Table 3: Results of anal manometry and pouch physiology testing in patients with intra-operative conversion to IPAA (*n*=17/21) (range in parentheses)

Anal manometry and pouch physiology	Mean patient values	Normal values
Resting pressure (kPa)	7.0 (2.7-13.0)	5-10
Squeezing pressure (kPa)	19.0 (6.3-32.7)	20-24
Squeeze time (s)	28.6 (9.4-60.0)	>45
First sensation (ml)	43.2 (11.0-113.0)	20-30
First urge (ml)	115.6 (39.0-321.0)	80-120
Maximum tolerated volume (ml)	221.3 (47.0-456.0)	200
Compliance (ml/kPa)	78.3 (9.3-340.3)	35

Complications

Results of reservoir-related complications and inflammatory responses are summarized in *Table 4*. Six patients (30%) had in total eight laparotomy-related complications; these are summarized in *Table 5*. Two patients (10%) had three ileostomy-related complications: one patient had a leakage of the ileostomy which required a surgical intervention which unfortunately was complicated by an incisional hernia. One patient underwent re-laparatomy for an intestinal perforation after ileostomy closure. Five patients (25%) had other complications related to prolonged hospital stay.

Table 4: Comparison of complications between patients with intra-operative conversion to IPAA compared to meta-analysis of patients with IPAA as procedure of choice (percentages in parentheses, 95% confidence intervals in square brackets, n.a.= not available data)

Complication	Intra-operative conversions *n*=20	Hueting et al.[21] *n*=9317
Pouch failure	3 (15)	(6.8), [5.4-8.4]
Pelvic sepsis	1	(9.5), [8.2-10.9]
Strictures/stenosis	3 (15)	(9.2), [6.8-12.4]
Bladder dysfunction	1	n.a.
Sexual dysfunction	1	(3.6), [2.7-4.7]
Pouchitis	3 (15)	(18.8), [15.7-22.4]

Table 5: Results of laparotomy-related complications in patients with intra-operative conversion to IPAA

Complication	*n*=21
Drainage of intra-abdominal hematoma or abscess	3
Wound infection	1
Intestinal perforation (conservative treatment)	1
Small bowel obstruction (re-laparotomy)	1
Fistula	1
Mortality	0

Endoscopy

After INRA and/or IPAA, all patients underwent endoscopy at the mentioned intervals: one patient showed ulcera and aphtoid lesions at endoscopy while three patients showed a mild inflammation of the pouch. All of which were all asymptomatic.

Quality of life

Scores on the facet overall QoL, and in the separate domains of the WHOQOL-100 are illustrated in *Table 6*. The results in this study neither showed a difference between patients with an intra-operative conversion to IPAA if compared with the healthy population nor did it show a difference if compared to patients with IPAA as their procedure of choice.

Table 6: QoL in patients with intra-operative conversion to IPAA for UC (n=20) compared to the healthy population and to patients whose procedure of choice was IPAA[20] (p>0.05 between all domains of QoL the two IPAA cohorts and the reference values of the healthy population)

Quality of life	*Reference values*	IPAA procedure of choice	Intra-operative conversion to IPAA
Overall QoL	*15.6*	13.9	15.1
Physical health	*14.6*	14.1	14.5
Psychological health	*14.7*	15.1	15.7
Level of independence	*16.3*	15.8	15.0
Social relationships	*15.1*	15.3	16.5
Environment	*15.8*	15.1	15.6
Spirituality	*13.3*	12.4	12.4

Discussion

INRA was developed to achieve a reduction in complication rate in comparison to patients who undergo an IPAA, and offer functional results in line with the gold standard, IPAA.[5;6] Twenty-seven percent of the INRA patients had to undergo a conversion to IPAA. All viable pouches showed normal results in function and during ano-reservoir physiology testing; hence, have their pouch function equally normal as in patients which underwent an IPAA.[21]

Three patients experienced pouch failure: in retrospect, one of these pouch failure patients was later diagnosed with CD, in itself a risk of pouch failure.[22;23] The other two failures were caused by strictures, one of which was the result of a pelvic sepsis. Our results do not differ from those of previous studies.[24;25]

The results of our assessment by endoscopy support the above reported functional outcomes, all showed mucosal coverage of the pouch together with no, or only mild, inflammation in three patients. Nonetheless, with a percentage of 15.8% we do report a relatively high rate of anal stenosis and strictures compared to those reported in the meta-analysis 9.2%; with individual reports ranging from 9-37%.[21;24;25] In this study a stenosis was defined as any stenosis needing manual dilatation, the use of dilator probes, or a surgical intervention.

Our study may be biased in reporting the functional outcome of the conversions since it was impossible to perform, during endoscopy, a mucosectomy in the majority of our patients. Latter had severely inflamed mucosa which result in large amounts of scar tissue and fibrosis, all explaining the predisposition to developing a stricture in this area. Therefore, the higher incidence of strictures observed in our study may be a result of the selection bias or due to a low threshold in defining after endoscopic detection. An additional bias may be the result of our methodology. The more than normal scrutiny by performing endoscopic assessments in all patients during follow up in our INRA study, in contrasts to the routine follow-up in restorative surgery with less assessments of their mucosa, may have resulted in a higher number than normally discovered stenosis in the included patients.

As restorative surgery in this patient population is called 'QoL surgery', the overall QoL and its assessment in the separate domains are comparable to the healthy population in patients after intra-operative conversion. Furthermore, QoL in these patients is comparable to patients who choose IPAA as their procedure of choice.[20;26] As INRA is not performed any more, a note of caution must be made interpreting our results.[5] Due to this limited performance the size of our cohort on intra-operative conversions is small. Notwithstanding that we conclude, based on these good results that INRA is a good – albeit for routine treatment cumbersome – and safe procedure.

In conclusion, the results of this study show that patients with an intra-operative conversion to IPAA have a comparable functional outcome and complication rate if compared to patients with IPAA as procedure of choice.

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Chapter 8

Summary, discussion and conclusions

Summary, discussion and conclusions

Ulcerative Colitis (UC) and Familial Adenomatous Polyposis (FAP) remain debilitating diseases despite advances made in therapeutical options. In patients with FAP and 20%-30% of the patients' refractory to medical treatment in the case of UC, proctocolectomy is the mainstay of cure.[1-4] Since 1976, the Ileal Pouch Anal Anastomosis (IPAA) has become the gold standard for patients considering intestinal continuity. Until 1996 with the introduction of the Ileo Neo Rectal Anastomosis (INRA), no alternative was available.[5;6] An evaluation was needed of this novel procedure to determine the place of INRA in the domain of restorative surgery. This was the rationale of this thesis. The four main aspects addressed in this thesis, the study questions and the answers to these questions are listed in *Table 1*.

Summary of the studies

Patient-reported outcome after restorative surgery

As reflected in the number of studies published over the last two decades, well-being is increasingly considered an important outcome of (restorative) surgery. In *Chapter 2*, a systematic review was carried out to determine well-being in patients after IPAA. We reviewed 10,565 studies of which eventually 33 were eligible for quantitative and qualitative analysis, comprising a total of 4,790 patients. Only three studies were of high quality.[7-9]

In the analysed studies, the aspects of Health Related Quality of Life (HRQoL) and Health Status (HS) were assessed. Due to the heterogeneity of the studies, analysis was challenging. Independent of methodological quality, all studies reported improvement in HRQoL and HS 12 months after IPAA. Moreover, patients' HRQoL and HS were comparable to those reported from the general healthy population.[10] None of the studies assessed Quality of Life (QoL) according to the definitions recommended by the World Health Organization (WHO).[11]

From a methodological point of view, the analysed results from this review are disappointing. Thirty of the 33 analysed studies are incomplete, poor and unsystematic in presenting the patients-reported outcome post-IPAA. The virtual absence of QoL aspects in this systematic review prompted us to carry out a multicentre prospective cohort study to evaluate the QoL and HS before and after IPAA in patients with UC. *Chapter 3* describes this study. We observed that certain aspects of QoL and HS deteriorated after proctocolectomy (before IPAA) when compared to the healthy population. However, during the six months after IPAA surgery, QoL levels in this population increased in four of the six domains of QoL reaching levels comparable to the healthy population. HS levels increased after IPAA as well, however HS took longer to achieve levels comparable to the healthy population.

Table 1: Answers to study questions addressed in this thesis

	Chapter	Study question and answers
Patient-reported outcome after restorative surgery	2.	For patients with Ulcerative Colitis, what is the patient-reported outcome after restorative surgery? **Health Related Quality of Life and Health Status improve after restorative surgery.**
	3.	For patients with Ulcerative Colitis, what is the outcome in terms of Quality of Life and Health Status before and after restorative surgery and how does it relate to the healthy population? **Quality of Life and Health Status improve after restorative surgery and are comparable to the healthy population.**
Evaluation of surgical innovation in restorative surgery	4.	For surgical innovations, is an evidence-based assessment possible warranting a safe and phased introduction into the realm of science? **Performing evidence-based surgical studies will improve surgical science with the consequence that progress in surgical care continues and interventions become safer, more efficient and allow a better Quality of Life in surgical patients.**
Long-term results of INRA	5.	For patients who require restorative surgery, INRA has a theoretical potential to be superior to the current technique (IPAA). Does this theoretical potential translate into clinical favourable results? **This potential was not confirmed in short- and long-term evaluations. Hence, IPAA is currently the best available alternative to a conventional ileostomy.**
		For patients who require restorative surgery, is a vascularised mucosal transposition a safe technique with good long-term results? **A vascularised mucosal transposition is a viable technique with good long-term results.**
	7.	For patients with restorative surgery, what is the outcome in terms of function, complications, and Quality of Life after intra-operative INRA conversions to IPAA compared to patients with IPAA as their procedure of choice? **Patients who undergo INRA with intra-operative conversion to IPAA have long-term function and complication rates comparable to patients with IPAA as their procedure of choice. Quality of Life scores are comparable to the healthy population.**
Comparison of INRA to IPAA	6.	For patients with restorative surgery, what is the outcome in terms of functional results, complications, and Quality of Life after INRA and IPAA? **Comparison of INRA and IPAA on an intention to treat basis was not considered to be realistic due to the high intra-operative conversion rate and the failures in the INRA group. IPAA remains the procedure of choice for restoring intestinal continuity after proctocolectomy for Ulcerative Colitis.**

The observation of a difference between QoL and HS in patients who underwent IPAA is an indication that patients undergoing restorative surgery after UC were less bothered by the physical impairments and apparently satisfied with the achieved change.[12] This is important information for the surgeon-patient relationship. The operating surgeon can now evidently inform and prepare his patient that, postoperatively, (s)he will first have to learn to accept a possible malfunction, especially in the first year after surgery. After the first year, the impact of the disease and surgery declines and levels are comparable to the healthy population.

Evaluation of the process of implementation of INRA as a surgical innovation in restorative surgery

The introduction of new techniques is considered an important part of surgical innovation as well as of daily surgical practice. Despite the emphasis to strengthen the evidence-based principles in the surgical discipline, not many clinical studies are available yet that follow the recommendations as published by the Balliol group on surgical innovation.[13-15] In *Chapter 4*, we evaluated the research process, developed for and used in the implementation of INRA, using the IDEAL paradigm.

Despite limitations our study established the safety and efficacy as recommended by IDEAL as well as the comparative value of INRA to IPAA. Although the Randomised Controlled Trial is considered the gold standard, especially in stage 3 and 4 of the IDEAL paradigm, this was not deemed possible for the following reasons: first, the (estimated) results of INRA were in line with IPAA, requiring a large amount of patients to participate and secondly, to be able to include such amounts of patients a multicentre study would be needed. Due to INRA's long learning curve and the fact that restorative surgery is low-volume surgery in the Netherlands, it would be an arduous task to train enough surgeons and their teams to participate in this study. Hence, we equally consider valid arguments on why we performed a non-randomised prospective case-matched cohort study comparing IPAA and INRA series (EBM level of evidence 2A).

While eventually after our studies INRA and IPAA have comparable benefit-to-harm profiles, a preference for IPAA from a surgeon's, rather than from a patient's, point of view is understandable. IDEAL helped to both evaluate and report INRA as surgical innovation in evidence-based terms.

In this analysis, both groups of a) INRA and b) conversion-IPAA patients had equal clinical outcomes to those of patients who underwent IPAA as their procedure of choice (*Chapters 3*, *5*, *6*, and *7*). Close long-term follow-up was provided by us through repeated detailed functional, endoscopic, histopathological and patient-reported outcome evaluation, warranting a safe 'journey' into a stable life which was evidenced by a reported good QoL. In summary, evidence-based surgical innovation was feasible, and future surgical practice and new surgical innovations should be modelled to fit the IDEAL criteria.

Long-term results of INRA

In 1999, the first series of 11 patients who underwent INRA were evaluated.[5] In 2004, a subsequent series on the first 37 patients, presenting their medium-term results, was published.[16] Since 2004 the INRA cohort has grown to 79 patients, and their overall follow-up extended to (a median of) more than 8 years. Hence, we are now able to report for the first time the outcome of twice as many INRA procedures, as well as their long-term results.

While INRA has the theoretical potential to be superior to IPAA; its long-term results (*Chapter 5*) showed that it neither differed in a reduction in complications nor in patient's eventual gastro-intestinal function. Essentially, the theoretical premises of INRA, namely that of preventing autonomic nerve damage as well as pelvic sepsis, were fulfilled.

Conversion from INRA to IPAA procedure

Unique for the surgical practice – to avoid complications from (innovative and) regular surgical procedures – is the aspect of 'conversion'. Interestingly, our studies offered the opportunity to study the consequences on short- and long-term clinical outcome of this conversion group as well as the procedural aspect of conversion while developing INRA. Separate evaluation of the series of conversion IPAA patients showed that both the short- and long-term clinical outcome was in line with patients who received IPAA as their procedure of choice (*Chapter 7*).

Comparison of a surgical innovation (INRA) to the gold standard (IPAA)

Part of the morbidity of the pelvic dissection in IPAA is iatrogenic. Conventionally the removal of the rectum follows the 'Total Mesorectal Excision' (TME) principle: the dissection is in the plane between the parietal and visceral pelvic fascia. In this plane the hypogastric plexus is at risk. Damage to the plexus may also occur as a result of pelvic sepsis, the most critical complication threatening the success of IPAA.[3] In three per cent of the patients, this results in bladder or sexual dysfunction.[17]

INRA was developed as a technique based on the theoretical potential to reduce the complication rate related to the pelvic dissection, without compromising resultant functions. Eventually, a comparison between INRA and IPAA had to be made to assess their respective merits and preferential position in the future surgical practice.

We describe in *Chapter 6*, while comparing these two techniques, the difficulties of such a study. In the evaluation of new surgical interventions versus an established control latter are often favoured by the established comparator, especially if the complexities of both procedures are different. Both INRA and IPAA have comparable benefit-to-harm profiles. However, as INRA is more cumbersome the preference for IPAA from the surgeon's perspective is understandable.

Taking into account the results described in *Chapter 6*, and 1) the high intra-operative conversion rates to IPAA, 2) INRA being an arduous, lengthy operation, and 3) INRA being a technically more demanding technique than the established IPAA, we eventually decided to stop offering and undertaking INRA as a reconstructive surgical procedure. Hence, after this assessment of INRA, we concluded that the well-established IPAA as the best available alternative to the conventional ileostomy.[18]

Discussion and conclusions

This thesis has provided answers to several clinical questions on patient-related outcomes after restorative surgery for UC and FAP. It has in an evidence-based manner evaluated and determined the position of INRA in the surgical realm. In the following paragraphs the studies are discussed and conclusions based on these studies are presented.

Patient-reported outcome after restorative surgery

Restoring intestinal continuity in UC and FAP patients after proctocolectomy brings QoL and HS in range with the healthy population (*Chapter 2*). QoL and HS are becoming increasingly important patient-reported outcome measures in (restorative) surgery. Since there is not yet a single and fully accepted definition of QoL in today's literature, this important patient-reported outcome assessment was addressed in our patient population.

Chapter 3 has illustrated the prospective course of QoL and HS, and in more detail drafted the separate domains of QoL and dimensions of HS. Too few surgical interventions have systematically presented the well-being of patients. Presenting this data is not only feasible but also should be essential in determining the position of any new surgical technique.

Future studies, therefore, should concentrate using international accepted definitions for well-being and validated questionnaires like the WHOQOL-100 and RAND-36. These questionnaires make it possible to detect subtle changes as they break down QoL and HS into domains and dimensions. This approach facilitates surgeons to tailor their counselling of patients in an evidence-based manner and herewith effectively restore the well-being and quality of life in the operated patient group.

Evaluation of the process of implementation of INRA as a surgical innovation

Introduction of surgical innovations and new interventions is associated with several methodological and practical challenges. Such assessment is complex because of idiosyncrasies related to surgical practice, but necessary so that introduction and adoption of surgical innovations can derive from evidence-based principles rather than trial and error. A regulatory framework is desirable to protect patients against the potential harm of any novel procedure. We have shown that such evidence-based approach in developing and implementing a new surgical technique – from bench to bedside and following

schemes like the IDEAL framework – is feasible and rewarding. In the case of INRA, innovation and evaluation evolved together in an ordered manner from concept through explorations, to validation of the technique and ultimately to its position in the surgical realm.

Future innovations should use a framework like the IDEAL five-stage paradigm to report on their progress. Using a model such as IDEAL will improve surgical science, offering the profession a justified manner of positioning new interventions in the public health system.

Long-term results of INRA

This thesis has clearly shown that INRA has proven not to have a distinct advantage (function, complications, and QoL) over the gold standard, and therefore it was decided to stop further developing this technique (*Chapter 5*). Nonetheless, this surgical innovation has left a footprint in the field of innovative surgery. INRA has proven that the technique of small bowel mucosal transposition with a vascular pedicle is both as safe as IPAA and feasible, though technically demanding; moreover, it results in good long-term results. As such the concept of epithelial removal with autografting is an applicable concept, possibly even throughout the digestive tract. As morbidity of the proctectomy part of restorative surgery by IPAA still remains considerable, INRA offers another advantage: the concept of mucosectomy as opposed to proctectomy, or 'tissue sparing pelvic dissection' in essentially benign disease reduces the risk of autonomic nerve damage and minimises the risk of a devastating pelvic sepsis.

It would be a significant step forwards if a reduction in morbidity could be attained by firstly reducing the morbidity of the pelvic dissection and secondly with a reduction of the severity of a pelvic sepsis in case of an anastomotic leakage. Part of the morbidity of pelvic dissection is iatrogenic due to surgery following the oncological 'TME' route between the parietal and visceral pelvic fascia. Furthermore, this dissection results in the resection of the mesorectum. From an oncological point of view this is mandatory; however, UC is a benign disease. The concept and our evaluation of INRA indirectly proved that there remains an on-going need to improve IPAA. Our studies illustrate that patients with INRA have fewer pelvic complications when compared to patients with an extensive pelvic dissection (IPAA). Perhaps it is not necessary for such an extensive dissection to take place in order to perform IPAA.

The concept of INRA has led to a reintroduction of a 'close rectal dissection' in IPAA. It is a dissection performed within the mesorectum, close to the rectal muscle wall. The aim of this technique is to remove the diseased rectum and at the same time minimizing damage to the pelvic nerves. Future surgery in UC and FAP should abandon the oncological resection and focus on an extra-anatomical 'close rectal dissection' in the pelvis. The latest developments in electrothermal bipolar vessel-sealers and ultrasound dissection have made this approach feasible and safe.[19] Studies on the outcome of this approach are in progress. (Clinical Trials.gov Identifier: NCT01111708).

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Summary in Dutch (Nederlandse samenvatting)

Leven met de consequenties van Colitis Ulcerosa en Familiaire Adenomateuze Polyposis: de rol van chirurgie

Colitis Ulcerosa (CU) en Familiaire Adenomateuze Polyposis (FAP) zijn belastende aandoeningen voor de patiënt. Patiënten met FAP en 20%-30% van patiënten met CU refractair voor medicamenteuze therapie komen in aanmerking voor chirurgie. Een proctocolectomie is de curatieve en gangbare behandeling bij deze patiënten waarbij aansluitend of in tweede instantie continuïteitsherstel gerealiseerd kan worden.[1-3]

In 1976 introduceerde Parks de 'Ileal Pouch Anal Anastomosis' (IPAA) als techniek om continuïteitsherstel te bewerkstelligen.[4] In de loop der jaren is IPAA verfijnd en is er over de hele wereld veel ervaring mee opgedaan. Een gevolg van deze verbetering was een daling van postoperatieve mortaliteit en morbiditeit met acceptabele functionele resultaten.[5] Ondanks deze verbeterde resultaten is er nog steeds sprake van een significante morbiditeit van 20%.[3] Vanwege het feit dat er geen goed alternatief bestond, behoudens een stoma, werd IPAA de gouden standaard voor patiënten die in aanmerking kwamen voor continuïteitsherstel na CU of FAP.

In 1996 ontwikkelde Van Laarhoven de 'Ileo Neo Rectale Anastomose' (INRA) als een alternatief voor IPAA.[6] INRA is onder andere gebaseerd op een techniek ontwikkeld door Peck in 1964.[7] INRA laat de anatomie van het kleine bekken intact en creëert een nieuwe en gezonde mucosale bekleding van het rectum. Aansluitend aan de mucosectomie van het rectum wordt een transplantatie van de mucosa van het ileum gerealiseerd met een intacte vaatsteel van dit terminale ileum. Hiermee werd INRA conceptueel een andere ingreep dan IPAA.

De resultaten van de eerste serie van patiënten na INRA (n=11) lieten zien dat de nieuwe techniek veilig en goed uitgevoerd kan worden.[8] In de daarop volgende 10 jaren groeide het INRA cohort. Evaluatie van de middellange termijnresultaten van de eerste 37 INRA's kwam overeen met die van IPAA, de gouden standaard.[9] Zes jaar later na 79 INRA procedures was er behoefte aan een meer definitieve analyse waarbij ook de lange termijnresultaten werden meegenomen. Het beoogde doel van deze vraag was om te bepalen of INRA, naast IPAA, een goed alternatief was voor patiënten die in aanmerking komen voor continuïteitsherstel. Dit was het uitgangspunt van verdere studies en de essentie van dit proefschrift.

Om in dit proefschrift een conclusie te kunnen trekken, of INRA naast IPAA een goed alternatief is, hebben wij de volgende aspecten onderzocht:

1. Patiënt-gerapporteerde uitkomstmaten na continuïteitsherstel
2. Evaluatie van de implementatie van INRA als een chirurgische innovatie
3. Lange termijnresultaten na INRA
4. Vergelijk van een chirurgische innovatie (INRA) met de gouden standaard (IPAA)

In *Tabel 1* staan de onderzoeksvragen, gebaseerd op de bovengenoemde doelen, en de antwoorden op deze vragen.

Tabel 1: Studievragen en antwoorden

	Hfst.	Studievragen en antwoorden
Patiënt-gerapporteerde uitkomstmaten na continuïteitsherstel	2.	Wat zijn de patiënt-gerapporteerde uitkomstmaten bij patiënten met continuïteitsherstel na Colitis Ulcerosa? **Gezondheidsgerelateerde Kwaliteit van Leven en de Gezondheidstoestand verbeteren na continuïteitsherstel.**
	3.	Wat is de Kwaliteit van Leven en de Gezondheidstoestand vóór en na continuïteitsherstel bij patiënten met Colitis Ulcerosa en hoe weerhoudt dit zich tot de gezonde populatie? **Kwaliteit van Leven en Gezondheidstoestand verbeteren na continuïteitsherstel en zijn vergelijkbaar met de gezonde populatie.**
Evaluatie van een chirurgische innovatie	4.	Voor chirurgische innovaties, is er een evidence-based evaluatie mogelijk zodat nieuwe behandelingen op een veilige en gefaseerde wijze geïntroduceerd kunnen worden? **De evaluatie van INRA laat zien dat evidence-based onderzoek naar chirurgische innovaties haalbaar is.**
Lange termijnresultaten na INRA	5.	Bij patiënten die in aanmerking komen voor continuïteitsherstel na proctocolectomie biedt INRA een theoretisch voordeel ten opzichte van IPAA. Geeft dit theoretische voordeel INRA een plek in de chirurgische praktijk? **Het theoretische voordeel van INRA werd door de korte als de lange termijnresultaten niet bevestigd. Derhalve is IPAA op dit moment de voorkeursbehandeling.**
		Is de techniek van het transplanteren van mucosa met een intacte vaatsteel veilig en haalbaar met goede resultaten bij patiënten die in aanmerking komen voor continuïteitsherstel na proctocolectomie? **De techniek van het transplanteren van mucosa met een intacte vaatsteel is een veilige en haalbare techniek met goede resultaten.**
	7.	Patiënten die in aanmerking komen voor continuïteitsherstel na proctocolectomie kunnen kiezen tussen INRA en IPAA. Zijn de resultaten van de INRA patiënten die peroperatief geconverteerd zijn naar IPAA vergelijkbaar met patiënten die IPAA als primaire procedure kozen? **De resultaten van de patiënten die werden geconverteerd van INRA naar IPAA zijn zowel op korte als op lange termijn vergelijkbaar met die van patiënten bij wie primair gekozen was voor IPAA.**
Vergelijk van INRA met IPAA	6.	Zijn de functionele resultaten, complicaties en Kwaliteit van Leven na INRA vergelijkbaar met IPAA bij patiënten die in aanmerking komen voor continuïteitsherstel na proctocolectomie? **Het vergelijken van INRA met IPAA werd niet mogelijk geacht door het hoge percentage conversies en de niet functionerende INRA's. Dientengevolge is IPAA op dit moment de beste keuze voor patiënten die na een proctocolectomie *niet* met een stoma door het leven willen of kunnen gaan.**

Discussie van de studies

1. Patiënt-gerapporteerde uitkomstmaten na continuïteitsherstel

Steeds vaker wordt welzijn gezien als een belangrijke uitkomst na een chirurgische ingreep. Dit wordt ondersteund door een toenemend aantal wetenschappelijke publicaties over dit onderwerp.

In *Hoofdstuk 2* zijn de resultaten weergegeven van een systematic review over het welzijn van patiënten die IPAA ondergingen voor CU. We hebben 10.565 studies beoordeeld, waarvan slechts 33 studies, met in totaal 4.790 patiënten, in aanmerking kwamen voor verdere analyse. Van deze 33 studies bleken slechts drie studies van methodologisch hoge kwaliteit. Uitgaande van de definitie opgesteld door de Wereld Gezondheid Organisatie (WGO) bleek kwaliteit van leven (KvL) in geen enkele studie te zijn gemeten.[10,11]

De drie studies van hoge kwaliteit rapporteerden over 'gezondheidsgerelateerde kwaliteit van leven' en de 'gezondheidstoestand'. Zowel de gezondheidsgerelateerde kwaliteit van leven als de gezondheidstoestand van de patiënten verbeterde in de 12 maanden na IPAA. Ook de studies van minder hoge kwaliteit lieten een vergelijkbaar resultaat zien. Twaalf maanden na IPAA waren de gezondheidsgerelateerde kwaliteit van leven en de gezondheidstoestand vergelijkbaar met die van de gezonde populatie.[10] Methodologisch bleken de resultaten van deze studies van een teleurstellende kwaliteit (*Hoofdstuk 2*). De heterogeniteit binnen en tussen de studies maakte vergelijking en analyse van de data uitdagend en vrijwel onmogelijk.

Het feit dat er in onze onderzoekspopulatie, volgens de internationaal geaccepteerde definitie van de WGO, nimmer onderzoek verricht was naar KvL, was voor ons aanleiding om een prospectieve studie hiernaar op te zetten. Hierin werd KvL en gezondheidstoestand zowel *vóór* als *na* IPAA onderzocht in een patiëntenpopulatie na een proctocolectomie voor CU.

Met deze studie tonen wij aan dat bij deze patiënten KvL en gezondheidstoestand na proctocolectomie lager was dan bij de gezonde populatie. Zes maanden na IPAA was KvL verbeterd en in vier van de zes domeinen vergelijkbaar met die van de gezonde populatie. Twaalf maanden na IPAA was ook de gezondheidstoestand vergelijkbaar met die van de gezonde populatie (*Hoofdstuk 3*).

KvL en gezondheidstoestand zijn verschillende entiteiten. KvL, in tegenstelling tot gezondheidstoestand, refereert aan de tevredenheid van een persoon aangaande verschillende aspecten van zijn of haar leven en is niet altijd een directe weerspiegeling van zijn of haar functioneren. Uit de bovengenoemde resultaten van onze studie (*Hoofdstuk 3*) blijkt dat patiënten, na continuïteitsherstel middels IPAA voor CU, leren omgaan met een veranderde situatie met betrekking tot hun lichamelijk functioneren.[12] Dat bij hen de KvL verbeterde, ondanks een verminderd lichamelijk functioneren na IPAA, is belangrijke informatie voor de chirurg en zijn patiënt.

2. Evaluatie van de implementatie van INRA als een chirurgische innovatie

Innovatie is een belangrijk onderdeel binnen de chirurgische praktijk. Het ontwikkelen en evalueren van nieuwe technieken is complex. Idealiter wordt de evaluatie uitgevoerd middels systematic reviews en RCT's. Veel innovaties worden echter ingevoerd op basis van het 'trial and error' principe. Wij hebben gezocht naar een manier om INRA zo goed mogelijk op evidence-based wijze te onderzoeken. Niettemin hebben we moeten afzien van een RCT om de volgende redenen.

Ten eerste waren de (geschatte) resultaten van INRA en IPAA zodanig vergelijkbaar dat het benodigd aantal proefpersonen voor deze studie zeer groot zou zijn om een vooraf gedefinieerd significant klinisch verschil waar te nemen. Ten tweede zou een dergelijk onderzoek een langdurige multicentre trial worden aangezien continuïteitsherstel een vorm van laag-volume chirurgie is. Ten derde hebben er te weinig chirurgen de leercurve van INRA doorlopen om een multicentre trial te kunnen faciliteren. De ervaring leert ons dat INRA een lange leercurve kent. Samenvattend is het jaarlijkse volume te laag en de aantallen operateurs te beperkt om binnen een redelijke tijd een vergelijkende RCT in Nederland voor INRA en IPAA uit te voeren.

Recent is in de Lancet een serie verschenen – de IDEAL aanbevelingen – die is bedoeld om chirurgische innovaties te toetsen op een evidence-based wijze.[13-15] Aan de hand van de IDEAL aanbevelingen hebben wij stap voor stap INRA geëvalueerd en gevalideerd. *Hoofdstuk 4* beschrijft deze ontwikkeling. Ondanks de beperkingen van INRA liet deze studie zien dat INRA op een veilige en verantwoorde wijze is geïntroduceerd.

Wij hebben een niet gerandomiseerde prospectief vergelijkend onderzoek naar de resultaten van INRA en IPAA uitgevoerd waarbij wij de resultaten van INRA hebben vergeleken met een 'gematchte' cohort patiënten na IPAA (prospectieve cohortstudie). Beide technieken bleken vergelijkbare uitkomsten te hebben wat betreft de functie van het reservoir, lange termijn complicaties, KvL en gezondheidstoestand. IPAA blijft echter de meest toegepaste techniek.

De evaluatie van INRA laat zien dat evidence-based onderzoek naar chirurgische innovaties haalbaar is. Toekomstig onderzoek naar nieuwe chirurgische technieken kan worden opgezet aan de hand van de IDEAL aanbevelingen. Tot nu toe zijn er nog maar weinig studies die in hun rapportage van de chirurgische innovaties de IDEAL aanbevelingen volgen.

3. Lange termijnresultaten van INRA

In 1999 werden de eerste 11 patiënten met INRA geëvalueerd.[8] Het cohort groeide naar 37 patiënten waarvan in 2004 de middellange termijnresultaten werden gepubliceerd.[9] In de periode tot 2006 is het INRA cohort toegenomen tot 79 patiënten. In 2011 was de mediane follow-up periode meer dan acht jaar waardoor het mogelijk werd om een twee keer zo groot cohort met ook de lange termijnresultaten na INRA te rapporteren (*Hoofdstuk 5*).

INRA was een chirurgische innovatie die curatie van de ziekte met herstel van intestinale continuïteit bewerkstelligde. Tevens had deze techniek als doel de complicaties na de proctectomie te voorkomen. Een uitgebreide evaluatie van INRA was wenselijk. Terwijl INRA een theoretisch voordeel kent ten opzichte van IPAA, lieten de lange termijnresultaten geen verschillen zien tussen INRA en IPAA ten aanzien van het voorkomen en de ernst van complicaties dan wel functionele gevolgen van de ingreep (*Hoofdstuk 5*).

Conversie van INRA naar IPAA
Tijdens de INRA procedure kan worden besloten om af te zien van INRA en een IPAA procedure uit te voeren. Redenen voor conversie zijn o.a. technisch onmogelijkheid om het mucosa uit het rectum te verwijderen of een te korte rectumstomp.

Voor de evaluatie van INRA was het van belang om de geconverteerde groep te bestuderen. De resultaten van de patiënten die werden geconverteerd van INRA naar IPAA waren zowel op korte als op lange termijn vergelijkbaar met die van patiënten bij wie primair gekozen was voor IPAA (*Hoofdstuk 7*).

4. Vergelijk van een chirurgische innovatie (INRA) met de gouden standaard (IPAA)
De wezenlijke complicaties van IPAA vormden de aanleiding INRA te ontwikkelen met minimaal behoud van functionele resultaten van de gouden standaard. Een deel van de morbiditeit, gerelateerd aan IPAA, kan ontstaan door de resectie van het rectum uit het kleine bekken.

Van oudsher werden de oncologische dissectievlakken van de 'Totale Mesorectale Excisie' gevolgd. Deze operatie is een *en-bloc resectie* van het rectum met het mesorectum door middel van scherpe dissectie in het a-vasculaire vlak tussen de viscerale en pariëtale fascie van het rectum, waarbij de autonome zenuwen in het kleine bekken schade kunnen oplopen. Deze schade bij IPAA kan iatrogeen ontstaan tijdens de feitelijke excisie, maar kan ook ontstaan ten gevolge van een ontsteking in het kleine bekken ('pelvic sepsis'). Laatstgenoemde complicatie is bepalend voor het succes van IPAA.[3] In drie procent van de gevallen leidt deze complicatie tot een afname van het functioneren van de blaas en/of seksueel disfunctioneren.[5]

Hoofdstuk 6 beschrijft het onderzoek, het proces en de evaluatie van de resultaten van INRA vergeleken met IPAA. Uit de evaluatie blijkt dat men in de praktijk vaak de bekende techniek verkiest boven een complexere innovatie.[14] De leercurve van een complexe innovatie is langer dan die van de gangbare en algemeen geaccepteerde techniek. INRA is technisch meer uitdagend dan IPAA en is een arbeidsintensieve techniek met lange operatietijden.

Vanwege bovenstaande redenen, de resultaten zoals beschreven in *Hoofdstuk 6* en het feit dat het conversie percentage van INRA naar IPAA hoog (21/79) was, is uiteindelijk besloten om INRA niet meer aan te bieden als een techniek voor continuïteitsherstel bij patiënten met CU en FAP. Dientengevolge is IPAA op dit moment de beste keuze voor patiënten die na een protocolectomie *niet* met een stoma door het leven willen/kunnen gaan.[16]

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Prof. dr. J. de Vries. Beste Jolanda, ik kan jou niet vaak genoeg bedanken. Toen ik als onderzoeker begon, had ik nooit gedacht dat ik zo vaak bij een psychologe aan tafel zou zitten! Dankzij jou is kwaliteit van leven een rode draad geworden door dit proefschrift en speelt het dagelijks een prominente rol in mijn vak als (oncologisch) chirurg. Onze gesprekken, vroeg vóór alle werkzaamheden uit, waren memorabel. Ik hoop nog vaak bij je aan te mogen schuiven.

Dr. D.J. de Jong. Beste Dirk, dit proefschrift is een kruisbestuiving van chirurgie, darmziekten en psychologie. Jij bent hierin als gedreven MDL-arts onmisbaar geweest. Mede dankzij jou hebben we INRA kunnen vergelijken met pouch chirurgie. Nu is het INRA onderzoek compleet.

Caroline Andeweg, een vertrouwd idee dat jij naast mij staat in deze laatste fase. Als we samen net zoveel hadden geschreven als we hadden gesproken over onderzoek en promoveren, dan was ons werk al veel eerder klaar geweest. We kunnen samen perfect overleggen, we zijn het altijd eens.

Boj Mirck, behoudens het feit dat je mijn paranimf bent met bijbehorende verplichtingen, zijn er (bijna) geen excuses meer om niet te gaan zeilen. Laten we dat ook vooral gaan doen op kleine en grote bootjes, op de Nederlandse meren, voor de kust, op de Solent of waar dan ook.

Maatschap St Elisabeth Ziekenhuis Tilburg 2004-2011
dr. D.P. van Berge Henegouwen, dr. J.D. Meeuwis, Prof. dr J.A. Roukema, dr. H.J.M. Oostvogel, prof. dr. J.F. Hamming, drs. T. van Egmond, prof. dr. C.J.H.M. van Laarhoven,

drs. D.H.C. Burger, prof. dr. M.H.J. Verhofstad, dr. P.W.H.E. Vriens, dr. J.M. Heyligers, dr. J. Heisterkamp en dr. F.H.W.M. van der Heijden. Jullie hebben mij gekneed en gevormd tot een jonge en enthousiaste klare chirurg. De atmosfeer waarin jullie dat hebben gedaan is ongekend. Een chirurg in opleiding kan zich geen beter klimaat wensen om in opgeleid te worden, veilig en met ruimte voor eigen verantwoordelijkheid en keuzes. Ik ben er trots op dat ik een product ben van uw samenspel.

Assistenten Heelkunde St Elisabeth Ziekenhuis 2004-2011. Beste passanten, dank voor al jullie wijze adviezen, tips en tricks en jullie flexibiliteit zodat ik op en neer kon gaan naar Nijmegen voor mijn onderzoek. Samenwerken met jullie was een feest waaruit dierbare vriendschappen zijn ontstaan. Lunch in de assistentenkamer blijft onvergetelijk net als EZ-CD's, de wintersporten en feestjes in de binnenstad.

Assistenten Heelkunde UMCN 2009-2010
Dank voor jullie geduld en al het rek in het elastiek. De assistenten bezetting was niet altijd royaal en toch maakten jullie het mogelijk voor mij om tijd te besteden aan mijn onderzoek.

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Lieve ouders, onvoorwaardelijk is jullie steun. Via de mail is mijn proefschrift de halve wereld afgereisd en beland o.a. in de binnenlanden van Afrika. 'Less is more' gaat niet op voor jou pa, maar je kritische blik en commentaar is van onschatbare waarde. Jullie vastberadenheid, idealen en doorzettingsvermogen zijn voor mij een voorbeeld.

Jasper, broer, maatje en vooral goede vriend. Ik begreep eerlijk gezegd niet veel van je thesis over de olie- en gasindustrie. Gelukkig zul je de inhoud van dit werk wel begrijpen. Ik bewonder je vermogen om je eigen weg te kiezen en het vervolgens ook uit te voeren. Het heeft je nooit afgeschrikt om een minder bewandeld pad te kiezen en daarin ben je een voorbeeld. Een zeiler die geen koers uitzet heeft nooit wind mee. Bon vents, het gaat je goed. Ik hoop dat we elkaar nog veel op het water mogen tegen komen, of we nou met of tegen elkaar varen. Lindsey, you are my favourite sister in law!

Babette, liefste, ondanks dat ik pretendeer iets te weten en te mogen schrijven over kwaliteit van leven, breng jij de kwaliteit in mijn leven. Jij geeft het leven nog meer kleur, samen met onze drie mooie kinderen Siebe, Féline en Joppe. Jullie zijn het mooiste dat me is overkomen.

Curriculum Vitae

Johannes (Joost) Tinyiko Heikens was born on the 19th of October 1976 in Elim, Louis Trichard, a small town in South Africa. Part of his childhood he spent abroad, living with his parents and brother. in 1995, he graduated from the Kandinsky College in Nijmegen. Prior to being admitted to medical school, he studied physiotherapy in Utrecht (1995-1996). In 1996, he started his medical training at the University Medical Centre Utrecht. Enjoying student life he finished his last 'in hospital training courses' in 2003.

In 2004, after graduating from medical school, he joined the Department of Surgery of the St Elisabeth Hospital in Tilburg (dr. J.F. Hamming), as a junior researcher writing the protocols for the PhD project described in this thesis.

In 2005, he started his residency in general surgery in the St Elisabeth Hospital in Tilburg (dr. C.J.H.M. van Laarhoven and later prof. dr. J.A. Roukema). In 2009-2010, he continued his training at the Radboud University Nijmegen Medical Centre (prof. dr. C.J.H.M. van Laarhoven). From 2010-2011, he returned for his last year of training to the St Elisabeth Hospital in Tilburg (dr. F.H.W.M. van der Heijden). In 2011, after his registration as a general surgeon, he was offered a position as a surgical fellow in oncological surgery in the Jeroen Bosch Hospital in 's-Hertogenbosch, The Netherlands (dr. K. Bosscha). During this period, his interest in surgical oncology grew and his interest in minimal invasive surgery was raised. In 2013, he was offered a position in the staff of Ziekenhuis Rivierenland in Tiel as an oncological surgeon.

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Stellingen behorende bij het proefschrift

Restorative surgery after proctocolectomy

Studies on functional results, complications, and quality of life after restorative proctocolectomie with Ileo Neo Rectal and with Ileal Pouch Anal Anastomosis

1. Patiënt-gerapporteerde uitkomstmaten zijn de belangrijkste resultaten als het gaat om de behandeling van patiënten. (dit proefschrift)
2. Bij patiënten na IPAA is de kwaliteit van leven eerder terug op het oorspronkelijke niveau dan de gezondheidstoestand. (dit proefschrift)
3. Bij een nieuwe chirurgische behandeling is een gestructureerde evaluatie en validatie niet alleen gewenst, maar zou verplicht moeten worden gesteld. (dit proefschrift)
4. Indien na een gestructureerde evaluatie behandeling *'B'* beter blijkt te zijn dan *'A'*, dan moet men behandeling *'A'* niet meer toepassen. (dit proefschrift)
5. INRA heeft de behandeling van patiënten die in aanmerking komen voor continuïteitsherstel verbeterd, ondanks het feit dat INRA niet meer wordt toegepast. (dit proefschrift)
6. IPAA is op dit moment de beste keus voor patiënten die na een proctocolectomie niet met een stoma door het leven willen of kunnen gaan. (dit proefschrift)
7. Vandaag de dag, waarin de Randomised Controlled Trial als gouden standaard wordt gezien, is een blik op de resultaten uit het verleden minstens zo belangrijk. (dit proefschrift)
8. Een arts dient in het gesprek met zijn patiënt verkleinwoorden en woorden zoals 'even' te vermijden.
9. The single biggest problem in communication is the illusion that it has taken place. (George Bernard Shaw 1856-1950, Ierse toneelschrijver en socialist)
10. Life is what happens to you, while you are busy making other plans. (John Lennon 1940-1980, popmusicus en vredesactivist)
11. There is no I in Team. (Author unknown)

Joost T. Heikens
23 oktober 2013