Reinforced Tension-Line suture for prevention of incisional hernia after colorectal cancer surgery

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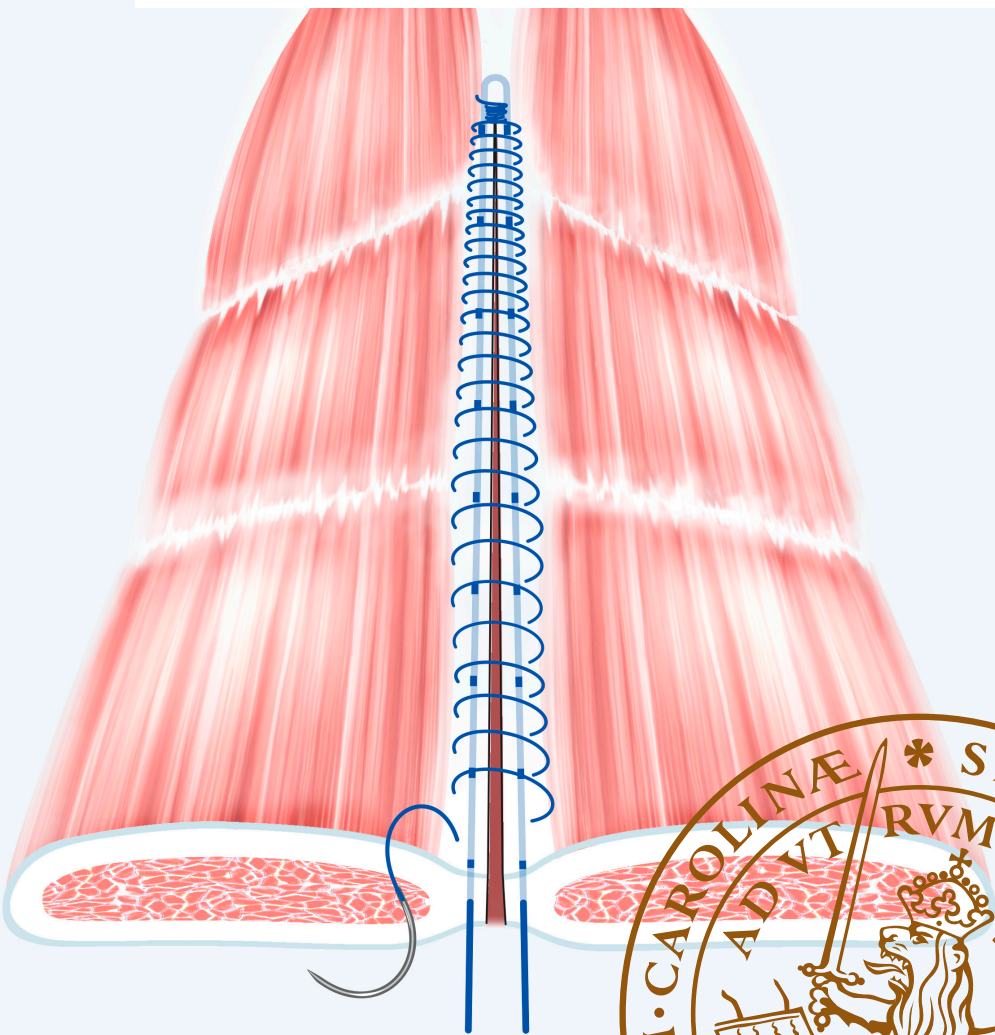

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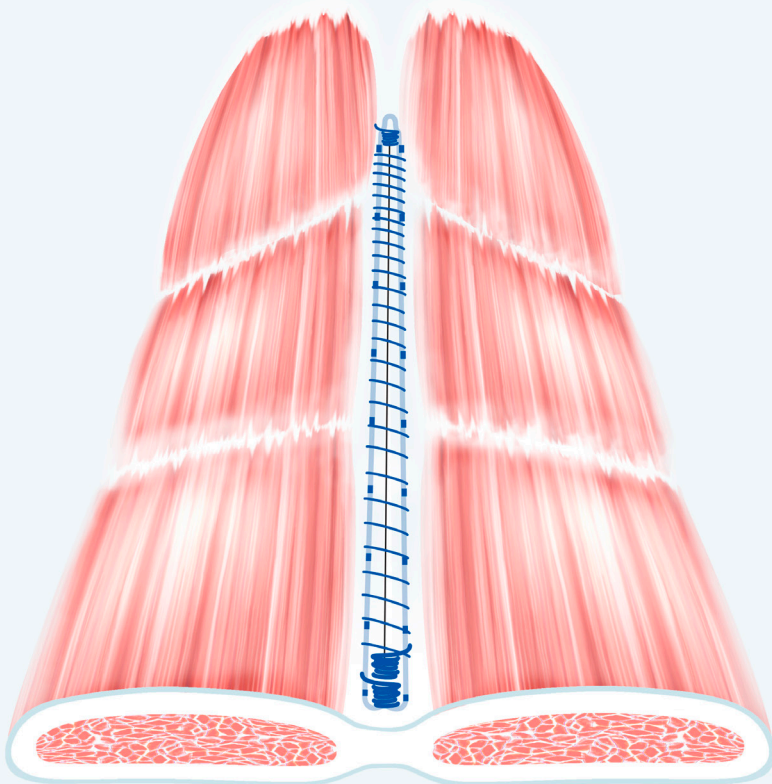

Cover illustrations of the RTL suture technique
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DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine, Lund University, to be publicly defended on April 25th 2025 at 09.00 in MFC Lilla aulan, Jan Waldenströms gata 5, Skåne University Hospital, Malmö

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Abstract

Incisional hernia (IH) is the most common complication after abdominal surgery with incidences up to 36% and more in high-risk patients. This causes suffering and increased health care costs due to need of IH repair. An alternative to mesh-prevention of IH is warranted when mesh is deemed unsuitable.

This thesis evaluates the reinforced tension line (RTL) suture technique compared to the gold standard 4:1 fascia closure technique for prevention of IH, as its primary outcome.

A retrospective study was conducted, comparing IH incidence for the two different closure techniques after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherpy (HIPEC). At the same time a two-centre prospective randomized controlled trial (RCT), the Rein4CeTo1-trial, was performed to investigate whether adding the RTL suture to the standard 4:1 small-bite closure would reduce the IH incidence after open colorectal cancer (CRC) surgery. Furthermore, IH risk factors and QoL were evaluated.

Paper I evaluates the IH incidence in 129 CRS/HIPEC patients resulting in a clinically relevant difference with 2% IH in the RTL-group and 11% IH in the 4:1 group, p=0.071.

Paper II covers the RCT with 160 randomized patients, evaluating 134 patients at 1 year postoperatively. The IH incidence was significantly reduced with the RTL technique (6%) compared to the 4:1 closure (21%), p=0.014.

Paper III is a long-term follow up of the RCT, evaluating 101 patients at 3 years postoperatively, showing a significant reduced IH incidence in favor of the RTL closure technique, p=0.003. The 4:1 closure and adjuvant chemotherapy were risk factors for IH.

Paper IV evaluates QoL in relation to IH in the RCT at 1 and 3-years postoperatively, showing no differences between patients with IH and those without. Having a stoma was an independent risk factor for decreased general QoL at 3 years.

Conclusions

Fascia closure with the RTL-suture technique reduces IH incidence in CRC patients.

Key words: Incisional hernia (IH), abdominal closure, Reinforced tention line suture (RTL), Colorectal cancer (CRC), Quality of life (QoL), Cytoreductive surgery (CRS), Hyperthermic intraperitoneal chemotheraphy (HIPEC), malignant disease.

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MADE IN SWEDEN

To my patients

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List of original papers

This thesis is based on following original work, which in this thesis will be referenced to by the Roman numeral.

I. Abdominal closure with reinforcing suture decreases incisional hernia incidence after CRS/HIPEC. Wenzelberg C, Petersson U, Syk I, Ekberg O, Rogmark P. Journal of Abdominal Wall Surgery. 2023 Mar 9; 2: 11188. doi: 10.3389/jaws.2023.11188.

II. Reinforced tension-line suture after laparotomy: early results of the Rein4CeTo1 randomized clinical trial. Wenzelberg CL, Rogmark P, Ekberg O, Petersson U. Reinforced tension-line suture after laparotomy: early results of the Rein4CeTo1 randomized clinical trial. British Journal of Surgery. 2024 Sep 3;111(10):znae265. doi: 10.1093/bjs/znae265.

III. Reinforced tension line suture after laparotomy: long-term results of the Rein4CeTo1 randomized clinical trial. Wenzelberg CL, Rogmark P, Ekberg O, Petersson U, Rønnow C-F. *In manuscript.*

IV. Impact of incisional hernia on Quality of Life after colorectal cancer surgery-results of the Rein4CeTo1 randomized clinical trial. Wenzelberg CL, Rønnow C-F, Petersson U, Rogmark P. *In manuscript.*

Abbreviations

ASA	American Society of Anaesthesiologists
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
CRS/HIPEC	Cyto Reductive Surgery/ Hyperthermic Intraperitoneal Chemotherapy
CT	Computed Tomography
EHS	European Hernia Society
HRQoL	Health-Related Quality of Life
IH	Incisional Hernia
NRS	Numerical Rating Scale
PDS	Polydioxanone
PP	Polypropylene
PROM	Patient Reported Outcome Measure
QoL	Quality of Life
RCT	Randomized Controlled Trial
SSI	Surgical Site Infection
VAS	Visual Analog Scale
VHPQ	Ventral Hernia Pain Questionnaire
WD	Wound Dehiscence
CI95%	Confidence Interval with 95% width
IQR	Interquartile Range
OR	Odds Ratio
SD	Standard Deviation

Thesis overview

Paper	Publication	Aim	Method	Results/conclusions
I	Abdominal closure with reinforcing suture decreases incisional hernia incidence after CRS/HIPEC	To compare IH rates after fascia closure with RTL and 4:1 technique, respectively, 1 year after CRS/HIPEC operations for peritoneal carcinomatosis	Retrospective chart- and register review, and CT-scan evaluation of IH in 129 CRS/HIPEC patients	IH was found in 7.8% of the patients, with 2% in the RTL-group and 11% in the 4:1-group (p=0.071), constituting a clinically relevant difference suggesting an advantage for the RTL-closure
II	Reinforced tension-line suture after laparotomy: early results of the Rein4CeTo1 randomized clinical trial	To compare early results and CT-diagnosed IH 1 year after colorectal cancer surgery, where fascia closure was done with RTL and 4:1 technique, respectively, in the Rein4CeTo1 RCT	RCT including 160 patients randomized at two study centres where 134 were eligible for 1-year clinical and CT follow-up	IH was significantly (p=0.014) reduced in the RTL-group (6%) compared to the 4:1 group (21%) at 1 year without difference in complications and the number needed-to-treat was 6.8
III	Reinforced tension line suture after laparotomy: long-term results of the Rein4CeTo1 randomized clinical trial	To compare CT-diagnosed long-term IH incidence and to assess potential risk factors for IH development in the Rein4CeTo1 RCT	3-year follow-up of the RCT where 101 patients were eligible for clinical and CT follow-up and logistic regression analyses were done for risk factor assessment	IH was long-term significantly (p=0.003) reduced in the RTL-group (14% cumulative IH rate) compared to the 4:1-group (36% cumulative IH rate) and closure with 4:1-technique and adjuvant chemotherapy were risk factors for IH
IV	Impact of incisional hernia on Quality of Life after colorectal cancer surgery-results of the Rein4CeTo1 randomized clinical trial	To compare general and abdominal wall specific QoL in patients with and without IH, respectively, at 1- and 3-year follow-up in the Rein4CeTo1 RCT	QoL was evaluated with the EQ-5D-5L- and the Ventral Hernia Pain Questionnaires	89% of eligible patients at 1 year and 80% at 3 years answered the questionnaires where EQ-5D-5L results were in accordance with the Swedish norm and VHPQ showed minor abdominal wall symptoms without differences between patients with IH and those without

Introduction

An incisional hernia (IH) is defined as an abdominal wall gap with or without a bulge in the area of a postoperative scar[1, 2] and is the most common long-term complication after abdominal surgery. In patients with an increased risk of IH development, incidences of over 35% of hernias have been reported[3]. IH leads to patient suffering with reduced quality of life (QoL)[4], and many times a new operation to repair the IH is needed, with increased healthcare costs[5-7]. With the aim of reducing IH development in patients at increased risk, reinforcing mesh has been used for abdominal closure with good results[8]. However, the fear of a difficult-to-treat infection in a reinforcing mesh and increased costs make many surgeons hesitant to use mesh for preventive purposes[9]. An alternative reinforcement measure to prevent IH is therefore warranted. Patients who are operated for colorectal cancer (CRC) have an increased risk of IH and would certainly benefit from a well-functioning prophylactic technique. Furthermore, they are postoperatively surveyed according to defined regimens which includes CT-scans. Taken together, these conditions make CRC patients suitable for IH prevention studies which has been utilized in this thesis.

Historical background

Surgical treatment of various conditions and diseases goes back to the ancient Egypt and was described already 1550BC in the Ebers as well as in several other papyrus scrolls. Wound care, splinting of fractures, use of sutures for wound closure, drainage of abscesses and more was depicted[10]. At that time, surgery was often performed together with religious rituals and possibly magic spells.

Figure 1. Ebers Papyrus, containing the first descriptions of the anterior abdominal wall
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In the ancient Greece, surgery was still limited to superficial procedures. Around the birth of Christ Cornelius Celsus, a Roman nobleman, encyclopaedist and physician, wrote one of the first descriptions of surgical techniques in Latin. Of many procedures he described was umbilical hernia repair with removal of the hernia sac and fascia suturing[11]. Handling of war trauma by field surgeons in the Roman military contributed to major advancement of surgical knowledge and skills.

How to enter and close the abdominal cavity after abdominal surgery is a knowledge that has been important to every surgeon, and patient, throughout the ages. Before the 19th century, the survival rates for abdominal surgery were poor due to difficulties in managing infections and bleeding and was considered extremely risky and at best avoided. Hernias were so far predominantly treated with girdles[12]. The absence of anaesthesia certainly prohibited development of surgical technique since the surgical procedures had to be performed so expediently that no time for technical perfection was available.

Despite the absence of anaesthesia, Doctor McDowell successfully performed extirpation of an ovarian cyst in a 46-year-old woman from Kentucky, USA, in 1809 through a left lower laparotomy. This may have been the first successful elective laparotomy[13].

With the introduction of ether as the first useful anaesthetics in 1842, major progress in developing surgery took place. Ether was the predominant anaesthetic method until the 1950s. Inhalation anaesthesia was further developed when halothane was

introduced followed by the highly fluorinated ethers sevoflurane and desflurane, used today. Shortly after the introduction of anaesthesia, Joseph Lister (1827-1912) professor of clinical surgery in Edinburgh, revolutionized surgical treatment through his research on antiseptic methods applied in surgery, saving countless of lives[14]. The next revolutionary discovery was penicillin which reduced the risk of postoperative infection and life-threatening sepsis[15].

Abdominal wall fascia closure was described already by Celsus, based on experience from penetrating abdominal trauma. He wrote: ”stitching of the surface skin only or of the inner membrane only is not enough, but both must be stitched. And there must be two rows of stitches, set closer together than in other places, partly because they can be broken here more easily by the abdominal movement”. Ancient sutures were made of either plant or animal material such as hemp, cotton, flax, hair, silk, tendons, arteries, nerves and intestines[16]. They were applied using eyed needles of different materials, invented several thousand years BC. Sutures derived from intestines, catgut, has stood the test of time but is today almost totally replaced by synthetic absorbable sutures.

Figure 2. Aseptic suture and chromic catgut (from sheep intestine)
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Besides choice of suture materials (non-absorbable or absorbable, rapidly or slowly absorbable, multifilament or monofilament, from natural sources or synthetic),

different techniques for fascia closure (one layer or multiple layers, mass or layered closure, interrupted or continuous sutures) have varied and trended over time. The aims that have driven the evolution of sutures and fascia closuring techniques are prevention of exaggerated inflammation, development of healthy and firm scar tissue and, in the long-run, prevention of IH.

Anatomy of the abdominal wall

Thorough anatomy knowledge is essential for every surgeon, and for hernia surgery the abdominal wall anatomy is central. The abdominal wall protects the abdominal cavity and its content and consists of different layers of muscles and connective tissue[17]. Besides protection of the internal organs, the muscles stabilize and facilitates flexible movement of the body and works as accessory expiratory muscles of importance for lung function. The abdominal muscles are active in increasing the abdominal pressure needed in activities such as coughing, defecation and vomiting.

From inside out the peritoneum separates the abdominal organs from the muscular abdominal wall. The anterolateral abdominal wall consists of four muscles on both sides, the lateral muscles and the rectus abdominis muscle, see figure 3a. The three muscles of the lateral abdominal wall are the innermost transversus abdominis muscle, the obliquus internus and the obliquus externus muscles. The aponeurotic parts of the lateral abdominal wall muscles form the aponeurotic sheath that encloses the rectus abdominis muscles. The transition between the lateral muscles and the rectus muscle is the tendinous linea semilunaris, the part of the abdominal wall where no muscle-coverage exists.

The rectus abdominis muscles extends from both sides of the xiphoid process and the cartilages of the 5th to the 7th ribs cranially, to the pubic bone and the pubic symphysis caudally. The posterior aponeurosis is made up of aponeurotic fibres from the transverse and internal oblique abdominal muscles and covers the backside of the rectus abdominis muscles from the xiphoid and down to some centimetres below the umbilicus, where it ends and forms the arcuate line or the linea semicircularis. Distal from this point the rectus muscle is separated from the abdominal cavity only by preperitoneal fat and the peritoneum. Anteriorly, the rectus muscles are covered by an anterior aponeurosis consisting of aponeurotic fibres from the internal and the external oblique abdominal muscles. The anterior aponeurosis is present all the way down to the symphysis. In the midline the aponeuroses from each side meat and form the linea alba. The pyramidalis muscle is a small triangular muscle with its origin at the pubic bones which extends cranially and anteriorly to the rectus abdominis muscles, covered by the anterior rectus aponeurosis.

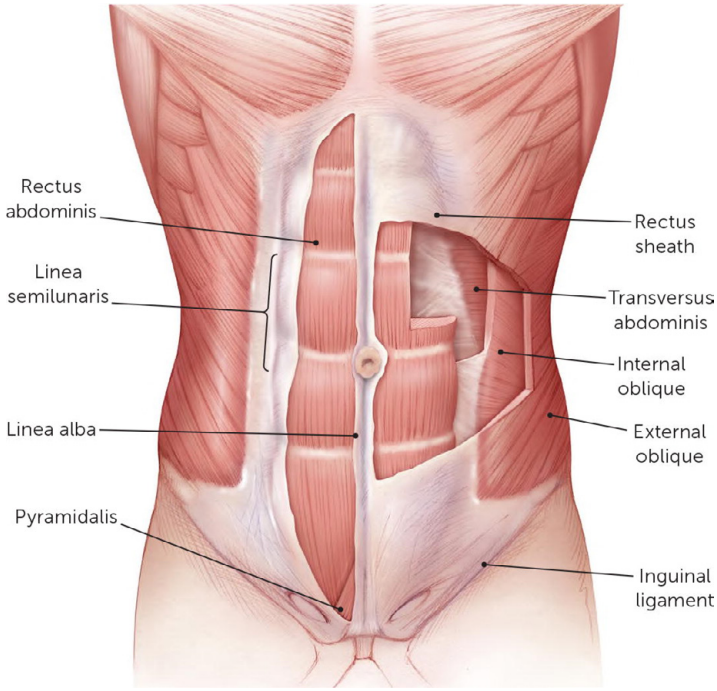

Figure 3a. The abdominal wall muscles
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The blood supply to the abdominal wall is mainly from arteria epigastrica inferior, arteria epigastrica superior and from the intercostal arteries that follow the intercostal nerves Th7-Th12. The intercostal neurovascular bundles run between the transversus abdominis and the obliquus internus muscles, entering the posterior rectus aponeurosis laterally, thereafter, continuing into the rectus muscles. After anastomoses with branches from the epigastric vessels, the vessels perforate the anterior aponeurosis in the midaxillary line together with the segmental nerve branches. These perforators together with vessels from the lateral cutaneous branches of intercostal vessels and superficial inferior epigastric vessels supply the subcutaneous fat and skin of the abdomen. The segmental nerve branches give of motor branches for rectus abdominis muscle innervation and sensory branches penetrates the anterior aponeurosis, together with the perforating vessels, for innervation of the skin over the rectus abdominis muscles. In the inguinal regions nervus ilioinguinalis and nervus iliohypogastricus supply motor and sensory innervation, see figure 3b.

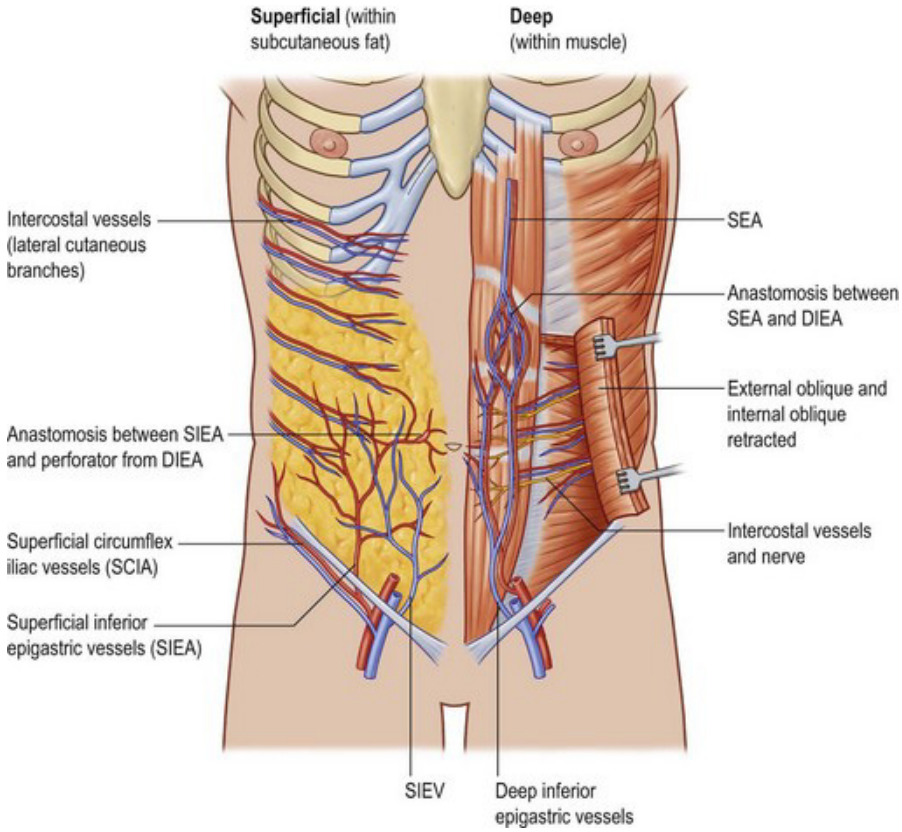

Figure 3b. The abdominal wall nerves and blood supply
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Wound healing

Preventing IH development after abdominal surgery include alignment to technical principles that promote uncomplicated wound healing, and the mechanisms of wound healing are essential to understand in this context. Before the laparotomy wound finally becomes a firm and stable scar, four phases including coagulation and haemostasis, inflammation, proliferation and wound remodelling take place[18], see figure 4.

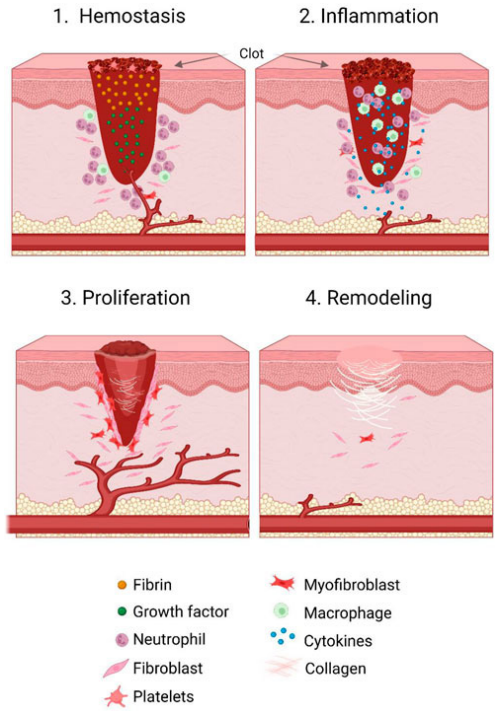

Figure 4. The wound healing process
 DOI:10.3389/fcell.2023.1252318.

The first haemostatic phase starts immediately, where platelets and fibrin deposited at the wound site leads to haemostasis and creation of a provisional matrix that influence the progress of a reparative process by attracting inflammatory cells and mediators. Haematoma due to inadequate haemostasis may disrupt the matrix and impair the possibility of uncomplicated wound healing, making haematoma to a fundamental cause of IH[19].

The aim of the secondary inflammatory phase is to establish an immune barrier against invading micro-organisms and to clear the wound from damaged tissue and present bacteria in the early inflammatory stage. This is done through phagocytosis by neutrophils attracted to the wound. In the later inflammatory stage, neutrophils are replaced by macrophages who continue wound debridement and release mediators that attract fibroblasts, endothelial cells and lymphocytes. It is of importance that this inflammatory phase progress successfully and infection is prevented since wound infection is a major risk factor for IH development.

The proliferative phase starts after approximately three days and lasts for about two weeks. During this phase fibroblasts migrate into the wound and produce a new extracellular matrix and shift into fibromyoblasts capable of wound contraction.

Furthermore, collagen synthesis, angiogenesis and granulation tissue formation occur. The inflammatory and proliferative phases are dependent on a functioning immune system, good nutritional status, manual debridement and optimal wound care in case of necrosis and infection.

In the wound remodelling phase collagen is reorganized and bundles increase in size and collagen is transformed from type III to I supplying increased stability and strength to the wound. The scar matures as the number of fibroblasts and macrophages decreases over time and new epithelium progressively covers the wound. This can take up to 1-2 years and sometimes even longer[20].

Wound healing is complex, and many negative influencing factors may disturb the process and result in the development of an IH after a laparotomy.

Wound classification

Wound infection increases the risk of developing an IH[21]after laparotomies and the risk of recurrence after IH repair[22, 23]. When evaluating IH incidence it is necessary to classify wounds from a wound infection risk perspective. The Centre for Disease Control and Prevention[24] classification of wounds into four grades is shown in figure 5. Colorectal cancer surgery, which is evaluated in this thesis, is at best classified as clean/contaminated due to opening of the alimentary tract.

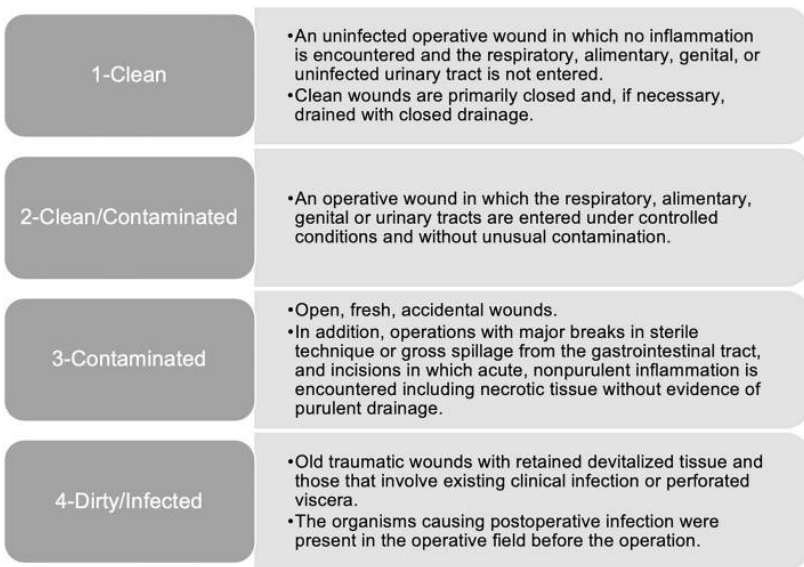

Figure 5. Wound class definitions from the American college of surgeons

Surgical access

Surgeons from different surgical disciplines perform surgery within the abdominal cavity. Different incisions are used for entrance and best access to the organs of interest. Even if minimal invasive surgery is becoming increasingly common, open abdominal surgery will still be needed in many cases.

There is some evidence that midline incisions have a higher risk of IH than off-midline incisions[25, 26]. Despite this, midline incisions are most used since it provides good access to many organs. Exactly what details are of importance when entering the midline is not known but an exact midline incision through the linea alba, without entering the rectus muscle compartment, is theoretically to be preferred[27] since the thicker linea alba has a better suture-bearing capacity than the anterior or posterior rectus aponeurosis alone[28], see figure 6.

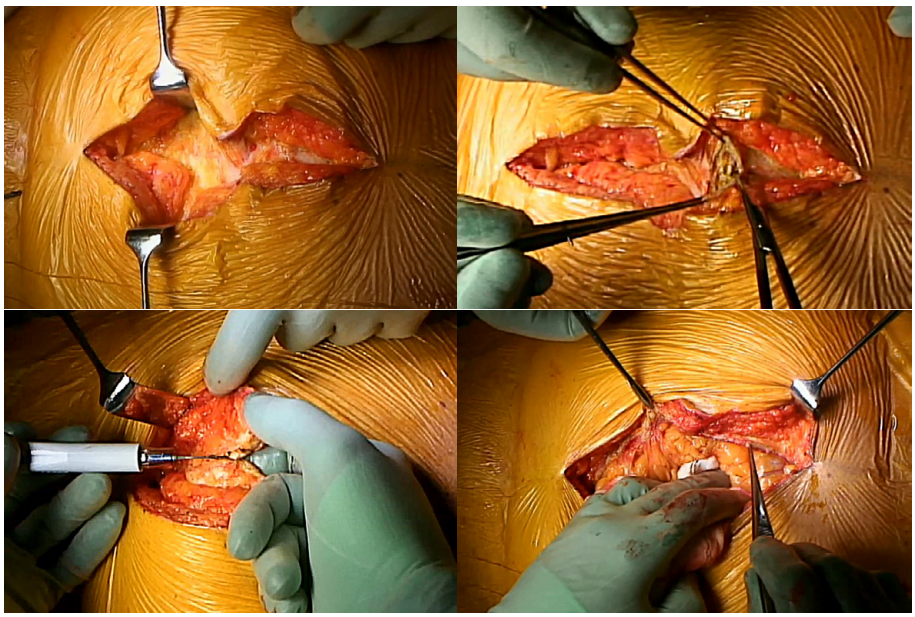

Figure 6. Precise midline incision as performed in the Rein4CeTo1 study
Anterior rectus aponeurosis dissected free of subcutaneous fat in the midline (upper left). Midline opened cranially to the umbilicus (upper right). Index finger used to palpate the midline (lower left). The incised line alba is shown (lower right). Photo by Petersson. Published with permission of the patient.

Another unanswered question is if only the anterior or both the anterior and posterior rectus aponeurosis should be sutured in case the rectus sheath has been opened.

Besides offering good access to the abdominal cavity, a midline incision has the advantage of being performed in an area where no vessels or nerves are present, minimizing possible effects of damaging such structures. In addition, IH developing

after a midline incision is easier to repair in a standardized manner than IH after off-midline and transverse incisions which many times requires dissection into the lateral compartments to achieve enough mesh-coverage laterally.

Wound dehiscence

Wound dehiscence (WD) or more adequately fascial dehiscence, also called burst abdomen (BA), occurs in a few percent[29] after laparotomy when fascia and skin sutures fail to keep the wound closed, resulting in partial or complete rupture of the wound and exposure of abdominal contents. WD and IH are related and constitutes two temporal extremes of incisional insufficiency, WD appearing early and IH late after a laparotomy. WD is associated with significant morbidity and mortality. A nationwide registry study in Denmark on patients electively operated on for CRC showed that patients suffering a WD had increased 90-day mortality rates, decreased 5-year survival and increased subsequent IH repair rates[30].

Risk factors for WD are both patient[31] and surgical technique-related[32]. The facial holding force of the suture is important and vary between patients e.g. due to wound contamination or infection, higher age or immunosuppression. The suturing technique, mass closure including the medial part of the rectus muscles or closure where only the fascia is included, and the tension put on the suture by the surgeon is also of importance. Failure of surgical knots is another pathogenetic factor. A tense knot, as well as high tension on the suture, may lead to tissue damage and cutting through of the knot or suture. Furthermore, tension of a suture is shown to decrease until a plateau phase is reached, and the slacking of the suture is more pronounced in tissue with lower collagen content[33]. If the plateau tension is low the wound edges tend to separate.

Already in 1976 Jenkin[34] suggested suturing laparotomies with continuous non-absorbable sutures with 1 cm bites and short distances between suture loops to achieve a 4:1 closure (suture-length four times longer than the incision) and lowering the risk of WD. Furthermore, experimental research has shown that a small-bite technique, suturing the aponeurosis only, decreases suture cutting-through compared to a mass closure technique, where also muscle is included in the stitches[35].

Even with good surgical fascia closing technique, WD will still occur. The EHS has published guidelines on handling burst and open abdomen (OA) and recommends dynamic closure techniques in treating both WD and OA[36]. The vacuum-assisted wound closure and mesh-mediated fascial traction (VAWCM) technique is an alternative for dynamic fascial closure in WD and OA patients[37]. Furthermore, mesh reinforcement was recommended when the fascia was sutured after a WD.

Incisional hernia

An IH is defined as any "abdominal wall gap in a post-operative scar, perceptible or palpable by clinical examination or imaging"[1, 2], and is thereby distinguished from primary hernias of the abdominal wall which arises without previous surgery at the hernia location.

IH show a wide variety in complexity. The European Hernia Society (EHS) endorsed a Delphi consensus process with the aim of defining a complex IH[38]. Complex hernias present factors reflecting difficulties in the surgical repair process and the risk of postoperative complications. Consensus on a total of 18 factors defining a complex hernia were met. Among those factors were: IH with a width >10cm; presence of enterocutaneous fistula; midline IH plus parastomal hernia; loss of domain; re-recurrent hernias; hernia occurring after bone resection; hernia after open abdomen treatment; BMI (>40); and cirrhosis with ascites[38-40].

IH symptoms can range from an asymptomatic hernia, mostly small fascial gaps or hernias, to life-threatening situations due to strangulation and ischemic bowel injury. Larger IH may entail mechanical discomfort due to size of the hernia and pain is common. Furthermore, negative effects on bowel function and abdominal stability may result in secondary backpain.

Incidence

The IH incidence ranged from 0-36% among the included studies in a large meta-analysis, where a weighted incidence of 12.8% was reported after 2 years. Incidences as high as 60% have been reported in specific high-risk populations[3, 41]. Even when standardized fascia closure techniques are used incidences of 13% (small-bite) and 21% (large-bite) are found after 1 year[42]. It is shown that the IH incidence increases over time[43, 44]. A retrospective study of almost 3000 patients, showed that over 50% of the IH development occurs within 6 months and 75% within two years after surgery[41]. In minimal invasive CRC surgery, IH at the specimen extraction site is reported to be as high as 16%[45]. A Swedish study on more than 1200 CRC patients concluded an equal IH incidence of 25% for open compared to minimal invasive surgery, but a higher risk of IH after conversion from minimal invasive surgery to open surgery[46]. The IH incidence after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) operations seem to be in accordance with the incidence of other abdominal cancer operations[47-52].

Classification

The importance of having an IH classification that is easily applicable and broadly accepted cannot be underestimated. The variety of surgical and patient morbidity-related complexity is great and effects outcome. Therefore, evaluation of treatment results in studies must be based on a classification system to be comparable and in the extension of this guidelines can become more evidence based.

Edouard Quenu distinguished IH from other types of hernias in the first documented classification already in 1896[12]. In 2000 Chevrel et al proposed a classification system based on the three parameters localization, width and number of previous hernia repairs[53]. Other parameters that have been suggested and used in different classification systems include the clinical implication of the hernia in lying and standing position, the ratio between the anterior abdominal wall surface and the hernia defect, body type and risk factors[2].

In 2009 the EHS published a classification on ventral and incisional hernias, where separating ventral non-IH (primary) hernias from IH was agreed upon due to the different etiopathology of the conditions[2]. This distinction had previously seldom been applied and interpretation of reported study results, including both entities, has been difficult. The bases in the EHS classification of IH is location, size and whether it is a recurrent hernia or not. The localisation is classified from M1 to M5 as described in figure 6. The reason for this division is the variable difficulties in repair and risk for recurrence where hernias close to bony structures constitute greater difficulties.

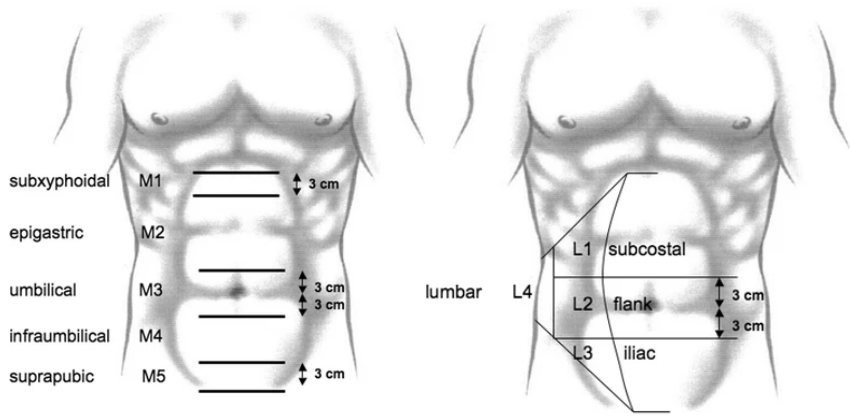

Figure 7. Localisation classification

DOI:10.1007/s10029-009-0518-x.

According to the classification, the width of the hernia defect is the most important measurement for determining the difficulty of successfully repairing the hernia with increasing difficulties with increasing width. The hernia width is defined as the greatest horizontal distance between the lateral margins of the hernia. The size for a small IH is W (width) <4 cm, a medium IH W=4-10 cm and a large IH W>10 cm, see figure 7 where length measurement is also shown.

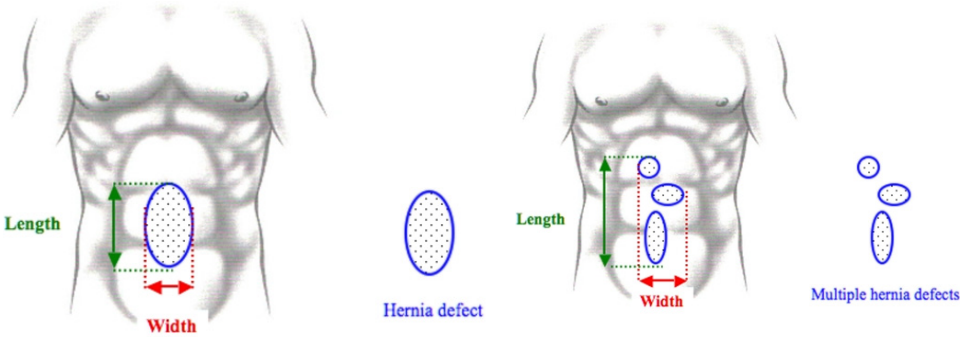

Figure 8. Size classification

DOI:10.1007/s10029-009-0518-x.

Finally, according to the suggested classification system it should be noted if the IH is recurrent or not.

Incisional hernia diagnosis

Different diagnostic modalities for IH diagnosis are being used. Patient's symptoms related to an IH most often initiate the first contact with a physician, and a clinical examination is the first diagnostic step taken. For further investigation ultrasound, CT and MRI can be considered, and the choice vary due to local tradition. CT is the dominating imaging modality and have a higher sensitivity than clinical examination[54]. A standardized ultrasound investigation in addition to a clinical examination revealed an additional 20% IH compared to the clinical examination[55] only but most of these IH was asymptomatic and the clinical value questionable in a Dutch study[56].

Clinical examination

When performing a clinical examination for IH diagnosis, the patient should be examined both standing and in the supine position, both in a relaxed state and when

straining and coughing, see figure 8. In case clinical examination reveals a definite IH diagnosis there is no need for imaging, unless as preoperative planning. The sensitivity of a physical examination alone has showed to be up to 75%[42, 56, 57].

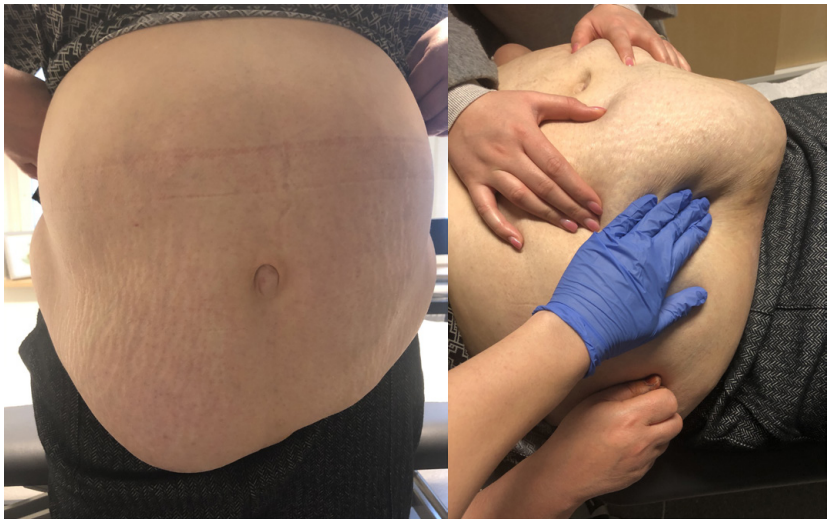

Figure 9. Clinical examination of IH
Inspection and palpation should be performed standing and in the supine position, in a relaxed state and during straining and coughing Photos by Wenzelberg, published with the patients permission.

CT-scan

CT scan is widely used for IH diagnosis and preoperative planning. It is more sensitive than clinical examination with a close to 100% sensitivity and specificity[58], and has the advantage of being available for interpretation by the surgeon compared to an ultrasound investigation[55]. When planning for IH operation, especially if the hernia is of complex nature, the EHS guidelines recommend performing a CT scan (good practice statement). If the radiation dose is considered a problem, an ultrasound or MRI with Valsalva can be used instead[26].

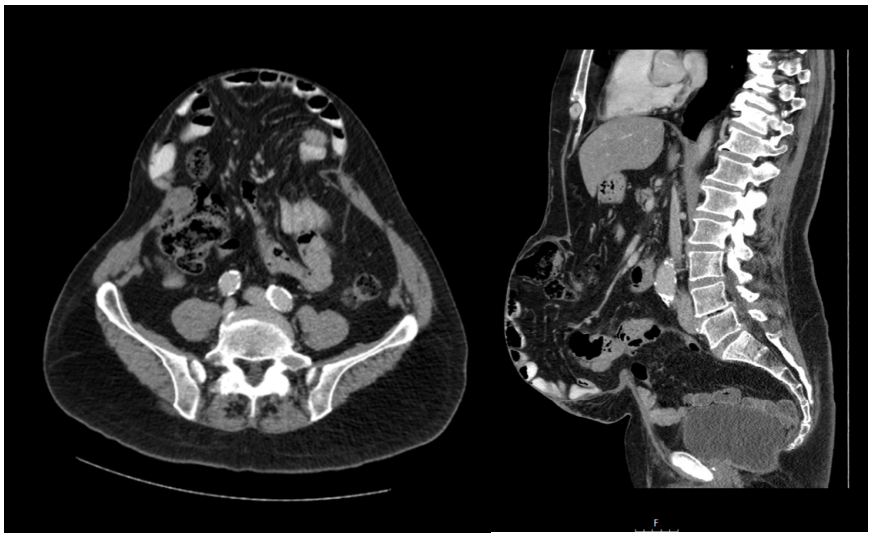

Figure 10. CT-scan as part of the preoperative planning of a large IH
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Risk factors for incisional hernia

Risk factors are patient-related, surgical technique or surgeon-related. Some are modifiable and others are not. Other non-modifiable risk situations are emergency and vascular surgery. Risk factors for IH all, alone or in combination, act through impaired wound healing[25].

Patient-related factors identified as risk factors for IH are co-morbidities (diabetes mellitus, chronic obstructive pulmonary disease – COPD, and diseases treated with immunosuppressants), genetics affecting collagen function (Ehler Danlos syndrome)[59], abdominal aortic aneurysm, health-related behaviour (obesity, smoking), and older age.

According to EHS guidelines[25], patient-related risk factors for IH that are manageable and worth-while to control are high BMI (the higher the more increased risk, proportionally with BMI≥25), smoking, diabetes and immunosuppression. Poor nutritional status and anaemia are two modifiable factors in elective cases and should be corrected before surgery.

A high BMI increases the abdominal pressure, putting excessive and extended strain on the abdominal wall, as do COPD and coughing[41, 60]. It is also associated with increased risk of postoperative complications, especially a higher risk of surgical site infection (SSI)[61] as is badly controlled diabetes and smoking.

Immunosuppressive treatment reduces the immune response which facilitates the biofilm formation and is then potentially working as a direct risk factor[62].

Surgical technique- and surgeon-related factors increasing the risk of IH are midline incisions, closure with fast-absorbable sutures and closure with other suture-technique than the 4:1 small-bite technique. Studies have shown that the combination of a continuous small-bite technique with a slowly absorbable suture reduces the risk of IH[25, 26]. The burst-strength after small-bite is better than with large-bite and it is easier to avoid slacking of the stitch[27, 63]. High suture tension have effect on the regenerating tissue, influencing the collagen synthesis negatively in the incisional region[64].

Of all factors involved, a postoperative SSI appears to be the most important risk factor for IH[65].

Risk factors for IH in colorectal cancer surgery

CRC surgery is classified as clean-contaminated procedures due to opening of the bowel per-operatively and constitutes an increased risk of SSI, and in the extension of this an increased risk for IH[66]. Furthermore, CRC patients may have additional risk factors for impaired healing, such as weight-loss and poor nutritional status and possible immunosuppression because of neo-adjuvant therapy.

CRS/HIPEC is an extensive surgical procedure to treat malignancies spread to the peritoneal surface in the abdominal cavity. Patients undergoing this surgery exhibit several risk factors for IH development, such as increased risk of SSI, earlier midline incisions, per-operative chemotherapy-induced immunosuppression, intestinal swelling and extended high intraabdominal pressure. The supposed increased IH incidence has so far not been verified[47, 49, 51, 52]. Higher age and BMI, female gender, neoadjuvant chemotherapy and fascial dehiscence (FD) have shown to be risk factors for later IH in earlier studies [48-52].

Incisional hernia treatment

In the early 19th century, a French surgeon, Pierre Nichollas Gerdy, performed the first IH repair that is documented. Otherwise IH was rarely repaired in those days. During the second half of the twentieth century documentation of IH surgery increased. Initial technique for surgical repair was simple suturing the defect under tension. At the end of 19th century, the various abdominal wall layers were repaired separately by suturing and the technique gradually developed. In the beginning of the 20th century the use of grafts for closing the hernia defect was explored. The

results were not encouraging, but as an extension of these attempts artificial meshes was introduced[12].

With the introduction of mesh, a tension free repair was made possible. A tension free repair and the abdominal wall reinforcement achieved with a mesh has been shown to be superior to suture repair[67].

Various mesh and mesh-placing techniques have been developed over the years with the aim of improving the results[68]. Spaces in the abdominal wall possible to use for mesh placement are shown in figure 10. There are pros and cons with all positions. The inlay technique is abandoned due to poor results with high recurrence rates. The retromuscular Rives-Stoppa, initially described by Rene´ Stoppa[69] is the most used technique today[70] and is recommended by the EHS, in their guidelines for repair of IH <10 cm, as the technique of choice. Among other studies, a systematic review of large IH repair states that the sublay mesh position should be used if possible[71, 72].

Placing the mesh on the anterior rectus aponeurosis, as suggested and described by Chevrel[73], show higher recurrence rates than retromuscular mesh placement and also more wound complications[26]. However, the technique may still have a place in the context of IH prophylaxis.

Laparoscopic repair with intraperitoneal mesh was reported in 1993 by LeBlanc[74] when improved mesh materials and composition reduced mesh adhesion to the intestine. Despite special meshes there is still a risk for adhesions and damage to the bowel. Because of that there is a trend in IH surgery today to place the mesh outside the abdominal cavity.

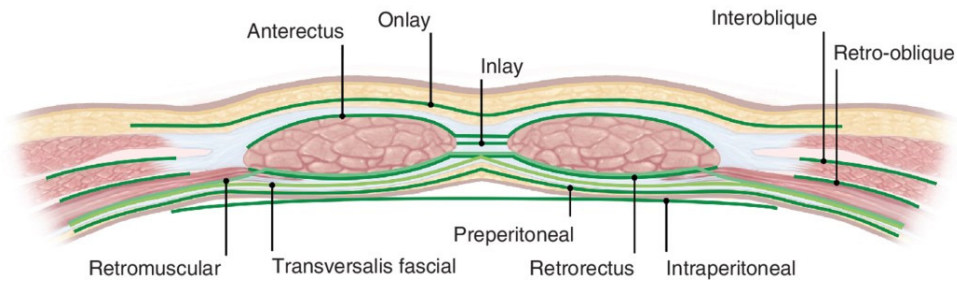

Figure 11. The abdominal wall layers with possible positions for mesh
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Approximately one third of the patients with IH undergo surgical repair[3]. The cumulative recurrence rate after repair varies between 23% and more than 50% after 5 years[62] and for every failed repair, the complications and re-recurrence increases[75].

With these aspects in mind, it is crucial to make a careful and accurate assessment of risks and benefits for each IH patient before surgical treatment is decided. The EHS guidelines from 2023 on primary IH with defect size <10 cm states that the

most important outcome measure for surgery should be QoL. Patients with symptoms that adversely affect them and who are medically fit for surgery should be offered treatment[26]. Also patients with increased risk of incarceration (a defect width of 3-4 cm compared to defects of 0-2 cm, age >65 years, BMI >30, female sex, diabetes mellitus and ASA III-IV) will benefit from surgery[76].

Patient-related risk factors with negative impact on successful and uncomplicated repair of IH are frequently present. In the EHS guidelines[26] it is suggested that modifiable risk factors such as BMI>30, poorly controlled diabetes mellitus and smoking should be addressed before elective surgery. Pre-optimization of pulmonary fitness is also recommended. The time it takes to optimize the patient for IH surgery, especially weight-loss, must be carefully weighed against the discomfort and risks of having an unoperated IH, especially since large IH tend to enlarge over time[77]. On the contrary, watchful waiting may be an alternative to surgery, especially in surgical high-risk patients[78].

Complex hernia repair

Components separation techniques can be applied in larger and more complex IH to achieve enough mesh overlap outside the hernia defect and to be able to reconstruct the line alba, i.e. to suture fascia-to-fascia from both sides of the hernia defect. The components separation can be made by an anterior components separation (ACS) or a posterior component separation (PCS) with transversus abdominus release (TAR)[79] as shown in figure 12. After retromuscular dissection, the posterior rectus sheath is incised medial to where the lateral nerves enter the posterior rectus sheath, whereafter the transverse muscle is divided. This releases abdominal wall tension, and the rectus sheath can be advanced towards the midline and adaptation of the linea alba made possible.

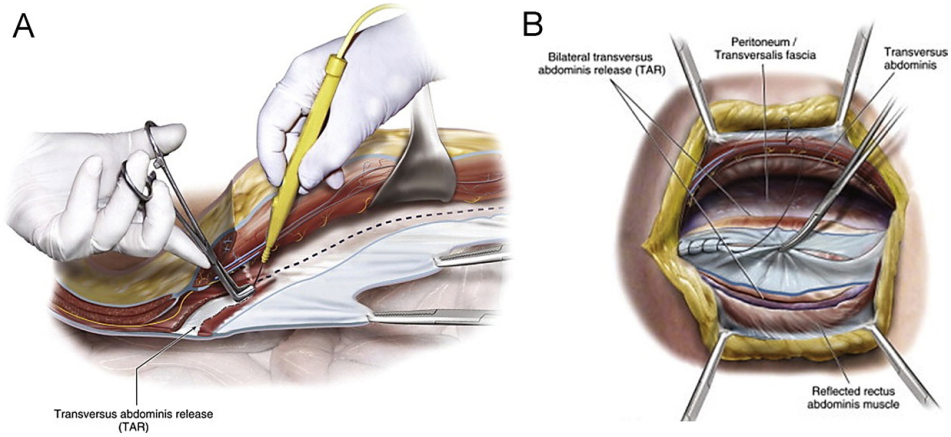

Figure 12. Posterior component separation with transverse abdominis release (PCS-TAR)
Reproduced with permission of the illustrator. ISBN:978-1-4377-2751-7.

Another technique utilizing the hernia sac for separation of the intestines from the retromuscular mesh posteriorly and covering the mesh from the subcutaneous fat anteriorly is the peritoneal flap- technique, initially described by Malik[80] and later modified by the abdominal wall surgery group in Malmö by adding suturing the fascial edges to the mesh everywhere fascia-to-fascia closure is not possible[81]. This technique can be used in all retromuscular repairs and in the majority of IH, also in larger ones, prevents the need of a component separation. The retro muscular space is entered through the posterior rectus fascia on one side and the anterior rectus fascia on the other side. Two flaps of circulated hernial sac are created. The abdominal cavity is closed by suturing the posterior fascial edges wherever possible and using the hernial sac where it's not. After placing the mesh retromuscularly the incised fascial edges, posteriorly as well as anteriorly, are sutured to the mesh, in some sense creating a bridged, but stable repair. Finally the anteriorly attached hernia sac is sutured to cover the rest of the mesh.

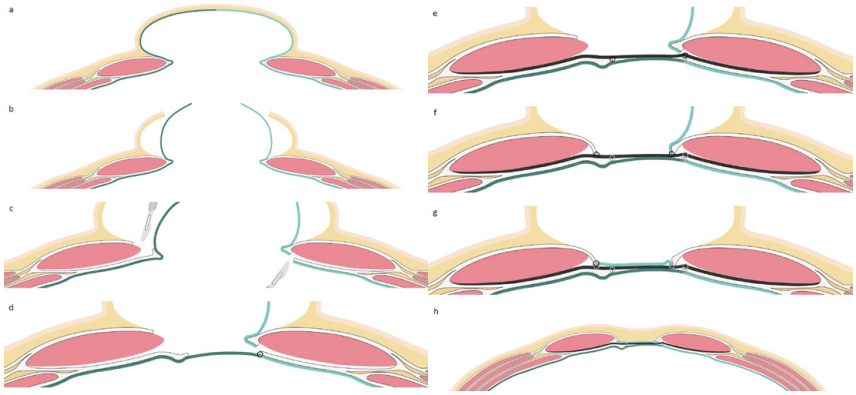

Figure 13. The modified peritoneal flap technique am Malmö
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Prevention of incisional hernia

IH has a multifactorial pathogenesis. Risk factors have been discussed earlier together with a brief outlining of preferred fascia closure techniques. A recent review[82] and existing guidelines[25] point out the importance of preoptimizing modifiable patient-related risk factors as well as aligning to the recommendations concerning fascial closure techniques which sometimes includes fascia reinforcing measures to decrease the IH incidence.

Fascia closure

Already in ancient Greece, Aelius Galenus or Galen of Pergamon (129 AD-216 AD) described a mass closure of the abdominal wall (including all layers) as he was aware of the risk of IH: “In stitching the needle should be thrust from without inwards through skin and rectus muscle, and then from within outwards through the muscle and skin, repeating this until the wound is closed”[12].

Even at that time there were different opinions concerning the best technique since Celsus in Rome described a layered closure: ”Stitching of the surface skin only or of the inner membrane only is not enough, but both must be stitched. And there must be two rows of stitches, set closer together than in other places, partly because they can be broken here more easily by the abdominal movement”.

In 1976 Jenkins calculated the ideal suture length to wound length ratio (SL:WL ratio) of 4:1 to prevent IH. He concluded that if the bites in suturing were not large enough, the suture may cut through the fascia resulting in a WD[34], and stated that the bite on each side should be at least 1 cm. The SL:WL ratio was further

investigated in the 1990s by Israelsson et al[83] in a prospective clinical trial, where they found a ratio of <4 to be an independent risk factor for IH development. Besides the suturing technique, wound infection and age was also found to be independent risk factors of IH[84]. In these studies larger bites resulting in mass closure partly including medial rectus muscle fibres was used.

The theory behind using small stitches was that it decreases the amount of devitalised tissue since it is only applied in the fascia and not in the muscle which is more prone to necrosis due to tension from the suture. Besides proposed higher risk of infection, cutting through of the suture in the less collagen-rich muscle compared to fascia would allow the wound edges to separate and increase the risk of IH and WD[33, 35].

Results of the small stitch closure technique was first reported in 2009 by Millbourn et al[85]. They randomized 737 patients in a prospective RCT to either long stitches or short stitches (<10 mm from the wound edge) in combination with a SL:WL ratio of at least 4. They found higher incidences of SSI and IH in the long stitch group (18% vs. 5.6%) and long stitches was an independent risk factor for both SSI and IH. This was the first prospective trial comparing large and small bites. After this study surgeons were recommended to place stitches 5-8 mm from the wound edge, 5 mm apart, and incorporating only the aponeurosis, and to measure and document the ratio at fascia closure[86]. Furthermore, a systematic review and meta-analysis 2010 showed lower IH rates using a continuous suture technique with slowly absorbable suture material[87] compared to interrupted suturing and rapid absorbable sutures.

In 2015 Deerenberg et al reported the results from a double-blind multicentre RCT, the STITCH trial, including 560 patients. They compared small stitches (5-8 mm from the wound edges and 5mm apart) with large bites (1cm with 1cm apart) and SL:WL ratio >4 in both groups. They confirmed the differences found by Millbourne of 13% IH in the small-bite group and 21% in the large-bite group at 1 year[42].

The ESTOIH randomized controlled trial by Fortelny et al 2022 concluded a clinical difference between short and long stitches, twice as many IH in the long-stitch group, without reaching statistical significance[88].

Three meta-analyses on materials and techniques for laparotomy closure 2018, 2023 and 2024 concluded that the IH rate is significantly reduced with the small-bite compared to the large-bite technique[89-91].

Fascia closure recommendations

The 4:1 small-bite technique with a continuous, slowly resorbable suture is considered the gold standard for fascia closure and is the recommended technique in the EHS guidelines from 2022[25].

Mesh reinforcement at fascia closure

Using a reinforcing mesh has repeatedly been shown to reduce IH compared to only suture for fascia closure and have been recommended for abdominal closure in patients at increased risk of IH, such as CRC patients, patients with abdominal aortic aneurysm disease, obese patients and those with high IH risk scores, and for reinforcement of more complex incisions[8, 92-101]. An onlay or retromuscular reinforcing mesh do not seem to increase wound complications or postoperative pain compared to only suturing of the fascia[102]. The use of prophylactic mesh has also been shown to be cost effective[103]. There is a discrepancy between the evidence and the willingness among surgeons to use a prophylactic mesh, even in patients with a high-risk for IH. In a survey from 2019 only 15% of answering surgeons used prophylactic mesh. The reasons for not using mesh were unfamiliarity with literature and fear of mesh complications, scepticism towards mesh benefits and believing evidence for mesh use in contaminated situations is insufficient[9, 32, 104].

The EHS guidelines from 2022 states that prophylactic onlay or retromuscular mesh can be considered but the evidence is still low, and the strength of the recommendation is weak.

Reinforce Tension Line suture (RTL)

In 2007 Hollinsky et al[105] described the RTL-suture with a non-absorbable polypropylene suture as an alternative to mesh repair of IH. They concluded that the RTL-suture is cheap and easy to perform and presented good results. The RTL-suture is threaded within the fascia parallel to the incision on both sides and the fascia closing suture is then applied including the RTL-suture in every stitch. Finally, the RTL-suture is tied, see figure 14.

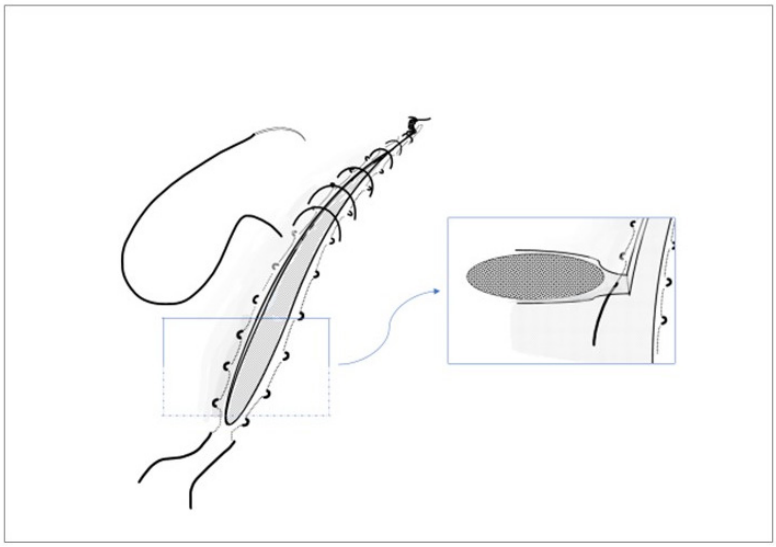

Figure 14. The RTL-suture technique
On the left closing the fascia with a continous 4:1 suture including the RTL-suture in every stitch. On the right a clarification of the principle threading the suture within the fascia. Copyright, published by Frontiers. Reproduced under Creative Commons CC-BY licence. DOI:10.3389/jaw.

In 2011 Agarwal et al evaluated the RTL-technique as a means of preventing fascia dehiscence (FD) in patients with acute peritonitis. They found significantly lower FD rates with the RTL-closure compared to the standard 4:1 closure, using slowly absorbable polydioxanone sutures[106].

The RTL-suture has so far only been evaluated for IH prophylaxis in one study presented in 2022 by Lozada-Hernandez et al. They compared RTL plus 4:1 closure with 4:1 large bite closure alone, using polydioxanone sutures in both groups and showed a lower IH with the use of RTL suture at 3-year follow-up (9.8 vs 28.3%)[107].

Reinforcing sutures in CRC patient cohorts is hardly tested or evaluated. In 2022 the randomized HART study[108] (Huges Abdominal Repair Trial), compared the Hughes interrupted stitches combined with mass closure to mass closure or surgeon´s choice of fascia closure in CRC patients, with IH incidence as primary outcome. After two years IH incidences in both groups were around 30% without differences.

The RTL suture as an IH preventive closure technique has not been studied earlier in CRC patient cohorts.

Quality of Life (QoL)

There are many ways to define QoL. It is a wide concept that is used to describe a person's or a group's general well-being and satisfaction. The World Health organisation's (WHO) definition states QoL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"[109]. QoL includes different dimensions, for example physical and mental health. Other subject areas are economy, social relations, work and leisure time, education, environment, safety and freedom. Centers for Disease Control and prevention (CDC) describes Health related quality of life (HRQoL) as "an individual's or a group's perceived physical and mental health over time"[110]. QoL can be measured objectively or subjectively, for example with surveys. Fitzpatrick et al described 1998 the purposes of the different questionnaire instruments that are available to assess the impact of health care from the patient point of view, as patient-based measures of outcome[111].

In a review from 2024 LaGuardia et al concluded that evaluation of QoL following abdominal wall reconstruction rely on several different assessment instruments and a standardized instrument for use in this patient group is not yet available[112].

Generic patient reported outcome measure (PROM)

Generic patient reported outcome measure (PROM) is used to assess overall health outcomes, relevant to a wide range of patient groups, that enables comparisons across treatments for different groups of patients. PROMs can for example detect positive or negative effects of an intervention. The generic instruments use data to generate "normative values" that patients with a health problem can be compared with. A disadvantage with generic instruments is that it may have fewer relevant items for a particular disease and thereby becomes less sensitive.

PRO (Patient Reported Outcome) is the patient's own reported health associated with the health care they have received. PROs include symptoms, functionality, QoL, mental health and the patient's perception of treatment principles. Tools for measuring PROs is for example SF-36, EQ-5D and VAS (visual analogue scale). The EQ-5D is often used in clinical trials and was used in the Rein4CeTo1 study in this thesis.

One of the most common generic instruments used is the SF-36 that measures health status in 8 dimensions where the response gives a score for each of the items that can be summed into a physical component score (PCS) and a mental component score (MCS). SF-36 is one of the most widespread and validated QoL instruments[113]. SF-36 is also the most common generic instrument for evaluation after abdominal wall reconstruction, even if it is not hernia-specific[112, 114]. The questionnaire, originally developed 1992, addresses the patient's pain, daily

activities and mental health status. There is also a shorter form of this questionnaire with 12 questions instead of 36 but this is more seldom used.

EQ-5D is a generic health status measure, that have been developed from economics, with a form of numerical weighting of health status[111]. It delivers a single QoL-index that is useful for summarising and comparison of health outcomes, and was developed in 1991 to be a fast, easy to complete and reliable instrument. It is available in more than 200 languages and has been used in 15 studies related to abdominal wall reconstruction outcomes until now, even though a validation for its use in abdominal wall and hernia patient cohorts is lacking[112]. The EQ-5D descriptive system was developed by the EuroQuol Group[115] to a 5-level version, with the aim that it could be used in a variety of health care sectors.

The EQ-5D-5L consists of five dimensions to describe the patient's unique health state: Mobility (MO), Usual Activities (UA), Self-Care (SC), Pain and Discomfort (PD) and Anxiety and Depression (AD). Each dimension has five number of levels that the respondent of the questionnaire ticks in: no, mild, moderate, severe and extreme or unable to. For example 1-1-1-1-1 means no problems in any of the dimensions and 5-5-5-5-5 is the worst health state resulting in 3.125 possible health profiles. The second part of the questionnaire is an EQ VAS (visual analogue scale) that is an overall assessment on a scale from 0-100. This provides complementary information to the EQ-5D profile, because some aspects of the health are not reflected in the profile.

To compare the health profiles a scoring system is needed since you, for example, cannot appreciate how much better 1-1-1-1-1 is compared to 1-1-1-1-2, or whether 1-1-1-1-2 is better or worse than 1-1-1-2-1. The EQ-5D profile data can be converted to a single number from ≤0 to 1, that is called EQ-5D value (or EQ-5D index), where each dimension is weighted reflecting the QoL. A value set is a country-specific full set of values for each possible EQ-5D profile.

The EQ5D value in the Rein4CeTo1 study was calculated using the TTO (time-trade-off) method. The TTO is based on a person's preferences in relation to QoL and lifespan; how many years a person is prepared to sacrifice in lifespan to live a shorter time in perfect health, QALYs (quality adjusted life years). A Swedish value set is available for comparison[116].

Disease specific PROM

Disease specific PROM is measuring outcomes for a particular disease or treatment. The intention is thus to have a relevant content for a specific disease (for example cancer) and an advantage with this type of questionnaire is that changes over time for a specific subject can be noted[111]. There are different disease specific surveys that are used to evaluate QoL in hernia patients.

The Hernia-Related Quality-of-Life Survey (HerQLes) implemented 2012[117] with 12 questions, is focusing on abdominal wall function and impact of ventral hernia and ventral hernia repair on QoL. The questionnaire captures outcomes also related to mental health and is the most common hernia specific outcome tool[112].

Carolinas Comfort Scale (CCS) published 2008[118] is another disease specific survey that focuses on patients' daily activities and pain, measuring QoL after hernia repair. CCS is the second most used hernia-specific instrument.

Another hernia specific questionnaire is the European Hernia Society Quality of Life Tool (EuraHS-QoL), developed by Muysoms et al in 2012[119], that in addition to evaluate pain and activity restrictions has a dimension of cosmetic discomfort.

The Ventral Hernia Pain Questionnaire (VHPQ) published 2012[120] (used in the Rein4CeTo1 study in a slightly modified version) measures QoL by assessing pain and impact on activities of daily living in hernia patients and consists of 19 questions.

The relatively new Abdominal Hernia-Q (AHQ) instrument was developed in 2020[121] and assesses pain, daily activities, mental health and secondary items. This questionnaire was not available when the Rein4CeTo1 RCT was designed.

QoL in colorectal cancer (CRC) patients

It is known that patients with CRC report low QoL[122], as do patients after CRS/HIPEC surgery[48]. Sjövall et al concluded an impaired QoL in patients after CRC in a Swedish population 2023[123]. Living with a stoma is also confirmed having an impact on QoL of CRC patients, influencing the QoL negatively[124, 125].

QoL in IH patients

Earlier studies have showed that IH is a complication that has negative impact on QoL assessed with different patient outcome measures[48, 126]. In 2012 van Ramshorst et al investigated the impact on IH on quality of life and body image and reported lower mean scores using the SF-36 instrument[127]. Studies have also showed an improvement in patients QoL after IH repair[4, 128-130].

A Danish register study indicated a reduced QoL several years after CRC surgery in patients developing an IH[130] using the cancer-specific questionnaire EORTC QLQ-C30, developed by the European Organisation for Research and Treatment of cancer (EORTC). The questionnaire contains 30 items in five aspects of function, global QoL and different areas of symptoms for use in cancer patients.

That the comparison of QoL inbetween studies is complicated, this due to the use of different instruments and length of follow-up variation, was concluded in a

systematic review by Jensen et al 2014, by Grove et al 2021 and again 2024 by LaGuardia et al[112, 114, 131]. Until today the gold standard for QoL evaluation after surgery is to use both a generic and a disease specific QoL questionnaire since a single standardized outcome measurement instrument is still lacking.

Aims

To retrospectively compare the CT-detected IH incidence for two different fascia closure techniques, RTL+4:1 and 4:1 suture only, 1 year after CRS/HIPEC surgery, and to evaluate possible risk factors for IH development.

To prospectively investigate whether adding an RTL suture to the standard 4:1 small-bite fascia closure technique reduces the CT diagnosed IH incidence after open CRC surgery 1 year postoperatively, and to evaluate short-term complications, in the Rein4CeTo1 randomized controlled trial.

To evaluate the 3-year CT diagnosed IH incidence after open CRC surgery and to identify potential risk factors for IH, in the Rein4CeTo1 randomized controlled trial.

To evaluate and compare general QoL and disease specific abdominal wall pain and discomfort 1 and 3 years after CRC surgery in patients with and without an IH in the Rein4CeTo1 randomized controlled trial.

Methods

This thesis is based on one retrospective and one prospective randomized trial, with the common main purpose to evaluate the IH incidence associated with the use of two different suturing-techniques for fascia closure after open surgical CRC treatment. At our institution the standardized 4:1 fascia closure technique was used at CRS/HIPEC operations since the beginning of the CRS/HIPEC era around year 2000. It was successively replaced by the RTL+4:1 technique which initially was introduced as an alternative to prophylactic mesh in high-risk patients and is now used in the majority of patients. In paper 1 we evaluated and compared the IH incidence of the two different techniques. Paper II-IV is based on the Rein4CeTo1 randomized controlled trial, where patients scheduled for open CRC surgery were randomized to fascial closure with either of the same two closure techniques. The patients sutured with RTL+4:1 was called the RTL group and the patients sutured with 4:1 only was called the PDS group. The aims for the study were to compare IH incidences 1 and 3 years postoperatively between fascia closure groups and to perform a risk factor analysis for IH development. Furthermore, to evaluate complications related to the techniques and QoL.

Fascia closure techniques in the studies

The 4:1 small-bite technique

The 4:1 small-bite technique as described by Millbourn et al in 2009 was used in both studies[85].

The fascia is dissected free from subcutaneous fat at the beginning of the operation to allow for a precise midline entrance to the abdomen and a precise suture placement at fascia closure, see figure 15.

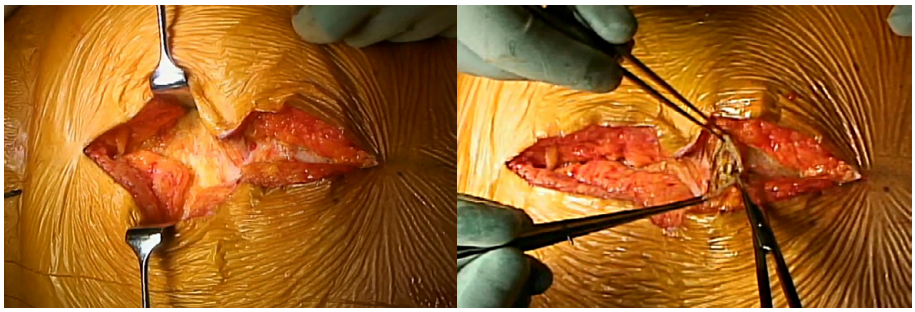

Figure 15. Precise mid-line incision
The midline fascia is dissected free of subcutaneous fat (left picture) and entrance to the abdominal cavity is started just carnially of the umbilicus. Photo by Petersson. Published with permission of the patient.

The fascia closure is done with a 2/0 polydioxanone suture (PDS®plus, Ethicon) on a CT-2 needle and the stitches are placed 5-8 mm from the fascial edge of the midline incision. The suture bites only include the fascia and not fat or muscles. The suture-bites are placed 5mm apart to ensure a SL:WL ratio > 4. Skin closure was done with a running intracutaneous 4-0 polydioxanone suture (PDS®Plus, Ethicon). The main principle of the technique is shown in figure 16.

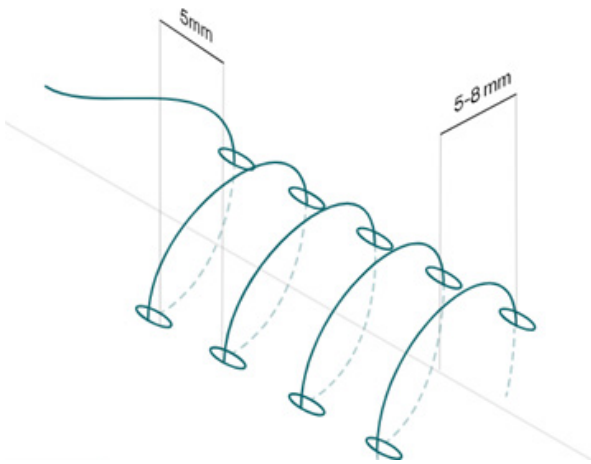

Figure 16. The small-bite 4:1 technique.
Reproduced with permission of the illustrator, Gabriel Börner, Suturion.

The RTL + 4:1 small-bite technique

In the RTL + 4:1 small-bite closure the fascia is dissected free of fat as described above. A reinforcing suture of 2/0 polypropylene (Prolene®, Ethicon, Raritan, NJ, USA) on a CT-2 needle is threaded within the linea alba on both sides of the fascia

incision, 5-8mm from the incision. In case of accidental opening in the rectus muscle sheath, the RTL suture is used to close the fascia layers again. After applying the RTL-suture the ends are initially left untied. The incision is then closed with the same type of suture according to the 4:1 small-bite technique described above, making sure to include the RTL-suture in every stitch, i.e. the 4:1 suture is placed lateral to the RTL-suture. After finishing fascia closure the RTL-suture is tied. Skin closure was done with a running intracutaneous 4-0 polydioxanone suture (PDS®Plus, Ethicon).

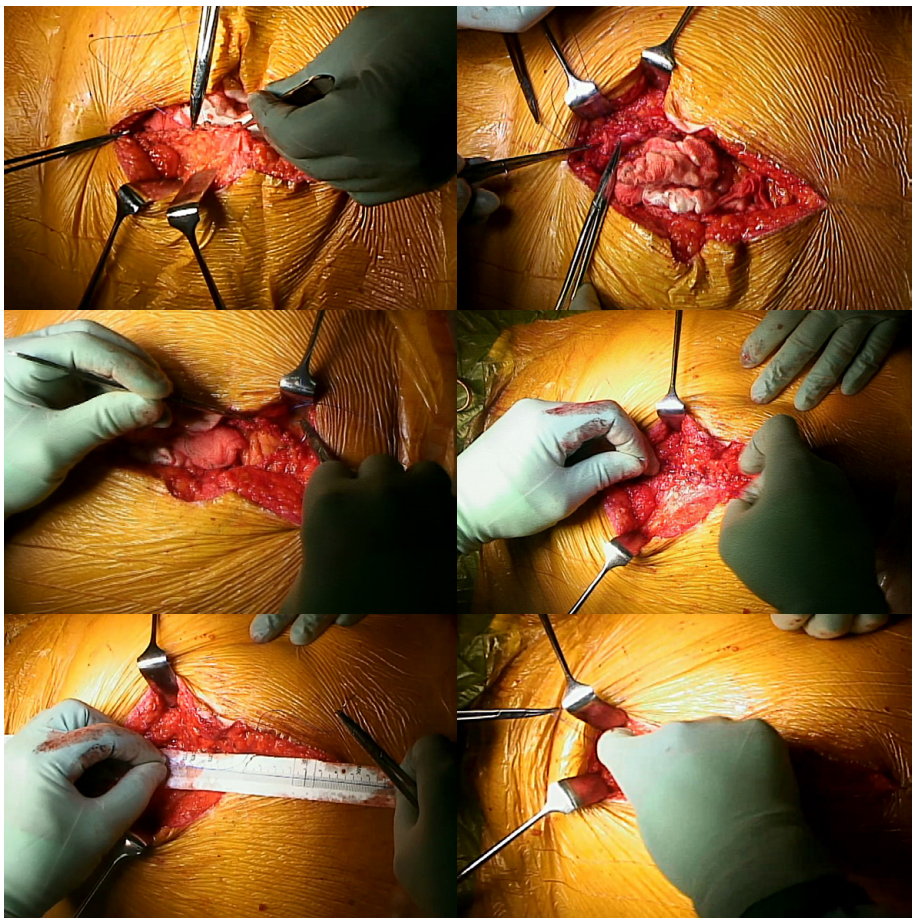

Figure 17. The RTL technique
The RTL-suture is threaded within the fascia on the left side of the incision (top left). An accidental opening of the rectus sheath is closed with the RTL-suture (top right). A cranially started small-bite 4:1 suture is applied outside the RTL-suture (middle left). Another small-bite suture is started caudally and the two sutures are tied at the umbilicus (middle right). The incision and suture lengths are measured (lower left) whereafter the RTL-suture is tied (lower right). Photo by Petersson. Published with permission of the patient.

The retrospective CRS/HIPEC study (paper I)

In this study patients treated with CRS/HIPEC between 2004 and 2019, at Skåne University Hospital in Malmö, were evaluated regarding CT diagnosed IH incidence 12 ± 3 months after surgery with midline laparotomy, comparing the two fascia closure techniques.

Exclusion criteria were patients closed in a different way than the two techniques studied, patients with an existing midline mesh, existing hernia or patients reoperated or deceased within 9 months after surgery. Patients not investigated with a CT scan 12 ± 3 months after surgery were also excluded from analysis.

Patient data was retrieved from clinical records and from a prospective CRS/HIPEC database. Peritoneal cancer index score (PCI) was used in staging carcinomatosis[132]. The completeness of cytoreduction score (CC-score), classifying the completeness of surgical extirpation of cancer[133] was noted. The Clavien-Dindo classification was used for documentation of postoperative complications[134]. CT-scans were scrutinized by two surgeons and one radiologist independently and in case of discrepancy a discussion was carried out to reach agreement.

The Rein4CeTo1 trial (paper II-IV)

The Rein4CeTo1 open parallel trial was conducted at two Swedish surgical units, Skåne University Hospital Malmö and the County Hospital Kristianstad, between 2017 and 2021. The overall primary endpoint was CT-diagnosed IH incidence 1 year ±3 months after open CRC surgery, comparing the two fascia closure techniques.

All patients over 18 years of age with CRC planned for surgery through a midline incision were assessed for eligibility and participation. Exclusion criteria were planned CRS/HIPEC, previous midline hernia surgery, current midline hernia (<1cm was accepted), inability to participate in follow-up and ASA>III.

Patients with per-operatively detected peritoneal carcinomatosis, midline hernia, need for fascia reconstruction, or for other reasons deemed inappropriate to participate by the surgeon, were excluded.

The randomization was done during the operation immediately before closing the fascia. Fascial closure time and accidental opening of the rectus sheath was documented per-operatively.

An instructive video of the closure techniques was produced and distributed to the surgeons. Several meetings were held before the start of the study and visits in the

operating rooms were conducted for inspection of performance of the closure techniques and alignment to protocol through the study period.

Follow-up

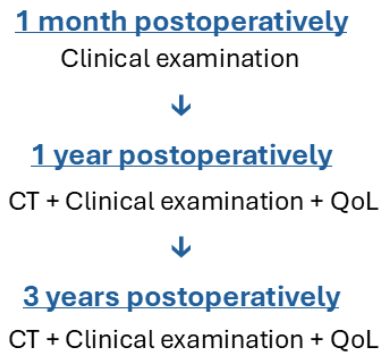

Figure 18. Follow-up schedule in the Rein4CeTo1 RCT

Patients were seen in the outpatient clinic 1 month after the operation by a colorectal surgeon. Short-term complications were registered, including wound healing (hematoma, seroma and surgical site infection).

As part of the routine CRC follow-up the patients underwent CT scans, without Valsalva manoeuvre, 1 and 3 years after surgery. Three examiners reviewed the CT scans independently and were blinded regarding fascia closure technique. Any discrepancy was discussed to reach consensus. IH was defined as "any abdominal wall gap in the post-operative scar, perceptible or palpable by clinical examination or imaging", in accordance with the EHS definition. Umbilical hernias <1 cm, present before and after surgery were not assessed as an IH.

Patients were invited to a clinical visit and examination of the abdominal wall 1 and 3 years postoperatively. The research group surgeon examining the patients was blinded for fascia closure technique. Abdominal wall examination was done in both standing and supine position in a relaxed state and when straining/coughing.

Patient data were registered prospectively according to the study protocol and after review of patients records to identify problems related to the operation appearing between the scheduled study visits.

When restrictions due to the COVID-19 pandemic existed, the patients were contacted by telephone and mail.

QoL

To evaluate QoL and abdominal wall pain were secondary aims of the Rein4CeTo1 trial, and the patients were asked to fill out two questionnaires for assessment of this at the 1- and 3-year follow-up visits. For assessment of general health QoL the EQ-5D-5L questionnaire was used. For assessment of abdominal wall pain and discomfort the hernia-specific ventral hernia pain questionnaire, VHPQ, was used.

The EQ-5D health states and EQ VAS were compared with the Swedish characteristics developed by Burstrom et al[116]. An EQ-$5D_{index}$ was calculated using the value set of the time trade-off (TTO) model. The EQ-$5D_{index}$ was used in multivariable linear regression analysis for evaluation of possible risk factors.

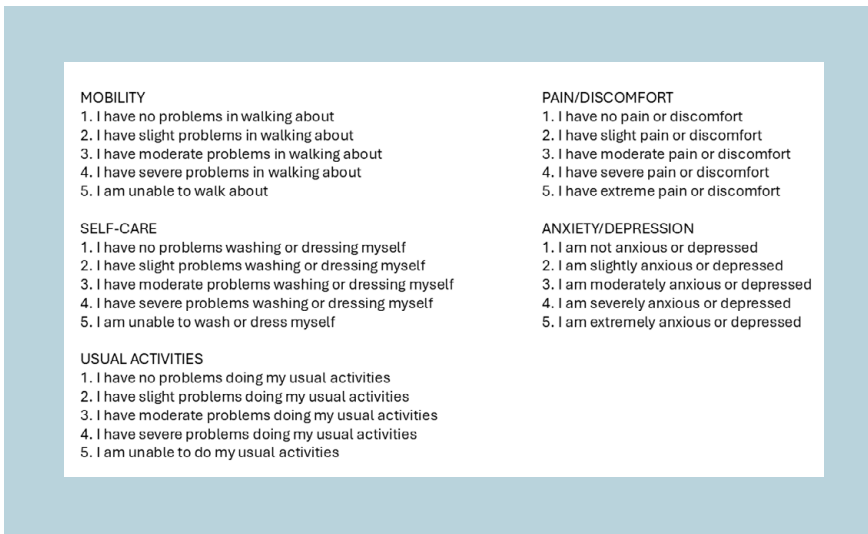

Figure 19. The five dimensions and the five levels in the EQ-5D-5L questionnaire

The two questions concerning abdominal pain "right now" and worst abdominal pain "last week" in the VHPQ questionnaire was graded from 1 to 7.

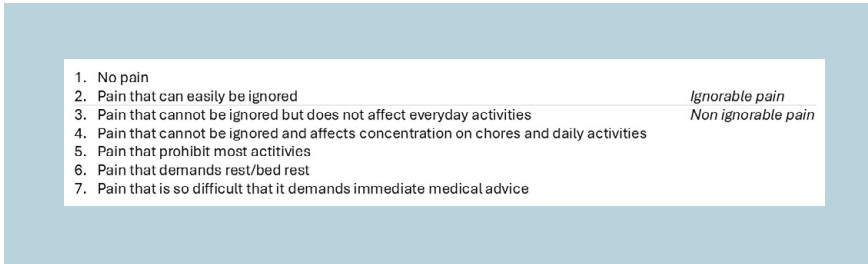

Figure 20. Pain grading scale in the VHPQ questionnaire

Statistical methods (paper I-IV)

Sample size calculations

The power computations of the Rein4CeTo1 trial were performed on CT detected IH incidence 1 year postoperatively that was the overall primary outcome of the study. Based on previous findings, the IH incidence in the PDS-group with small-bite 4:1 closure was set to 20%. Since no publication on IH incidence using the RTL suture closing technique was available at that time it was assumed to be 5%. With a decided power of 80%, a significance level of 0.05, and assuming a 20% drop-out rate, a minimum of 90 randomized patients was required in each group.

Randomization

Randomization to the two different study groups in the Rein4CeTo1 trial was created using Microsoft® Excel 365 for Windows® (Microsoft, Redmond, WA, USA) with a 1:1 allocation using random block sizes of 4, 6 or 8. Sealed opaque envelopes was used for the group allocation and recruiting and operating surgeons were blinded. The study was based on the intention to treat principle, which means that they remained in the initial allocation group.

Statistical analysis paper I

Statistical analysis was performed using IBM SPSS Statistics version 26.0.0.1. A p-value of ≤ 0.05 was considered statistically significant. Continuous variables were expressed as means with standard deviation (SD) or median with interquartile range (IQR). The Student's t test, Pearson's chi-square test or Fisher's exact test, if the number for any expected outcome was below 5, was used for comparisons between groups.

Statistical analysis paper II-IV

Statistical analysis was done using IBM SPSS Statistics version 26.0.0.1. A p-value of ≤0.05 was considered statistically significant. Continuous variables were expressed as means with SD and evaluated with Student's t-test. Categorical variables were analysed with Pearson's Chi^2-test or Fisher's exact test, if the number for any expected outcome was below 5. Risk factors were analysed with uni, bivariate- and multivariate logistic regression. OR with 95% confidence interval was used.

The predefined risk factors included in the risk factor analysis for IH were those stated in the EHS guidelines: diabetes mellitus, BMI, smoking, wound infection and immunosuppressive treatment. Additional factors tested in the bivariate analysis were factors interesting for this study, tumour location and adjuvant chemotherapy.

When adjusting for fascia closure technique in the bivariate analysis the risk factors with the highest OR were chosen for the multivariate logistic regression. In the multivariate analysis the fascia closure technique was adjusted with those three factors. Considering the risk of overfitting, the amount of 27 IH allowed us to analyse 4 risk factors.

Ethics

All studies followed the principles of the Declaration of Helsinki 1964.

Paper 1

The CRS/HIPEC study was approved by the Swedish Ethical Review Authority (Dnr. 2020-03504). Informed consent was not required.

Paper II-IV

The Rein4ceTo1 study was approved by the Regional Ethics Committee at Lund University, Sweden (2017/459) and registered at https://clinicaltrials.gov (NCT03390764). EuroQol provided authorization for research use of EQ-5D-5L, ID:21776.

All patients signed informed consent to participate in this study after oral and written information. Patients were informed that withdrawal of their consent was possible at any time during the study. The patients were also informed about similar complication rates and unintended effects in both study groups with already established surgical techniques.

Evaluation of risks and benefits

Patients included in the retrospective study were already operated and no risk with the evaluation was anticipated.

No risk was anticipated for the patients participating in the Rein4CeTo1 RCT either. Adding an RTL-suture to the standard small-bite 4:1 technique for fascia closure after laparotomy must be considered a minor variation in fascia closure technique, theoretically without any significant risk for complications. Furthermore, the RTL-suture technique had been used in selected cases in emergency surgery without observed negative effects. If a difference in IH incidence could be shown, as hypothesized, some of the patients in the study may, on the contrary, benefit from their participation.

Results

The main aim and overall primary outcome of this thesis was to evaluate IH development after CRC surgery, comparing the gold standard 4:1 fascia closure technique (PDS-group) with the RTL+4:1 suture technique (RTL-group).

Included and evaluable patients

The retrospective CRS/HIPEC study (paper I)

A total of 193 patients, treated with CRS/HIPEC between 2004 and 2019, were identified and 129 patients were included for analysis: 82 in the PDS- and 47 in the RTL-group, as shown in figure 21.

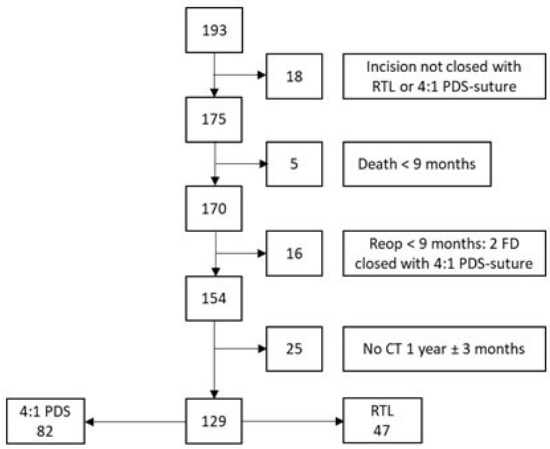

Figure 21. Flowchart CRS/HIPEC study

DOI: 10.3389/jaws.2023.11188.

The Rein4CeTo1 RCT (paper II-IV)

In the prospective Rein4CeTo1 trial, 248 patients were assessed for inclusion between 2017 and 2021. When 204 patients were scheduled for surgery, the trial was stopped due to marked slowing down of inclusions. This was the result of the Covid-19 pandemic which necessitated a reorganisation of care for CRC patients in the Region of Skåne to other hospitals, as well as an increased amount of minimal invasive CRC-surgery.

A flowchart for the study is shown in figure 22.

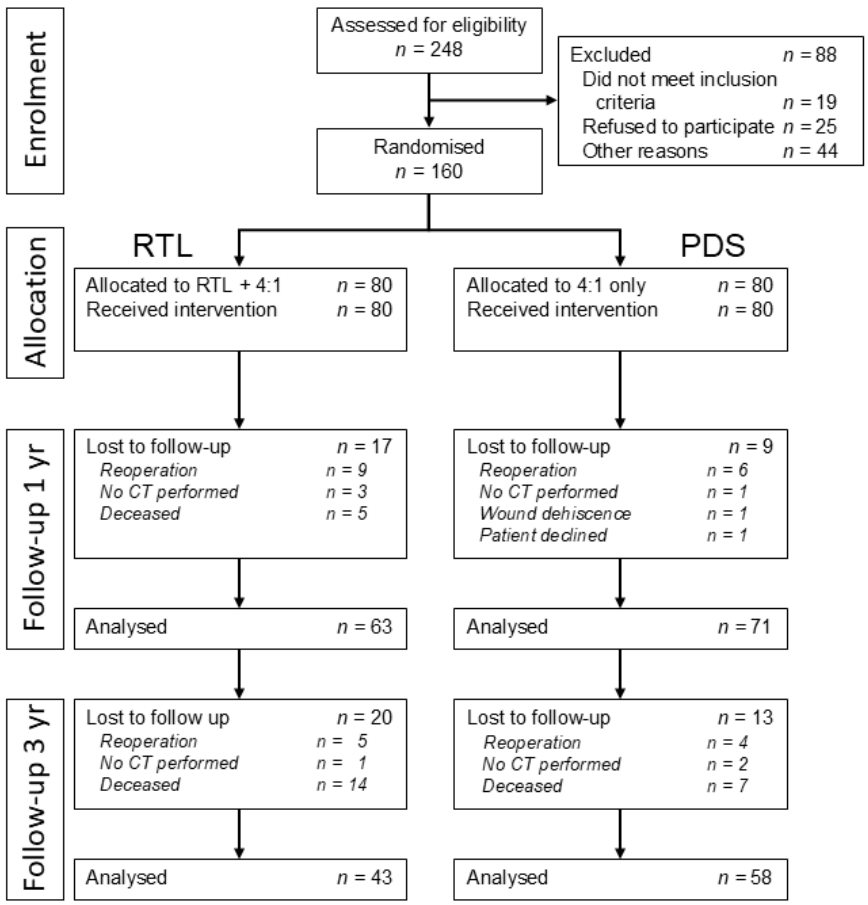

Figure 22. Flowchart for the Rein4CeTo1 trial

Of the 204 patients scheduled for operation, a total of 160 patients equally divided between groups were finally randomized. Besides 19 patients that did not meet the inclusion criteria and 25 declining participation, other reasons for perioperative exclusion were: detected hernia, need for fascia reconstruction, peritoneal carcinomatosis and the surgeon's decision in some cases.

At the end the study reached a power of 75.1% and not the desired 80%. At 1 year ±3 months, 134 patients remained for analysis: 63 in the RTL-group and 71 in the PDS-group. The corresponding figures at 3 years±3 months were 101 patients: 43 in the RTL-group and 58 in the PDS-group.

Incisional hernia (paper I-III)

The retrospective CRS/HIPEC study (paper I)

Of the 129 evaluable patients, 9 (11%) were diagnosed with an IH in the PDS-group and 1 (2.1%) in the RTL-group, p = 0.071. Furthermore, 2 cases of fascia dehiscence were noted, both in the PDS-group.

The Rein4CeTo1 RCT (paper II-III)

The CT-assessment of IH at 1- and 3-year follow-up is shown in figure 23.

	IH		OR (CI95%)	p-value
	PDS	RTL		
1 year	15/71 (21.0%)	4/63 (6.3%)	3.95 (1.24-12.60)	0.014
	19/134 (14.2%)			
	PDS	RTL		
3 years	21/58 (36.2%)	6/43 (14.0%)	4.39 (1.67-11.58)	0.003
	27/101 (26.7%)			

Figure 23. IH in the Rein4CeTo1 trial at 1- and 3-years

There was a risk difference for CT-diagnosed IH at 1 year of 14.7% (OR 3.95, CI95% 1.24-12.60, p=0.014), in favour of the RTL-group in the per protocol

analysis. Besides the significant difference in IH incidence, one patient in the PDS-group suffered a fascia dehiscence early postoperatively, as a manifestation of an acute wound insufficiency.

At 3 years ±3 months, 8 new IH were diagnosed, 2 in the RTL-group and 6 in the PDS-group. The cumulative IH incidence within 3 years was per protocol 27/101 (26.7%), 6 (14.0%) in the RTL-group and 21 (36.2%) in the PDS-group with a risk difference of 22.2% (OR=4.39, CI95% 1.67-11.58, p<0.003). No patient with known IH at 1 year was lost to follow up at 3 years.

The IH rate was similar between the two operating centres at 1 year (OR=1.08, CI95% 0.28-4.11, p=1.000) as well as at 3 years (OR=0.733, CI95% 0.224-2.391, p<0.606).

The CT-measured widths of the hernias, at the time of diagnosis, were <4 cm in 11 patients, 4-10 cm in 14 patients and >10 cm in 2 patients.

The fragility index for IH at 1 year, i.e. the number of additional IH in the RTL-group needed to lose statistical significance, was 2 which corresponded to 50% of the incisional hernias in the RTL group. The number needed to treat to avoid one IH was 6.8.

Baseline characteristics (paper I-III)

The retrospective CRS/HIPEC study (paper I)

In the retrospective CRS/HIPEC study, 52% of the patients were women, the mean age was 57 years, and the mean BMI 26. The only difference in preoperative characteristics was that patients in the RTL-group were 5 years younger.

The Rein4CeTo1 RCT (paper II-III)

In the Rein4CeTo1 trial, 46% were women, the mean age was 68 years, and the mean BMI was 25,6. Baseline characteristics were similar between groups regarding cardiovascular disease, COPD, diabetes mellitus, steroid treatment, smoking, previous midline incision, haemoglobin and albumin levels.

In the drop-out analysis, comparing the evaluable 134 patients with the 26 dropouts, no difference in baseline characteristics was demonstrated apart from ASA class where the dropout patients had a higher score.

Pre- and perioperative data (paper I-III)

The retrospective CRS/HIPEC study (paper I)

There was less blood loss and more frequent postoperative neutropenia in the RTL group.

No differences were found in peritoneal cancer index, midline scar resection, duration of surgery, complete cytoreduction, or adjuvant chemotherapy, between the groups.

The Rein4CeTo1 RCT (paper II-III)

For patients evaluable at 1 year, neoadjuvant radiotherapy was more frequent in the RTL-group (33/63 RTL, 24/71 PDS, p=0.030), as was stoma creation (41/63 RTL, 32/71 PDS, p = 0.020), and fascial closure time was longer (42 versus 30 min, p<0.001).

There were no differences in neoadjuvant cytostatic treatment, duration of operation, blood loss, accidental opening of the rectus fascia, stoma reversal, or perioperative complications. A SL:WL ratio >4 was achieved in all but 4 patients, without difference between the groups. Data on the ratio was missing in 4 patients, 2 in the RTL and 2 in the PDS group. Furthermore, there were no differences in adjuvant chemotherapy between groups.

The surgical complexity in the study is shown in table 1. Fifty-nine percent were rectal procedures (including 6 pelvic exenterations and 17 musculocutaneous flap reconstructions) and 41% colonic resections.

Table 1. Surgical complexity ih the Rein4CeTo1 trial

 DOI:10.1093/bjs/znae265.

	No. of patients	
Patients available for 1-year evaluation	134	(100.0)
Colon resection	55	(41.0)
Colon resection only	43	(78.2)
Colon resection and resection of other organ	12	(21.8)
APR/rectal resection	73	(54.5)
APR/rectal resection only	35	(47.9)
APR/rectal resection and gluteal flap	7	(9.6)
APR/rectal resection and resection of other organ	25	(34.2)
APR/rectal resection and resection of other organ and gluteal flap	6	(8.2)
Pelvic exenteration	6	(4.5)
Pelvic exenteration only	2	(33.3)
Pelvic exenteration and gluteal flap	3	(50.0)
Pelvic exenteration and resection of other organ and gluteal flap	1	(16.7)

Among the patients evaluable for follow-up at 3 years, 51/101 patients (25/43 RTL, 26/58 PDS) had received a stoma, and 44/101 patients (17/43 RTL, 27/58 PDS) had received adjuvant chemotherapy.

Complications other than incisional hernia (paper I-II)

The retrospective CRS/HIPEC study (paper I)

Complications according to the Clavien-Dindo classification were similar in both groups in the CRS/HIPEC study.

The Rein4CeTo1 RCT (paper II)

Any complication was noticed in 62% but only 6% had complications 3b or worse according to the Clavien-Dindo classification, without differences between groups. There were no differences in specific complications as anastomotic insufficiency which was detected in 3/61 patients with anastomosis (4.9%) or wound infection (8.2%).

Six patients in the PDS-group and 9 patients in the RTL-group were reoperated within 9 months, and 5 patients died in the RTL-group before 1-year follow-up, for reasons not associated with the fascia closure. At the 3-year follow-up 9 additional patients had been reoperated and a further 21 patients had died for other reasons than IH.

Clinical examination results in the Rein4CeTo1 trial

Pandemic restrictions for research visits and that some of the patients lived far from Malmö, contributed to a relatively low frequency of clinical follow-up and examination. After 1 year, 79/134 (59%) attended a clinical visit and the corresponding figure for the 3-year visit was 75/101 (74%).

Of the 27 patients with CT-diagnosed IH, 21 patients attended 1- and/or 3-year clinical visits. Fifteen (71%) of CT-confirmed IH were correctly diagnosed with clinical examination but 6 (29%) were missed, 5 that were <4 cm and 1 that was >4 cm in width.

Risk factors for incisional hernia

The retrospective CRS/HIPEC study (paper I)

In the univariate analysis, cardiovascular disease was more frequent among patients with an IH compared to those without, (p=0.024).

There were no differences between patients with and without an IH in regard to sex, age, ASA, BMI, COPD, diabetes mellitus, immunosuppression therapy, haemoglobin, serum creatinine, serum albumin, earlier midline laparotomy or midline laparotomy within 8 weeks prior to CRS/HIPEC surgery, neoadjuvant chemotherapy, peritoneal cancer index score, resection of midline scar, duration of surgery, blood loss, complete cytoreduction, neutropenia, complications, or adjuvant chemotherapy.

Due to the low number of IH in the study, a multivariate analysis of risk factors was not carried out.

The Rein4CeTo1 RCT (paper III)

In the Rein4CeTo1 trial, uni- and bivariate logistic regression of the potential risk factors for IH was performed including BMI (>30), smoking, diabetes, tumour localization, wound infection and adjuvant chemotherapy. The risk factors found in the analyses after adjusting for fascia closure technique were wound infection (OR 5.82), BMI >30 (OR 3.55) and adjuvant chemotherapy (OR 3.58). In the multivariate logistic regression, the closure technique was adjusted with these three factors and the difference between the RTL- and PDS-groups remained statistically significant (OR 4.810, CI95% 1.39-10.142, p=0.028). Besides the PDS-group, adjuvant chemotherapy was the only additional significant independent risk factor for IH (OR 4.592, CI95% 1.098-8.083, P=0.032).

Wound infection was diagnosed in 8/101 (7.9%) and 5/8 (62.5%) developed an IH. BMI >30 was present in 15/101 (14.9%) and an IH was detected in 7/15 (46.7%). The corresponding figures for patients receiving adjuvant chemotherapy were 44/101 (43.6%) and 18/44 (40.9%), respectively.

Incisional hernia surgery in the Rein4CeTo1 trial

Of the 27 patients with IH, 9 (30%) were symptomatic. IH surgery was performed in 2 patients within the 3-year follow-up period. One patient was scheduled for operation but died from metastasized disease before the planned IH operation. One

patient with major symptoms have been recommended and is awaiting surgery, four patients were hesitant to undergo IH operation and one patient, with a small oligosymptomatic IH was not recommended surgery.

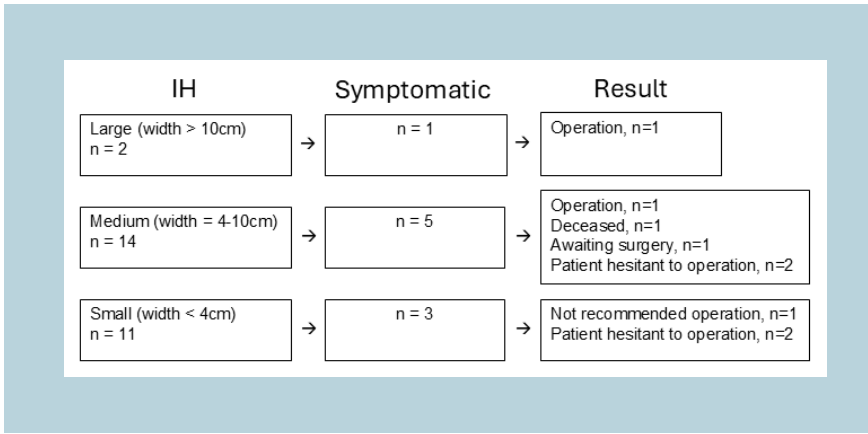

Figure 24. Symptoms and treatment recommendations of IH in the study

Quality of life in the Rein4CeTo1 trial

At 1 year follow-up 119/134 (89%) patients answered the EQ-5D-5L and the VHPQ and at 3 years 81/101 (80%) patients filled out the questionnaires. Reasons for patients not answering the questionnaires are shown in figure 24.

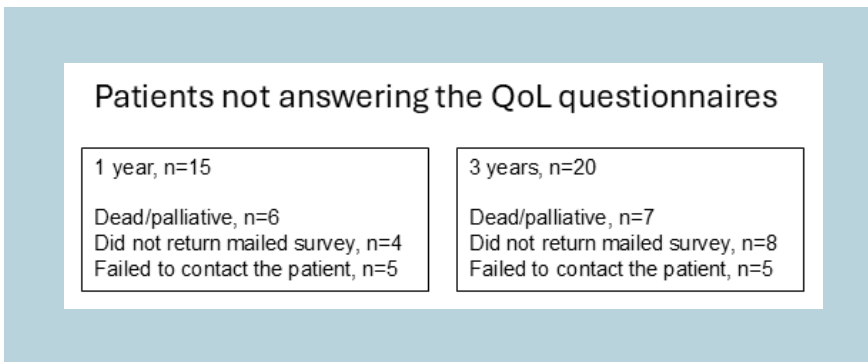

Figure 25. Reasons for patients lost to QoL follow-up

EQ-5D-5L

The descriptive results at 1 and 3 years, for the 5 dimensions of the EQ-5D-5L and the EQ VAS, were compared and no significant differences were found, see figure 26.

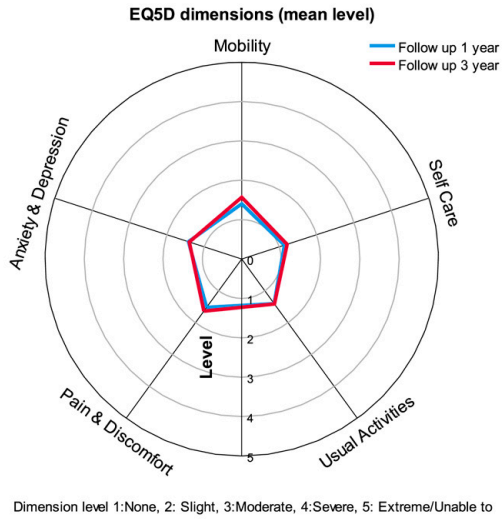

Figure 26. Mean values for the 5 dimensions in the Rein4CeTo1-patients at 1 and 3-years

These EQ-5D-5L results were equivalent to the Swedish characteristics[116], with the only exception that some study patients scored a lower level in the dimensions "usual activity" and "pain/discomfort". The mean values for the dimensions were corresponding to "no/slight" problems.

The results were also similar for patients with an IH and patients without (p<0.276 at 1 year and p<0.404 at 3 years), see figure 27.

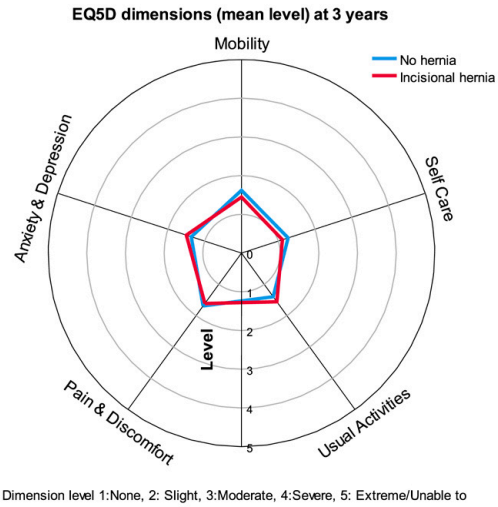

Figure 27. Mean values for the 5 dimensions in patients with and without IH at 3 years

In the risk factor analysis at 3 years the presence of a stoma was found to be an independent risk factor for impaired general QoL, $p<0.004$. IH, recurrent CRC or new malignant disease was also included as potential risk factors in the multivariable linear regression analysis but were not found to be independent risk factors.

VHPQ

Abdominal wall-related problems were evaluated with the VHPQ. Non-ignorable pain ("pain that cannot be ignored but do not affect everyday activities" and worse) "right now" was 5.0% and 1.2%, at 1 years and at 3 years, respectively. Non-ignorable pain "last week" was 2.4% at 1 year and 3.5% at 3 years. Sensation of stiffness in the abdominal wall was reported by 11.0% and 7.4% at 1 year and 3 years, respectively. Corresponding incidences for other discomforting symptoms were 11.9% and 6.3%. No patient was on sick-leave due to pain which generally was of low frequency, short duration and had low impact on daily activities.

As for cosmesis, almost one of four patients reported their scar as cosmetically disturbing at 1 year, and one of five at 3 years. At both follow-up occasions, one of ten patients regarded the appearance of their abdomen as socially limiting in some way. Anyhow, 87% of patients were satisfied with the result at 1 year, and 93% at 3 years.

Concerning overall VHPQ-results, no differences were seen between the RTL- and PDS-groups or between patients with IH and those without.

Discussion

Background and study design

This thesis consists of one retrospective and one prospective randomized study with the common primary aim to compare two fascia closure techniques for CT diagnosed IH incidence 12±3 months after elective open CRC surgery. The results of a retrospective study could thereby further be evaluated within a prospective study.

Open surgical access through the midline will always be performed, even if use of different minimal invasive techniques, laparoscopic or robot-assisted, have increased rapidly over the last years. Despite fewer laparotomies, IH is the most common long-term complication after abdominal surgery with high incidences and it is a major cause of surgical morbidity.

At the time that the included studies in this thesis were designed, open surgery was still performed more frequently than minimal invasive surgery for CRC in Malmö. The fascia closure at our surgical unit followed the gold standard technique for closure with continuous small stitch using a slowly resorbable suture and with an ambition of a SL:WL ratio>4. When the RTL-technique first was described, surgeons started to use that technique in situations when mesh reinforcement was considered but deemed unsuitable, for example in patients assessed as high risk of fascia dehiscence or IH and at the same time having contaminated surgical fields. An IH-preventive fascia closure technique without the use of mesh was thus desirable.

As for other abdominal surgery, the 4:1 suturing technique was applied for fascia closure after CRS/HIPEC procedures at our institution. The RTL-technique was gradually introduced and since 2016 it has been the predominant method. A retrospective study on this patient group with several risk factors for IH development, including per-operative chemotherapy, that had been treated in a standardized way and where register data was available, provided a good opportunity to evaluate the technique.

When designing the Rein4CeTo1 study, no RCT was earlier reported comparing the two suture techniques for prevention of IH. Therefore conducting a multicentre RCT, with a high scientific value, was of interest for evaluation of this intervention. During the study period minimal invasive techniques increased and at the same time

open CRC surgery was re-localized to smaller hospitals in the Region of Skåne to mobilize resources at the larger hospitals demanded by the COVID-19 pandemic. The Rein4CeTo1 trial was at first designed as a multicentre study at the three surgical units in Malmö, Kristianstad and Ystad, but unfortunately Ystad could not complete the study participation.

When designing the Rein4CeTo1 trial, decisions on detailed suturing technique and choice of suture to be used was needed. The small-bite 4:1 technique with a continuous slowly absorbable suture according to Milbourn et al[85] had been used for several years at our department and was not questioned as the gold standard suturing technique for fascia closure, which also is found evidence for in the STITCH RCT[42], EHS guidelines[25] and meta-analyses[91, 135]. The ESTOIH trial 2022 showed a better outcome with small-stich compared to long-stich technique but without reaching statistical significance [88], possibly due to a relatively low IH incidences. Recently an RCT by Ozcan et al 2024[136]investigated 5 mm small bite to 10 mm bites in open CRC surgery with results favouring the small bites technique also in this cohort of CRC-patients. It is also of importance to use a needle size and suture size to fit the short stich technique with a standardized approach[27]. The choice of a 2/0 polydioxanone suture on a CT-2 needle in the Rein4CeTo1 trial is in accordance with the above-mentioned literature.

The RTL suture, described in 2007 by Hollisky et al[105] as a mesh-free alternative for IH repair used polypropylene sutures whilst Argawal et al[106] used slowly absorbable sutures in their RCT concluding a reduced incidence of burst abdomen in emergency surgery by the use of RTL-suture. The RCT performed by Lozada-Hernandez et al[107]published 2022, also used slowly absorbable sutures for the RTL as well as for the mass closure technique in the other arm of the study. The use of a non-absorbable suture instead of slowly absorbable sutures has been studied without difference in IH or abdominal wall dehiscence[137] but non-absorbable suture may cause prolonged wound pain and sinus formation. Decision was taken on use of non-absorbable polypropylene sutures in the Rein4CeTo1 trial, to mimic the properties of a mesh i.e. as a permanent reinforcement.

Outcomes in the CRS/HIPEC study

In the retrospective CRS/HIPEC study, the primary outcome IH 1 year ± 3months after surgery, was clinically but not statistically different between the groups. The IH incidence after fascia closure with the 4:1 technique only was 11%, which is in line with other reports, and for the RTL-technique it was 2.1%, which is 5% lower than reported in any other study. However, in addition to the primary outcome, two patients in the PDS-group suffered a fascia dehiscence, which is the acute

manifestation of a wound insufficiency. Taking that into account, the advantages of using the RTL+ 4:1 closure in this patient group is strengthened and encouraging.

Considering that patients treated with CRS/HIPEC generally have several factors associated with an increased risk of IH, it is somewhat surprising that the IH incidences do not seem to exceed incidences after laparotomies in general[48, 49, 52]. This was also found in our study with an incidence of 7.8% at 1 year, where the only risk factor for IH development was cardiovascular disease. None of the risk factors described in earlier studies (higher age, higher BMI, female gender, fascia dehiscence and neoadjuvant chemotherapy) were demonstrated here. Some of previously described risk factors, and chemotherapy that also has been shown associated with IH[138], may affect the wound healing process and thus predispose for wound infection and an increased risk of IH.

A possible explanation for the results in our and other studies with relatively low incidences of IH may be that the patients are carefully selected and must be healthy enough to cope with the CRS/HIPEC treatment. They may thereby have less co-morbidity than the average laparotomy patient. In our study the mean age was 57 years, 75% of the patients was ASA I or II, mean BMI was 26, 6% had COPD and 8% diabetes. The surgeons´ skill and expertise may also influence the results. In our study this was reflected in complete cytoreduction in 95%, fascia dehiscence in 1.5%, and only 5% of the complications being Clavien-Dindo 3b or worse. Intraperitoneal chemotherapy leads to immunosuppression which may impair normal wound healing but on the other hand it stimulates formation of adhesions following the peritonectomy procedure which may distribute the intraabdominal pressure on the entire abdominal wall, reducing the burden on the midline incision and in the extension of this possibly contribute to lower IH incidence.

Outcomes in the Rein4CeTo1 trial

IH

The primary outcome of the Rein4CeTo1 trial, CT- detected IH 1 year after elective open CRC surgery, showed a statistically significant reduction in IH incidence with the RTL+ 4:1 suture technique compared to the 4:1 small bite technique alone (per protocol 6% vs 21%, p=0.014). The difference remained at 3 years with an increasing cumulative IH incidence per protocol (14.% vs 36.2%, p<0.003). Increasing IH incidences over time have been reported previously and is to be expected[41, 43, 87].

In the RCT by Lozada-Hernandez both elective and acute patients with different pathologies were included and followed for 3 years. They reported IH incidences of

9.8% with RTL+4:1 closure and 28.3% for 4:1 mass closure[107], diagnosed with clinical examination and when uncertain IH diagnosis CT was performed. In comparison, the IH incidences in the Rein4CeTo1 study were somewhat higher. An explanation can be that the IH incidences at both 1 and 3 years postoperatively were evaluated with CT scans in all patients in the Rein4CeTo1 study. At clinical examination 6 of 21 IH detected on CT were missed which is almost 1/3 of the patients, underlining the higher sensitivity of CT for IH diagnosis. Using clinical examination only or in combination with different imaging techniques in selected cases may underestimate the incidence. The HART study evaluated the IH incidence by clinical examination and CT after 1 year, and the incidence was more than doubled with CT[108]. Another explanation could be that patients with previous mid-line incisions were excluded in the Lozada-Hernandez study and that they did not report cumulative IH incidence. Furthermore, patients included in the Rein4CeTo1 study are relatively high-risk patients, all with clean-contaminated surgical procedures of rather high complexity (59% rectal resection or pelvic exenterations whereof 20% needed gluteal flaps and 54% had stoma creation) in a generally elderly patient cohort (mean age 68 years), with comorbidities (50% cardiovascular disease, 9% COPD, 14% diabetes) reflected in many deceased and lost to follow-up (36.7% at 3 years). The Rein4CeTo1 cohort underwent complex surgical treatment as indicated above and an overall anastomotic insufficiency rate of 4.9% and an 8.2% wound infection rate indicates good surgical performance.

Risk factors for IH

Obesity, wound infection and adjuvant chemotherapy were found to be risk factors in the Rein4CeTo1 study. High BMI and wound infection are previously described and well-known risk factors. BMI>30kg/m^2 was chosen as cut-off in our study analysis. Hoer et al have showed an increased risk for IH with a of BMI of >25[41] whilst Söderbeck et al[139] concluded that men, patients <70 years, BMI>30, operation time >3h, and postoperative wound complications are risk factors for IH after CRC surgery. The PDS-group and adjuvant chemotherapy was found to be strong independent risk factors for IH in the multivariate analysis in our study which also was shown by Santos et al[138], likely through the mechanism of impaired wound healing.

The responsible surgeons in the study were experienced, skilled and were thoroughly instructed in the fascia closure techniques to certify strict adherence to the surgical protocol of the study. Good adherence to the 4:1 technique was shown by Israelsson in 1998 to be the most important factor for reducing IH variability among surgeons[140]. Four cases of SL:WL<4 and additional 4 missing notes on SL:WL ratio indicates good adherence to the protocol. Individual surgeons were not evaluated but there was no difference in IH incidence between the study centres which increases the generalizability of the results.

QoL

To measure QoL in patients with an IH, several different tools can be used[114]. The generic EQ-5D-5L measures health related QoL within 5 dimensions and was used in the study with the hypothesis that patients with an IH would experience decreased QoL compared to those without an IH. In the Rein4CeTo1 study follow-up, however, no statistically significant differences were found between patients with and without IH, not even when excluding fascial gaps (<2cm) that can be presumed to have less clinically significance. Independent of IH or not the cohort scored as the Swedish norm and reported no-slight problems in all dimensions.

This contradicts findings from some previous studies showing that IH has a negative impact on QoL [88, 128] and that QoL improves after IH repair[4]. Recently, Toma et al showed an improvement of QoL and abdominal wall functionality after abdominal wall reconstruction using EQ-5D-5L[129]. In the STITCH study patients answered both the SF-36 and the EQ-5D. Patients with IH showed a decreased general health in the SF-36 and in EQ-5D-5L more problems were revealed in the mobility dimension. A Danish register-study on CRC patients indicate an additional reduced QoL in CRC patients having an IH[130] and Sjövall et al[123] concluded that Swedish CRC patients report a decreased QoL.

One thing, needed to be taken into consideration, is that the cohort of patients in our study is complex with several factors possibly affecting QoL. The EQ-5D-5L mirrors 5 dimensions covering much more than symptoms from the abdominal wall and makes it conceivable that the symptoms of an IH are not reflected strong enough to make an impact on the QoL. Furthermore, QoL was a secondary aim of the study, and no power calculation was performed for this outcome, why there is a risk that the study is underpowered for this specific outcome. Even if the presence of an IH did not decrease QoL, the presence of a stoma did and was found to be an independent risk factor of impaired general QoL at 3 years.

The abdominal wall specific VHPQ was used for evaluation of abdominal wall pain and discomfort. Also with this questionnaire only discrete problems were reported and despite concerns with cosmetic changes almost all patients were content with their operation.

The results of the QoL evaluation indicate that this cohort of patients have few problems affecting their everyday activities or how they appreciate their general QoL.

Methodological considerations.

A retrospective study can never present results with high scientific value but is of interest to display historical data, to find out relationships, and to evaluate a problem

over time. It is relatively inexpensive to conduct since data of interest is readily available in records and easy to access. In the CRS/HIPEC study, the data was retrieved from clinical records and from a prospective CRS/HIPEC database. The limitations it entails regards collected data. Since data is collected prior to design of the study there is always a risk that interesting and desirable data may be missing. For example, the SL:WL ratio was not documented and could not be supplemented afterwards because it was not registered in the clinical records. However, the operations in the study were either performed or supervised by the same surgeon who had a standardized way of closing the fascia according to the small-bite 4:1 technique. Furthermore, the prospective database was maintained by the same surgeon and new data collected during the study was registered in the database by one researcher, which ensures equivalent assessment and data quality.

It is also important to consider the risk of bias and confounders that can be a disadvantage when performing a retrospective study. Baseline characteristics, perioperative and postoperative findings were found to be similar between the groups, indicating that the study groups were comparable. The only differences were that the RTL-patients were 5 years younger, had less blood loss and more frequent neutropenia, which must be considered when interpreting the findings. Another strength is that CT scans were scrutinized independently by three different persons. The study reflects a longer period of CRS/HIPEC surgery at our department, with two separate standardized techniques used during different periods of the study. Other changes over time may affect outcome but since only one surgeon performed or supervised the operations there is little risk of deviation from the standardized fascia closure manner.

An RCT have a high scientific value and is a reliable method for evaluating the effect of an intervention, only exceeded by the scientific value of meta-analyses of randomized trials. The high scientific value is not achieved without effort. Performing an RCT is both time-consuming and costly and the outcome of interest to investigate must be frequent enough to allow the study to be conducted within a reasonable timeframe. The purpose of an RCT is to examine possible changes in a specific primary outcome as a result of different interventions. In the Rein4CeTo1 trial, the CT-diagnosed IH incidence after 1 year was the primary outcome for which the power-calculation was performed. When first designing the study, the proposed IH incidence with the 4:1 fascia closure technique was set to 15% but was changed to 20% based on findings at our department[46]. The IH incidence after RTL sutures was unknown and assumed to be 5%, which also would be a clinically relevant improvement. With a larger effect size, the number of evaluable patients needed in the study decreased. We expected a 20% dropout rate, but this turned out to be an underestimation. Furthermore, the study had to be closed prematurely due to a dramatic drop in inclusions over time. This was caused by the reorganization of CRC surgery in the Region of Skåne as a result of the pandemic and by marked increase in minimally invasive CRC surgery approach. Finally, the study reached a

power of 75.1% and not the desired 80%. This inflicts a risk of a type-II error for some of the investigated outcomes, especially the secondary ones. However, we could demonstrate a statistically significant difference for the primary endpoint with the number of patients evaluable both at 1 and 3 years.

With the inclusion and exclusion criteria in the RCT the intention was to create a homogeneous cohort concerning characteristics important for the study. The inclusion criteria were adult CRC patients, scheduled for open surgery through a midline laparotomy, not planned for CRS/HIPEC or having a previous midline hernia surgery or current midline hernia, with ASA<III and available for follow-up. The exclusion criteria were hernia detected perioperatively, need for fascia reconstruction, peritoneal carcinomatosis, and those deemed not suitable by the responsible surgeon. This last criterion was necessary from a clinical perspective but was unfortunately applied to a larger extent than anticipated resulting in 44 patients, preoperatively planned for participation, not being randomized.

Except for the factors we can control in the inclusion and exclusion criteria, the randomization process reduces the risk of systematic errors and bias by randomly assigning the participants to the two different study groups. If the randomization works as planned, different factors will be distributed equally or at random between groups that will be as similar as possible. The randomization process also eliminates confounders, for example if there is any underlying cause that we are not aware of that affects outcome it will be randomly distributed between the groups. To minimize the impact of confounders we also controlled that there was no difference between study centres. We used® Excel 365 for Windows® (Microsoft, Redmond, WA, USA) with a 1:1 allocation using random block sizes of 4, 6 or 8. Sealed opaque envelopes was used for the group allocation. In addition, both the recruiting and operating surgeons were blinded in all aspects of the randomization, including block sizes. The patients were informed of the allocated technique afterwards.

Data was registered according to the study protocols, ensuring that important information was collected at the right time. The fascia closure techniques were also strictly described and presented in an instruction video produced for the trial. Adherence to the techniques was controlled by announced and unannounced operation room visits aiming at conformity and high internal validity. Altogether, prerequisites exist to reproduce the study. Furthermore, all data from patients' records registered in between visits were extracted and registered by one researcher. This ensured few missing data, except for the QoL questionnaires that sometimes were incompletely filled out by the patient. The external validity of the results of this study is not tested. We can state that the participating centres had similar outcomes and may speculate that the results are likely applicable to a wider patient group since the primary outcome, IH after laparotomies, are depending on the same risk factors, whether surgery is performed for CRC or other pathologies. To ascertain the external validity more studies, preferably a larger multicentre study, applying the same protocol are needed.

Finally, the limited number of IH allowed us to analyse only 4 risk factors in the multivariate risk factor analysis, according to the relaxing rule of events per variable[141].

Evaluating QoL requires carefully consideration about what is measured. The CRC patient group is a group with known decreased QoL from the beginning. We were primarily interested in investigating whether QoL was affected by IH development since the whole study was focused on IH. We assumed that the general QoL would be affected the day before the operation and we chose not to ask the patients to complete a preoperative questionnaire, of course resulting in not being able to make a comparison before and after the CRC operation. It is difficult to appreciate at what point the patient should have completed a preoperative questionnaire without risking a major impact of their recent malignant diagnosis. The Swedish colorectal cancer register started collecting PROM in 2022, which is after the Rein4CeTo1 trial was conducted, and will provide more information on these questions in the future. Although the QoL outcomes may be underpowered in this study, with a relatively small number of patients, the results of general QoL postoperatively were in accordance with the Swedish characteristics[116], suggesting that the patients may have improved after the CRC operation and that the presence of an IH did not have a great enough impact to be detected as a decreased QoL. This is contrasted by earlier studies showing improvement of QoL after abdominal wall reconstruction[4, 128, 129] even in CRC patients[130]. Both the generic questionnaire and the modified disease specific questionnaire VHPQ, measuring impact on activity and function related to ventral hernia and ventral hernia repair, might have shown different results if the study population would have been larger. For clarifying how IH affects QoL in a cohort like this, further studies with QoL as the primary endpoint and power calculations based on that, is necessary.

Conclusions

Using the RTL+4:1 fascia closure instead of 4:1 suture only, in patients undergoing CRS/HIPEC surgery, seems to be clinically relevant for IH prevention even though statistical significance was not reached in our study. Presence of cardiovascular disease was the only risk factor for IH that was found.

To add an RTL suture to the standard 4:1 small-bite fascia closure technique significantly reduces the CT diagnosed IH incidence 1 year after open CRC surgery, without differences in short-term complications.

The long-term 3-year CT diagnosed IH incidence after open CRC surgery is significantly reduced by using the RTL+4:1 small bite fascia closure technique compared to the 4:1 suture alone. Besides the 4:1 small bite suture technique, adjuvant chemotherapy was an independent risk factor for IH.

No statistically significant difference was found in general QoL or disease specific abdominal wall pain and discomfort 1 and 3 years after CRC surgery in patients with and without an IH. Having a stoma was an independent risk factor for decreased general QoL after 3 years.

The future

"The best way to predict the future is to invent it"

Alan Kay 1971

The results of the RTL-suture as an IH prophylactic measure are encouraging both in the context of CRS/HIPEC surgery and in elective CRC surgery, as presented in this study. Since there is only one other RCT[107] evaluating the effect of the technique in IH prophylaxis, further research is needed.

The results for the small-bite 4:1 technique are reasonably as shown in several RCTs by now[42, 85, 88] indicating that further reduction in IH development is hard or impossible to achieve without other measures, like reinforcing mesh or perhaps the RTL-technique.

Quite recently, results from an interesting comparison between on-lay mesh reinforcement and the RTL-technique for prevention of fascia dehiscence was presented[142], where no difference in incidence was seen. As an extension of that study a multicentre RCT with IH prophylaxis as primary outcome comparing mesh and RTL is warranted. In such a study it would also be possible to compare other outcomes like infection, time consumption and costs for the different techniques. In the framework of such a multicentre study the external validity of the techniques would also be possible to evaluate.

Although IH incidence after CRS/HIPEC operations do not seem to be higher than after other laparotomies, a reduction of the incidence in this group of heavily burdened patients would be long awaited. To study a comparison between mesh reinforcement and RTL-suture would be of interest but certainly would demand a nationwide study.

Another study proposal is evaluation of IH at extraction sites after robotic or laparoscopic CRC surgery. A comparative RCT between small-bites 4:1 and RTL+4:1 technique, as in the Rein4CeTo1 trial would be of interest since minimal invasive CRC surgery is becoming so frequent. If our friends at the urology department could be made interested, the frequently performed robot-assisted prostatectomy procedures would also be suitable for such a study.

In summary, more RCTs need to be conducted to evaluate the RTL suture technique. Maybe the RTL-technique can challenge the mesh recommendation for preventing IH in high-risk patients, and the small-bite 4:1 technique in laparotomy patients overall?

Populärvetenskaplig sammanfattning

Ärrbråck kan beskrivas som en utbuktning av vävnad från bukhålan på platsen för tidigare operationssår efter bukkirurgi och beror på att förslutningen av bukväggen under huden spricker upp. Detta är den vanligaste långtidskomplikationen efter operation med ett längsgående snitt i bukens mittlinje och kan inträffa i upp till en tredjedel av alla patienter som opereras med så kallad öppen kirurgi. Mindre eller större defekter kan uppkomma och patienter som drabbas av ärrbråck kan beskriva mildare symptom, såsom endast en bula på buken som går att trycka tillbaka, till värre symptom. Mer uttalade symtom kan vara tyngdkänsla, smärta till följd av att det buktande innehållet kommer i kläm, eller kosmetiskt störande buktning av större bråck där kläder inte längre passar. Ärrbråck kan leda till sänkt livskvalitet och ökade vårdkostnader, på grund av att behov av ytterligare operation för att laga ärrbråcket uppkommer. Det är därför viktigt att minimera uppkomst av ärrbråck, framför allt för att minska patientens lidande men också ur ett sjukvårdsperspektiv.

För att minimera risken av att drabbas av ärrbråck har ibland ett förstärkande nät använts vid förslutningen av buken med gott resultat. Många kirurger är dock tveksamma till att använda nät i ärrbråcksförebyggande syfte på grund av infektionsrisken i ett operationssår. Därför är ett alternativ till nät för att minska risken för ärrbråck vid bukförslutning önskvärt. I vissa patientgrupper är risken för ärrbråck ökad och patienter som opereras för tarmcancer utgör en sådan grupp. Såret vid operation av patienter med tarmcancer betraktas inte som helt rent på grund av att tarm öppnas under operationen och en del tas bort tillsammans med tumören. Patienter med tarmcancer är också en enhetlig patientgrupp som genomgår planerad kirurgi och följs upp med planerade skiktröntgenundersökningar (CT). Den ökade ärrbråcksrisken och standardiserade uppföljningar gör gruppen passande för en klinisk studie, i syfte att utvärdera åtgärder tänkta att minska risken för ärrbråck på det sätt som är gjort och beskrivs i denna avhandling.

Hur en buk ska öppnas och stängas vid bukkirurgi är en kunskap som är och har varit viktig för varje kirurg och patient genom tiderna. Före 1900-talet var överlevnaden efter bukkirurgi dålig på grund av svårigheter att hantera infektioner och blödningar och var något man avrådde från i största möjliga mån på grund av den extrema risken. När anestesimedel i form av eter introducerades ledde detta till en revolution för kirurgiska behandlingar. Joseph Listers (1827–1912) forskning på antiseptiska metoder inom kirurgin och därefter upptäckten av penicillinet, var andra avgörande orsaker till att kirurgiska behandlingar kunde utvecklas.

Valet av suturmaterial, som förr oftast bestod av växt eller djurmaterial har idag nästan helt blivit ersatt av syntetiska suturer. Själva tekniken för hur och var man har öppnat och sedan sytt ihop buken har också varierat över tid. Förutom god kunskap i bukväggsanatomi behövs kunskap om sårläkning för att optimera möjligheterna till ett lyckat slutresultat och för att minska risken för ärrbråcksutveckling. Det finns vissa bevis för att det är bättre att undvika att öppna buken i mittlinjen, men oftast har kirurgen bättre tillgång till det som ska opereras genom denna snittföring.

Hur bukförslutningen ska göras optimalt för att minska risken för utveckling av ärrbråck har studerats genom åren. 1976 räknade Jenkins ut det ideala förhållandet mellan hur mycket suturmaterial som bör användas i förhållande till hur långt snitt som ska förslutas, så kallat ”suturlängd:sårlängd kvot” (SL:WL). Några decennier senare, 2009, gjordes en s.k. prospektiv randomiserad studie i Sverige där slutsatsen drogs att om patienterna försluts med så kallad ”small-stich”, dvs små suturtag, med en SL:WL kvot på minst 4:1, minskade incidensen av ärrbråck. Detta konfirmerades sedan i en multicenterstudie 2015 (STITCH- studien). Europeiska bråckföreningen, European Hernia Society (EHS), ger ut riktlinjer för behandling av olika tillstånd utifrån tillgängliga forskningsresultat, däribland hur bukförslutning bör göras. Rekommendationen är idag att använda 4:1 teknik med små suturtag och med en kontinuerlig sutur av resorberbart suturmaterial. Gällande patienter som bedöms ha en högre risk för ärrbråckutveckling rekommenderas att överväga förstärkning med nät vid bukförslutningen.

”Reinforced Tension Line” (RTL) sutur, beskrevs 2007 som en teknik för att behandla ärrbråck, med bra resultat. Det finns även bevis för att tekniken är bra för att förebygga ruptur av operationssåret efter akutkirurgi, utan att komplikationer orsakade av tekniken kunde påvisas. Akut ruptur av operationssåret drabbar några procent av patienter som opereras. Såret spricker då upp tidigt i efterförloppet till operationen. Denna komplikation liknar ärrbråcksutveckling, men utvecklas snabbare efter den kirurgiska operationen och är ett tillstånd som är förknippat med hög sjuklighet och dödlighet.

Den övergripande hypotesen som prövas i denna avhandling var att utvärdera om en kombination av den standardiserade bukförslutningstekniken 4:1 och RTL-suturen skulle kunna förebygga ärrbråck jämfört med att endast använda sig av 4:1 tekniken. Avhandlingen är baserad på en tillbakablickande s.k. retrospektiv studie och en s.k. prospektiv (framåtblickande) randomiserad studie.

I den retrospektiva studien utvärderades patienter som hade genomgått så kallad CRS/HIPEC operation som är en avancerad kirurgisk behandling för olika typer av cancer i bukhålan där spridda cancertumörer opereras bort varefter bukhålan sköljs med uppvärmd cytostatika (cellgift). Patienterna som ingick i studien behandlades mellan 2004 och 2019. Under den första tidsperioden syddes bukväggen ihop med 4:1 sutur, som under den senare tidsperioden ersattes med RTL+4:1 tekniken.

Ärrbråcksincidensen utvärderades genom att granska de CT-undersökningar som patienterna genomgått under uppföljningstiden 12±3 månader efter operationen. CT-undersökningarna bedömdes av tre oberoende granskare, en radiolog och två kirurger. Data insamlades från journaler och en CRS/HIPEC databas. Totalt 193 patienter identifierades, varav 129 inkluderades för analys i studien och slutresultatet visade en kliniskt relevant skillnad mellan grupperna som jämfördes, till fördel för RTL tekniken, men skillnaden var inte statistisk signifikant (säkerställd).

Den prospektiva studien utfördes på universitetssjukhuset i Malmö och på centrallasarettet i Kristianstad. Patienter som var planerade för öppen kolorektal cancerkirurgi inkluderades, förutsatt specifika inklusions- och exklusionskriterier. Patienterna valdes slumpvis ut till de två olika studiegrupperna där bukväggen förslöts antingen med 4:1 suturteknik (PDS-gruppen) eller med RTL + 4:1 suturteknik (RTL-gruppen). I RTL-gruppen valdes en beständig sutur, med avsikt att efterlikna ett förstärkande näts egenskaper. Patienterna följdes upp kliniskt med mottagningsbesök efter 1 månad, 1 år och 3 år. CT-bilder granskades avseende ärrbråcksutveckling efter 1 och 3 år och patienterna fick även fylla i livskvalitetsenkäter vid dessa tillfällen. Totalt randomiserades 80 patienter i varje studiegrupp och efter 1 år var 134 patienter utvärderingsbara (63 i RTL-gruppen och 71 i PDS-gruppen). Efter 1 år kunde en statistisk signifikant skillnad mellan grupperna påvisas, där RTL-gruppen hade 6% ärrbråck och PDS-gruppen 21% ($p=0.014$). Vid tre år var det 101 patienter kvar som var möjliga att utvärdera. Resultatet visade en fortsatt signifikant skillnad mellan grupperna med 14.0% ärrbråck i RTL-gruppen och 36.2% i PDS-gruppen ($p<0.003$). Vid riskfaktoranalys visade det sig att cellgiftsbehandling som givits efter operationen samt bukförslutning med endast 4:1 suturteknik var oberoende riskfaktorer för ärrbråcksutveckling.

Slutligen gjordes en utvärdering av patienternas livskvalitetsenkäter som de fyllt i både vid 1 och 3 år. Hos de patienter som svarade på enkäterna kunde inga skillnader ses, vare sig mellan de båda grupperna eller mellan de patienter som utvecklat ett ärrbråck eller inte. Att ha en stomi (kirurgiskt skapad öppning för tarmen på buken) var en oberoende riskfaktor för sänkt generell livskvalitet efter 3 år.

När planeringen av denna avhandling gjordes, fanns det ingen tidigare studie som jämförde 4:1 suturteknik med RTL+4:1 teknik vid bukförslutning i syfte att minska ärrbråcksutveckling på sikt. Under studieperioden har en randomiserad studie gjorts som jämför RTL+4:1 tekniken med ”vanlig bukförslutning” och således inte de rekommenderade små suturtagen. Den studien påvisade också ett mindre antal ärrbråck med RTL-tekniken.

Resultaten av samtliga studier i denna avhandling talar för möjligheterna att kunna förebygga ärrbråck i en större utsträckning genom att använda en förstärkningssutur (RTL-suturen) i kombination med 4:1 tekniken och inte bara använda den nu

rekommenderade 4:1 suturtekniken vid bukförslutning. Det finns många fördelar med att ha ett alternativ till nätförstärkning när det bedöms opassande att använda, till exempel vid högre risk för infektion i såret. Med denna nya kunskap skulle många patienter, som genomgår en öppen bukoperation, kunna slippa ytterligare operationer och efterföljande lidande på grund av ärrbråck på ett billigt och relativt enkelt sätt.

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