

Anterior abdominal wall hernia in adults

Clinical studies on treatment and prevention

Doctoral thesis by Jan Roland Lambrecht



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“This could not have been done better by the same man in America!”

(proverb salubriously used by my father when he is content with his achievements)

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Preface

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Definitions and abbreviations

Definitions

Incisional hernia: a hernia developing in an incisional scar after surgery

Primary Hernia: a hernia developing without previous trauma or surgery; in literature frequently confusing as some authors nominate a primary hernia as a first occurrence of an incisional hernia

Ventral Hernia: joint denomination for all hernias in the anterior abdominal wall; confused by some authors who define ventral hernia as a primary hernia

Bulging after hernia repair: a protrusion/eventration where the implanted mesh is stretched or pushed into the hernia defect, but the defect is covered (bridged) and abdominal content is retained by the prosthesis

Stoma: an exteriorized intestine for deviation of stool, created through the abdominal wall

Ostomy: opening in the abdominal wall for passage of the intestine

Parastomal hernia: a hernia at the site of a stoma

Abbreviations

3D	Three-dimensional
AAA	Abdominal Aortic Aneurysm
ASA-score	American Association of Anesthesiologists physical score
BMI	Body Mass Index; kg/m ²
CI	Confidence Interval
cIH	Concurrent Incisional Hernia; concurrent with a Parastomal Hernia
COPD	Chronic Obstructive Pulmonary Disease
CST	Components Separation Technique
CT	Computed Tomography
EHS	European Hernia Society
ePTFE	Expanded PolyTetraFluoroEthylene
HR	Hazard Ratio; risk estimation by adjusted survival analysis
IH	Incisional Hernia
IPOM	Intra Peritoneal Onlay Mesh
IPOM+	Intra Peritoneal Onlay Mesh with defect closure by suture (+)
LIHR	Laparoscopic Incisional Hernia Repair
LIVHR	Laparoscopic Incisional and Ventral Hernia Repair; oxymoronic: see definition of VH
LVHR	Laparoscopic Ventral Hernia Repair; repair of PH or IH by laparoscopy
mTOR	mammalian Target Of Rapamycin inhibitor; anti-rejection medication
Non-IS	Not Immuno-Suppressed
OR	Odds Ratio; risk estimation by univariate or multivariate statistical analysis
OVHR	Open Ventral Hernia Repair
PH	Primary Hernia
PSH	Parastomal Hernia
QoL	Quality of Life
rIH	recurrent Incisional Hernia
rPH	recurrent Primary Hernia
rPSH	Recurrent Parastomal Hernia
SAR	Serratus Anterior muscle Release; anterior components separation
TAPP	Trans Abdominal Preperitoneal (patch) Plasty; laparoscopic hernia repair
TAR	Transversus Abdominis muscle Release; posterior components separation
TEP	Totally Extraperitoneal (patch) Plasty; endoscopic hernia repair
Tx/IS	Solid organ transplanted and immunosuppressed by medication
VH	Ventral Hernia

List of papers

Paper 1

Laparoscopic ventral hernia repair: outcomes in primary versus incisional hernias: no effect of defect closure

Jan R. Lambrecht, Arild Vaktskjold, Erik Trondsen, Ole M. Øyen and Ola Reiertsen

Published in Hernia 2015

Paper 2

Laparoscopic repair of incisional hernia in solid organ-transplanted patients: The method of choice?

Jan R. Lambrecht, Morten Skauby, Erik Trondsen, Arild Vaktskjold and Ole M. Øyen

Published in Transplant International 2014

Paper 3

Prophylactic mesh at end-colostomy construction reduces parastomal hernia rate: a randomized trial

Jan R. Lambrecht, Stein G. Larsen, Ola Reiertsen, Arild Vaktskjold, Lars Julsrud and Kjersti Flatmark

Published in Colorectal Disease 2015

Thesis at a glance

Paper 1

Questions	Are there differences in outcomes between primary (PH) and incisional hernia (IH) treated with laparoscopic ventral hernia repair (LVHR)? Does defect closure benefit outcomes?
Materials and Methods	37 patients with PH and 70 patients with IH treated with LVHR and randomised to defect closure with absorbable suture before placement of coated intraperitoneal mesh.
Results	Follow-up 38 months. 1/3 of PH were recurrences compared to 10% IH. PH were smaller, had less adhesions and were operated faster. No late mesh infections occurred. Recurrence rate was 0 vs. 4%, bulging rate 5 vs 13% and complication rate 16 vs. 27% favouring PH, but not significantly. Defect closure led to more overall complications and did not benefit recurrence/bulging rate.
Conclusions	In spite of different aetiology LVHR is effective in both PH and IH. Defect closure with absorbable suture was associated with higher complication rate without long-term benefits. PH and IH should be analysed and reported separately.

Paper 2

Questions	Is LVHR for IH safe and effective in solid organ transplanted and immunosuppressed (Tx/IS) patients? Do outcomes compare to non-immunosuppressed (non-IS) patients with IH?
Materials and Methods	31 Tx/IS (liver or kidney) and 70 non-IS patients with IH treated with LVHR and randomised to defect closure. Follow-up with clinical examination and supplementary Ultrasound/Computed Tomography.
Results	Follow-up 37 months. Tx/IS hernias were larger than non-IS. Polycystic kidney disease overrepresented in the Tx/IS group. One conversion to open surgery in the Tx/IS group. No late infections or mesh removals. No infected seromas. Recurrence rate was 4 vs. 10% and complication rate 19 vs. 27% favouring non-IS but not significantly. Bulging rate 13 vs 29%, $p=0.09$.
Conclusions	Incisional hernia in Tx/IS patients may be treated with the same low complication and recurrence rate as non-IS patients. By LVHR the seroma complications with open surgery can be avoided. LVHR is particularly rational in Tx/IS patients.

Paper 3

Questions	In creating a colostomy, can an implanted synthetic mesh in the retromuscular plane prevent parastomal herniation (PSH)? Is it associated to increased risk of complications?
Materials and Methods	60 patients with primary or recurrent rectal cancer or scheduled for curative open surgery and permanent end-colostomy were randomised to mesh prevention vs. no mesh. Follow-up with clinical and CT evaluation.
Results	Follow-up 40 months. 40 patients completed – 20 censored. Comparable groups. PSH rate was 6% vs. 46% ($p<0.001$) favouring mesh prevention without any observed increase in early or late complications. Ostomy orifice increased in the non-mesh group but was stable in the mesh group ($p=0.001$).
Conclusions	Retromuscular mesh insertion at the time of end-colostomy creation reduces the risk of PSH without increase in adverse reactions. Mesh prophylaxis should be offered to the patients.

Introduction

A brief history of hernia

Let me start with quoting Sir Astley Paston Cooper from his text on the Anatomy and Surgical Treatment of Inguinal and Congenital Hernia, Cox, London, 1804: “No disease of the human body, belonging to the province of the surgeon, requires in its treatment, a better combination of accurate, anatomical knowledge with surgical skill than hernia in all its varieties”.

The surgery of hernia was possibly conceived >3000 years ago in Egypt, as discovered by the Norwegian Egyptologist G. M. Ebers, who in collaboration with the Norwegian physician B. Ebbell in the late 19th century translated a papyrus suggesting a high level of surgical skill and development of procedures to treat hernia and aneurysm, substantiated by studies on mummies. Refined surgical techniques were described in the first millennium B.C by Hippocrates, sophisticated in Alexandria and inherited by the Roman empire. The scientific inguinal hernia tradition was continued with some regression (sacrifice of ipsilateral testicle) by the Moorish and Byzantine cultures, but largely lost to European medieval culture of dogmatic faith – and unmatched until this ignorance was overcome in the European renaissance period, where vessel ligation and anatomical awareness were reinvented.

Crucial mediators for the emergence of modern surgery on hernia were anesthesia and aseptic methods, although there was no understanding of microbiota in the middle of the 19th century. Before this, the treatment was restricted to reduction (in Greek: taxis) and trusses (Picture 1) – and in the middle ages, bestial procedures as hot iron application to induce scarring have been described and depicted. The date of the first surgical management is unknown – but before anesthesia, this was restricted to absolute emergencies – often by illiterate “cutters”. The medieval knight wore trusses even for prophylaxis and quoting from a description of truss fabrication and use from Roger of Salerno, descendant of crusaders and regent of Antioch 1112-1119: *“If a patient does not wish to undergo treatment by extraction of the member and by cautery, the hernia may thus be reduced.”* The development of surgery started with hernia and was dependent of the study of hernia.

Picture 1: Plates of ancient healing. Taxis for reduction of an incarcerated hernia and various trusses for containment of groin hernias.



As one of the fathers of modern hernia surgery, Sir Cooper's quote is surpassed by surgical evolution, as many other refined surgical treatments have emerged and demand no less skill or knowledge than hernia surgery. In fact, hernia surgery has been discounted during this development as a rather simplistic procedure useful for introduction to surgery, but to be successful even today there is a need for dedication and skill. In the hands of the hernia specialist good results can be achieved, but with the great abundance of hernia repairs the treatment is widespread and performed by many non-dedicated surgeons, which is why research and standardization are essential factors. With a life incidence rate of 10%, although $\frac{3}{4}$ of that is inguinal hernia, which is not a topic of this thesis, hernia repair has an enormous impact on the health of the individual, on society and health economics and thus deserves interest. Hernia summons a substantial part of unapproached health treatment worldwide, with 5 billion people without access to rudimentary surgical and anesthetic needs [1], incapacitating humans and assisting in deprivation of realms [2], thus adding a backdrop for reflection on minor refinements of treatment in high-income countries.

In the last decades, abundant research on hernia has been conducted, and worldwide cooperating hernia societies have been formed in order to promote and improve hernia

research and teaching. The European Hernia Society (EHS), first called GREPA, was formed in 1979 and has chapters in many European countries, but among the Nordic countries only in Sweden. The American Hernia Society (AHS) was formed in 1997, the Asia-Pacific Hernia Society (APHS) in 2004 and the Afro Middle East Hernia Society (AMEHS) was founded in 2009. Hence, herniology is maturing as a scientific field.

Characterization of abdominal wall hernia

Primary hernia (PH)

Herniology was developed around spontaneous hernias, primarily inguinal and umbilical. In this thesis the primary hernias (PHs) of the anterior abdominal wall are addressed – specifically the umbilical and epigastric hernias, which may be of quite different etiology – with a prevalence of almost 50%, although rarely representing a clinical problem, as only about one per thousand end up with a repair, still amounting to a considerable number. A (spontaneously acquired) PH may develop along embryological openings into the abdominal cavity: alongside the esophagus passing through the diaphragm, along the spermatic cord in the inguinal canal, along the femoral vessels or in the umbilicus, which may represent a specific etiology. The direct inguinal, lumbar, diaphragmatic, Spigelian or epigastric hernias may denote a different etiology [3, 4].

Incisional Hernia (IH)

Except in the rare survivors after accidents or war with abdominal wall wounds, the (secondary) incisional hernias (IHs) arrived with the appearance of anesthesia, which made surgery in the abdominal cavity feasible. Surgery through laparotomy wounds in the anterior abdominal wall is now an everyday procedure with an incisional hernia rate as high as 20% after one year [5] and increasing thereafter [6], despite focus on laparotomy incisions and closure techniques. Mini-invasive techniques have developed in recent years partly to alleviate this problem, but they have not eradicated IH which still has a great impact on individual health, health resources and economics [7, 8].

Parastomal Hernia (PSH)

The first recorded survivors of “spontaneous” ostomies in history were in the early 18th century after a battle lesion and later in the same century in succession to an incarcerated

umbilical hernia, resulting in the formation of a fistula with fecal drainage (Picture 2). The first successfully attempted procedure was carried out late in the 18th century for anal atresia. Forming a deliberate stoma is a common event in surgery today and made indispensable by the increased ability to perform curative pelvic surgery, both in bowel cancer and inflammatory disease. Thus, many non-palliative stomas have longevity. Ten thousand Norwegians live with a stoma and 2.500 receive a stoma every year [9]. A common complication to a stoma, which in essence is an IH in itself, is parastomal herniation of abdominal content alongside the bowel passing through the abdominal wall. This can lead to deformation, pain, leakage, social inhibition and obstruction of bowels. The incidence of PSH is likely more than 50% and up towards a third need surgical intervention [10, 11].

Picture 2: Ms. Margreth White was in 1740 treated by Mr. Cheselden for an incarcerated umbilical hernia that formed a spontaneous ostomy.



Classification of abdominal wall hernias

PH classification

In order to study and compare results of treatment standardized classification systems are essential. Before the EHS classification in 2009 [12] no proposals for PH classification existed. The EHS classification for PH distinguishes between midline and lateral hernia, and subdivides these in epigastric and umbilical – and Spigelian and lumbar – respectively. It furthermore considers defect size and divides between small, medium and large: <2cm, ≥2-4cm and ≥4cm respectively.

Despite absence of a classification system at the inception of our research, we have recorded size and topography in an analogous manner to the EHS classification (Grid 1).

Grid 1: EHS grid for classification of PH [12] (reprinted with permission from Springer)

E H S		Diameter cm	Small <2cm	Medium ≥ 2-4cm	Large ≥ 4cm
Primary Abdominal Wall Hernia Classification					
Midline	Epigastric				
	Umbilical				
Lateral	Spigelian				
	Lumbar				

IH classification

In year 2001 the first proposal for a classification of IH was published by V. Schumpelick [13] and an understanding of the need was emerging. Most early proposals considered defect size, recurrence and topography to some extent. In the EHS classification (Grid 2), which arrived in 2009 after a consensus meeting [12], a definition of IH was made: a gap in a scar with or without a bulge which is perceptible by clinical examination or imaging. Next, a distinction of medial and lateral hernias was made, where all hernias within the confines of the rectus abdominis sheath were considered medial. The medial hernias were divided into subgroups according to cranio-caudal topography: subxiphoid, epigastric, umbilical, infraumbilical and suprapubic. The lateral hernias were grouped in subcostal, flank, iliac and most latero-dorsally: lumbar, defined by the anterior axillary line. No consensus on classification of overlapping hernia was reached, but an understanding of classification according to the most difficult repair was proposed. Regarding size, because many incisional hernias are “swiss-cheese” – i. e. more than one defect, an agreement on a single one-dimensional size measure as e.g. area was not agreed upon, but a registration of vertical length and horizontal width. Also, the width was grouped in 3 classes: <4cm, ≥4-10cm and ≥10cm and a note of recurrence. In case of “swiss-cheese” it was agreed that the outer borders should be used for measurement.

An interesting element is the consensus that a recurrent PH (rPH) should be considered an IH, despite the probable difference in etiology. This chimera is intricate, as we still know too little about causes and effects, although we are aware of a communal systemic predisposition in collagen metabolism in patients with PH and rPH. In this thesis, incepted before the EHS classification, rPH was therefore retained in the PH group. Although the EHS classification was not available at the onset of our research, we have used a similar classification, except that we have based our defect size analysis on measurement of an ovoid area and not just width. Especially concerning mesh overlap measurement, accounting for both directions seems relevant [14].

Grid 2: EHS grid for classification of IH [12] (reprinted with permission from Springer)

E H S			
Incisional Hernia Classification			
Midline	subxiphoidal	M1	
	epigastric	M2	
	umbilical	M3	
	infraumbilical	M4	
	suprapubic	M5	
Lateral	subcostal	L1	
	flank	L2	
	iliac	L3	
	lumbar	L4	
Recurrent incisional hernia?		Yes <input type="radio"/>	No <input type="radio"/>
length:	cm	width:	cm
Width	W1	W2	W3
	<4cm	≥ 4-10cm	≥10cm
cm	O	O	O

PSH classification

In classification of PSH, systems based on Computed Tomography (CT) evaluation have been proposed in 2009 by J. Moreno-Mathias [15] and in 2011 by H. S. Seo [16] and anatomical systems have been proposed before that in 1994 by M. Rubin [17] and in 1983 by H. B. Devlin [18], but they had little practical use in prediction of outcomes of repair. In 2011 G. Gil [19] published a system based on therapeutic approach that became the forerunner of the rather self-explanatory EHS Parastomal classification grid [20] from 2014, depicted hereunder (Grid 3).

Our research, focusing on prophylaxis of PSH, was initiated before publication of the proposed CT and therapeutic classification systems. The CT evaluation in our study was performed post-hoc using the Moreno-Mathias CT PSH classification (Table 1). Additionally, proxies for direct aperture size measurements (CT measurements and not intraoperatively observed dimensions) of the EHS classification were applied.

Grid 3: EHS grid for classification of PSH [20] (reprinted with permission from Springer)

EHS Parastomal Hernia Classification		Small ≤ 5 cm	Large > 5 cm
		Concomitant incisional hernia?	No
Yes	II		IV
P: Primary R: Recurrent		P <input type="checkbox"/>	R <input type="checkbox"/>

Table 1: Moreno-Mathias CT classification of PSH [15] (reprinted with permission from Wiley)

Type	Content of hernia sac
0	Peritoneum follows the wall of the bowel forming the stoma, with no formation of a sac
Ia	Bowel forming the colostomy with a sac < 5 cm
Ib	Bowel forming the colostomy with a sac > 5 cm
II	Sac containing omentum
III	Intestinal loop other than the bowel forming the stoma

Hernia treatment

PH

The surgical treatment of PH in the anterior abdominal wall was traditionally an open suture repair, as standardized in the vertical Mayo repair [21]. Most PHs are small or medium sized and are easily repaired with minor tension. However, even small PHs may have a higher recurrence risk after a suture repair compared to a repair with reinforcement [22, 23]. In inguinal hernia repair, open as well as endoscopic, the tension-free approach has been embraced for the last couple of decades, as was envisaged by Bilroth in the 19th century even before the Bassini “anatomical” repair became popular, but has not been equally frequently applied in open anterior abdominal wall hernia. Although challenged, in laparoscopic repair of PH in the anterior abdominal wall the tension-free bridging repair by reinforcing mesh is normative, conforming to the principles of modern reinforcing and tension-free inguinal hernia repair.

IH

The sutured repair of IH has been abandoned for lack of efficiency, with a recurrence rate of 43%, which can be halved with the use of reinforcing mesh [24]. Mesh repairs is the norm in both open and laparoscopic incisional hernia repair (LIHR). In open repair most midline hernias are closed by suture and augmented by mesh in the retromuscular position (sublay) or an onlay position above the muscle fascia – and rarely an intraperitoneal mesh position (IPOM). In large hernia a components separation technique – anterior or posterior – can be applied to make it possible to join the hernia edges. This is also applicable in endoscopic

surgery, but the question of affixing the hernia edges in laparoscopic ventral hernia repair (LVHR) is not fully answered [25]. The norm has been a non-tensile bridging approach. However, laparoscopic surgeons are increasingly focused on closing the defect in addition to reinforcement (intraperitoneal on-lay mesh repair with closure (+), IPOM+), to counter the risk of pseudo-hernia, which is a protrusion of the mesh through the hernia gap but where the abdominal contents are held in place by the mesh [26]. Reconstruction of the linea alba should supposedly improve the function of the abdominal wall [27, 28], but there is no firm evidence concerning the physiological impact of this muscle realignment [29].

Most very large incisional hernias (above 15 cm in width) are probably best treated by an open approach, with posterior components separation (transversus abdominis muscle release, TAR) or endoscopic anterior components separation (serratus anterior muscle release, SAR) and a skin plasty. For the hernias smaller than 15 cm a very low mesh infection rate with need for mesh removal in less than 1% in comparison to a rate of 4% in open repair, a lower overall wound infection rate of 3% vs. 13% , a shorter time for convalescence and otherwise no disadvantages are in favor of the laparoscopic approach [30], which has therefore risen in popularity throughout the last two decades.

Exceptions to abandonment of mesh repair are cases of contaminated fields, high-risk and immunocompromised patients. However, evidence is emerging that also in these cases biologic [31] as well as synthetic mesh reinforcement is safe [32-38].

PSH

Suture repair of PSH fail in more than 50 % of cases and relocation of the stoma without reinforcement fares no better. Great reluctance to repair the parastomal hernia has therefore been exerted, leaving the patients with a reduced quality of life (QoL) [39, 40], addressing only the seriously complicated hernias. More recent techniques with mesh repair have given somewhat better results, but the “keyhole” technique, where the defect is repaired with an augmenting mesh surrounding the intestine in the already damaged abdominal wall – in open or laparoscopic setting - has been a disappointment with recurrences in up to 30% [41, 42]. The Sugarbaker repair, an intraperitoneal approach with lateralization of the intestine has so far been the most promising [43]. An alternative is relocation of the stoma with a prophylactic mesh [44], which can also be applied intraperitoneally [45].

Risk factors

Genetics and acquired factors

Development of hernia may be associated with patient specific features. The preponderant primary hernia developing in the groin has been proposed to be a feature of an erect posture, not considered by the physiology architect in evolution of the human being. However, the risk of umbilical and other anterior wall hernias that are also observed in mammalian quadrupeds should be reduced by this posture. Some significant features in the quality of scar tissue and remodeling defects have been proposed as part of heterogeneous genetic and extracellular matrix disorders leading to biomechanical failure as well as behavioral and occupational causes [46]. Cigarette smoking and old age are well-known causes of tissue weakening and retarded healing - and some families carry a history of hernia [47, 48]. Studies have shown differences in fibroblast quality/relation but whether this is cause or effect is not fully understood [4, 49-52] and has thus far not provided tools for risk estimation. However, we know that some monogenetic disorders give rise to connective tissue disorders (e. g. Ehler-Danloss) and the risk of an incisional hernia after laparotomy for treatment of abdominal aortic aneurysm (AAA) approaches 70% [53]. Vice versa, contracting a primary hernia seems to increase the risk of AAA [54].

Male gender, obesity and lung disease (increased abdominal pressure) have been identified as risk factors for PH, IH and rPH. Patients with hepatic cirrhosis or on steroids and other immunosuppressive treatment, as well as postoperative infection and reoperation, also have increased risk for herniation after surgery, impacting the properties of the scar tissue. These are aspects that need consideration for provision of tailored treatment.

Dissection and surgical wound closure

No surgeon wants to harm her patient. There has been meticulous attention to establish standards for correct dissection and tissue handling technique and to provide the best closure of the laparotomy incision. Currently the small bites technique, single layer closure with slowly absorbable, running monofilament suture, and otherwise avoid midline laparotomy whenever possible, is advocated as the best technique to prevent IH and infection, the latter being a cause of wound dehiscence [55]. Specifically for stoma patients, muscle atrophy caudally to the ostomy and a midline shift may be associated to PSH and IH

development [56]. Changes towards more preemptive measures with tissue augmentation are emerging, as will be discussed later.

Mesh technology

The first attempts of alloplastic tissue augmentation at the end of the 19th century were with silver thread in inguinal hernia, which was stiff and painful, degraded, migrated, caused fistulae and intestinal perforation. Similar results were seen with tantalum. Also, gold-thread has been used. The development of the ideal tissue support material is still ongoing and a very large variety of meshes are available. For a very basic overview; modern mesh materials can be divided into three categories.

Non-absorbable synthetic

A mesh should be strong enough, flexible enough, shrink little and incorporate easily in the host tissue with controlled inflammatory response and good host-tissue ingrowth; the ideal non-absorbable mesh should be inert and with little host reaction [57]. The first attempts with synthetic mesh in human inguinal hernia were performed by Usher in 1958, rapidly followed by application to IH repair. A tightly woven mesh of polypropylene proven inert in animal studies, that did not allow the hosts immune cells or fibroblasts to enter between polymers was used, and resulted in some infectious problems, fistula formation and migration even after several years [58]. Misconceptions regarding details of mesh density; heavy-, middle- and light-weight meshes, that are still heard in everyday discussion about mesh technology, in an interim lead surgeon to believe that light-weight was more suitable, although there is a close relation between weight and porosity in most meshes. The understanding that large pore-size is the determining factor for good ingrowth and adequate inflammatory response, and that light-weight meshes may be too flexible and cause too much shrinkage, is very new [59]. Textile meshes can thus crudely be subdivided in macro- and micro-porous and further subdivided according to the type of polymers used; mono- or multi-filament and mixed structure (i. e. combined with absorbable textile) [60]. Meshes can be flat or 3D-constructed, weaved or knitted and bioactive meshes with enhanced healing properties are in the horizon. As for type of material there is no evidence to support superiority of polypropylene or polyester, however, for historical reasons

polyester is mostly used in Europe. Modern synthetic macroporous monofilament meshes are relatively inexpensive, perform well and are widely used in hernia surgery where the mesh is not exposed to the abdominal cavity, and therefore provide the bulk of meshes used in hernia surgery.

Another sub-category of mesh material, expanded polytetrafluoroethylene (ePTFE) was a milestone for intraabdominal mesh placement (IPOM), as this mesh, in contrast to the other synthetic meshes, did not adhere extensively to the intestines, and thus reached high popularity and facilitated the development of LVHR. However, this hydrophobic sheet mesh without natural porosity does not incorporate well into the host tissue, and is often encapsulated, shrinks more and is not resistant to infection.

In an interlude the mesh materials ePTFE and polypropylene were combined, trying to achieve optimal mesh ingrowth and antiadhesive properties, which resulted in abundance of material and incompatibility because of difference in inflammatory response that resulted in uneven shrinking. Absorbable barrier membrane types, that interchange with the hosts own parietal peritoneum in only a few days, were developed to achieve reduced adhesions [61]. The large pore mesh type with absorbable membrane (special features) is now the most popular in IPOM, as the handling features also outperform the ePTFE mesh and the controlled ingrowth features allow absorbable mesh fixation, but also non-absorbable coatings as e.g. titanium and polyvinylidene fluoride are used for composite mesh fabrication. When infection occurs, the modern large-pore meshes can often be rescued with drainage or vacuum therapy and the infection can be resolved without mesh explantation [62].

Biologic scaffolding

Biologic meshes, derived from decellularized human or animal connective tissue, are divided in two groups: collagen cross-linked meshes (a partial tanning procedure mimicking the natural crosslinking in healthy connective tissue) that withstand degradation longer than non-cross-linked meshes, but which also induces a larger degree of foreign body reaction. The primary rationale for using a biologic mesh is scaffolding, initially augmenting or bridging the repair, but then gradually being replaced by the host's own connective tissue. The cross-linked meshes have shown little ability to instigate this remodeling, but a supporting scar plate develops as a function of encapsulation. The non-crosslinked meshes perform better in

remodeling, but in the long-term they do not reinforce the native tissue as well [63, 64]. In addition, in case of infection the biologic meshes degrade rapidly.

However, biologic meshes have been reported favorable in contaminated fields and can be placed intraabdominally because of the non-adhesive features, resembling the ePTFE materials non-adhesive qualities. The biologic meshes therefore have a role in bridging in a sandwich mesh repair in combination with a non-degradable mesh in very large hernias [65] and burst abdomen where the fascial edges cannot be brought together – and in grossly contaminated fields where a planned secondary repair is not the preferable option. Biologic meshes therefore occupy an important niche although a higher recurrence rate can be expected, but can then be dealt with under sterile conditions. However, use of biologic mesh alone in complex abdominal hernia repair is susceptible to a higher recurrence rate [66]. The enthusiasm for biologic mesh, as advocated by the industry sponsored Ventral Hernia Working Group [67], is progressively opposed as the standard solution for hernia repair [38, 68, 69].

Biologic meshes are used as bridging in prophylaxis of perineal hernia in abdominoperineal excision (APE) after introduction of the cylindrical rectal excision and the increased use of neoadjuvant radio-chemo therapy that inflicts impaired healing. The scientific evidence for this prophylaxis is limited [70, 71], and although perineal IH is rare, there is a perception that the risk of perineal IH is higher after a laparoscopic procedure because of reduced intraabdominal adhesions - and the recurrence rate after perineal hernia repair is high [72, 73]. Biologic meshes have been used for open PSH repair, but the keyhole technique has proven inferior in open and laparoscopic PSH repair. Some small observational studies report good outcomes of biologic mesh in PSH prevention [74, 75], but less advantageous in IH prevention [76, 77].

Absorbable synthetic

Polyglactin meshes have been around for many years. They are rapidly absorbed and create a high degree of inflammation. They have no role in hernia surgery as they completely lack fortifying effect after a short period, but newer synthetic slow-absorbable meshes have arrived and their role is yet undetermined. They are introduced as reinforcement in repair and prevention, purportedly performing as fibrous scaffolding for remodeling like the

biologic meshes were supposed to. Clinical tests are underway and the long-term performance will be interesting to evaluate.

Bioactive meshes

Bioactive meshes are special features meshes feasibly from any of the mentioned mesh categories. Mesh with anti-infectious proxies are available, developed for the less infection-resistant mesh material ePTFE, but technologies with active growth-promoting agents are immature. Animal experiments have suggested decreased IH and rIH rates with deployment of topical growth hormone, demonstrating increased angiogenesis and collagen protein production [78]. Conceivably, a combinatory technology with mesh from any category and growth promoters can be developed, but as yet not available.

The role of laparoscopy

With the emergence of laparoscopy in general surgery in the 1980'ies, some advantages became evident. Generally, laparoscopy inflicts a lesser trauma compared to open surgery and offer less risk of adhesion. A shorter time in hospital and to rehabilitation has been observed. Wound infections and IH were reduced. The disadvantages are more expensive equipment and a new skill-level to be cultured. However, studies have shown an overall cost-benefit when accounting for complications, readmissions and socio-economic effects of a shorter absence from daily routines.

More specifically, in anterior abdominal hernia repair, the need for intraabdominal dissection gives an added risk of intestinal damage in laparoscopy compared to open repair, where entrance to the abdominal cavity often can be avoided. Inherent to the laparoscopic methodology is also a potential risk of adhesions from intraperitoneal mesh placement and fixation devices. In summary, these disadvantages are nevertheless overcome by a decrease in reoperations and overall complications in comparison to open surgery, in keeping with results from laparoscopy in general [30, 79-86] and even more accentuated in obese individuals [87-90] – and also cost-effective [91-93].

PH

Small umbilical hernias < 3 cm are easily managed with an open repair, preferably with mesh, but in risk patients, e. g. adipose, the technical difficulty and infection risk increase.

The laparoscopic method provides excellent exposure and a very low infection risk at the hernia site [94-96]. In epigastric hernia, which is a direct hernia type, due to connective tissue quality multiple defects are frequently present, which are easily discovered and dealt with by laparoscopy, as are larger defects. The lateral hernias are also more easily accessed by laparoscopy and the cosmetic result often better [97]. In small umbilical hernia the suture repair still has a role, especially in infected fields, but the patient should be informed of an increased recurrence risk and the possibility of a laparoscopic mesh repair in case of failure.

IH

Various degrees of intraabdominal adhesions are encountered in IH. Along with the risk of intestinal damage in laparoscopic dissection, the foremost argument against this technique is that the intraabdominal mesh placement may potentially result in formation of additional adhesions by adhesion to the prosthesis or fixation devices [96]. Open reduction of hernia content, dissection and fascial closure may be necessary in an abdomen with massive adhesions. This can be combined/hybridized with laparoscopic intraperitoneal mesh placement, which may be advantageous as a better aseptic control with the prosthesis may be accomplished. The cosmetic aspect is not as valid an argument as there is already a scar, indeed when there is a need for an abdominoplasty an open or hybrid method could be preferable. However, the vast majority of incisional hernias are relatively small and without the need of skin excision. The difficult subxiphoidal and suprapubic hernias are more easily accessed with adequate mesh overlap and fixation [98]. Still, the method has not been completely standardized and questions such as mesh fixation, mesh overlap and defect closure are unresolved [99]. The special features meshes with barrier for intraperitoneal use are many times more expensive than the same synthetic meshes without barrier.

Giant IH and loss of domain

In complex ventral abdominal hernia repair, accessory steps may be necessary and the role of laparoscopy is not as obvious. In loss of domain, where there is not enough room in the abdominal cavity for the contents, the abdominal wall needs to be mobilized preoperatively or stretched preoperatively and even organ resection may be needed.

In open surgery of anterior abdominal wall hernia professionals agree that the defects should be closed whenever possible, avoiding bridging techniques. However, bridging may be the only alternative to close the abdomen and/or to avoid abdominal compartment

syndrome. Expansion of the anterior wall is possible with intraperitoneal balloons or pneumoperitoneum, but is little used. Relaxing incisions and mobilization (Components Separation Technique, CST) are common and may be done in the external oblique aponeurosis where 4-5 cm of mobilization towards the midline on each side can be obtained [100]. Due to significant wound morbidity with open anterior CST the endoscopic anterior CST is becoming increasingly popular [101]. This technique can be applied in conjunction with a totally laparoscopic repair, a hybrid repair with open closure and intraperitoneal mesh placement by open or laparoscopic technique, and by laparoscopy with bridging mesh also in very large hernias without loss of domain.

Alternatively to anterior, a posterior CST (TAR) has been proposed in complex hernia repair [102] and reported for use in hernia after open abdomen [103] or in closure after laparostomy [104]. Some reports of the use of botulinum toxin, named chemical component paralysis, note a useful temporary tension-relief and decompression of the abdominal cavity postoperatively [105, 106], which decreases pain and potentially decreases recurrence and may even replace mechanical CST in closure of the “open abdomen” [107].

PSH

In PSH repair, laparoscopy delivers the same advantages and caveats of mini-invasive surgery as in other procedures and is more powerfully adapted in concurrent IH. As in IH repair, laparoscopic PSH repair can be demanding and requires a high skill level. Dense adhesions and contamination is a relative contraindication. In Sugarbaker repair [108], an implanted intraperitoneal mesh covers the ostomy and lateralizes the bowel. When modified to laparoscopy a full laparotomy is avoided [109, 110], thus making the laparoscopic approach more appealing in comparison to the open local mesh repair that has a higher failure rate [111]. An alternative is stoma relocation with a preventive mesh [44] and preferably with a reinforcing mesh at the previous stoma site [112]; combined procedures which are also feasible by laparoscopy [113].

Hernia prevention

IH, suture technique

Studies on closure techniques after abdominal incisions agree on the use of small bites and running suture, but there is no consensus regarding suture material [114, 115]. Proper tissue handling and small stitches with a running, slowly absorbable suture four times the length of the wound is now the reference method [55].

IH, augmentation

The benefit of augmentation in addition to suture closure in patients at risk of IH, as defined in the risk factors chapter, is becoming increasingly evident. A number of randomized controlled trials (RCTs) have been published and reviewed in metaanalyses [116-118]. In studies with synthetic mesh augmentation at the primary surgery there is a noticeable reduction in incisional hernia rate, most prominent after repair of AAA and in obesity surgery, but also after colon resection in average risk patients – all without additional adverse reactions. The role of absorbable mesh is awaiting evidence from ongoing studies. Primary mesh prevention is a very interesting concept with potential to reduce patient ailments and socioeconomic expense. In specific risk groups, i.e. organ transplantation and other medication-induced immunosuppressed patient groups, the concept has scarcely been investigated for abdominal wall replacement [119]. In transplantation the seroma/lymphocele problem [120, 121], and especially in liver transplantation the rate of re-intervention, does pose potential infection problems which may be accentuated by inserting a preventative mesh [122].

PSH, topography and technique

Trephine method and placement of a stoma has been discussed, but no conclusive evidence of the best method between lateral to m. rectus abdominis, transrectus or extraperitoneal route is available [123], although a metaanalysis suggest the extraperitoneal route to be preferable [124]. The currently most used method in Scandinavia, directly through the rectus muscle; rely on one Swedish and one Danish retrospective study [125, 126]. Evidence of ostomy size and trephine method is inadequate as well as evidence of stoma fixation technique.

PSH, augmentation

The first description of ostomy mesh augmentation using a dense Marlex mesh was by Rosin and Bonardi in 1977 [127] and later in a clinical series by Bayer in 1986 [128], reporting restricted scope of complications. However, when placing a high-density mesh with a high inflammatory response against the intestine the risk of erosion and fistulation is high. As described in a previous chapter, new developments in hernia technology has facilitated such an approach. Several reports on the effects of mesh augmentation with modern meshes when constructing a stoma have a favorable outcome, and a metaanalysis concludes that augmentation not only reduces parastomal herniation, but also reduces the relative proportion in need of repair [129]. One review concludes that all permanent stomas should be routinely augmented [130]. However, the published studies are relatively small and the routine of augmentation has not been applied in a larger scale. The published RCTs report no increase in adverse reactions with augmentation in both short and long term. However, the method of ostomy augmentation has not been standardized. The most researched method is a sublayer application of a non-absorbable large-pore mesh through a midline laparotomy. In recent years, stomas are frequently created by laparoscopy and a different approach is required. A digital retromuscular dissection and mesh placement through the trephine [131], intraperitoneal keyhole and modified Sugarbaker methods have been proposed, as well as a standardized stapled trephine with mesh fixation. The trephine must accommodate the bowel size, which is variable. One retrospective study suggests that the otherwise inevitable ostomy expansion is reduced with augmentation [132].

Principles and controversies in hernia repair

Tension repair or bridging

The non-tension repair is a concept evolving from surgery for inguinal hernia, developed from Bassini's method with a relaxing incision, to finally avoiding any suture tension with a plugging or bridging mesh. Stoppa/Nyhus and Gilbert/Lichtenstein, with a preperitoneal and anterior approach, respectively, popularized the open tension-free inguinal hernia mesh technique as late as in the 1980'ies while Rives prepared for the highly successful laparoscopic posterior approach. The traditional LVHR is a non-tension procedure with bridging mesh, first published by LeBlanc in 1993.

Augmentation is in literature also referred to as a non-tension procedure, however, in surgical practice this is not exactly the circumstance – like in cases with hiatal- and ventral hernia (PH and IH). In open PH and IH, the tension repair with reinforcing mesh in various layer positions has developed and reserves bridging only to unusual cases. Relaxing incisions to make this possible are increasingly used, also in complex abdominal wall reconstruction after open abdomen, but need in addition augmentation to yield acceptable recurrence rates [133].

Proponents of defect closure by tension suture in LVHR, IPOM+, claim better results concerning recurrence, pseudo-hernia, pain and muscle function, but no comparative studies have been published. However, the concept is gaining momentum despite lack of good evidence of superiority and studies with this aim are unattended.

Mesh fixation

In open mesh repair with defect closure, mesh fixation method is not emphasized, since modern large-pore meshes integrate well and do not migrate in the typical retromuscular position. Mesh fixation in IPOM is contentious, with traditionally two camps who are proponents for either transfascial suture or for tacking. In the ePTFE era there was need for permanent fixation to avoid migration and counter mesh shrinkage. The suture concept with non-absorbable suture had problems with pain as a result of nerve irritation, mesh shrinkage and even herniation at the suture sites. The permanent tacker gave rise to problems with adhesions, pain and tacker migration. No difference in outcome has been shown with a recurrence rate of about 4 % for both approaches in studies with mixed PHs and IHs. The first shift towards a better suited mesh with a proper anti-adhesive barrier but also good ingrowth properties, led to usage of absorbable suture for mesh fixation and thus relying on ingrowth to keep the mesh from migrating, but many surgeons continued with non-absorbable tacking. Only lately the absorbable tackers came to market and were welcomed by surgeons, who were concerned about the pain generated from tacking (and the occasional need for removal of fixation material [134]) and the improved anti-adhesive properties [135]. This concept has not been validated neither in regard of recurrence- or complication rates. In fact only one cohort study on incisional hernia based on questionnaires from a registry has been published; showing increased risk of recurrence with absorbable compared to permanent tacker of 28.5% vs. 18%, respectively [136]. The risk of

prolonged pain after mesh fixation is still not solved, and the absorbable tacker fixation does not seem to improve this, according to this report. Fibrin glue as alternative or accessory fixation is little researched and difficult to manage in laparoscopic IPOM; an RCT report less immediate pain after glue fixation of mesh in umbilical hernia but no long-term benefit and a significantly higher recurrence rate of 26%, compared to 6% with permanent tacker fixation [137]. The self-gripping mesh type, that is very useful as alternative to tacker or glue fixation in laparoscopic extraperitoneal hernia repair (TEP and TAPP) primarily for inguinal hernia, and used in anterior inguinal hernia approach as well as open incisional hernia and primary prophylaxis, is not yet developed for use intraperitoneally.

Contaminated field

In contaminated fields there are several options and controversies. Referring to the earlier discussion of mesh technology, the role of the expensive biologic mesh may primarily lie in this setting [31]. However, unless grossly contaminated or infected, emerging evidence suggests that also the modern synthetic meshes perform well [138]. Increasingly, when having minor contamination, reports confirm no adverse reaction by placing a large-pore synthetic mesh intraperitoneally – and studies on stoma prophylaxis, where mesh is also placed in a potentially contaminated area, show no increase in adverse reaction. Studies on use of synthetic mesh in risk patients, e.g. patients on immunosuppressive therapy, also report very little adverse reactions and restrained use is not justified [139, 140]. The biologic mesh may be advantageous in this setting, but with worse outcome in regard of herniation in prophylaxis and in recurrence of hernia. So a small shift of paradigm is taking place towards using synthetic mesh more boldly, as long as the placement is intraperitoneally or adjacent to tissue with good blood circulation as e.g. the retromuscular position. However, a valid alternative to primary use of biologic mesh in a grossly contaminated operating field is temporary closure and a second procedure for hernia repair after infection recovery. Generally, in mesh placement routine use of prophylactic antibiotics is considered advisable [95] – and even topically and prolonged systemically in case of infection/gross contamination may be considered.

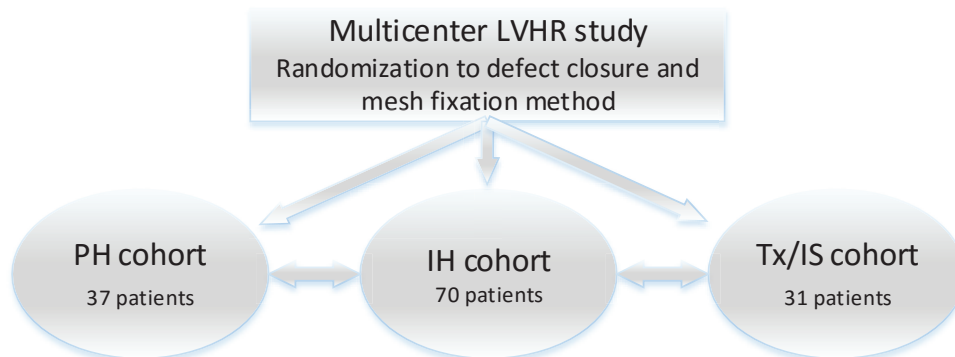
Study aims

The aims of the present study were to

- Compare outcomes of LVHR in patients with PH vs. IH (Paper 1)
- Compare outcomes of LIHR in solid organ transplanted and immunosuppressed vs. non-immunosuppressed patients with IH (Paper 2)
- Evaluate the effects of defect closure with absorbable suture and reinforcement with synthetic mesh as opposed to bridging with synthetic mesh in LVHR (Paper 1 and 2)
- Assess the efficacy and side effects of mesh prophylaxis for prevention of PSH in end colostomy creation (Paper 3)

Material and methods

Paper 1 and 2; a shared protocol



Three cohorts were included from 2006 to 2010: a cohort of patients with PH and another with IH, who were operated at Sykehuset Innlandet, Gjøvik and Oslo University Hospital, Ullevål. The IH cohort was further subdivided in patients with and without prior solid organ (liver or kidney) transplantation and immunosuppression (Tx/IS patients). The patients in the Tx/IS cohort were operated at Oslo University Hospital, Rikshospitalet (all institutional names are present names). The three cohorts were included and treated according to the same study protocol, and prospectively investigated after intervention with mesh fixation by suture and tack vs. just tacks and closure of the hernia defect (reinforcement) vs. no closure (bridging) during LVHR. The randomization procedure was blinded, but the follow-up was by the operating surgeons and not blinded; planned for 3 years and involved out-patient visits with clinical examination at two month and three years postoperatively. Additionally, ultrasonography or CT were implemented if there was any doubt of re-herniation or bulging.

Surgery

LVHR was introduced to the doctoral candidate at the turn of the millennium and standardized towards the beginning of the studies as described in the protocol, with technicalities aimed at the principal questions at the time: mesh fixation method and +/-

defect closure. All patients were operated with laparoscopic technique: Open access or Verres' needle for creation of pneumoperitoneum, three trocars—and, in a few patients, one or two trocars were added for dissection or to accomplish secure mesh fixation. The hernia sac contents were completely reduced, and the mesh-receiving abdominal wall was stripped of preperitoneal fat. A polyester-based mesh with collagen barrier for intraperitoneal use (Parietex Composite, Covidien, Mansfield, MA, USA) was introduced - targeted in size for a minimum of 5 cm overlap of the hernia in primary hernia or the whole previous incision in incisional hernia - and fixated to the abdominal wall. Half of the patients were to have approximated the defect before mesh placement according to allocation by randomization. Intracorporeal sutures in figures of eight and extrafascial knotting achieved defect closure. The sample was also split in a cross-design for two fixation techniques: four non-absorbable corner stay-sutures and one ring of non-absorbable tackers (ProTack, Covidien) and the other half with only tack fixation with an outer and an inner ring of tackers.

Paper 1

Aims

In paper 1 [141], LVHR in PH was compared to LVHR in IH. The primary endpoints were recurrence of hernia and bulging at the previous hernia site after three years of follow-up. Secondary endpoints were infection, seroma, overall complications and persistent pain at two months postoperatively. In addition, we wanted to assess the effect of hernia size, mesh overlap and defect closure (raphe) on the study endpoints perioperative events, complications and long-term outcome.

Material

The PH cohort in the prospective study comprised 11 female patients and 26 male patients with two Spigelian, 15 epigastric and 20 umbilical hernias. 13 (35%) of those were recurrent hernias. In the IH cohort there were 55 female patients and 15 male patients; 57 of those had hernia in the midline, six in the sub-costal region, three suprapubic, two sub-xiphoid and two in the right iliac fossa. Seven (10%) hernias were recurrent.

Analysis

Four possible confounding variables were included for adjustment in data analysis: Two continuous variables were categorized into ordinals: Body Mass Index (BMI) and age, and two were dichotomous: gender and chronic obstructive pulmonary disease (COPD). The mesh overlap was defined and calculated as a coefficient and categorized into ordinals. The associations between treatment group (PH vs. IH) and hematoma and re-operation, respectively, were analyzed bivariately using Fisher's exact test, independent samples t test and Mann–Whitney U Test where applicable (two-tailed). Randomization groups were analyzed in contingency tables with Fisher's exact test and with Freeman–Halton extension. The other endpoints were analyzed in four multiple logistic regression models. The adjusted odds of recurrence and protrusion, respectively, were estimated for randomization to defect closure, hernia area, overlap coefficient and treatment group; adjusted for BMI, age, COPD and sex. The significance level was set at five percent in all tests.

Additional retrospective study

In addition to the prospective data in paper 1, a decision was made to include data from a previously unpublished retrospective study with prospective follow-up, also conducted by the doctoral candidate. This was a study with an approved protocol and patient consent forms, which had the same aims as in the prospective study, representing the first and all the consecutive LVHR at Sykehuset Innlandet, Gjøvik from 2002 to 2006. In the IH group were 37 female and 14 male patients whereof five (10%) had recurrent hernia and in the PH group there were 17 female and 19 male patients whereof 12 (33%) had recurrent hernia. In December 2006 these patients underwent ambulatory examination after the same concept as in the prospective studies. The variables were subjected to the same data analysis as in the prospective study, however, the results were only presented in tables and not discussed in the manuscript and although valid, is not an integral part of this thesis.

Paper 2

Aims

In paper 2 [142], LVHR in Tx/IS patients with IH was compared to LVHR in non-immunosuppressed (non-IS) patients with IH. The aim of this study was to assess whether LVHR is a safe and effective solution to IH in a Tx/IS cohort in comparison with a non-IS

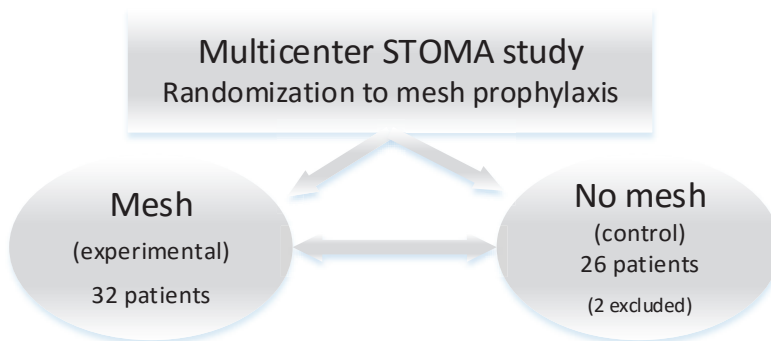
cohort, and study how mesh overlap, hernia size, and randomization to closure/not closure of the defect is associated with recurrence, bulging, infection and seroma.

Material

The Tx/IS group had 15 liver and 16 kidney transplanted patients; nine were female. The liver transplanted all had Mercedes incisions. Seven of the kidney transplanted had polycystic kidney disease and were mostly transplanted through an oblique extraperitoneal incision. At the time of LVHR, the recipients received 2.5–15 mg prednisolone, while in two liver recipients, steroids had been withdrawn. Four and five, respectively, were on mammalian target of rapamycin inhibitor (mTOR) antirejection treatment, whereas all had mycophenolate mofetil (MMF) and corticosteroids. The kidney transplanted patients additionally received basiliximab. Six of the hernias were recurrent (19%).

The data analysis was similar to the plan in paper 1.

Paper 3



Study design

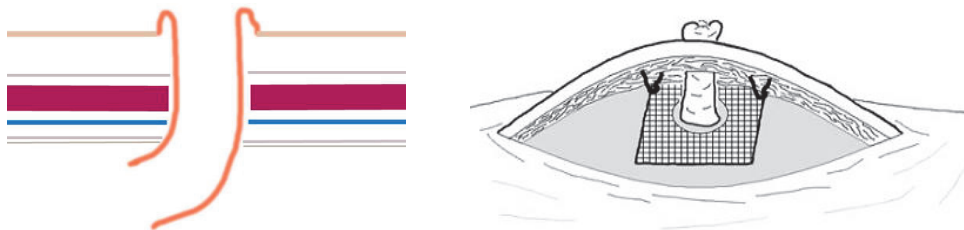
The study in paper 3 [143] was a multicenter design with blinded randomization of patients to two groups, namely mesh prophylaxis (study group) and no mesh prophylaxis (control group), in the creation of an end-colostomy. A 90% power estimation with $\alpha = 0.05$, based on a published study [15], suggested a sample size of 50 patients. After adjustment for expected mortality, a sample size of 60 was planned. Patients having abdominoperineal excision (APE)

with curative intent for low rectal cancer and those having surgery with curative intent for recurrent rectal cancer or other pelvic cancer resulting in an end-colostomy were included. Patients having palliative resections were excluded. Two surgical centers in Norway participated, including a specialized research center (Oslo University Hospital, the Norwegian Radium Hospital) and a district teaching hospital (Sykehuset Innlandet Hospital Trust, Gjøvik).

Patients and surgical procedures

Sixty patients were included from September 2007 to September 2011. The mean age was 64 years and 25% of patients were female. Three patients underwent pelvic exenteration, nine Hartmann's operation and 48 APE. Thirty-two patients were randomly allocated to the study group and 28 were randomly allocated to the control group, but two patients in the control group were excluded from the trial as palliative status was identified during surgery. The remaining 26 patients in the control group underwent an APE. The stoma trephine was made through the rectus abdominis muscle. A large-pore, low-weight polypropylene mesh, measuring 10 x 10 cm was used; the mesh was trimmed to fit in the space between the rectus muscle and the posterior rectus sheath, most often 7 or 8 cm wide. A cruciform incision, 2 x 2 cm was made in the center of the mesh to allow passage of the colon. The lateral corners of the mesh were sutured to the rectus sheath with a single multifilament fast-absorbable stitch and medially included in the main wound fascial closure with continuous monofilament slow-absorbable suture (figure 1). In the control group, no mesh was applied.

Figure 1: Mesh placement in the rectus sheath behind the rectus abdominis muscle; mesh in blue color, rectus sheath in grey color [144] (reprinted with permission from Springer)



Follow-up

Patients underwent clinical assessment and CT scan of the chest, abdomen and pelvis as part of the cancer follow up at 6-month intervals for the first 2 years and thereafter annually for a total of 4 years. This regime was interrupted in the event of incurable cancer recurrence or death. The stoma was assessed by inspection and palpation with the patient in the supine and erect positions and during a Valsalva maneuver. A bulge associated with the stoma was defined as a clinical PSH and was graded similarly to the classification of the European Hernia Society (EHS). CT assessment of PSH was not part of the original protocol, but the sizes of the orifices in the anterior abdominal wall (the ostomies) were, instead of direct measurements, substituted with measurements from the CT scans. The CT scans were also evaluated for PSH by an experienced radiologist who was unaware of the randomization categories.

CT-assessed PSHs were categorized according to the classification of Moreno–Matias. In addition, the orifices were measured in transverse and sagittal planes and the areas were calculated using the geometric formula for an ellipse, at the first and at the last postoperative CTs.

Statistical analysis

Fisher's exact test was used for binomial data, and parametric or nonparametric tests were used for continuous variables and in multiple logistic regression models. The adjusted odds of PSH were estimated for mesh prophylaxis and adjusted for body mass index (BMI) (≤ 25 kg/m²; > 25 and ≤ 30 kg/m²; or > 30 kg/m²), age (≤ 60 years, > 60 and ≤ 70 years; or > 70 years), the size of the stoma aperture at the time of the first postoperative CT examination (≤ 500 mm², > 500 and ≤ 750 mm²; or > 750 mm²), acquired other incisional hernia (IH), chronic obstructive pulmonary disease (COPD) and gender. The cumulative occurrence of PSH was determined by Kaplan–Meier and Cox regression analyses. Possible differences in stoma aperture sizes from CT measurements were calculated. The significance level was set at five per cent in all tests. ORs with 95% CI were determined, with the control group as reference.

Summary of results

Paper 1

Clinical parameters

Except for gender distribution and distribution of recurrent hernia, the two groups were similar in age (mean: 57 years), body mass index (mean: 30 kg/m²), pulmonary disease and American association of anesthesiologists physical score (ASA-score). Hernia size was significantly larger in the IH group (19 vs. 7 cm², ellipsoid area), as was operating time (100 vs. 79 minutes), admission time (2.8 vs. 1.6 days) and adhesion score. Defect closure did not influence operating time significantly.

Recurrence

The recurrence rate in the IH cohort was 4.3 % vs. 0 % in the PH cohort. The observed difference was not significant in bivariate analyses ($p = 0.55$) and since no recurrence occurred in the prospective PH cohort adjusted analysis was not applicable. All three hernia recurrences were in patients operated for their first instance of IH, i.e. not recurrent hernia repairs. COPD was removed from the adjusted analysis model, since none of the 19 patients with this condition acquired a recurrence. There were no trocar site hernias in the study period, however trocar hernias have occurred later in two cases, in one patient from each cohort.

Bulging

Mesh protrusion was found in 13 % in the IH group and 5 % in the PH group ($p = 0.32$). The adjusted OR was 3.51 (95 % CI 0.47–26.18). More protrusions were found among males in the IH group ($p = 0.02$), but males also had larger hernias ($p = 0.03$). All cases of protrusions were asymptomatic. Defect closure had no significant effect on recurrence, protrusion or seroma formation. Full closure was achieved in all allocated patients. For patients with large hernia size (ellipsoid hernia area > 20 cm²) the OR for protrusion was 2.30 (CI 0.73–7.19). Large overlap (overlap coefficient ≥ 1.0 i.e. overlap ≥ 5 cm) seemed to counter this risk (OR 0.59; CI 0.16–2.13).

Complications

The total complication rates were 27 % vs. 16 % and the inadvertent enterotomy rate 1.4 % vs. 0 % in favor of PH, but these differences were not statistically significant. One quarter of the patients had pain at two-month control with no difference between cohorts (OR 0.59; CI 0.18–1.94). There were also no significant difference between the two-month pain rates in patients with or without defect closure (OR 0.54; CI 0.21–1.37). Seroma formation was not associated with infection, recurrence or protrusion. None of the studied factors were associated with infection, but higher BMI (adjustment factor) was associated with overall complications (OR 1.87; CI 1.14–3.05). In bivariate analysis overall complications related to defect closure was primarily a feature of the PH group ($p < 0.01$), and not significant in the IH group ($p = 0.43$), however, in adjusted analysis the proportion of patients with overall complications increased with hernia defect closure (OR 3.42; CI 1.25–9.33), but was not associated to PH or IH. Mesh fixation method was not associated with complications or primary endpoints in bivariate analysis and was therefore removed from adjusted analysis.

Additional retrospective study

The results from the retrospective study were comprehensively in resemblance to the prospectively randomized cohort study. Recurrence rates were 7.8 % and 2.8 % for the IH and PH groups, respectively.

Paper 2

Clinical parameters

Two patients in the Tx/IS cohort and three patients in the non-IS cohort with IH died of causes unrelated to hernia surgery before 3 years follow-up but with updated status at the time of death, leaving 96 patients (95%) with a complete follow-up period of 3 years. The studied cohorts were similar regarding age, body mass index and ASA-score, but not in gender. There was no difference in operating time (median 110 min vs. 90 min) or time to normal activity. Of significance were male majority, longer admission time, larger hernias, less mesh overlap and a smaller adhesion score in the Tx/IS group.

Recurrence

The recurrence rates in the studied cohorts were similar (9.7% vs. 4.2%, $p = 0.368$) in bivariate comparison. The three patients with recurrences in the Tx/IS group were leaner [mean BMI 27 (25–29) vs. 32 (28–38)] and younger (mean age 54 vs. 62) than the three patients with recurrences in the non-IS cohort. Both sexes (two males and one female) were represented in the Tx/IS group with recurrence—in the non-IS group, there were only female patients. There was no correlation between mTOR immunosuppressive therapy at the time of LVHR and recurrence. The mean hernia area size in the Tx/IS cohort was higher ($p < 0.001$), but the mean mesh size used was equal to the control cohort. This is reflected by the mean overlap coefficient, which in the Tx/IS cohort was 0.7 (i.e. mean overlap 3.5 cm), and the targeted overlap of 5 cm was reached in only five of 31 patients (16%). 14 patients (45%) had a coefficient of 0.8 or higher (i.e. ≥ 4 cm overlap). In the non-IS cohort, the mean overlap coefficient was 1.1 (i.e. mean overlap 5.5 cm) and the target was reached in 47 of 70 patients (67%), and 66 patients (94%) had an overlap coefficient of 0.8 or more. One recurrence occurred in a patient who previously had radiotherapy for treatment of malignant lymphatic abdominal disease. After surgery a colonic perforation was detected, probably from an unrecognized iatrogenic lesion during dissection. She was consequently re-operated with mesh explantation - and thus regained her hernia. She also developed enteric fistulae and had a long hospital stay. No other mesh-related infection or explantation has been observed. Another recurrence was a technical failure as the mesh positioned at primary repair was found to be fixated only just tangential to the defect and therefore not augmenting the defect. These recurrences were in the non-IS group.

Bulging

The adjusted odds ratio for protrusion was 3.69 (CI: 0.70–19.47) in the Tx/IS group compared with the non-IS group. As there were no women with protrusion in the Tx/IS cohort, sex was removed from the model. However, this tendency for the Tx/IS group was also observed when including only men in the analysis (OR = 3.63; CI: 0.42–31.30). Male sex was significantly associated with protrusion in a bivariate analysis ($p < 0.001$; Fishers exact test). In either cohort, there were no differences in mesh overlap between subgroups with or without protrusion. The hernias in the respective protrusion subgroups were larger. However, hernia size was not associated with an increased risk of protrusion, but larger mesh ingrowth

area was (OR = 3.46; CI: 1.16–10.35), with additional accentuation in the men-only analysis (OR 6.14; CI: 1.19–31.68). The estimated ORs for seroma, recurrence, and protrusion were independent of how the patients were randomized, as randomization to defect closure was adjusted for in the regression models. However, we found a protective tendency of defect closure in regard to protrusion when including only men in the regression analysis (OR = 0.16; CI: 0.02–1.18). There were no missing values for any of the variables included in the analysis.

Complications

There were no differences in hematoma, reoperation or infection rate. Treatment group and the study factors were not associated with the adjusted risk of recurrence or seroma, but there was a tendency toward less seroma incidence in the Tx/IS cohort (OR = 0.23; CI: 0.02–2.27). No difference was seen in percentage of patients with pain recorded at 2 months ($p = 0.318$), but five patients in the non-IS group have had fixation devices removed: three with removal of suture and two with tacker removal. None of the transplanted patients had long-term fixation device-related pain.

Paper 3

Clinical parameters

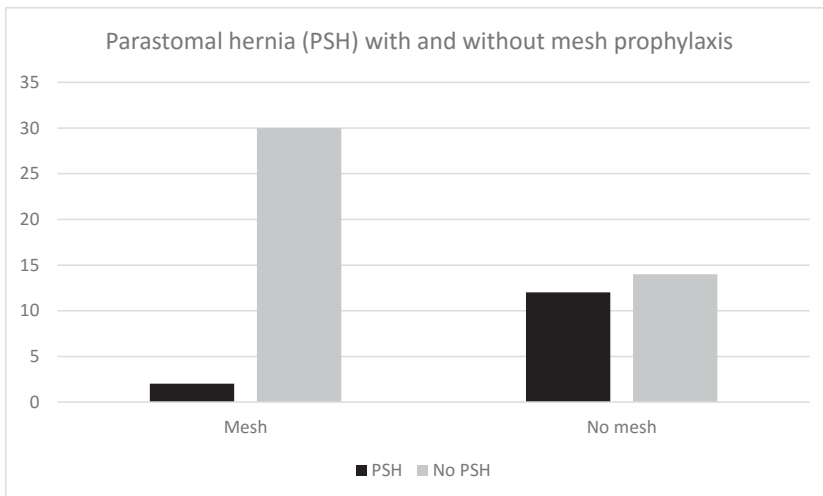
There were no differences in the patient characteristics between the 32 patients in the study group and the 26 patients in the control group. One patient in the study group received steroid therapy and did not develop PSH or complications. The median follow-up was 36 (range: 81) months in the study group and 48 (range: 71) months in the control group. Twelve and six patients in the study and control groups, respectively, developed recurrence of cancer and subsequently died.

Clinical detection of parastomal hernia (PSH)

Two (6%) patients with mesh developed PSH compared with 12 (46%) in the control group (Figure 2, $p < 0.001$, exact test). The adjusted OR for PSH with mesh vs no mesh was 0.032 (95% CI: 0.003–0.333). Adjustment for hernia in previous history and COPD was omitted in the analysis because of the low prevalence and even distribution of these between the groups. The presence of an IH of the main abdominal wound did not influence the results

and without this adjustment a more precise estimate was revealed (OR = 0.043; 95% CI: 0.006–0.304). In contingency table analysis the relative risk for PSH with mesh was 0.14 (95% CI: 0.02–0.55) and the number of mesh implants needed to avoid one PSH were 2.5 (95% CI: 1.9–6.9).

Figure 2: Parastomal hernia distribution in experimental and control groups

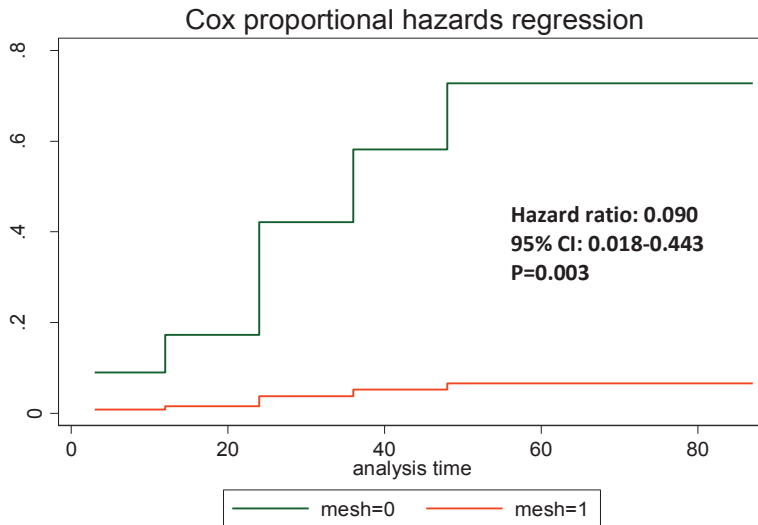


The two patients with PSHs in the study group died shortly after three years of follow-up. They both had a BMI in the normal range (23 and 24 kg/m²) and were in their early 60's. They developed no other complications and did not have hernia in their previous history. In adjusted analysis of only the patients who were alive at three years, the reduction of the risk of PSH was retained (OR = 0.019; 95% CI: 0.001–0.352).

The survival analysis demonstrated a significant difference between the groups (Kaplan–Meier analysis, log–rank test: $p < 0.001$). In adjusted Cox regression analysis, the hazard ratio for PSH with mesh prophylaxis was 0.090 (95% CI: 0.018–0.443, $p = 0.003$). The results regarding adjusted survival analysis given here deviate insignificantly from the published results, as they are founded on ordinal collapse of adjustment variables equal to the multinomial regression analysis, whereas the results in the article were based on continuous variables. The risk of developing PSH continued over time in the control group, whereas this was not the case in the study group: in the study group, both instances of PSHs occurred

after 3 and 12 months; in contrast, eight of the 12 instances of PSHs in the control group occurred later than 18 months after surgery.

Figure 3: Cumulative hazard of clinical parastomal hernia development. Cox regression analysis on randomization between protective mesh or no mesh applied at the formation of an end-colostomy, adjusted for age, BMI and stoma orifice size at 1st postoperative CT. Analysis time in months.



Factors associated with PSH and clinical detection of PSH

Eleven of the 12 patients with PSHs in the control group and the two patients with PSHs in the study group were men ($p = 0.330$), but the estimate for gender as an adjustment factor was imprecise. In multinomial regression analysis of male patients, the OR for developing PSH with mesh in comparison with no mesh was 0.036 (95% CI: 0.003–0.390). A postoperative IH of the main abdominal wound occurred in eight (31%) patients in the control group, concurrently with PSHs in seven. In contrast, five (16%) patients in the study group developed an IH without PSH ($p = 0.213$). Development of IH was associated with PSH (OR = 10.11; 95% CI: 1.22–83.55; $p = 0.032$) and is a complicating factor in stoma care and PSH repair, as exemplified by the EHS classification. BMI was associated with development of PSH in the control group (OR = 1.31; 95% CI: 1.00–1.72; $p = 0.050$). Applying the CT measurements of the aperture in the anterior abdominal wall, the clinical distribution

corresponding to the EHS classification was as follows: Type I (n = 3), Type II (n = 6), Type III (n = 2) and Type IV (n = 1) in the control group; and Type I (n = 2) in the study group.

CT evaluation of the stoma aperture (= ostomy)

The mean interval from stoma creation to the first postoperative CT scan was 4 months in both groups and at this time the median size of the stoma aperture was similar in the groups. After controlling for age, a large aperture size at the first CT scan was associated with a higher BMI in the study group ($p = 0.038$) but not in the control group ($P = 0.495$). At the last CT examination, the median aperture size was 688 mm^2 in the control group and unaltered, at 494 mm^2 , in the study group ($p = 0.024$), at a mean respective interval of 33 ± 23 months and 28 ± 18 months between CT studies. This significant increase of aperture size in the control group was highly associated with the development of PSH. BMI was associated with a change in the area of the aperture in the control group (increase of 37 mm^2 per BMI point increase, $p = 0.011$) and was correlated with the size of the stoma orifice at the last CT scan in both groups ($p = 0.015$, study group and 0.024 , control group).

In the control group, CT failed to detect four clinical PSHs, one of which were in need of surgical repair, and three patients in the control group with a PSH diagnosed by CT did not have clinical evidence of PSH. PSHs were detected in eight patients by both methods. In the experimental group, six patients with non-clinical PSHs were diagnosed by CT. One of these had abdominal surgery two years after creation of the colostomy and no PSH was found. The two clinically detected PSHs in the study group were both also diagnosed by CT. Although there was poor agreement between the clinical and CT diagnosis of PSH, even when these methods of diagnosis were combined, there was a difference in the rate of PSH between the groups (25% vs 58%; $p = 0.016$, Fisher's exact test).

Stoma-related complications

There were no stoma-site infections, stoma retraction or fistula formation. Two patients in the study group had a stomal stenosis in the immediate postoperative period. Both needed intervention; this involved digital distention of the stoma orifice in one patient and enlargement of the mesh aperture in the other patient. One patient without mesh had stomal necrosis and needed surgical revision.

Discussion of the results

The discussion is divided in two sections: Hernia treatment and hernia prophylaxis. In section one, we reflect on the results after laparoscopic treatment of abdominal wall hernia in three patient groups: primary hernia, incisional hernia and incisional hernia in immunosuppressed patients.

In section two, we discuss hernia prevention in the context of parastomal hernia, but also contemplate how it may relate to prevention of incisional hernia.

Hernia treatment

Primary abdominal wall hernia

Umbilical hernia treated with open suture closure as compared to open mesh repair, recur significantly more often in a RCT: 11% vs. 1% [23] and in a metaanalysis with studies of variable quality 8.2% vs. 2.7%, but at the insignificant expense of a higher rate of surgical site infection rate (6.6% vs. 7.3%) [145]. In epigastric hernia the same relations are reported: 14.9% vs. 10.9% [146]. In a registry-based cohort study with questionnaire and clinical follow-up a recurrence rate of 21% vs. 10% with no difference in pain (5% vs. 6%) [22] and the cumulative risk of repair of recurrent umbilical and epigastric hernia according to a registry study is also higher with suture repair: 5.6% vs. 2.2% [147]. The infection- and recurrence-risk is higher with obesity. In our study on laparoscopic primary hernia repair (LPHR) we observed a 5.4% incidence of minor and untreated infection/erythema at a trocar site, but no infection at the hernia site occurred. In addition, no recurrences were observed and purportedly the recurrence rate after LPHR is very low. Only a very few studies report recurrence rates on LPHR alone, 0%-1.4%, [148, 149] and in comparison to open repair also significantly lower incidence of adverse outcome and in-hospital time. Most studies pool PH and IH in LVHR and repeatedly report a recurrence rate close to 5% in these pooled analyses [30, 86, 150]. That epigastric and umbilical hernia have different outcome has been elucidated by a registry study [151], and may have diverse etiologies [152]. In synopsis, the results from the PH cohort treated with LVHR in our study do not differ from published reports and seem to add to the pool of evidence that favors this methodology. However, in our PH cohort a third of the hernias were recurrent after suture repair. EHS suggest that a

recurrent PH (rPH) should be classified as IH, but we have retained rPHs in the PH group in agreement to the underlying primary pathology.

Incisional abdominal wall hernia

IHs have a more dispersed topography, although the majority occur in the midline. The propensity to be located close to an osseous structure is higher than in PH and IH is most often larger. In addition, a certain dissection of abdominal contents due to adhesions after previous surgery is required and add to the risk of adverse outcome, in fact laparoscopic dissection may in rare cases be impossible. These inherent differences lead to expectation of a more difficult procedure and with greater risk for complications and recurrence. In a recent metaanalysis the overlooked enterotomy rate in LIHR is 6% and in open surgery 2%, where this parameter was the only to reach a statistical significant difference [153]. This rate of missed enterotomy is larger than in our prospective study, where it was 1.4% (one patient). However, in the retrospective study we had an inadvertent enterotomy rate of 3.3%, but all events were detected and repaired intraoperatively; two intracorporeally and two by minilaparotomy, without postoperative complications. In addition, in the retrospective study a cardiac tamponade occurred due to a tacker. Such an event is only described twice previously. Fortunately, after treatment the patient recovered without further morbidity and was dismissed on day three after surgery. In the metaanalysis the overall complication rate was 39% compared to 27% and the mean operating time was 89 minutes compared to 98 minutes in our study and the hernias in the metaanalysis were slightly larger. The wound infection rate in the metaanalysis was 6% compared to 7.1% and the recurrence rate was 9% but with shorter follow-up than in our study, where the recurrence rate was 4.3%, all outlining that the quality of the treatment in our study is equal to expected standards. This is compounded by a large register study reporting a cumulative IH recurrence rate of 37% and a cumulative reoperation rate for IH recurrence of 15% after 40 months, with no significant difference between open and laparoscopic mesh repair [154].

Comparison of LVHR in PH and IH

In the PH group, 34% of the hernias were recurrent, whereas the expected proportion would be closer to 10% after suture repair [23, 145] and the group had significant male majority, in contrast to the IH group with female majority and an rIH rate of 10%. Otherwise the groups were similar in biometric data and comorbidities. Similar distributions were seen in the

retrospective, consecutive study. This may reflect that the recurrence rate by suture-only repair is high and equally insufficient in IH and PH patients. Many cases of IH are considered to be caused by infectious problems or insufficient closure technique whereas PH may be associated with inherent abdominal wall weakness. Thus, it seems at least as important to treat PH patients by a reinforcing mesh, as many of these may suffer from congenital polymorphisms/defects in collagen or other structural proteins. However, a fraction of the IH patients must also be expected to have inherent/pre-existing weaknesses with regard to structural protein and scar repair. In this study we have allocated recurrent PHs (rPHs) to the PH group. This allocation choice should be challenged, as a recurrent open repair of a PH would share many characteristics of an IH, regarding both perioperative challenges and long-term outcomes. We have therefore performed uni- and bi-variate post hoc analyses allocating rPHs to the IH group and with eliminating recurrent hernia from the dataset. These analyses did not alter the study results compared to the a priori analysis plan.

The larger hernia sizes, adhesion scores and operating times (98 min vs. 80 min) in the IH group were anticipated. We found no significant difference in operating times between randomization groups. We had also expected a higher complication rate in the IH group, but the difference of 27% vs. 16% was not statistically significant, probably due to small sample size as is probably also the cause for lack of difference in bulging (12.8% vs 5.4%) and recurrence rate.

In multinomial regression analysis obesity and the randomization to defect closure were identified as risk factors for overall complications in joint analysis of the groups, but in bivariate analysis the latter was a feature of the PH group ($p=0.046$), and not significant for the IH group ($p=0.428$). This is reciprocated in a study with IPOM+, but with non-absorbable suture; a seroma rate of 7.6% as opposed to 12.8% in our study, and a recurrence rate of only 0.6% after a mean of 48 months follow-up [28]. Unfortunately they did not assess bulging and maybe there was none – adding to the evidence of the performance of IPOM+, as described by the originator of the procedure in a chart review reporting seroma rate of 2.6%, bulging rate of 1.5% and recurrence rate of 4.7% [27]. Bulging can be a serious problem, demanding a new procedure [26], however, this it is not our experience that this is very common, as for most of the reported bulges in our study, patients were oblivious and bulging was discovered during physical examination. The use of absorbable suture for defect

closure in our study was apparently counter effective in PH and with no added benefit in IH, but this is so far the only RCT published on the question of IPOM+ and only retrospective comparative studies, and supporting IPOM+, have been published [155, 156]. RCTs with non-absorbable suture are needed.

In our study, having IH and having a large hernia showed a tendency towards a higher bulging rate. Although questionable, we have pooled the prospective and retrospective studies for analysis and in joint analysis of the groups: having a large hernia was a significant risk factor for bulging and seroma – and the IPOM+ remained a risk factor for overall complications, but in segregated bivariate analysis overall complication risk with IPOM+ was only a feature in PH group ($p=0.670$ vs. $p<0.001$). However, seroma as a complication in LVHR is quite dissimilar to seroma in open surgery. Intervention for seroma after LVHR is contraindicated, as spontaneous regression consistently occurs and persistency for a period of more than two months is sporadic. Seromas after LVHR are not associated to infection unless aspirated. Thus, since seroma constituted half of the complications in both the PH and IH groups, to remove this from analysis, the difference in overall complications between the IPOM+/IPOM randomization groups may not be apparent in our dataset. The issue of the possible benefits of IPOM+ is still not settled and larger randomized studies seem essential [25].

The other randomization arm: mesh fixation with Protack in Double Crown formation [157] vs. corner anchor suture and one row of tackers did not show any difference on any parameter, substantiated by other studies [150, 158-160]. The increased use of tacker-only fixation has been controversial and is still countered by experts. Some studies even report more complications with suture fixation; pain and so-called suture hernia [134, 161]. However, the pain problem after LVHR is still not solved. We have explanted both sutures and tackers for pain problems and have, like many other surgeons altered strategy towards absorbable tacking devices recently put on the market. We do not know if this actually decreases pain or has a negative impact on the long-term outcome. Only one study has been published on the subject, a register study indicating a higher risk of recurrence with absorbable tackers and no benefit regarding chronic pain [136].

The overlap of mesh in LVHR seems to be an important element to consider [14, 162] and also sufficient coverage of the whole incisional scar [149]. In our study we have analyzed the

overlap by a proprietary overlap coefficient [163]. We targeted a 5 cm mesh overlap, translated to a coefficient of 1.0. This was reached in most patients, but analysis did only reveal a weak tendency towards less bulging with such an overlap in reference to a reduced overlap, supporting the general perception on this theme; possibly counteracting the potential mesh migration due to a larger ingrowth area [162, 164].

In spite of differences in etiology, hernia size and hernia topography, LVHR in PH and IH produce satisfactory—and almost comparable outcomes—suggesting LVHR with synthetic mesh to be safe and effective for both patient groups. In this study defect closure with absorbable suture was associated with a higher overall complication risk and with no long-term benefits compared to bridging repairs, distinctly in PH patients. Although we only saw trends of differences, we recommend that LVHR studies segregate analysis of outcomes to etiology (PH and rPH vs. IH and rIH) – in addition to topography.

Incisional hernia in immunosuppressed, organ transplanted patients

The Tx/IS population

The solid organ transplant population has increased risk of wound complications, IH and recurrence of IH, due to delayed and incomplete wound healing, involving impaired fibroblast proliferation. The impact of these immunosuppressive effects may be illustrated by the fact that lymphocele/lymph leakage is a major problem after allograft kidney transplantation (KTx) (3–18% requiring re-interventions) [121], while in renal auto-transplantation, this problem is almost nonexistent [165]. Previous studies have shown the hernia defects in the Tx/IS population to be definitely larger [120, 140, 166]. Our data support this observation. During recent years, the immunosuppressive treatments have been increased and optimized, resulting in fewer rejection episodes, but probably with more severe adverse effects also regarding wound healing.

Polycystic kidney disease (PKD) is a congenital, systemic disorder affecting fibrous tissue development and structure [167]. Interestingly, PKD was overrepresented in our material comprising seven of 16 KTx (44%), while the PKD proportion in our KTx population is only 10–12% [168]. The debilitating effect of PKD on fibrous healing seem to potentiate the immunosuppressive, antiproliferative effect. The Mercedes incision used in all liver recipients in the present study was probably a major risk factor for hernia due to simple

vascular reasons. The now preferred L-shaped incision [169] will probably instigate a lower hernia incidence in the future. The likely explanation of the majority of men (71%) in the Tx/IS group is that more men suffer from both kidney and liver failure [28].

Complications

One of the most conspicuous features regarding the Tx/IS patients in this study, was the low rate of major postoperative complications (19%). The problem of seroma formation and thereby increased infection hazard above the mesh, seemed to be almost eliminated with the LVHR approach, quite obviously affected by omitting the skin incision above the mesh. Prior to the minimally invasive era, the open procedure—with a large incision above the mesh—gave rise to huge problems, often involving a seroma with communication to mesh and cutaneous incision. All detected seromas (predominantly in the non-IS group) regressed spontaneously prior to 3 months without treatment. The tendency toward a lower incidence of seromas in the Tx/IS group may be explained by a reduced inflammatory response caused by the immunosuppressive drugs, in particular, corticosteroids and mycophenolate mofetil [170]. Our study indicates that the low rates of complications in the non-IS population when using LVHR, compared with open methods [168, 171], can indeed be conveyed to the Tx/IS patient population. The previous reluctance to use synthetic mesh in immunosuppressed patients for hernia repair seems a surpassed stage.

Recurrence

A recurrence rate of about 10% in the Tx/IS population must be considered satisfactory and comparable to non-IS patients (OR 1.35; CI: 0.45-14.18). Previous studies have also been able to show an equally low recurrence rate with LVHR [140, 172-174]. The inherently larger hernias and immunosuppression (and PKD incidence) in the Tx/IS group would be suspected to cause at least 50% more recurrences with open methods [120, 139, 166, 175-179].

Furthermore, the regression analysis on both collective IH cohorts revealed a tendency to harmful effect on recurrence from the factors 'Hernia size (ellipsoid)' and COPD.

The factor 'Overlap coefficient' only prompted an insignificant OR of 1.75. Several authors emphasize the importance of sufficient overlap in LVHR to compensate for mesh shift, positioning, and shrinkage, but no randomized study has substantiated these claims [95]. Recurrences may also be related to awkward hernia localizations, particularly with larger defects in the Tx/IS group extending toward the iliac crest or ribs/sternum [180, 181]. The

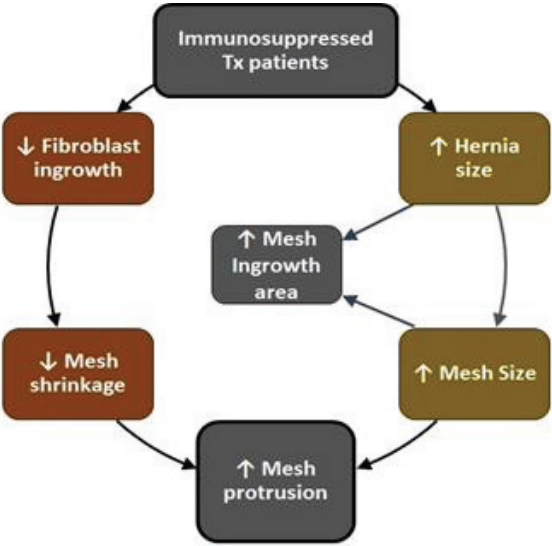
single conversion in the Tx/Is group and one of the three recurrences were caused by a potentially insufficient mesh overlap between the kidney graft and the iliac crest. In these cases, an open approach should be considered. Furthermore, in other locations with osseous proximity - in particular toward the costal margin, the exact placement of transfascial sutures and tackers should be deliberate to prevent adjacent organ damage.

Protrusion

The Tx/IS hernias seemed more at risk of mesh protrusion (OR 3.69; CI: 0.70–19.47), probably due to larger defects and inferior wound healing, with retarded scar formation and diminished mesh shrinkage. These relationships have been depicted in Figure 3. For obvious physical reasons, we consider a larger mesh to be subjected to more peripheral tension and thus protrusion, further accentuated with immunosuppression. Even though we did not find any association between hernia size and protrusion in the combined cohorts (OR 0.98; CI: 0.39–2.51), we think the basic data and theoretical considerations are consistent [26]. In our study, male sex was associated with protrusion overall and within each cohort. The great baseline discrepancy regarding sex distribution (71% males in Tx/IS vs. 71% females in non-IS) represents a methodological weakness. However, by segregating ‘Men only’ in the regression analysis, the same observed elevated risk for protrusion was sustained. Furthermore, there is no support from the literature, nor from basic pathophysiological considerations, to suggest a sex difference regarding protrusion. Increased ‘mesh ingrowth area’ was also associated with development of protrusion (OR 3.46; CI: 1.16–10.35), which may be explained by the fact that a larger hernia, for simple mathematical reasons, will require a larger mesh size/area, to secure a 5 cm overlap all around the perimeter, thus theoretically a surrogate parameter for hernia size. The increased protrusion rate in the Tx/Is group with significantly larger defects and the potential protective effect of defect closure (IPOM+) suggested by the men-only regression analysis does support defect closure in large defects. Thus, we would consider an open, laparoscopic, or hybrid procedure in the Tx/IS population with large defects (> 8–12 cm); attempting total fascial closure above the mesh by layer separation (CST) [182, 183]. This is also proposed in the EHS guidelines [95]. Many small and medium bulges (<5 cm) are indolent and even unrecognized by the patient. In our experience, lean patients seem to be less compliant to a bulge and are more perceptive to

its presence. This may influence clinical detection and explain the protective association of a high BMI (OR 0.46; CI: 0.22–0.98).

Figure 4: Factors/Relationships favoring net-protrusion in immunosuppressed/Tx patients (reprinted with permission from Wiley)



Type of mesh/fixation devices

In this study, a mesh made of polyester with a good ingrowth ability [184] and antiadhesive absorbable inside layer was used. Superior ingrowth ability is a key feature in the choice of mesh [57, 167, 185] and probably even more so in the immunosuppressed population. Proposing the use of biologic meshes in the Tx/IS population seems rational in fear of infection, however, the performance of a scaffolding mesh in a population with compromised fibroblast function is uncertain and still needs to be investigated [57, 186]. This study supports the feasibility of synthetic mesh implantation in the intraperitoneal space. Though not statistically significant, it is remarkable that no fixation device was found related to long-term pain in the Tx/IS group, as opposed to the non-IS cohort, with five patients in need of fixation material removal. The immunosuppressive medication (involving corticosteroids) may have exerted an anti-inflammatory—and thereby analgesic—response [187]. As no undesired effects were observed from permanent fixation devices and impaired inflammation/fibrous repair required for ingrowth of mesh is expected, a permanent (non-absorbable) fixation method may still seem advisable in the Tx/IS group. However, no firm evidence has been presented regarding the difference between absorbable and non-absorbable fixation, and particularly not any concerning the Tx/IS population.

We found no difference between an immunosuppressed cohort and a non-immunosuppressed cohort regarding recurrence or complications after LVHR. We observed a higher rate of bulging in the Tx/IS group. We conclude that Tx/IS patients can be treated with LVHR with similar results as in non-IS patients—avoiding the troublesome infected seromas above the mesh—and thus the minimally invasive method qualify as the favored procedure.

Hernia prophylaxis

PSH

The conducted RCT suggests that a fully non-absorbable synthetic large-pore mesh placed on the posterior sheath of the abdominis rectus muscle at the time of fashioning an end-colostomy protects against PSH. The risk of mesh-related complications was low, although the study was not powered for detecting such differences, and in keeping with previously published results. The significant difference in the development of PSH is in accordance with previously reported results from four RCTs [75, 188-190] and five observational studies [45, 191-194]. Two of the RCTs, with 27 patients in each arm, employed a partially degradable synthetic mesh placed in the retromuscular space [189, 190]. One of the other RCTs used a similar technique with a biologic mesh but it included only 10 patients in each arm [75], and in the fourth RCT, with 18 and 16 patients in the experimental and control groups, respectively, the mesh was placed intraperitoneally [188].

Three systematic reviews [195-197] and one meta-analysis [129] evaluating the first three RCTs concluded that retromuscular mesh prophylaxis has short-term efficacy without increased morbidity, but further studies, as we have now provided, were needed before a recommendation could be made. The results of our study substantiate the conclusion regarding efficacy and further suggest that this strategy also provides long-term effectiveness regarding PSH prevention, in agreement with another report of the long-term outcome [198]. In one very heterogenic study by Fleshman et al. [199], which was an evaluation of synthetic and biologic mesh prevention in a mixture of stoma types, the efficacy of mesh prophylaxis was not supported. They found no difference in the rate of PSH between the groups, but almost 40% of stomas were ileostomies, PSH rates for separate stoma types were not reported and the PSH rate in the control group was exceptionally low, at just 13% at 24 months, which is well below reported incidence for colostomies, however,

at the expected level for mesh-protected stomas. Another recent populations based study that compared historic cohorts without and with prophylactic mesh, found equal PSH rates of 25% by clinical examination and 53% by CT evaluation in both cohorts with a median follow-up of 31 months [200], and no mesh related complications. In a RCT published after our study with intraperitoneal key-hole mesh prophylaxis, reduction after one year is reported in clinically - but not in CT - detected PSHs [201]. Additionally, in a larger Dutch study with retromuscular mesh position, which at this moment has only been presented orally and also with one year of follow-up, a significant reduction in PSH occurrence was displayed with both modalities of detection (Brandsma et al., publication expected 2016).

A reduction in the incidence of PSH will have a critical impact on the quality of life of stoma patients [39, 202-204]. The number needed to treat (NNT) to prevent one PSH repair within the study period was 13 ($p = 0.24$, CI: 7, ∞), approaching results that can be derived from an analogous study [189]. As survival after treatment for rectal cancer is increasing, PSH will also increase [205, 206] and this will lead to an even lower stoma NNT with mesh to avert PSH repair. In summary, prevention of PSH by mesh insertion should reduce the complications resulting from development of PSH and the need for a PSH repair (which has a high risk of failing), demonstrating that this is an improvement in the treatment of patients who require a permanent colostomy.

Poor correlation between the clinical and CT detection of PSH was found in the present study. If clinically diagnosed PSH were to be the reference, CT detected nine false positives and four false negatives, suggesting that detection of a hernia sac without a Grade III PSH category is difficult and that a CT aimed mainly to detect recurrence of cancer disease is unreliable in distinguishing omentum from mesocolic or epiploic fat, whereas a dedicated CT scan, namely one that is focused on detecting PSH, has previously been shown to correspond well with the clinical findings [207]. Furthermore, the clinical significance of a diagnosis by a non-dedicated CT scan is indeterminate [11] and clinical evaluation and patient-reported symptoms seem more relevant.

Interestingly, the CT-assessed median size of the fascial orifice increased significantly over time in patients without a mesh; and was markedly associated with development of PSH. Stabilization of the fascial opening conceivably explains – and is possibly a crucial factor for – the prophylactic effect of the mesh against PSH. In accordance with previously published

studies, in the present RCT, placement of a retromuscular mesh dramatically reduced the rate of PSH formation in the experimental arm without increasing complications. Patients scheduled for a permanent colostomy should be considered for a prophylactic mesh procedure to reduce the risk of PSH.

IH

Prophylaxis of IH is not within the confines of this thesis. However, a few comments relevant to the study results are required:

Concomitant IH (cIH)

The implications of a cIH i.e. IH simultaneous with PSH are important. PSH appears to be an independent risk factor for development of (c)IH [208]. We observed a larger proportion of patients with IH in the control group without mesh prophylaxis for PSH, but the difference was not significant. As a utility of reduced PSH rate in the mesh group, the cIH rate was significantly reduced (to zero). Repair of cIH, and reciprocally repair of PSH with cIH, are more complex procedures susceptible to amplified failure and morbidity rates. Thus, as a side-effect the prospect for successful repair of an IH was amply improved. This has general inference potential.

IH after stoma reversal

If a possible option; the best repair of a PSH is stoma reversal. Nevertheless, IH rates after stoma reversal approaches 30% in addition to about 50% IH in the midline when reversal of colostomy incorporates a laparotomy [209]. This calls for adjustment of strategy in line with the proposed method of PSH prophylaxis, namely tissue augmentation, as suggested in a recent study [210].

IH in general

With growing evidence of effectiveness, tissue augmentation with mesh to prevent IH is a focus area for a prominent research body within the EHS. It is very probable that the planned EHS guidelines update in 2017 will include advice of reinforcement at index surgery, as several studies show significant preventive effect without increased morbidity [116, 118, 211], also in non-risk patients [212, 213].

Conclusions and future perspectives

Fortunately, the incidence of IH is in decline as the effect of increasing use of laparoscopy for most intraabdominal conditions. This is not the case for stoma creation, although refined technique and equipment has given potential to avert some cases of permanent stoma. However, both IH and the virtually inevitable accessory hernia as consequence of a stoma have a substantial impact on patient QoL and health economics. Amenities to repair or prevent the hernia disease with the least indisposition or disruption from daily life should be endeavored. The research in this thesis, presenting assessment of miniinvasive abdominal wall hernia repair in three distinct patient groups – and assessment of mesh prophylaxis in end colostomy construction, is with this goal in mind. The probable economic side-effect on the patients and society's behalf is an adjunct benefit.

From paper 1 we learned that there were no significant differences between the outcomes of LVHR in PH and IH, although this result was probably caused by inadequate sample size. In addition, the characteristics of hernia size differed between the groups. We also learned from randomization in this study, that defect closure in small hernia/PH probably is counterproductive, with a higher morbidity rate and no effect on long-term outcome. In both patient groups a very low recurrence rate and no infections were observed - and the method seems commendable. In the study there was a randomization to two different fixation methods, tackers only or a combinatory suture/tacker mesh attachment, without association to any outcome parameters. However, the problem of postoperative pain from the fixation utensils still needs to be addressed and alternative ways of securing the mesh should be explored. Absorbable tacking needs further inquiry as well as methods with glue or meshes with self-affixing technology. No quality studies are published on the subjects and the available evidence does not show superiority of one particular alternative.

In paper 2 the study of an organ transplanted cohort treated with LVHR for IH also returned favorable results in terms of morbidity and recurrence – comparable to a cohort without immunosuppression. This was the first published prospective cohort study comparing LVHR in these patient groups. The absence of otherwise complicating surgical site infections in open hernia surgery in transplanted patients, along with the favorable recurrence rate exceedingly advocate the modality and has after the study become the method of choice in

cooperating departments. The hernias in the Tx/IS group were larger than in the non-IS group and there was a tendency towards more bulging and recurrence in this group. In this study the randomization to defect closure tended to counteract this risk and is probably beneficial in larger hernia. In fact, we advocate extended procedures as CST, hybrid or open surgery if closure is not attainable by laparoscopy. However, studies with randomization to defect closure have not been published previously. Paper 2 were in conjunction with paper 1 so far the only published trials with randomization to this effect parameter. In the Tx/IS cohort no prolonged pain was observed. We explain this with the use of steroids in anti-rejection therapy and an attenuated fibrous response. As incorporation of mesh in the host tissue is theoretically weaker and we found no pain issues, we advise permanent fixation of mesh in this patient category.

Paper 3 was the largest published RCT series on PSH prophylaxis and increased the aggregated sample size in published RCTs on mesh prevention in colostomy against PSH with 46%. The consistency of decreased PSH incidence in RCTs solidify that the message is important to convey to health professionals as well as patients. Although the follow-up is relatively short with up to five years in these studies, the procedure with mesh prophylaxis appears safe and effective. Comparative studies that have not indicated advantages have puzzlingly low PSH rates in patients without mesh prophylaxis, but in conjunction with non-randomized prospective series they also support the safety in use of mesh. Thus, the effect of prevention with this particular open approach seems well founded with the addition of our study - and is an easy and inexpensive additional procedure, which holds the promise to avoid patient suffering and save money and time for both the patient and the health system. The procedure has become standard of care in the collaborating divisions. Patients destined to be recipients of a permanent colostomy should be considered for PSH prevention with mesh.

We know that the keyhole technique in PSH repair with a central hole in the mesh does not work well, so it is slightly perplexing that this approach is successful in primary prophylaxis and as secondary prophylaxis in stoma relocation for treatment of PSH. One retrospective comparative study [132] from 2012 examined the aperture change and found the same stabilizing effect of mesh as we found in our study, purporting the difference of primary amplification of a healthy -, in comparison to repair of a partly degenerated abdominal wall.

Despite weaknesses as lack of power to detect morbidity in our study, this knowledge is provided by several prospective series and metaanalyses of RCTs, further strengthened by our study and compounded by a very recent published RCT with short-time outcomes of 150 patients [214]. However, as mentioned earlier the modality of stoma creation is changing with increasing use of laparoscopy, and mesh procedures in this setting are not validated, although one study describes similar PSH risk with retromuscular mesh placement through the trephine [131] and some evidence that the Sugarbaker approach seems promising [45]. A future obligation is to provide randomized series of the options available in the laparoscopic setting, especially the more costly intraperitoneal key-hole and Sugarbaker prevention methods in comparison to the simple retromuscular mesh application through the trephine – and also the performance of various meshes in these settings.

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Appendix

Unpublished and extended tables

Supplementary tables to Paper 1:

Table 6a. Laparoscopic ventral hernia repair: Impact of **defect closure** on **overall complications**, prospective data.

	Complications, n/n	Fischers exact test, p value
Primary hernia with closure (a+c)	9/21	0.005
Primary hernia without closure (b+d)	0/16	
Incisional hernia with closure (a+c)	12/36	0.433
Incisional hernia without closure (b+d)	8/34	
Primary and incisional hernia with defect closure (a+c)	21/57	0.004
Primary and incisional hernia without defect closure (b+d)	8/50	

Table 6b. Laparoscopic ventral hernia repair: Impact of **mesh fixation method** on **overall complications**, prospective data.

	Complications, n/n	Fischers exact test, p value
Primary hernia with suture + SC (a+b)	4/17	1.000
Primary hernia with DC (c+d)	5/20	
Incisional hernia with suture + SC (a+b)	13/33	0.069
Incisional hernia with DC (c+d)	7/37	
Primary and incisional hernia with suture + SC (a+b)	17/50	0.191
Primary and incisional hernia with DC (c+d)	12/57	

Table 6c. Laparoscopic ventral hernia repair: Impact of **mesh fixation method and defect closure** on **overall complications**, prospective data.

	Complications, n/n	Fischers exact test, Freeman-Halton ext, p _A value
Primary hernia with suture/SC and raphe (a)	4/11	0.016
Primary hernia with suture/SC and no raphe (b)	0/6	
Primary hernia with DC and raphe (c)	5/10	
Primary hernia with DC and no raphe (d)	0/10	
Incisional hernia with suture/SC and raphe (a)	8/16	0.170
Incisional hernia with suture/SC and no raphe (b)	5/17	
Incisional hernia with DC and raphe (c)	4/20	
Incisional hernia with DC and no raphe (d)	3/17	
Primary and incisional hernia with suture/SC and raphe (a)	12/27	0.048
Primary and incisional hernia with suture/SC and no raphe (b)	5/23	
Primary and incisional hernia with DC and raphe (c)	9/30	
Primary and incisional hernia with DC and no raphe (d)	3/27	

Table 7a. Laparoscopic ventral hernia repair: Impact of **defect closure** on **protrusion**, prospective data.

	Protrusion, n/n	Fischers exact test, p value
Primary hernia with closure (a+c)	0/21	0.180
Primary hernia without closure (b+d)	2/16	
Incisional hernia with closure (a+c)	5/36	1.000
Incisional hernia without closure (b+d)	4/34	
Primary and incisional hernia with defect closure (a+c)	5/57	0.752
Primary and incisional hernia without defect closure (b+d)	6/50	

Table 7b. Laparoscopic ventral hernia repair: Impact of **mesh fixation method** on **protrusion**, prospective data.

	Protrusion, n/n	Fischers exact test, p value
Primary hernia with Suture/SC (a+b)	0/17	0.490
Primary hernia with DC (c+d)	2/20	
Incisional hernia with suture/SC (a+b)	3/33	0.485
Incisional hernia with DC (c+d)	6/37	
Primary and incisional hernia with suture/SC (a+b)	3/50	0.213
Primary and incisional hernia with DC (c+d)	8/57	

Table 7c. Laparoscopic ventral hernia repair: Impact of **mesh fixation method and defect closure** on **protrusion**, prospective data.

	Protrusion, n/n	Fischers exact test, Freeman-Halton ext, p_A value
Primary hernia with suture/SC and raphe (a)	0/11	0.158
Primary hernia with suture/SC and no raphe (b)	0/6	
Primary hernia with DC and raphe (c)	0/10	
Primary hernia with DC and no raphe (d)	2/10	
Incisional hernia with suture/SC and raphe (a)	2/16	0.814
Incisional hernia with suture/SC and no raphe (b)	1/17	
Incisional hernia with DC and raphe (c)	3/20	
Incisional hernia with DC and no raphe (d)	3/17	
Primary and incisional hernia with suture/SC and raphe (a)	2/27	0.428
Primary and incisional hernia with suture/SC and no raphe (b)	1/23	
Primary and incisional hernia with DC and raphe (c)	3/30	
Primary and incisional hernia with DC and no raphe (d)	5/27	

Table 8a. Laparoscopic ventral hernia repair: Impact of **defect closure** on **seroma**, prospective data.

	Seroma, n/n	Fischers exact test, p value
Primary hernia with closure (a+c)	3/21	0.243
Primary hernia without closure (b+d)	0/16	
Incisional hernia with closure (a+c)	6/36	0.479
Incisional hernia without closure (b+d)	3/34	
Primary and incisional hernia with defect closure (a+c)	9/57	0.134
Primary and incisional hernia without defect closure (b+d)	3/50	

Table 8b. Laparoscopic ventral hernia repair: Impact of **mesh fixation method** on **seroma**, prospective data.

	Seroma, n/n	Fischers exact test, p value
Primary hernia with Suture/SC (a+b)	1/17	1.000
Primary hernia with DC (c+d)	2/20	
Incisional hernia with suture/SC (a+b)	6/33	0.290
Incisional hernia with DC (c+d)	3/37	
Primary and incisional hernia with suture/SC (a+b)	7/50	0.541
Primary and incisional hernia with DC (c+d)	5/57	

Table 8c. Laparoscopic ventral hernia repair: Impact of **mesh fixation method and defect closure** on **seroma**, prospective data.

	Seroma, n/n	Fischers exact test, Freeman-Halton ext, p_A value
Primary hernia with suture/SC and raphe (a)	1/11	0.470
Primary hernia with suture/SC and no raphe (b)	0/6	
Primary hernia with DC and raphe (c)	2/10	
Primary hernia with DC and no raphe (d)	0/10	
Incisional hernia with suture/SC and raphe (a)	4/16	0.462
Incisional hernia with suture/SC and no raphe (b)	2/17	
Incisional hernia with DC and raphe (c)	2/20	
Incisional hernia with DC and no raphe (d)	1/17	
Primary and incisional hernia with suture/SC and raphe (a)	5/27	0.365
Primary and incisional hernia with suture/SC and no raphe (b)	2/23	
Primary and incisional hernia with DC and raphe (c)	4/30	
Primary and incisional hernia with DC and no raphe (d)	1/27	

Table 9a. Laparoscopic ventral hernia repair: Impact of **defect closure** on **pain** at 2 months, prospective data.

	Pain at 2 months, n/n	Fischers exact test, p value
Primary hernia with closure (a+c)	9/21	0.723
Primary hernia without closure (b+d)	4/16	
Incisional hernia with closure (a+c)	6/36	0.102
Incisional hernia without closure (b+d)	12/34	
Primary and incisional hernia with defect closure (a+c)	13/57	0.384
Primary and incisional hernia without defect closure (b+d)	16/50	

Table 9b. Laparoscopic ventral hernia repair: Impact of **mesh fixation method** on **pain** at 2 months, prospective data.

	Pain at 2 months, n/n	Fischers exact test, p value
Primary hernia with Suture/SC (a+b)	7/17	0.2793
Primary hernia with DC (c+d)	4/20	
Incisional hernia with suture/SC (a+b)	8/33	1.000
Incisional hernia with DC (c+d)	10/37	
Primary and incisional hernia with suture/SC (a+b)	15/50	0.663
Primary and incisional hernia with DC (c+d)	14/57	

Table 9c. Laparoscopic ventral hernia repair: Impact of **mesh fixation method and defect closure** on **pain** at 2 months, prospective data.

	Pain at 2 months, n/n	Fischers exact test, Freeman-Halton ext, p _a value
Primary hernia with suture/SC and raphe (a)	5/11	0.545
Primary hernia with suture/SC and no raphe (b)	2/6	
Primary hernia with DC and raphe (c)	2/10	
Primary hernia with DC and no raphe (d)	2/10	
Incisional hernia with suture/SC and raphe (a)	3/16	0.303
Incisional hernia with suture/SC and no raphe (b)	5/17	
Incisional hernia with DC and raphe (c)	3/20	
Incisional hernia with DC and no raphe (d)	7/17	
Primary and incisional hernia with suture/SC and raphe (a)	8/27	0.495
Primary and incisional hernia with suture/SC and no raphe (b)	7/23	
Primary and incisional hernia with DC and raphe (c)	5/30	
Primary and incisional hernia with DC and no raphe (d)	9/27	

Table 10a. Laparoscopic ventral hernia repair: Impact of **defect closure** on **recurrence**, prospective data.

	Recurrence, n/n	Fischers exact test, p value
Primary hernia with closure (a+c)	0/21	1.000
Primary hernia without closure (b+d)	0/16	
Incisional hernia with closure (a+c)	2/36	1.000
Incisional hernia without closure (b+d)	1/34	
Primary and incisional hernia with defect closure (a+c)	2/57	1.000
Primary and incisional hernia without defect closure (b+d)	1/50	

Table 10b. Laparoscopic ventral hernia repair: Impact of **mesh fixation method** on **recurrence**, prospective data.

	Recurrence, n/n	Fischers exact test, p value
Primary hernia with Suture/SC (a+b)	0/17	1.000
Primary hernia with DC (c+d)	0/20	
Incisional hernia with suture/SC (a+b)	2/33	0.599
Incisional hernia with DC (c+d)	1/37	
Primary and incisional hernia with suture/SC (a+b)	2/50	0.598
Primary and incisional hernia with DC (c+d)	1/57	

Table 10c. Laparoscopic ventral hernia repair: Impact of **mesh fixation method and defect closure** on **recurrence**, prospective data.

	Recurrence, n/n	Fischers exact test, Freeman-Halton ext, p _A value
Primary hernia with suture/SC and raphe (a)	0/11	1.000
Primary hernia with suture/SC and no raphe (b)	0/6	
Primary hernia with DC and raphe (c)	0/10	
Primary hernia with DC and no raphe (d)	0/10	
Incisional hernia with suture/SC and raphe (a)	2/16	0.130
Incisional hernia with suture/SC and no raphe (b)	0/17	
Incisional hernia with DC and raphe (c)	0/20	
Incisional hernia with DC and no raphe (d)	1/17	
Primary and incisional hernia with suture/SC and raphe (a)	2/27	0.343
Primary and incisional hernia with suture/SC and no raphe (b)	0/23	
Primary and incisional hernia with DC and raphe (c)	0/30	
Primary and incisional hernia with DC and no raphe (d)	1/27	

Multinomial regression on protrusion and overall complications on incisional and primary hernia cohorts, prospective data

	Protrusion		Complications	
	Incisional hernia	Primary hernia	Incisional hernia	Primary hernia
Defect closure	1.22	N/A	2.01	N/A
Reference category: no defect closure	(0.23-6.38)		(0.65-6.20)	
Hernia size	2.02	N/A	0.99	0.05
Reference category: ≤20cm2	(0.35-11.59)		(0.29-3.44)	(0.00-9.27)
Overlap coefficient	2.46	0.73	0.64	8.43
Reference category: ≥1.0	(0.38-16.11)	(0.04-13.44)	(0.20-2.02)	(0.26-273.43)

Adjusted for age, BMI and sex, N/A: not applicable (regression analysis not applicable as no PH patients with closure had protrusion and no PH patients without closure had complications)

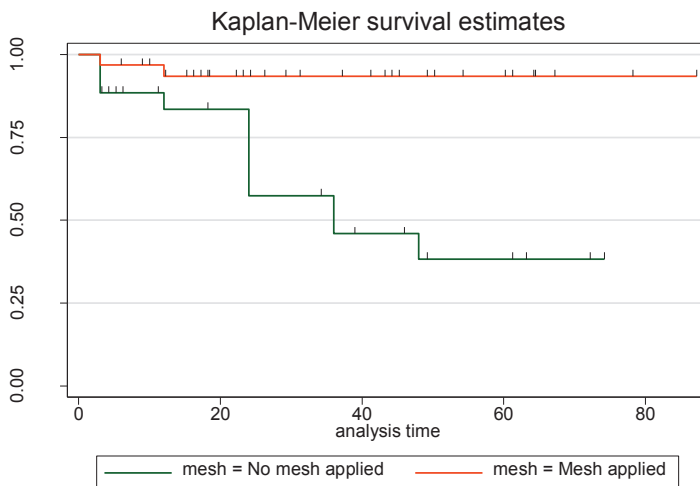
Supplementary table and figure to Paper 3:

Mesh prophylaxis against parastomal hernia (PSH) in end-colostomy creation: Distribution of PSH according to Moreno-Mathias' (M-M) computed tomography (CT) classification and modified European Hernia Society (EHS) clinical PSH classification.*

	Hernia type	Mesh applied	No mesh
Modified* classification of PSH according to EHS	I	2	3
	II	0	6
	III	0	2
	IV	0	1
Classification of CT-detected PSH according to M-M	Ia	2	2
	Ib	2	1
	II	4	2
	III	0	6

* Exchange of directly measured ostomy diameter at PSH repair with diameter measured by CT, table not provided in original manuscript

Cumulative incidence of disease-free (clinical parastomal hernia) survival. Kaplan-Meier analysis on randomization between protective mesh or no mesh applied at the formation of an end-colostomy. Analysis time in months.



Log-rank test: P<0.001

Popular summaries of papers 1-3

English language

Paper 1:

PEEPHOLE SURGERY AS TREATMENT FOR ABDOMINAL WALL HERNIA

At operation for hernia in the abdominal wall with peephole/keyhole technique, a reinforcing mesh is placed inside the abdominal cavity to permanently support the abdominal wall. The operation is equally effective in spontaneously arisen hernia or hernia after previous surgery, a scar hernia. Furthermore, there is no proven effect of sewing the defect before the mesh reinforcement, especially at the smaller spontaneously arisen abdominal wall hernia. This is what a randomized study with 3 years of follow-up after surgery reveals.

Hernia in the abdominal wall

Hernia occurs after weakness in the abdominal wall where fat or bowel escapes forward through muscle layers, forming a noticeable bump under the skin. Hernias can cause pain, ileus and more. Such hernias can occur spontaneously or after surgery through the abdominal wall: scar hernia. Up to 20% develop abdominal wall hernia after surgery and most people need another surgery to close the defect.

Operations

Modern open and laparoscopic (peep-hole) techniques for hernia repair includes use of mesh reinforcement. Mesh materials are either synthetic (nylon or polyester) which is the most used and which do not degrade in the body, biodegradable synthetic meshes - or biologic meshes (made from pig skin or other animal tissue) which degrade at different rates, but serves as a matrix for the body's own connective tissue in scar healing.

Using meshes a recurrence rate of hernia at under 10% can be obtained, but there is a greater risk of infection by open surgery and there is shorter convalescence after keyhole surgery. Keyhole surgery is not equally applicable to quite large hernia defects of more than 15 cm and "loss-of-domain", which is a situation where the

lesion has become so large and the abdominal wall simultaneously has withdrawn so far aside, that viscera no longer fits inside the abdominal cavity; but these represent a small proportion of abdominal wall hernia.

The study's purpose and method

With the study, we wanted to show that keyhole method for operation of both spontaneous hernia and scar hernia is efficient and with acceptable scope of complications. To do this, 37 patients with spontaneous abdominal wall hernia and 70 patients with scar hernia were included in a prospective treatment study with standardized operation with the keyhole method, but also randomly allocated to +/- closure of the hernia defect. In this study was used soluble thread to sew up the defect. All patients were followed up for 3 years after surgery and complications and recurrence of hernia was recorded. Patients were operated on two hospitals: Ullevaal and Gjøevik hospitals. One such study with randomization to +/- closing of the hernia defect is not previously disclosed.

Results and discussion

The compared patient groups were comparable in age, other illnesses and body mass index, but there was unequal gender distribution. One third of the spontaneous hernia were recurrence after open surgery without mesh reinforcement, while this was only the case for 10% in the scar hernia group. Scar hernias were in average larger than the spontaneous hernia.

There were no differences in complications between the patient groups. The adjustment factor BMI proved to be associated with increased risk of complications (OR 1.87; CI 1.14 to 3.05). We also found that with closing the hernia defect occurred more complications, such as fluid retention at the hernia site and inflammation of the skin (OR 3.42; CI: 1.25 to 9.33). This difference was most pronounced in the spontaneously arisen hernia.

The recurrence rate after scar hernia was 4% and after spontaneous hernia 0%. This was not a significant difference, but this may be because the study groups were too small. Bulging of the mesh into the previous hernia defect occurred in 13% in the scar hernia group and in 5% in the group with spontaneous hernia. This was also not

significantly different but mostly a result of differences in hernia size between the patient groups.

There was no significant benefit of closing the defect, since there was no difference between the randomized groups in recurrence or bulging of the mesh in the defect. Sewing the defect with soluble thread proved thus not useful and caused more complications. Changed method with non-soluble thread and more and stronger stitches, may possibly have an effect on the primary endpoints: bulging and relapse - and thus offset the increased complication rate, but it does require new studies to clarify this question.

Conclusion

Although there are differences in cause, size and also localization of hernia in the abdominal wall by comparing spontaneously arisen hernia and scar hernia, keyhole surgery for this condition is effective and safe for both hernia types.

Closure of the defect with soluble thread gave no useful effect and increased the overall complication rate in this study.

The study "Laparoscopic ventral hernia repair: Outcomes in primary versus incisional hernias - No effect of defect closure, Lambrecht JR et al" was published in the journal *Hernia* on February 7th 2015:

Hernia (2015) 19: 479-486, DOI: 10.1007 / s10029-015-1345-x

Paper 2:

PEEP-HOLE SURGERY AS TREATMENT FOR INCISIONAL HERNIAS AFTER LIVER OR KIDNEY TRANSPLANTATION

The peep-hole method for operation of incisional hernias in organ transplanted patients is just as effective and safe as in the normal population. This is shown by a study with 3-year follow-up after surgery.

Scar hernia

is a weakness in the abdominal wall after surgery, in which fat or bowel escapes forward through muscle layers, forming a noticeable and often troublesome bump under the skin. Incisional hernias can be large or small and provide both cosmetic and functional problems, as ileus, pain and skin wounds. The problem is huge as 1 of 5 who is operated in the abdominal cavity develop a hernia in the scar. Most patients need a second operation to close this defect.

Immunosuppression

Patients operated with kidney or liver transplantation have an even greater risk of scar hernia, as they receive medicine that suppress the immune system so that organs should not be repelled by the host body, but simultaneously also dampens the formation of strong scar tissue. Because of transplant patients' reduced immune system and hence increased risk of infection in surgical scars, doctors have been reluctant to use synthetic mesh reinforcement in these patients and contented themselves with sewing the hole without reinforcement. This has resulted in a large number of recurrences of hernia.

Operations

Modern technique for operation of incisional hernias include use of a reinforcing mesh which is attached to the abdominal wall and supports the natural tissue. These meshes are usually made of polypropylene (nylon) or polyester, that do not disintegrate in the body. Hernia in the abdominal wall is operated either as a traditional open surgery with cutting in the old scar, closing the hole and placing a

reinforcing mesh behind or in front of the abdominal muscles. The method is efficient, with relapse rate of approximately 10%, but there is a risk of infections and in some cases meshes have to be removed because of that. Alternatively, a peep-hole method can be used, which avoids the large opening, but the reinforcing mesh is then placed completely inside the abdominal cavity - and therefore must have been coated on the inside to prevent adhesions against the intestines. The peep-hole method has proven to be beneficial in several areas: patients are hospitalized a shorter time after a peep-hole operation, but the most significant is that the risk of infection is decreased. At the same time, it has proven to be as effective as the open repair method of hernia defects below 10-15 cm.

The study's purpose and method

With the study, we wanted to show that the peep-hole method for surgery of scar hernia is efficient and with acceptable rates of complications also in patients who are liver or kidney transplanted. To do this, 31 transplant patients and 70 "normal" patients with scar hernias were included in a treatment study with standardized operation with the peep-hole method. All patients were followed up for 3 years after surgery and any complications or recurrence of the hernia was recorded. Patients were operated on 3 hospitals: The transplanted patients at Rikshospitalet and the "normal" patients at Ullevaal and Gjøevik hospitals. Such a prospective study on transplanted patients with a control group is not previously disclosed.

Results

Patient groups were similar in age and body mass index, but there were unequal gender distributions. As expected we saw less scar tissue formation in the abdominal cavity in the immunocompromised transplanted patients. Hernias were also larger in this group and these patients were hospitalized for a longer time after surgery. Fluid accumulation under the wound or in the previous hernia cavity after hernia operation, is a major problem for open surgery, with frequent infection problems. In our study, there were fewer cases of fluid collections in the transplanted patient group - and no infections in either group. There was no significant difference in relapse rate between the two groups (9.7% vs. 4.2%, $p = 0.4$). However, there was a

tendency towards an increased proportion of patients with bulging of the supporting mesh through the previous defect in the transplanted patient group - a situation where the mesh still keeps the abdominal contents inside the abdominal cavity, but escapes slightly forward - also called a pseudo-hernia. We partly attribute this tendency to the fact that the transplanted patient group had larger hernias than the control group, but also that they form less strong connective tissue. This was more pronounced for the male gender but this gender difference has not been reported previously. In the study, patients were also randomly assigned to close the defect or not - and by closing the defect we saw a tendency to lower the risk for pseudo-hernia.

Recommendations

Based on the results we recommend peep-hole surgery as the preferred method of operation for incisional hernia in a liver or kidney transplanted population. The major problem with infection seems eliminated in relation to the open method and a relapse rate below 10% is highly satisfactory in this patient group.

The study "Laparoscopic repair of incisional hernia in solid organ transplanted Patients: the method of choice ?, Lambrecht JR et al" was published in the journal *Transplant International* on May 9th 2014:

Transplant Int (2014), 27: 712-720, DOI: 10.1111 / tri.12327

Paper 3:

SYNTHETIC MESH AS PREVENTION AGAINST HERNIA WHEN BRINGING THE BOWEL THROUGH THE ABDOMINAL WALL FOR STOOL DRAINAGE

In conditions such as cancer in the lower part of the rectum and in chronic enteritis, it is often necessary to lead the intestine out through the abdominal wall as a permanent solution for stool drainage. A colostomy (large intestine brought out) provides besides hernia rarely problems that cannot be solved by a specialized nurse, e.g. skin irritation, difficulty in attaching the bag (pouch) that collects feces and retraction of the bowel during which can result in leakage. About 10,000 Norwegians are living with a colostomy and every year approximately 2,500 patients have to be operated with a colostomy in Norway.

Hernia beside the stoma

More than 50% with a colostomy develops hernia beside the colostomy. This can cause deformation and problems fitting the pouch, leak and cause pain, ileus and social and cosmetic distress. These problems from this condition leads to that about 1/4 of hernias at the colostomy site will need surgery to repair the hernia. The recurrence rate after surgery for hernia at the colostomy site is unfortunately high, but new techniques with keyhole surgery and mesh reinforcement are promising.

Prevention

Intestines can be brought out through the abdominal wall through different muscle layers, but no specific method appears to reduce the risk of hernia significantly. Few and small studies, including three randomized, have demonstrated the efficacy of preventive mesh placement around the bowel where it passes the abdominal muscles, but many surgeons have been reticent against placing a synthetic mesh in a contaminated area because of fear of infectious complications. Meanwhile, former experience with mesh ingrowth through the intestinal wall forming so-called fistulas and pus collections (abscesses) are historical fallouts, where the meshes were of an entirely different nature than the material reduced meshes in use presently.

The study's purpose and method

With the study we wanted to examine whether prevention with mesh in construction of permanent colostomy prevents a hernia along the exteriorized bowel as a colostomy without causing complications. To do this, 60 patients were included in a prospective study and randomly assigned to receive mesh around the bowel in open surgery (laparotomy) where permanent colostomy had to be planned. The majority of patients were operated at the Norwegian Radium Hospital – the remaining at Inlandet Hospital Trust in Gjøevik. Follow-up was scheduled for 4 years, with clinical examination and CT, which also measured the size of the opening in the abdominal wall, with half-year intervals the first two years and hereafter annual checks.

Results and discussion

The experimental group with mesh prophylaxis and the control group were comparable in age, body mass index, other diseases, gender and previous hernia disease. Because of the underlying disease that necessitated operation there was a high mortality and only 20 patients in each group survived to the three-year control. There were no differences in complications between the groups. Six % of patients in the experimental group with mesh developed hernia at the stoma, in contrast to 46% in the control group without mesh ($p < 0.001$, Fisher's exact test). In the experimental group there was a significantly decreased risk for hernia at the stoma site (Odds Ratio (OR) 0.04; 95% Confidence Interval (CI): 0.00, 0.35) for all enrolled patients, in analysis adjusted for age, body mass index and size of the opening in the abdominal wall at the first CT. By the same analysis on only those who survived three years there were also smaller odds for hernia (OR 0.04; 95% CI: 0.00, 0.68). Likewise, at adjusted survival analysis there was a reduction in the risk of hernia at the stoma site in the experimental group (Cox regression hazard ratio 0.09; 95% CI: 0.02, 0.44), which translates to a risk reduction of 90%. To avoid one hernia at the stoma site only 2.5 patients must receive a prophylactic mesh at the operation (CI: 1.9, 6.9). With our study, the number of patients included in published randomized trials increased by 50% and the results are comparable and support the earlier studies.

Another finding from CT controls was that the opening in the abdominal wall was constant over time in the experimental group with mesh ($p = 0.64$, related samples sign test), but increased in size in the control group without mesh ($p = 0.003$). The change in size between groups was also significant ($p = 0.001$, Independent samples t-test). An interesting result is that the increase in orifice size was only in the subgroup of patients with hernia by clinical examination. Mesh thus appears to stabilize the abdominal wall, so there is less risk of hernia and thus expansion of the opening created for the bowels departure from the abdominal cavity.

Conclusion

In line with previous studies this randomized trial confirms that the mesh to strengthen the abdominal wall, and enclosing the intestine at construction of a colostomy, protects against hernia formation adjacent to the intestine through the opening in the abdominal wall. There is no increased risk of complications when using the mesh in this setting. Increased size of the opening in the abdominal wall over time is associated with the development of the hernia and the mesh seems to stabilize the abdominal wall and prevent this expansion. Patients receiving permanent colostomy should receive a preventive mesh.

The study " Prophylactic mesh at end-colostomy construction reduces parastomal hernia rate: a randomised trial, Lambrecht JR et al " was published in the journal Colorectal Disease on July 14th 2015:

Colorectal Dis. 2015 Oct; 17 (10): 0191-7, DOI: 10.1111 / codi.13065

Norwegian language

Artikkel 1:

KIKKHULLSKIRURGI SOM BEHANDLING FOR BUKVEGGS-BROKK

Ved operasjon for brokk i bukveggen med kikkhullskirurgi, også kallet laparoskopi, legges et forsterkende nett som støtte for bukveggen inn i bukhulen.

Operasjonstypen er like effektiv om det er spontant oppstått brokk eller brokk etter tidligere kirurgi, arr-brokk. Videre er det ingen god effekt av å sy igjen defekten før nett forsterkning, spesielt ikke ved de mindre spontant oppståtte bukveggs-brokk.

Det viser en randomisert studie med 3 års oppfølging etter operasjon.

Bukveggsbrokk

Brokk oppstår etter svakhet i bukveggen hvor fett eller tarm tyter frem gjennom muskellagene og danner en merkbar kul under huden. Brokk kan gi smerter, tarmslyng m.m. Slike brokk kan oppstå spontant eller etter kirurgi gjennom bukveggen: arrbrokk. Helt opp mot 20% utvikler bukveggsbrokk etter kirurgi og mange trenger ny operasjon for å lukke defekten.

Operasjon

Moderne åpne og laparoskopiske (kikkhull) teknikker for brok reparasjon innbefatter bruk av nettfosterkning. Nettmateriale er enten kunstnett (nylon eller polyester) som er det mest brukte og som ikke nedbrytes i kroppen - eller biologiske nett (laget av grisehud e.l.) som nedbrytes i varierende hastighet, og erstattes av kroppens eget bindevev i arrdannelsen.

Ved bruk av nett kan man holde tilbakefallsrate av brokk på under 10%, men det er større risiko for betennelse ved åpen operasjon og det er kortere rekonvalesens etter kikkhullskirurgi. Kikkhullskirurgi er imidlertid ikke like anvendelig når brokkåpningen er over 10-15 cm og ved «loss-of-domain», som er en situasjon hvor brokket har blitt så stort og bukveggen samtidig har trukket seg så mye sammen at det ikke lenger er plass til innvollene inne i bukhulen; men disse utgjør en liten andel av bukveggsbrokk.

Studiens formål og metode

Med studien ønsket vi å vise at laparoskopisk operasjon for både spontane brokk og arr-brokk er effektiv og med akseptabelt komplikasjonsomfang. For å gjøre dette ble 37 pasienter med spontane bukveggs brokk og 70 pasienter med arr-brokk inkludert i en prospektiv behandlings studie med standardisert operasjon med kikkhulls metode, men også tilfeldig utvalgt (randomisert) til lukking av brokk defekten. I denne studien ble anvendt oppløselig tråd til å sy sammen defekten. Alle pasienter ble fulgt opp i 3 år etter operasjon og komplikasjoner og tilbakefall av brokk ble registrert. Pasientene ble operert på 2 sykehus: Ullevål og Gjøvik sykehus. En slik studie med randomisering til lukking eller ikke lukking av brokkdefekten er ikke tidligere publisert i internasjonale fagtidsskrifter.

Resultater og diskusjon

Pasientkohortene var sammenliknbare i alder, andre sykdommer og kroppsmasseindeks (KMI), men det var ulik kjønnsfordeling. En tredjedel av de spontane brokk var tilbakefall etter åpen operasjon uten nettførsterkning, mens dette kun var tilfellet for 10% i arr-brokk gruppen. Arr-brokk var gjennomsnittlig større enn de spontane brokk.

Det var ingen forskjell i komplikasjoner mellom brokkgruppene. Justeringsfaktoren KMI, dvs. overvekt viste seg å være en forbundet med økt komplikasjonsrisiko (OR 1.87; CI 1.14-3.05). Vi fant også at med lukking av brokkdefekten oppsto flere komplikasjoner, som væskeansamling ved brokket og betennelse i hud (OR 3.42; CI: 1.25-9.33). Denne forskjellen var mest uttalt hos de mindre og spontant oppståtte brokk.

Tilbakefallsraten etter arrbrokk var 4% og etter spontant brokk 0%. Dette var ikke en signifikant forskjell. Frembuling av nett i defekten oppsto hos 13% i arrbrokk gruppen og 5% i gruppen med spontane brokk. Heller ikke dette var signifikant forskjellig og mest et utslag av forskjell i brokkstørrelse.

Det var ingen statistisk signifikant nytte av å lukke defekten, siden det ikke var forskjell mellom de randomiserte gruppene på tilbakefallsraten eller frem buling av nett i defekten.

Sammensying av defekten med oppløselig tråd viste seg altså ikke nyttig og forårsaket flere komplikasjoner. Endret metode med ikke-oppløselig tråd og flere og tettere sting, kan muligvis gi effekt på de primære endepunkter: frem buling og tilbakefall – og således oppveie den økte komplikasjonsrate, men det krever nye studier for å avklare dette spørsmål.

Konklusjon

Selv om det er forskjell i årsak, størrelse og også lokalisering av brokk i bukveggen ved sammenlikning av spontant oppståtte brokk og arrbrokk, er kikkhullsoperasjon for denne tilstanden effektiv og sikker for begge brokktyper.

Lukking av defekten med oppløselig tråd ga ingen nyttevirkning og økte den samlede komplikasjonsrate i denne studien.

Studien "Laparoscopic ventral hernia repair: Outcomes in primary versus incisional hernias - No effect of defect closure, Lambrecht JR et al" er offentliggjort i tidsskriftet *Hernia* d. 7 Februar 2015:

Hernia (2015) 19:479-486, DOI: 10.1007/s10029-015-1345-x

KIKKHULLSKIRURGI SOM BEHANDLING FOR ARRBROKK HOS ORGANTRANSPLANTERTE PASIENTER

Kikkhullsmetoden for operasjon av arrbrokk på organ transplanterte pasienter er like effektiv og sikker som på ikke-transplanterte pasienter. Det viser en kohort studie med 3 års oppfølging etter operasjon.

Arrbrokk

er en svakhet i bukveggen etter operasjon, der fett eller tarm tyter frem gjennom muskellagene og danner en merkbar kul under huden. Arrbrokk kan være store og små å gi både kosmetiske og funksjonelle problemer, som tarmslyng, smerter og sår i huden. Problemet er stort idet helt opp mot 1 av 5 som er operert i bukhulen utvikler brokk i arret etter operasjon med stort snitt. De fleste pasienter trenger en ny operasjon for å lukke denne defekten.

Immunsuppressjon

Pasienter operert med nyre- eller lever-transplantasjon har enda større risiko for arrbrokk, da de for at organene ikke skal avstøtes av vertskroppen får medisin som demper immunforsvaret, men samtidig også demper dannelsen av sterkt arrvev. På grunn av transplanterte pasienters nedsatte immunforsvar og derav økte risiko for infeksjon i operasjonsarr, har man vært tilbakeholdende med å bruke kunstnett på disse pasienter og nøyert seg med å sy sammen hullet uten forsterkning. Det har medført et stort antall tilbakefall av brokk.

Operasjon

Moderne teknikk for operasjon av arrbrokk inkluderer bruk av et forsterkende nett, som festes til bukveggen og støtter det naturlige vev. Disse nett er som regel laget av polypropylene (nylon) eller polyester, som ikke nedbrytes i kroppen. Brokk i bukveggen opereres enten som en tradisjonell åpen operasjon med oppskjæring av

det gamle arret, lukking av hullet samt innsyng av et forsterkende nett bak musklene. Metoden er effektiv, med tilbakefalls rate på ca. 10 %, men det er risiko for betennelse i såret og i noen tilfeller må nettet opereres ut igjen. Alternativt kan anvendes en kikkhullsmetode (laparoskopi), der man unngår den store åpningen, men det forsterkende nett legges da helt inne i bukhulen – og må derfor være behandlet på innsiden for å unngå sammenvoksninger mot tarmene. Laparoskopi har vist seg å være gunstig på flere områder: pasienter er innlagt i kortere tid etter en laparoskopisk operasjon, men det mest vesentlige er at risikoen for infeksjon er mindre. Samtidig har metoden vist seg å være like effektiv som den åpne metoden på brokkdefekter under 10-15 cm.

Studiens formål og metode

Med studien ønsket vi å vise at laparoskopisk operasjon av arrbrokk er effektiv og med akseptabelt komplikasjonsomfang også hos pasienter som er organtransplantert. For å gjøre dette ble 31 transplanterte pasienter og 70 «normale» pasienter med arrbrokk inkludert i en prospektiv behandlingsstudie med standardisert laparoskopisk operasjonsmetode. Alle pasienter ble fulgt opp i 3 år etter operasjon og komplikasjoner og tilbakefall av brokk ble registrert. Pasientene ble operert på 3 sykehus: Transplantasjonskohorten på Rikshospitalet og de «normale» pasienter på Ullevål og Gjøvik sykehus. En slik prospektiv studie med kontrollgruppe er ikke tidligere publisert i fagtidsskrifter.

Resultater

Pasientgruppene var ens med hensyn til alder og kroppsmasseindeks, men det var ulik kjønnsfordeling. Som forventet så vi mindre arrvevsdannelse i bukhulen hos de immunosupprimerte pasienter. Brokkene var også større i denne gruppen og disse pasienter var innlagt i lengre tid etter operasjonen. Seromdannelse, som er ansamling av væske under såret/i brokkhulen etter brokkoperasjon, er et stort problem ved åpen kirurgi, med hyppige infeksjonsproblemer. I vår studie var det færre tilfeller av seromdannelse i den transplanterte gruppen – og ingen infeksjoner i noen av gruppene. Det var ikke forskjell i tilbakefallsraten mellom gruppene (9.7% vs. 4.2%, $p=0.4$). Derimot var det en tendens henimot større andel pasienter med

frembuling av nett gjennom den tidligere defekt i den immunsupprimerte gruppen – en situasjon der nettet fortsatt holder mageinnholdet på plass i bukhulen, men tyter litt frem – som også kalles pseudobrokk. Denne tendens tilskriver vi dels at gruppen hadde større brokk enn kontrollgruppen, men også at de danner mindre sterkt bindevev. Dette var mest uttalt for menn og denne kjønnsforskjell er ikke rapportert tidligere. I studien var pasientene også tilfeldig fordelt til å lukke defekten eller ikke – og ved å lukke defekten så vi en tendens til mindre risiko for dette pseudobrokk.

Anbefalinger

Basert på resultatene anbefaler vi kikkhullskirurgi som den foretrukne metode ved operasjon for arrbrokk i en transplantert befolkningsgruppe. De store problemer med infeksjon synes eliminert i forhold til den åpne metode og en tilbakefalls rate på under 10% er svært tilfredsstillende i denne gruppen.

Studien “Laparoscopic repair of incisional hernia in solid organ-transplanted patients: the method of choice?”, Lambrecht JR et al” er publisert i tidsskriftet *Transplant International* d. 9. Mai 2014:

Transplant Int (2014), 27: 712–720, DOI: 10.1111/tri.12327

NETT SOM FOREBYGGELSE MOT BROKK VED UTLAGT TARM

Ved tilstander som kreft i nederste del av endetarmen og kronisk tarmbetennelse er det ofte nødvendig å lede tarmen ut gjennom bukveggen som permanent løsning. Utlagt tarm (stomi) gir relativt sjelden problemer som ikke kan løses ved hjelp av en spesialisert sykepleier, e.g. hudirritasjon, problemer med å feste posen (stomiposen) som samler opp avføringen samt inntrekning av tarmløpet som kan gi lekkasje. Ca. 10000 nordmenn lever med utlagt tarm og hvert år får ca. 2500 pasienter utlagt tarm i Norge.

Brokk ved siden av stomien

Mer enn 50% med utlagt tykktarm utvikler brokk ved siden av den utlagte tarm. Dette kan føre til deformering og problemer med å feste stomiposen, lekkasje samt gi smerter, tarmslyng og sosiale og kosmetiske gener. Problemene fører til at omtrent 1/4 av stomibrokk får behov for operasjon for denne tilstanden. Tilbakefallsraten etter operasjon for stomibrokk er dessverre også stor, men nye teknikker med kikkhullskirurgi og nett er lovende.

Forebyggelse

Tarmen kan føres ut gjennom bukveggen gjennom forskjellige muskellag, men ingen metode synes å bedre brokkrisiko vesentlig. Noen få og små studier, herunder 3 randomiserte, har vist effekt av forebyggende innlegging av nett rundt tarmløpet der den passerer bukens muskulatur, men mange kirurger har vært reservert mot å legge kunstnett i et forurenset område på grunn av frykt for betennelseskomplikasjoner. Samtidig har man fra tidligere sett innvokst nett gjennom tarmveggen med såkalte fistler og bylledannelse, men det er historiske resultater der nettene hadde helt andre kvaliteter enn de moderne kunstnettene vi nå benytter.

Studiens formål og metode

Med studien ønsket vi å undersøke om forebyggelse med nett ved anleggelse av permanent utlagt tarm virker forebyggende mot brokk ved siden av den utlagte tarm,

uten å påføre pasienter komplikasjoner. For å gjøre dette ble 60 pasienter inkludert i en prospektiv studie og tilfeldig utvalgt til å motta nett ved åpen operasjon (laparotomi) hvor permanent utlagt tykktarm var planlagt. Hovedparten av pasientene ble operert ved Radiumhospitalet – resten ved Sykehuset Innlandet i Gjøvik. Oppfølging var planlagt i 4 år, med klinisk undersøkelse og CT, hvor man også målte størrelsen på åpningen i bukveggen, med halvårsintervall første 2 år og heretter årlige kontroller.

Resultater og diskusjon

Forsøksgruppen med nett og kontrollgruppen var sammenliknbare i alder, kroppsmasseindeks (KMI), andre sykdommer, kjønnsammensetning, og tidligere brokksykdom. På grunn av grunnsykdommen var det stor dødelighet og kun 20 pasienter i hver gruppe overlevet til 3-års kontrollen. Det var ingen forskjell i komplikasjoner mellom gruppene. Seks % av pasientene i forsøksgruppen utviklet brokk ved stomien, hvorimot 46 % i kontrollgruppen fikk brokk ($p < 0,001$, Fishers exact test). I analyse justert for alder, KMI og størrelse på åpning i bukveggen ved første CT undersøkelse, var det i forsøksgruppen betydelig minsket risiko for brokk ved stomien (Odds Ratio (OR) 0,04; 95% konfidensinterval (KI): 0,00, 0,35) for alle inkluderte pasienter. Ved samme analyse på kun de som overlevet 3 år var det også mindre risiko for brokk (OR 0,04; 95% KI: 0,00, 0,68). Også ved justert levetidsanalyse var det reduksjon i risiko for brokk ved stomien i forsøksgruppen (Cox regresjon: Hazard Ratio 0,09; 95% KI: 0,02, 0,44). For å unngå ett brokk ved stomien må man legge inn nett på 2,5 pasienter (KI: 1,9, 6,9). Med vår studie økes antallet pasienter inkludert i publiserte randomiserte studier med ca. 50% og resultatene er sammenliknbare og støtter de tidligere studier.

Et annet funn fra CT kontrollene var at åpningen i bukveggen var konstant over tid i forsøksgruppen ($p=0,64$, related samples sign test), men økte i størrelse i kontrollgruppen ($p=0,003$). Størrelsesendring mellom gruppene var også signifikant ($p=0,001$, Independent samples t-test). Det interessante er at økning i åpningens størrelse kun var i undergruppen av pasienter med brokk ved klinisk undersøkelse. Nettet synes således å stabilisere bukveggen, så det er mindre risiko for brokk og dermed utvidelse av åpningen.

Konklusjon

I tråd med tidligere undersøkelser bekrefter dette randomiserte forsøk at nett i bukveggen, som omslutter tarmen ved konstruksjon av permanent utlagt tykktarm, beskytter mot brokkdannelse ved siden av tarmen gjennom denne åpningen i bukveggen. Det er ingen økt risiko for komplikasjoner ved bruk av nett i denne setting. Størrelses økning i åpningen i bukveggen over tid er forbundet med utvikling av brokk og nettet synes å stabilisere bukveggen. Pasienter som får permanent utlagt tykktarm bør få forebyggende nett.

Studien "Prophylactic mesh at end-colostomy construction reduces parastomal hernia rate: a randomised trial, Lambrecht JR et al" er offentliggjort i tidsskriftet *Colorectal Disease* d. 14. Juli 2015:

Colorectal Dis. 2015 Oct;17(10):O191-7, DOI: 10.1111/codi.13065

Errata list

Name of PhD candidate: Jan Roland Lambrecht

Title of Thesis: Anterior abdominal wall hernia in adults, Clinical studies on treatment and prevention

Abbreviations for correction types: Cor – correction, Celtf – change of page layout or textformat

May 27, 2016

Page	Line	Foot note	Original text	Cor type	Corrected text
6	14	1	Paper 2 (reprinted with permission from Springer)	Cor	Paper 2 (reprinted with permission from Wiley)
35	27		was	Cor	were
36	21		was	Cor	were
40	27		...i.e., overlap...	Cor	...i.e. overlap...
41	27		was	Cor	were
42	2		P	Cor	p
44	3		was	Cor	were
44	5		3	Cor	three
44	8		3	Cor	three
44	12		P	Cor	p
44	15		was	Cor	were
45	4		end-colostomy	Cor	end colostomy
45	9		P	Cor	p
45	17		P	Cor	p
46	15		was	Cor	were
46	18		nonclinical	Cor	non-clinical
46	19		2	Cor	two
48	4		Incisional hernias	Cor	IHs
84	1	1	(reprinted with permission from Springer)	Cor	(reprinted with permission from Wiley)
102	10	2	Laparoscopic ventral hernia repair: Impact of mesh fixation method on overall complications , prospective data and data <i>pooled with retrospective clinically controlled study data</i>	Cor	Laparoscopic ventral hernia repair: Impact of mesh fixation method on overall complications , prospective data

1: Error in reference of publisher for reprint permission, 2: Header error of table 6b in description of analyzed data

