UNIVERSITY OF
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SANNA KOUHIA

**COMPLICATION AND COST ANALYSIS OF
INGUINAL HERNIA SURGERY**
Comparison of Open and Laparoscopic Techniques

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of Inguinal Hernia Surgery

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ABSTRACT

Inguinal hernia repair is the most common elective surgical procedure, with over 20 million procedures performed worldwide every year. The aim of this study was to evaluate inguinal hernia surgery from the complications' and society costs' perspective.

Study I was a prospective randomized trial comparing open mesh repair to laparoscopic repair (47 + 49 patients, respectively) in the treatment of recurrent inguinal hernia. The laparoscopic group had faster recuperation from surgery compared to the open group (average convalescence 14.8 days *versus* 17.9 days, respectively, p=0.05), and suffered less from chronic pain symptoms (0.0% vs. 12.8% at three years follow-up, respectively, p=0.03).

Study II evaluated the possibility of preoperative magnetic resonance imaging (MRI) to diagnose the origin of intense pain in 22 patients to be operated for painful (visual analogue score (VAS) > 50/100) inguinal hernias. Changes in pain scores and quality of life (QoL) were measured after laparoscopic surgery for inguinal hernia. MRI was unable to diagnose the origin of pain, and thus to predict the outcome of surgery. Laparoscopic inguinal hernia repair significantly improved the patients' QoL and reduced pain. Four patients had prolonged pain at six months after surgery. These patients' preoperative pain scores were significantly higher, and QoL scores significantly lower than the scores in patients without prolonged pain symptoms.

Study III evaluated the prevalence of complications in inguinal hernia surgery using nationwide patient insurance registry data. Open non-mesh hernia repairs, open mesh repairs and laparoscopic repairs were compared. The complication data was available for 335 patients. Both laparoscopic and open non-mesh repairs were associated with significantly increased probability of complications, and these complications were more severe compared to complications after open mesh repairs. After open non-mesh repairs, recurrences and severe chronic pain were overrepresented, whereas after laparoscopic surgery, visceral complications, deep infections and major hemorrhagic complications predominated.

Study IV explored the total societal costs of inguinal hernia repair. Over a ten-year period, 458 laparoscopic repairs were compared to 528 open mesh repairs. All visits, treatment episodes and surgical procedures associated with the inguinal hernia treatment were identified from patient files, and their costs were calculated. Also costs from convalescence were calculated for employed patients. The in-hospital costs of laparoscopic repairs were significantly higher, but convalescence costs lower than respective costs of open mesh repairs. The total costs of a laparoscopic repair in an employed patient were 8,606 € as opposed to 9,042 € for open mesh repair (p=0.036).

In conclusion, this study indicated that endoscopic totally extraperitoneal (TEP) surgery is beneficial when operating a recurrence after open inguinal hernia surgery, and is less expensive than Lichtenstein operation. However, the risk of serious complications is elevated in laparoscopic surgery, and thus the surgeons' proper training and education play an important role in minimizing the risk of complications.

TIIVISTELMÄ

Nivustyräleikkaus on yleisin pehmytkudoskirurginen toimenpide, joita tehdään maailman-laajuisesti yli 20 miljoonaa vuosittain. Tästä johtuen pienetkin erot leikkaustekniikoiden välillä voivat olla yhteiskunnan kannalta merkittäviä. Tämän tutkimuksen tarkoituksena oli analysoida nivustyräleikkausten komplikaatioita ja niiden kustannuksia.

Ensimmäisessä osatyössä verrattiin satunnaistetusti avointa ja tähystystekniikalla tehtyä nivustyrän verkkokorjausta uusiutuneen nivustyrän hoidossa 96 potilaalla. Tähystysryhmän potilaiden sairausloma (14.8 päivää) oli merkittävästi lyhyempi kuin avoleikkausryhmän (17.9 päivää). Lisäksi tähystystekniikalla leikatuilla potilailla ilmeni merkittävästi vähemmän pitkittynyttä kipua, joka on yleisin nivustyräleikkauksen jälkeinen komplikaatio.

Toisessa osatyössä 22 voimakkaan kivuliaasta nivustyrästä kärsivää potilasta kuvattiin magneettikuvauksella ennen tähystysleikkausta, tarkoituksena selvittää kivun alkuperä. Lisäksi kyselyin selvitettiin koettua kipua ja elämänlaatua. Magneettikuvauksessa ei näkynyt tyrää lukuun ottamatta poikkeavuuksia, joten kivun alkuperän osoittaminen tai leikkaustuloksen ennustaminen ei kuvauksen avulla onnistunut. Elämänlaatu parani ja kipu väheni merkitsevästi tyräkorjauksen avulla, mutta neljällä potilaalla oli kipuja vielä puoli vuotta leikkauksesta. Heidän kipunsa oli ennen leikkausta selvästi voimakkaampi ja elämänlaatumittareiden pisteet matalammat kuin kivuttomilla verrokeilla.

Kolmas osatyö oli Potilasvakuutuskeskuksen rekisteritutkimus, jossa selvitettiin komplikaatioiden yleisyyttä kolmessa ryhmässä: avoin korjaus ilman verkkoa, avoin verkkokorjaus ja tähystysleikkaus. Yhteensä 335 komplikaatiota ilmoitettiin rekisteriin. Sekä tähystysleikkausten että avointen ommelkorjausten jälkeen komplikaatioita oli merkittävästi enemmän ja ne olivat seurauksiltaan vaikeampia kuin avointen verkkokorjausten jälkeen. Tähystysleikkausten jälkeen oli enemmän suolivaurioita, syviä tulehduksia ja verenvuoto-ongelmia, kun ommelkorjausten jälkeen tyrän uusiutumiset ja pitkäkestoinen kipu olivat tavallisempia komplikaatioita.

Viimeisessä osatyössä selvitettiin nivustyräleikkauksen kokonaiskustannuksia yhteiskunnan kannalta. Vertailtavana oli 458 tähystysleikkauksella ja 528 avoimella verkkokorjauksella hoidettua potilasta. Tähystysleikkaus oli sairaalahoidon osalta selvästi kalliimpaa, mutta työssäkäyvien potilaiden osalta pienemmät sairauslomakustannukset tasapainottivat korkeampia sairaalakustannuksia siten, että kokonaiskustannukset olivat pienemmät tähystysleikkauksella (8606€ tähystysleikkaus vs 9042€ avoleikkaus).

Yhteenvetona voidaan todeta, että tähystysleikkaus on hyödyllinen uusiutuneen nivustyrän hoitona, ja se on myös kokonaiskustannuksiltaan halvempi. Tähystysleikkauksiin liittyy kuitenkin suurempi riski vaikeisiin komplikaatioihin, joten kirurgien koulutus ja opetus on tärkeää komplikaatioiden minimoimiseksi.

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My mother, for your support through thick and thin. Without counting hours or distance, you have always been there for me. Words cannot express my gratitude.

My son Janne, for his unconditional love.

Helsinki, August 2016

Sanna Kouhia

List of the original publications

This dissertation is based on the following original publications:

I   Kouhia ST, Huttunen R, Silvasti SO, Heiskanen JT, Ahtola H, Uotila-Nieminen M, Kiviniemi VV, Hakala T. Lichtenstein hernioplasty versus totally extraperitoneal laparoscopic hernioplasty in treatment of recurrent inguinal hernia – a prospective randomized trial. *Ann Surg 249: 384-387, 2009.*

II   Kouhia S, Silvasti S, Kainulainen J, Hakala T, Paajanen H. Magnetic resonance imaging has no role in diagnosing the origin of pain in patients with overwhelmingly painful inguinal hernia. *Hernia 19: 557-563, 2015.*

III Kouhia S, Vironen J, Hakala T, Paajanen H. Open mesh repair for inguinal hernia is safer than laparoscopic repair or open non-mesh repair: a nationwide registry study of complications. *World J Surg 39: 1878-1884, 2015.*

IV   Kouhia S, Aro E, Paajanen H. Actual costs of Lichtenstein and laparoscopic inguinal hernia repairs in a non-randomized study. Submitted.

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Contents

Abbreviations

ASA	American Society of Anesthesiologists
BHS	British Hernia Society
BME	Bone marrow oedema
BMI	Body mass index
CPIP	Chronic Postoperative Inguinal Pain
CT	Computed Tomography
EHS	European Hernia Society
FPIC	Finnish Patient Insurance Centre
IPOM	Intra-Peritoneal Onlay Mesh
LAP	Laparoscopic
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic Resonance Imaging
OM	Open Mesh
OS	Open Sutured (non-mesh)
RAND-36™	RAND 36-Item Health Survey (by RAND Corporation)
RCT	Randomised Controlled Trial
QALY	Quality-Adjusted Life-Year
QoL	Quality of Life
SD	Standard Deviation
SPSS®	Statistical Package for the Social Sciences
STIR	Short Tau Inversion Recovery or Short T1 Inversion Recovery (MRI sequence)
TAPP	TransAbdominal PrePeritoneal hernioplasty
TEP	Totally ExtraPeritoneal hernioplasty
US	Ultrasonography
VAS	Visual Analog Scale

Introduction

Inguinal hernia has been present in the human history from the very beginning. The first literary description of an inguinal hernia can be dated to ca. 1555 BC. The Ebers Papyrus described inguinal hernia as a swelling that comes out during coughing. Also Hippocrates (460-375 BC) mentions hernias of the umbilical and pubic region in his writings.

The first anatomical cadaver studies containing information about the inguinal canal were those by Galen ca. 150-200 AD. Galen studied pigs and monkeys, and in spite of this limitation, his knowledge of the inguinal canal anatomy was considered valid until 1543, when Andreas Vesalius published his book on human anatomy, *De Humani Corporis Fabrica* (On the Fabric of the Human Body). The Renaissance is therefore considered to end the first of five eras in inguinal hernia history.

The second era of inguinal hernia history is mainly to be credited for advances in understanding the anatomical structure of the inguinal canal and inguinal hernias. Despite these achievements, the treatment of inguinal hernias did not flourish. It was not until the late 1800s that the first descriptions of real surgical techniques emerged, and the third era of inguinal hernia history began; the era of hernia repair under tension. The first attempts to reduce the hernia opening were recorded by Marcy (1871), Steele (1874) and Czerny (1887) (Legutko et al 2008, Van Hee 2011). However, an Italian surgeon Eduardo Bassini, was the first surgeon to describe a surgical technique to reconstruct the posterior wall of the inguinal canal, a surgical procedure known today as the Bassini hernioplasty. The technique was introduced in 1884, but published between 1887 and 1889 in Italian and 1890 in German (Bassini 1887, Bassini 1888, Bassini 1889, Bassini 1890). The Bassini technique became accepted outside Italy only during the 1890s.

The next significant advances in inguinal hernia surgery happened in 1940s, when Chester McVay together with Barry Anson in 1942, and Edward Shouldice in 1945 developed repair methods eponymously known today. Both these techniques emphasize the role of tranversalis fascia in hernioplasty, and tension was reduced by making relaxing incisions. These technical modifications substantially decreased the incidence of hernia recurrence, and thus mark the beginning of the fourth era in inguinal hernia history.

Techniques using fascia grafts to close large defects and recurrent hernias had been described in the beginning of 1900s by famous surgeons such as Halstedt (1903) and Kirschner (1908). The discovery of synthetic polymers in 1930s provided hernia surgeons with yet another reconstructive option: the use of alloplastic material in the form of mesh. These materials were first used by Stock (1954) and Usher (1962). It was Sir Francis Usher, who originally discovered the suitable properties of polypropylene (Marlex®) mesh already in 1950s, and worked tirelessly with chemists and engineers to produce the hernia mesh with optimal properties. He also made numerous experiments in implanting Marlex® meshes to both sterile and contaminated environments (Read 1999). Placing the mesh preperitoneally was described by Rives (1965) for unilateral and Stoppa (1968) for bilateral inguinal hernias.

The beginning of the fifth era of inguinal hernia history – the era of tension-free repair – is credited to Irving Lichtenstein, who described an open anterior hernioplasty with Marlex® mesh in 1970. The results of the first 1,000 operations were astonishing with no recurrences over a 5-year follow-up period. The technique relied on reinforcing the posterior wall of the inguinal canal with prosthetic material. This method remains unchanged until the present day, and has been considered the gold standard of inguinal hernia surgery against which all other techniques are compared and validated.

In inguinal hernia history, the laparoscopic techniques are usually included in the fifth era of tension-free repairs. However, it may be justified to state, that laparoscopic repairs initiated the sixth era of inguinal hernia history – the era of mini-invasive repairs. Laparoscopy was first introduced in the early 20th century as a technique that facilitated exploring the abdominal cavity without the significant morbidity of performing a laparotomy. The first physicians to use laparoscopy were the gynecologist von Ott, the gastroenterogist Kelling, and the

gastroenterologist Jacobaeusc. In 1901, von Ott examined the abdomen of a pregnant woman in Russia and Kelling performed an experimental laparoscopy to a dog in Germany. Until 1910, Jacobaeusc had performed around a dozen laparoscopies for Swedish patients with ascites. During the first decades the use of laparoscopy and its' achievements were of little importance, until in the 1970s when gynecologists and surgeons became increasingly interested in the possibilities of laparoscopy. The first laparoscopic inguinal hernia repair is credited to Dr. P. Fletcher of the University of West Indies, who successfully closed the hernia opening of an indirect inguinal hernia by using metallic clips in November 1979. The first 20 patients operated for inguinal hernia laparoscopically using mesh plug repair were reported by Schultz in 1990. Today, three different laparoscopic techniques have been established for laparoscopic inguinal hernia repair: the intraperitoneal onlay mesh repair (IPOM), the transabdominal preperitoneal mesh repair (TAPP) and the totally extraperitoneal preperitoneal mesh repair (TEP).

In short, the surgical intervention for inguinal hernias has developed from a life-saving procedure for incarcerated hernias into elective ambulatory surgery in just over a century. Inguinal hernia surgery is the most common elective procedure in general surgery today, with over 20 million hernioplasties performed each year worldwide, and over 10,000 in Finland. Thus the importance of short- and long-term surgical outcomes, minimizing complications and perfecting cost-effectiveness cannot be underestimated.

This study aims at exploring prevalence, prediction, treatment and costs of complications in inguinal hernia surgery with a special focus on laparoscopic surgery. Complication profiles and their costs are compared between treatment modalities.

2 Review of the literature

2.1 DIAGNOSIS OF INGUINAL HERNIA

2.1.1 Physical examination

The description of an inguinal hernia from the Ebers papyrus is still valid, and the most common way of diagnosing an inguinal hernia is visual inspection and palpation. Typical palpation finding is a soft protrusion which enlarges when the patient coughs. In supine position, the hernia is usually easily reduced, either spontaneously, or with only a little pressure on the hernia. The patients themselves most often recognize the bulging in the groin as a hernia. A reliable clinical test for small hernias is performed with the patient in an upright position, and the physicians' index finger pressed against the external opening of the inguinal canal through scrotum. When the patient coughs, a hernia impulse from the protruding hernia can be palpated in the inguinal canal. Sometimes the patients present only with pain but no visual or palpable bulge especially in obese patients, or the bulge is not a typical hernia; it is irreducible, there is no hernia impulse on provocation, or the consistence of the bulge is atypical. In these circumstances additional imaging may be needed. Differential diagnoses include, for example, lymph node enlargement, aneurysm, soft-tissue tumors, abscess, ectopic testis, adductor tendinitis, pubic osteitis, hip arthrosis, ileopectineal bursitis, and radicular low back pain (Simons et al. 2009).

2.1.2 Herniography, ultrasonography and computed tomography

Radiological imaging may be needed in cases where the diagnosis of a hernia is not evident in clinical examination. Traditional herniography has the longest history in revealing occult hernias (Robinson et al. 2013). Positive herniographies may detect hernias in many asymptomatic patients, as the inguinal canal may remain open and the contrast medium demonstrates an incipient hernia with no clinical significance, as demonstrated by radiological and laparoscopic studies (Paajanen et al. 2006). Injecting the contrast medium blindly into the abdominal cavity harbors a risk of visceral perforation and allergic reactions to contrast medium, both of which could be fatal (Ekberg 1983). Ultrasonography (US) examination has been proposed as an alternative, since it is a dynamic and virtually risk-free modality, but since it is largely operator-dependent, concerns about broader applicability have been raised (Light et al. 2011). Computed tomography (CT) has been proposed as an accurate tool in inguinal hernia diagnostics (Harrison et al. 1995), but it has the obvious disadvantage of radiation exposure.
A systematic review and meta-analysis of imaging in occult hernias was performed in 2013 (Robinson et al. 2013). The conclusion was that the sensitivity and specificity are 86% and 77% for ultrasonography, 80% and 65% for computed tomography, and 91% and 83% for traditional herniography. Based on these values, the authors suggested herniography as the first line examination in cases of suspected hernias. US should be used if herniography is not available, and, if diagnostic uncertainty persists, magnetic resonance imaging (MRI) should be considered. However, the authors did not consider the possible detection of other pathologies in the groin region. The European Hernia Society (EHS) guidelines suggest ultrasound (US) as the first line examination, if expertise is available. MRI is recommended as a second-line examination, whereas herniography only follows MRI in diagnostic order (Simons et al. 2009).

2.1.3 Magnetic resonance imaging

The literature on MRI in inguinal hernia diagnostics is scarce and inconclusive. Until early 2015, less than 20 articles examining the use of MRI in inguinal hernia diagnostics have been published. Excluding editorials, case reports and reviews on the radiologic anatomy of the inguinal area,

only ten articles thus far have evaluated MRI in inguinal hernia diagnostics. The first mention of MRIs capability in inguinal hernia diagnostics is from 1989. This publication merely states that MRI enables the visualization of epigastric vessels, and thus allows the differential diagnosis between an indirect and a direct inguinal hernia (Wechsler et al. 1989). There have been two time spans with more enthusiasm on studying MRI, the first between 1997 and 2000, and the second beginning in 2013.

The first phase of publications is mainly credited to a group of Dutch radiologists and surgeons (van den Berg et al. 1997, van den Berg et al. 1998, van den Berg et al. 1999, van den Berg et al. 2000). They used 0.5 T MRI and described an imaging protocol utilizing four sequences with the patient in supine position; T1, T2 and two dynamic sequences (i.e., imaging during Valsalva manoeuver). These sequences were used both pre- and postoperatively with success. At the same time a Swedish group advocated the use of T1, STIR, and MRCP sequences in a 1.5 T MRI with the patient in a prone position with arms raised (Leander et al. 2000). They were able to identify only 8/11 hernias demonstrated in traditional herniography, but also identified inflammatory findings in the pubic symphyses of three patients. These inflammatory findings were interpreted as *osteitis pubis* and its early forms.

From 2013 onwards, five publications have addressed the use of MRI with inguinal hernia. Instead of describing the sequences used, recent research has focused on visualizing the mesh postoperatively. A German research group has used iron-embedded meshes in TAPP repair of inguinal hernia, and the mesh's postoperative visualization, shrinkage and folding pattern was investigated in gradient echo sequences in 1.5 T MRI (Hansen et al. 2013, Ciritsis et al. 2014, Hansen et al. 2015, Ciritsis et al. 2016). In addition, one report has retrospectively evaluated the sensitivity and specificity of US, CT and MRI (Miller et al. 2014). This report concludes that in case of a suspected hernia, MRI is preferable to both US and CT owing to its better sensitivity and specificity to detect occult hernias. Table 1 summarizes the sensitivity and specificity values of different imaging modalities.

Table 1. Sensitivity and specificity of imaging modalities in inguinal hernia diagnostics (van der Berg et al. 1999, Robinson et al. 2013, Miller et al. 2014).

Subgroup	Modality	Sensitivity	Specificity	Positive predictive value*	Negative predictive value*
All hernias	US	0.56 – 0.93	0 – 0.82	1.00	0
	CT	0.77 – 0.83	0.25 – 0.83	0.96	0.04
	MRI	0.75 – 0.91	0.92 – 0.96	0.97	0.79
Occult hernias	US	0.33 – 0.86	0 – 0.77	1.00	0
	CT	0.54 – 0.80	0.25 – 0.65	0.86	0.06
	MRI	0.75 – 0.91	0.92 – 0.96	0.95	0.85

US=ultrasonography; CT=computed tomography; MRI=magnetic resonance imaging
* according to Miller et al. 2014

To date, only three publications have attempted to correlate MRI findings with pain symptoms or surgical outcome (Aasvang et al. 2009, Hansen et al. 2015, Burgmans et al. 2016). Based on these studies, postoperative inguinal MRI findings, such as oedema and spermatic cord calibre increase, do not correlate with the intensity of pain (Aasvang et al. 2009, Burgmans et al. 2016). In addition, postoperative mesh shrinkage and folding pattern do not correlate with pain symptoms after TAPP repair (Hansen et al. 2015). MRI has also been criticized for poor interobserver agreement (Aasvang et al. 2009), although systematic collaboration between surgeons and radiologists has been shown to be beneficial in improving the interobserver agreement (Amid 2009). More recent reports have presented better interobserver agreement reaching excellent in some aspects (Burgmans et al. 2016).

Until now, no studies have been made attempting to correlate preoperative MRI findings with hernia symptoms.

Although scientific evidence of MRI in inguinal hernia diagnostics is scarce, this is not the case for reports of MRI findings in the groin region in general. During the last decade, chronic inguinal pain syndrome known as "sportman's hernia" or "athletic pubalgia" or "inguinal disruption" has been intensely studied, and numerous imaging findings typical to this entity have been described (Sheen et al. 2014). Typical MRI findings in athletic pubalgia include bone marrow oedema (BME), osteitis pubis, tendon disruption and fluid in the symphysis (Figure 1). Also asymptomatic athletes present with similar findings, especially with milder forms, and the findings' association to pain is somewhat unclear (Robinson et al. 2004, Paajanen et al. 2008). Nevertheless, it has been shown that the presence on bone marrow oedema may predict the immediate recovery from athletic pubalgia after endoscopic surgery (Kuikka et al. 2015). MRI has not been used to evaluate the origin of pain in patients with painful inguinal hernias, thus, it is currently not known, whether the pain may be explained by similar findings as detected in patients with inguinal disruption, and if the presence of these findings may predict the postoperative course in these patients.
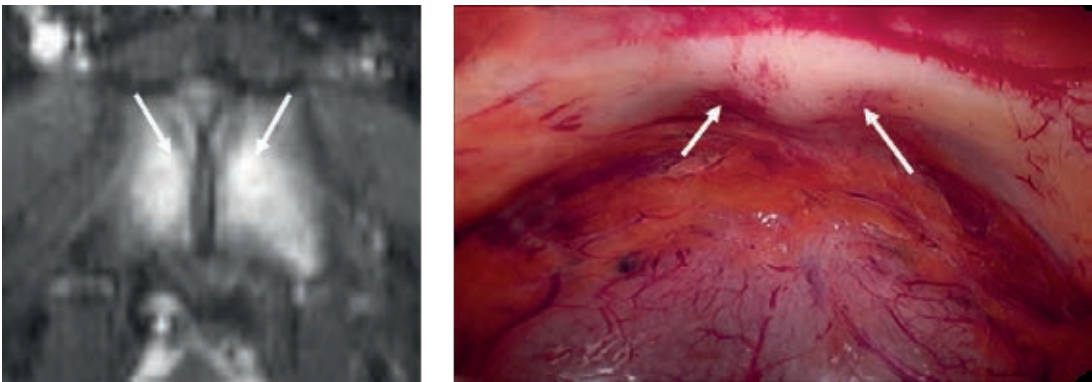
Figure 1. Oedema of the pubic symphysis (white arrows) in an elite athlete undergoing TEP surgery for sportman's groin. © Hannu Paajanen

2.2 CONSERVATIVE AND SURGICAL TREATMENT

2.2.1 Conservative treatment

Traditionally, the existence of an inguinal hernia has been seen as an indication for surgery. Recently conservative treatment ("watchful waiting") has been recommended for asymptomatic or minimally symptomatic inguinal hernia by some authors, especially in older patients with significant comorbidities and increased risks associated with administration of anesthesia (Fitzgibbons et al. 2006, O'Dwyer et al. 2006, Miserez et al. 2014). However, after a follow-up of seven years or more, between 62% and 79% of the observed patients cross over to surgical treatment, mainly owing to development of symptoms (Chung et al. 2011, Fitzgibbons et al. 2013). Although the first reports found no significant increase in emergency repairs associated with watchful waiting, a retrospective analysis in a less selected population found a 59% increase in emergency procedures, which were also associated with increased morbidity and mortality (Hwang et al. 2014). Thus, watchful waiting may in fact add to morbidity, mortality, and costs of inguinal hernia treatment.

2.2.2 Operative treatment

The surgical treatment of inguinal hernias began to flourish after the widespread use of general and local anesthesia in the latter half of the 19th century. The techniques discovered then were pure tissue repairs, whereas the use of synthetic material to reinforce the repair became feasible only during the 20th century. Since then, a vast array of different inguinal hernia repair methods has been presented, without a single method being superior to all others.

A structured overview of possible surgical techniques for inguinal hernia repair is presented in Figure 2. In addition to these groups, the ONSTEP technique lies between groups 2 and 3. The advocates of this technique promote the method, since all hernias openings can be covered with a 3-4 cm incision, the operating time is short, and there is no long learning curve of laparoscopic repairs (Lourenço and da Costa 2013). However, since the mesh is placed both in the anterior and posterior planes, the repair of a potential recurrence may be more difficult than after a simple anterior or posterior approach.

	Group 1	Group 2	Group 3	Group 4
Technique	Bassini Shouldice McVay/ Lotheisen Kirschner Zimmerman	Lichtenstein Mesh plug (Rutkow) (Gilbert) PHS	Rives Stoppa Wantz Nyhus TIPP Ugahary	TAPP TEP IPOM
Access	open			endoscopic
Prosthesis	none	mesh		
Localization of prosthesis	-	anterior	posterior	

Figure 2. A structured overview of surgical techniques to repair an inguinal hernia (Schmedt et al. 2005). Reproduced with the permission of Springer Science + Business Media. PHS=Prolene Hernia System®; TIPP=transinguinal preperitoneal repair; TAPP=transabdominal preperitoneal repair; TEP=totally extraperitoneal preperitoneal repair; IPOM=intraperitoneal onlay mesh.

2.2.2.1 Bassini hernioplasty

Introduced by Eduardo Bassini in 1884 and published in 1887 (Bassini 1887), this technique remains in use more than a century later, especially in resource-limited settings (Kassab et al. 2013, Savoie et al. 2014). Some authors state that the Bassini hernioplasty only carries historical status, and should not be used in current practice (Bittner and Schwarz 2012). Nevertheless, many surgeons consider the Bassini hernioplasty useful in adolescents and young adults, in cases of incarcerated hernia, and also if the patient does not want foreign material to be used in the repair. Despite the criticism faced by this technique by some authors, it has been used up to recent years with success (Osifo and Amusan 2010).

The surgical technique itself has remained largely the same for over a century. An inguinal incision is performed, the hernia dissected and reduced. A medial hernia sack is inverted, but a lateral sack is usually resected. After hernia reduction, the posterior wall of the inguinal canal is reconstructed. All three tissue layers are approximated using a single row of interrupted sutures. The transversalis fascia, the transversus abdominis muscle and the internal oblique muscle are sutured together with the inguinal ligament, thus also reconstructing the internal inguinal ring (Figure 3). The original description of the technique utilized non-absorbable sutures. The Bassini hernioplasty has also been made with slowly absorbable sutures (polyglycolic acid), but this has resulted in more recurrences than using non-absorbable sutures (12.8% vs. 8.7%, Kux et al. 1994).

Several modifications of the Bassini hernioplasty have been described. For example, the so-called "American Bassini" omits the incision of the transversalis fascia, and thus only two layers of tissue are approximated with sutures. The American Bassini is in fact more commonly used than the original Bassini hernioplasty, although it is claimed to have inferior results (Fitzgibbons et al. 2003).
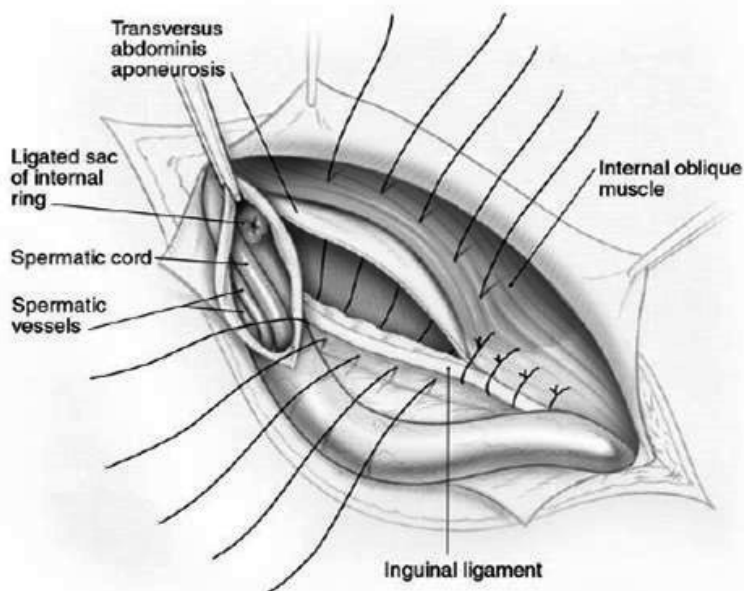
Figure 3. Bassini hernioplasty (Wartz 1989). Reprinted with permission from the Journal of the American College of Surgeons, formerly Surgery Gynecology and Obstetrics.

2.2.2.2 Shouldice hernioplasty

This technique, as described by Edward Shouldice in 1952, utilizes the concept of reconstructing the posterior wall of the inguinal canal, as suggested by Bassini. However, the repair is more complex and consists of four layers of continuous sutures. The first two layers consist of the divided transversalis fascia, and the lateral flap of the cremaster muscle sutured to the inguinal ligament (Figure 4a). The third and fourth layers of the repair are made by suturing the external/internal oblique muscle and the conjoined tendon to the inguinal ligament to cover the medial portion of the repair (Figure 4b). Traditionally, the Shouldice repair is made with stainless steel wire, but may be substituted with 3-0 polypropylene suture (Fitzgibbons et al. 2003, Chan and Chan 2006). The Shouldice hernioplasty is still used today, as demonstrated by the success of the technique in the Shouldice Clinic in Canada with approximately 1% recurrence rate (Chan and Chan 2006). However, in the hands of surgeons less dedicated to the Shouldice technique, the recurrence rate is around 6% in 5 years (Hay et al. 1995). Also, over 10% recurrence rates have

been reported with a long-term follow-up of 10 years (Junge et al. 2006). Because of the more complex structure of the repair, the Shouldice repair has a longer learning curve than the Bassini hernioplasty or anterior mesh plasties. Thus its role has been diminishing, and in many surgical units, it has almost completely been replaced by the anterior tension-free techniques.
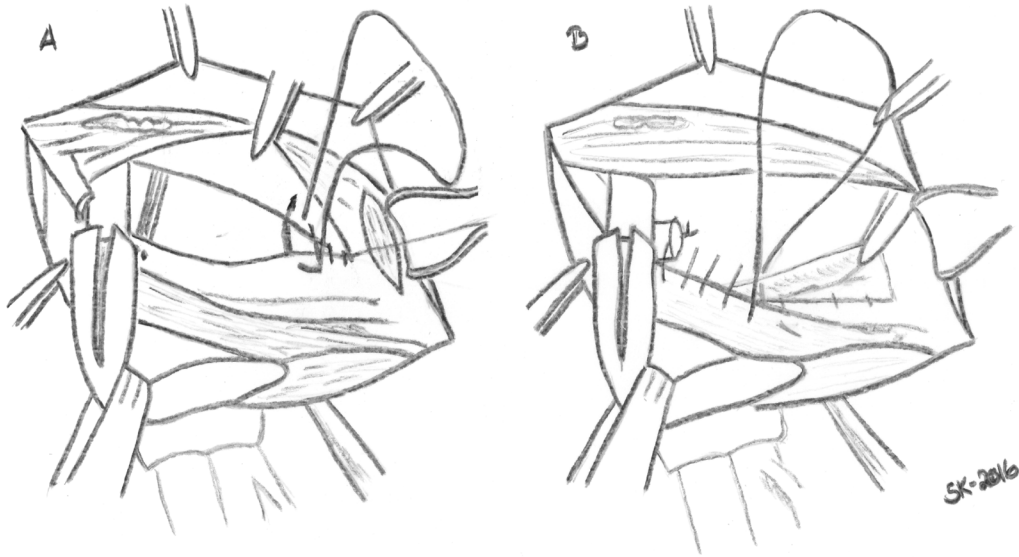
Figures 4a and 4b. Shouldice hernioplasty. Figure 4a depicts the first suture of Shouldice repair, completing the first and second layers of the repair. Figure 4b depicts the second suture and completion of the third and fourth layers of the Shouldice repair.

2.2.2.3 Lichtenstein hernioplasty
Introduced by Irving Lichtenstein in 1970, the Lichtenstein hernioplasty started the fifth era of inguinal hernioplasty – the era of tension-free repair. The original description of the technique utilized Marlex® mesh, and the reported results were astonishing with no recurrences in 1,000 patients after a follow-up exceeding 5 years (Lichtenstein et al. 1989). The method has been shown to be relatively simple and the learning curve short (Danielsson et al. 1999). After the inguinal incision and hernia dissection, a piece of polypropylene mesh is placed over the defect and sutured to the inguinal ligament and internal oblique muscle and its aponeurosis, thus recreating the posterior wall of the inguinal canal (Figure 5a). Mesh overlapping of minimum 2 cm to the pubic bone has to be achieved in order to avoid the most common type of recurrence, a medial recurrence (Amid et al. 1995). For the spermatic cord, the lateral part of the mesh is divided into two tails that cross around the spermatic cord and thus reform the internal inguinal ring (Figure 5b).
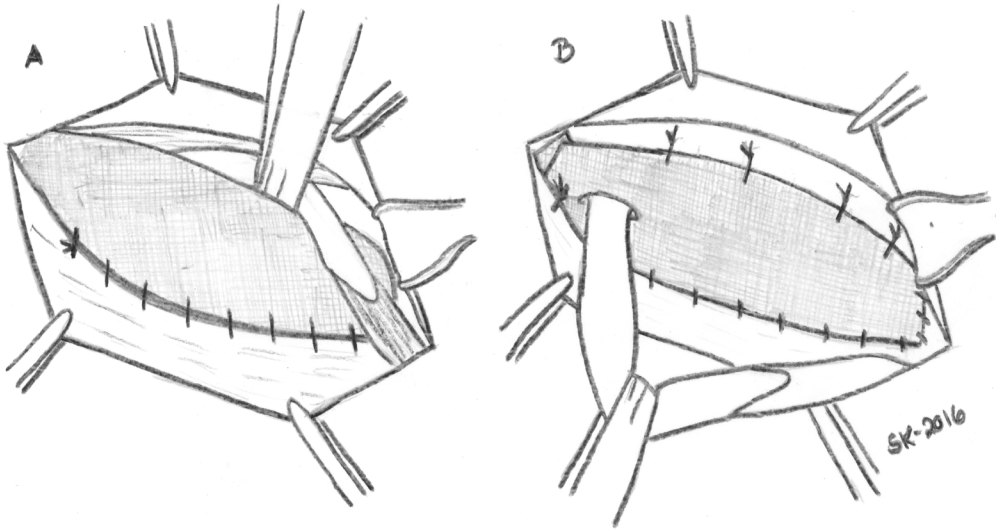
Figures 5a and 5b. Lichtenstein hernia repair.

2.2.2.4 Laparoscopic hernioplasties (TAPP and TEP)

Two main approaches to laparoscopic or endoscopic repair of inguinal hernia are in use today: transabdominal preperitoneal repair (TAPP) and totally extraperitoneal repair (TEP). Earlier, intra-peritoneal onlay mesh (IPOM) was also used, but owing to higher rates of recurrences and other complications, in today's practice it is mainly used only in complicated cases with preperitoneal fibrosis or multiple recurrences, where TAPP or TEP are not viable options (Tran et al. 2014, Hyllegaard and Friis-Andersen 2015). Nomenclature of the laparoscopic techniques is not uniform: it has been suggested that the term "laparoscopic" should be reserved for TAPP, and TEP should be referred to as "endoscopic" or "video-assisted" hernioplasty. However, since the majority of published data include both TAPP and TEP in the category of laparoscopic repairs, the same term will be used here.

In both TAPP and TEP, the mesh is placed in the preperitoneal space, the difference of these techniques is the approach to the preperitoneal space (Figure 6a). In TAPP, a pneumoperitoneum is established, as in other intra-abdominal laparoscopic procedures, the peritoneum is opened followed by the dissection and placement of mesh. At the end of the procedure, the peritoneum is closed over the mesh repair, and desufflation of the abdominal cavity performed. In TEP operations the abdominal cavity is never entered. The preperitoneal space is reached from between the rectus abdominis muscle and the posterior rectus sheath, and insufflation performed completely in the preperitoneal space (Figure 6b). In both techniques, the peritoneum together with the hernia sac is then dissected away from the anterior abdominal wall, Cooper's ligament and the psoas muscle. The dissection is extended laterally to the anterior iliac spine, and caudally beyond the ileopubic tract. Important preperitoneal anatomical landmarks are depicted in Figure 6c. A wide dissection ensures that all potential hernia openings are covered with mesh, and also enables the use of large enough mesh without the risk of mesh folding. A piece of mesh, usually 10 x 15 cm size, is placed over hernia openings, and either fixed with staples or glue, or left unfixed if the correct placement and sufficient overlap of hernia openings is achieved (Teng et al.
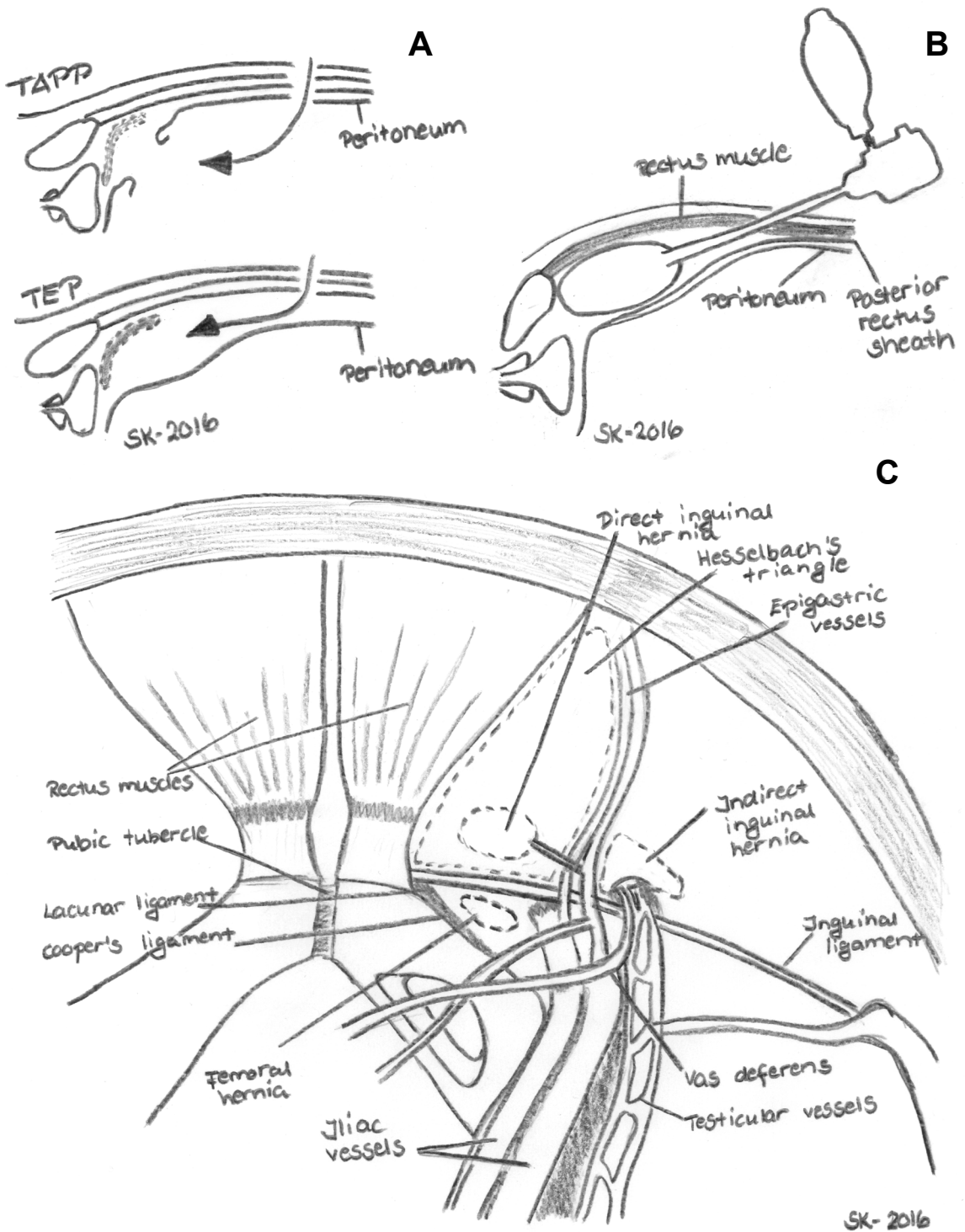
Figures 6a-c. Laparoscopic hernia repairs. Figure 6a shows the difference in the approach between TAPP and TEP. Figure 6b illustrates the insufflation of the preperitoneal space in TEP repair. Figure 6c depicts the important anatomical landmarks in laparoscopic hernia repairs.

2011, Kaul et al. 2012, Sajid et al. 2012, Sajid et al. 2013a). Also self-adhesive meshes have recently been used (Mangram et al. 2014).

Both TAPP and TEP are acknowledged today as appropriate options for laparoscopic inguinal or femoral hernia repair, and both techniques have their own advocates. TEP is criticized for a longer learning curve than TAPP, but TAPP harbors an increased risk for intra-abdominal organ injury (Edwards and Bailey 2000, Neumayer et al. 2004, Wake et al. 2005). In Finland and Sweden, over 90% of laparoscopic repairs are performed with the TEP technique (P. Nordin and H. Paajanen, personal communications).

2.2.2.5 EHS guidelines

The European Hernia Society published guidelines on the treatment of inguinal hernia in adult patients in 2009 (Simons et al. 2009), and updated the guidelines in 2014 (Miserez et al. 2014). The recommendations for hernia repair techniques were given in 2009, and the update in 2014 did not change the basic recommendations. Watchful waiting strategy can be considered for asymptomatic or minimally symptomatic inguinal hernias, but bearing in mind, that approximately 70% of the patients will eventually need surgical treatment owing to development of symptoms. The guidelines committee suggests that TEP repair should be preferred over TAPP for laparoscopic repairs. For primary hernias (both unilateral and bilateral), the guidelines suggest either Lichtenstein repair or endoscopic approach, if endoscopic expertise is available. For recurrent hernias, the previous mesh repair method should be taken into consideration. If the previous repair was anterior, an open or endoscopic preperitoneal approach should be used, whereas a recurrence after a previous posterior surgery should be treated with anterior technique (Simons et al. 2009). The update in 2014 added, that for recurrences after conventional sutured hernioplasties an endoscopic approach is preferred owing to faster convalescence and significantly less chronic pain (Miserez et al. 2014). For female hernias, an endoscopic approach should be considered, since the risk of a femoral hernia is greater, and females are at a greater risk of chronic pain, but the grade of evidence is only D (Simons et al. 2009).

2.3 OUTCOMES OF INGUINAL HERNIA REPAIR

2.3.1 Duration of surgery and length of hospital stay

Laparoscopic inguinal hernia repairs have been criticized for the longer duration of surgery and thus claimed to be less cost-effective than open mesh hernioplasties. The criticism is mainly attributed to the data collected in randomized controlled trials (RCTs) in the 1990s, which were summarized in a Cochrane review (McCormack et al. 2003). The lost operating room (OR) time was estimated to be around 15 minutes on average compared to mixed open procedures. Since the learning curve for laparoscopic repairs is long, it can be speculated, as to whether the data from the 1990s are still valid in todays practice or not.

Figure 7 summarizes the operative times from randomized controlled trials comparing open mesh and laparoscopic procedures in a two-decade time span (total number of patients 7,128). It is clear, that the operative times for both open and laparoscopic procedures vary greatly. In addition, most of the trials do not define the competence of the participating surgeons for each procedure. In many studies the operative time for laparoscopic repairs is in fact shorter than that of the open mesh repair (Lau et al. 2006, Butler et al. 2007, Dahlstrand et al. 2013). It is also widely debated, whether the duration of operation for bilateral hernia is shorter when utilizing the laparoscopic method. Naturally, the number of operating surgeons in open procedures and the surgeons' expertize plays an important role regarding the duration of the bilateral procedure.
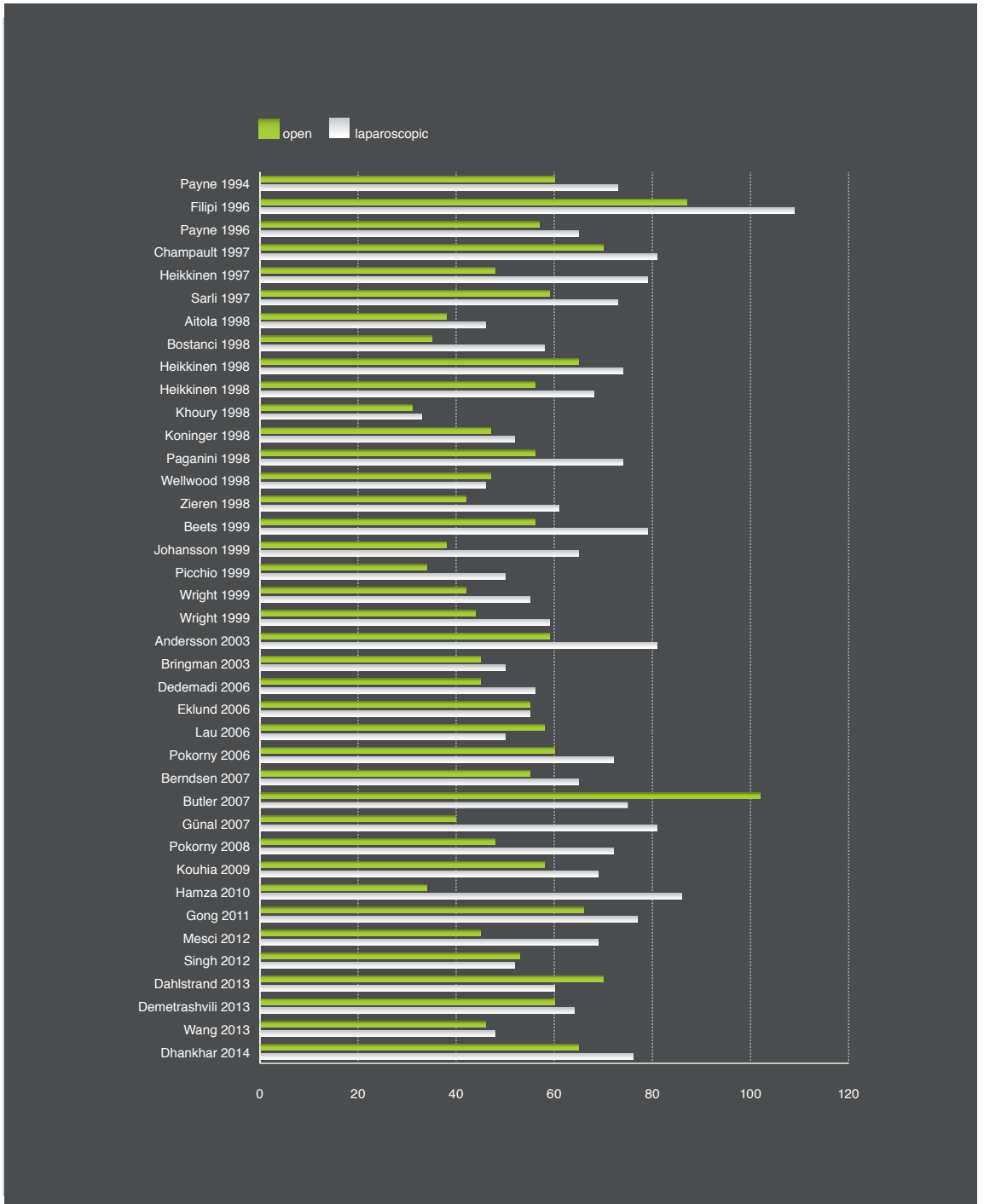
Figure 7. Operative times in minutes for open and laparoscopic hernia repairs in RCTs between 1994 and 2014.

The length of hospital stay (LOS) has been regarded as an important cost factor in hernia surgery, mainly because the patient volume is large, and even small differences in LOS may therefore result in significant economical differences between the surgical methods. Major variations in LOS exist between different surgical units and countries, since the local practices, treatment cultures and patient expectations may be more influencial factors than the clinical course alone. In the Cochrane review, mean length of stay is between 0 and 9.46 days for open inguinal hernia repairs, and between 0 and 8.17 days for laparoscopic repairs (McCormack et al. 2003). Based on the available data, mainly from the 1990s, the shorter length of stay has been seen as an advantage of the laparoscopic methods. However, in current practice, most inguinal hernia repairs are ambulatory procedures in many countries including Nordic countries irrespective of the technique used (Eklund et al. 2010, Aly et al. 2011).

Therefore, significant scope for speculation remains on the potential benefits on reduced operative time and hospital stay, because the duration of surgery and length of stay may reflect local practices and surgeons' expertize more than the impact of the procedure.

2.3.2 Early postoperative outcome

The amount of early pain is often measured in conjunction with measuring the return to normal activities or convalescence from work. The results are mainly derived from earlier RCTs, with approximately 75-80% of the trials showing statistically significant difference in pain scores and/or early analgesic requirements favoring laparoscopic approach (EU Hernia Trialists Collaboration 2000, Anderson et al. 2003, Eklund et al. 2006). The more recent RCTs usually do not measure early pain scores as intently as the early trials, possibly owing to the convincing evidence provided by the prior publications.

2.3.3 Duration of convalescence

Shorter convalescence has been regarded as an advantage of minimally invasive techniques such as laparoscopic inguinal hernia repair. The average difference favoring laparoscopic repairs is approximately one week, 14.8 versus 21.4 days (McCormack et al. 2003, Schmedt et al. 2005). However, marked heterogeneity remains between studies, with sick leaves between 5 and 46 days for laparoscopic, and between 7 and 43 days for open mesh repairs (Schmedt et al. 2005). More recent meta-analyses present savings of only 3 to 5 days of convalescence (Aly et al. 2011, Bobo et al. 2014). It has been speculated, that, similarly to the length of hospital stay, the duration of sick leave may reflect social, cultural and economic differences, since together they are more influencial factors than clinical recovery.

2.4 COMPLICATIONS

2.4.1 Minor complications

Minor complications include superficial or wound infections, haematoma and seroma, and several miscellaneous complications not limited to hernia surgery, such as urinary retention, deep vein thrombosis and pneumonia. These complications do not usually require major interventions. They can often be treated without readmission and they rarely have long-term harmful consequences.

2.4.1.1 Haematoma / seroma

The prevalence of haematomas in RCTs is between 10.5%-16.0% for open and 8.6%-13.1% for laparoscopic repair, significantly favoring the laparoscopic approach (McCormack et al. 2003, Schmedt et al. 2005). However, in registry data, the prevalence of haematomas is significantly lower, approximately 3.3% for laparoscopic, 3.5% for open anterior mesh and 4.4% for open preperitoneal mesh repairs (Lundström et al. 2012). In the registry data haematoma was defined

as bleeding causing significant tissue distension, and thus the RCTs may be reporting such hematomas that do not carry any clinical significance.

Inguinal hernia surgery is considered minor surgery, and thus also many patients with anticoagulative or anti-platelet medication undergo inguinal hernia repairs. There is limited evidence on the perioperative continuation of these medications in the context of non-cardiac surgery. The continuous use of acetylsalicylic acid has not been associated with an increased risk of haemorrhagic complications in a pilot study (Antolovic et al. 2012). Also, no increased risk has been noted with the use of clopidogrel in a retrospective study (Chu et al. 2011). Some evidence about the safety of continued warfarin therapy exists; studies suggest a slightly increased or similar risk of wound haematoma in patients continuing warfarin therapy during hernia surgery. (McLemore et al. 2006, Sanders et al. 2008, Smoot et al. 2008, Stucky et al. 2015). All these reports are limited by either the retrospective nature of the study, or the small number of patients.

Some surgeons use compression during the immediate postoperative period to reduce the likelihood of a haematoma, but this method is empiric and has not been subjected to controlled studies.

The frequency of seromas is 3.8%-8.9% after open and 5.8%-12.2% after laparoscopic repairs, favoring open surgery (McCormack et al. 2003, Schmedt et al. 2005). However, there is evidence that when operating recurrent hernia, the frequency of seromas might not be influenced by the choice of operative technique (Dedemadi et al. 2010). The seroma formation after laparoscopic inguinal hernia repair may easily be explained by the wider dissection typical for the surgical procedure.

2.4.1.2 Superficial infection

According to the Cochrane review, superficial wound infections are significantly more often observed after open inguinal hernia repair compared with laparoscopic techniques (3.1% vs. 1.5%, respectively, McCormack et al. 2003). A similar conclusion was made by Schmedt and colleagues, with an incidence of 2.4%-2.7% for open and 1.0%-1.2% for laparoscopic repairs (Schmedt et al. 2005). Also, a large registry-based study has effectively reached the same conclusion: 0.6% of patients with laparoscopic repairs had infections compared to 1.4% with anterior mesh repairs, and 1.9% with open preperitoneal repairs (Lundström et al. 2012). Based on registry data it is known that increased operative time predisposes to wound infection, as do: emergency surgery; a surgeon's low annual operative volume; and operating for recurrent hernia (van der Linden et al. 2011, Lundström et al. 2012). Although most individual RCTs have failed to show benefit from a prophylactic antibiotic in the prevention of superficial infections, a meta-analysis has detected a significant benefit of an antibiotic prophylaxis, with a number-needed-to-treat (NNT) of 41 (Mazaki et al. 2013).

2.4.1.3 Other immediate complications

Based on a meta-analysis of almost 5,000 patients, the frequency of urinary retention is 1.1%-2.7% for open repairs and 2.3%-3.5% for laparoscopic repairs (Schmedt et al. 2005). However, in individual studies the frequency of urinary retention after laparoscopic inguinal hernia surgery has varied between 1% and 22% (Sivasankaran et al. 2014). The problem in evaluating these data is that urinary retention is defined relatively rarely. Registry data defines urinary retention as a need for catheterisation and presents with a frequency of 0.6% for open anterior mesh, and 1.5% for laparoscopic repair (Lundström et al. 2012). Benign prostate hyperplasia, increased age, emergency surgery, regional or general anesthesia (as opposed to local anesthesia), and operation for recurrent hernia have been shown to predispose to urinary retention (Sivasankaran et al. 2014, Lundström et al. 2012).

Several complication types not specifically related to inguinal hernia surgery exist, but most publications do not address the frequency of them. Typically, urinary tract infections, pneumonia, venous thromboembolism, and/or pulmonary embolism are such complications. Johansson and colleagues reported one venous thromboembolism, one pulmonary embolism,

two cases of unknown fever, one allergic skin reaction, and two cases of urinary tract infection in 590 patients undergoing either conventional sutured repair, open mesh repair, or TAPP repair for inguinal hernia, with an overall incidence of 1.2% (Johansson et al. 1999). Registry data report an average incidence of 2.1% for other complications, but these complication types are not further specified (Lundström et al. 2012 , Sivasankaran et al. 2014).

2.4.2 Recurrence

Hernia recurrence is one of the main end-points in publications. It should be easy to define, and often results in undesirable and costly additional surgery. Several etiological factors regarding recurrence after inguinal hernia repair have been proposed, both operation dependent and patient dependent. Furthermore, the best way to treat a recurrent hernia remains a controversial subject.

2.4.2.1 Definition and prevalence

Hernia recurrence should be easy to define, but only approximately half of the RCTs have defined the criteria for a recurrence (Bhangu et al. 2015). Even in those with defined criteria for recurrence, 70% of the studies accepted an unspecified clinicians' opinion of a recurrence, and supplementary imaging was used routinely in just 10% of the studies, and selectively in 7.5% of the studies (Bhangu et al. 2015). The mesh may bulge without an actual hernia, mimicking a recurrence, and thus the presence of a recurrence may be confirmed or negated only during an operation for any suspected recurrence.

Early sutured techniques of inguinal hernia repair without a mesh, such as the Bassini hernioplasty, had recurrence rates up to 30% after the primary hernioplasty. In regard to recurrent hernias, the incidence of a re-recurrence was 35% in the pre-mesh era (Gopal and Warrier 2013). The only sutured repair with an early recurrence rate significantly below other sutured repairs has been the Shouldice repair with a 1% incidence (Bendavid 1995). However, these results are only achieved at the Shouldice clinic, where the surgeons concentrate on inguinal hernia treatment, and the Shouldice technique comprises over 90% of the procedures. In fact, results from randomized controlled trials from less selected hospitals provide an overall recurrence rate of 2.4% for the Shouldice repair and 4.9% for all non-mesh repairs combined (Scott et al. 2002). In addition, long-term results suggest an over 10% recurrence rate at 10 years after the Shouldice repair, even in expert hands (Junge et al. 2006). Thus, there have been recommendations against the use of conventional repairs in all other groups other than young patients with small indirect hernias.

With the introduction of tension-free mesh techniques, the recurrence rates have fallen significantly. The gold standard of inguinal hernia repair today, the Lichtenstein hernioplasty, is credited for having a recurrence rate lower than 1% by both expert and non-expert surgeons (Shulman et al. 1995, Kingsnorth et al. 2003). There are several other repair techniques using mesh, such as plug-and-patch (i.e., a Rutkow-Robbins repair) or the preperitoneal mesh repairs by Rives and Stoppa (Rives 1967, Stoppa et al. 1984, Rutkow and Robbins 1993, Rutkow and Robbins 1998). Combining all mesh repairs, the total recurrence rate is today around 3% in RCTs today (McCormack et al. 2003). This may demonstrate either the feasibility and efficacy of the Lichtenstein repair compared to other mesh repairs, or the selection of more demanding cases to undergo preperitoneal mesh repairs that then present with 7-10% recurrence rates (Gopal and Warrier 2013).

Regarding laparoscopic inguinal hernia repairs, recurrence rates similar to those achieved by open mesh repairs have been achieved (McCormack et al. 2003). However, several meta-analyses have criticized laparoscopic repairs for an increased risk of recurrence (Schmedt et al. 2005, O'Reilly et al. 2012), while others have detected similar prevalence of recurrence between open and laparoscopic repairs (Koning et al. 2013, Zhu et al. 2014). The meta-analyses detecting a difference favoring open surgery have generally included RCTs in which the patients have been operated in the 1990s or the early 2000s. Since the learning curve of laparoscopic repairs,

especially TEP, is known to be lengthy (and suggested to be up to 450 procedures; Schouten et al. 2013), it is likely that the majority of surgeons participating in the included trials had not yet been through their learning curve process. Despite this, the majority of the data included from trials in one meta-analysis considered 5-30 prior procedures enough to achieve competence in laparoscopic hernia repairs (O'Reilly et al. 2012).

2.4.2.2 Mechanisms

According to Gopal and Warrier, there are two basic groups of recurrences (Gopal and Warrier 2013). The early recurrences are mainly attributed to operation dependent factors, such as technical errors, suture line tension or infectious complications. The second group of recurrences that usually present late, even decades after the initial repair, are more often associated with patient dependent factors, also referred to as "tissue failure". In addition, different techniques of repair carry their own typical operation-dependent risk factors for recurrence. These different mechanisms of recurrence have been summarized in Table 2.

Table 2. Potential mechanisms of recurrence after inguinal hernia repair with mesh (Gopal and Warrier 2013).

Patient-dependent factors	Smoking and chronic lung diseases
	Obesity and diabetes
	Collagen disease and aging
	Prolonged use of corticosteroids
	Prolonged infections
	Malnutrition, anemia
Surgery-dependent factors	Surgeon experience
	Infection and/or haematoma
	Incomplete dissection
	Missed hernias and preperitoneal lipomas
	Too small mesh / mesh shrinkage (LAP repairs)
	Mesh slitting (LAP repairs)
	Folding or migration of the mesh (LAP repairs)
Debated mechanisms	Mesh properties (microporosity, weight, etc.)
	Fixation of the mesh (LAP repairs)
Mechanisms avoided by using mesh	Suture line tension
	Size of hernia
	Femoral canal opening
	Suture material
	Suturing technique

2.4.2.2.1 Surgeon experience

Data on the effect of surgeon competence on recurrence are controversial. Based on registry data it is acknowledged that the yearly operative volume of the surgeon is associated with the rate of complications in hernia surgery. Laparoscopic repairs have a long learning curve, most often estimated between 30 and 100 repairs (Liem et al. 1996, Ferzli et al. 1998, Wright and O'Dwyer 1998, Aeberhard et al. 1999, Miserez et al. 2009). However, a retrospective analysis of over 1,000 cases demonstrates that even after 200 repairs the performance of the surgeon improves as

measured by conversion and recurrence rates (Feliu-Pala et al. 2001). Another analysis suggests continued improvement after 400 repairs (Schouten et al. 2013). Adequately supervised residents have been shown to be able to achieve comparable results to consultants both with open mesh and laparoscopic techniques (Paajanen and Varjo 2010a, Zendejas et al. 2011). When competence is achieved, an annual volume of 30 procedures is enough for excellent results (AlJamal et al. 2016).

2.4.2.2.2 Infection or hematoma
It has been claimed that 50% of the recurrences are caused by an infectious complication, and that one third or more of the infected inguinal hernia repairs result in the development of a recurrent hernia (Gopal and Warrier 2013). This may be an overestimation of the problem, but a data analysis on a large nationwide register demonstratedthat both infection and haematoma were risk factors for recurrence, with 23% and 22% increased risk, respectively (Lundström et al. 2012).

2.4.2.2.3 Incomplete dissection, missed hernias and preperitoneal lipomas
Understandably, if the primary hernia is completely missed and not repaired, there is a "recurrence", especially in cases of simultaneous multiple hernias. The incidence of this phenomenon is not known, but is most likely related to a surgeon's experience. If the patient has more than one hernia during the primary surgery, there is a greater risk for a missed hernia. Preperitoneal and spermatic cord lipomas, if left in place, may sometimes be misinterpreted as hernia recurrences. Incomplete dissection has been proposed as the primary and most important mechanism of recurrence after laparoscopic surgery (Gopal and Warrier 2013). Wide dissection and the ability to cover all potential hernia openings has been seen as an advantage of laparoscopic techniques. However, inadequate dissection also leads to secondary mechanisms of recurrences, including: insufficient mesh size, incomplete fixation, and insufficient overlap of mesh (Lowham et al. 1997, Gopal and Warrier 2013).

2.4.2.2.4 Mesh-relates issues
Especially with laparoscopic repairs, mesh shrinkage, mesh folding or migration, mesh slitting, and insufficient mesh size have been shown to predispose to recurrence (Felix et al. 1998, Leibl et al. 2000, Gopal and Warrier 2013). Earlier reports also stress the importance of the adequate fixation of the mesh (Felix et al. 1998, Gopal and Warrier 2013), but, recently, meta-analyses have confirmed that the non-fixation of mesh does not increase the risk for recurrent hernia (Tam et al. 2010, Teng et al. 2011, Sajid et al. 2012). In addition, differences between the fixation methods, such as staples/tacks or glue have not been shown to associate with recurrence (Kaul et al. 2012, Sajid et al. 2013a) and neither does mesh weight (Currie et al. 2012, Sajid et al. 2013b).

2.4.2.3 Treatment
Relatively few publications have aimed at determining the best surgical treatment of recurrences. Current guidelines suggest taking into consideration the previous repair method. If an anterior mesh has been placed, a laparoscopic technique is recommended, whereas, after a previous laparoscopic repair, the recurrence should be treated with an anterior open technique (Simons et al. 2009, Bittner et al. 2011a, Sanders and Kurzer 2013, Miserez et al. 2014). Considering the potential for late recurrences because of tissue failure even decades after primary surgery, it is likely that surgeons will also continue to face recurrences after sutured repairs. The latest update of the EHS guidelines recommended a TEP approach to any recurrence after conventional repairs based upon the lower incidence of chronic pain and faster convalescence (Miserez et al. 2014).

The Cochrane review of 2003 analyzed 41 RCTs, out of which one study included recurrent hernias singularly (Beets et al. 1999) and 19 included recurrent hernias as part of their broader study (McCormack et al. 2003). They concluded that there is no difference in the re-recurrence rates between open and laparoscopic surgery for recurrent hernia, but a return to normal

activities is faster after laparoscopic surgery in exchange of the longer operating time. The major weakness of the Cochrane review is combining open non-mesh repairs, open anterior mesh repairs, and open preperitoneal mesh repairs all into one single category of open surgery.

Some RCTs, especially those on recurrent hernias, have been published after the Cochrane review. To date, five subsequent prospective randomized trials have compared open anterior mesh repair against laparoscopic repair in the treatment of recurrent inguinal hernia, one of them being study I of this thesis (Table 3). In addition, a laparoscopic approach has been evaluated against an open preperitoneal mesh repair of recurrent inguinal hernia in one RCT (Beets et al. 1999). Differences in several coagulation- and inflammation-related parameters were investigated in one RCT (Rahr et al. 2006). Furthermore, four meta-analyses have evaluated open and laparoscopic techniques in the treatment of recurrent inguinal hernia (Table 4). Two of these meta-analyses also included the study by Neumayer and colleagues (Neumayer et al. 2004), despite that study including both primary and recurrent hernias, and not being strictly confined to recurrent hernias. Generally these meta-analyses conclude that laparoscopic repairs for inguinal hernia are superior to open repairs in terms of return to normal activities, wound infections, and postoperative pain, but at an expense of longer operating times (Table 4).

2.4.3 Chronic postoperative inguinal pain (CPIP)
Persistent pain after inguinal hernioplasty is a well-known complication. Since the rate of hernia recurrence has decreased significantly with the introduction of mesh-based repairs, chronic pain has become the most important single outcome measure of inguinal hernioplasty.

2.4.3.1 Definition
Despite its importance, the definition of chronic pain after inguinal hernia repair is far from clear. The International Association for the Study of Pain (IASP) first defined chronic postsurgical pain as a pain that fulfills all of the four criteria: 1) the pain developed after a surgical procedure, 2) the pain has lasted at least 2 months, 3) other causes of pain have been excluded (continuing malignancy, chronic infection, etc.), and 4) the possibility that the pain is continuing from a pre-existing problem must be excluded (Macrae and Davies 1999). However, most of these criteria can be problematic when trying to apply them to pain after inguinal hernioplasty.

1) Most patients present with symptoms associated with their hernias. Pain is a common symptom caused by an inguinal hernia. Thus, it can be challenging to differentiate, whether the pain after inguinal hernioplasty is "similar" or "different" than the preoperative pain (criterion 1).
2) The duration of pain over 2 months can be too short a time, especially considering mesh repairs. The mesh causes inflammatory response that may last well over 2 months, without the process being unusual in any terms. This may prolong the postoperative pain in some individuals, without being a sign of chronic condition (criterion 2).
3) Sometimes a recurrent hernia may present with pain only, and thus it can be difficult to rule out the other causes of pain without extensive diagnostic work-up. Also, several other diseases may cause inguinal pain, and thus the exclusion of other causes of pain may be time-consuming and difficult (criteria 3 and 4).

These criteria have been modified (Macrae 2001), and, more recently, upgraded criteria have been proposed (Werner and Kongsgaard 2014a). Despite the criteria offered by the IASP and others, uniform criteria for persistent postsurgical pain after inguinal hernia repair are lacking. Most publications do not classify the intensity of pain using a visual analog scale (VAS) or any other repeatable scale, but rather classify persistent pain simply present or absent without actual definition of the pain or its intensity.Certain studies with a special focus on postsurgical pain even

Table 3. Randomized controlled trials on treatment of recurrent inguinal hernias.

Publication	Operative methods and number of patients	Duration of follow-up	Open better	Outcomes	
				LAP better	
Beets, 1999	GPRVS 37 vs. TAPP 42	2.8 years	Recurrence OR time	Return to normal activity Wound infection	
Kumar, 1999	Lichtenstein 25 vs. TEP 25	1.6 years		Postoperative pain Seroma/wound hematoma	
Dedemadi, 2006	Lichtenstein 32 vs. TAPP 24 vs. TEP 26	3 years	OR time	Postoperative pain Return to work Seroma/wound hematoma	
Eklund, 2007	Lichtenstein 74 vs. TAPP 73	5 years		Postoperative pain Return to work Hematoma	
Kouhia, 2009 (study 1)	Lichtenstein 47 vs. TEP 49	5.6 years		Postoperative pain Return to work Chronic pain	
Demetrashvili, 2011	Lichtenstein 28 vs. TAPP 24	5 years	urinary retention	Postoperative pain Return to work	

GPRVS=giant preperitoneal reinforcement of visceral sack (open preperitoneal repair)

Table 4. Meta-analyses evaluating open *versus* laparoscopic treatment of recurrent inguinal hernias.

Author	Included studies	Open groups	Laparoscopic groups	Outcomes No differences	Outcomes Open better	Outcomes LAP better
Karthikesalingam, 2010	4 RCTs	Lichtenstein & GPRVS	TAPP & TEP	Re-recurrence Chronic pain Hematoma Reoperations	OR time	Postoperative pain Wound infections Return to normal activity
Dedemadi, 2010	5 RCTs (+ 7 comparative studies)	Lichtenstein & open preperitoneal mesh repairs	TAPP & TEP	Wound infection Urinary retention Testicular pain or discomfort Pain / neuralgia Re-recurrence Hematoma / seroma		Hematoma / seroma (re-recurrence: TEP better than TAPP)
Yang, 2013	5 RCTs	Lichtenstein	TAPP & TEP	Re-recurrence Urinary retention Wound hematoma		Wound infection Chronic pain
Pisanu, 2014	7 RCTs	Lichtenstein	TAPP & TEP	Re-recurrence Ischemic orchitis Wound infection Hematoma / seroma Urinary infection Urinary retention Postoperative hospital stay	OR time	Chronic pain Return to normal activities

refuse to give any cutoff values for pain scales, but instead report verbal definitions such as mild/moderate/severe impairment of daily activities (Cunningham et al. 1996, Aasvang et al. 2008). One group has defined VAS scores (0-100) under 10 as mild pain, 10-50 as moderate pain, and over 50 as severe pain (Nikkolo et al. 2010, Nikkolo et al. 2012, Nikkolo et al. 2014, Nikkolo et al. 2015).

In addition, the time limit when pain is considered persistent or chronic is variable. Several authors consider 3 months as the limit of persistent pain, while others use 6 months. However, a prospective trial using open mesh repair concluded that even after 3 years the incidence of persistent pain diminishes compared to the pain at 6 months (Nikkolo et al. 2012). Thus, the natural course of CPIP seems to be self-limiting in many patients, and a need to accurately determine CPIP for research purposes still exists. This need has been admitted already in 2002, but up to date, no uniform consensus over the definition has been reached (Kehlet et al. 2002, Kehlet et al. 2013).

2.4.3.2 Prevalence

Table 5 presents the rates of chronic pain after different inguinal hernia repair techniques. The incidence of chronic postoperative pain varies between studies, depending on several factors: the definition of chronic pain, the method of follow-up, and the duration of follow-up. An average of 11.5% has been given for the incidence of CPIP (Perkins and Kehlet 2000). In some trials, chronic numbness is reported as a separate entity, whereas other trials do not report numbness at all (Cunningham et al. 1996, Wellwood et al. 1998, Andersson et al. 2003, Nikkolo et al. 2010). In addition to the wide variety of chronic pain rates in trials, many trials have completely omitted the evaluation of chronic pain rates, possibly owing to the difficulty of defining chronic pain.

Table 5. Chronic pain rates and different inguinal hernia repair techniques.

Method	Lowest rate	Highest rates	References
Open non-mesh repair	3.7%	63% (any) 12% (moderate to severe)	Cunningham et al. 1996 Perkins and Kehlet 2000
Open mesh repair	0%	59.4% (any) 23.4% (moderate to severe)	Rutkow and Robbins 1998 Nikkolo et al. 2010
Laparoscopic	1.5%	29%	MRC 1999 Zendejas et al. 2011

As Perkins and Kehlet acknowledge, publications from specialised hernia centres usually present low rates of chronic pain, whereas the rates are higher in series from teaching institutions (Perkins and Kehlet 2000). The individual surgeon's operative volume has been shown to reversely correlate with the incidence of all inguinal hernia repair complications (Nordin and van der Linden 2008, Lundström et al. 2012,), and this may be one explanation for the differences between specialised centres and teaching hospitals with regard to chronic pain. Regarding Lichtenstein repair, results achieved by unsupervised residents have been comparable to those of consultants (Paajanen and Varjo 2010a). Supervised surgical trainees have performed laparoscopic inguinal hernia repairs with an astonishingly low complication rate, including a chronic pain rate of 1.5% (Zendejas et al. 2011).

One meta-analysis of RCTs has concluded that the laparoscopic approach is associated with less chronic pain compared to open repairs (13.8% vs. 19.1%, McCormack et al. 2003). Another meta-analysis reached the same conclusion for laparoscopic compared to open mesh repairs (6.8% vs. 10.8%, Schmedt et al. 2005). A Cochrane review of open mesh versus non-mesh repairs

reported a higher incidence of pain after non-mesh repair (7.1%) than after mesh repair (5.2%), although the follow-up time was only three months (Scott et al. 2002).

2.4.3.3 Mechanisms

The biological basis of pain can be divided into three major groups: nociceptive pain, inflammatory pain, and neuropathic pain. The molecular mechanisms of each pain type have been carefully described in a number of publications, providing a thorough understanding of the different pathways that induce acute pain, and may play a role in the development of chronic pain after a surgical procedure (Kehlet et al. 2006). In CPIP, inflammatory and neuropathic pain are proposed as potential sources. Prolonged inflammatory response is suggested to be associated with the use of mesh and the foreign-body reaction induced by the mesh (Kehlet et al. 2006). Nevertheless, neuropathic pain is considered to be the most important mechanism of chronic pain, and the damage of major nerves an almost absolute prerequisite for development of any neuropathic pain (Aasvang and Kehlet 2005, Kehlet et al. 2006, Figure 8). This nerve damage can in turn be a result of either direct surgical injury, or inflammation caused by the mesh (Mikkelsen et al. 2004). However, the mechanism by which the nerve damage is followed by neuropathic pain is unclear. Only a few well-conducted studies have performed thorough neurophysiological sensory testing before and after the hernia repair (Mikkelsen et al. 2004, Aasvang et al. 2008, Linderoth et al. 2011). Quantitative sensory testing and pressure algometry results have not been extremely different in patients with chronic pain compared to pain-free patients (Mikkelsen et al. 2004). Repetitive punctuate and brush stimulation has resulted in significantly more intense pain on the affected side, and this finding was also not present in control patients without chronic pain (Aasvang et al. 2008). Neurophysiological sensory testing has been latterly performed in patients with severe chronic pain after laparoscopic hernia repair, and three distinct pain patterns have been found. In one group, the suggested mechanism is ongoing deep inflammation or irritation caused by the mesh with or without a neuropathic pain component. In the second group, neuropathic pain was the leading mechanism of pain without a substantial inflammatory component. In the third group, a general absence of responses to deep tissue stimulation was seen, suggesting the most probable mechanism to be a partial nerve lesion (Linderoth et al. 2011). Also, temporal summation of pain, as detected by repetitive punctuate and brush stimulation, has been detected in many patients with chronic pain after inguinal hernia repair, suggesting a central nervous system sensitisation (Aasvang et al. 2008, Linderoth et al. 2011).

2.4.3.4 Predictive factors and prevention

Several factors associated with increased likelihood of chronic postoperative pain after any surgical procedure have been described. Older age, female gender, presence of certain diseases (fibromyalgia, migrainous headaches, irritable bowel syndrome, Raynaud's disease), psychosocial factors (anxiety, depression and catastrophising beliefs), lower socio-economic status, certain geographical and cultural backgrounds, employment status and occupational factors, and history of abuse or interpersonal violence have all been patient-related factors associated with an increased risk for chronic pain after surgery (Macrae 2001, van Hecke et al. 2013). Genetic factors have been shown to play an important role in chronic pain syndromes. Although it is considered unlikely that there might be a unique "pain gene", the catechol-O-methyltransferase (*COMT*) gene has been the most widely studied candidate (van Hecke et al. 2013).

Table 6 summarizes some of the factors associated with the development of chronic pain specifically after inguinal hernioplasty. Several of the surgical and mesh-related factors have been intensely studied, but patient-related factors have recently been ignored, apart from the interest in gene studies. A recent prospective study reported certain haplotypes in *COMT* and guanosine triphosphate cyclohydrolase (*GCH-1*) genes to be associated with chronic pain after mesh repair of
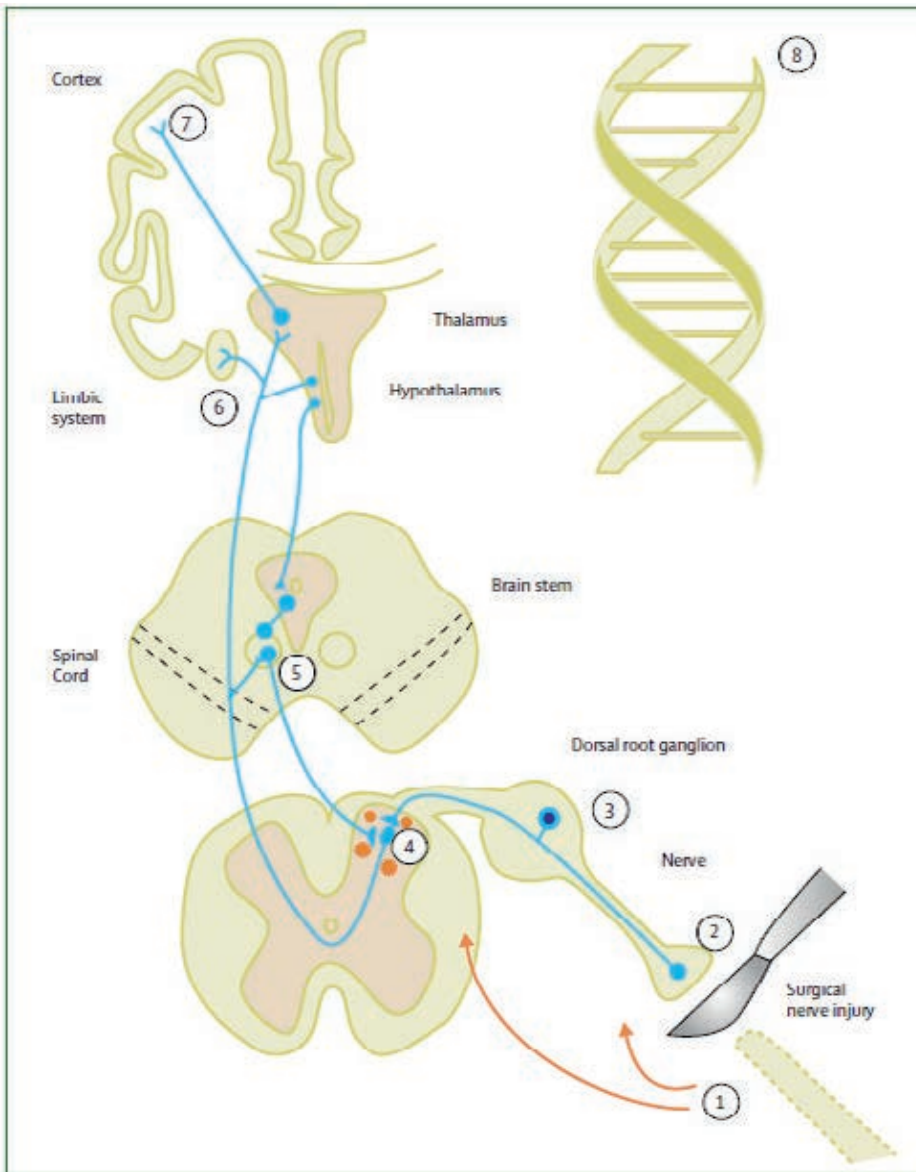
Figure 8. Sites and mechanisms responsible for chronic postsurgical neuropathic pain. (1) Denervated Schwann cells and infiltrating macrophages distal to nerve produce local and systemic chemicals that drive pain signaling. (2) Neuroma at site of injury is source of ectopic spontaneous excitability in sensory fibres. (3) Changes in gene expression in dorsal root ganglion alter excitability, responsiveness, transmission, and survival of sensory neurons. (4) Dorsal horn is site of altered activity and gene expression, producing central sensitization, loss of inhibitory interneurons, and microglial activation, which together amplify sensory flow. (5) Brainstem descending controls modulate transmission in spinal cord. (6) Limbic system and hypothalamus contribute to altered mood, behavior and autonomic reflexes. (7) Sensation of pain generated in cortex (past experiences, cultural inputs, and expectations converge to determine what patient feels). (8) Genomic DNA predispose (or not) patient to chronic pain and affect their reaction to treatment. (Kehlet et al. 2006) Reproduced with permission from Elsevier Ltd.

inguinal hernia (Belfer et al. 2015). The authors suggest that combining one single nucleotide polymorphism (SNP) from each of the candidate genes to certain clinical data (preoperative Activity Assessment Scale, preoperative pain response to 47°C stimuli, the difference of warmth detection in groin area, and Hospital and Depression Scale anxiety score) increased the predictive value of the model from "fair" to "good" in detecting persistent postherniotomy pain. Also a certain haplotype of the major histocompatibility complex, class II, DR beta 1 (*HLA DRB1*) gene has recently been associated with an increased risk of pain after inguinal hernia repair (Dominguez et al. 2013).

Several intraoperative factors may affect the incidence of chronic postoperative pain after inguinal hernia repair. The decreased likelihood of chronic pain with laparoscopic approach compared with open techniques may be owing to the avoidance of nerve damage during surgery (Aasvang et al. 2010). Based on trials including 7,658 patients with open repairs and 7,998 patients with laparoscopic repairs, the average chronic pain rate is 18% after open repairs (non-mesh and mesh repairs combined) and 6% after laparoscopic repairs (Aasvang and Kehlet 2005). However, as the authors acknowledge, the study designs and definitions of chronic pain vary to such degree that the figures should be interpreted very cautiously.

The type of mesh is another intraoperative factor of great controversy. Less chronic pain has been detected after the use of light-weight meshes in several meta-analyses (Smietanski et al. 2012, Sajid et al. 2013b, Zhong et al. 2013), and also beta-glucan coated meshes have given good results (Champault et al. 2007). A major drawback in these studies of mesh types is the short follow-up, not extending beyond one year (Bringman et al. 2005a, Bringman et al. 2005b, Chowbey et al. 2010, Peeters et al. 2010, Bittner et al. 2011b, Bittner et al. 2011c). The importance of follow-up is well illustrated by a three-year follow-up after an RCT, where light-weight mesh provided better immediate results at six months, but was equivalent to heavy-weight mesh at three years (Nikkolo et al. 2010, Nikkolo et al. 2012). A five-year follow-up also provides similar results when comparing light-weight and heavy-weight meshes (Paajanen et al. 2013).

The fixation method or non-fixation of the mesh is another great controversy. Glue-fixation has resulted in less pain than fixation with penetrating methods (Fortelny et al. 2012, Colvin et al. 2013, Shah et al. 2014), but surprisingly self-adhesive meshes and non-fixation of (laparoscopic) meshes have failed to show any significant benefit (Sajid et al. 2012, Fang et al. 2014, Rönkä et al. 2015, Gutlic et al. 2016).

The role and efficacy of pre-emptive and preventive analgesia in the prevention of chronic pain after surgery is still not very well documented. Several different methods – systemic analgesics, local anaesthetics, neural blokades, N-methyl-d-aspartate (NMDA) receptor antagonists (ketamine, gabapentin, pregabalin), steroids – have been studied in conjunction with several different types of surgical procedures (Kehlet et al. 2006, Kehlet et al. 2013, Vadivelu et al. 2014). In addition, in most studies the data on the potential surgical nerve injury, the disease-specific data, the adequacy of the afferent blockade, as well as detailed assessment of wound hyperalgesia are lacking, thus drawing an incomplete picture of the effect of the intervention (Brennan and Kehlet 2005, Kehlet et al. 2006). These data on preventive analgesia unfortunately allow very few conclusions to be drawn regarding the possibility to prevent CPIP.

2.4.3.5 Treatment

Pharmacological management of pain, local anesthetic blockades, sensory stimulation methods and finally, surgical interventions have all been used in the treatment of CPIP (Werner 2014b, Table 7).

Local anesthetic blockades seem to offer benefit in over 50% of patients (Thomassen et al. 2013), but since 42% of the patients are placebo-responders (Bischoff et al. 2012c), the actual benefit seems limited. Several different techniques of neuromodulation have been used in the treatment of CPIP (Werner 2014b). In CPIP, the evidence is still limited, but early results are promising (Kastler et al.

Table 6. Factors associating with a risk of chronic pain after inguinal hernia repair.

	Factor	Increased likelihood	Decreased likelihood or no difference
Patient-related factors	Younger age	Aasvang 2005 Kehlet 2006	
	Preoperative pain	Poobalan 2001 Wright 2002 Kehlet 2006	Liem 2003
	Intense early postoperative pain	Callesen 1999 Lau 2003 Heikkinen 2004	
	Recurrent hernia repair	Callesen 1999 Poobalan 2001 Aasvang 2005	Courtney 2002 Haapaniemi 2002 Liem 2003
	Employment	Poobalan 2001	
	Workers' compensation	Saldeco-Wasicek 1995	
	HLA, COMT and GCH-1 genes	Dominguez 2013 Belfer 2015	
Factors related to surgical technique	Open repair (versus laparoscopic repair)	Liem 1997 MRC 1999 EU Hernia Trialists Collaboration 2002 Kumar 2002 Bringman 2003 Liem 2003 Aasvang 2005	Dirksen 1998 Gillion 1999 Neumayer 2004
	Open anterior surgery (versus posterior open approach)	Koning 2012	
	Not identifying nerves / routine nerve dividing	Alfieri 2006 Smeds 2010 Reinpold 2011	Picchio 2004 Hsu 2012 Bischoff 2012
Mesh-related factors	Sutured repair (versus open mesh repair)	EU Hernia Trialists Collaboration 2002 Scott 2002 Poobalan 2003 Aasvang 2005	
	Heavy-weight mesh	Nikkolo 2010 Smietanski 2012 Zhong 2013 Sajid 2013	Currie 2012 Nikkolo 2012
	Penetrating fixation (versus glue or non-fixation or self-adhesive mesh)	Fortelny 2012 Colvin 2013 Shah 2014	Pierides 2012 Sajid 2012 Fang 2014 Rönkä 2015a

Table 7. Studies on non-surgical treatment of chronic posthernioplasty pain.

Treatment	Method	Results	Reference
Pharmagological	Topical lidocaine	No benefit	Bischoff 2013
	Topical capsaisin	No benefit	Bischoff 2014
Local anesthetic blockades	Bupivacain-triamcinolone	21/38 patients benefitted	Thomassen 2013
	Lidocaine vs. placebo	50% response to lidocaine 42% response to placebo	Bischoff 2012
Neuromodulation	Continuous radiofrequency (CRF) vs. local anesthetic blockade	Good response in both groups, pain relief lasted longer in CRF group	Kastler 2012a Kastler 2012b
	Peripheral nerve stimulation (selective implantation of electrodes)	Average VAS decrease during 29-month follow-up from 8.1 to 3.1	Possover 2013

2012a, Kastler et al. 2012b, Werner et al. 2012, Possover 2013). Also neuro-destructive botulinum toxinum, alcohol and phenol have been used. The use has not been subjected to controlled trials and thus is largery empiric (Kehlet et al. 2013). In addition, spinal neuromodulation has successfully been used both alone and combined with peripheral neuromodulation in severe cases of CPIP (Yakovlev et al. 2010, Lepski et al. 2013).

   The largest portion of studies on the treatment of persistent inguinal pain concentrates on surgical treatment (Werner 2014b). Nearly all of these trials based presurgical diagnostics on diagnostic neural blockades, electromyography (EMG) measurements and/or radiological imaging (CT, US or MRI). In 80% of studies, the surgical approach was open. The surgical treatments used consist of neurectomies (selective/tailored or triple or extended triple), partial or total removal of the mesh with or without replacement, removal of fixation devices, spermatic cord adhesiolysis or microsurgical cord denervation (Kehlet et al. 2013, Werner 2014b). These studies are criticised for heterogenous reporting of pain outcomes, inadequate follow-up times, not reporting pain-related impairment of functional performance, not using structured assessment questionaires and neurological testing, etc. Despite these shortcomings, neurectomy or the removal of the mesh may provide long-lasting total or partial relief in CPIP, although it has been advocated as the last treatment option (Kehlet et al. 2013, Werner 2014b).

2.4.4 Major complications
Major complications after inguinal hernia repair are rare. However, since the vast majority of inguinal hernia repairs are elective, and performed to improve the individual patient's QoL, virtually no major complications should be tolerated. With approximately 20 million procedures each year worldwide (Bittner and Schwarz 2012), even small incidences of major complications are important.

2.4.4.1 Urological
Long-term complications after inguinal hernioplasty, excluding infection, recurrence, and pain, are mostly urogenital in nature; ischemic orchitis, testicular atrophy, chronic testicular pain or discomfort, and sexual dysfunction in the forms of dysejaculation or pain during sexual activity.

   According to a meta-analysis, testicular problems are rare with an overall incidence of 0.8% after open mesh repairs and 0.6% after laparoscopic repairs (Schmedt et al. 2005). A large RCT reported 0.3-2.0% frequency of individual urogenital complications including orchitis, hydrocele, testicular pain, and pain during sexual activity (Eklund et al. 2010). However, major urological

complications, including ischemic orchitis, chronic testicular pain with or without testis atrophy, and bladder perforation have been the primary reason for claims after inguinal hernia repair in nearly one fifth of patients (Rönkä et al. 2015a).

Based on randomized controlled trials, sexual dysfunction is rare with less than 1% prevalence in RCTs (Eklund et al. 2010). However, nationwide questionnaire studies focusing on sexual dysfunction after inguinal hernioplasty have found dysejaculation or coital pain in 9.8-10.9% of the patients (Aasvang et al. 2006, Bischoff et al. 2012b). These questionnaire-based studies are criticised for over-estimating the prevalence, since the response rate has been around 68.5% and symptomatic patients may be more likely to respond. In addition, a prospective evaluation of sexual activity impairment before and after endoscopic inguinal hernia repair revealed a prevalence of 32.1% preoperatively and 9.1% postoperatively. Only 2.3% of the patients with no preoperative pain experienced significant pain postoperatively impairing sexual activity (Schouten et al. 2012).

Chronic testicular pain may have severe long-term consequences and may even require orchiectomy as part of the treatment. However, similarly to CPIP, chronic testicular pain has been noted to have separate components of nociceptive, inflammatory, and neuropathic pain, and thus orchiectomy is not universally beneficial in the treatment of testicular prolonged pain (Rönkä et al. 2015a).

Concerns have also been presented, that a previous laparoscopic inguinal hernia repair may significantly increase the difficulty of subsequent pelvic operations, or even make them impossible to perform (Katz et al. 2002, Cook et al. 2003). This concern is especially strong in cases of bilateral repair. These concerns were originally raised in a few case reports, and more recently wider analyses have been made with no significant differences between patients with or without previous hernia repairs (Erdogru et al. 2005, Laungani et al. 2007). Recent reviews also conclude that the oncological and surgical outcomes of laparoscopic prostatectomy are similar irrespective of the presence or absence of a previous laparoscopic inguinal hernia repair (Picozzi et al. 2015). Thus the potential future need of radical prostate surgery for cancer should not be a determining factor against laparoscopic inguinal hernia surgery (Haifler et al. 2012).

2.4.4.2 Visceral and vascular complications

Visceral injuries have been reported in up to 0.3% in laparoscopic repairs, but only up to 0.07% in open repairs (Scott et al. 2002, McCormack et al. 2003, Schmedt et al. 2005, Bittner et al. 2011a). Compared to TEP in general (0.11% visceral injury rate on average), TAPP (0.21% on average) harbors an increased risk of visceral injury (Bittner et al. 2011a).

The average rate of vascular injuries varies between 0.09% and 0.3% for laparoscopic repairs based on RCTs (McCormack et al. 2003, Schmedt et al. 2005). However, in comparative and case series that do not fulfill the criteria of meta-analyses, the rates tend to be higher; 0.42% for TAPP repairs and 0.25% for TEP repairs on average (Bittner et al. 2011a). In RCTs, the rate of vascular injuries is up to 0.2% for open hernia repairs combined, with 0.07% rate for open non-mesh repairs (Scott et al. 2002, McCormack et al. 2003, Schmedt et al. 2005).

2.4.4.3 Deep infections

Deep infections are also considered rare. According to a Cochrane review, only three cases of deep infections were found in the 41 RCTs analysed, comprising 7,161 patients (McCormack et al. 2003). Based on the included studies, the deep infection rate is 0.08% for laparoscopic and 0.14% for open repairs. Also, case series of laparoscopic repairs have shown deep infection rates between 0.02% and 0.08% (Bittner et al. 2011a). However, this low rate of deep infections has not been achieved in all studies. Specifically, studies on the efficacy of antibiotic prophylaxis, and studies focused on the consequences of deep infections after mesh repairs claim more than tenfold larger rate of deep infections: up to 2.1% in the immediate postoperative period of under one month, and between 0.03% and 1.4% presenting as late-onset infections even years after the original mesh repair (Aufenacker et al. 2004, Fawole et al. 2006, Delikoukos et al. 2007, Othman

et al. 2011, Rehman et al. 2012). The available data have not demonstrated the use of antibiotic prophylaxis to be beneficial in prevention of deep infections (Mazaki et al. 2013). Lack of long-term follow-up data casts doubt over the reliability of the results. One retrospective study also reported no association between antibiotic prophylaxis and the development of a deep infection (Delikoukos et al. 2007).

2.4.4.4 Mortality
Based on an existing national register in Sweden, the mortality associated with inguinal hernia repair is approximately 0.1%, ranging from less than 0.1% in elective repairs to 1.5% in emergency repairs (Lundström et al. 2012). Emergency repairs are known to associate with increased mortality compared to elective repairs, both in the general population and in elderly patients (Lundström et al. 2012, Huerta et al. 2014, Hwang et al. 2014). The mortality rates for emergency repairs have varied between 1.5% and 5.4%, and have been reported to be up to 13% in elderly patients (Lundström et al. 2012, Huerta et al. 2014, Hwang et al. 2014, Venara et al. 2014, Beadles et al. 2015). The health policy change in the UK from active surgery to watchful waiting has been criticised for causing a 59% increased risk of emergency repair, and, consequently, an increased total mortality mainly attributed to the increase in emergency surgeries (Hwang et al. 2014).

2.5 QUALITY OF LIFE

2.5.1 Quality of life questionnaires
Different questionnaires addressing the quality of life (QoL) have been used in an attempt to measure the effects of a certain disease or treatment on the patients' QoL. These questionnaires can be divided into general and disease-specific questionnaires. General questionnaires, such as Short-Form 36 (SF-36®), RAND-36®, EQ-5D® and 15D© scales can be used widely in different patient groups or populations. However, they have been criticised for not taking into consideration the specific problems that may arise in patients with a certain condition or after a certain type of treatment (Heniford et al. 2008). Therefore, disease-specific questionnaires have been developed for a number of surgical patient groups. For inguinal hernia surgery, the Carolinas Comfort Scale (CCS®), Inguinal Pain Questionnaire (IPQ©) and Core Outcome Measures Index (COMI) hernia have been validated (Fränneby et al. 2008, Heniford et al. 2008, Staerkle and Villiger 2011). The IPQ is designed as a retrospective tool for long-term follow-up (Fränneby et al. 2008), and COMI-hernia is a modification of a 5-item survey originally designed for evaluating QoL in patients with back pain (Staerkle and Villiger 2011). Together with COMI-hernia, EQ-5D and EQ-VAS were used both pre- and postoperatively in a validation study. It was concluded that the reproducibility is good, and that COMI-hernia could alone be used in defining the result of inguinal hernia repair (Staerkle and Villiger 2011). The CCS is a 23-item survey, were pain, movement limitations and sensation of mesh are evaluated across eight categories using a Likert-type scale (Heniford et al. 2008). As with IPQ, the CCS can only be used postoperatively. Therefore, neither of these questionnaires can be used to evaluate the effect of an inguinal hernia on the QoL, or the effect of inguinal hernia repair on the QoL. Thus, generic QoL –questionnaires are still mainly used in evaluation of inguinal hernia treatment.

2.5.2 The impact of inguinal hernia and inguinal hernia surgery on QoL
Although QoL measurements have gained popularity among surgeons, relatively few data exist on the preoperative impact of inguinal hernia on QoL. Most publications do not compare the QoL-scores with those of the general population. Based on three trials it can be concluded that the average QoL of hernia patients is preoperatively lower than the general population's, most likely owing to pain or other disturbing symptoms (Mathur et al. 2006, Pierides et al. 2013, Magnusson et al. 2014). Since most studies addressing the QoL-changes after surgical treatment have shown that inguinal hernia surgery significantly improves QoL (Nikkolo et al. 2010, Pierides

et al. 2013, Christoffersen et al. 2014, Magnusson et al. 2014, Nikkolo et al. 2014), it can be indirectly concluded that having an inguinal hernia decreases the QoL of an individual.

Hernia surgery has been shown to increase QoL in patients undergoing open or laparoscopic inguinal hernia repair (Bansal et al. 2013, Coronini-Cronberg et al. 2013, Pierides et al. 2013, Christofferssen et al. 2014, Magnusson et al. 2014, Nikkolo et al. 2014). Even though relatively few publications have compared open and laparoscopic techniques in terms of QoL, laparoscopic surgery seems to increase QoL more than open surgery (Singh et al. 2012, Coronini-Cronberg et al. 2013, Christofferssen et al. 2014).

2.6 COST

2.6.1 Cost of inguinal hernia repair

Considering the frequency of inguinal hernia repair, with over 10,000 procedures yearly in Finland, 200,000 in Germany and almost 800,000 in the United States (Rutkow 2003, Paajanen et al. 2010b, Bittner and Schwarz 2012), the total cost of inguinal hernia treatment is significant. Several attempts have been made to evaluate the difference between costs of open mesh repair and laparoscopic repair (Table 8). Most of the individual studies conclude that laparoscopic repair is more costly from the hospitals' perspective, but suggest that the expected shorter convalescence after laparoscopic repair might make the laparoscopic approach less expensive from a societal perspective.

Several of the studies addressing the cost of inguinal hernia repair have been criticised for long operation times, high conversion rates, and high complication rates in laparoscopic repairs, all these factors potentially depicting effects of the learning curve (Paganini et al. 1998, Hildebrandt and Levantin 2003, Schneider et al. 2003, Khajanchee et al. 2004, Butler et al. 2007, Langeveld et al. 2010, Smart and Castles 2012, Bittner et al. 2015). Most of the randomized cost data reviewed by Bittner and Köckerling (Bittner et al. 2015) are from the 1990s, when laparoscopic hernia repair was a relatively new technique and expensive disposable equipment were used freely without cost containment measures (Jacobs and Morrison 2008). In fact, data from a large volume laparoscopic centre with minimal use of disposable equipment shows the hospital costs of open and laparoscopic methods to be comparable (Khajanchee et al. 2004). An evaluation of costs based on an administrative database also revealed no difference in the hospital costs between open mesh and laparoscopic repairs (Wittenbecher et al. 2013).

Most of the previous studies on costs are byproducts of randomized clinical trials treating men with unilateral primary hernias (Lawrence et al. 1995, Heikkinen et al. 1998b, Hynes et al. 2006, Butler et al. 2007, Eklund et al. 2010), whereas current guidelines suggest laparoscopy to be most effective when treating women and bilateral or recurrent hernias (Simons et al. 2009, Sanders and Kurzer 2013, Bittner et al. 2015). This casts a doubt over the reliability and applicability of the results of these cost analyses. Also, most of the cost analyses omit the societal perspective by only calculating the in-hospital costs, or the cost calculations may be an estimate based on a smaller subgroup of patients (Eklund et al. 2010). In addition, the cost of complications is lacking from all but four trials (Wellwood et al. 1998, Andersson et al. 2003, Hynes et al. 2006, Eklund et al. 2010).

The costs of inguinal hernia repair are not easy to define, because of the nearly endless variables associated with the treatment. Some of them are patient or institution/society dependent, whereas others can be controlled by the surgeon (Bittner et al. 2015). Also the treatment protocols and the societal costs can vary significantly between countries or even within the same institution (Coronini-Cronberg et al. 2013, Bittner et al. 2015). It has been shown, that, for example, reducing the amount of disposable equipment can decrease in-hospital costs as much as 20% (Farinas and Griffen 2000). In addition, the reimbursement rates and hospital charge policies may have a significant effect on the profitability of laparoscopic repair from the hospital's perspective (Khajanchee et al. 2004, Jacobs and Morrison 2008).

Table 8. Previous studies evaluating the costs of open flat mesh versus laparoscopic hernia repairs.

Publication	Country	Study type[a]	Patients	Hernia types[b]	Techniques[c]	Institutional costs Open	Institutional costs LAP	Costs of complications Open	Costs of complications LAP	Costs of convalescence Open	Costs of convalescence LAP
Payne 1994	USA	RCT	100	A	L vs. TAPP	US$ 2 494	US$ 3 093	-	-	-	-
Heikkinen 1997	Finland	RCT	38	A	L vs. TAPP	US$ 1 367	US$ 1 884	-	-	US$ 3 952	US$ 2 912
Heikkinen 1998	Finland	RCT	40	U, P	L vs. TAPP	3 915 FIM	5 976 FIM	-	-	22 113 FIM	14 742 FIM
Heikkinen 1998	Finland	RCT	45	M, U, P	L vs. TEP	US$ 782	US$ 1 239	-	-	US$ 3 892	US$ 2 747
Wellwood 1998	UK	RCT	400	A	L vs. TAPP	272 £ (GB)	675 £ (GB)	140 £ (GB)	72 £ (GB)	-	-
Paganini 1998[d]	Italy	RCT	108	A	L vs. TAPP	US$ 306	US$ 1 249	-	-	-	-
Zieren 1998[d]	Germany	RCT	160	U, P	P&P vs. TAPP	US$ 124	US$ 1 211	-	-	-	-
Papachristou 2002	Greece	RS	320	A	PHS vs. TAPP vs. TEP	484 €	763 € (TAPP) 573 € (TEP)	-	-	-	-
Andersson 2003[e]	Sweden	RCT	168	M, U	L vs. TEP	US$ 2 817	US$ 1 726	incl.	incl.	US$ 2 682	US$ 1 940
Schneider 2003[f]	USA	RCT	56	A	L vs. TEP	US$ 2 009 (3 999)	US$ 2 861 (5 509)	-	-	-	-
Hildebrandt 2003	Germany	PS	138?	A	L vs. TEP	1 988 €	2 428 €	-	-	-	-
Anadol 2004	Turkey	RCT	50	M, U, P	L vs. TAPP	US$ 629	US$ 1 100	-	-	-	-
Khajanchee 2004[g]	USA	RS	85	U, P	open flat mesh vs. TEP	US$ 666 (1 385)	US$ 795 (3 064)	-	-	-	-
Hynes 2006[h]	USA	RCT	1395	M, mostly U and P	L vs. TAPP/TEP	US$ 773	US$ 1 589	incl.	incl.	-	-
Butler 2007[j]	USA	RCT	66	U, P	L vs. TAPP vs. TEP	US$ -1 200	0 (TAPP) US$ +125 (TEP)	-	-	-	-
Langeveld 2010	Netherlands	RCT	660	A (mostly M, U, P)	L vs. TEP	1 333 €	1 758 €	-	-	1 839 €	1 327 €
Eklund 2010[k]	Sweden	RCT	1370	M, U, P	L vs. TEP	1 952 €	2 663 €	23 €	108 €	2 270 €	1 767 €
Wang 2013	China	RCT	252	NS	L vs. TAPP vs. TEP	5 852 RMB	9 504 RMB (TAPP) 9 351 RMB (TEP)	-	-	-	-

a RCT = randomized controlled trial; RS = retrospective series; PS = prospective series
b A = all hernias (both genders, uni- and bilateral, primary and recurrent); M = men; U = unilateral hernias; P = primary hernias; NS = not specified
c L = Lichtenstein; P&P = plug&patch; PHS = Prolene Hernia System
d In-hospital costs only include the cost of disposables
e the costs of complications requiring re-operation were included in the in-hospital costs
f patient charge rate in parentheses
g reimbursement rate in parentheses
h the costs of complications were included in the total 2-year costs of medical service use
j absolute prices were not given for the procedures
k the cost calculations were based on an average of 27 patients/group from a single hospital participating in a multicenter trial

2.6.2 Cost-effectiveness of inguinal hernia surgery

Quality-adjusted life years (QALYs) are an important measure in calculating the cost-effectiveness of treatment. One QALY corresponds to one year in perfect health. As very many diseases are not fatal, but instead may lower the patients' QoL, survival alone is not enough to evaluate the effect of a treatment. In diseases like inguinal hernia, QALYs are typically used in estimating the effect of surgical treatment. The cost of treatment may be then divided by the QALYs gained, and thus the price/QALY is evaluated. A threshold value of £30,000/QALY has been set by the National Institute of Clinical Excellence (NICE) in Great Britain as a limit to what is an acceptable price for a treatment (McCabe et al. 2008). When calculating the price/QALY, usually only direct hospital/healthcare costs are included, but the costs of convalescence are omitted.

Relatively few publications have addressed the cost-effectiveness of inguinal hernia surgery from a societal perspective. Most cost analyses have not taken into consideration any societal costs such as convalescence from work. In addition, data on QALYs gained from inguinal hernia surgery are still scarce. For open inguinal hernia mesh repair, gained QALYs vary between 0.13 and 0.95 for the first year (Coronini-Cronberg et al. 2013, Palmqvist et al. 2013, Sgourakis et al. 2013). Laparoscopic repair provides approximately 0.70-0.92 QALYs (Coronini-Cronberg et al. 2013, Sgourakis et al. 2013). The most extensive cost-effectiveness analysis thus far is based on over 17,000 inguinal hernia patients returning patient-reported outcome-measure (PROM) questionnaires pre- and postoperatively. This analysis concludes that on average laparoscopic inguinal hernia surgery provides 0.92 QALYs as opposed to 0.82 QALYs for open repairs. The price per QALY was £1,540 (€2,053) for laparoscopic and £1,746 (€2,328) for open repairs, thus indicating that laparoscopic repair is more cost-effective (Coronini-Cronberg et al. 2013). According to another analysis, the prices per QALY were $1,942 (€1,618) for Nyhus repair, $1,948 (€1,623) for Stoppa repair and $2,011 (€1,675) for TEP repair (Sgourakis et al. 2013). Both of these analyses have only included in-hospital costs to their analyses, not taking into consideration costs of convalescence or potential complications.

3 Aims of the study

The aims of this study were to evaluate the outcome and complications of open and laparoscopic hernia repair surgery, and to determine the cost of treatment. The specific aims were as follows:

1. To compare open and laparoscopic inguinal hernia repair in treating recurrent inguinal hernias, with a specific focus on long-term outcomes.
2. To evaluate the potential of preoperative MRI in predicting the outcome of laparoscopic inguinal hernia repair of overwhelmingly painful inguinal hernias.
3. To assess the QoL in patients with painful inguinal hernias, and the change in QoL following laparoscopic TEP repair of the hernia.
4. To evaluate the possibility of predicting postoperative pain with preoperative pain and QoL scores.
5. To assess the complication profiles of open and laparoscopic inguinal hernia repair by using national registry data.
6. To compare cost and outcome of open mesh and laparoscopic inguinal hernia repairs in a single surgical unit.

4 Patients and methods

4.1 PATIENTS

The overview of patients in each study is presented in Table 9. All patients in the two prospective studies (study I and II) were adult patients, and their written informed consent was obtained prior to inclusion. The local ethics committee approved the study protocols of all four studies. In addition, the Finnish Patient Insurance Center approved the study protocol of study III and gave the permission to access and to evaluate the material.

Table 9. Patients included in studies I-IV.

Study	Patients	Type of study	Surgical techniques	Enrolment period	Final data collection	Length of follow-up (years)
I	99	RCT	Lichtenstein *versus* TEP	Feb 1997 - Feb 2002	May 2007	5-10
II	22	Prospective series	TEP	May 2012 - May 2013	June 2015	2-3
III	395	Registry data	Open mesh *versus* open non-mesh *versus* laparoscopic	2002 - 2010	N/A	N/A
IV	986	Retrospective series	Lichtenstein *versus* TEP	2002 - 2011	June 2015	3.5-13.5

4.1.1 Treatment of recurrent inguinal hernia (study I)

The study included 99 consecutive patients from the surgical outpatient clinic of North Karelia Central Hospital. Two patients were excluded because femoral hernias were found during surgery, and one patient because of a surgical correction of a hydrocele. Thus, the final sample size was 96 randomized patients, 47 in the Lichtenstein group and 49 in the TEP group. All but one patient had recurrences after open hernia repair, and the most common previous repair technique was open sutured repair (38 patients in the Lichtenstein group and 39 patients in the TEP group).

4.1.2 MRI in painful inguinal hernia (study II)

Between May 2012 and May 2013, 42 patients aged less than 50 years were evaluated for inclusion at the surgical out-patient clinic of North Karelia Central Hospital, and 22 patients were included. The inclusion criteria were a painful inguinal hernia, with the VAS score over 50/100, and the patients' agreement to participate. The exclusion criteria were previous lower midline laparotomy or Pfannenstiel incision, contraindications to either MRI, general anesthesia or laparoscopy, only mild or moderate pain (VAS score less than 50/100), or the patients' refusal to participate. The flow-chart of the study is depicted in Figure 9.
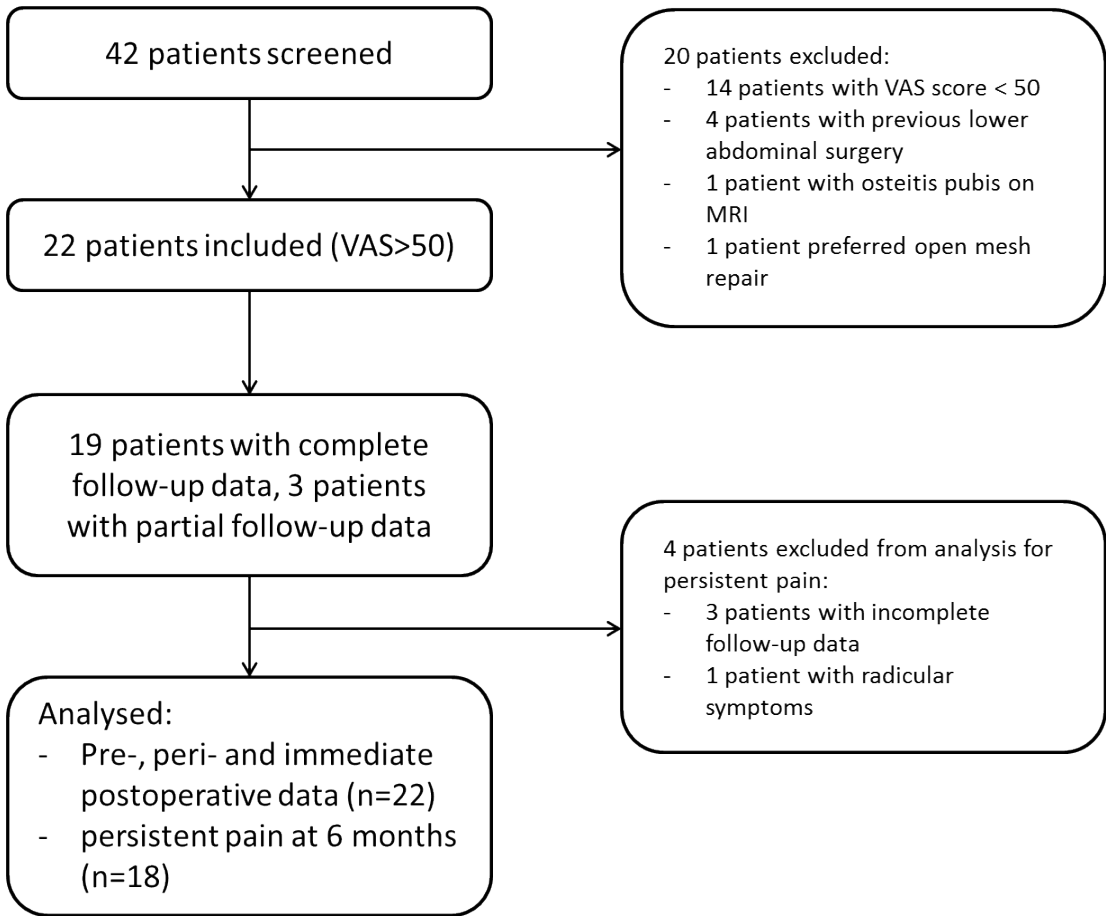
Figure 9. Flow-chart of study II

4.1.3 Complications in inguinal hernia surgery (study III)

This retrospective analysis includes 335 patients who filed claims to the Finnish Patient Insurance Centre (FPIC) after inguinal or femoral hernia repair in 2002-2010. Of these patients, 245 had open mesh repair, 40 had open sutured repair and 50 had laparoscopic repair (36 TEP and 14 TAPP repairs).

4.1.4 Cost of inguinal hernia repair (study IV)

This retrospective material was collected from North Karelia Central Hospital. All patients having laparoscopic inguinal hernia repair between January 2002 and December 2011 were identified from the hospitals' annual reports to the Finnish Hospital Discharge Registry. The individual patient files of these 458 patients were reviewed and data regarding demographic factors, details of the surgical treatment, and potential complications were collected. In addition, a control group of randomly selected 528 patients undergoing a Lichtenstein repair was collected and similar data were extracted from the patient files. Complications were categorized into eleven categories similarly to study III. Any hospital appointments, treatment episodes, and re-operations related to the hernia surgery were recorded until June 2015, providing a minimum follow-up time of 3.5 years. For deceased patients, death certificates were examined to confirm the cause of death.

4.2 METHODS

4.2.1 Randomization in study I
The randomization to treatment groups took place at the ward for gastrointestinal surgery upon the patients' arrival for surgery. The treatment allocations were placed in sealed envelopes before the inclusion of the first patient. Envelopes were prepared by the secretary of the surgical clinic, who did not participate in the treatment of patients. The treatment group was determined by opening the next envelope in sequence.

4.2.2 Magnetic resonance imaging in study II
Prior to operative treatment, all patients underwent magnetic resonance imaging (MRI) of the groin area, using both short tau inversion recovery (STIR) and T1-weighted sequences in axial and coronal directions, both sequences from pubis to sacrum. No Valsalva manoeuver was performed. All scans were evaluated by a senior consultant in radiology. The MRI scan was repeated at 6 months, if abnormal findings were present, or if the patient experienced prolonged pain.

4.2.3 Surgical treatment

4.2.3.1 Lichtenstein repair
In study I, the Lichtenstein procedure was performed as described by Lichtenstein and colleagues (Lichtenstein et al. 1989), using a heavy-weight polypropylene mesh (Prolene®, Ethicon, 80 to 85 g/m^2) and suturing the cranial edge of the mesh with interrupted sutures. Spinal anesthesia was administered to 46 patients, and one patient had general anesthesia. No routine prophylactic antibiotic treatment was used. All patients were managed as in-patients.

In study IV, patients in the Lichtenstein group were operated with a similar technique, but using a light-weight mesh (Optilene®, B. Braun, 36 g/m^2). The procedure was completed in local (n=156), spinal (n=324) or general (n=48) anesthesia. All but four patients received antibiotic prophylaxis. More than half of the patients (57.1%) were treated as ambulatory patients.

4.2.3.2 Laparoscopic TEP repair
The laparoscopic TEP was performed as described by Heikkinen and colleagues (Heikkinen et al. 2004). In study I, a heavy-weight polypropylene mesh (Biotech, 100 g/m^2) was used. Tackers were used to attach the mesh in all but three patients. Prophylactic antibiotic treatment was not routinely used.

In study II, the operative technique was a laparoscopic TEP with a light-weight polypropylene mesh (TiMesh® light, Pfm Medical, 35 g/m^2) and no fixation. Routine prophylactic antibiotic of intra-venous cefuroxime 3 g was administered to all patients. The majority of patients (n=18, 82%), were managed as ambulatory patients.

In study IV, the laparoscopic TEP was performed with light-weight meshes (TiMesh® light, Pfm Medical, 35 g/m^2), and in 43% of the patients the mesh was not fixed. The fixation method, when used, was tackers in all but two patients. Some 44.3% of the patients received antibiotic prophylaxis. Only 7.6% of the patients were treated as ambulatory patients.

4.2.4 The Finnish Patient Insurance Centre (FPIC) registry
All communal and private clinics are obliged to have insurance against patient injury within the FPIC, which is a non-profit organization. Over 80% of the claims received by FPIC are related to surgical interventions (personal communication, FPIC / statistician Mari Saukko). Although a scientific report on the coverage of the FPIC registry is lacking (personal communication, FPIC / development manager Minna Plit-Turunen), the FPIC registry has been regarded as all-inclusive

by Finnish surgeons, especially regarding major complications (Rantanen et al. 2008), and thus it provides an excellent insight into severe surgical complications.

4.2.5 The Finnish Hospital Discharge registry
The annual number of inguinal and femoral hernioplasties and the distribution of the patients' gender and age were obtained from the Finnish Hospital Discharge Registry, which is maintained by the National Board of Health. Data are collected from all communal and private hospitals in Finland and automatically sent into the registry at the end of each year. The data have been verified to be accurate and reliable (Keskimäki and Aro 1991).

4.2.6 Follow-up and questionnaires
In study I, the first visit at the out-patient clinic was at three weeks after surgery and yearly visits were scheduled up to three years. The patients were contacted via telephone in March-May 2007. The primary outcomes of interest were pain in the inguinal region, and recurrence.

In study II, two questionnaires were filled in on the day of surgery and at 6 months postoperatively. The RAND-36 QoL –questionnaire was filled in at both times, and general health issues, preoperative hernia symptoms, the postoperative course, and the intensity of pain symptoms pre- and postoperatively were defined using custom-made questionnaires. If a response was not obtained at 6 months, a reminder was sent twice.

The RAND-36 was scored from 0 to 100 according to the standard method and missing values were handled according to the RAND-36 instructions (the half-scale rule). The values were compared to the age-matched average provided by the validation study (Aalto et al. 1999).

4.2.7 Data collection in study III
The FPIC registry was searched for claims after inguinal or femoral hernia repair. Some 335 claims were identified and individual patient files were reviewed. Each claim was evaluated by at least two surgeons independently of each other. Demographic data and details from the surgical procedure were recorded. The complications were categorized into eleven categories based on the type of complication. The complications were also categorized into mild/moderate and severe/unreasonable complications.

4.2.8 Cost calculations in study IV
For economic evaluation in study IV, the numbers of out-patient visits, emergency room visits, bed-days, ICU days, as well as additional surgical procedures were recorded. For each patient, it was determined which of these costs were attributed to primary treatment, and which to complications. Thus it was feasible to calculate the costs of primary treatment and complications on an individual level. The established prices from 2015 were used in the calculation of costs, and the most common prices are depicted in Table 10.

Since the treatment process of inguinal hernias within the hospital has changed from 2012 onwards, especially for laparoscopic repairs, cost estimates were also calculated based on the current treatment process. A new ambulatory surgery unit with a larger capacity was opened in North Karelia Central Hospital in 2012, and after this, all patients qualifying for ambulatory surgery have been treated there. This has significantly shifted the focus of laparoscopic inguinal hernia surgery from in-patient treatment to day-case surgery. For this analysis it was estimated that 90% of the patients with ASA risk class 1, 55% of ASA class 2 patients and 10% of ASA class 3 class patients could be treated in the ambulatory surgery unit. These figures were derived from the control group of Lichtenstein repairs, although it is likely that the actual current percentages for ambulatory surgery are higher than this estimate. For this cost update, it was assumed, that the complications and their treatment as well as the durations of sick leave would remain similar to the originally collected data.

Table 10. Typical prices in inguinal hernia treatment.

Unit	Type of visit / surgery	Patient	Municipality	Total
Out-patient clinic	First visit	30 €	201 €	231 €
	Follow-up visit	30 €	141 €	171 €
Ambulatory surgery	Lichtenstein	97 €	1132 €	1229 €
	TEP	97 €	1375 €	1472 €
Surgical ward	Basic treatment / day	35 €	465 €	500 €
	Demanding treatment / day	35 €	792 €	827 €
	Elective procedures	-	1398 € (Lichtenstein) 1699 € (TEP)	1398-1699 €
	Emergency procedures	-	2516 € (Lichtenstein) 3058 € (TEP)	2516-3058 €
Emergency room	Visit (basic)	30 €	84 €-134 €	114-164 €
	Visit (demanding)	30 €	220 €-353 €	250-383 €
	Visit (very demanding)	30 €	461 €-738 €	491-768 €
	Overnight observation	35 €	400 €	435 €
Intensive care	Standard price / day	35 €	2088 €	2123 €
	Additional price	-	26,66 € / TISS point	26,66 € / TISS point

For calculating the costs of convalescence from work, the estimate provided by Confederation of Finnish Industries (EK) was used (EK 2009). In short, the cost of a patients' sick leave is estimated to be three times the actual salary. This estimate includes not only the actual salary and social cover, but also takes into account the costs of productivity and quality losses, administration costs, costs for finding a substitute, overtime work, delays, etc. The average salary in Finland in 2014 was 3,284 €/month, and this figure was used to calculate the daily cost of sick leave, which in turn was multiplied by the amount of days of convalescence.

4.2.9 Statistical methods

All the statistical analyses were performed with the IBM SPSS Statistics –package. Version 15.0 was used in study I, version 19.0 in study III and version 21.0 in studies II and IV. The analyses were performed on an intention-to-treat basis in studies I, III and IV. A p-value threshold of 0.05 was considered the upper limit for statistical significance.

For categorized variables, the Pearson Chi-square and Fisher's exact test were used, as appropriate. The categorized variables are presented in absolute numbers (percentages).

In studies I, II and IV, the independent samples t-test and the Mann-Whitney U-test were used for continuous variables, depending on the normality of the variable. In study III, the Kruskal-Wallis test was used. In addition, the Wilcoxon signed rank test was used in study II to analyze the changes in VAS and RAND scores. The continuous variables are presented in mean (SD).

5 Results

5.1 TREATMENT OF RECURRENT INGUINAL HERNIA (STUDY I)

5.1.1 Preoperative and intraoperative factors
The average age of the patients was 56.8 years. No differences in preoperative factors was detected. The mean operative time for Lichtenstein repair (58 minutes) and TEP (69 minutes) were also similar (p=0.99). Two conversions in the TEP group were required.

5.1.2 Early outcomes
Most early outcomes were similar between the groups, but the TEP group needed less pain medication at the ward: 4.4 doses in the Lichtenstein group and 3.0 doses in the TEP group (p=0.02). Primary complications did not differ between the groups. The duration of sick leave was longer in the Lichtenstein group (average 17.9 days) than in the TEP group (average 14.8 days, p=0.05).

5.1.3 Long-term outcomes
The follow-up time was on average 5.3 (± 3.6) years, the first patients in the study were followed-up until 10 years from surgery. Further recurrences were detected in three patients in the Lichtenstein group as opposed to none in the TEP group (p=0.11). Chronic pain in the operated inguinal area was significantly more common after Lichtenstein repair compared to TEP repair (p=0.02), although this difference became evident only after two years of follow-up (Table 11).

Table 11. Main outcomes in study I.

Variable		Lichtenstein (n=47)	TEP (n=49)	Univariate *p*
Non-opiod doses		4.4	3.0	0.02
Duration of sick leave (days)		17.9	14.8	0.05
Chronic pain	Total	13	4	0.02
	1. year	8	3	0.19
	2. year	7	0	0.01
	3. year	6	0	0.03
	During phone interview	5	0	0.05

5.2 MRI IN PAINFUL INGUINAL HERNIA (STUDY II)

5.2.1 Preoperative factors and MRI findings
The patients were 35 years old on average (range 19-49), and the majority (17/22 patients, 77%) of them had heavy physical labor. The preoperative MRI showed no signs of pubic periostal irritation, haemorrhage or soft tissue abnormalities (Figure 10), and thus was unable to predict the outcome of the TEP repair. Only 9/22 (41%) of the hernias were detected in the MRI in resting state.
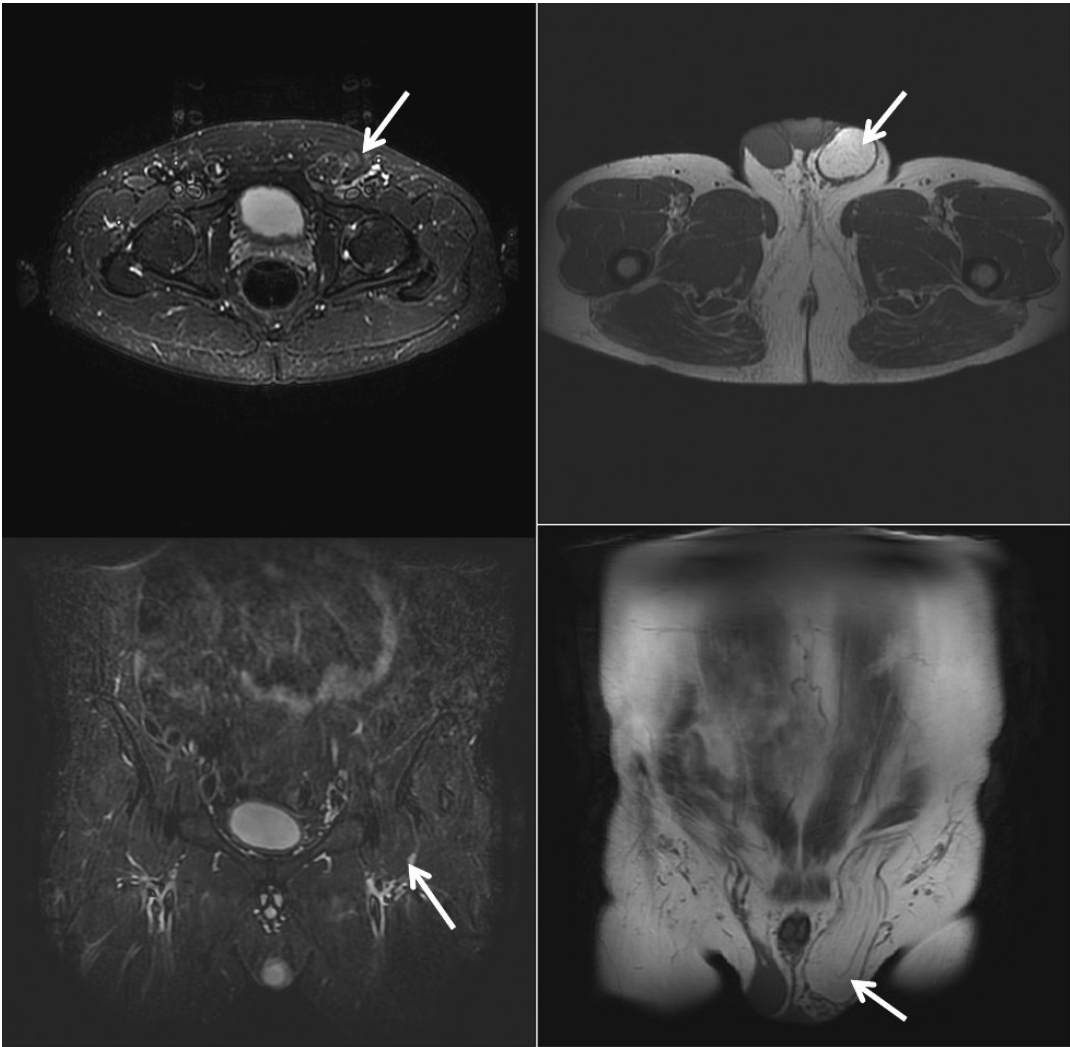
Figure 10. A preoperative MRI showing a left-sided inguinal hernia (white arrows), but no other pathologies. Left column - STIR sequences, right column – T1-weighted images, upper row – transverse sections, lower row – coronal sections

5.2.2 Operative details and early surgical outcomes

The mean operative time was 43 (13) minutes. Most patients (16/22) had lateral hernias. The majority, 18/22 patients (82%), were treated as ambulatory patients. Postoperatively, 12/22 (55%) of the patients reported having minor hematomas either at the wound area or scrotal/labia major area, and one patient (1/22, 4.5%) had a seroma collection that resorbed spontaneously. No recurrences have been noted until June 2015. The average length of sick leave was 17 days (range 0-35).

5.2.3 Pain scores and persistent postoperative pain

At six months after surgery, the VAS scores for pain were significantly lower than preoperative scores for most patients (Table 12). Four patients (18%) were still experiencing pain in the operated inguinal area at the time of the six-month follow-up (Table 13). Their preoperative VAS scores for pain were significantly higher than the scores for those patients, who did not have pain during the follow-up.

Table 12. Pre- and postoperative VAS scores for pain in study II.

Pain dimension	Preoperative	Postoperative	p-value
VAS at worst	57 (17)	14 (22)	< 0.001
VAS at rest	1 (2)	1 (4)	0.394
VAS during exercise	33 (22)	14 (26)	0.003
VAS disturbance last week	28 (23)	7 (16)	< 0.001
Average VAS	24 (11)	7 (11)	< 0.001

VAS scores are expressed as mean (SD).

Table 13. Factors predisposing to postoperative long-term pain in study II.

Factor	Subgroup	Inguinal pain at 6 months (n=4)	No pain at 6 months (n=14)	p-value
Preoperative VAS scores for pain	during physical exertion	60 (12)	29 (20)	0.012
	disturbance last week	56 (16)	23 (20)	0.008
	average score	38 (3)	22 (10)	< 0.001
Preoperative Score on Physical Ability (PA)		66 (17)	83 (12)	0.025
Preoperative VAS score "disturbance last week"	low (< 30)	0 (0.0%)	10 (71.4%)	0.023
	high (> 30)	4 (100.0%)	4 (28.6%)	

Continuous variables are expressed as mean (SD).

5.2.4 Changes in quality of life
As the patients in the study were relatively healthy apart from the inguinal hernia, their QoL is also rather good compared to the age-matched average. Only dimensions associated with physical abilities (Physical Functioning, PF; Role/Physical, RP; Pain, P) were significantly lower than the age-matched average, most likely reflecting the impact of the painful inguinal hernia (Figure 11).

After surgery, the three dimensions of physical abilities (PF, RP and P) improved significantly. The only dimension with postoperative values below the age-matched average was Pain (P), which is thoroughly explained by the values of the four patients who had prolonged postoperative pain.

5.3 COMPLICATIONS IN INGUINAL HERNIA SURGERY (STUDY III)

5.3.1 Inguinal hernia surgery in Finland during the study period
Between January 2002 and December 2010, over 91,000 adult hernioplasties for inguinal of femoral hernias were performed in communal and private hospitals in Finland (Table 14). Nearly 80% of them were open mesh hernioplasties, and in the years 2006-2010 open mesh repairs comprised over 80% of all repairs.

5.3.2 Claims reported to the FPIC
During the study period, altogether 335 claims were reported to the FPIC after inguinal or femoral hernia surgery; 245 claims after open mesh hernioplasty, 40 after open non-mesh surgery and 50 after laparoscopic surgery. In spite of the highest absolute number of complaints, the open mesh repair is associated with the lowest relative complication rate; 3.3 per 1,000 procedures for open mesh surgery, 5.2 per 1,000 for open non-mesh surgery and 5.0 per 1,000 for laparoscopic surgery,
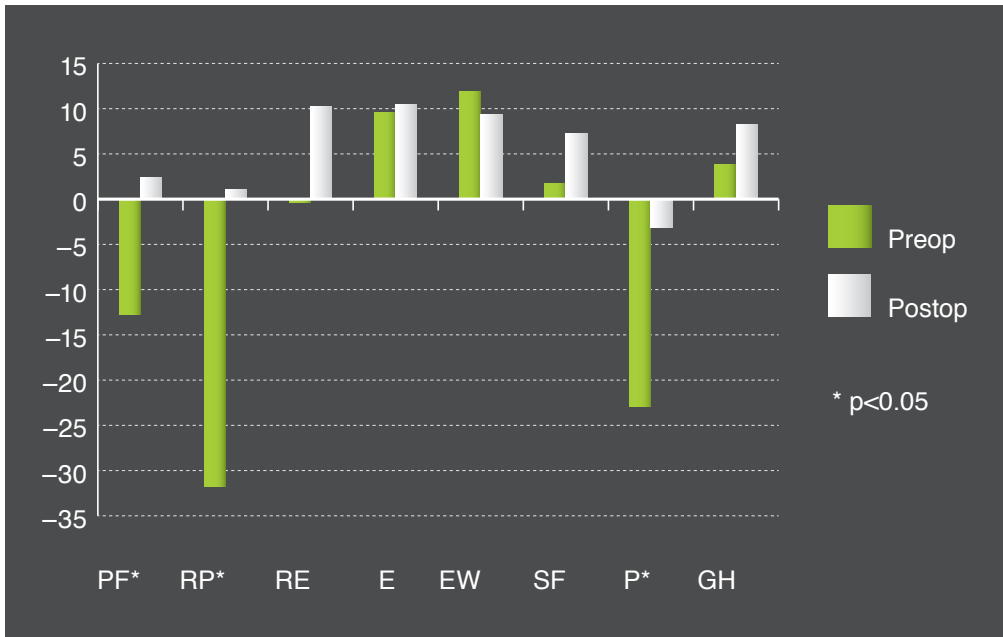
Figure 11. Changes in RAND-dimensions in study II. PF=physical function, RP=role/physical, RE=role/emotional, E=energy, EW=emotional wellbeing, SF=social function, P=pain, GH=general health perceptions, * p<0.05

p=0.007. Three deaths were associated with inguinal hernia repair as previously described (Paajanen et al. 2010b).

5.3.3 Patient demographics and perioperative data
The average age of the patients was 56 years with no statistically significant difference between the groups. Most of the demographic data were similar between the two groups. The patients receiving open repairs had higher BMI, more often primary and unilateral repair performed by residents with a heavy-weight mesh.

5.3.4 Claimed complications
The open mesh group, open non-mesh group and the laparoscopic group had similar amounts of haemorrhagic and infection complications in total (Figure 12). However, a significant difference between the groups favoring the open mesh repair over open non-mesh or laparoscopic repair was observed in early complications (p=0.001) and immediate reoperations (p=0.006). In addition, open non-mesh repair harboured an increased risk of late complications (p<0.001) compared to mesh repairs. The open non-mesh and laparoscopic groups had more severe complications (p<0.001).

Individual complication types are presented in Figure 13. Superficial infections were significantly more often claimed after open repairs (p=0.022), and deep infections after laparoscopic repairs (p<0.001). Deep haemorrhage predominated after laparoscopic repairs (p<0.001). Visceral injuries were significantly more often observed after laparoscopic and open non-mesh repairs (p<0.001), whereas non-mesh repairs harbored an increased risk of both recurrence (p=0.001) and neuropathic pain (p<0.001).

Table 14. Inguinal and femoral hernioplasties in Finland 2002-2013.

Type of repair	Type of hernia	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total
Open sutured	Inguinal	908	860	608	583	448	346	330	305	318	300	226	151	5,383
	Femoral	122	137	114	97	88	73	79	78	68	62	63	68	1,049
Open mesh	Inguinal	8,298	8,022	8,421	9,313	8,550	7,836	8,145	8,309	8,067	8,353	8,279	8132	99,725
	Femoral	30	29	57	58	77	51	70	84	74	89	74	98	791
Laparoscopic	Inguinal	912	895	1,098	1,328	1,204	1,162	1,082	1,121	1,101	1,258	1,419	1590	14,170
	Femoral	11	11	8	12	11	4	12	2	16	26	22	25	160
Other repair	Inguinal	100	117	95	77	50	63	56	61	44	49	50	40	802
	Femoral	0	0	0	0	0	0	0	0	0	0	0	0	0
Total repairs	Inguinal	10,218	9,894	10,222	11,301	10,252	9,407	9,613	9,796	9,530	9,960	9,974	9,913	120,080
	Femoral	163	177	179	167	176	128	161	164	158	177	159	191	2,000
	All repairs	10,381	10,071	10,401	11,468	10,428	9,535	9,774	9,960	9,688	10,137	10,133	10,104	122,080
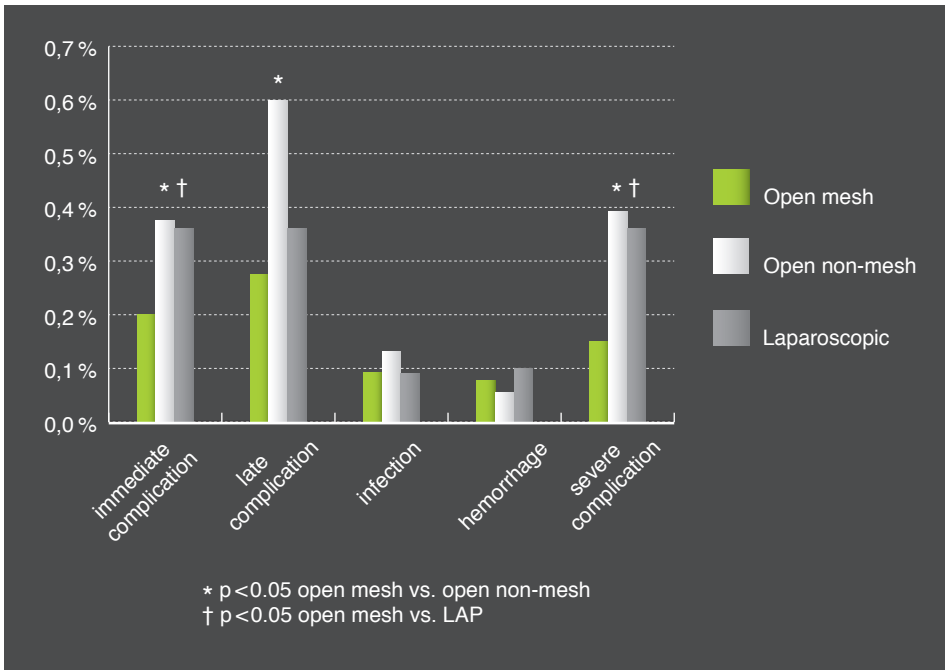
Figure 12. General features of claimed complications to FPIC 2002-2010 (study III).

5.4 COSTS OF INGUINAL HERNIA REPAIR (STUDY IV)

5.4.1 Patient demographics and operative details
Between January 2002 and December 2011, altogether 458 patients were operated laparoscopically for 753 inguinal hernias. The control group consisted of 528 patients with 568 inguinal hernias repaired with the Lichtenstein technique. The sociodemographic factors of the groups were comparable, but significantly more patients in the laparoscopic group were operated for recurrent or bilateral hernia, indicating the good adherence to current guidelines on inguinal hernia repair (Simons et al. 2009, Sanders and Kurzer 2013).

The average operative time was 61 minutes in both groups (p=0.694). For bilateral and recurrent hernias, laparoscopic repair was significantly faster than Lichtenstein repair. Only 7.6% of the patients in laparoscopic group were treated as outpatients during the study period, as opposed to 57.1% in the Lichtenstein group.

5.4.2 Surgical outcomes and complications
The treatment episode and recovery was uneventful in 801 patients (82.7%), and complications of any severity or type were detected in 185 patients, with no differences between the groups. Some 82.2% of the complications were classified mild or moderate. Urological and bowel complications were more frequent in the laparoscopic group, whereas prolonged pain was observed more often after a Lichtenstein repair.
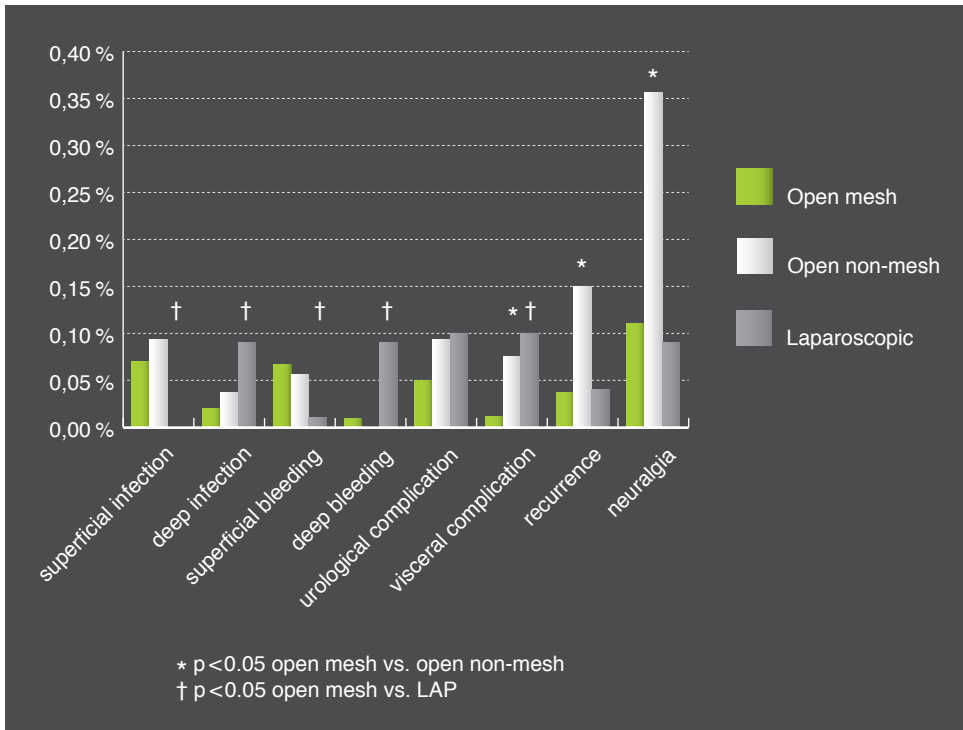
Figure 13. Specific complication types in claimed complications (study III).

5.4.3 Economical evaluations

The mean in-hospital price of an uncomplicated primary treatment episode was significantly higher for laparoscopic surgery (3,035 € vs. 1,986 €, p<0.001, Figure 14). The same result was confirmed in all subgroups (bilateral hernias, recurrent hernias and unilateral primary hernias, Figure 15). The average cost of complications was also higher for laparoscopic repairs (2,099 € vs. 1,087 € per complicated case, p=0.003).

Convalescence after laparoscopic surgery was significantly shorter (16 vs. 21 days, p<0.001), and thus also the cost of convalescence from uncomplicated treatment (5,150 € vs. 7,060 €, p<0.001). Similar findings were also observed in the subgroup analyses, with even more pronounced difference favoring the laparoscopic approach for recurrent hernia repairs (16 vs. 29 days, p<0.001, Figure 15).

When the cost calculations were updated to the current treatment protocols with a concomitant increase in the utilization of ambulatory surgery, the difference between hospital costs of open and laparoscopic repair decreased from 1,256 € to 607 €. However, despite this reduction in the costs of laparoscopic surgery, the difference of in-hospital costs was still significantly favoring open surgery (p<0.001).
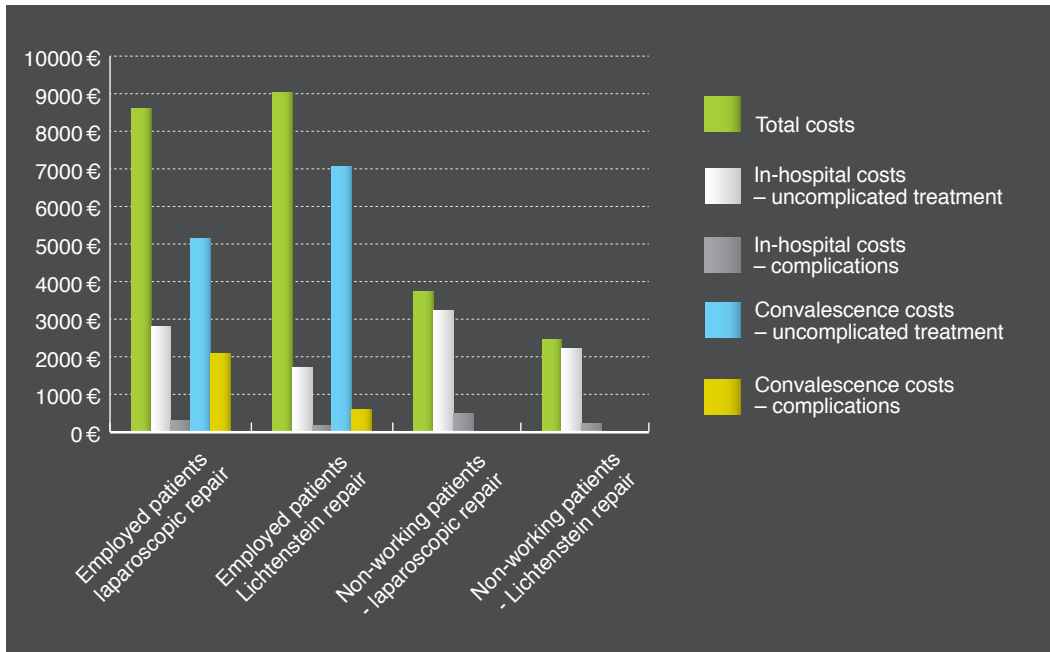
Figure 14. Distribution of costs in laparoscopic and Lichtenstein repairs divided by employment status.
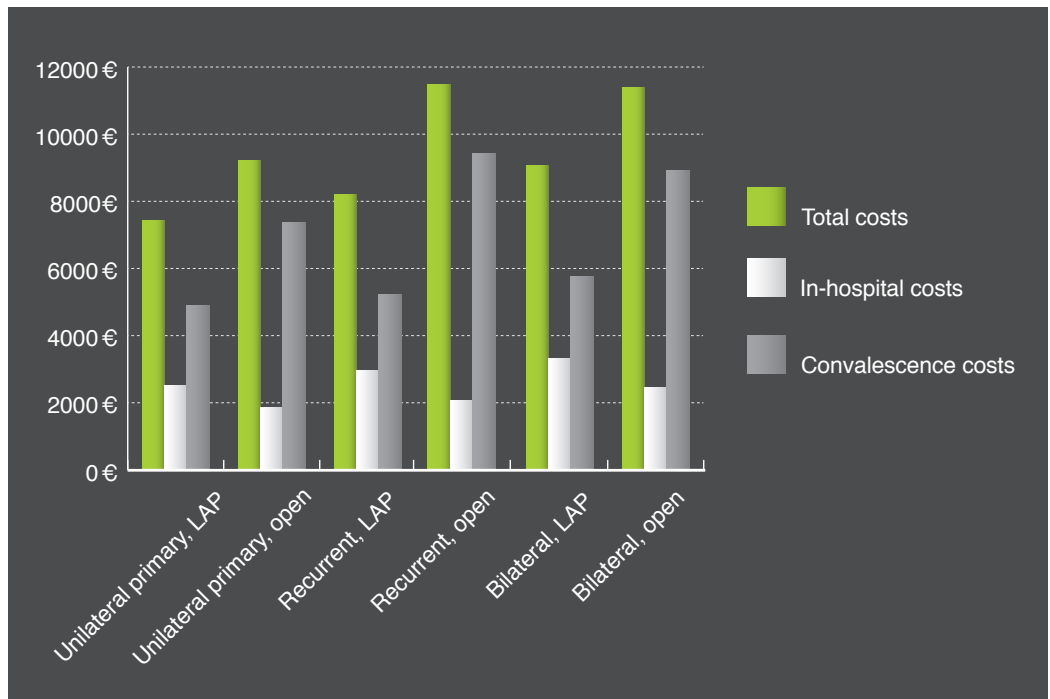
Figure 15. Costs of inguinal hernia treatment of employed patients according to subgroups of bilateral, recurrent, and unilateral primary hernias.

6 Discussion

6.1 GENERAL DISCUSSION

The results of this study show, that a recurrent inguinal hernia following a sutured repair should be treated with laparoscopic TEP, and the total societal costs of laparoscopic inguinal hernia surgery are less than the costs of Lichtenstein repair. The origin of intense pain in an inguinal hernia patient cannot be evaluated using MRI, but laparoscopic repair of these hernias significantly improves the patients' QoL. However, laparoscopic methods harbor an increased risk of serious complications.

The results of study I have already been evaluated in several meta-analyses (Dedemadi et al. 2010, Karthikesalingam et al. 2010, Yang et al. 2013, Li et al. 2014, Pisanu et al. 2015), and they potentially have had a partial influence in the update of the EHS guidelines regarding the treatment of recurrent hernia after a previous non-mesh repair (Miserez et al. 2014). As MRI is increasingly used, it is important to justify the use of additional imaging. In the context of painful inguinal hernias, MRI does not provide additional information regarding the origin of pain, and thus should be omitted from routine preoperative assessment, as shown in study II. Study III futher demonstrated that previous suspicions of an increased risk of severe complications after laparoscopic inguinal hernia repair were justified (EU Hernia Trialists Collaboration 2000, McCormack et al. 2003). Study IV demonstrated that despite of the risk for severe complications, the overall costs of laparoscopic inguinal hernia repairs are lower than open repair, thus the use of laparoscopic methods is justified, especially in the working population. Understanding these factors affecting the outcome of laparoscopic inguinal hernia repairs, proper attention has to be paid to training curricula of surgeons utilising laparoscopy in inguinal hernia treatment.

All these four studies were aimed at performing analyses from a clinical perspective, and therefore rigorous exclusion criteria was only applied in study II. On the contrary, studies I, III and IV include patients with concomitant coagulation disorders and in higher ASA risk classes, and thus represent the true cross section of patients undergoing inguinal hernia repair. Study I is the first published study to compare Lichtenstein hernioplasty and laparoscopic TEP repair in the treatment of recurrent hernias with an average of over 5 years of follow-up. Study II is fundamental in examining the potential role of MRI in detecting the origin of pain in inguinal hernia patients. Study III, on the other hand, is the first study to evaluate different inguinal hernia repair methods with a special focus on the severity of complications. Finally, study IV is the first study to examine total societal costs of inguinal hernia repair according to current guidelines using individual patient-level data.

6.1.1 Evaluation of patient selection

The patients in the prospective studies I and II were consecutive patients from the outpatient clinic of North Karelia Central Hospital. Rigorous exclusion criteria regarding previous lower abdominal surgery were only applied in study II to ensure a small risk of conversion during laparoscopic TEP. Conversion to open anterior repair could have distorted the postoperative evaluation of prolonged pain. Study I included also patients in higher ASA risk classes and patients on anticoagulative medications. These are patient groups that have been excluded in a number of other studies on recurrent inguinal hernias (Beets et al. 1999, Dedemadi et al. 2006, Eklund et al. 2007); the patients in study I thus better represent the actual population undergoing surgery for recurrent hernias. In the retrospective studies III and IV, the patients present the general population undergoing inguinal hernia repair, and thus the results of these

studies are easily generalisable to clinical practice. Also, the EHS guidelines for inguinal hernia surgery were followed in over 90% of the cases in study IV, indicating the hospital's good adherence to these international guidelines.

6.1.2 Evaluation of methods

The surgical techniques used in these studies are generally accepted and commonly used worldwide. The Lichtenstein repairs were performed according to the original description of the technique in studies I and IV, with the exception of fixating the cranial edge of the mesh with interrupted resorbable sutures, whereas the original description of the technique utilizes a continuous non-resorbable suture (Lichtenstein et al. 1989). However, this modification of the technique does not seem to have affected the recurrence or chronic pain rates in these studies. The meshes in open anterior hernia repairs (Prolene® and Optilene®) have been commonly in use during the years of inclusion.

The laparoscopic TEP was also performed in a widely accepted manner, with the only variations over the time being the changes from heavy-weight mesh (Biotech®) to light-weight mesh (TiMesh® light) and the decrease in usage of penetrating fixation (tackers). However, during studies I and IV both open and laparoscopic repair were performed using similar mesh weight; heavy-weight during study I and light-weight during study IV. Thus there is no risk that the choice of mesh could have influenced the rates of chronic pain favoring one method over the other.

The MRI protocol in study II was designed to detect possible inflammatory changes in the inguinal area. The sequences used were obtained from the authors of a previous publication studying these factors in the context of inguinal disruption (Paajanen et al. 2008).

The QoL questionnaire used was a widely adopted RAND-36 which has been validated in the Finnish population and whereby the average population level scores were available for comparison. Hernia-specific questionnaires were not used, since the only questionnaire available for both pre- and postoperative assessment is COMI-hernia. With only five questions, the COMI-hernia is a very course scale, and not likely to detect small differences in patient samples. Instead, hernia-specific symptoms were asked through a custom-made questionnaire which could be used both pre- and postoperatively.

The evaluation of costs of a treatment can be made by a number of different methods. The method chosen here was based on the actual monetary value of the treatment which is charged from the community and patients. Several publications have made very thorough calculations including the value of operating room minutes, pain medication pills and injections, as well as physicians' and nurses' salaries, and administratory expenses. The calculation of all these factors is difficult and leads to a potential of significant bias. In the Finnish healthcare system the treatment is charged in "packages" which include all medications, laboratory tests and radiology, as well as the salaries of personnel and the operating room use. These prices are actual prices charged from the community, and thus represent the true costs of the treatment. This method of cost calculation is obviously not suitable in heathcare systems where every medication and laboratory test is charged separately. However, in Finland, it gives a very good picture of the true costs of hernia treatment.

The allocation concealment and randomization in study I were performed in a widely used manner, and the risk of bias in these methods have been considered to be low (Pisanu et al. 2015). The statistical methods employed were kept relatively simple throughout the studies in order not to lose the relevance of the results in overly complicated statistical testing.

6.2 RECURRENT INGUINAL HERNIA REPAIR (STUDY I)

The results of this randomized clinical trial show, that TEP repair of recurrent inguinal hernia after previous open repair is superior to Lichtenstein repair in several important aspects affecting patient satisfaction. The results of this study are easily adapted to clinical practice, since no rigorous exclusion criteria were applied, but rather all consecutive recurrent hernias were included. The results are also in line with the current EHS guidelines (Simons et al. 2009, Miserez et al. 2014). As this study was published before the update of the guidelines, it is reasonable to believe that the results have had an influence on the conclusion of the update.

Preoperatively, the groups were comparable, and intraoperatively, there were no major differences between the groups. Laparoscopic techniques are often criticised for longer operative times also in the context of recurrent hernias (McCormack et al. 2003, Dedemadi et al. 2010, Karthikesalingam et al. 2010, Yang et al. 2013, Li et al. 2014, Pisanu et al. 2015), but this was not observed in this study. All consultants operating patients in this study were experienced in laparoscopic repairs prior to the beginning of the study, and this may eliminate the difference from the operating times between the two surgical methods.

The incidence of additional recurrences was higher in the open group, although this did not reach statistical significance. Also in the meta-analyses, no significant difference in re-recurrence rates have been noted (McCormack et al. 2003, Dedemadi et al. 2010, Karthikesalingam et al. 2010, Yang et al. 2013, Li et al. 2014, Pisanu et al. 2015). In individual studies, the re-recurrence rates vary between 0.4% and 8.3% for laparoscopic repairs and between 1% and 15.6% for open mesh repairs (Amid et al. 1995, Kumar et al. 1999, Scheuerlein et al. 2003, Feliu et al. 2004, Dedemadi et al. 2006, Eklund et al. 2007, Demetrashvili et al. 2011). With a follow-up of over 5 years on average, it is unlikely that new re-recurrences should be noted in this study group (Feliu et al. 2004).

The incidence of persistent postoperative pain after inguinal hernia repair is higher after open mesh repair than after laparoscopic repair (McCormack et al. 2003, Schmedt et al. 2005). In treatment of recurrent hernias, some studies have found significantly reduced rates of chronic pain after laparoscopic surgery (Yang et al. 2013, Pisanu et al. 2015), whereas others have failed to find any difference (Eklund et al. 2007, Dedemadi et al. 2010, Karthikesalingam et al. 2010, Demetrashvili et al. 2011, Li et al. 2014). In this study, laparoscopic repair of recurrent hernia resulted in significantly less persistent pain compared to open flat mesh repair. This difference was observed only more than a year after the surgery. Since the mesh causes a temporary inflammatory response, that may last over 6 months in some cases, it may explain why the difference between the groups only became evident after the first year.

Similarly to other trials and meta-analyses, the patients in the laparoscopic group experienced less early pain, and their duration of sick leave was shorter (Dedemadi et al. 2006, Eklund et al. 2007, Karthikesalingam et al. 2010, Demetrashvili et al. 2011, Pisanu et al. 2015). It is estimated, that for working patients, these immediate advantages may be able to financially counterbalance the higher absolute hospital cost of the laparoscopic procedure (Pisanu et al. 2015). However, no cost analysis has been made regarding the treatment of recurrent hernias.

In this study, there were no differences between the open and laparoscopic groups regarding other complications than the above-mentioned. Meta-analyses have suggested, that a laparoscopic procedure for recurrent hernia may result in less wound infections (Karthikesalingam et al. 2010, Yang et al. 2013, Li et al. 2014) and haematomas (Dedemadi et al. 2010), but these differences were not observed in this study.

6.3 MRI IN DIAGNOSTICS OF PAINFUL INGUINAL HERNIA (STUDY II)

The preoperative MRI showed no signs of pubic periostal irritation, haemorrhage, or soft tissue abnormalities, and thus was unable to recognize the source of preoperative pain, or to predict the outcome of the TEP repair.

The severe pain in some patients with inguinal hernia may be explained by several possible reasons. Hernia bulge may cause muscle tear, haemorrhage, inguinal nerve irritation, adjacent pubic bone irritation, or radiating scrotal pain. Preoperative MRI should be able to detect at least muscle tears, haemorrhage, and oedema around the pubic structures (Genovese et al. 2013). Earlier studies have shown some correlation between groin pain and the intensity of bone marrow oedema (BME) of the pubic symphysis in both elite athletes and physically active adults (Paajanen et al. 2008). The presence of BME findings may even correlate to immediate recovery from athletic pubalgia treated laparoscopically (Kuikka et al. 2015). In this study the hypothesis was that the overwhelming groin pain present in some patients with inguinal hernias could be a result of similar inflammatory changes in the pubic symphysis area. However, no pathological inflammatory findings could be detected in this series of patients with painful inguinal hernias. Also no differences were observed in the preoperative MRI between patients with prolonged postoperative pain at 6 months compared to their pain-free counterparts.

Therefore, MRI does not provide additional information for predicting prolonged pain after TEP repair of painful inguinal hernia.

6.4 PREDICTING POSTOPERATIVE PAIN AFTER TEP REPAIR OF INGUINAL HERNIA (STUDY II)

Previous studies have found several factors influencing the development of persistent postoperative pain; age, gender, psychosocial factors, genetic predisposition and the intensity of preoperative pain have all been shown to affect the likelihood of prolonged pain after surgical treatment (Kehlet et al. 2006, van Hecke et al. 2013). Specifically for inguinal hernia repair, younger age, preoperative pain, intense early postoperative pain, repair of recurrent hernia, the use of mesh and method of repair (open or laparoscopic), have variably been associated with development of persistent posthernioplasty pain (Callesen et al. 1999, Poobalan et al. 2001, Aasvang and Kehlet 2005, Kehlet et al. 2006). Nerve injury by some mechanism has been seen as an almost absolute prerequisite for development of chronic pain, but all patients with inguinal nerve damage do not develop chronic postsurgical pain. In addition, neurectomy has been successfully used in the treatment of CPIP (Kehlet et al. 2013, Werner 2014b). Currently it is not clear whether the nerve damage resulting in chronic pain is a result of a direct surgical injury to the nerve, or rather postoperative inflammatory changes associated especially with the use of mesh (Aasvang et al. 2008).

In this study, the four patients with prolonged postoperative pain at six months had higher preoperative VAS scores for pain than those patients without pain at six months. This repeats the findings of several previous studies (Poobalan et al. 2001, Wright et al. 2002, Bansal et al. 2013). Also, for the preoperative VAS score "disturbance caused by pain during last week" a cut-off value of 30/100 was detected; none of the patients with a VAS score under 30 developed prolonged pain, whereas all four painful patients rated this VAS score over 30.

6.5 CHANGES IN QUALITY OF LIFE FOLLOWING TEP REPAIR OF PAINFUL INGUINAL HERNIA (STUDY II)

The results of this study show, that laparoscopic TEP repair of painful inguinal hernia significantly improves quality of life.

Hernia surgery improves QoL irrespective of the surgical method used (Myers et al. 2010, Bansal et al. 2013, Coronini-Cronberg et al. 2013, Pierides et al. 2013). There are some data suggesting that laparoscopic repairs may improve QoL measures more than open repair techniques (McCormack et al. 2005, Myers et al. 2010, Coronini-Cronberg et al. 2013). For open mesh repair, some of the studies have found almost all categories in QoL scores (RAND-36/SF-36) improving significantly (Nikkolo et al. 2010, Nikkolo et al. 2014, Nikkolo et al. 2015), while others have shown, that hernia repair only increases QoL in more physical dimensions of RAND-36 (Pierides et al. 2013). For laparoscopic hernia repair the few available data suggest that an improvement can be reached in all dimensions of SF-36, without a significant difference between TAPP and TEP procedures (Bansal et al. 2013).

In this study, statistically significant improvement was reached in the dimensions bodily pain (P), physical function (PF), and role functioning/physical (RP). These three dimensions scored preoperatively significantly lower than the age-matched average, but returned to normal level after the hernia repair. Only the dimension of bodily pain remained below age-matched average, reflecting the lower values from the four patients with prolonged pain. Non-significant improvement was also seen in dimensions role functioning/emotional, social functioning, and general health perceptions.

6.6 COMPLICATION PROFILES AFTER INGUINAL HERNIA REPAIR (STUDY III)

The results of this registry-based study show that both laparoscopic and open non-mesh repairs of inguinal hernia are associated with a more severe complication profile than open mesh hernioplasties.

Compared to the open anterior approach, the proximity of major vascular and visceral structures makes them more vulnerable during laparoscopic repairs, where dissection takes place within deeper layers of the abdominal wall. A similar potential for visceral and bladder injuries is present in open non-mesh repairs during the suturing of deeper layers of the repair. However, both vascular and visceral injuries during inguinal hernia repair are rare. Based on over 31,000 laparoscopic repairs, the average rate for vascular injuries is 0.25% for TAPP and 0.42% for TEP (Bittner et al. 2011a). Based on RCTs, the rate of vascular injuries is up to 0.2% for open repairs (mixed non-mesh and mesh) and 0.09-0.3% for laparoscopic repairs (Scott et al. 2002, McCormack et al. 2003, Schmedt et al. 2005). In line with these results, the vascular complication rate was 0.01% for open mesh repairs, 0.00% for open non-mesh repairs and 0.05% for laparoscopic repairs, significantly favoring open surgery over laparoscopic repairs.

The frequency of visceral injuries is also low, and on average lower for TEP (0.11%) than for TAPP (0.21%) repairs (Bittner et al. 2011a). However, significantly lower visceral injury is observed in mixed open repairs (0.04-0.06%) than in laparoscopic repairs (0.1-0.3%) (McCormack et al. 2003, Schmedt et al. 2005), but open non-mesh repairs seem to carry somewhat higher risk for visceral injuries (0.07%, Scott et al. 2002). Accordingly, the visceral complications were significantly more prevalent in the open non-mesh (0.07%) and laparoscopic (0.1%) groups than in the open mesh group (0.01%).

The risk of infection is present in all surgical procedures. Superficial wound infections usually carry less long-term consequences, but deep infections extending to the mesh may lead to prolonged treatment, repeated surgery and ultimately require the removal of mesh. Superficial infections are significantly more prevalent after open than laparoscopic surgery (McCormack et al. 2003, Schmedt et al. 2005, Lundström et al. 2012), although the rates of superficial infections vary between 1.4% and 3.1% for open repairs, and between 0.6% and 1.5% for laparoscopic repairs in large patient materials (McCormack et al. 2003, Schmedt et al. 2005, Lundström et al. 2012). In this study, the number of claims after superficial wound infections was too small to draw any

conclusions of their true frequency. However, the relative number of claims was significantly higher after open procedures than laparoscopic surgery.

Based on RCTs, the frequency of deep infections seems very similar between methods since only three cases were found from 41 RCTs; one in each of the groups (McCormack et al. 2003). RCTs and comparative series have found the rate of deep infections between 0.02% and 0.08% in all groups (Scott et al. 2002, McCormack et al. 2003, Schmedt et al. 2005, Bittner et al. 2011a). In the present study, deep infections were claimed by 0.02% of patient in the open mesh group, 0.04% of the patients in the open non-mesh group and 0.09% of the patients in the laparoscopic group, statistically significantly favouring open surgery.

Chronic groin pain after inguinal hernioplasty is a well-known complication to surgeons, but difficult to evaluate. The rates of chronic pain or numbness vary greatly between trials from almost zero to over 50%, depending on the definition of chronic pain and the method and length of follow-up. The majority on clinical trials as well as meta-analyses conclude, that the laparoscopic approach reduces the likelihood of chronic postoperative pain (Wright et al. 1996, Wellwood et al. 1998, Johansson et al. 1999, Andersson et al. 2003, Mahon et al. 2003, McCormack et al. 2003, Heikkinen et al. 2004, Schmedt et al. 2005, Eklund et al. 2006). However, a number of studies challenge this view, especially regarding recurrent hernias (Khoury 1995, Kozol et al. 1997, Zieren et al. 1998, Dedemadi et al. 2010, Karthikesalingam et al. 2010). The average rate of chronic pain has been set at 12% (Perkins and Kehlet 2000), while 2-4% of the patients experience severe pain (Werner 2014b). In this study, the claimed rates of chronic pain were significantly lower, between 0.09% and 0.36%. Unlike in RCTs, in the present study only patients with significant impairment of everyday life were likely to report their pain. Another explanation is, that most patients were preoperatively warned about the possibility of chronic pain, and they did not perceive it as a complication. Nevertheless, the greatest prevalence of chronic pain seemed to be in the open non-mesh group, replicating the findings of a meta-analysis (Scott et al. 2002). The probable mechanisms include the tension created in sutured repairs, and the entrapment of nerves within the sutures.

An increased risk of hernia recurrence is reported with non-mesh repairs (Scott et al. 2002, McCormack et al. 2003). This is well demonstrated in this study, as the risk of early recurrence was low (0.04%) for both open mesh and laparoscopic repairs, whereas a significantly higher risk of a recurrence was observed in the open non-mesh group (0.15%).

In conclusion, the claimed complications after both laparoscopic and open non-mesh repairs are more frequent and more severe compared to open mesh repairs. In laparoscopic repairs, deep infections, vascular and visceral injuries are more frequent whereas in open non-mesh repairs, visceral complications, recurrences, and chronic pain predominate.

6.7 TOTAL SOCIETAL COSTS OF INGUINAL HERNIA REPAIR (STUDY IV)

The results of this study confirm that from a societal perspective laparoscopic inguinal hernioplasty is more cost-effective than open flat mesh repair in employed patients. This finding is true even when laparoscopic technique was more often employed in repairing complicated hernias, ie. bilateral and recurrent, as current guidelines suggest. Also, the same finding persisted in all subgroup analyses of bilateral, recurrent, and unilateral primary hernias.

The surgical outcomes in this study compare favorably with previous studies. Based on a meta-analysis, the total morbidity is up to 28% for both laparoscopic and Lichtenstein repairs (Schmedt et al. 2005). In this study, the registered complication rates are between 18.4% and 19.2%. Most individual complication types were also less prevalent in this series compared to meta-analyses (Table 15). In contrast to RCTs, the current study registers only complications that lead to additional usage of health services.

Table 15. Complication rates in study IV compared to previous meta-analyses.

Complication type	Study IV	McCormack 2003	Schmedt 2005
Superficial infection	0.6% / 0.0 %	3.1% / 1.5%	2.7% / 1.0%-1.2%
Deep infection	0.0% / 0.2 %	0.08% / 0.05%	N/A
Hematoma	6.3% / 5.7%	10.5% / 8.7%	16% / 8.6%-13.1%
Bowel complications	0.0% / 2.2%	0.04% / 0.3%	0.06% / 0.1%
Recurrence	1.9% / 1.7%	3.1% / 2.7%	2.7% / 3.2%-5.5%
Prolonged pain / neuralgia	8.1% / 3.9%	19.1 % / 13.8%	4.5%-12.7% / 5.2%-7.6%
Urinary retention	1.5% / 5.0%	N/A	2.7% / 3.5%
Other urological complications	0.6% / 1.7 %	N/A	0.8% / 0.7%
Other complications	1.5% / 0.9%	N/A	N/A

Open mesh / laparoscopic group.

Several earlier studies have dissected the in-hospital costs of open and laparoscopic inguinal hernia surgery (Table 8). Several factors may create a potential for bias in these studies (Table 16). In an attempt to evaluate the true economic impact of inguinal hernia surgery, such results are of limited value. In this study, the economic analysis of in-hospital costs was based on actual invoicing determined by the use of medical services in a non-profit organization, thus presenting more than an estimate of the costs. This revealed a significant difference favouring Lichtenstein repair (1,986 € vs. 3,035 €, p<0.001). Because of differences in the treatment protocols during the study period, the costs of treatment at the surgical ward were overrepresented, especially in the laparoscopic group. Based on the current treatment protocols, inguinal hernia repair would still be more expensive laparoscopically (2,181 € vs. 2,788 €, p<0.001), but the difference would be significantly smaller than previously (1,256 vs. 607 euros more for the laparoscopic repair).

Table 16. Potential biases in earlier cost studies

Factor	Limitation	Concern	References
By-product of RCT	Limited to primary unilateral hernias	Guidelines on hernia surgery are not followed	Heikkinen 1998a Heikkinen 1998b Zieren 1998 Anadol 2004 Khajanchee 2004 Hynes 2006 Butler 2007 Langeveld 2010 Eklund 2010
Long operating times and large conversion rates	Surgeons may have not passed the learning curve	Overestimation of OR time and cost in laparoscopic repairs	Paganini 1998 Hildebrandt 2003 Khajanchee 2004 Butler 2007 Schneider 2003 Langeveld 2010 Bittner 2015
Calculating only the cost of disposable equipment	Assuming otherwise similar resource consumption between groups	Cost calculations do not consider all variables of treatment	Paganini 1998 Zieren 1998 Butler 2007

The costs of convalescence from work are rarely included in the cost analyses. It has been estimated by many authors, that the shorter sick leave after laparoscopic surgery may offset the expenses from the more expensive surgical treatment itself (Schneider et al. 2003, Stylopoulos et al. 2003, Gholghesaei et al. 2005, McCormack et al. 2005). However, not all authors have reached the same conclusions (Eklund et al. 2010). The large differences in the duration of convalescence

between different trials suggest that the differences in cultural and sociodemographic factors may be more influential than the repair method alone. In addition, the type of insurance has been shown to affect the duration of convalescence (Feliu-Pala et al. 2001). For the non-working population, laparoscopic hernia repair cannot be justified by economic calculations since there is no monetary benefit from shorter convalescence. If only economics were considered, the non-working patients should be treated with open techniques in all subgroups.

Very few cost analyses have considered the cost of complications. Laparoscopic inguinal hernia repair is known to associate with more severe complications than open mesh repair (EU Hernia Trialists Collaboration 2000, McCormack et al. 2003, study III). Since complications increase the use of health care resources, their costs should be included in the cost analyses of surgical treatments. Only four publications have attempted to include the cost of complications in their analysis (Table 17). All of them present with methodological concerns, and the results may not be applicable to regular practice. In this study, complications after laparoscopic procedures were significantly more expensive than those after open surgery (in-hospital costs 2,099 € vs. 1,087 €, p<0.001, and costs of convalescence 2,083 € vs. 590 €, p<0.001), but they were unable to offset the savings obtained from the shorter convalescence of the employed patients after the index repair.

Table 17. Previous studies on costs of complications

Reference	Method of complication-related cost calculation	Problems in the cost analysis
Wellwood 1998	All in-hospital costs related to complications	Time frame only 3 months – recurrences? chronic pain?
Andersson 2003	In-hospital costs of three reoperations	Costs attributable to other complications not requiring reoperations?
Hynes 2006	included in the costs of all health care resource use within 2 years of the index repair	Costs of hernia surgery complications are not separated from other health care costs
Eklund 2010	All in-hospital and societal costs related to complications	1) Only men with unilateral primary hernias 2) Cost calculations based on 27 patients/group from a single hospital 3) 33% of recurrences in TEP group attributable to a single surgeon

6.8 LIMITATIONS OF THE STUDY

Specifically in studies I and II, the main limitation is the small number of subjects. For study I, recruiting hundreds of patients would have been increasingly difficult, when most repairs are performed with mesh-based techniques, and the number of recurrences steadily decreases. At the same time, care had to be taken not to modify the surgical techniques significantly during the study period. Thus, five years was determined as an adequate time to reach a relevant number of recurrent hernia repairs, while the surgical techniques remained without significant changes. Study II was designed as a pilot study to search for possible changes in the MRI of patients with painful inguinal hernias. As there is no literature on the subject, sample size estimation was not feasible. Pain scores and QoL measurements were secondary end-points. Therefore it may be criticised that the study was not adequately powered to evaluate changes in these measurements, and type II error may be present. This calls for verification of the pain and QoL score results in larger patient groups.

Studies III and IV were both retrospective, and thus carry the evident limitations of such studies. Most importantly, the registry data are only as reliable as the data entries into the registry. Because of the passive reporting to the FPIC, it is probable that not all complications were reported. This is most likely true especially for minor complications such as superficial wound infections that do not require additional in-hospital treatment or have otherwise severe consequences. The FPIC does not usually compensate for complications that are considered common (frequency of over 2%), unless the complication has had severe consequences. It is naturally possible, that even some severe complications could have been left out of the registry data. However, there is no reason, why more complications would go unreported in the group of open mesh repairs when compared to both open non-mesh and laparoscopic repairs.

In study III, there is a chance that the learning curve effect contributes to more complications after laparoscopic surgery. In most Finnish hospitals, the laparoscopic repairs became more widely used in late 1990s, and, thus, in 2002 all surgeons could not have been yet through the learning curve. This may overrepresent the frequency of complications after laparoscopic repairs. However, since new generations of surgeons are constantly along the learning curve of laparoscopic repairs even today, the learning curve effect in laparoscopic repairs can never be eliminated at a population level, and thus it will continue to show in registries such as the FPIC registry.

The results of study IV may not be applicable to health care systems very different from the Finnish system. Specifically, if the treatment unit is a private clinic aiming for profit, the economic analyses may be weighted very differently. In addition, patient charges and reimbursement rates have been shown to differ between open and laparoscopic repairs much more than might be expected from the actual costs (Khajanchee et al. 2004, Jacobs and Morrison 2008). This may cause the price of laparoscopic surgery to increase to a level, where it is no longer a valid option from the payers' point of view, irrespective of the clinical results.

6.9 IMPLICATIONS AND FUTURE PERSPECTIVES

Based on the assumption that "tissue failure" accounts for late recurrences even decades after primary repair, it is likely that surgeons will continue to face recurrent hernias after previous sutured repairs, although in declining numbers. According to the result in study I, these recurrent hernias should be treated with laparoscopic TEP rather than open Lichtenstein repair, in order to avoid the most common complaint, long-lasting pain after surgery. Faster recuperation from surgery is another benefit in laparoscopic treatment of recurrent inguinal hernias.

Since the incidence of recurrences after inguinal hernia repair decreases, chronic pain has become the single most important outcome measure in inguinal hernia surgery. As prolonged pain after inguinal hernia repair is observed in over half of the patients at some interval (Nikkolo et al. 2010), the effects of CPIP on both the patients and the society cannot be ignored. The definition of CPIP should finally reach a consensus, and all publications thereafter should be demanded to adhere to the definitions decided. Only then will the results of studies on CPIP be comparable with each other, and the surgical community will be able to truly move forward in finding solutions in both prevention and treatment of this complication.

As there were significant differences in preoperative pain scores between those patients experiencing pain at six months after surgery, and those without pain in study II, it would be interesting to replicate these relatively simple measurements in a larger population. If the result persists, it might be able to provide clinicians with a simple tool to preoperatively screen patients to find those in greater risk of prolonged pain. Also, as preoperative and early postoperative pain predict the development of prolonged pain, it would be interesting to test the effect of aggressive multimodal pain control pre- and perioperatively, for example using anti-inflammatory pain medication, corticosteroids, gabapentinoids and possibly an infusion of local anesthetic to the

operative area. Another interesting possibility for pain control would be a mesh releasing local anesthetic into the operative area for several weeks.

Severe but rare complications are more common after laparoscopic inguinal hernia repairs. Since RCTs are not powered to detect these rare complications, prospective all-inclusive registries are needed for quality control everywhere, including Finland. Inguinal hernia repair is a high-volume surgery, and even small differences in treatment results may be significant at a society level. Therefore, forming nationwide registries on inguinal hernias has to be promoted at last. In Denmark and Sweden, national hernia databases have provided the surgical community with data on surgical results and complications, and recommendations have led to decreased recurrences, higher use of ambulatory surgery, and better documentation on chronic pain (Kehlet and Bay-Nielsen 2008). A similar effort in evaluation of methods and quality control should be an absolute prerequisite of inguinal hernia surgery in Finland.

Being aware of cost-effectiveness is an inevitable part of todays' surgical practice. With the era of increasing demands without similar increase in resources, all physicians must be aware of the total financial impact of the treatments offered to patients. In the future, calculations of costs have to be combined with information on the QoL both pre- and postoperative, in order to fully understand the costs and gains of different procedures or treatments. A nationwide registry would also be helpful in collecting these data. As only a small fraction of costs can be directly controlled by the surgeon, the distribution of total costs must be made known to the policy-makers to facilitate the decisions on resource distribution.

7 Conclusions

Based on this study, the following conclusions regarding inguinal hernia treatment can be drawn:

1) For recurrent hernias after previous open repairs, laparoscopic TEP should be preferred over the Lichtenstein technique in order to avoid chronic pain symptoms and to decrease the duration of convalescence.
2) Preoperative MRI is unable to detect reasons for preoperative pain, nor to predict prolonged postoperative pain after laparoscopic TEP for painful inguinal hernias.
3) Painful inguinal hernias significantly impair the patients' quality of life, but laparoscopic TEP returns quality of life postoperatively back to age-matched average.
4) Intense preoperative pain seems to predict postoperative prolonged pain after laparoscopic TEP.
5) Complications after laparoscopic surgery for inguinal hernia are more severe than complications after open surgery with mesh.
6) Total societal costs, including costs derived from convalescence and treatment of complications, are lower for laparoscopic TEP than Lichtenstein repair in employed patients. For the non-working population, the Lichtenstein hernioplasty is more cost-effective, if quality of life measures are not considered.

8 References

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Inguinal hernia repair is the most common elective procedure in general surgery. Most repairs are performed to improve quality of life (QoL). In this study, laparoscopic totally extraperitoneal (TEP) repair provides less immediate and chronic pain than Lichtenstein operation when operating a recurrence after open inguinal hernia repair. TEP also significantly improves QoL, and is less expensive in working population. However, the risk of serious complications is elevated in laparoscopic surgery.

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