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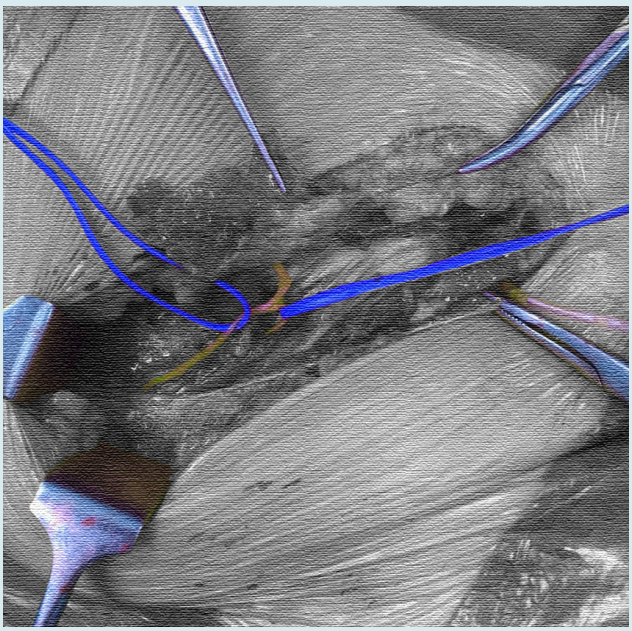

Long term evaluation of pain, sexual discomfort, and comparison of pain assessment scales after inguinal hernia surgery

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LUND UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on February 14th 2025, at 13:00, in MFC lilla Aulan, Skåne University Hospital, Malmö, Jan Waldenströms gata 5.

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Title:
Long term evaluation of pain, sexual discomfort, and comparison of pain assessment scales after inguinal hernia surgery

Abstract:

Background:

Chronic postoperative inguinal pain (CPIP) affecting daily activities is reported in 8-12% and more severe pain between 0.6-6% after inguinal hernia repair. CPIP incidences are based on a variety of PROMs and definitions of pain, making comparison between studies difficult. Pain during sexual activity (SEX-P) is rarely studied in randomized settings. Few RCTs with large cohorts report on CPIP after 5-year follow-up. The TEPLICH RCT compares TEP to Lichtenstein repair in men with primary inguinal hernia, in a setting where all surgeons were department-certified hernia-specialists, trained according to the same curriculum. Long-term CPIP, SEX-P and comparison of three pain assessment instruments were the study´s main objectives.

Paper I compare 416 patients regarding short-term outcomes, CPIP, recurrence, QoL and sensory disturbances up to 3 years. No difference in CPIP, recurrence or QoL was observed but TEP had shorter operative time, shorter time to recovery, less complications and sensory changes.

Paper II compare the subgroup of 30–60-year-old men regarding SEX-P, without differences between groups up to 3 years.

Paper III is a long-term questionnaire- and patient record-based follow-up including 322 patients, mean 8 years after surgery. CPIP present at 3 years persisted without differences between groups. No additional recurrence occurred after 3 years.

Paper IV evaluates VAS, Cunningham pain scale and Inguinal Pain Questionnaire for correlation and interchangeability between scales. Interchangeability couldn't be confirmed between any of the pain scales. Optimized VAS cut-offs based on Cuningham categories were calculated.

Conclusion: TEP showed favorable short-term outcomes and less sensory changes. No differences in CPIP, SEX-P, recurrence or QoL were found at any follow-up occasion. Compared PROMs were not interchangeable underlining the difficulties in comparing pain between studies, and motivates the use of 2 PROMs when evaluating pain. Calculated optimal VAS cut-offs may be used as a reference in future studies.

Key words: Inguinal hernia, TEP, Lichtenstein, chronic pain, recurrence, pain at sexual activity, comparison of pain assessment scales

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To my family

Table of Contents

List of papers

This thesis is based on the following articles, which in the text will be referenced to using Roman numerals.

I. Randomized clinical trial comparing total extraperitoneal with Lichtenstein inguinal hernia repair (TEPLICH trial). Gutlic N, Gutlic A, Petersson U, Rogmark P, Montgomery A. The British journal of surgery. 2019;106(7):845-55.

II. Pain with sexual activity at 1 and 3 years: Comparing total extraperitoneal with Lichtenstein inguinal hernia repair in a randomized setting (TEPLICH trial). Gutlic A, Rogmark P, Gutlic N, Petersson U, Montgomery A. Surgery. 2022;172(5):1463-70.

III. Long term inguinal pain after TEP or Lichtenstein repair: the TEPLICH RCT 8 years follow-up. Gutlic A, Petersson U, Rogmark P, Montgomery A. Hernia: the journal of hernias and abdominal wall surgery. 2024;29(1):49.

IV. Comparison of Inguinal Pain Questionnaire, Cunningham pain scale and VAS in inguinal hernia surgery. Gutlic A, Rogmark P, Montgomery A, Petersson U. *In manuscript.*

Abbreviations

ASA = American Society of Anesthesiologists (physical status classification system)

BMI = Body Mass Index

CI = Confidence Interval

CPIP = Chronic Postoperative Inguinal Pain

EHS = European Hernia Society

GFN = Genitofemoral Nerve

IHN = Iliohypogastric Nerve

IIN = Ilioinguinal Nerve

IPQ = Inguinal Pain Questionnaire

IQR. = Interquartile Range

NRS = Numerical Rating Scale

OR = Odds Ratio

PROM = Patient Reported Outcome Measure

QoL = Quality of Life

RCT = Randomized Controlled Trial

SD = Standard Deviation

SEX-P = Sex Pain, pain at sexual activity

SHR = Swedish Hernia Register

TAPP = Transabdominal Preperitoneal Patch

TEP = Totally Extraperitoneal Patch

VAS = Visual Analog Scale

Thesis Overview

Publication	Aim	Method	Results/conclusions
Paper I Randomized clinical trial comparing total extraperitoneal with Lichtenstein inguinal hernia repair (TEPLICH trial)	To compare TEP to Lichtenstein regarding pain, QoL, recurrence and surgical harm at 1 and 3 years in men with unilateral primary inguinal hernias	RCT including 480 men, 30-75 years, randomized to TEP or Lichtenstein repair where physical exam, pain questionnaires (IPQ, Cunningham) and SF-36 preop, 1 and 3 years postop were used for evaluation	Low rates of pain, harm, recurrence, and improved QoL with high patient satisfaction after surgery, without differences between groups were observed, while complications and sensory changes were more frequent in Lichtenstein
Paper II Pain with sexual activity at 1 and 3 years: Comparing total extraperitoneal with Lichtenstein inguinal hernia repair in a randomized setting (TEPLICH trial)	To specifically compare pain at sexual activity (SEX-P) and QoL 1 and 3 years after TEP and Lichtenstein repair in the TEPLICH trial	A subgroup of men, 30-60 years old, in the TEPLICH trial answered a questionnaire on pain/discomfort at sexual activity in addition to physical examination and questionnaires mentioned above	Low rates of SEX-P and improved QoL after surgery without differences between groups was observed, while a neuropathic pain type was more frequently reported in Lichtenstein, and risk factors for SEX-P were preoperative SEX-P and a Lichtenstein procedure
Paper III Long term inguinal pain after TEP or Lichtenstein repair – the TEPLICH RCT 8 years follow-up	To evaluate long-term pain, QoL, recurrence rate and harm due to surgery after 8 years	Questionnaire based follow-up of 322 patients answering the TEPLICH questionnaires with an additional chart review and telephone interviews performed for new pain/discomfort or recurrence	The low chronic pain rates observed at 3 years remained at 8 years and few patients reported new onset of pain occurring between 3-8 years, without differences between groups, and no additional recurrences occurred
Paper IV Comparison of Inguinal Pain Questionnaire, Cunningham pain scale and VAS in inguinal hernia surgery	To evaluate VAS, IPQ and Cunningham in TEPLICH patients available for follow-up at 8 years, regarding interchangeability between scales	Individual patient´s Cunningham results were compared to their IPQ and VAS notes and scrutinized for evaluation of correlation and agreement	Pain scales were overall not interchangeable but the calculated optimal VAS cut-offs based on Cunningham can serve as a reference for future studies measuring CPIP using VAS

Introduction

Background

History of groin hernia treatment

The history and management of groin hernias can be categorized into five eras, ranging from the ancient to the modern era of tension-free hernia repair. (1).

During the ancient era, signs of potential hernia surgery have been found on the mummy of Pharaoh Merneptah (†1203 BC) who showed a large groin wound with the scrotum excised which might be suggestive of hernia surgery. In 900 BC physicians in Alexandria used fitting bandages to treat inguinal hernias. Five centuries later, the ancient Greeks learned to differentiated between a hernia and a hydrocele by the former being reducible and the latter illuminable. The Roman nobleman Cornelius Celsus wrote one of the first descriptions of surgical techniques for hernia repair around the birth of Christ which included removal of the hernia sac through a groin incision where the cord was dissected from the sac and the wound was left open to granulate. There was no major progress in surgical techniques during the Middle Ages and customized hernia belts were probably the recommended treatment. In the sixteenth century, the Italian anatomist Gabriele Fallopio came to advocate surgical treatment with wide excision of the hernia, including the skin and hernia contents (2). It is not difficult to image the life-threatening consequences of such treatment, and the barber-surgeons of that time seem to have considered surgery “only for marked hernias, which could not be held even with the strongest and sturdiest bands at their right place” (3).

During the 17th to 19th century the groin anatomy was elucidated through detailed dissections and many well renowned physicians such as Richter, de Gimbernat, Cooper and Hesselbach made contributions to herniology which have withstood the test of time. The development of more modern surgical techniques did, however, not begin until the mid-19th century. Despite increased knowledge of anatomy, opening the inguinal canal was frequently complicated by severe sepsis and recurrences due to inadequate sterile conditions and lack of surgical technique. It was not until Bassini's contributions in 1887, with his description of the first open anterior tissue reconstructive repair (4), that hernia surgery transitioned into a more modern era with acceptable recurrence and mortality rates.

The Bassini repair aims to restore the inguinal canal to its pre-hernia state by suturing the conjoined tendon of the transversus abdominis muscle and the internal oblique muscle to the inguinal ligament, thereby closing the hernia orifice and re-creating the posterior wall of the inguinal canal. The Bassini repair became a breakthrough with improved results, and numerous modifications of the Bassini technique have been presented over the years. To various extent all these methods creates tension on the tissues used to close the hernia orifice which is a risk for recurrence.

Elaboration of techniques with the intent to decrease recurrence rates and to facilitate the procedure have continuously been ongoing over time, and a major evolutionary step in open anterior hernia repair was the introduction of reinforcing synthetic mesh, first introduced by Uscher in 1959 (5). Mesh made it possible to perform a durable repair without tension. The most extensively used tension-free mesh technique today is the Lichtenstein repair, presented in 1984 (6).

The preperitoneal space allows access to both the inguinal and the femoral regions for hernia repair. Stoppa described a preperitoneal approach for mesh repair of complex inguinal and femoral hernias in 1969 (7). He applied a giant mesh, reinforcing the entire preperitoneal space on both sides through a midline preperitoneal dissection. Another technique is the Nyhus approach which initially was a sutured repair with access to the hernia through a transverse incision above the groin.

The development of laparo-endoscopic techniques for inguinal and femoral hernia repair, followed the introduction of laparoscopic and endoscopic minimally invasive surgery. The principle is minimally invasive dissection of the preperitoneal space to enable application of a mesh covering the groin from the inside. This can be achieved through a laparoscopic transabdominal (TAPP=transabdominal preperitoneal patch) or endoscopic extraperitoneal (TEP=totally extraperitoneal patch) approach.

With atraumatic techniques, inguinal hernia surgery, open or laparo-endoscopic, is today almost exclusively performed as day case surgery and decreasing recurrence rates has shifted the postoperative complication focus from recurrence towards persisting or postoperatively arising chronic pain. The main purpose of this thesis is to humbly contribute to some further elucidation on chronic pain.

Incidence and gender differences

Groin hernia is divided in inguinal hernia appearing above the inguinal ligament, and femoral hernia appearing below the inguinal ligament in the femoral canal. Inguinal hernia is furthermore divided into medial or direct hernias, appearing medially of the inferior epigastric vessels, and lateral or indirect hernias appearing laterally of the inferior epigastric vessels.

Inguinal hernias requiring surgery in men exhibit a bimodal age distribution, with prevalence peaking in two distinct age groups: 0-5 years and 75-80 years (8). From

the 25th gestational week, the testicle descends from its retroperitoneal position into the inguinal canal carrying with it a part of the peritoneum which becomes the processus vaginalis (9, 10). During normal development the processus vaginalis closes and becomes the tunica vaginalis severing the connection between the intraperitoneal cavity and the inguinal canal. If the processus vaginalis fails to close, it results in a patent processus vaginalis, which is a predisposing factor for developing an indirect inguinal hernia in young age. The 20-year cumulative incidence of developing an inguinal hernia among men aged 60-74 is 23% (11) and the lifetime risk of having an inguinal hernia repair is 27% for men, indicating that the incidence is particularly high in older age groups (12), and 3% for women.

The lower incidence of inguinal hernia in women compared to men can be attributed to anatomical differences in the pelvis. A study has shown that men have an internal inguinal ring that is nearly twice as wide, while women have a broader rectus abdominis muscle (13). These anatomical distinctions likely contribute to the reduced likelihood of inguinal hernia development in women. Women are, on the other hand, more prone to develop femoral hernias than men which may be explained by women having a wider pelvis.

The high incidences are reflected in the fact that inguinal hernia surgery is one of the most common surgical procedures and the most frequently performed groin operation, with some 20 million operations annually worldwide. Operations are performed with a ratio of 9:1 between men and women, corresponding to the differences in hernia incidence.

The Swedish Hernia Register – SHR

The SHR was founded in 1992 by Professor Erik Nilsson with the aim of nationally surveying hernia repair techniques and outcomes and has been assigned the task to assess the quality of hernia care in Sweden. Around 95% of all groin hernia procedures performed in Sweden today are registered in the SHR and so far, more than 360 000 hernia operations are registered. On-site evaluations at selected participating centers are performed yearly where register data is compared with patient records to ascertain register data validity. The primary quality indicator assessed is the 5-year reoperation rate. Among many other indicators are patient-reported outcomes including chronic pain and satisfaction with surgery. A questionnaire is sent to patients 1 year postoperatively to assess these PROMs.

A yearly report is launched, presenting national trends regarding type of operation, the risk for reoperation, type of anaesthesia, number of emergency vs elective operations, 30-day complications and more. The SHR database is used for prospective and retrospective research, which has resulted in 70 publications until the end of 2023. Data from the register has contributed to new and improved recommendations in hernia surgery, both on a national and international level.

Furthermore, analysis of data for each participating center can be compared with the national means, providing a valuable opportunity for internal quality control, adherence to guidelines and improvement.

SHR provides valuable updated data available for everyone. The number of operations for groin hernia, i.e. inguinal and femoral hernia, performed and registered in the SHR during 2023 was 18 425 (www.svensktbrackregister.se/images/Årsrapporter/Årsrapport2023.pdf). Some data from the SHR 2023 annual report is summarized in Table 1.

Table 1. Compilation of data from the SHR annual report 2023

SHR 2023	Total	Men	Women
Hernia op (n)	18 425	16 475	1 950
Op for recurrence (%)	8.2	8.7	3.4
Lateral (%)		54	53
Medial (%)		34	20
Femoral (%)		1.5	25
Bilateral (%)	9.7	9.5	13.3
Emergency op (%)	4.2	3.5	10.8

The change in surgical techniques over the years is also reported from the SHR and in figure 1 data for men is extracted and divided in open and endo/laparoscopic operations. Among techniques, a decreasing trend in the use of Lichtenstein is seen with a shift towards an increased use of TEP which constitutes 83% of the endo/laparoscopic operations for groin hernias in Sweden today, see Figure 1.

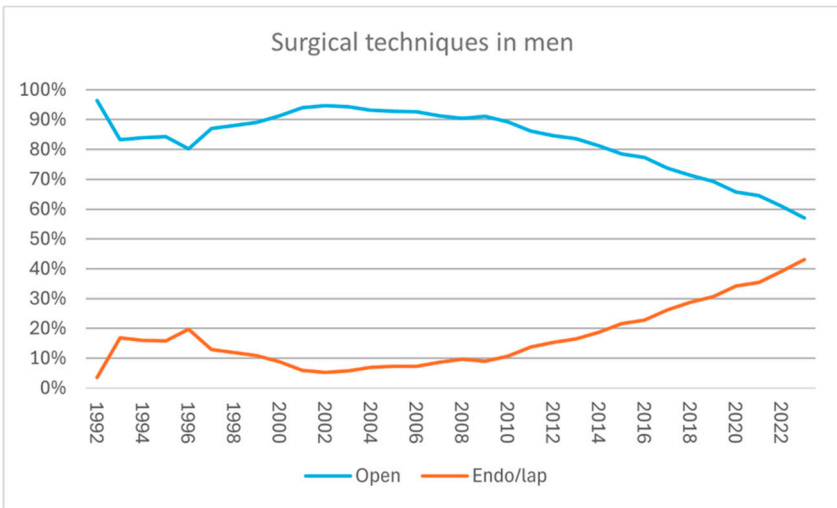


Figure 1. Changes in surgical techniques in men 1992-2023 (data from the SHR)

With the 95% coverage on a national basis, data obtained from SHR reflects the hernia population, treatment and outcome in a wider sense than data from randomized controlled trials and therefore provide better generalizability and external validity. The advantage of randomized studies, on the other hand, lies in the standardization of surgical performance, the randomization effect itself with elimination of confounders, and the added internal validity that comes with it.

Risk factors for inguinal hernia development and recurrence

Risk factors for primary inguinal hernia

As mentioned earlier, a patent processus vaginalis increases the likelihood of developing a lateral inguinal hernia. A prolonged increase in intra-abdominal pressure from activities like coughing is associated with the formation of lateral, but not medial hernias, likely due to a simultaneous presence of a patent processus vaginalis (14).

A family hernia history also elevates the risk across all ages, with the strongest hereditary link observed in female-to-female inheritance patterns (15).

Alterations in connective tissue may predispose to the development of inguinal hernias. Fibrillar type I and III collagen are the dominating components of the interstitial matrix. The tensile strength of fibrillar type I collagen is superior to that of type III, and inguinal hernia patients have been shown to have a decreased type I:III collagen ratio, possibly more so in patients with direct hernias (16). Collagen type IV is essential for basement membrane assembly and the turnover has been shown to be increased, due to increased synthesis and decreased breakdown, in inguinal hernia patients compared to healthy controls (17).

Enzymes involved in maintaining collagen ratios and connective tissue homeostasis are matrix metalloproteinases (MMPs), which break down the extracellular matrix, and lysyl oxidase that cross links elastin and collagen which provides strength and elasticity to connective tissues (18, 19). Increased levels of MMPs are seen in both medial and lateral hernias, while intraoperative specimens of transversalis muscle showed lower levels of lysyl oxidase and increased levels of elastase in direct compared to indirect hernias (19).

Furthermore, patients with connective tissue disorders, such as Ehlers-Danlos and Marfan syndromes, are at increased risk of developing inguinal hernias (20, 21), underlining the importance of collagen disorders in inguinal hernia pathogenesis.

Additional patient related risk factors are age, male gender, earlier open radical prostatectomy and low BMI (14). Heavy smoking and black race, on the other hand, have shown inverse correlation with inguinal hernia incidence (21, 22).

Risk factors for recurrence

Risk factors for a recurrence after a previous inguinal hernia repair can be patient-related or due to factors associated with surgery. Patient-related risks for inguinal hernia recurrence are female gender, obesity, earlier repair of a medial hernia, smoking, occurrence of bilateral hernias, yearly hernia-center repair volume, and mode of admission at operation. The pooled relative risks for recurrence for some risk factors according to a meta-analysis by Buchart et al. are presented in Table 2 (23).

Table 2. Risk factors for recurrence and their pooled relative risks

Risk factors for recurrence	Relative risk (95% CI)
Female sex	1.38 (1.28-1.48)
BMI 25-30 vs 20-25	1.19 (1.0-1.4)
Medial hernia	1.91 (1.62-2.26)
Smoking	2.53 (1.43-4.47

The surgeons´ experience is a decisive factor for both TEP and Lichtenstein regarding incidence of recurrence (24, 25). For TEP, the recurrence rate has been seen to decrease after the surgeon has performed at least 25 procedures and for Lichtenstein higher recurrence rates are reported for surgeons who perform less than 5 repairs yearly (25, 26).

The proportion of all patients being reoperated later due to recurrence after a primary hernia operation 2008-2014 (the years the operations in the TEPLICH trial were performed) according to the SHR annual report 2023, divided in primary open and endo/laparoscopic operations is shown in Figure 2. The proportion of reoperations during these years is approximately 1% higher after primary endo/laparoscopic operations compared to open.

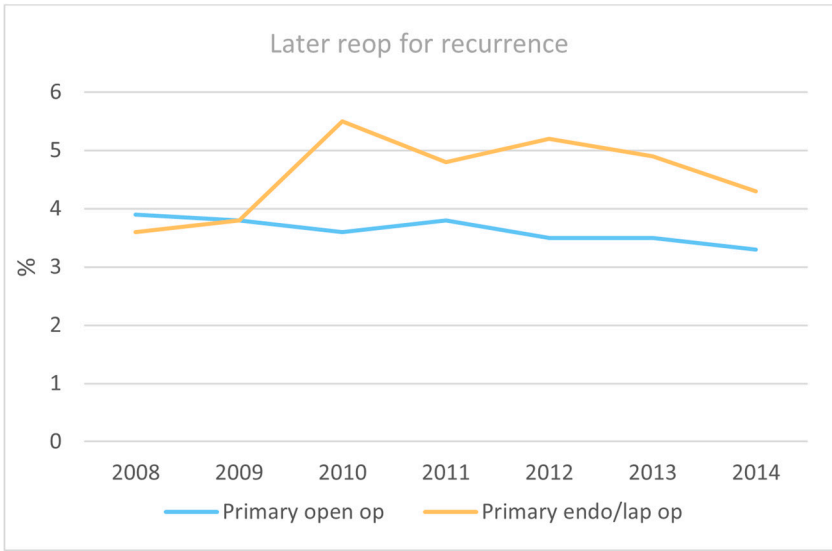


Figure 2. Proportion of patients operated 2008-2014 who have been reoperated for recurrence later (data from the SHR)

The cumulative risk for men to be reoperated due to recurrence over 8 years after primarily being operated for groin hernia is reported in the SHR annual report. The risk after 3 years is approximately 1.6% for open and 2.9% for endo/laparoscopic operations and the corresponding figures after 8 years are 3% and 4.3%, respectively. See Figure 3.

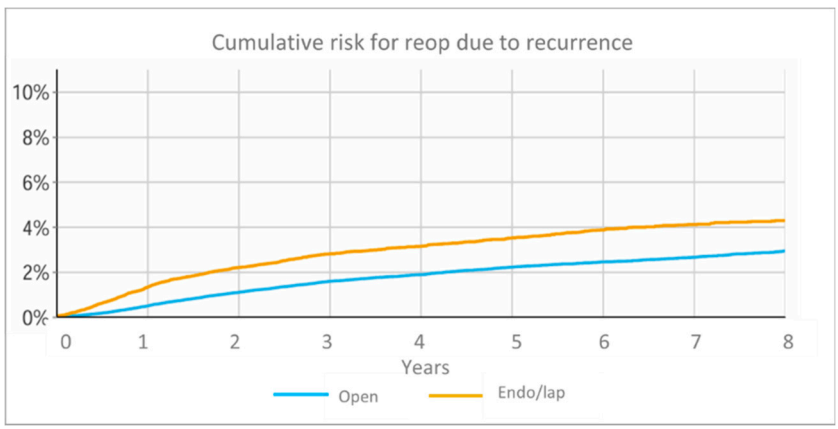


Figure 3. Cumulative risk for reoperation in men due to recurrence between 2014-2023 (data from the SHR)

Anatomical considerations

The anatomy of the groin is essential to understand for optimal performance of inguinal hernia surgery, for prevention of complications, and for understanding mechanisms of postoperative pain.

The main landmark for the division between a medial and a lateral hernia is, as mentioned above, the inferior epigastric vessels. A medial hernia is delineated by the inferior epigastric vessels laterally, the rectus abdominis muscle medially, and the inguinal ligament inferiorly. A lateral hernia is delineated by the inferior epigastric vessels medially, the lateral part of the internal inguinal ring laterally, and the inguinal ligament inferiorly, see Figure 4.

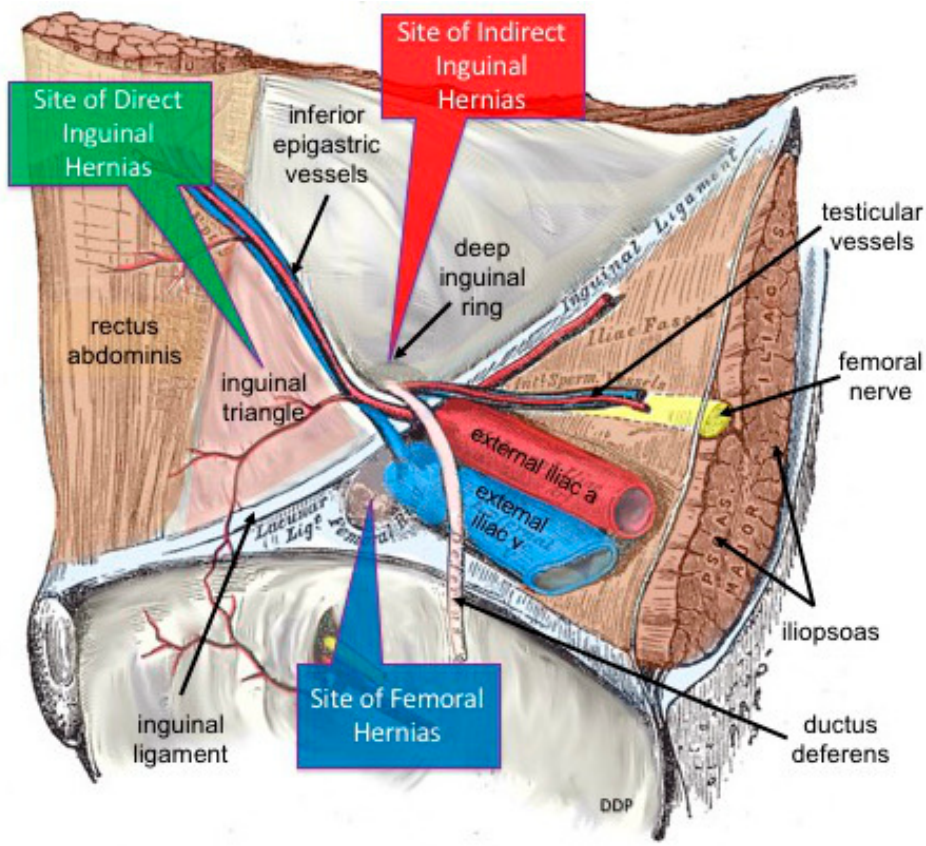


Figure 4. Preperitoneal view of right groin anatomy ("Common Sites of Lower Abdominal Hernias" by Dennis M. DePace, PhD is licensed under CC BY-SA 4.0)

Muscles

To fully grasp the compartments where these hernias arise, one must visualize the groin as a three-dimensional space built-up by the three muscles present in the groin and understand their relationship.

The **external oblique** is the most superficial muscle of the three and the lowermost part of its' aponeurosis forms the inguinal ligament which extends from the anterior superior iliac spine laterally to the pubic tubercle medially and constitutes the inferior border of the inguinal canal. Further, the aponeurosis of the external oblique muscle constitutes a part of the superficial inguinal ring and the anterior wall of the inguinal canal. The deeper situated **internal oblique** muscle aponeurosis forms the conjoined tendon together with the innermost located transversalis muscle aponeurosis. This tendon provides stability to the inguinal canal and form its superior wall. The deep inguinal ring is formed by the internal oblique and the transversalis muscle. The **transversalis** muscle aponeurosis forms the posterior wall of the inguinal canal and provides structural integrity.

Nerves

The innervation of the inguinal region originates from the lumbar plexus formed by the anterior rami of the L1 to L3 nerves, part of the L4 nerve, and occasionally a branch from the subcostal (T12) nerve (27). Since there is a considerable variability in the branches, innervation and course of these nerves (28), there is also a variability and overlapping in the dermatome distribution of the nerves. All branches of the lumbar plexus are susceptible to injury during inguinal hernia repair, with the ilioinguinal (IIN), iliohypogastric (IHN), and genitofemoral (GFN) nerves being the most frequently involved. Less commonly affected nerves are the lateral femoral cutaneous (LFC) and femoral nerve (FN). All nerves are mixed sensorimotor nerves except for the LFC nerve being solely a sensory nerve.

There is consensus about the importance of identifying and preserving the nerves during an anterior approach for inguinal hernia repair (29), which also applies when performing posterior repairs. Thus, a solid understanding of standard neuroanatomy and common variations is essential for a hernia surgeon. Identification of the nerves is not always easy and according to a recent systematic review, the identification rates for the IIN, IHN and GFN were 82%, 62% and 41% respectively (30).

The **IIN** arises from the anterior ramus of L1 and runs on the anterior surface of the quadratus lumborum muscle before entering the transversus abdominis muscle close to the iliac crest. It then perforates the internal oblique muscle and enters the inguinal canal. In the inguinal canal, it runs anteriorly on the spermatic cord in two thirds of cases and leaves the canal through the external inguinal ring (27, 31). It gives off motor fibres to the transversus abdominis and the internal oblique muscles. The IIN provides sensory innervation to the proximal medial skin of the thigh, the

skin above the inguinal crease, the upper scrotum and the lateral base of the penis. It is the most frequently injured nerve during anterior inguinal hernia repair.

The **IHN** also originates from the anterior ramus of L1 and initially runs as the IIN. It gives of an anterior and lateral cutaneous branch between the transversus abdominis and internal oblique muscles, cranially to the IIN. In the majority of cases, the IHN traverses the inguinal canal and leaves it by perforating the external oblique muscle at the level of the conjoined tendon, just superior to the external inguinal ring (28, 31). It gives off motor fibres to the transversus abdominis and the internal oblique muscles (anterior branch). The IHN provides sensory innervation to the posterolateral aspect of the gluteal skin (lateral branch) and the suprapubic skin (anterior branch).

The **GFN** is derived from the anterior ramus of L1 and L2. It is the most variable of the nerves from the lumbar plexus and its course in the retro- and preperitoneal spaces is highly inconsistent (28, 31). Typically, the GFN traverses the psoas muscle and on its way caudally divides into a femoral and a genital branch as it approaches the inguinal ligament. The femoral branch passes underneath the inguinal ligament and maintains the most lateral position in relation to the femoral artery and vein as they all enter the femoral canal together. The genital branch instead continues ventrally and enters the inguinal canal through the deep inguinal ring in most cases (27). It can be found in the inguinal canal in 97% of cases (28, 31). It gives off motor fibres to the cremaster muscle (genital branch) and supplies sensory innervation to the upper scrotal skin (genital branch), upper anterior thigh and the skin overlying the femoral triangle (femoral branch).

Chronic Postoperative Inguinal Pain - CPIP

Incidences of chronic pain

Clinically relevant CPIP interfering with daily activities or work have a reported incidence of 10-12% (32-34) and more severe debilitating pain incidences of 0.6%-6% (33). It is important to consider that an underlying bias in pain-reporting exists due to different definitions of pain among studies, which will be further discussed later in this thesis.

Several meta-analyses based on RCTs have examine the difference in CPIP incidence between TEP and Lichtenstein, with some favouring TEP (35-37) while others finding no significant differences between the two (38, 39), see Table 3 for pooled odds and risk ratios.

Table 3. Meta-analyses reporting pooled odds and risk ratios for incidence of CPIP in TEP compared to Lichtenstein

Meta-analysis	
Aiolfi et al	RR=0.36 (95% CrI, 0.21-0.54)
Bobo et al	RR=0.70 (95% CI, 0.59-0.85)
Bullen et al	OR=0.41 (95% CI, 0.3-0.56)
Gavriilidis et al	OR=0.26 (95% CI 0.66–1.00)
Lyu et al	OR=0.62 (95% CI 0.2–1.4)

RR= risk ratio, OR= odds ratio,
CI= confidence intervals, CrI= crude confidence intervals

Risk factors for chronic pain

Risk factors for chronic pain are young age, postoperative complication, hernial sac defect < 3 cm, female gender, preoperative pain, postoperative pain and operation for recurrence. The pooled relative risks are based on a meta-analysis by Chu et al. and presented in table 4 (40). The impact of the surgeons experience on the risk of chronic pain has not been thoroughly studied and a prospective study is required (41).

Table 4. Risk factors for chronic pain and their relative risks according to Chu et al (40)

Risk factors for chronic pain	Relative risk (95% CI)
Young age	2.26 (1.3-4.55)
Postoperative complication	1.85 (1.03-3.31)
Hernia sac <3 cm	1.37 (1.01-1.85)
Female sex	1.89 (1.02-3.47)
Preoperative pain	2.32 (1.35-3.98)
Postoperative pain	1.55 (1.28-1.89)
Operated for recurrence	2.71 (1.45-5.07)

Mechanisms of pain

Injuries to the nerves in the groin can occur in both open anterior and laparo-endoscopic posterior repair (27). Direct nerve injury may occur during dissection, by the use of electrocautery close to nerves, by entrapment in sutures or mesh, and also indirectly as a result of scarring or inflammation engaging the nerves, see Figure 5 and 6.

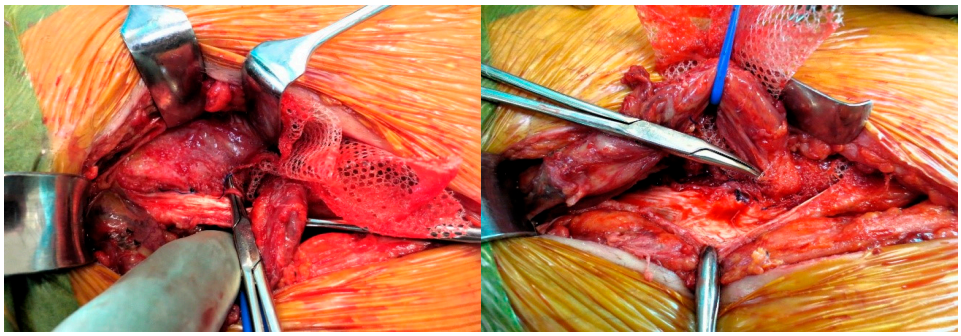


Figure 5. The genital branch of the genitofemoral nerve trapped when suturing the mesh to the inguinal ligament during a Lichtenstein repair (left), and entrapment of the ilioinguinal nerve by a mesh applied too tightly around the deep inguinal ring (right) (pictures by Ulf Petersson)

All three nerves are at a higher risk of injury during a Lichtenstein procedure compared to a TEP due to their anatomical location in relation to the operative field in respective technique.

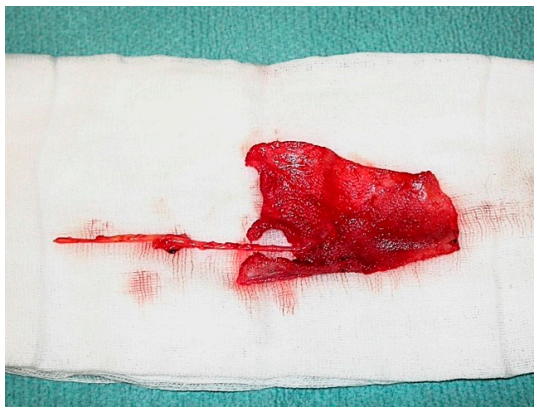


Figure 6. The ilioinguinal nerve stuck to the mesh after a Lichtenstein repair (picture by Ulf Petersson)

However, nerve injury can still occur during a TEP operation due to direct trauma from dissection, thermal injury, improper mesh placement or mesh fixation.

Besides pain caused by damage to or entrapment of nerves - neuropathic pain, pain may also be mediated by inflammation – nociceptive or inflammatory pain.

Neuropathic pain

The damaged nerve serves as a focus for aberrant propagation of action potentials affecting adjacent nerves and eventually leading to ”tactile allodynia” and central

sensitization (42). At the level of the spinal cord, microglial cells release pro-inflammatory cytokines such as TNF α which further worsens pain hypersensitivity. The surgical damage of peripheral nerves leads to lack of sensory input which induces apoptosis of inhibitory dorsal horn neurons and eventually loss of cortex and cortical grey matter. This drives the balance in the pain modulation pathway in favour of a more excitatory system.

Neuropathic pain can be divided into spontaneous and stimulus induced pain. The spontaneous pain is episodic and is reported as electric, shooting or stabbing in character (43). The stimulus needed to trigger pain can vary from normally non-painful stimulus (allodynia) to painful stimulus resulting in worse pain than normal (hyperalgesia). The stimuli that induce pain are vibration, blunt, pricking or thermal in nature. Patients with neuropathic pain often have altered sensations such as dysesthesias and paraesthesia or hypo/hyperesthesia that accompany the pain. Sensory phenomena of dysesthesia and paraesthesia are tingling, itching, numbness and "pins and needles".

Nociceptive/Inflammatory pain

Nociceptive pain can arise as a consequence of tissue injury mediated through a mechanical, thermal or chemical force. The consequent tissue injury results in inflammation and release of inflammatory mediators that increase sensitivity to pain (peripheral sensitization). Central sensitization occurs at the level of the dorsal root ganglion if the tissue injury is extensive such as in surgery. The intensity of the stimuli leads to upregulation of excitatory transmitters and reduction of inhibitory transmitters. The process usually last for days and is often reversible (44, 45). Kehlet has described nociceptive pain as throbbing pain and pain elicited by heat (42).

The distinction between nociceptive and neuropathic pain could be important from a therapeutic aspect. In patients with severe neuropathic pain, a trial with peripheral nerve blockade followed by triple neurectomy plus/minus mesh extirpation can be considered (46).

Indications for inguinal hernia surgery and "watchful waiting"

It is evident that surgery should be offered to patients with a symptomatic inguinal hernia causing discomfort or pain. However, for as many as 1/3 of patients who present with asymptomatic or mildly symptomatic inguinal hernias, the indication for surgery is less clear-cut (47). Traditionally, patients with inguinal hernias, symptomatic or asymptomatic, were offered surgery due to fear of the potential risk for bowel obstruction or strangulation which could occur over time (48). However, randomized controlled trials comparing watchful waiting with surgery in asymptomatic or mildly symptomatic patients have shown that the risk of

incarceration is negligible in these groups (49-51). The eventual need for surgery was also evaluated in these RCTs. The long-term RCT by Fitzgibbons reported a crossover rate from watchful waiting to surgery of 31.9% and 68% at 3 and 10 years, respectively (52). While a watchful waiting approach is safe, this study concluded that a large proportion of patients eventually end up needing surgery due to increased symptoms from their inguinal hernia. De Goede showed that 37.8% of patients had crossed over from watchful waiting to receiving surgery at 3 years (49), out of which 2.3% had emergency surgery. The main reason for cross over in this study was worsening symptoms. Another and recent RCT compared watchful waiting with surgery for asymptomatic or mildly symptomatic patients over a period of 12 years (50). They found that the time when 50 % of asymptomatic patients had crossed over to surgery was 6 years and for mildly symptomatic patients the corresponding time point was 2 years. They drew the conclusion that mildly symptomatic patients might benefit from early surgery. Additionally, patients in the watchful waiting group expressed more regret about their allocated treatment strategy compared to those in the surgery group.

Currently, the main reason for recommending a repair is the patient´s subjective experience of discomfort or pain and whether the symptoms affect their usual activities. The risk of new postoperative chronic pain in patients with no pain preoperatively must be accounted for and patients need to be informed about this before undergoing surgery.

To summarize, watchful waiting is an acceptable option for patients with asymptomatic inguinal hernias, although new evidence suggests that mildly symptomatic patients might benefit from early surgery without the added risk of persisting pain, according to the authors (50).

Patient-reported outcome measures (PROMs) in inguinal hernia surgery

The goal of a PROM is to measure a specified construct of interest. To understand the limitation of a PROM and its appropriateness of use in research, a certain degree of knowledge about the validation of a PROM is necessary.

A validation process has been proposed by the COSMIN group (53) consisting of 3 main domains which are validity, reliability and responsiveness, see Figure 7 for graphical presentation of the relationship between validity and reliability.

Validity determines the instruments' ability to measure the construct it intends to measure. Briefly, the different types of validity are as follows:

- *Criterion validity* can be measured if there is a gold standard that the instrument can be measured against. Criterion validity is often lacking.

- *Construct validity* assesses the degree to which the instrument measure the construct. One way to measure construct validity is by comparing an instrument´s score with the scores of other instruments measuring the same construct.

- *Content validity* assess how precisely a test measures all aspects of the construct it intends to measure.

- *Structural validity* checks if the instrument measures the domains it is intended to measure.

Reliability indicates that the reported outcome for a group of patients is consistent when measured with the same instrument. There are several aspects of reliability being test-retest reliability, measurement error and internal consistency. For instance, test-retest reliability and measurement error can be evaluated by asking a group of patients to fill in the same questionnaire two weeks apart to see if their own reported outcomes are in agreement. Internal consistency (Cronbach's alfa) shows how correlated the PROMs items are and if they capture the same or different constructs. For example, a PROM containing separate items (questions) measuring QoL and chronic pain, contain at least 2 constructs (54).

The *responsiveness* measures the ability of the instrument to detect a change in the outcome of interest before and after a certain intervention, for example pain before and after inguinal hernia repair.

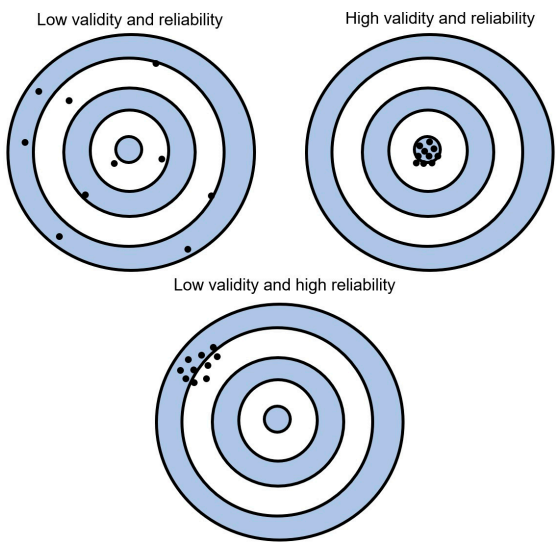


Figure 7. The relationship between validity and reliability

Questionnaire or PROMs used to assess CPIP as an outcome after inguinal hernia surgery are either generic (designed to assess general aspects of health) or hernia specific, henceforth referred to as disease specific. One problem with generic PROMs in this context is that they are not validated to specifically measure outcomes after inguinal hernia surgery and are as such not appropriate to use as a sole measure of patient-reported pain. The Visual Analog Scale (VAS) is the most used scale to measure patient-reported pain in inguinal hernia surgery (55, 56). It is unidimensional for pain and does not account for other inguinal hernia specific postoperative symptoms, for example mesh sensation in the groin or restriction in activity due to CPIP. Furthermore, it is typically used to measure pain right now and does not include pain over time. Early on, due to the lack of consensus regarding assessment of CPIP, Kehlet and colleagues proposed several parameters to be used in a PROM when evaluating CPIP (57). Some of these parameters were CPIP frequency, a pain over time perspective, physical activity impairment, leisure activity level, need for pain medication, and occupation. Most PROMs assessing CPIP do not encompass all these proposed parameters.

Gram-Hanssen et. al recently published a systematic review article where they examined the usage of generic and disease specific PROMs, which included 929 studies from 2000-2019(58), and found a trend towards increased use of disease specific PROMs over time, see Table 5 for a compilation of the results.

Among the disease specific PROMs, the Carolina Comfort Scale was by far the most used questionnaire, followed by the Inguinal Pain Questionnaire and the Activity Assessment Scale. The disease specific PROMs are further described in order, based on their frequency of use.

The Carolina Comfort Scale (CCS) is widely used for measuring CPIP and in addition focuses on mesh sensation (59), why it is not possible to use fully in the preoperative setting. It consists of 23 questions, each compromised of 6 grades from no symptoms to disabling symptoms. The questions concern sensation of mesh, pain and movement limitation in relation to certain activities. Grade 3 (“moderate and/or daily symptoms) is the only part of the scale that incorporates time or frequency.

The Inguinal Pain Questionnaire (IPQ) was created based on the parameters proposed by Kehlet et al. (60). The PROM is composed of 18 questions assessing pain and its impact on activities “right now” and “past week” (60). The grades concerning pain are scaled from “No pain” to “Pain present, prompt medical advice sought”.

The Activity Assessment Scale (AAS) was launched with the aim of comparing open to laparoscopic inguinal hernia repair pre- and postoperatively (61). It comprises 11 questions assessing the potential limitations an inguinal hernia or its surgical treatment may impose, ranging from interference with sedentary activities to more physically demanding tasks during the last 24 hours. The scale is made up of 5 grades from “No difficulty” to “Not able to do it”.

The Surgical Pain Scales (SPS) is another questionnaire developed by the same author who was involved in creating the (AAS) (62). This PROM estimates pain intensity on a VAS scale, “within the last 24 hours”, based on pain at rest, during normal activities, during exercise or more intense activities and the unpleasantness of the worst pain felt during a day. 0 on the scale equals “No Pain sensation or Not bad at all” to a maximum of “Most intense pain imaginable or Most intense bad feeling imaginable”.

The Core Outcome Measure Index-Hernia (COMI-hernia) includes a VAS scale for measuring pain intensity “in the last week”, ranging from 0-10. It also assesses the impact of pain on "normal work", quality of life, sexual dysfunction, and satisfaction with the groin surgery, using a grading scale from 1 to 5.

The Hernia Quality of Life (HERQL) was developed by Taiwanese hernia surgeons with inspiration from the AAS, CCS, COMI-hernia, Brief Pain Inventory and IPQ, and includes 20 questions. It was designed to examine three constructs: pain, quality of life and patient satisfaction (63). Not to be confused with HERQL, HERQLES is another widely used PROM specifically designed to evaluate outcomes after ventral hernia repairs (64).

Gram-Hanssen concluded that these disease specific PROMs all lack content and structural validity (65), see Table 5. They emphasized that further validation is needed to ensure that these tools are suitable for use as PROMs in inguinal hernia surgery.

Generic instruments measuring pain are by far more commonly used in inguinal hernia surgery compared to disease-specific PROMs, see Table 5 (56, 58). The generic instruments are described below in order of their frequency of use.

The Visual Analog Scale (VAS) is a unidimensional, easy to use instrument, often used to measure pain intensity in patients with inguinal hernias. VAS typically consists of a 100mm horizontal line starting with “no pain” and finishing with “worst pain imaginable”. Compared to multidimensional instruments that measure several constructs, VAS is more susceptible to patient misinterpretations regarding the specific construct intended to be measured (66). Additionally, with the lack of other references, the interpretation of the “worst pain imaginable” can be highly variable.

The short form 36 (SF-36) is a widely used quality of life questionnaire composed of 36 questions, examining 8 health status domains within the past 4 weeks (67).

Like VAS, *the Numeric Rating Scale (NRS)* consists of a line with the addition of numerical grades from 0 “no pain” to 10 “worst pain imaginable”.

The Verbal Rating Scale is generally defined by 4 ordinal categories of pain: no pain, mild, moderate and severe pain but occasionally an additional category, “very severe pain” is used. *The Cunningham pain scale* is similar but also includes a time perspective and relation to activities (68).

Table 5. Pros and cons for PROMs frequently used in inguinal hernia surgery

	Total No. of studies	No. of items	No. of categories in items	Domains and constructs measured	Time frame included	Activity restriction included	Suitable for pre-and postop	Measurement properties lacking
Disease-specific PROMs								
CCS	46	23	6	Pain Mesh sensation Movement limitation	Partially[a]	Yes	No	Reliability Content validity? Structural validity?
IPQ	29	18	Binary, 5, 6 or 7 (pain)	Pain, ADL	Past week	Yes	Yes	Reliability Construct validity
AAS	20	13	5	Sedentary/Exercise /Ambulatory activities/ Limitation of sexual activity	24h	Yes	Yes	Content validity? Structural validity?
SPS	9	4	Continuous scale	Pain	24h	Yes	Yes	Content validity? Reliability?
COMI-Hernia	4	12	Continuous scale (pain), dichotomous, 5 or 6	Pain, ADL, QoL, satisfaction with surgery	Past week	Yes	Yes	Content validity? Structural validity?
HERQL	1	20	Binary, 5, 7 or 10 (pain)	Pain, QoL, satisfaction with surgery	Past week	Yes	Yes	Content validity? Structural validity Internal consistency?
Generic PROMs								
VAS	654	1	Continuous scale	Pain	No			
SF-36	132	36	Binary, 3, 5 or 6	8 health status domains	Past 4 weeks			
NRS	109	1	10	Pain	No			
VRS	48	1	4 or 5	Pain	No			

This table is based on the systematic review of PROMs used in inguinal hernia surgery and validation issues discussed by Gram-Hanssen et al. Question mark indicates that data is lacking. [a] Includes a category “moderate and/or daily symptoms”.

Pain at sexual activity and aspects of sexual dysfunction

Pain at sexual activity

Pain at sexual activity is a sparsely studied outcome after inguinal hernia surgery and have only come into focus the last 10-15 years. Sexual dysfunction is a broader concept but what constitutes sexual dysfunction is not clearly defined. However, various aspects of sexual dysfunction associated with inguinal hernia or inguinal hernia repair have been studied. These aspects include pain at sexual activity and

impairments in sexual function, such as ejaculatory dysfunction, impotence, and infertility, or a combination of these (69).

No RCT comparing TEP to Lichtenstein regarding pain at sexual activity exists, apart from the study presented in this thesis. However, two studies based on the Danish Hernia Database have reported frequencies of pain at sexual activity of 10,9% and 22,1 %, respectively, with 5.3% and 6,7% of patients having moderate to severe pain after inguinal hernia repair, in the respective studies (70, 71), see Figure 8.

Proposed mechanisms of pain at sexual activity are intraoperative nerve damage, traumatization of VAS while dissecting the hernia sac from the spermatic cord and inflammation associated with mesh repair, all of which can lead to chronic groin and genital pain with subsequent pain at sexual activity (70). N. Schouten et. al reported a decrease of moderate-severe pain at sexual activity from 21,2% to 3,4%, before compared to after TEP repair (72). A retrospective study comparing TAPP and Lichtenstein in 317 patients, showed a reduction in moderate-severe pain at sexual activity from 23.4% to 2.6% for TAPP and from 21.7% to 5.9% for Lichtenstein, when comparing preoperative pain levels to those at 6 months postoperatively (73). New pain (pain of any degree, not present preoperatively) was seen in 3,4% in TAPP and 3,7% in Lichtenstein.

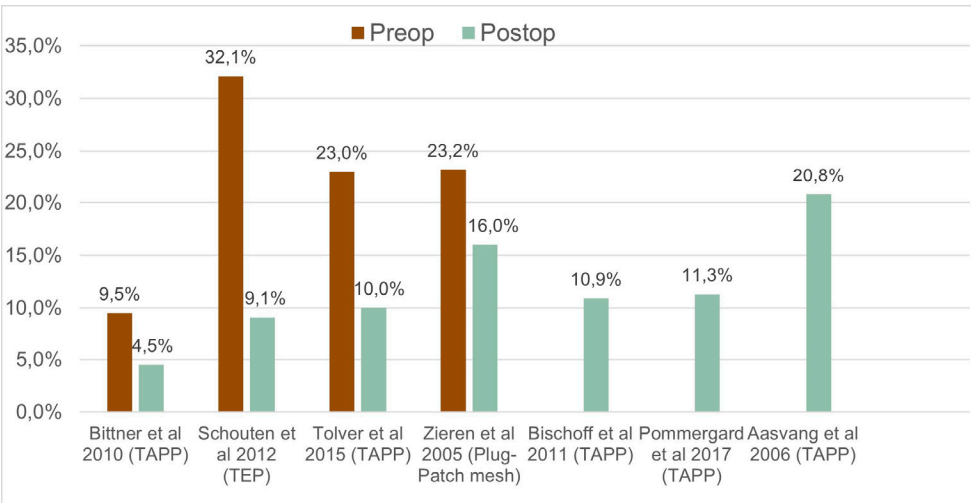


Figure 8. Reported incidences of pain at sexual activity

Ejaculatory pain and sexual dysfunction

Ejaculatory pain after inguinal hernia surgery is less common than pain at sexual activity. A review by Ece et al. compared the total incidences of dysejaculation following inguinal hernia repair across 10 studies with a total of 5521 patients,

where 3317 underwent laparoscopic and 2204 open repair (74). The incidence of dysejaculation was 2,4% for TEP and 1,1% for open repair, with the Lichtenstein procedure used in 82% of the open repair cases. The total incidence of pain at sexual activity for all types of repairs was 8,2%.

Aasvang et al. explored the pathophysiological mechanisms behind dysejaculation by comparing 10 patients with severe dysejaculation causing sexual dysfunction to 20 patients having CPIP but no dysejaculation (75). A detailed mapping of sensory disturbances was performed and compared between the groups, quantifying areas of hypoesthesia, hyperesthesia and allodynia. The locations of patients' maximum pain were also noted. Furthermore, pain detection thresholds for tactile and mechanical pressure were determined. All patients underwent psychosexual evaluation including their sexual and psychosocial history and status. The external inguinal ring was the point of maximum pain for all patients with dysejaculation. Pain thresholds for heat and tactile stimulus were significantly decreased for patients with dysejaculation compared to patients with CPIP only. The psychosexual evaluation showed that the observed findings between the groups were of somatic origin. 80 % of patients with dysejaculation compared to 55 % of patients with CPIP only, experienced increased pain on repetitive tactile testing ("windup phenomenon"), which is suggestive of neuropathic pain. Although no power analysis was performed in this study, it does give some insight into the possible pathophysiological mechanism behind postoperative dysejaculation. With the maximum pain localized at the external inguinal ring and the predominance of neuropathic pain in the group of patients with dysejaculation, injuries to the VAS and surrounding nerves have been proposed as a potential cause for this pain.

A study by Verhagen et al evaluated 100 patients operated with neurectomy due to intolerable CPIP and dysejaculation (76). A neurectomy, funicular release/mesh removal or both were performed. Preoperatively, 34 patients reported dysejaculation, among them 20 reported a preoperative VAS score of 5.5 which decreased to 2.1 postoperatively ($p<0.001$). Another study histologically examined vas deferens specimens of 13 patients undergoing surgery due to severe CPIP (77). Intraoperatively vas deferens was successfully separated from the ingrown mesh and scar tissue in 4 patients, while in 9 patients it could not be separated from the mesh, resulting in a complete excision of vas deferens and mesh in 6 patients, and in 3 patients only the mesh was excised leaving a partial mesh remnant on vas deferens. The 6 excised vas deferens specimens demonstrated more invasive mesh involvement in patients reporting dysejaculation and pain at sexual activity. Additionally, mesh separation was unachievable in all patients reporting dysejaculation or sexual activity-related pain, compared to only 44% of patients without these symptoms. This suggests that dysejaculation alone by itself might indicate a need for mesh removal to improve quality of life and sexual functioning.

Erectile function following inguinal hernia repair is sparsely reported after inguinal hernia surgery. A score used to measure the degree of impaired erectile dysfunction

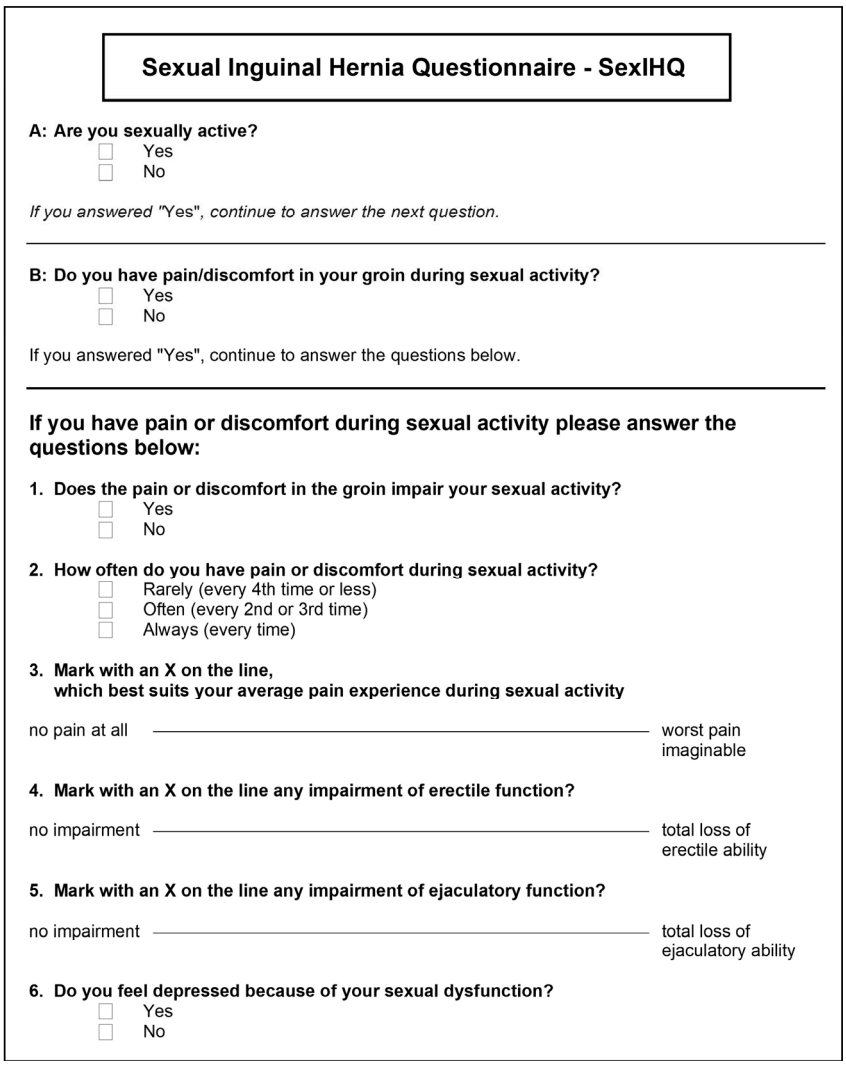
is the International Index of Erectile Function (IIEF) (78). IIEF is composed of 5 domains concerning erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. A shorter version, the IIEF-5, contains only 5 questions focused on erectile function, each scored from 1-5 (79). In total 25 points are achievable, with the severity of erectile dysfunction categorized as follows: 5-7 indicate severe erectile dysfunction, 8-11 moderate, 12-16 mild to moderate, 17-21 mild and 22-25 represents no erectile dysfunction.

A study evaluated the erectile function of 57 patients operated with Lichtenstein with the IIEF-5 before, at 1 and 6 months after surgery (80). Their mean IIEF scores were 18.04 preoperatively, 19.53 at 1 month, 21.26 at 6 months, showing an improvement in their erectile function from mild ED preoperatively to almost no ED at 6 months. A randomized controlled trial by Gupta et al. compared sexual function and impact on fertility in 41 TAPP and 40 TEP and Lichtenstein patients aged 25-50 years, evaluating these primary outcomes preoperatively and at 3 months postoperatively. They were given the Brief Male Sexual Function Inventory (BMSFI), which measures almost identical domains as the IIEF but is shorter. Fertility was assessed by measuring anti-sperm antibodies and conducting semen analysis that included sperm count and microscopy to study sperm morphology and motility. Anti-sperm antibodies may become elevated if the blood-testes barrier becomes disrupted, which may happen if vas deferens is manipulated roughly intraoperatively. Anti-sperm antibodies were found to be elevated for Lichtenstein patients but were still within the normal reference values. Even though experimental data suggest that elevated anti-sperm antibodies can cause decreased sperm counts and potential infertility (81), sexual function improved significantly in all domains equally among the groups, except for erectile function, showing some but non-statistically significant improvement. Interestingly, the semen analysis showed increased sperm count, concentration and volume, which could be partly explained by the improved temperature conditions for spermatogenesis following the removal of the hernia sac, as the sac itself may raise testicular temperature.

A potential problem associated with assessing sexual dysfunction after inguinal hernia repair is the risk of underreporting as patients might feel uncomfortable answering intimate questions. The incidence of pain at sexual activity after inguinal hernia repair remains uncertain, and further studies are needed to determine the total prevalence, and RCTs to determine the differences in prevalence between techniques. Apart from pain at sexual activity, sexual dysfunction and its consequences ejaculatory pain/dysfunction and erectile dysfunction are additionally important outcomes that need to be analyzed and added to hernia registries. Distinguishing between pain at sexual activity and dysejaculation is crucial as they may have different causes and may require different treatment approaches.

Aasvang et al. launched a questionnaire for assessment of pain at sexual activity after inguinal hernia surgery focusing on pain frequency, intensity, localization, pain descriptors and pain-related sexual dysfunction (70). This questionnaire served as

an inspiration for Gutlic et al. to develop the Sexual Inguinal Hernia Questionnaire (SexIHQ) (82). As a further development of Aasvangs' questionnaire, the SexIHQ added additional questions regarding depression, and erectile and ejaculatory function, see Figure 9. The first 2 questions in the SexIHQ are discriminatory questions, enquiring whether the patient is sexually active and has pain at sexual activity. If the answer to both questions is yes, the patient proceeds with the rest of the questionnaire. The domains of the SexIHQ still need to be validated against already established questionnaires.



Sexual Inguinal Hernia Questionnaire - SexIHQ

A: Are you sexually active?

☐ Yes
☐ No

If you answered "Yes", continue to answer the next question.

B: Do you have pain/discomfort in your groin during sexual activity?

☐ Yes
☐ No

If you answered "Yes", continue to answer the questions below.

If you have pain or discomfort during sexual activity please answer the questions below:

1. **Does the pain or discomfort in the groin impair your sexual activity?**
   ☐ Yes
   ☐ No

2. **How often do you have pain or discomfort during sexual activity?**
   ☐ Rarely (every 4th time or less)
   ☐ Often (every 2nd or 3rd time)
   ☐ Always (every time)

3. **Mark with an X on the line, which best suits your average pain experience during sexual activity**

no pain at all ——— worst pain imaginable

4. **Mark with an X on the line any impairment of erectile function?**

no impairment ——— total loss of erectile ability

5. **Mark with an X on the line any impairment of ejaculatory function?**

no impairment ——— total loss of ejaculatory ability

6. **Do you feel depressed because of your sexual dysfunction?**
   ☐ Yes
   ☐ No

Figure 9. The SexIHQ according to Gutlic et al. (82) (licensed under CC BY 4.0)

Aims of the thesis

To analyze pain and QoL before and long-term after inguinal hernia surgery, comparing TEP with Lichtenstein repair in a randomized setting where both techniques were highly standardized and performed by department-certified specialized hernia surgeons trained according to the same curriculum.

To analyze pain at sexual activity before and up to 3 years after surgery, the impact of pain at sexual activity on QoL, and risk factors for pain at sexual activity in a sub-group of 30–60-year-old men, operated in the same setting.

To analyze long-term pain and pain at sexual activity patterns over time for the individual patient, and to describe possible long-term harm of surgery and hernia recurrence, based on data from the same study.

To analyze correlation and interchangeability between the different pain assessment scales used in the study, to determine optimal cutoffs for the VAS scale based on the Cunningham pain scale, and the impact of time and activity on pain frequency and intensity.

Methods

The TEPLICH randomized controlled trial

This thesis is based on results from the randomized controlled TEPLICH trial. It is a single-center trial designed to compare TEP to Lichtenstein repair in terms of postoperative outcomes. Patients were included and operated between 2008 and 2014. Figure 10 displays the study plan of the trial, presenting each evaluation the patients underwent preoperatively and at the different follow-up occasions. One month postoperatively patients were scheduled for a follow-up visit to a study nurse where any complication, time of sick leave, and time to recovery was noted. Patients were asked to answer the IPQ questionnaire, the Cunningham pain scale and SF-36 preoperatively, at 1, 3 and 8 years and were clinically examined preoperatively, at 1 and 3 years. Men between 30 and 60 years were, in addition, asked to complete a questionnaire on pain at sexual activity preoperatively, at 1 and 3 years. All patients were checked for a potential sensory disturbance or sign of a recurrence during the postoperative clinical exams. A lost to follow-up analysis was performed where patients lost to follow-up between 1 and 8 years were compared to patients who remained in the study at 8 years. Differences in non-ignorable pain and age at 1 year between these groups were compared for both techniques.

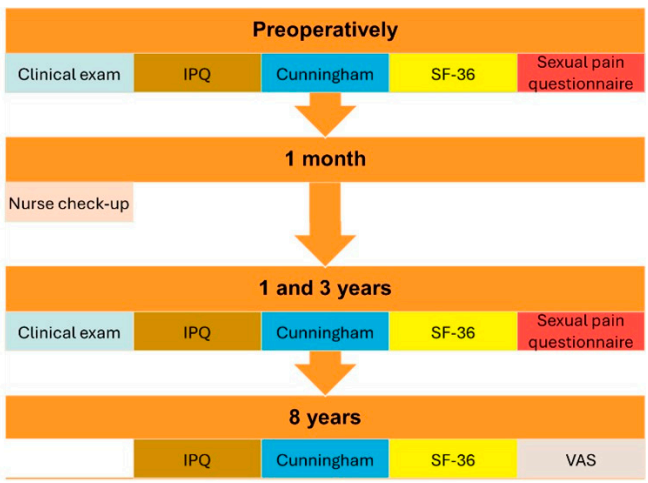


Figure 10. TEPLICH trial - flowchart

The TEPLICH trial's **overall primary endpoint** was *non-ignorable pain* last week according to IPQ, 1 year postoperatively. Ignorable pain was defined as no pain or pain present but could easily be ignored (grade 1 and 2 on the 7-grade scale) and non-ignorable pain was defined as pain present but does not interfere with everyday activities or worse (grade 3-7). Any pain was defined as pain present but could easily be ignored or worse (grade2-7).

Pain as secondary outcomes were *pain at other time points and pain measured with other PROMs*: IPQ non-ignorable pain last week preoperatively, at 3 and 8 years; non-ignorable pain right now preoperatively, at 1, 3 and 8 years; any pain right now and last week preoperatively, at 1, 3 and 8 years; pain according to the Cunningham pain scale preoperatively, at 1, 3 and 8 years; and, pain right now and last week measured with VAS at 8 years. *Each individual patient´s pain status* was followed from preoperative to 8 years.

Other secondary outcomes were: *perioperative data* including operation time, conversion rate, operation difficulty level, and surgeons' performance-satisfaction; *postoperative data* including complications and reoperations within the first month, sick leave and recovery time; *sensory disturbances* in the operated groin preoperatively, at 1 and 3 years; *physical function* tested by climbing stairs, squatting, and raising from bed preoperatively, at 1 and 3 years; *quality of life* according to SF-36 preoperatively, at 1, 3 and 8 years; *cumulative recurrence* based on clinical exam at 1 and 3 years and by questionnaire at 8 years; *surgical harm* defined as a new-onset non-ignorable pain last week not existing preoperatively or testicular atrophy due to surgery, based on clinical exam at 1 and 3 years and by questionnaire at 8 years; and *patient's satisfaction* with surgery at 1, 3 and 8 years.

Pain at sexual activity was investigated in a cohort of men, 30-60 years old, and included in the study. They were asked to complete a questionnaire for assessment of pain experienced at sexual activity (SEX-P) preoperatively, at 1 and 3 years postoperatively. If they reported pain, they answered further questions about intensity, frequency and the potential negative impact the pain had on their sexual activity and function. Each patient's pain at sexual activity status was followed individually from preoperatively to 3 years and new-onset, relief of or persisting pain at sexual activity was noted. They were also asked to map the location of pain at sexual activity and to describe the pain using specified pain descriptors, to discriminate whether the pain was of neuropathic or nociceptive origin.

Physical activity level and activity limitation due to pain were evaluated by addition of questions concerning this at 8 years. The questions were mailed to the patients together with the IPQ questionnaire, the Cunningham pain scale, SF-36 and VAS. A chart review was performed for all in- and -outpatient visits, scanning the records for a potential recurrence or chronic pain.

Eligible patients for inclusion were men between 30 and 75 years, with a primary unilateral hernia. Exclusion criteria were large scrotal hernia, ASA > II, non-

Swedish speaking in need of an interpreter, unable to cooperate or a history of prior lower abdominal surgery. In paper II, when evaluating pain at sexual activity, a sub-group of 30-60-year-old patients were included.

Comparison of PROMs assessing pain in the TEPLICH trial was the basis for paper IV. IPQ, Cunningham and VAS were compared concerning their correlation and potential interchangeability (agreement). In accordance with IPQ´s question on pain right now and during the last week, VAS scales for pain right now and last week were used to include a time frame for the patient´s pain experience. The best cut-offs between Cunningham and VAS right now and VAS last week were determined.

Hernia surgery training for study participating surgeons

In the early 1990s, laparo-endoscopic techniques for hernia repair were introduced at the Abdominal wall surgery unit at the Department of Surgery, Skåne University Hospital in Malmö. Initially, TAPP was used but in the mid-1990s TEP became popular and has since then been the technique of choice. Lichtenstein became popular approximately at the same time and came to replace Shouldice as the preferred open technique. The surgeons working together at that time learned and implemented the techniques and have had consensus about how to perform both operations. They have continued to work at the unit and have trained all the surgeons participating in the TEPLICH trial, ensuring uniform and standardized operations. All surgeons were department-certified for one or both techniques and far beyond the learning curve for the techniques. The study was conducted at a single center, reasonably improving adherence to protocols and facilitating study information and unannounced quality controls during the procedures.

The surgical procedures in the study

Lichtenstein

All procedures were performed under general anesthesia. Antibiotics or thrombosis prophylaxis were not routinely used. Iodine skin protection film was applied before making the groin incision. After opening the external muscle aponeurosis, effort was made to identify the 3 inguinal nerves, and a no-touch approach was exercised (Figure 11). The number of nerves found, spared or divided was noted. The cremaster muscle was left intact and if a cord lipoma was encountered, it was excised. In case of an indirect hernia, the hernia sac was dissected, ligated and divided at the internal inguinal ring after palpation for a femoral hernia through the

opened sac (Figure 11). In case of a large scrotal sac, the sac was divided and the caudal part left in situ. In case of a direct hernia, the transversalis fascia was incised to enable palpation of a potential femoral hernia. The incision was closed and the hernia invaginated with a continuous absorbable suture. A lightweight polypropylene mesh with large pores was applied (Parietene® Light, 10×15cm; Medtronic, Dublin, Ireland) with a 2 cm overlap at the pubic tubercle. Once proper mesh placement was achieved, the mesh was fixated to the inguinal ligament with a continuous polypropylene suture and the slit made in the mesh was closed laterally to the cord. The mesh was medially and cranially fixated to the internal oblique fascia at 2 points with absorbable sutures, whereafter the external muscle aponeurosis was closed with the same suture (Figure 11). Finally, the skin was closed intracutaneously.

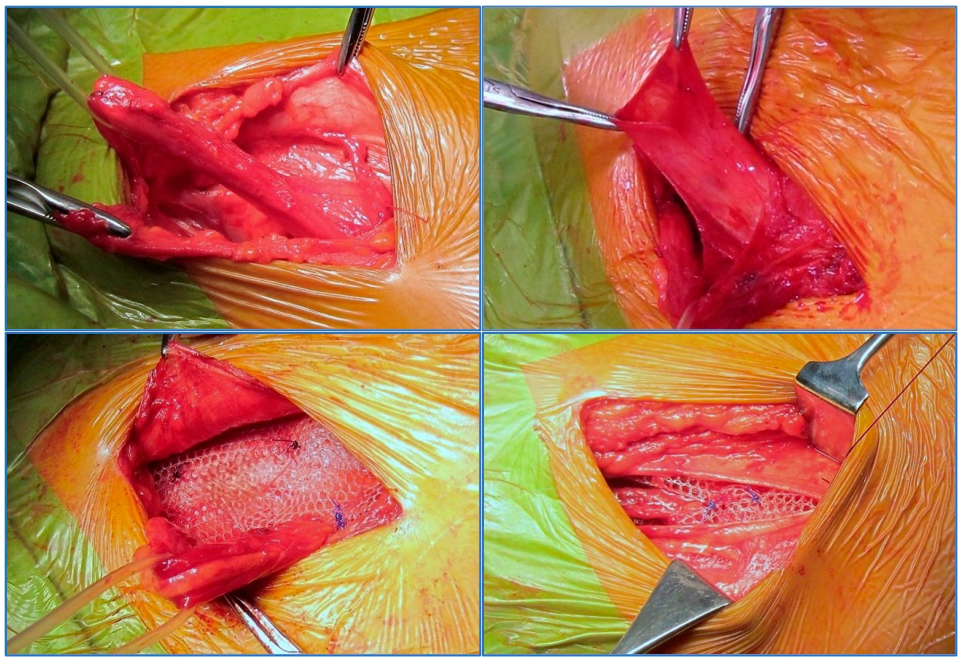


Figure 11. The upper left photo shows the opened external aponeurosis, and the spermatic cord lifted with a plastic tube. The upper right photo shows the opened lateral sac with split but not divided cremasteric muscle fibers. The lower left photo shows the mesh in place with the split mesh parts sutured together laterally from the deep ring and the absorbable fixating sutures cranially. The lower right photo shows closure of the external aponeurosis (pictures by Ulf Petersson)

TEP

All procedures were performed under general anesthesia. Antibiotics or thrombosis prophylaxis were not routinely used. To gain access to the retromuscular and preperitoneal space, a sub-umbilical centimeter-long skin incision was made, the

anterior rectus fascia incised, and the rectus muscle lateralized whereafter a camera port was introduced. Two 5 mm ports were placed caudally to the umbilicus in the midline. A standard procedure for dissection was applied where the pubic symphysis and Coopers ligament were first exposed. The next step was identifying the peritoneum laterally after advancing the dissection underneath the epigastric vessels. The peritoneum is successively brought down from lateral and alongside the bladder to the internal ring, thereby reducing the hernia. The peritoneum was mobilized laterally to the iliac spine, incising the arcuate ligament laterally if necessary to gain access, and 5 cm down from the deep ring for good exposure of the triangle of doom. Care was taken to keep the dissection close to the peritoneum, leaving the fascial coverage over the triangle of pain and triangle of Doom intact. A heavy weight polypropylene pre-shaped mesh (3DMax® large, 12×17cm; Bard Medical, Covington, Georgia, USA) was placed with good overlap outside the hernia orifice, covering both the inguinal and femoral areas (Figure 12). No mesh fixation was used.

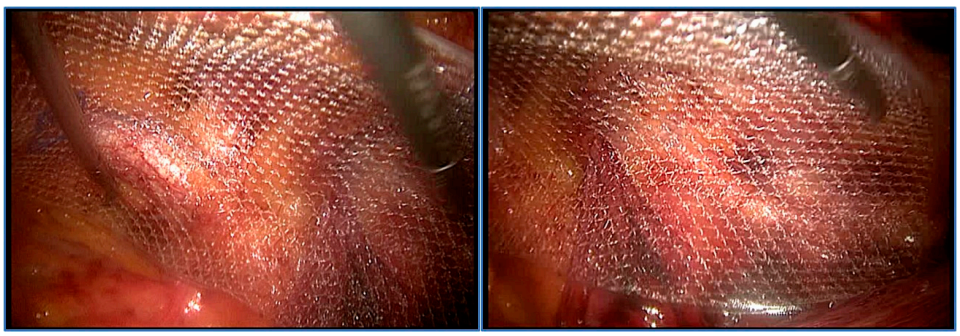


Figure 12. The left photo shows the medial view with the mesh covering the symphysis, Cooper's ligament and the Hesselbach´s triangle. The right photo shows the lateral view with the mesh covering the spermatic cord, iliac and spermatic vessels and the triangle of pain laterally (pictures by Ulf Petersson)

PROMs used in the study

The Inguinal Pain Questionnaire

The pain questionnaire consists of 18 questions on pain experience and the pain's impact on activities and functions. The two questions concerning pain, right now and worst pain during the last week, have the same alternative answers shown in Figure 13. The patients answered the questionnaire preoperatively, 1, 3 and 8 years postoperatively.

Estimate the pain you feel right now in the groin on the same side as the operation

Estimate the worst pain you felt in the operated groin during this past week

1. No pain
2. Pain present but can easily be ignored
3. Pain present, cannot be ignored, but does not interfere with everyday activities
4. Pain present, cannot be ignored, interferes with concentration on chores and daily activities
5. Pain present, cannot be ignored, interferes with most activities
6. Pain present, cannot be ignored, necessitates bed rest
7. Pain present, cannot be ignored, prompt medical advice sought

The red line divides ignorable vs non-ignorable pain

Figure 13. IPQ pain right now and pain last week

The Cunningham pain scale

The Cunningham pain scale was also answered preoperatively, 1, 3 and 8 years postoperatively and is shown in Figure 14.

1. No pain
2. Mild pain (occasional feeling of pressure and discomfort)
3. Moderate pain (occasional pain, pain during exertion)
4. Severe pain (daily discomfort/pain)

Figure 14. Cunningham pain scale

VAS

The questions concerning pain right now and last week was answered with VAS scales at 8 years, shown in Figure 15.

Estimate the severity of pain right now in your groin by putting a cross on the line below

No pain ——— Worst pain imaginable

Estimate the severity of pain during the past week in your groin by putting a cross on the line below

No pain ——— Worst pain imaginable

Figure 15. VAS questions

Pain at sexual activity questionnaire

Patients between 30 and 60 years of age were asked to answer the following questions (Figure 16) preoperatively, at 1 and 3 years postoperatively.

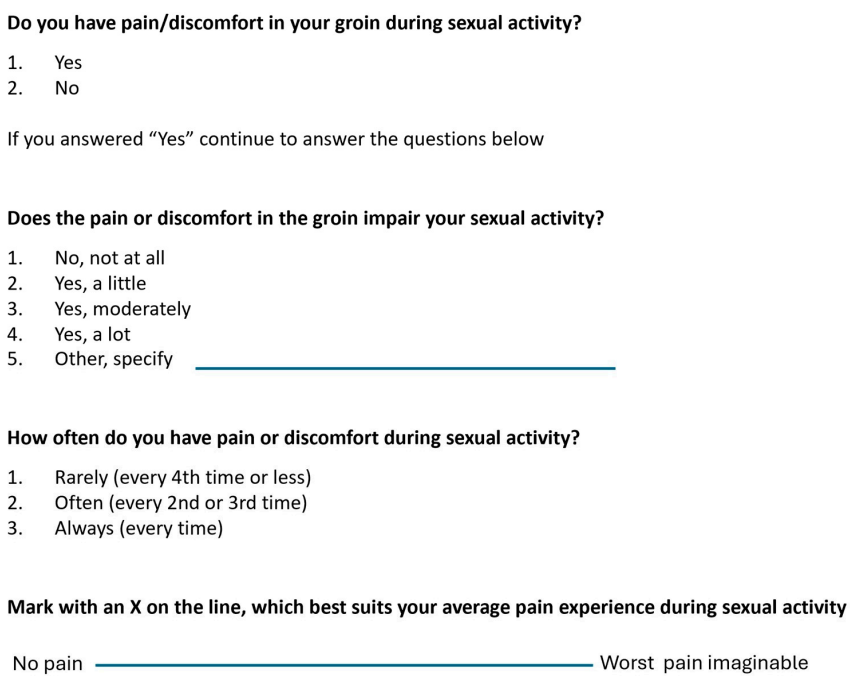


Figure 16. Pain at sexual activity questionnaire

Clinical examination for sensory disturbances and mapping of pain at sexual activity

A clinical examination was performed for all patients preoperatively, at 1 and 3 years follow-up checking for the sensory disturbances tenderness, hyposensitivity to touch, hyposensitivity to sharpness, hypersensitivity and radiating pain based on 5 locations in the groin mapped on the left side of Figure 17. A sensory change was defined as either hyposensitivity to touch/sharpness or hypersensitivity. A potential recurrence and other reason for pain such as adductor tendinopathy or pain with adduction or rotation of the hip were excluded through examination. Sensory disturbances were compared between TEP and Lichtenstein procedures, and the association between sensory changes and the presence or absence of non-ignorable pain last week was analyzed within each group.

Patients were asked to map the location in the groin in which they felt pain during sexual activity (see right part of Figure 17) and to use 1 of 13 pain descriptors for characterizing the pain. The locations were later divided into 4 quadrants, corresponding to the lateral groin, upper groin, lower groin and testicle. Additionally, the sensory disturbances and location were mapped for patients with pain at sexual activity and compared to those having non-ignorable pain without pain at sexual activity to detect possible differences.

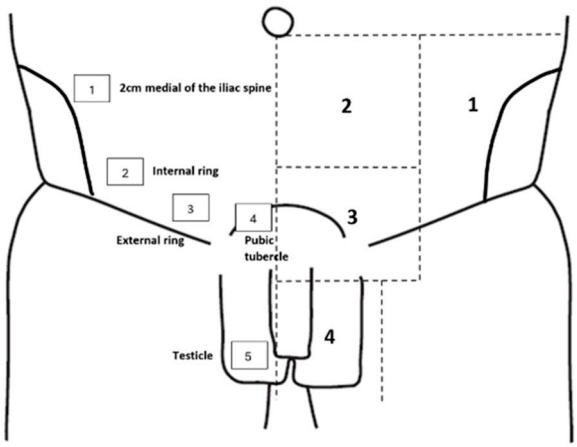


Figure 17. The left side of the schematic picture was filled out by the doctor according to sensory disturbances found at clinical examination, and the right side shows the quadrants used by patients to categorize their areas of pain at sexual activity

Statistical methods

Sample size calculations

The sample size calculation for the TEPLICH study was based on the presumption that non-ignorable pain last week according to IPQ last week 1 year after surgery would be 20% in the Lichtenstein group and 8% after TEP, i.e. a 12% difference between groups, which was chosen based on a previous RCT by Eklund et al. (83). To be able to detect this difference with 90% power and α=0.05 with a drop-out rate of 13%, 200 patients in each group were to be included.

An equal effect size of 12% was calculated for pain at sexual activity, necessitating the inclusion of 131 patients in each group to achieve a power of 80% and α=0.05.

IBM SPSS 25 and 29 were used for all statistical analyses.

Paper I-III

Values were presented as mean (SD) or median (IQR) as appropriate. A p-value of 0.05 was considered significant. Pearson's chi square and Fischer's exact test were used to analyze binary variables and Student's t-test was used for continuous variables. McNemar's test was used for paired nominal variables. Multivariate logistic regression and univariate logistic regression were used in the risk factor analysis for chronic pain and pain at sexual activity, respectively. The Swedish norm-based SF-36 scores according to age and sex were used as a reference when comparing the SF-36 scores in the study. The population-specific norm-based scores have a mean (SD) of 50 (10). An effect size of 5 corresponds to 0.5 standard deviations, which is considered a medium seized effect size (Cohen's D).

Paper IV

Descriptive statistics mean (SD), median (95 percentile range) and mode were used to describe distribution of data. Scatterplots were used for visual distribution and relationships between scales. Data was tested for normal distribution using Kolmogorov-Smirnov, Shapiro Wilk and histogram plots. Non-parametric methods were used for non-normally distributed data. Spearman's (r_s) and Kendall's Tau-b (τ_b) were used to measure correlation between Cunningham, VAS and IPQ. VAS-reported pain "right now" and "last week", later referred to as categorized VAS, was divided into four pain intensity levels as follows: no pain (0.0), mild pain (<3.0), moderate pain (≥3.0 and <6.0), and severe pain (≥6.0). Optimal VAS cut-offs based on Cunningham were calculated using Cohen's kappa (k). The agreement between categorized and optimal VAS vs Cunningham was calculated with percentage agreement and linear weighted kappa (k_w). Pearson's chi-square and Fischer's exact test were used for analysis of binary variables. A risk factor analysis for non-ignorable pain was performed, using binary logistic regression, with the independent risk factor being the patient's activity level.

The calculated correlation coefficient ranges from -1 to 1, where -1 indicates a perfect negative correlation, 1 indicates a perfect positive correlation, and 0 indicates no correlation (84). Proposed reference values for interpreting correlation coefficients are as follows (84, 85): 0.00–0.10 indicates negligible correlation, 0.10–0.39 indicates weak correlation, 0.40–0.69 indicates moderate correlation, 0.70–0.89 indicates strong correlation, and 0.90–1.00 indicates very strong correlation.

Correspondingly, the kappa value has an interval from -1 to 1 and a similar interpretation of the value apply. Landis and Koch suggested the following reference values for weighted kappa (86): 0 indicates poor agreement, 0.21–0.40 indicates fair agreement, 0.41–0.60 indicates moderate agreement, 0.61–0.80 indicates substantial agreement, and 0.81–1.00 indicates almost perfect agreement.

Results

The TEPLICH trial (Paper I and III)

Between 2008-2014, a total of 416 patients underwent surgery, 202 with TEP and 214 using the Lichtenstein technique, see Figure 18 for the flowchart up to 3 years.

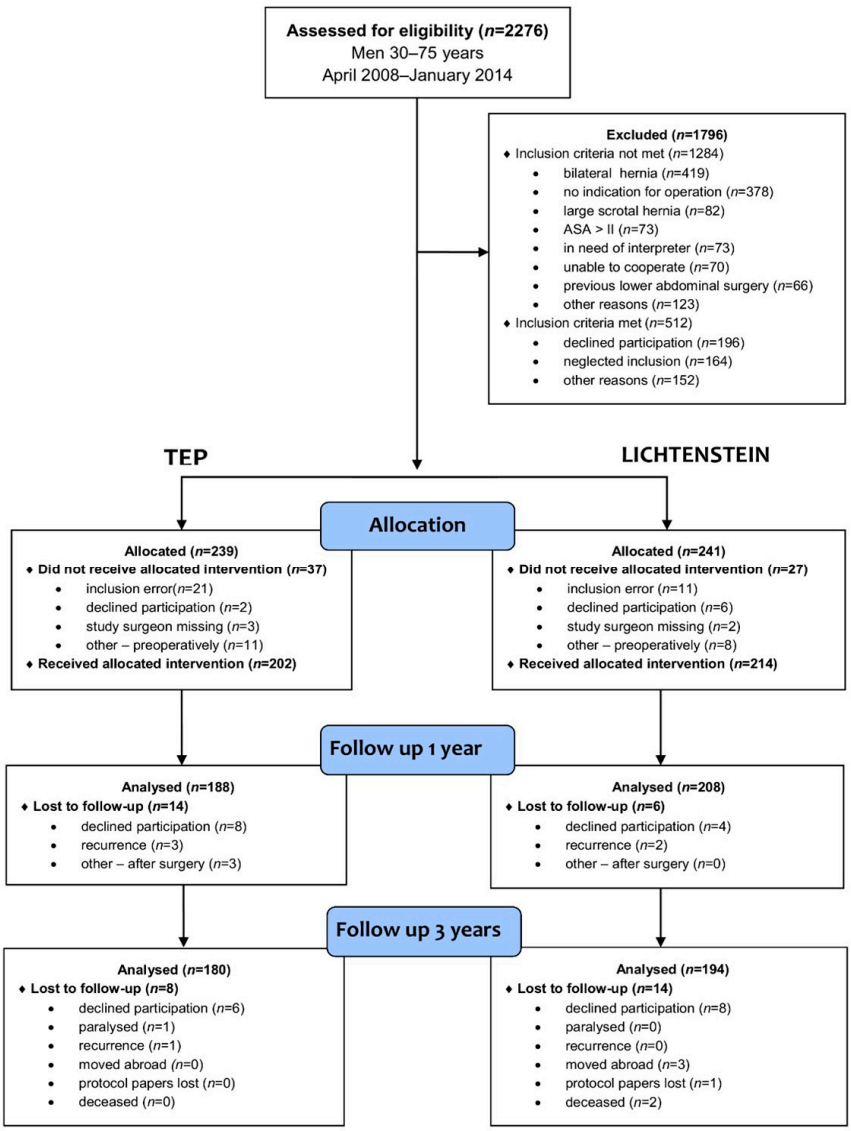


Figure 18. Study flowchart up to 3 years

Of 386 patients eligible for a long-term follow-up, 322 answered the questionnaires after a mean of 8 years (range 5-10.75 years), corresponding to 77% of the patients receiving the allocated operation, see Figure 19 for the flowchart for the long-term follow-up.

Out of 392 patients, 72 (18.4%) were lost to follow-up between 1 and 8-year follow-up, Table 1. No differences in non-ignorable pain or age were observed between patients lost to follow-up and patients remaining at 8 years, for either TEP or Lichtenstein.

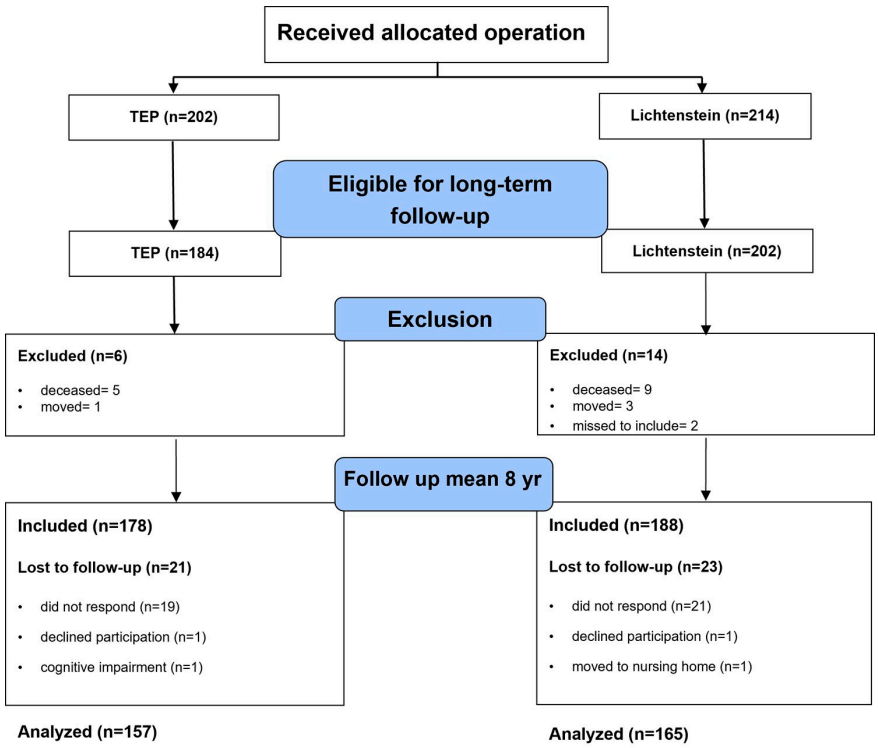


Figure 19. Flowchart for long-term follow-up

Preoperative, operative and short-term data (Paper I)

Overall, there were no differences in patients' preoperative characteristics between groups, see Table 6.

Table 6. Preoperative data

	TEP	Lichtenstein	Total
	n=202	n=214	n=416
Age, mean (SD)	55(12)	54(12)	54 (12)
BMI, mean (SD)	26(3)	25(3)	51 (3)
ASA (%) ASA I ASA II	n=189 133(70.4) 56(29.6)	n=206 161(78.2) 45(21.8)	n=395 294(74.4) 101(25.6)
Occupational physical strain (%) Light Heavy Unemployed/Retired	n=188 40(21.3) 103(54.8) 45(23.9)	n=204 44(21.6) 109(53.4) 51(25.9)	n=392 84(21.4) 212(54.1) 96(24.5)

A total of 10 surgeons performed all operations; of these, 8 performed both techniques, while 2 specialized in either TEP or Lichtenstein exclusively.

TEP had a shorter median operative time than Lichtenstein, 48 (IQR 37-60) minutes compared to 60 (IQR 49-70) minutes ($p<0.001$). There were no conversions, but TEP was considered more difficult by the surgeons ($p<0.001$). The surgeons were in general more satisfied with their performance after a Lichtenstein (100%) compared to a TEP procedure (95.5%) ($p=0.002$).

No patients in the TEP group but four patients in the Lichtenstein group were reoperated within the first week, 2 due to bleeding, 1 due to severe pain and 1 due to testicular ischemia ($p=0.055$). In total, 7.2% short-term complications occurred after Lichtenstein and 2.2% after TEP ($p=0.018$), with hematoma formation being the predominant complication.

Sick leave and recovery time for TEP were 9.6 and 13.2 days, respectively, averaging 3 and 6 days shorter than for Lichtenstein ($p < 0.001$).

In summary, there was no difference in baseline characteristics, TEP operations were faster, early reoperations were only needed in the Lichtenstein group, and sick leave and time to recovery was shorter in the TEP group.

Chronic pain (Paper I and III)

IPQ non-ignorable pain last week

This is the primary endpoint for the TEPLICH trial. A significant proportion of patients, 72% in the TEP group and 74% in the Lichtenstein group, reported non-ignorable pain preoperatively without difference between groups (Figure 20).

Non-ignorable pain last week at 1 year follow-up was reported by 6.9% in TEP and 9.8 in Lichtenstein (p=0.30). At 3 years, the figures were 4.5% for TEP and 6.8% for Lichtenstein (p = 0.49), and at 8 years 7.6% in TEP and 6.7% in Lichtenstein (p=0.73). Thus, no significant differences were found preoperatively or at 1, 3 and 8 years, see Figure 20.

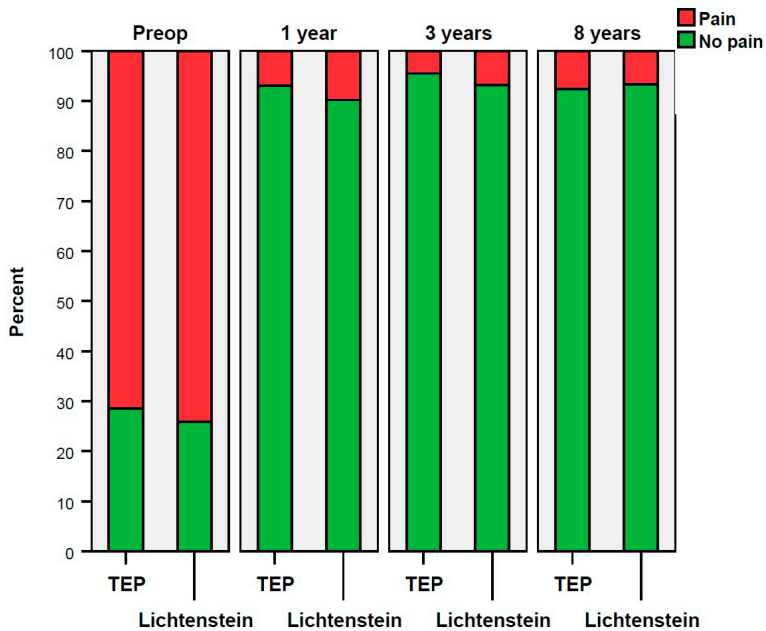


Figure 20. Non-ignorable pain last week according to IPQ last week throughout the study

IPQ non-ignorable pain right now

Preoperatively, 46 % in the TEP group and 50% in Lichtenstein reported non-ignorable pain right now. One year after surgery the corresponding values were 3.7% and 5.9% (p=0.32), at 3 years 3.5% and 5.2%, (p=0.38), and at 8 years 5.1% and 4.8% (p=0.56), respectively.

IPQ any pain

Preoperatively, 69.2% in both groups reported “any pain” right now. One year after surgery the corresponding values were 10.6% and 21.7% (p=0.32), at 3 years 3.5% and 14.1%, (p=0.38), and at 8 years 10.2% and 12.1% (p=0.58), respectively.

Preoperatively, 91.0% in the TEP group and 90.2% in Lichtenstein reported “any pain” last week. One year after surgery the corresponding values were 18.1% and 25.5% (p=0.08), at 3 years 9.0% and 19.0%, (p=0.008), and at 8 years 15.3% and 18.2% (p=0.49), respectively.

IPQ reported pain in summary

Overall IPQ pain was frequently reported preoperatively and decreased significantly postoperatively. Higher incidences are reported for questions incorporating a time frame, i.e. pain during last week compared to pain right now. Generally, the frequencies of “any pain” are higher than those of non-ignorable pain for any given time-point. No differences between the groups were found except for “any pain” last week at 3-year follow-up where the Lichtenstein group had a significantly higher incidence. In the context of this study, with department certified surgeons trained according to the same curriculum and a strictly standardized study protocol, preoperative non-ignorable pain was relieved in 9 of 10 patients.

Cunningham moderate-severe pain

Preoperative moderate-severe pain according to Cunningham was reported by 57% in TEP and 63% in Lichtenstein (p=0.21). The corresponding findings at 1 year were 2.7% in TEP and 5.0% in Lichtenstein (p=0.09), at 3 years 4.1% for TEP and 4.9% for Lichtenstein (p=0.80), and at 8 years 3.8% for TEP and 5.5% for Lichtenstein (p=0.48). Thus, no significant differences were found preoperatively or at 1, 3 and 8 years, see Figure 21.

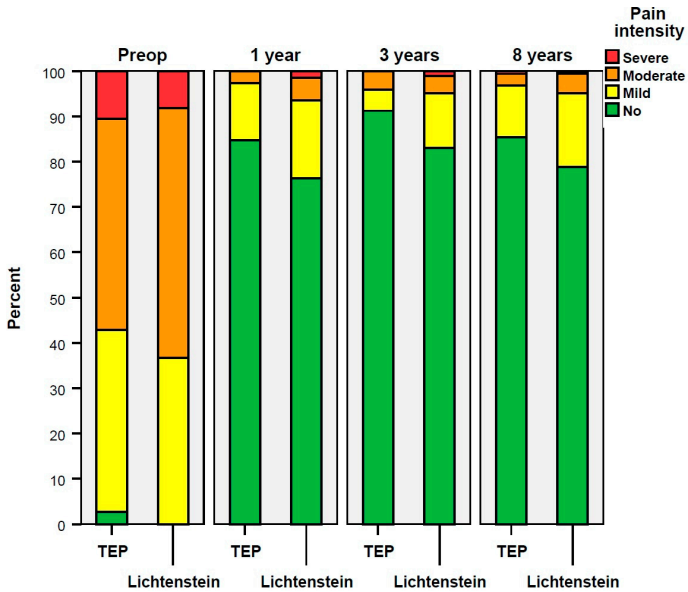


Figure 21. Pain over time according to Cunningham

No patients reporting severe preoperative pain had severe postoperative pain at 1, 3 or 8-years follow-up. Out of the 34 patients reporting severe preoperative pain, 22 and 21 reported no pain at 1- and 3-year follow-up, respectively, see Figure 22. At 3-year follow-up, 3 of the 34 patients with preoperative severe pain (8.9%) reported mild and 2 (5.9%) moderate pain. In this study, severe preoperative pain was alleviated by surgery and few patients reported remaining mild or moderate pain.

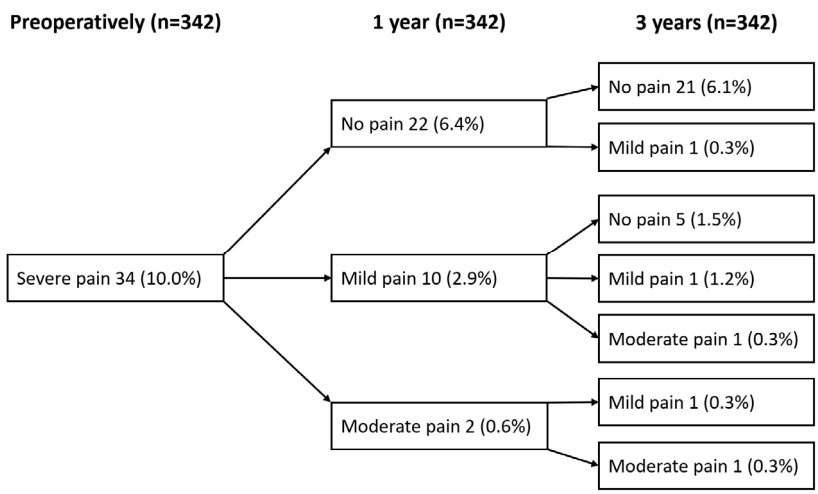


Figure 22. Changes in pain over time for patients with preoperative severe pain according to Cunningham

Physical activity level and activity limitation due to pain (Paper IV)

When asking the patients about their activity level and experienced pain last week at the 8-year follow-up, there was no difference in pain between those with no/light physical activity (10.8%) compared to those with moderate/heavy physical activity (6.7%). Also, no difference in non-ignorable pain was found for patients with a no-moderate activity level compared to those with a heavy activity level. The binary logistic regression model for the same activity levels revealed no difference in the risk of non-ignorable pain. Furthermore, there was no difference in physical activity limited by pain for any of the physical activity level groups.

Pain status over time and surgical harm (Paper I and III)

Among the patients without preoperative non-ignorable pain and participating at all follow-up occasions, 4.9% in the TEP group and 6.4% in the Lichtenstein group reported pain after 8 years, which may have been caused by surgery. The new non-ignorable pain arose between 3 and 8 years. The percentage of patients relieved from preoperative pain was 91.3% in the TEP group and 93.2% in the Lichtenstein group. Among those with preoperative pain, 8.7% and 6.8%, respectively, reported persistent pain. A summary of pain over time is presented in Figure 23.

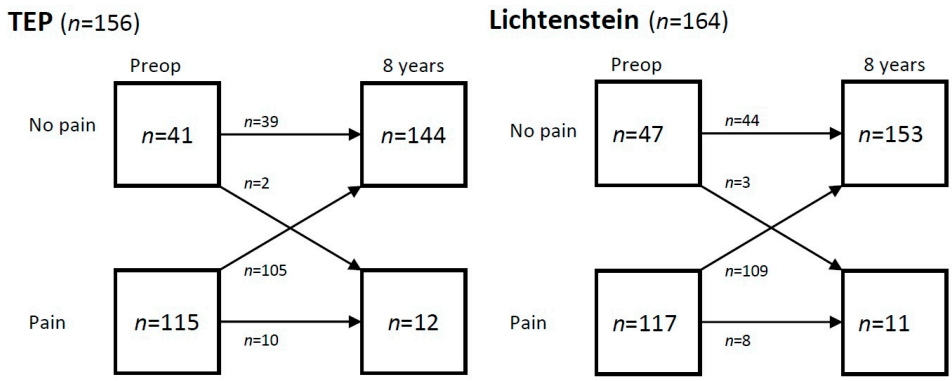


Figure 23. Changes in non-ignorable pain based on each individual patient´s status throughout the study

Besides new pain possibly inflicted by surgery, harm in terms of testicular atrophy was found in one patient in each group at 1 year. At 3 years, 2 additional patients in the Lichtenstein group had developed testicular atrophy.

Sensory disturbances (Paper I)

Sensory disturbances (sensory changes, tenderness and radiating pain) were noted preoperatively, at 1 and 3 years, see Figure 24. Tenderness was seen in almost all patients preoperatively and most of the tenderness disappeared postoperatively. Preoperatively, sensory changes were noted in 18.4% of patients. At 1 year 7.6% of patients in TEP and 36% in Lichtenstein had sensory changes ($p<0.001$). Corresponding figures for sensory changes at 3 years were 5.4% and 24.3% for TEP and Lichtenstein, respectively ($p<0.001$).

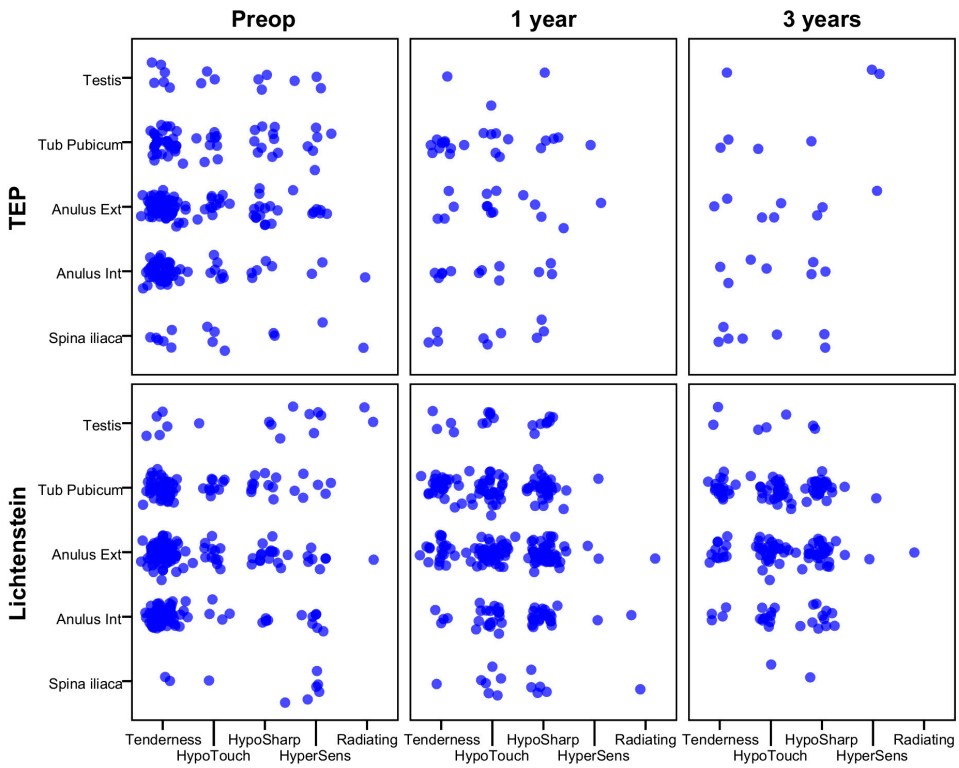


Figure 24. Tenderness, sensory changes and radiating pain at clinical examination

Sensory changes vs non-ignorable pain

For both techniques, a sensory disturbance (sensory changes, tenderness and radiating pain) was noted more frequently in patients with non-ignorable pain last week than in patients with ignorable pain at all follow-up occasions (preoperatively, 1 and 3 years), except for Lichtenstein preoperatively where the difference was non-significant.

For patients having sensory changes preoperatively, no difference in frequencies of sensory changes were observed, regardless of whether they reported non ignorable pain last week or not. Postoperatively, patients with non-ignorable pain last week had sensory changes more frequently after Lichtenstein at 1 and 3 years, but only at 1 year after TEP, see Table 7.

Table 7. Sensory changes vs non-ignorable pain last week by operative technique

	Non-ignorable pain last week		p-value	Non-ignorable pain last week		p-value
	No	Yes		No	Yes	
Preoperatively	**TEP (n=187)**			**Lichtenstein (n=198)**		
No sensory change (%)	47 (87.0)	106 (79.7)	p=0.24	39 (76.5)	124 (84.4)	p=0.20
Sensory change (%)	7 (13.0)	27 (20.3)		12 (23.5)	23 (15.6)	
1 year	**TEP (n=181)**			**Lichtenstein (n=196)**		
No sensory change (%)	157 (93.5)	10 (76.9)	p=0.07	120 (68.2)	6 (30.0)	p<0.01
Sensory change (%)	11 (6.5)	3 (23.1)		56 (31.8)	14 (70.0)	
3 years	**TEP (n=162)**			**Lichtenstein (n=174)**		
No sensory change (%)	148 (95.5)	5 (71.4)	p=0.05	128 (79)	5 (41.7)	p<0.01
Sensory change (%)	7 (4.5)	2 (28.6)		34 (21.0)	7 (58.3)	

Sensory changes include hyposensitivity to touch/sharpness or hypersensitivity

Physical function (Paper I)

Preoperatively 37.7% of TEP and 44.5% of Lichtenstein patients had some degree of discomfort executing the tests (climbing stairs, squatting, and raising from bed). At 1- and 3-year follow-up the corresponding values were 2.5% and 1.9% for TEP and 3.5% and 2.3% for Lichtenstein. In TEP, 35.2% of patients had improved and 1.2% of patients decreased scores at 1 year. The corresponding values for Lichtenstein were 44.5% and 1.7%, respectively. The corresponding values at 3-year follow-up compared to preoperative findings were 37.7% and 1.2% for TEP and 42.8% and 1.7% for Lichtenstein, respectively. The overall improved physical function and changes of scores are shown in Figure 25.

		Follow up 1 year						
		0	1	2	3	4	5	6
Preop TEP	6	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	3	7	0	0	1	0	0	0
	2	16	0	0	0	0	0	0
	1	34	1	0	2	0	0	0
	0	101	0	0	0	0	0	0
Preop Lichten-stein	6	1	0	0	0	0	0	0
	5	0	0	0	0	0	0	0
	4	1	0	0	0	0	0	0
	3	10	0	1	0	0	0	0
	2	33	2	0	0	0	0	0
	1	29	0	0	0	0	0	0
	0	93	0	1	1	1	0	0

		Follow up 3 years						
		0	1	2	3	4	5	6
Preop TEP	6	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	3	7	1	0	0	0	0	0
	2	16	0	0	0	0	0	0
	1	37	0	0	0	0	0	0
	0	99	1	0	1	0	0	0
Preop Lichten-stein	6	1	0	0	0	0	0	0
	5	0	0	0	0	0	0	0
	4	1	0	0	0	0	0	0
	3	9	0	0	1	0	0	1
	2	34	0	0	1	0	0	0
	1	29	0	0	0	0	0	0
	0	95	0	1	0	0	0	0

improved functional score

unchanged functional score

impaired functional score

Figure 25. The physical functional scores range from 0-6 points, where 0=without discomfort, and 6=severe discomfort, for all three activities (climbing stairs, squatting, and raising from bed). Individual changes are based on the number of patients completing the tests preoperatively, at 1- and 3-years follow-up (TEP n=162, Lichtenstein n=173)

Recurrences and reoperations (Paper I and III)

A total of 6 recurrences were diagnosed, 5 at the 1-year follow-up and 1 at the 3-year follow-up, with no significant difference between the groups (p=0.36). No further recurrences were found between the 3- and 8-year follow-up. The cumulative recurrence rate at 8-year- follow-up, was 2.5% in the TEP group (4/157), and 1.2% (2/165) in the Lichtenstein group.

Out of the patients with a recurrence, all were reoperated except for one patient without symptoms in the TEP group.

Of all patients operated in the study, 9 (2.2%) patients were reoperated due to a recurrence (n=5) or a postoperative complication (n=4).

Quality of life (Paper I and III)

Preoperative a 7-point reduction in the physical composite score (PCS), corresponding to a medium to large clinical decrease compared to the norm, was seen without impairment of the mental composite score (MCS). Postoperatively, at all follow-up occasions, the PCS increased above the Swedish norm, see Figure 26. Between 1 and 8 years a significant decrease in PCS was observed in both groups, (p=0.001). During the same period, MCS decreased in the Lichtenstein (p=0.003) but not in the TEP group (p=0.67). Despite this decrease, the patients still scored above the Swedish norm at 8 years.

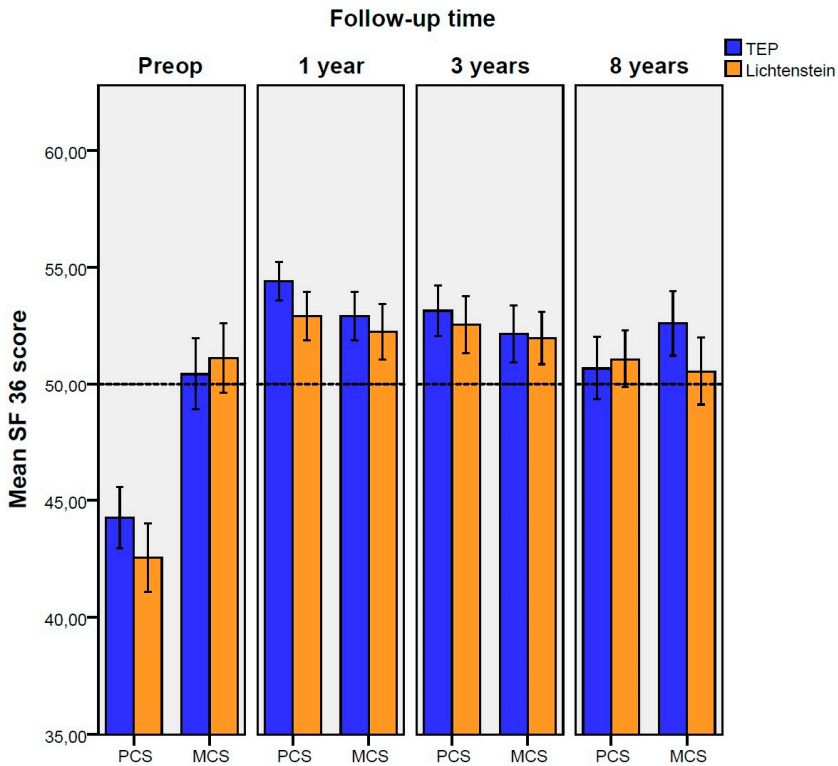


Figure 26. SF-36® scores for PCS=physical composite score and MCS=mental composite score, before and 1, 3 and 8 years after surgery

Patients' satisfaction after surgery (Paper I and III)

Overall, few patients were not satisfied with surgery. At 1 year, 0.6% in TEP and 2.7% in Lichtenstein were not satisfied with surgery. Corresponding numbers at 3 years were 1.8% and 3.4%, and at 8 years 1.3% and 2.4%. No differences were observed between groups at any follow-up occasion.

A subgroup of patients with preoperative no or mild pain according to Cunningham were analyzed whether they were satisfied with or regretted surgery. Of these patients, 1 (1.5%) patient in TEP at 3 years and 2 (2.7%) patients at 8 years were dissatisfied with surgery. No patients in Lichtenstein were dissatisfied with surgery at any follow-up occasion. Patients regretting surgery were 1 (1.5%) patient in TEP and 1 (1.6%) in Lichtenstein at 3 years. In this subgroup, no difference between groups was seen in satisfaction or regret undergoing surgery at any follow-up occasion.

The TEPLICH trial: pain at sexual activity and sexual impairment (Paper II)

A subgroup of 304 patients (111 in TEP and 132 in Lichtenstein) from the TEPLICH cohort was evaluated for pain at sexual activity and sexual impairment. At 1 year, 96.4% of TEP and 97.7% of Lichtenstein patients remained for follow-up. The corresponding numbers at 3 years were 90.1% in TEP and 89.4% in Lichtenstein.

Baseline characteristics, pre- and postoperative data

No differences in baseline, pre- and postoperative data was seen between TEP and Lichtenstein, see Table 8.

Table 8. Baseline, pre- and postoperative data

	TEP n=111	Lichtenstein n=132	*p*-value
Age [mean (SD)]	46[8.1]	46[8.3]	
BMI [mean (SD)]	25[2.4]	25[2.5]	
ASA (%) ASA I ASA II Missing	 93(84) 17(15) 1 (1)	 119(90) 13(10) 0 (0)	
Hernia type (%) Direct Indirect Combined Missing	 26(23) 68(61) 4 (4) 13(12)	 34(26) 82(62) 8 (6) 8 (6)	
Profession (%) Light Heavy Missing	 30(27) 80(73) 1 (1)	 36(27) 94(71) 2 (2)	
Out-patient (%) In-patient (%) Missing (%)	61(55) 1 (1) 49(44)	71(54) 3 (2) 58(44)	< 0.625[a]
Complications within 4 weeks (%) Hematoma/Seroma Infection Neuralgia Testicular pain Missing	2 (2) 0 0 0 2 9 (8)	8 (6) 3 2 1 2 19(14)	< 0.112[b]

[a] Out-patient vs in-patient
[b] Any postoperative complications vs no complications

Pain at sexual activity and sexual impairment

Before surgery, a total of 35% of patients reported pain at sexual activity, with no difference between techniques. At 1-year follow-up, 9.5% of patients experienced pain at sexual activity, 5.9% in the TEP group and 12.5% in the Lichtenstein group (p=0.10). At 3 years, corresponding rates were 8.2%, with 7.0% in TEP and 9.3% in Lichtenstein (p=0.57).

The intensity of pain at sexual activity was measured with VAS. VAS ≥3 was reported preoperatively by 70.0% of patients with pain at sexual activity. At 1 year postoperatively, 33.3% reported VAS ≥3, 0% in TEP and 46.2% in Lichtenstein (p=0.11). Correspondingly, at 3 years the total number was 66.7%, 60.0% in TEP and 71.4% in Lichtenstein (p=1.00).

The frequency of pain at sexual activity reported as occurring often or always was 63.4% preoperatively. 1 year after surgery, the rate was 38.1%, 0% in TEP and 53.3% in Lichtenstein (p<0.05). The corresponding figures at 3 years were 46.7% for both groups, 33.3% for TEP and 55.6% for Lichtenstein (p=0.61).

Moderate to severe impairment in sexual function was observed in 40.2% of patients who reported pain at sexual activity preoperatively. At 1-year follow-up, 9.5% experienced moderate/severe impairment, 0% in TEP and 33.3% in Lichtenstein (p=0.26). At 3 years, the rates were 28.6% overall, with 20.0% in TEP and 33.3% in Lichtenstein (p=1.00).

The intensity, frequency and impact on sexual activity of pain at sexual activity is shown in Figure 27.

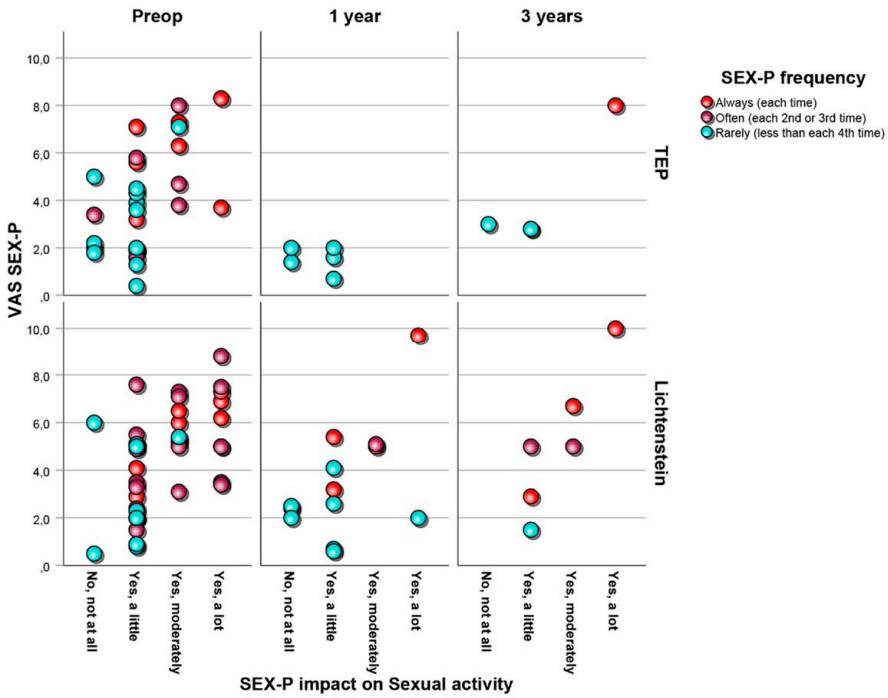


Figure 27. Pain at sexual activity (SEX-P) intensity, frequency and impact on sexual activity

Quality of life in relation to pain at sexual activity

SF-36 scores were calculated and compared between patients with and without pain at sexual activity. Preoperatively all patients scored below the Swedish norm, particularly in the PCS score, with notably lower scores in patients with pain at sexual activity. Postoperatively patients with pain at sexual activity equalled the Swedish norm-based scores and patients without pain at sexual activity had overall increased scores compared to the Swedish norm, particularly for PCS. No differences in PCS or MCS scores were seen between TEP and Lichtenstein when comparing patients with and without pain at sexual activity.

Risk factors for pain at sexual activity

A multivariate risk factor analysis that included preoperative pain at sexual activity status (yes/no), surgical technique (TEP/Lichtenstein), and age (<45/>45 years) was performed. Presence of pain at sexual activity preoperatively (p=0.004) and a Lichenstein operation (p=0.045) were identified as independent risk factors for postoperative pain at sexual activity.

Patients with non-ignorable pain last week had more pain at sexual activity compared to those without non-ignorable pain last week, except for TEP at 1 year where no difference was observed (Table 9).

Table 9. Pain at sexual activity (SEX-P) in relation to non-ignorable pain last week

	Non-ignorable pain last week		p-value	Non-ignorable pain last week		p-value
	No	Yes		No	Yes	
Preoperatively	**TEP (n=111)**			**Lichtenstein (n=132)**		
No SEX-p	23 (85.2)	55 (65.5)	p=0.06	27 (87.1)	53 (52.5)	p<0.001
SEX-P	4 (14.8)	29 (34.5)		4 (12.9)	48 (47.5)	
1 year	TEP (n=101)			Lichtenstein (n=120)		
No SEX-p	89 (94.5)	6 (85.7)	p=0.36	97 (91.5)	8 (57.1)	p<0.001
SEX-P	5 (5.3)	1 (14.3)		9 (8.5)	6 (42.9)	
3 years	**TEP (n=86)**			**Lichtenstein (n=108)**		
No SEX-p	77 (96.3)	3 (50.0)	p=0.004	93 (93.9)	5 (55.6)	p=0.004
SEX-P	3 (3.8)	3 (50.0)		6 (6.1)	4 (44.4)	

Percentages in parenthesis are proportions of patients with or without non-ignorable pain last week

Pain at sexual activity status through the follow-up period

Each individual patient´s pain at sexual activity status was followed from preoperatively to 3 years, and only patients with data available at all 3 occasions were included, see Figure 28.

Relief of, persisting, and new-onset pain at sexual activity at 1- and 3-year follow-up is shown in Table 10.

New-onset pain at sexual activity was observed in 3 (4.3%) patients in TEP and 5 (6.8%) in Lichtenstein between preoperatively to 1 year. The corresponding numbers, preoperatively to 3 years were 1 (1.7%) for TEP and 4 (6.0%) for Lichtenstein.

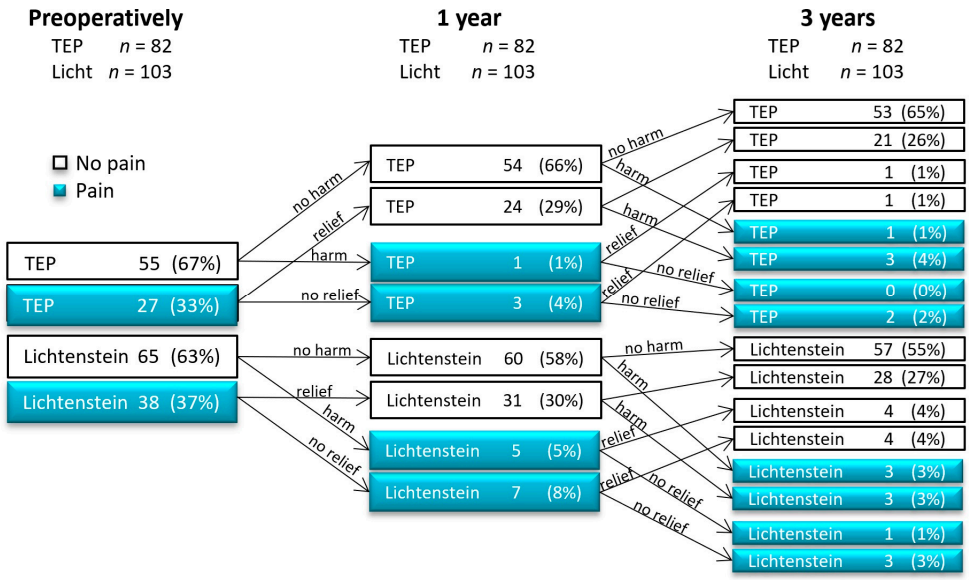


Figure 28. Assessment of pain at sexual activity over time in patients participating at all three follow-up occasions

Table 10. Changes in pain at sexual activity

Preop-1yr		**TEP**		**Lichtenstein**
Relief (%)	n=31[a]	28 (90.3)	n=46[a]	36 (78.3)
Persisting (%)		3 (9.7)		10 (21.7)
Remaining free of pain (%)	n=70[b]	67 (95.7)	n=74[b]	69 (93.2)
New onset (%)		3 (4.3)		5 (6.8)
Preop-3yrs		**TEP**		**Lichtenstein**
Relief (%)	n=28[a]	23 (82.1)	n=41[a]	35 (85.4)
Persisting (%)		5 (18.9)		6 (14.6)
Remaining free of pain (%)	n=58[b]	57 (98.3)	n=67[b]	63 (94.0)
New onset (%)		1 (1.7)		4 (6.0)

[a]Number of patients with preoperative pain at sexual activity
[b]Number of patients with no preoperative pain at sexual activity

Mapping of pain at sexual activity and pain descriptors

When asking the patients to map the location of pain at sexual activity and describe it with pain descriptors, the results indicated that Lichtenstein patients described pain at sexual activity with descriptors of more neuropathic origin compared to TEP patients. This pain was of pricking nature and most frequently located in the lower groin (Figure 29).

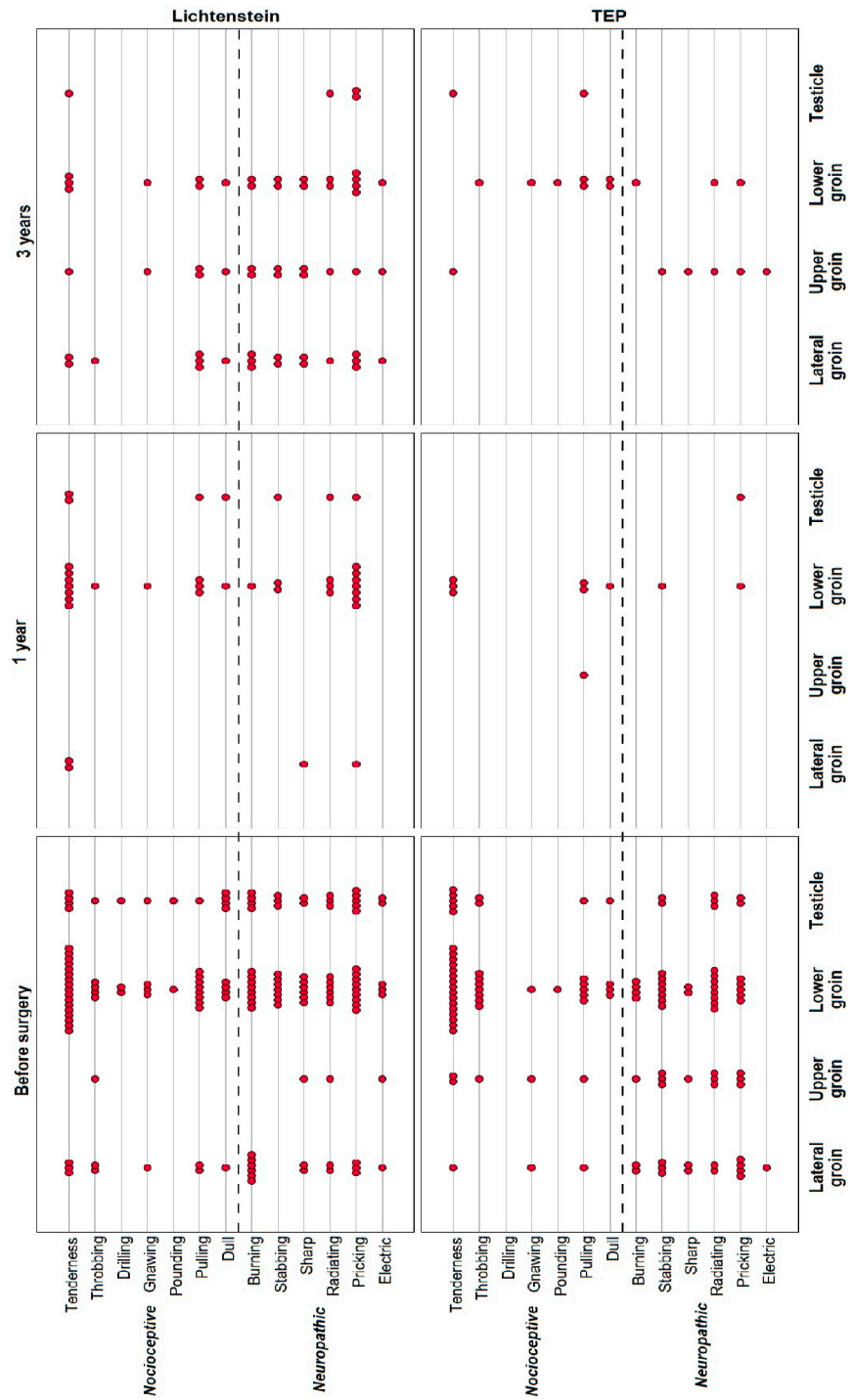


Figure 29. Pain descriptors and location for patients with SEX-P

Pain at sexual activity in relation to sensory disturbances

The difference in sensory disturbances and location for patients with pain at sexual activity compared to those having non-ignorable pain without pain at sexual activity is presented in Table 11 and 12.

Table 11. Number of patients with pain at sexual activity and their mapped sensory disturbances at 1 and 3 years

Sensation	Hypersens[c]		Hyposharp[d]		Hypotouch[e]		Radiating[f]		Tenderness	
	TEP	Lich	TEP	Lich	TEP	Lich	TEP	Lich	TEP	Lich
1 year Total (%)[a]	0	0	33	53	0	47	0	7	17	60
3 year Total (%)[a]	17	0	17	70	17	47	0	0	50	60
Locations	Testicle		Pubic tubercle		Deep ring		Iliac spine		Superficial ring	
1 year Total (%)[b]	0	20	33	47	0	27	0	7	17	73
3 year Total (%)[b]	17	0	17	80	17	30	17	0	17	50

[a] Total percentage is solely based on reported sensation, if the same patient reported the same sensation at multiple locations, these are counted as one. [b] Total percentage solely based on location, if the same patient reported multiple sensory disturbances at the same location, these are counted as one. Total number (N) of patients with SEX-P. N=6 for TEP and N=15 for Lichtenstein at 1 year. N=6 for TEP and N=10 for Lichtenstein at 3 years. [c] hypersens=hypersensitivity; [d] hyposharp=hyposensitivity to sharpness; [e] hypotouch=hyposensitivity to touch; [f] radiating=radiating pain.

Table 12. Number of patients with non-ignorable pain but no pain at sexual activity and their mapped sensory disturbances at 1 and 3 years

Sensation	Hypersens[c]		Hyposharp[d]		Hypotouch[e]		Radiating[f]		Tenderness	
	TEP	Lich	TEP	Lich	TEP	Lich	TEP	Lich	TEP	Lich
1 year Total (%)[a]	0	0	0	75	17	75	0	0	33	63
3 year Total (%)[a]	0	0	0	60	0	38	0	0	33	40
Locations	Testicle		Pubic tubercle		Deep ring		Iliac spine		Superficial ring	
1 year Total (%)[b]	17	13	50	63	0	25	0	13	0	60
3 year Total (%)[b]	0	20	0	40	0	40	33	0	0	63

[a] Total percentage is solely based on reported sensation, if the same patient reported the same sensation at multiple locations, these are counted as one. [b] Total percentage solely based on location, if the same patient reported multiple sensory disturbances at the same location, these are counted as one. Total number (N) of patients with non-ignorable pain last week with no Sex-P. N=6 for TEP and N=8 for Lichtenstein at 1 year. N=3 for TEP and N=5 for Lichtenstein at 3 years. [c] hypersens=hypersensitivity; [d] hyposharp=hyposensitivity to sharpness; [e] hypotouch=hyposensitivity to touch; [f] radiating=radiating pain.

In summary, the sensory disturbances did not differ between patients with pain at sexual activity compared to those having non-ignorable pain without pain at sexual activity. The disturbances were also located at similar anatomical areas, mostly at the pubic tubercle and the external iliac ring.

Comparison of Inguinal Pain Questionnaire, Cunningham pain scale and VAS in inguinal hernia surgery (Paper IV)

Optimal VAS cut-offs based on Cunningham and IPQ last week

Three optimal cut-offs for VAS right now and VAS last week based on Cunningham were found. For VAS right now, these were: no pain ≤0.3, no-mild pain ≤3.4, and no-moderate ≤5.2. For VAS last week these were: no pain ≤0.3, no-mild pain ≤4.0, and no-moderate ≤6.0. The optimal cut-off for VAS right now and VAS last week based on IPQ last week was ≤0.8 and ≤1.1, respectively. Cut-off values and Cohen's kappa values are summarized in Table 13.

Table 13. The optimal cut-offs for VAS right now and last week based on Cunningham and IPQ non-ignorable pain last week

VAS cut-offs based on Cunningham	No vs mild-severe (k)[a]	No-mild vs moderate-severe (k)[a]	No-moderate vs severe (k) [a]
Optimal VAS right now	≤0.3 (0.60)	≤3.4 (0.68)	≤5.2 (1.00)
Optimal VAS last week	≤0.3 (0.65)	≤4.0 (0.65)	≤6.0 (0.66)

VAS cut-off based on IPQ	No-easily ignorable pain vs non-ignorable pain last week (k)[a]
Optimal VAS right now	≤0.8 (0.61)
Optimal VAS last week	≤1.1 (0.67)

[a] Cohen's kappa (k) for each cut-off.

Distributions between pain scales

The distribution of VAS last week, Cunningham and IPQ non-ignorable pain last week are presented in Figure 30. Among the 263 patients who reported no pain on the Cunningham scale, 1 reported non-ignorable pain last week according to the IPQ, and 3 had a VAS score of ≥3. Among the 45 patients with mild pain, 10 reported non-ignorable pain, and 5 had a VAS score of ≥3. Of the 11 patients with moderate pain, 3 reported pain that interfered with daily activities, with VAS scores ranging widely from 1.7 to 6.9. The 2 patients who experienced severe pain on the Cunningham scale reported pain interfering with most activities and had VAS scores of 6.3 and 7.0.

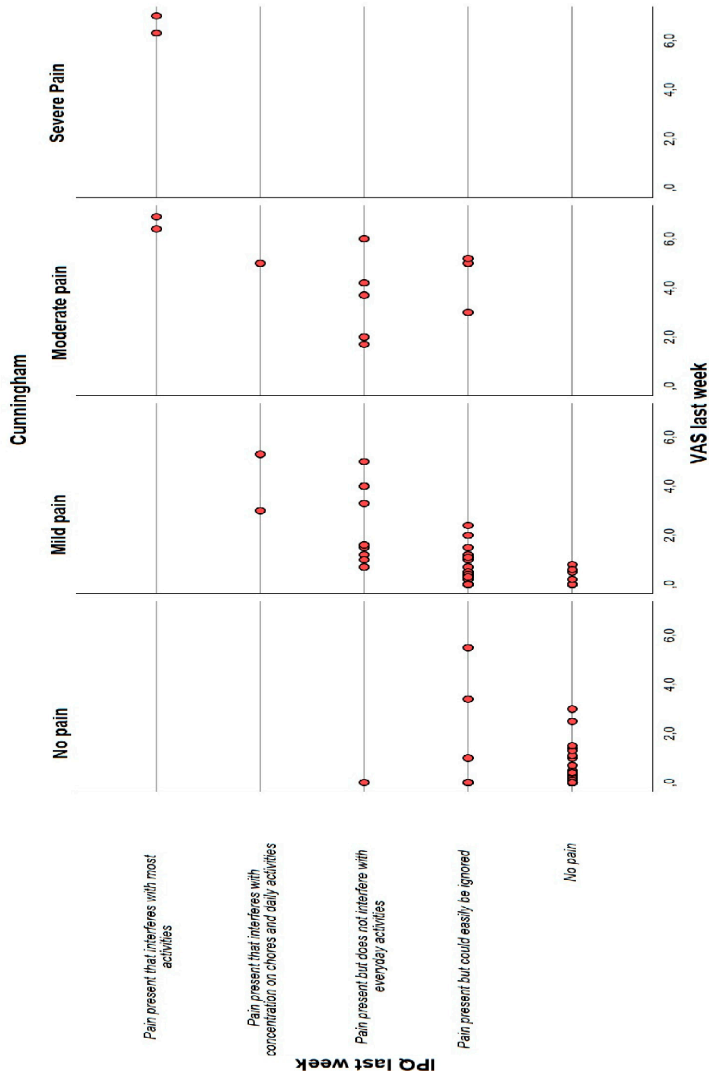


Figure 30. The distribution of VAS last week against Cunningham and IPQ last week

Cunningham and IPQ scores for pain last week were compared preoperatively and at 8 years, see Figure 31. Discrepancies were noted between the two scales in pain reporting preoperatively versus at 8 years. Preoperatively, among patients reporting moderate pain on the Cunningham scale, 56% described their pain as non-ignorable on the IPQ, 34% as easily ignorable, and 30% as no pain. Overall, the Cunningham scale reflected higher pain intensity than the IPQ for preoperative pain over the last week.

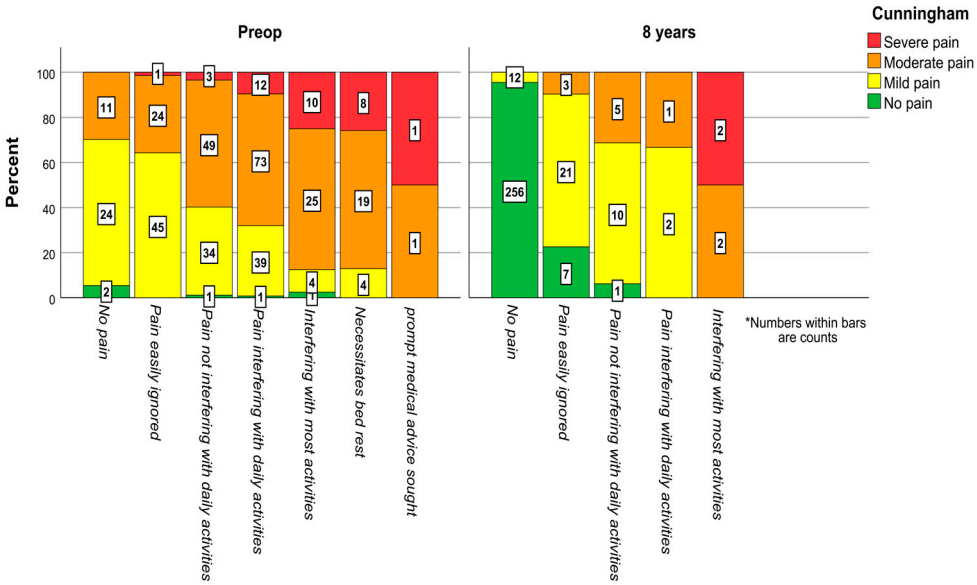


Figure 31. Pain distributions between IPQ last week and Cunningham preoperatively and at 8 years

Correlations and agreements between pain scales

The correlation between Cunningham and IPQ last week was weak preoperatively (τ_b=0.36) and strong at 8 years (τ_b=0.78), see Table 15. The correlation was moderate at 1 year (τ_b=0.57) and strong at 3 years (τ_b=0.73). For additional correlation coefficients between pain scales, see Tables 14 and 15.

Table 14. Correlations between continuous VAS right now/last week and ordinal scales Cunningham and 7-graded IPQ right now/last week at 8 years follow-up

Compared pain scales	r_s[a] (95% CI)
VAS right now vs VAS last week	0.93 (0.92-0.95)
VAS right now vs Cunningham	0.59 (0.5-0.66)
VAS right now vs IPQ right now	0.63 (0.55-0.70)
VAS right now vs IPQ last week	0.63 (0.55-0.69)
VAS last week vs Cunningham	0.62 (0.54-0.69)
VAS last week vs IPQ right now	0.58 (0.50-0.66)
VAS last week vs IPQ last week	0.65 (0.58-0.72)
	τ_b[b] (95% CI)
IPQ last week vs IPQ right now	0.78 (0.75-0.81)
IPQ last week vs Cunningham	0.78 (0.75-0.81)
IPQ right now vs Cunningham	0.64 (0.60-0.69)

[a] Spearman's correlation coefficient, [b] Kendall's tau-b

Table 15. Measures of correlation and agreement between Cunningham, IPQ, categorized and optimal VAS at 8 years follow-up

Compared pain scales	PA[a] (%)	τ_b[b] (95% CI)	k_w[c] (95% CI)
VAS right now vs VAS last week	95 %	0.93 (0.88-0.97)	0.89 (0.84-0.94)
IPQ right now vs IPQ last week	92%	0.78 (0.75-0.81)	0.77 (0.68-0.86)
Cunningham vs VAS right now	82%	0.55 (0.45-0.66)	0.57 (0.47-0.67)
Cunningham vs VAS last week	81%	0.58 (0.48-0.68)	0.56 (0.45-0.67)
Cunningham vs optimal VAS right now	87%	0.62 (0.57-0.66)	0.64 (0.53-0.75)
Cunningham vs optimal VAS last week	88%	0.67 (0.63-0.71)	0.67 (0.57-0.76)

[a] Percentage agreement (PA). [b] Kendall's tau-b (τ_b) measuring monotonic relationship. [c] Linear weighted kappa (k_w) measuring the agreement between pain variables

Categorized and optimal VAS last week compared to Cunningham are presented in contingency tables, see Figures 32 and 33. Categorized and optimal VAS last week showed moderate (k_w=0.56) and substantial (k_w=0.67) agreements with Cunningham, respectively, see table 16. Categorized VAS right now vs VAS last week showed an almost perfect agreement (k_w=0.89), while IPQ right now vs IPQ last week showed a substantial agreement (k_w=0.78).

VAS last week

Cunningham	VAS=0	0<VAS<3	3≤VAS<6	6≤VAS≤10	Total Cunningham
Severe Pain	0	0	0	2	2
Moderate Pain	0	2	6	3	11
Mild Pain	14	25	6	0	45
No pain	228	32	3	0	263
Total VAS last week	242	59	15	5	321

Figure 32. Contingency table of Cunningham vs Categorized VAS last week. Distributed frequencies of Cunningham vs categorized VAS last week. Overlapping values are marked with thicker boxes

	Optimal VAS last week				
Cunningham	0≤VAS≤0.3	0.3<VAS≤4	4<VAS≤6	6<VAS≤10	Total Cunningham
Severe Pain	0	0	0	2	2
Moderate Pain	0	4	5	2	11
Mild Pain	18	25	2	0	45
No pain	249	13	1	0	263
Total Optimal VAS last week	267	42	8	4	321

Figure 33. Contingency table of Cunningham vs Optimal VAS last week. Distributed frequencies of Cunningham vs optimal VAS last week. Overlapping values are marked with thicker boxes

Discussion

Short-term postoperative data

The short-term postoperative data in this study showed a shorter median operative time for TEP of 48 vs 60 min, a faster average recovery of 6 days (13 vs 19 days) and sick leave of 3 days (9 vs 12 days). Complications were more frequent in Lichtenstein, with overall 7.0% complications observed in the Lichtenstein group and 2.0% in TEP (p=0.018). Hematoma was observed in 3.7% in Lichtenstein and 1.0% in TEP, being the most common complication overall. Testicular pain was seen in 1.0% in TEP and 1.4% in Lichtenstein, where orchidectomy was necessary due to ischemic orchitis in 1 Lichtenstein patient. Surgeons were more satisfied after performing a Lichtenstein procedure compared to a TEP and found the Lichtenstein procedure technically easier.

A meta-analysis on existing RCTs comparing TEP with Lichtenstein regarding postoperative outcomes performed a pooled analysis, calculating the odds ratio for differences in short-term postoperative data between the techniques (38). The pooled analysis concluded that TEP had a lower risk of postoperative hematoma and faster return to daily activities, while, in contrast to our study, vascular injuries and operative time (mean difference, 11.05 min) favoured Lichtenstein. In the context of the study with primary, non-recurrent and non-scrotal hernias, the TEP procedure is in experienced hands often straightforward with fewer dissection steps, possibly explaining the faster operative times.

This systematic review additionally evaluated the methodological quality and potential biases of all included RCTs. This evaluation was based on Cochrane's criteria consisting of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcomes, completeness of outcome data and selective reporting (87). The TEPLICH study distinguished itself by being the only one scoring low for all biases.

Eklund et al. and Langeveld et al. performed RCTs comparing TEP to Lichtenstein studying similar outcomes as in the TEPLICH trial (25, 88). The observed complications rates in Eklunds study were 17.1% in TEP and 17.5% in Lichtenstein (p=0.89) and in Langeveld's study 33% for both techniques. 0.2% in TEP and 0.2% in Lichtenstein were reoperated due to a complication in the former study, and 4.2% in TEP and 3.5% in Lichtenstein in the latter study. No difference between

hematoma formation between techniques were observed in either study. In the RCT by Ekelund et al. all surgeons were board-certified for the techniques with median operating times of 55 min for both techniques. TEP had a median of 5 days (7 vs 12 days) shorter sick leave and 11 days (20 vs 31 days) shorter time to recovery compared to Lichtenstein. In the RCT by Langeveld et al., board-certified surgeons occasionally supervised a resident. Operative times were on average 5 minutes longer for TEP compared to Lichtenstein (54 vs 49 min). TEP patients returned faster to their daily activities and had shorter time of sick leave (1 vs 1.4 weeks). In summary, these RCTs reported similar operative time, time to recovery and sick leave as in our RCT. Although, the complications rates were considerably more frequent, especially in the study by Langeveld et al.

Chronic pain

Incidences of CPIP up to 5 years

The current literature on chronic pain after Lichtenstein and TEP is conflicting due to heterogeneity in definitions of pain, pain assessment tools utilized and non-consistent experience of surgeons between studies (89). In the TEPLICH study, no difference between TEP and Lichenstein was observed for IPQ “non-ignorable pain” or “any pain” last week or right now, or for Cunningham no-mild vs moderate-severe pain at 1, 3 and 8 years, except for less frequently reported “any pain” last week for TEP at 3 years (p=0.008).

Most existing RCTs generally report more favourable chronic pain outcomes for TEP compared to Lichtenstein (83, 90-92). However, another RCT reported no difference in mean VAS scores between TEP and Lichtenstein during the first week and 3 months postoperatively (93). Notably, Lichtenstein was performed under local anesthesia and only 29 patients in TEP and 30 patients in Lichtenstein completed the study, raising concerns about the statistical power. A more recent RCT, included 302 patients followed for a mean of 40.95 months, showed a clear advantage with less chronic pain for TEP compared to Lichtenstein (3.5% vs 25.2%, p=0.001) (91). A definition of pain was lacking for the long-term chronic pain, and VAS was used to estimate early postoperative pain. Similarly, VAS without a clear pain-definition was used in the LEVEL trial, the large RCT by Langeveld et al., reporting advantageous pain rates for TEP compared to Lichtenstein in the early postoperative period, but comparable chronic pain rates at 1 year (25% for TEP and 28% for Lichtenstein) (25). Westin et. al compared TEP to Lichtenstein repair in 375 patients after 1 year, defining pain as any pain last week according to IPQ (90). Any pain last week was reported by 39 (20.7%) patients in TEP and 62 (33.2%) patients in Lichtenstein (p=.007), compared to our figures of 18.1% for TEP and 25.5% for Lichtenstein at 1 year follow-up (p=0.077).

A large propensity score-matched registry study from Germany included 12 564 matched TEP and Lichtenstein patients. Pain (yes/no) at rest and on exertion was assessed at 1 year. Pain at rest was reported by 4.3% and 5.2% (p=0.003), and pain at exertion by 7.7% and 10.6% (p<0.001) in TEP and Lichtenstein, respectively. The corresponding odds ratio for pain at rest was 1.19 (CI, 1.06-1.34), and for pain at exertion was 1.373 (CI, 1.26-1.49), favouring TEP. While no optimal definition for pain in our study specifically reflects pain on exertion, the IPQ describes pain in relation to activity, thus non-ignorable pain last week could be used as a potential proxy for pain on exertion. In our study, non-ignorable pain last week was reported by 13 (6.9%) in TEP and 20 (9.8%) in Lichtenstein at 1 year follow-up (p=0.30), consistent with the German registry study.

Accordingly, most meta-analyses comparing RCTs on chronic pain rates after TEP vs Lichtenstein, suggest that TEP is associated with less chronic pain (35-37). Bullen et al. conducted the only meta-analysis that did not specifically compare TEP to Lichtenstein but instead calculated pooled odds ratios for TEP/TAPP vs Lichtenstein. In contrast, two additional meta-analyses found no significant difference in chronic pain between TEP and Lichtenstein (38, 39). The pooled odds and risk ratios for chronic pain between TEP and Lichtenstein, as reported in the studies, are presented in the introduction, Table 3.

Incidences of persisting CPIP after 5 years and longer

Only a few RCTs have reported chronic pain rates comparing TEP to Lichtenstein after 5 years of follow-up or longer (83, 94-96).

A 5-year follow-up of the LEVEL trial by Eker et al. reported decreasing chronic pain rates in TEP but unchanged for Lichtenstein from 1- to 5- year follow-up (94). In TEP the chronic pain decreased from 25% to 14.9% and for Lichtenstein it remained at 28%. In the Eker study, pain was assessed using VAS and although probable, it remains unclear if any score other than 0 was defined as no pain. Assuming this was the case, it resembles the results in our study, where VAS right now >0 was reported by 14.0 % of patients in TEP and 32.1% in Lichtenstein at 8 years. The mean VAS scores in the LEVEL trial at 5 years were 0.9 for TEP and 1.5 for Lichtenstein (p=0.03), compared to our 8 years results of mean VAS right now of 0.3 for TEP and 0.42 for Lichtenstein (p=0.001).

In the Eklund study (SMIL II-trial), comparing TEP and Lichtenstein, chronic pain was assessed using the Cunningham pain scale 1 and 5 years postoperatively. Mild-severe pain did not decrease between 1 and 5 years and was reported by 9.4% in TEP and 18.8% in Lichtenstein at 5 years (p<0.001). In the Lichtenstein group, moderate-severe pain decreased from 7.1% to 3.5% (p=0.001), but no significant decrease was observed in TEP (2.7% to 1.9). In comparison, our findings showed mild-severe pain in 14.6% of TEP and 21.2% of Lichtenstein patients (p<0.13) and

moderate-severe pain in 3.8% of TEP and 5.5% of Lichtenstein (p<0.48) patients at 8 years. In contrast to the SMIL II-study, moderate-severe pain did not decrease between 1 and 8 years in our study. Grant et al. compared TEP to Lichtenstein at 1 and 5 years using a 5 graded verbal rating scale that also included very mild pain (95). At 1 year, 27.7% of TEP patients and 35.6% of Lichtenstein patients reported very mild or more severe pain (p=0.15), with these numbers decreasing at 5 years to 18.1% in TEP and 20.1% in Lichtenstein (p=0.55). In an underpowered RCT by Hallen et al. that compared TEP to Lichtenstein 6 years postoperatively, chronic pain was observed in 21.9% of TEP and 23.5% of Lichtenstein patients (96).

In summary, there is conflicting data between RCT studies whether pain persists or decreases 5 years or longer after surgery. However, the SMIL II-study, using the same pain scale, reached the same conclusion as ours, that mild or more severe pain can persist a long time after surgery.

Pain status over time, surgical harms and satisfaction with surgery

In this study, we examined the pain status over time for all patients to identify those with new non-ignorable pain last week, i.e. pain not existing prior to surgery, defined by us as a harm since it might be inflicted by surgery. Of the 5 patients who preoperatively reported ignorable pain last week, 2 in each group reported a worsening in their pain status to non-ignorable pain not interfering with everyday activities, and one TEP patient reported non-ignorable pain last week interfering with most activities, at 8-years follow-up. Thus, low numbers of harm were observed. Persistent pain was observed in 8.7% of patients in TEP and 6.8% of patients in Lichtenstein. Over 90% of patients were relieved of their pain postoperatively, indicating high effectiveness of surgery for relieving preoperative pain.

Watchful waiting vs surgery has been discussed in the introduction of this thesis. Based on the studies presented there, surgery should generally be recommended for patients with pain or other symptoms affecting their desired activity but could also be recommended to patients with mild preoperative pain, according to a recent RCT where a crossover rate of 50% at 2 years for patients with mild and 6 years for patients with no pain, was observed (50). The main reason for crossover was increasing groin pain. These patients often regretted not having surgery immediately. Hence, also patients with mild preoperative symptoms benefited from immediate surgery in this study. To put this into perspective in relation to the present thesis, patients reporting no or mild pain were asked if they regretted the operation or were dissatisfied with the surgery. Of these patients, all but 1 (1.5%) patient in TEP at 3 years and 2 (2.7%) patients at 8 years were satisfied with their surgery. No patients in the Lichtenstein group were dissatisfied at any follow-up occasion. The corresponding figures for patients regretting the operation at 3 years were 1 (1.5%) in TEP and 1 (1.6%) in Lichtenstein. There was no difference in satisfaction or

regret about undergoing surgery between the TEP and Lichtenstein groups at any follow-up occasion. In the RCT by Eker et al., patient satisfaction was compared between 336 TEP and 324 Lichtenstein patients using the NRS scale with 10-points to quantify the level of post-surgical satisfaction at 5 years (94). The total score for TEP (8.0 points) was 0.5 point lower than for Lichtenstein (8.5 points) (p=0.004). Additionally, when evaluating satisfaction concerning their operative scar, TEP patients scored 8.8 points and Lichtenstein patients 8.4 points (p=0.02). Other studies have shown similar results of satisfaction after inguinal hernia surgery, with levels of satisfaction for Lichtenstein between 90.0%-95.8%, and for TEP between 92.3%-98% respectively (97-101).

Preoperative pain as a risk factor for postoperative pain

Preoperative pain has previously been shown to be a risk factor for postoperative pain after inguinal hernia surgery in register studies and systematic reviews (102-104). However, one of the studies, a registry-based study involving 4016 patients reporting pain using the VRS scale, concluded that moderate-severe pain at 1 month was a greater risk factor for CPIP than moderate-to severe pain preoperatively (104). Univariate and multivariate risk factor analyses are most frequently used to calculate the risk of postoperative pain in these studies. A drawback using logistic regression is that the calculated odds ratio does not equal absolute risks. Few studies, and no RCT, have followed individual patients over time to estimate the actual number of patients experiencing a specific level of pain pre- compared to postoperatively (97). We found that all the 34 patients having severe preoperative pain were cured of this pain at all follow-up occasions (1, 3 and 8 years). Only 2 (6%) of these had a moderate pain, while 64 % and 76% reported no pain at 1 and 3 years, respectively. Our results are in line with a registry-based study by Romain et al. that assessed pain preoperatively to 2 years in 5670 inguinal hernia patients operated with Lichtenstein, TIPP or TEP (97). The patients reported their pain using the VRS scale (no, mild, moderate and severe). Of the patients having severe postoperative pain, 0.4% had no-mild or severe, and 0.2% had moderate pain preoperatively. Of the patients having moderate postoperative pain, the corresponding preoperative pain distributions were no pain 3.1%, mild pain 3.4%, moderate pain 4.1%, and severe pain 6.8%. Thus, postoperative severe pain did not depend on the preoperative VRS pain status, but both mild and moderate postoperative pain showed a positive relationship with higher pain proportions with increasing preoperative pain severity, while a no postoperative pain status showed a negative relationship with higher proportions of no pain with decreasing preoperative pain severity. In other words, patients with severe preoperative pain reported similar proportions of severe or no pain at 2 years postoperatively as those with no preoperative pain.

Recurrence

In the TEPLICH study, the cumulative recurrence rate was 1.9%, corresponding to 6 patients throughout the study, with 3 diagnosed in TEP and 2 in Lichtenstein at 1-year follow-up and one additional recurrence in TEP at 3 years. No recurrences were observed between 3 and 8 years.

In the Swedish Hernia Registry (SHR) the reoperation rate serves as quality indicator for surgical performance as well as a proxy for recurrence. Patients were operated in the TEPLICH trial between 2008-2014, during the same period the SHR reported a cumulative reoperation rate due to recurrences of 2.4% for laparoscopic and 1.8% for open repairs at 3 years, and 4% and 2.4%, respectively, after 8 years. In our study, 1.5% of patients in TEP and 0.9% in Lichtenstein were reoperated due to a recurrence within 8 years. All the reoperations for recurrences were performed within a couple of months after the 1-year follow-up. Another 4 reoperations were performed due to complications within the first week, all in the Lichtenstein group, 2 for bleeding, 1 for severe pain, and 1 for testicular ischemia. With these numbers added to the Lichtenstein group, the reoperation rate increased to 2.8% which is still better than reported in SHR.

The number of recurrences has been shown to be dependent on surgical skill, especially for TEP. Eker et al. graded the proficiency of their surgeons depending on the number of TEP or Lichtenstein procedures they previously had performed. Level 1 surgeons were those who had performed <10 procedures, level 2 had performed 10-25 and level 3 had performed > 25 (94). Patients were clinically examined postoperatively at 1 and 5 years. A few recurrences occurred within the first year, but most developed between the 1- and 5-year follow-up. Surgeons with a higher level of experience were found to have less recurrences after TEP but having performed less operations was not found to increase recurrence after a Lichtenstein procedure. Eklund et al. reported cumulative recurrence rates of 3.5% for TEP and 1.2% for Lichtenstein and most recurrences occurred at 3 years follow-up. Likewise, a prospective study by Berndesen et al. presented a 5-year recurrence rate of 2.3% for primary hernias after TEP and Lichtenstein procedures (105). Three additional RCTs with a follow-up of 5 years, recorded that most recurrences occurred within the first 2 years and all within 3 years (106-108). However, Pieredes et al. reported 1 additional recurrence at 5-year follow-up (109). Thus, based on current RCTs and prospective studies, most recurrences develop within the first 3 years, although a small number may also occur later than 3 years after surgery. Low rates are observed in all studies mentioned, indicating excellent quality of inguinal hernia repair in these studies.

Quality of life

In this study, long-term quality of life was measured using SF-36, assessing physical and mental quality of life. The total Mental Composite Scores (MCS) did not seem to improve substantially from the pre- to the postoperative period. The Physical Composite Score (PCS) improved at all postoperative follow-up occasions compared to preoperative scores. Patients with pain during sexual activity scored worse on the MCS and particularly the PCS scores compared to those without, both before and after surgery, indicating that pain during sexual activity plays an essential role in patients' quality of life. Only a limited number of studies have examined quality of life using the SF-36, and most have reported their results shortly after surgery. An RCT by Isil et al. evaluated the quality of life of 176 patients operated with TEP or Lichtenstein preoperatively and at 30 and 90 days postoperatively (110). The differences in SF-36 scores favoured TEP at 30 days but the scores were evenly distributed between groups at 90 days with a predominant improvement in physical health domains. Palmquist et al. assessed quality of life with SF-36 in 225 patients operated with Lichtenstein, preoperatively at 3 and 12 months (111). At 3 and 12 months, all physical and mental health domains improved at least 5 points or more except for the general health domain. In another study by Mier et al., quality of life was evaluated after TEP and Lichtenstein based on preoperative pain status (no-mild vs moderate-severe pain) at 6 and 12 months postoperatively (112). Patients with no-mild preoperative pain had a higher postoperative PCS score (52.2 ± 7.2) than patients with moderate-severe pain (46.9 ± 10.9) (p=0.04). Conversely, MCS scores were the same regardless of preoperative pain status. As in our study, no difference between TEP and Lichtenstein was seen regarding PCS and MCS scores, and PCS but not MCS improved postoperatively. A limitation of the study was its small sample size and the fact that all analyses were done using retrospective data. Therefore, in addition to pain during sexual activity, preoperative moderate-severe pain may be a potential risk factor for worse physical health postoperatively.

Pain during sexual activity, pain descriptors and sensory disturbances

Distinguishing between CPIP, pain during sexual activity and sexual impairment

It can be difficult to discriminate between CPIP and pain at sexual activity since both cause pain during a certain activity. To elucidate this to some degree a comparison between patients' pain status (non-ignorable/ignorable pain last week) and their pain at sexual activity status (pain at sexual activity/no pain at sexual activity) was performed. At 3 years, 50.0% of patients in TEP and 44.4% of patients

in Lichtenstein with non-ignorable pain also reported pain at sexual activity. Correspondingly at 3 years, 3.8% of patients in TEP and 6.1% of patients in Lichtenstein with ignorable pain last week also reported pain at sexual activity, concluding that patients with ignorable pain last week reported pain at sexual activity less frequently than those with non-ignorable pain. Even though not specifically asked, 3 patients with ignorable pain having pain at sexual activity commented on the type of pain they felt during sexual activity. Out of these, 1 patient in the Lichtenstein group noted a burning sensation in the testicle/spermatic cord and 1 additional patient in Lichtenstein noted ejaculatory pain. In TEP, 1 patient noted a pulling sensation in the groin during sexual activity. Furthermore, patients could potentially interpret pain during sexual activity as ejaculatory pain, sensory disturbances or even postoperative erectile dysfunction. A drawback in Paper II, was not including these parameters when examining the underlying mechanisms which could potentially impact sexual function negatively. To address these parameters, the research group launched the SexIHQ (82). Further, in this thesis, additional analyses were done to compare sensory disturbances between patients with pain at sexual activity and ignorable pain last week and those with non-ignorable pain last week without pain at sexual activity. We found no major differences in frequency, type or location of sensory disturbances.

As previously discussed, severe ejaculatory pain has been shown by Aasvang et al. to have a proposed neuropathic origin with the pain being located at the external inguinal ring in all patients (113). In the histological study by Iakovlev et al., mesh ingrowth into VAS and surrounding nerves was most severe in patients with ejaculatory pain and pain at sexual activity (77). Including ejaculatory pain in a PROM might capture these patients with severe ejaculatory pain and offer them tailored surgical treatment.

Sensory disturbances and pain descriptors

The TEPLICH RCT is first in comparing sensory disturbances between TEP and Lichtenstein in a randomized setting. Sensory disturbances and sensory changes were both more frequent in Lichtenstein at 1 and 3 years. A retrospective study examined sensory changes in the groin with a questionnaire, comparing open anterior to endoscopic inguinal hernia repair (114). Out of a total of 490 patients, 45 patients experienced sensory changes, and they occurred 10 times more frequently in open repairs. In our study, sensory changes were 4-5 times more common in Lichtenstein than TEP at 1 and 3 years. A proposed explanation for the smaller difference in sensory changes between TEP and Lichtenstein in our study could be that a no-touch approach when handling the nerves was included in the operative protocol, and that all procedures were performed by board-certified hernia surgeons.

Magnusson et al. have previously evaluated the association between sensory disturbances and CPIP through clinical examinations, in a prospective, non-

randomized setting. The types of sensory disturbances tested for were touch (cotton swab), sharpness (pinprick) and temperature (cold/warm) (115). They included 116 patients, 28% operated with TEP and the rest with Lichtenstein. The Lichtenstein procedure was chosen for primary inguinal hernias and TEP for bilateral or recurrent inguinal hernias, according to their current local routines at that time. Sensory disturbances were noted in 34 % of patients and no difference in sensory disturbances were seen between patients with simultaneous pain and those without. The definition of pain was "any pain" according to IPQ, though it was not specified if any pain right now or last week was used. Our definition of pain for the same analysis was non-ignorable pain last week. We found that patients with sensory changes reported non-ignorable pain last week more frequently in Lichtenstein at 1 and 3 years, and in TEP at 3 years. An additional analysis using any pain last week yielded the same results, except a difference was also observed for TEP at 1 year. There was no difference in sensory disturbances preoperatively, regardless of which pain definition was used.

Mikkelsen et al. performed sensory tests in 72 patients, 6-12 months after open hernia repair. They found hypoesthesia and tactile allodynia in 50.0% of patients. The frequency of sensory changes did not differ between patients with pain 70.0% compared to those without pain 44.2% ($p<0.3$) (116).

Unlike Magnusson and Mikkelsen et al. we evaluated sensory disturbances both pre- and postoperatively in a randomized setting, including a considerably larger study group. Furthermore, besides our larger study group, the clinical exam was repeated at 3 years, providing an overall greater statistical power and reliability to support our findings. The finding that sensory changes differ between pain groups post- but not preoperatively, suggests that post-surgical pain accompanied by sensory changes may have a neuropathic origin.

Comparison of pain assessment scales

Optimal cut-offs for VAS based on Cunningham

The Visual Analog Scale (VAS) is the most used tool to assess CPIP and is often categorized into no pain, mild, moderate, or severe pain based on specific cut-offs (56). However, inconsistencies in the choice of cut-offs between studies pose a challenge for meta-analyses when assessing CPIP as an outcome. While some studies use similar cut-offs as the optimal cut-offs we found for VAS right now, other studies either underestimate moderate and severe pain by setting to high cut-offs (117) or underestimate moderate and sever pain by setting to low cut-offs for these pain categories (118, 119).

A study by Collins et al. aimed to find the most appropriate cut-offs for VAS for moderate and severe pain on the 4-graded Verbal Rating Scale (120). They used pooled data from 11 RCTs estimating the effect of a pain-relieving medication in the postoperative period. The cut-offs were determined by calculating at which cut-off level on VAS more than 85% of patients were correctly classified as having moderate or severe pain according to the VRS. Correspondingly, the most appropriate cut-off for moderate pain was ≥ 3 and for severe pain was ≥ 5.4. To reflect this, our optimal cut-off for moderate and severe pain right now were > 3.4 and > 5.2, respectively. Another study by Loos et al. used Cohen's kappa to calculate the optimal cut-offs for VAS based on VRS, and these were: >0.8 for mild pain, >3.2 for moderate pain and >7.1 for severe pain (121). The calculated Cohen's kappa value was 0.78 for these cut-offs. An error in their agreement calculations was applying Cohen's kappa to ordinally categorized VAS instead of using it to assess each cut-off individually.

To conclude, the optimal cut-offs calculated in our study for VAS right now and last week were of substantial agreement and could serve as a reference for future inguinal hernia research, to enable more accurate comparisons between studies.

Pain distributions and associations between scales

The incidences of CPIP reported in studies are highly dependent on which PROM is used to estimate the pain, complicating the comparison of CPIP incidences between studies. Each PROM has its own domains it measures, and current hernia-specific PROMs have been designed to measure not only pain, but also pain-related activity restrictions often including a time frame. With this in mind, we included IPQ, Cunningham, and VAS at 8 years follow-up with the goal to examine the potential association between pain scales.

At 8 years, no patient reported more intense pain than IPQ last week interfering with most activities. At 1 year, 2 patients reported an IPQ last week grade of pain necessitating bed rest, while at 3 years, only 1 patient reported the same intensity. In other studies, pain according to IPQ last week did not score higher than pain limiting most activities (122-124). This suggests that the highest categories in the IPQ may be unnecessary for assessing CPIP, which generally falls within the lower categories. In this study, Cunningham and IPQ last week were shown to be moderately correlated when measuring CPIP, thus considering the excessive categories in IPQ, Cunningham might be preferentially used. However, the disadvantage of Cunningham is that it is not made for assessing CPIP especially, hence lacks validity which is a problem also shared by most hernia specific questionnaires (65).

Interestingly, VAS right now and last week both showed a very strong correlation and almost perfect agreement. Conversely, IPQ right now and last week only

showed moderate correlation and substantial agreement. A potential explanation might be that despite being provided with a time frame in VAS, referencing pain to activities, as in IPQ, could be necessary for patients to recall a painful stimulus last week. In conclusion, patients report their pain differently on IPQ right now compared to last week, whereas VAS right now and last week could be viewed as potentially interchangeable. This highlights the increased complexity patients face in interpreting postoperative pain when transitioning from a unidimensional scale like VAS to a multidimensional scale like IPQ. Because when a time frame is added to IPQ, it decreases interchangeability between the IPQ right now and last week to a higher degree than it does to the unidimensional VAS right now and last week scales, despite the fact that both questionnaires originate from the same questionnaire or scale.

Ethics

All studies in this thesis followed the principles set in the Declaration of Helsinki 1964 and approval was received by the Ethical review board in Lund, Sweden. Initial approval (DNR 596/2007) was received for Paper I and II and a complementary approval (DNR 2019-00304) was received for Paper III and IV.

Patients were included at the out-patient clinic after thoroughly being informed about the overall low and comparable risk of harm associated with both procedures. After signing the informed consent, patients were randomized to already established techniques and were operated by department-certified surgeons, ensuring that the interventions did not differ from standard of care. They were informed that withdrawal of their consent was possible at any time during the study and that their social security numbers were concealed. A study nurse was available to answer additional questions regarding the study at any time.

Methodological considerations

External validity

In clinical research, RCTs are the study type with the highest scientific value, since confounders are eliminated in the randomization process. Furthermore, the setting and the methods can be controlled, as in our case, patients were operated by board-certified surgeons using standardized protocols. The exclusion and inclusion criteria enabled us to specifically study men with a primary unilateral hernia. The results correctly reflect the patients and characteristics of that particular setting but may not be applicable to the general population. Thus, there is a lack of external validity (generalizability). An effective, but expensive approach to address the problem of external validity to some extent would be to initiate a large multi-center RCT. To further address the lack of external validity that an RCT is affected by, CPIP, pain at sexual activity and recurrence rates from registry-based studies and the Swedish Hernia Registry are used for comparisons in the discussion section of this thesis.

Power of an RCT and secondary outcomes and subgroup analyses

RCTs are designed and powered to examine a specific primary outcome between two or more interventions. Secondary outcomes and subgroup analyses may be underpowered and even though results are statistically significant, the observed difference may be false negative, meaning that there is a higher risk of a type 2 error, not finding a difference that exists. On the contrary, the risk for a type 1 error, finding a difference when none exists, is higher the more analyses that are performed in a study. To account for type 1 errors, it is possible to use the Bonferroni or Hochberg corrections (125).

The power analysis for paper I and II is presented in the methods section of this thesis. For paper III, a retrospective power analysis confirmed a power of 87.5% based on a 12% difference in effect size (non-ignorable pain last week) and a significance level of $\alpha=0.05$ as used in paper II. In paper IV, power was gained by combining both TEP and Lichtenstein when comparing correlations, agreements and determining the optimal cut-offs.

The Randomization process

The randomization order for patient allocation was generated using Excel® (Microsoft, Redmond, Washington, USA). Cards with the allocated treatment group written on them were made and contained in non-transparent envelopes, which were locked in the office of the research coordinator. Block randomization was conducted using randomly selected block sizes of 8-18, with the surgeon remaining blinded. The allocation occurred once the patients were planned for surgery, but the type of operation was only revealed to patients at the day of the surgery. In the outpatient clinic, surgeons were briefed on the study and the patient enrolment process. The study was based on the intention to treat principle. For instance, if a patient was converted from open to laparoscopic surgery, or vice versa, they remained in the initial allocation group.

Risk factor analysis (logistic regression) vs frequency distributions (Chi square)

In the papers of the present thesis, both logistic regression and Chi square were used for analyzing outcomes. The statistical methods each have their own limitations and advantages. Chi-square is a non-parametric statistical test that is used to compare the frequencies of two independent categorical variables. It analyzes if the distribution of patients between categories in one variable differs in distribution between categories compared to another variable, by calculating expected frequencies and comparing them to observed ones. Chi-square does not account for potential confounding variables and is simpler than logistic regression. It is preferentially used in RCTs where confounding variables are not a problem. On the other hand, logistic regression can be used in most study designs, due to its ability to handle potential confounders when performing multivariate analyses. Logistic regression is a parametric method used to determine the association between a dependent binary variable and one or several exposure variables, allowing for the creation of a prediction model.

Choosing optimal cut-offs

Cohen's kappa is not the only method that could be used to calculate the optimal cut-off for a binary variable. Another such method is the use of Receiver-Operating Characteristic (ROC) curves. ROC curves determine the specificity and sensitivity of a test given that there is a true underlying rater that it is measured against. The area under the curve (AUC) of ROC curves is a measure of the overall accuracy of a test. The best cut-off of a ROC curve is the one yielding the highest sensitivity and specificity. In ROC curves, the Y-axis represents sensitivity, and the X-axis represents 1-specificity, resulting in bi-dimensional curves. This means that as

sensitivity increases, specificity decreases and vice versa. The issue with ROC curves arises when multiple cut-offs are needed, such as in an ordinal scale. In that case, multiple ROC curves would need to be combined to find each optimal cut-off, requiring the use of multidimensional ROC curves, which is not practically applicable (126). On the contrary, Cohen's kappa is more appropriate for determining cut-offs in ordinal scale variables (126).

The optimal cut-offs identified in our study are specific to the postoperative pain intensity levels observed in our patient population. Due to slight differences in postoperative pain intensity levels and patient characteristics compared to other studies, full generalizability of these results cannot be confirmed. Additional research using the same methodology to confirm the optimal cut-offs is needed. Until then, our cut-offs can serve as a reference for future studies.

Agreement vs correlation - limitations and differences

Cohen's kappa is appropriate to use when the variables are binary, but for ordinal variables weighted kappa should be used. The term "weight" is derived from the weighted kappa calculations, where weights are calculated based on the level of agreement between two scales with the same number of ordinal categories. If two separate ordinal scales rate pain within the same ordinal category, then no weight is added. However, for example, if one scale rates the pain as no pain and the other as severe pain, a weight is added. Additionally, the magnitude of the weight increases as the ratings on each ordinal scale become more divergent. A limitation to linear weighted kappa used in this study is that it gives the same weight to the difference between no to mild pain as it does to the difference between moderate to severe pain. In addition, weighted kappa value can differ depending on the distribution of pain across categories (127). Although, the distribution of CPIP after inguinal hernia surgery is similar among studies, usually being clustered in the lower pain categories. Another limitation of the agreement analysis in this study is the subjective nature of pain interpretation among patients. Each individual may perceive and rate their pain differently on the Cunningham pain scale compared to the 4-graded VAS scales, introducing inherent bias that can vary between patients. However, meaningful conclusions about agreement can still be drawn, given the inclusion of a relatively large patient cohort.

Agreement calculated with kappa statistics and correlation calculated with Spearman's or Kendall's Tau both measure the associations between variables but there are big differences. For instance, a strong correlation between two variables would mean that an increase in one variable would correspond to an increase in the other across pairs. This is called monotonic association. However, correlation does not consider the magnitude of the increase, but so does agreement. For example, two pain scales may show a strong correlation but weak agreement if one consistently rates pain slightly higher than the other. Greater agreement between

scales indicates that they are more interchangeable (128, 129). Additionally, agreement tend to decrease while correlation increases with increasing number of categories in a scale (130). Correlation can be calculated for two independent variables, whereas the variables chosen for agreement analysis must assess the same underlying construct (129).

Conclusions

In the TEPLICH trial, all patients underwent surgery in a highly standardized setting with strict operative protocols, by department-certified hernia-specialized surgeons. This strict setting is important to consider when interpreting the results.

Conclusions:

- In the short-term, TEP showed faster operative time, faster recovery with less sick leave days and less complications.
- Overall low rates of chronic pain, pain at sexual activity and recurrences, high patient satisfaction and improved QoL with no difference between TEP and Lichtenstein at 1-, 3- or 8-year follow-up.
- No risk factors for chronic pain were identified and none of the patients with severe preoperative pain retained a severe pain status at 1-, 3- and 8-year follow-up.
- In total, approximately 9/10 the patients were relieved of their preoperative pain, less than 1/10 reported persisting chronic pain and 1/18 reported new-onset chronic pain at 8-year follow-up.
- In total, approximately 8/10 of the patients were relieved of their preoperative pain at sexual activity, less than 1/6 reported persisting pain at sexual activity and 1/25 reported new-onset pain at sexual activity at 3-year follow-up.
- The independent risk factors for pain at sexual activity were preoperative pain at sexual activity and a Lichtenstein operation.
- In the Lichtenstein group, patients more often used neuropathic pain descriptors to characterize their pain at sexual activity.
- Sensory changes were more frequent in the Lichtenstein group and sensory changes were more frequent in patients with non-ignorable pain last week compared to those without at 3-year follow-up.
- A significant overlap of VAS scores within Cunningham categories was observed, raising concerns about the overall interchangeability between the two

pain scales. However, the optimal VAS cut-offs calculated based on Cunningham categories showed a substantial agreement between the scales and can serve as a reference for further studies evaluating CPIP.

- Cunningham and IPQ last week strongly correlated postoperatively, suggesting that the more user-friendly Cunningham pain scale may be used in registries until a new sufficiently validated user-friendly PROM, design to be used for assessment of inguinal hernia patients, is launched.

Future perspectives

Studies assessing chronic pain after inguinal hernia surgery use different PROMs that are not always user-friendly. In current inguinal hernia specific PROMs, different cut-offs and time intervals are presented. Furthermore, not all are suitable for pre- and postoperative assessment of pain, nor do all include pain in relation to daily activities. All are insufficiently validated and generic PROMs that lack validation for assessing CPIP are predominantly used (58, 65). Because of this heterogeneity between studies when reporting CPIP, the answer to which technique is advantageous remains questionable.

A suggested approach for developing new and more accurate user-friendly disease specific PROMs would be to first have an expert group compose a set of questions relevant for assessing CPIP. These questions could then be refined through a qualitative approach consisting of patient interviews, identifying which questions patients consider important in assessing CPIP. Subsequently, methods like Exploratory factor analysis or Rasch analysis could be used (131, 132). Such a new PROM would need to be validated before inclusion in registries and larger cohorts. A new inguinal hernia PROM, HERO, has been developed with the use of Rasch analysis by Associate Professor Agneta Montgomery and is currently in the process of validation.

We showed that both sensory changes and pain at sexual activity were more frequent when non-ignorable pain last week was reported, except for TEP at 1 year. To further study the potential impact of sensory changes on pain at sexual activity, pain at sexual activity could be run in a multivariate logistic regression model together with sensory changes, preoperative pain at sexual activity, operative technique and age. The same analysis could be performed for severe CPIP to confirm that it frequently is of neuropathic origin and is accompanied by sensory changes.

The LEVEL trial showed that surgical skill influences the risk of developing a recurrence after TEP but not after Lichtenstein (25). However, the impact of surgical skill for TEP and Lichtenstein on the risk of developing CPIP needs to be evaluated in randomized settings. Of special interest are patients with no preoperative pain that are experiencing moderate or severe pain postoperatively, possibly due to surgical harm. In the TEPLICH trial, where all surgeons were long past the learning-curve for the operations they performed in the study and with low recurrence rates indicating skilled performance, we could show that preoperative severe pain was

not present after surgery, in other words surgery relieved severe pain instead of being a possible causative mechanism. Severe CPIP may thus serve as a proxy for inferior surgical skill, just as recurrence. Conducting an RCT and/or a register-study on the impact of surgical skills on CPIP would be another interesting project.

Considering how frequently inguinal hernia repair is performed, implementation of a national educational curriculum focused on standardizing surgical techniques, may enhance outcomes following inguinal hernia surgery. Such efforts are ongoing in Sweden through mandatory national hernia courses. Adding supervised practical skills training according to a standardized protocol for each technique, as was done prior to starting the TEPLICH trial, may improve future results. Further, regular monitoring of surgical skills through collaborations and exchange programs with hernia centers is a potential way forward in achieving better patient outcomes nationally.

Larger randomized controlled studies comparing TEP to Lichtenstein need to be launched to fully understand to which extent chronic pain persists years after surgery, and to better study the few patients with the most severe CPIP or pain causing sexual dysfunction after groin hernia surgery. Validated PROMs, that accurately assess chronic pain and the key factors causing pain-induced sexual dysfunction, are needed to correctly identify these patients.

In recent years, robotic TAPP has been introduced and the technique is predominantly used in the United States. The main obstacle for wider implementation is the cost associated with the procedure and in general a lower availability of robotic systems compared to laparoscopic surgery. Thus, robotic TAPP has not yet been included as a recommended technique in the EHS guidelines. However, current knowledge shows similar short-term results concerning postoperative pain, quality of life and readmission rates but longer operative times and more surgeon's frustration with the robotic procedure (133). Long-term results of this RCT that initially included 102 patients showed no difference in chronic pain, quality of life or recurrences rates at 1- and 2-year follow-up (134). For now, robotic TAPP might be reserved for more complex inguinal hernias and performed at specialized centers. In the future, as robotic systems become cheaper and more available, new and better research with larger study populations will determine the possible advantages or disadvantages with the technique.

Populärvetenskaplig sammanfattning

Varje år utförs omkring 18 000 ljumskbråcksoperationer i Sverige, vilket gör ljumskbråcksoperationer till en av de vanligast förekommande operationerna nationellt. Av de som drabbas av ljumskbråck är cirka 90% män och den vanligaste operationsåldern för dessa är 70–75 år. Den teknik som används idag för att minska risken för återfall i bråck är lagning av bråckområdet med syntetiskt nät, s.k. nätplastik. Detta innebär att man placerar ett nät med god överlappningsmarginal och utan spänning i nätet över det område där bråcket är lokaliserat. Den öppna Lichtenstein-metoden, där nät placeras framför bråcket, är vanligast och anses som "gold standard" för män. Dryg hälften av män som opereras för ljumskbråck opereras med denna metod, medan titthålskirurgi används i andra fall. Titthålskirurgi blir allt vanligare och i Sverige är den vanligaste titthålsoperationen för ljumskbråck Total Extraperitoneal Plastik (TEP). I det svenska bråckregistret (SBR), registreras 95% av alla bråckoperationer, vilket gör det möjligt att studera och förbättra metoder för bråckkirurgi på en nationell nivå. Registret har lett till viktiga insikter kring bästa behandlingsmetoder för att minska risken för att återfall. Det har också har bidragit med värdefull forskning inom bråckområdet genom att möjliggöra utvärdering av operationsmetoder när de tillämpas på en större patientgrupp och utförs både av bråckspecialister och kirurger under utbildning.

Användningen av nätplastik har minskat antalet patienter som drabbas av återfall, en komplikation som tidigare stod i fokus. Med minskande antal återfallsbråck har kronisk smärta och sexuella besvär efter bråckkirurgi kommit att hamna i fokus. Till skillnad från Lichtenstein, undviker man vid en TEP operation i större utsträckning nerver i operationsområdet, dock finns det ändå en risk för nervpåverkan. För kvinnor rekommenderas TEP eftersom förekomsten av lårbråck är hög, och Lichtensteintekniken täcker inte det område där denna typ av bråck uppkommer.

Denna avhandlings fyra delarbeten utgår alla från TEPLICH studien, en randomiserad kontrollerad studie som jämför TEP- med Lichtensteinoperation för ljumskbråck hos 416 män, med kirurger som alla lärt sig genomföra operationerna på ett likadant standardiserat sätt och som utfört betydligt fler operationer än vad som brukar beskrivas krävas för att ha passerat inlärningsfasen för respektive operation, vilket inte är beskrivet i andra studier. Huvudmålen med studiens första tre delarbeten var att mäta och jämföra förekomst av kronisk smärta, smärta i samband med sexuell aktivitet, livskvalitet och antalet återfallsbråck från operationen och upp till 8 år efter, en tidsperiod som bara någon enstaka studie

tidigare redovisat. Dessutom jämföra hur många patienter som botades från smärta som fanns innan operationen, hur många som inte förbättrades och hur många som eventuellt tog skada av operationen med ny smärta som resultat, d.v.s. varje individuell patients smärtutveckling kartlades, vilket också bidrar med ny information. Förutom optimering av kirurgernas träning gjordes omfattande kartläggning av patienternas tillstånd med undersökning av patienterna samt användande av flera metoder/formulär för smärtutvärdering och livskvalitet. Det senare skapade förutsättningar för delarbete 4 som jämför de 3 smärtformulären som användes i TEPLICH studien, för att se om de var utbytbara mot varandra och i så fall hur resultaten från andra studier som använt något av dessa kan tolkas i förhållande till varandra.

Vid jämförelse av teknikerna fann vi att TEP gick snabbare att utföra, patienterna blev fortare återställda, hade kortare sjukskrivningstider och färre komplikationer efter operation. Den ljumskundersökning som genomfördes på alla patienter visade att patienter som genomgått en Lichtenstein hade en högre förekomst av nedsatt känsel i ljumsken jämfört med de som hade genomgått TEP.

Kronisk smärta efter ljumskbråckskirurgi är undersökt i flertalet studier som visar på en förekomst på 10–35%. För en del kan smärtan vara så uttalad att den påverkar det dagliga livet, vilket drabbar cirka 6% av de opererade. Variationen i smärtförekomst kan förklaras av att studier utvärderar olika operationstekniker och använder varierande definitioner av smärta. Dessutom skiljer sig frågeformulären, som används när patienterna skattar sin smärta, stort mellan studier. Jämfört med TEP är Lichtenstein tekniskt enkel och har en kort inlärningskurva för att uppnå en låg återfallsfrekvens, dock till priset av en relativt hög andel kronisk smärta. När Lichtenstein utförs av erfarna specialister är dock andelen som får kronisk smärta förhållandevis låg. TEP har däremot visat sig ge snabbare återhämtning, kortare sjukskrivning och i vissa studier mindre risk för kronisk smärta. I TEPLICH studien fann vi att drygt 70% av patienterna rapporterade smärta som inte kunde ignoreras innan operation jämfört med 7% efter 8 år, utan skillnad mellan TEP och Lichtensteinpatienter. När patienternas smärtstatus följdes över tid såg vi att 9/10 patienter med smärta innan operation blev smärtfria, knappt 1/10 hade kvar sin smärta och 1/18 patienter som var smärtfria innan operation rapporterade smärta efter 8 år.

Sexuella problem efter ljumskbråcksoperation är betydligt mindre studerat än kronisk smärta, men studier visar att över 20 % av patienter kan uppleva smärta vid samlag flera år efter ingreppet. Nätet som placeras i ljumsken vid en öppen operation (Lichtenstein) är i nära anslutning till ljumsknerver samt sädesledaren med dess nerver och kärl. Detta tros kunna påverka sexuell funktion och leda till obehag/smärta vid sexual aktivitet. Titthålstekniker tros ha en lägre risk för dessa besvär eftersom känsliga områden påverkas mindre. Studier har än så länge inte kunna visa på någon skillnad mellan Lichtenstein och TEP avseende smärta vid sexuell aktivitet och inga randomiserade studier bortsett från TEPLICH-studien

finns. Vi fann att 35% av patienterna rapporterade sexuella problem i form av smärta i samband med sexuell aktivitet innan operation. Efter operationerna sågs dessa besvär i 8% av patienterna utan skillnad mellan grupperna vid 3-års uppföljning. När patienternas smärtstatus följdes individuellt från innan operation fram till 3 år efter operation, visade det sig att 8/10 blev av med smärtan, 1/6 hade kvarvarande smärta och 1/25 fick ny smärta. Riskfaktorer för smärta vid sexuell aktivitet som identifierades var smärta i samband med sexuell aktivitet innan operation och att patienten hade genomgått en Lichtenstein operation. Dessutom karakteriserade Lichtenstein patienter sin smärta i större utsträckning som nervskadeorsakad (neuropatisk) smärta jämfört med TEP patienter. Totalt sätt ökade livskvaliteten för patienter efter operation medan patienter som upplevde smärta i samband med sexuell aktivitet hade en lägre livskvalitet jämfört med de utan smärta.

Livskvalitet mätt med SF-36, ett formulär som är använt i stor omfattning, var lägre i TEPLICH patienterna än hos befolkningen i stort avseende fysiskt välbefinnande innan operation. Efter operation sågs i båda grupperna en livskvalitet som översteg normalbefolkningens, utan skillnad mellan grupperna.

Rapporterad förekomst av återfallsbråck varierar mycket i litteraturen. TEP och Lichtenstein är båda tekniker med relativ låg frekvens av återfallsbråck. I Svenskt Bråckregister (SBR) finner man en reoperationsfrekvens på grund av återfallsbråck för patienter opererade 2008-2014, de år då TEPLICH patienterna opererades, på drygt 3% för öppen operation, där majoriteten var Lichtenstein, och drygt 4% för de laparoskopiska operationerna TEP och TAPP (Transabdominell Preperitoneal Plastik). De som opererats för ett återfallsbråck är bara en del av de patienter som verkligen har drabbats av ett återfall. I TEPLICH-studien undersöktes patienterna efter 1- och 3 år och tillfrågades i enkät om symtom på återfall vid 8 års uppföljning, ett tillvägagångssätt som påvisar en sannare bild av antalet återfall än uppgifterna i SBR. Vi fann att det inte var någon skillnad mellan grupperna och att förekomst av återfallsbråck efter 3 år var 1,6 %.

Det är problematiskt att jämföra smärta efter ljumskbråckskirurgi eftersom det inte finns något specifikt allmänt använt eller vedertaget frågeformulär. I TEPLICH-studien användes flera formulär för att möjliggöra jämförelse med andra studier samt för att utvärdera om formulären är utbytbara mot varandra. Inguinal Pain Questionnaire (IPQ) har utvecklats specifikt för att mäta smärta efter ljumskbråcksoperationer och består av 18 frågor, en del med många svarsalternativ, vilket gör att användarvänligheten kan ifrågasättas. Andra formulär som användes var allmänna, inte ljumskbråcksspecifika frågeformulär. Visual Analog Scale (VAS) baseras en 10 cm lång linje, där patienten sätter en markering som svarar mot hur de uppfattar sin smärta och där 0=ingen smärta och 10=värsta tänkbara smärta. Vidare användes Cunningham pain scale som är en 4-gradig skala (ingen, mild, måttlig, svår smärta). Ovanstående formulär utvärderar specifikt smärta medan Short Form 36 (SF-36), som är en 36-frågor lång enkät, mäter livskvalitet generellt. I delarbete 4 kunde påvisas att IPQ, VAS och Cunningham inte var utbytbara mot

varandra även om det förekom en stark korrelation mellan IPQ och Cunningham när postoperativ smärta utvärderades. Efter att ha delat in VAS i grader baserat på beräknade gränsvärden utifrån Cunninghamskalan, visade det sig att VAS stämde väl överens med Cunningham. Dessa beräknade gränsvärden för VAS kan med fördel användas i framtida studier när VAS delas in i fyra grader.

Sammanfattningsvis har de fyra delarbetena som alla grundas på TEPLICH-studien, som jämför resultat efter ljumskbråcksoperationer utförda med antingen TEP eller Lichtensteinteknik av bråckspecialiserade kirurger utbildade att utföra operationerna på samma sätt, kunnat påvisa: en fördel för TEP avseende de tidiga operativa och postoperativa resultaten; påtaglig förbättring efter operation av den smärta som föreligger hos många ljumskbråckspatienter och liten risk att få smärta som följd av operationen, utan skillnader mellan grupperna; samma resultat som ovan gällande smärta vid sexuell aktivitet och sexuella problem; förbättrad livskvalitet efter operation av ljumskbråck med båda tekniker till en nivå överstigande normalbefolkningens; låg andel återfallsbråck jämfört med nationella resultat, utan skillnader mellan operationsteknikerna, samt; svårigheter med jämförande av resultat mellan studier avseende smärta då använda smärtinstrument inte är utbytbara mot varandra.

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