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ABDOMINAL WALL COMPLICATIONS AFTER UROLOGICAL SURGERY

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ABDOMINAL WALL COMPLICATIONS AFTER UROLOGICAL SURGERY
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Maria Hermann

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To past, presence and future me

POPULAR SCIENCE SUMMARY OF THE THESIS

Abdominal wall complications such as incisional hernia, bulging, and pain are anticipated side-effects of surgery within the abdominal wall. Most of previous research in this field has been conducted on patients that have undergone general surgery such as gallbladder and intestinal procedures. Few studies have been performed on urological surgery and other treatments for cancer in the urological organs such as prostate and kidneys. This thesis explores abdominal wall complications after surgery and other treatments for kidney and prostate cancer.

Prostate cancer is the single most common cancer in Sweden, more common than both breast cancer and colon cancer. Historically, prostate cancer has been detected late in the course of the disease when little can be done to cure it. Over the last two decades, there has been a rapid development both in curative treatments with either radiation therapy or surgical procedures, and new oncological treatments when cure is no longer achievable. Whereas our knowledge of the outcome and safety of these cancer treatments are well-known, less is known about side-effects such as those related to the abdominal wall. In Study I, the risks for incisional hernia after open and laparoscopic surgery with curative intent for urological cancer were compared. The risk for developing incisional hernia was higher after a laparoscopic procedure than after open surgery. In Study III, inguinal hernia among men on castration treatment for advanced prostate cancer was investigated. It has long been suspected that low concentrations of the male hormone, testosterone, may play an important role in the development of inguinal hernia. This study showed that over more than nine years treatment with hormones aimed to eradicate testosterone levels, there was an increased risk for developing inguinal hernia.

Kidney cancer, or renal cell carcinoma as it is also called, is diagnosed in around 1,300 patients each year in Sweden. The only curative treatment for kidney cancer is surgery with radical removal of the tumor. Over the last decade, laparoscopically performed surgery has rapidly taken over from open surgery. Both methods have been evaluated and found to be safe regarding cancer-specific survival but less is known about side-effects on the abdominal wall such as the ones addressed in this thesis. The kidneys are located laterally in the abdomen towards the back, and the easiest way to reach them during open surgery is through an incision beneath the ribs potentially damaging several muscles, vessels and nerves. Such tissue damage may result in adverse effects such as incisional hernia or bulging of the abdominal wall due to weakening of the muscles in the area. In Study II, the risks for incisional hernia after open and laparoscopically performed surgery for kidney cancer were compared. The risk for incisional hernia was lower after laparoscopic than after open surgery. In Study IV, the extent of atrophy of the abdominal wall was measured up to 18 months after open surgery for kidney cancer. The association between severe atrophy and pain from the abdominal wall was also explored. Three months after surgery, 51% of patients reported pain from the abdominal wall. The degree of atrophy of the abdominal wall, however, was not correlated to the intensity of pain.

Kort populärvetenskaplig översikt på svenska

Komplikationer från bukväggen så som ärrbråck, utbuktning av bukväggen och smärta är förväntade bieffekter efter kirurgi i bukhålan. De flesta tidigare studier på området är inom allmänkirurgiska operationer som till exempel kirurgi på gallblåsa eller tarmar. Få studier har gjorts angående påverkan på bukväggen efter cancerbehandling av de urologiska organen så som prostata och njurar. I denna avhandling undersöks komplikationer från bukväggen efter kirurgi av prostata- eller njurcancer och under hormonell behandling av avancerad prostatacancer.

Prostatacancer är den vanligast cancerformen i Sverige, vanligare än både bröst och tjocktarmscancer. Tidigare fann man oftast prostatacancer sent i förloppet och det fanns inte mycket att erbjuda föra att bota eller behandla cancern. Under de två sista decennierna har utvecklingen gått fort både avseende den botande behandlingen med antigen strålning eller kirurgi, och för behandling när sjukdomen inte längre är botbar. Behandlingseffekten och säkerheten av de nya behandlingsmetoderna är väl undersökta. Ännu är kunskaper om bieffekter bukväggen begränsade. I studie I jämförs risken att utveckla ärrbråck efter botande prostatacancerkirurgi utförd med antingen öppen eller titthålskirurgi. Ärrbråck efter titthålskirurgi var vanligare än ärrbråck efter öppen kirurgi. I studie III undersöktes om män med låga testosteronnivåer på grund av hormonell behandling för prostatacancer har högre risk att utveckla ljumskbråck. Man har länge trott att låga nivåer av testosteron kan bidra till utveckling av ljumskbråck. I studien sågs att hormonell behandling i mer än nio år ökade risken för ljumskbråck.

Njurcancer diagnostiseras hos 1300 personer i Sverige årligen. Den enda botande behandlingen för njurcancer är kirurgi där hela tumören tas bort. Under de senaste tio åren har utvecklingen gått fort mot användandet av titthålskirurgi i stället för sedvanlig öppen kirurgi vid behandling av njurcancer. Båda operationsmetoderna är jämförbara avseende canceröverlevnaden, men begränsad forskning har gjorts på bieffekterna som tas upp i denna avhandling så som utbuktning och smärta från bukväggen efter kirurgin och ärrbråck. Njurarna ligger bukens övre del mot ryggsidan. Det enklaste sättet att få åtkomst till njurarna vid öppen kirurgi är genom att göra ett snitt nedom revbensbågen då samtliga muskellager och kärl och nerver delas. Detta kan ge upphov till en utbuktning av bukväggen efter kirurgin till följd av muskelförtvining, vilket kan orsaka obehag, smärta och ge negativt kosmetisk påverkan. I studie II jämförs risken för ärrbråck mellan öppen kirurgi och titthålskirurgi vid njurcancer. Risken för ärrbråck efter njurcancerkirurgi visades vara låg men var högre efter öppen kirurgi än efter titthålskirurgi. I studie IV undersöktes hur mycket musklerna i bukväggen förtunnas efter öppen njurcancerkirurgi och om uttalad muskelförtunning orsakar mer smärta från bukväggen. Musklerna i bukväggen förtunnas gradvis under de 18 månader patienterna följdes men graden av förtvining kunde inte förutspå graden av smärta från bukväggen.

ABSTRACT

Background

Abdominal wall complications such as incisional hernia, bulging, and pain are known complications of surgery in the abdominal cavity. Most previous studies have been conducted on general surgical procedures, whereas few have been conducted on patients treated for urological cancer. The urological organs differ from other abdominal organs since they are situated outside the peritoneum i.e., retroperitoneal. It has also previously been hypothesized that the levels of androgens such as testosterone may play a crucial role in the formation of inguinal hernia. The aims of this thesis were to:

I) Investigate and compare the incidence and risk factors for development of incisional hernia after prostate cancer and renal cell carcinoma surgery with either open or minimally invasive surgery.

II) Investigate the extent of muscle atrophy in the rectus abdominis after open renal cell carcinoma surgery, and whether the extent of muscle atrophy after surgery relates to degree of pain from the abdominal wall.

III) Test the hypothesis that low bioavailable levels of testosterone caused by treatment for prostate cancer may be related to an increased risk for development of inguinal hernia.

Methods

Study I. All men with prostate cancer who underwent radical prostatectomy in Sweden between 2004 and 2013 were identified from the National Prostate Cancer Register Sweden (NPCR) and linked with the National Patient Register (NPR) to determine comorbidity and diagnosis of or surgery for incisional hernia.

Study II. All patients diagnosed with renal cell carcinoma in Sweden between January 2005 and November 2015 were identified in the Renal Cell Cancer Database Sweden (RCCBaSE) n=9638. Of these, 6417 were included in the analyses to determine the cumulative rate of incisional hernia after surgery comparing open or minimally invasive surgery for radical nephrectomy or partial nephrectomy. Patient-related risk factors for incisional hernia were identified.

Study III. All men that had not received curative treatment for prostate cancer identified in the Prostate Cancer Database Sweden (PcBaSe) between 1st January 2008 and 31st December 2016 were included in a population-based nested case-control study on risk for inguinal hernia while on androgen deprivation therapy (ADT). Cases were men diagnosed with inguinal hernia or had undergone inguinal hernia repair (n=1,324) and controls were men without inguinal hernia, matched only on birth year (n=13 240). A conditional multivariate logistic regression model was used to assess any temporal association between

ADT and inguinal hernia adjusting for marital status, education level, prostate cancer risk category, Charlson Comorbidity Index, type of ADT, time since prostate cancer diagnosis, and primary prostate cancer treatment.

Study IV. Forty-three patients were included in a randomized study on patients undergoing open renal cancer surgery with a transverse unilateral incision at Karolinska University Hospital, Stockholm, between 2016 and 2019. The thickness and attenuation of abdominal wall muscles were measured on computer tomography (CT) scan before surgery and on two separate occasions after surgery. Three months postoperatively, patients were asked to report pain from the abdominal wall in a questionnaire. Repeated measure ANOVA was used to determine any decrease in rectus abdomni muscle thickness at first and second postoperative CT scans. Ordinal regression was used to determine correlation between patient-reported degree of pain three months after surgery and change in abdominal wall muscle thickness (>30 % decrease or <30% decrease) age (<65 year and >65 year), or gender.

Results

Study I. During the study period, 19,743 men underwent radical prostatectomy for prostate cancer. The cumulative rate of incisional hernia five years after surgery was 1.4% (95% confidence interval (CI95%) 1.2–1.7%) and 2.7% (CI95% 2.3%-3.2%) for open or minimally invasive radical prostatectomy. Age above the median was associated with increased risk for incisional hernia in both groups. Prostate volume above the median and lymph node dissection were associated with increased risk for incisional hernia in the minimally invasive group ($p<0.05$ for all).

Study II. Of the 6,417 patients that underwent surgery for renal cell carcinoma between January 2005 and November 2015, 5,216 (81%) underwent open surgery and 1,201 (19%) underwent minimally invasive surgery. In total, 140 patients were diagnosed with incisional hernia. The cumulative rate of incisional hernia after five years for all renal cell carcinoma surgery was 5.2 % (95% confidence interval (CI) 4.0%-6.4%) after open surgery and 2.4% (CI 1.0%-3.4%) after minimally invasive surgery ($p<0.05$). In Cox proportional hazard analysis, age and left-sided surgery were associated with incisional hernia in the open surgery group (both $p<0.05$). In the minimally invasive group, no statistically significant risk factors for incisional hernia were found.

Study III. Odds Ratio (OR) for diagnosis or repair of inguinal hernia 0-1 years after start of ADT was 0.5 (95% confidence Interval (CI)) 0.38-0.68), between 1 and 3 years after, the OR was 0.35 (95% CI 0.26-0.47), 3-5 years after, the OR was 0.39 (95% CI 0.26-0.56), 5-7 years after, the OR was 0.6, (95% CI: 0.41-0.97), and > 9 years after, the OR was 3.68 (95% CI 2.45-5.53).

Study IV. Compared to preoperative CT scans, there was a decrease in abdominal wall muscle thickness from 8.9 ± 2.2 mm to 6.2 ± 2.3 mm ($P<0.001$) at the first and to (5.2 ± 1.9

mm, P<0.001) at the second postoperative scan. Age below 65 years was associated with a statistically significant odds of perceiving more severe pain from the abdominal wall after surgery (OR 5.20 CI95% 1.16 to 23.41). However, no statistically significant association between the extent of muscular atrophy and level of pain was observed.

Conclusions

Study I. The rate of incisional hernia is significantly higher after minimally invasive radical prostatectomy for prostate cancer compared to open radical prostatectomy. Awareness of the risk and appliance of appropriate surgical technique may lower the risk.

Study II. Open surgery for renal cell carcinoma is associated with a significantly higher risk for developing incisional hernia than minimally invasive surgery. When open surgery for renal cell carcinoma is the only option, attention should be taken when choosing placement for incision and when closing the wound. Future studies are needed to find strategies to reduce the risk for abdominal wall complications after open renal cell carcinoma surgery.

Study III. The marked increase in OR for inguinal hernia after 9 years of ADT supports the hypothesis that low testosterone levels increase the risk for inguinal hernia. The apparently low risk for inguinal hernia during the first eight years on ADT is likely caused by selection of men with advanced cancer unlikely to be diagnosed or treated for inguinal hernia.

Study IV. Flank incisions lead to abdominal wall muscular atrophy that progresses over time, but the impact of atrophy on pain is difficult to predict. Low age is one of the most important factors for persisting pain.

LIST OF SCIENTIFIC PAPERS

The thesis is based on following studies

I. Incidence of incisional hernia after minimally invasive and open radical prostatectomy: a population-based nationwide study.

Maria Hermann Ove Gustafsson and Gabriel Sandblom
Scand J Urol. 2017;51(4):264-268.

II. Rate of incisional hernia after minimally invasive and open surgery for renal cell carcinoma: a nationwide population-based study.

Maria Hermann, Ove Gustafsson, Pernilla Sundqvist and Gabriel Sandblom.
Scand J Urol. 2021 Jul 21;1

III. Androgen Deprivation Therapy and the Risk for Inguinal Hernia – an Observational Nested Case Control Study.

Maria Hermann, Hanna Vikman, Pär Stattin, Asmatullah Katawazai, Ove Gustafsson, Johan Styrke, and Gabriel Sandblom.

In manuscript

IV. Abdominal muscle atrophy after Open Renal Cancer Surgery in Relation to perceived Pain and abdominal Wall Function – a prospective cohort study.

Maria Hermann, Lovisa Hult-Ericson, Helena Thulin, Ove Gustafsson, Gabriel Sandblom, and Yngve Forslin.

In manuscript

CONTENTS

LIST OF ABBREVIATIONS

AA	antiandrogen
ADT	androgen deprivation therapy
CDC	Center of Disease Control
CDR	Swedish Cause-of-Death Register
CI	confidence interval
CCI	Charlson Comorbidity index
CT	computer tomography
DHEA	dehydroepiandrosterone
GnRH	gonadotropin-releasing hormone
HRQoL	health-related Quality of life (QoL)
ICC	Intra Class Correlation Coefficient
ICD-10	International Classification of Diseases 10th Revision
IPOM	Intraperitoneal Onlay Mesh
MIRP	minimal invasive radical prostatectomy
NCCN	National Comprehensive Cancer Network
NPCR	Swedish National Prostate Cancer Register
NPR	National Patient Register
NSKCR	National Swedish Kidney Cancer Register
OR	odds ratio
QoL	Quality of life
ORP	open radical prostatectomy
PcBaSE4	Prostate Cancer Database Sweden
RCC	Renal Cell Carcinoma
RCCBaSE	Renal Cell Cancer Database Sweden
SCB	Statistics Sweden
SSSB	Small-stitch-small-bites technique

1 INTRODUCTION

1.1 HISTORY OF SURGERY AND HERNIAS

Modern surgery began in the mid-19th century when anesthesiology was first introduced (1). It rapidly developed from dental surgery to orthopedic surgery (mostly amputation) and finally to abdominal surgery after the introduction of aseptic technique. Even though Ignaz Semmelweiss already in 1847 showed that handwashing reduced childbed fever, decades passed before handwashing prior to surgery was introduced as routine. In the 1880s, sterilization of surgical equipment, use of cap, mask, and gown was introduced in the largest hospitals on the East coast of USA. Gloves were first introduced as a result of surgical nurses' reaction to chloride used for skin wash prior to surgery. Following Alexander Fleming's discovery of penicillin in 1928 and the introduction of penicillin V into clinical use some decades later, the fear of complications decreased, and the success rate of abdominal surgery increased. The introduction of antibiotics also made surgery unnecessary in some cases.

Minimally invasive surgery was first performed by the Swedish surgeon and later Professor Hans Christian Jacobeaus at the beginning of the 20th century. (2) Jacobeaus used a cystoscope inserted into the abdominal cavity to perform diagnostic laparoscopy. (3) The first nephrectomy after which the patient survived is believed to have been conducted in Heidelberg in 1869 and thereafter in Sweden 1881. The Swedish patient survived four hours before dying of circulatory chock. Autopsy revealed thrombosis the in vena cava. (4)

The first prostatectomy for prostate cancer was conducted 1904 in USA. In 1945, the first series of retropubic prostatectomies was published, and in 1991 the first minimally invasive prostatectomy was performed. (3)

Abdominal wall hernia is defined as an abnormal protrusion of abdominal cavity content through an opening in the abdominal wall. The term "Hernia" comes from Latin and means "rupture". In Greek, hernia means "bud". Protrusion of the content of the abdominal wall not only causes disfiguration of the abdominal wall, but it can also be painful and in the worst-case scenario cause death by strangulation, necrosis, and sepsis. Hernias occur in various parts of the abdominal wall, usually where communicating structures penetrate such as blood vessels (femoral and obturator vessels), where structures have migrated during embryonic stage as in inguinal and umbilical hernias, transition zones between different muscle aponeuroses (spigelian hernia), or areas where muscle continuity is interrupted such as in the groin (fig 1) The anatomy of the abdominal wall was first described 6000 years ago. First reports of incisional hernia repair are from latter part of the 19th century. (5)

Groin hernias were first described by the Egyptians, and since the introduction of abdominal surgery incisional hernia has been a well-known complication for all surgeons. (6)

Incisional hernia repair has always been a demanding surgical challenge, with poor long-term results. After a condition requiring surgery has been cured, many patients suffer from an incisional hernia that replaces the original problem.

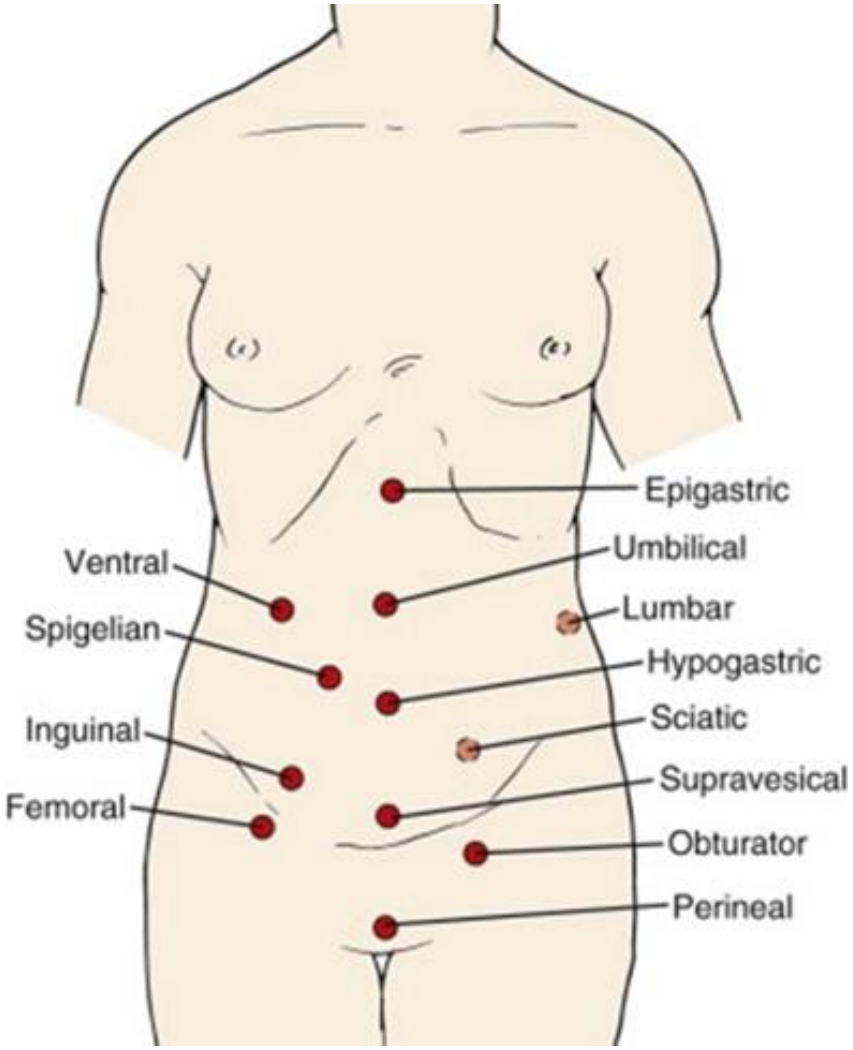

Figure 1 Location and types of primary hernias of the abdominal wall. (7) *Used by permission from Elsevier for thesis non-profit university use.*

1.2 ANATOMY OF THE ABDOMINAL WALL

The abdominal wall surrounds the abdominal cavity, the cranial margin being the lower ribs, cartilage of the costae, and the processus xiphodeus in the midline, the caudal margin being the iliac crest, inguinal ligament, and the pelvic bone (i.e., tuberculum pubicum) merging at the symphysis. It consists of muscles, nerves, vessels, tendons, and aponeuroses. Each one of these structures fulfills a crucial role in the complex process of stabilizing the outskirts of the abdomen. The muscles and aponeuroses form a barrel that protects the abdominal contents, supports the breathing cycle, and stabilizes posture. Detailed knowledge of the anatomy of the abdominal wall as well as its function is of crucial importance for all surgeons entering the abdominal cavity. Damage to the muscles, vessels, and nerves, must be reduced to a minimum since it can be irreversible. If the abdominal wall does not heal properly after surgery, it can have a great impact on both general health and quality-of-life (QoL).

1.2.1 Muscles

On either side of the midline, the rectus abdominis muscles run in a craniocaudal direction from the xiphoid process and costal cartilages 5-7, with insertion on the pubic symphysis and pubic crest. The rectus abdominis muscles are important for maintaining abdominal pressure, flexure of the trunk, and exhalation. Lateral to the rectus abdominis muscles are three flat muscles called the obliques. The innermost, the transverse abdominal muscle, originates from the lower five costae, the lumbar fascia, the anterior part of iliac crest, and from the lateral part of the inguinal ligament. It also forms the posterior wall of the inguinal canal and inserts on the linea alba. The next lateral muscle is the internal oblique, extending from the thoracolumbar fascia, iliac crest, and inguinal ligament in a diagonal cranial direction inserting on the cartilages of the eight to twelfth rib and the linea alba. It supports flexion of the trunk as well as rotation. The outermost of the obliques is the external oblique that supports side-flexion and pulls down the thoracic region elevating the pressure in the abdominal cavity as in the Valsalva maneuver. It originates from the lower eight ribs and inserts on the lateral iliac crest, thereby forming the inguinal ligament and the anterior wall of the inguinal canal.

In 80% of the population there is also a pyramidalis muscle that originates from the pubic crest and inserts on linea alba below the umbilicus. The pyramidalis muscle is not particularly important for stabilization of the abdominal wall.

The linea alba comprises a 1-2 cm wide combined aponeurosis of all the abdominal muscles in the midline running from the xiphoid process to the pubic symphysis. It largely consists of connective tissue with almost no vessels or nerves. The linea alba is stretched during pregnancy and obesity, and in some cases after pregnancy, the linea alba remains distended with weakness of function. This may look like a hernia of the abdominal wall, but it is not and should not be mistaken for one.

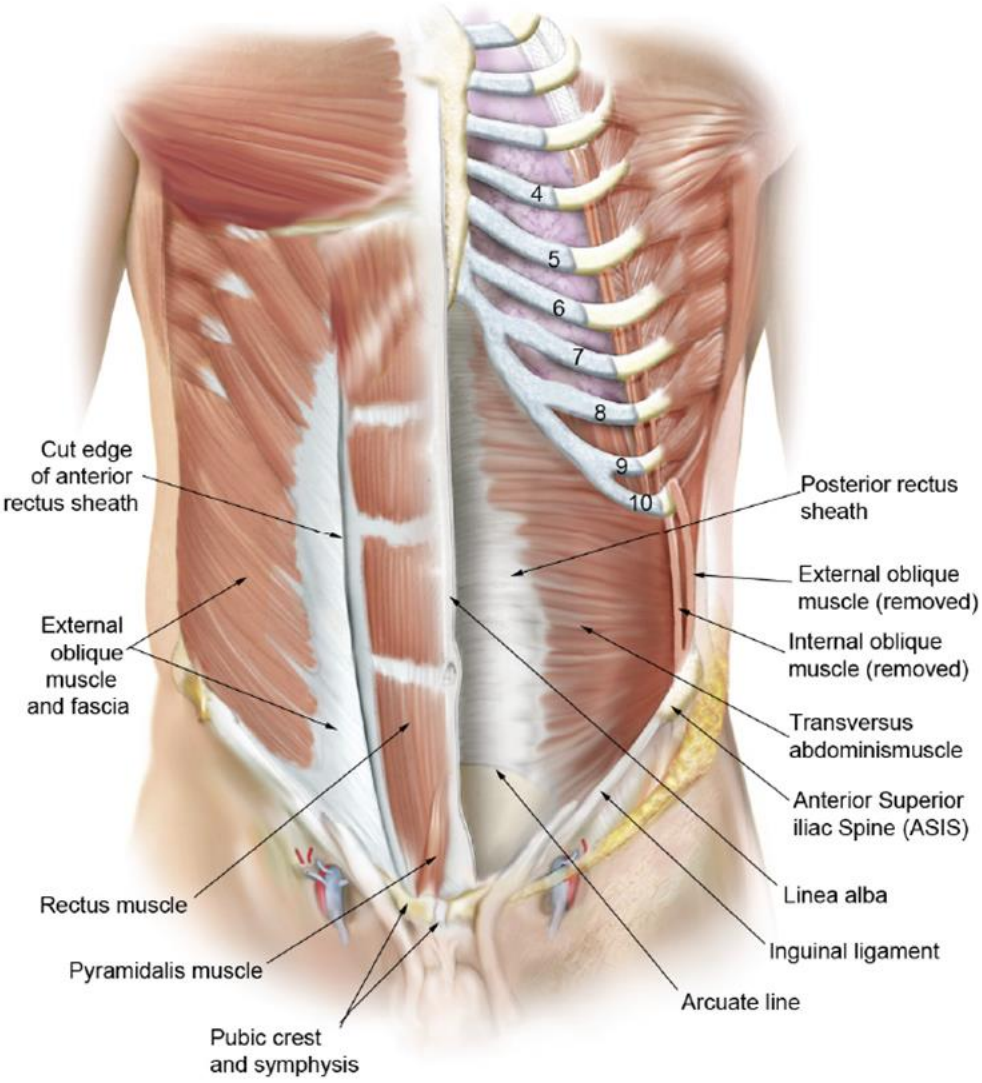

Figure 2. Anatomy of the ventral abdominal wall (8) *Used by permission from Elsevier for thesis non-profit university use*

1.2.2 Nerves

Sensory nerve innervation of the abdominal wall is derived from Th1-L1 and follows the dermatomes in a slightly caudo-medial direction towards the linea alba.

Motor innervation comes from thoracoabdominal, lateral cutaneous, subcostal, iliohypogastric, and ilioinguinal nerves, providing not only motor function but also sensory innervation when giving off sensory nerves to the overlying skin.

1.2.3 Blood supply

The arterial blood supply of the abdominal wall is derived from four deep systems: the internal thoracic artery; the aorta; the external iliac; and femoral arteries. These branch more distally to give the superior epigastric, inferior epigastric, musculophrenic, subcostal and posterior intercostal, deep circumflex iliac, superficial circumflex iliac, and superficial epigastric arteries.

A large venous plexus drains the entire abdominal wall and merges in the upper part to the internal thoracic vein and lateral thoracic vein and in the caudal part to the superficial and inferior epigastric veins.

Most larger vessels run between the transversus abdominis and internal oblique muscles.

1.2.4 Lymphatic system

The lymphatic drainage of the abdominal wall is divided into two systems. The superficial lymphatic system which drains the skin and subcutis into the axillary, parasternal, and superficial lymph nodes, and the deeper system mainly draining muscles and skeletal structures into the lumbar lymph nodes. The deep lymphatic system is not only of importance for the immune system in the abdominal wall, it also contributes to the removal of substances (water, fat, cellular waste, and proteins) from the interstitial fluid through the peritoneum, and transports some of the cells responsible for wound healing (see below).

1.3 WOUND HEALING

Wound healing follows the same pattern regardless of organ or tissue. The time it takes to completely heal differs between organs and tissues. Healing of an aponeurosis takes considerably longer than healing of the skin or oral mucosa. (9)

Healing of an incisional wound, or any wound, may be divided into four phases that seamlessly overlap each other: hemostasis (hours); inflammation (3-5 days); proliferation (5 days-3 weeks); and remodeling (3 weeks – two years) (10). The hemostasis phase is characterized by vasoconstriction and accumulation of thrombocytes. Blood loss is prevented, and formation of fibrin clots serve as a matrix for the inflammatory cells in the inflammatory phase to clean the wound and start the rebuilding process of the abdominal wall that continues into the proliferation phase (also called fibroplasia). Release of various cytokines, such as growth factors, stimulates angiogenesis and is crucial in the formation of collagen as the first new tissue in the wound. This first collagen is weak with a strength equivalent to 15-20% of the original abdominal wall tissue. (9) (11) The original collagen is then transformed into stronger permanent cross-linked collagen during the remodeling phase, lasting from three weeks to two years, finally providing a tensile strength of around 60-90% of the original strength (10) (11) (12) (13).

During the first 3-5 days i.e., the inflammatory phase, the wound itself has no tensile strength and sutures must support the tension (12) (14). It is during this period that most cases of wound dehiscence occur (see below) (12) (13) (15).

1.3.1 Collagen

There are at least 28 kinds of collagen in the body of which collagen types I and III are the most important for wound healing.

Over 90% of collagen in the body is collagen I. Collagen I is created by cross-linkage and aggregation of fibrils into fibers. The creation of cross-linkage is dependent on vitamin C and various proteinases. Prolonged deficiency of vitamin C may result in scurvy. Alterations or defects in the genes coding for proteinase and/or collagen has been associated with connective tissue disorders such as Ehlers-Danlos syndrome.

The collagen created by fibroblasts during the proliferation phase is collagen type III comprising fibrils that are converted into collagen by special proteinases called metalloproteinases (16). During this phase, wound healing is very sensitive to interfering factors such as infection, poor blood supply, and impaired nutrition, all of which may lead to prolonged proliferation with weak collagen III fibrils that aggregate instead of being converted to collagen I in the remodeling phase. This subsequently leads to poorer tensile strength in the final scar.

1.4 ABDOMINAL WALL INCISIONS

The midline incision through the linea alba is the most commonly used for access to the abdominal cavity. Other approaches may be preferable to gain optimal access to the targeted organ (Fig 3).

The choice of incision is of great importance both for access and exposure of the targeted organ, while efforts to limit harm to the components of the abdominal wall must be made.

A midline incision limits damage to the abdominal wall, avoiding division of muscles or nerves, and providing rapid and wide entry to the abdominal cavity (17) (18) (19) (20) (21). The midline incision can run at most from the processus xiphoideus to the symphysis or be limited to just a part of the linea alba. Midline incisions are, however, associated with a greater risk for wound dehiscence and development of incisional hernia compared to other abdominal wall incisions (22) (20).

Apart from the usual midline incision, paramedian, transverse, oblique, and muscle splitting incisions are common in abdominal surgery. (Fig 3)

A common incision in urological surgery is incision below the arcus or a subcostal incision, providing good access to the kidneys. This, however, implies dividing the oblique muscles, and part of the rectus abdominis muscle, injuring nerves, and vessels. This type of incision is less associated with the development of incisional hernia, since the lateral forces in the abdominal wall differ from those in the midline (21) (23) (24) (25) (26). If, an incisional hernia occurs in a lateral incision, it is more difficult to repair (27).

For open surgical procedures in the pelvic region such as bladder, prostate, and distal ureter surgery, a muscle-splitting technique such as Pfannenstiel is an option instead of a lower midline incision. Muscle splitting techniques are considered to be less associated with wound complications (17) (28) even though other studies show that wound dehiscence, nerve damage, and incisional hernia repair are quite common after muscle-splitting techniques (28) (29) (30).

In minimally invasive surgery, placement of the incisions for port entry as well as the number of ports used differ depending on the targeted organ and planned surgery

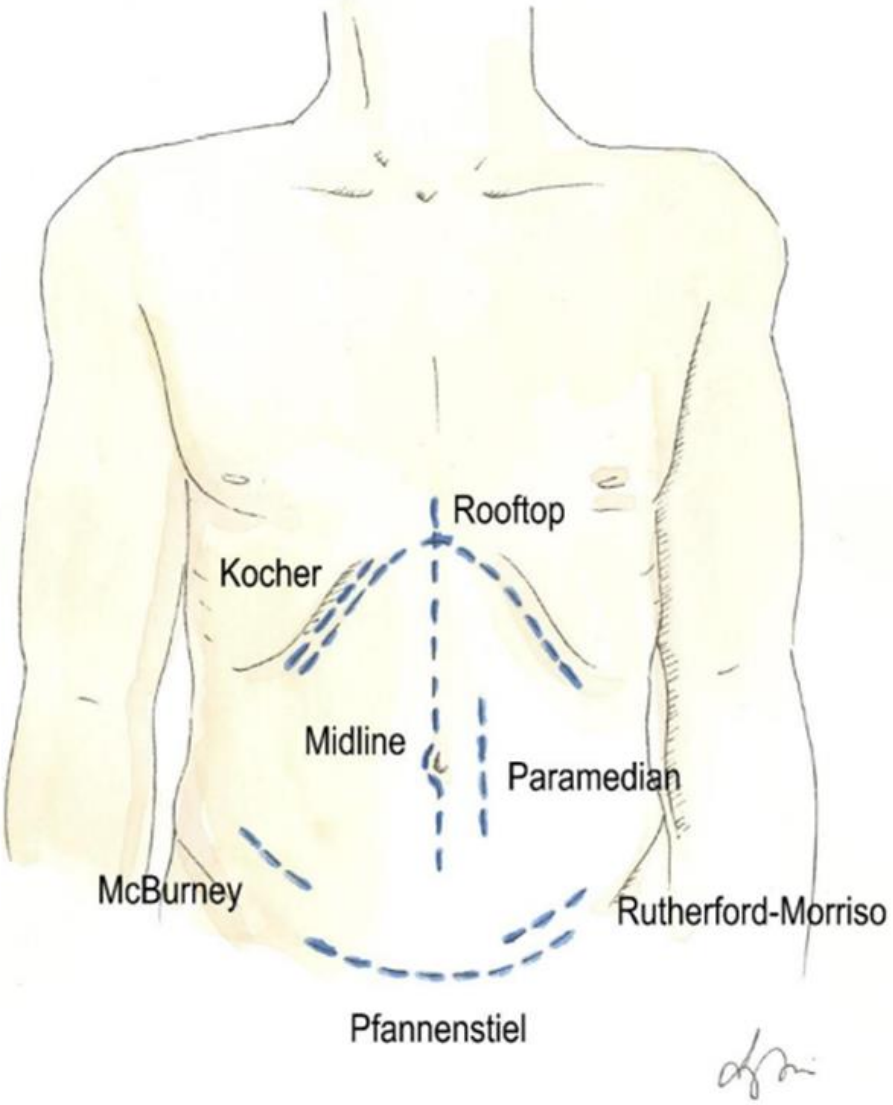

Figure 3. Different types of abdominal wall incision © Lucy Bai 2021

1.5 WOUND DEHISCENCE

Separation of the abdominal fascia after surgery it is called a wound dehiscence. The four predominating causes of wound dehiscence are: break of the suture, slipped knot, slack thread, or most commonly, the suture cutting through the fascia. (15) (31) (32) (33).

Wound dehiscence often occurs within the first days after surgery when the tensile strength of the wound is solely dependent on the suture and the capacity of the tissue to retain the suture (30) (32) (33). Wound dehiscence may be dramatic, with evisceration of the intestines through the wound, usually called a burst abdomen. Burst abdomen is a rare complication with a rate of up to 4% following elective abdominal surgery (13) (34) (35) (21) (32). In the acute setting, the incidence of burst abdomen may range between 2,4% and 35% (13) (34) (35). Burst abdomen is associated with a postoperative mortality rate of up to 35% (32) (34) (36) (35) (37).

Wound dehiscence often presents with secretion of serosanguinous fluid through the wound and is often mistaken for infection. Deeper palpation, however, usually reveals a weakening along the suture line (15) (38). If deficiency in the suture line is wide enough, abdominal contents can protrude through the wall and strangulate (13).

Wound dehiscence is usually diagnosed around postoperative day seven but may be confirmed anytime from postoperative day one to more than 21 days postoperatively (15) (36) (38), often with delay in diagnosis.

The major risk factor for wound dehiscence is poor technique when closing the incision, causing the wound edges to separate due to inappropriate suture material or anchoring knots. In a large study, use of the SSSB technique for wound closure reduced the rate of wound dehiscence to 0.6% (39).

There is yet no consensus on how to treat wound dehiscence. If there is a large closure defect, emergency surgery to close the fascia is indicated. However, this may not be appropriate due to infection, intra-abdominal swelling, or weak fascia (40). If immediate repair of the wound dehiscence is chosen, there is no consensus on how to close the deficit. Nestors in the field Israelsson and Millbourn argue that a wound dehiscence should be sutured by mass-stitching of all tissues in the abdominal wall apart from the skin at least 3 cm from the wound edges to secure holding capacity in the tissue, and that sutures should be 4-5mm apart to distribute the forces over a wide segment of tissue. This technique yields a suture length 10-15 times the length of the incision. No study has been published on this closing technique, but Israelsson and Millbourn argue that they have had almost 100% success rate with this technique. Another alternative is to leave to abdomen open for some time with or without negative pressure treatment. This is suitable when there is a risk of abdominal compartment syndrome, presence of deep surgical infection, or other complicating factors for wound healing. Another option is to place a mesh between the two fascial edges to reduce the pressure, creating a neo-abdominal wall (40) (41) (42).

A Cochrane review comparing midline incisions with transverse incisions (including oblique and sub-arcus incision) showed a lower rate of wound dehiscence with transverse incisions, but none of the included studies had sufficient statistical power to independently show that. (24).

Repeated surgery for burst abdomen is associated with a high incidence of incisional hernia formation (32) (35).

1.6 INCISIONAL HERNIA

The most accepted definition of an incisional hernia is that of Korenkov et al: “Any abdominal wall gap, with or without a bulge, in the area of a postoperative scar perceptible or palpable by clinical examination or imaging” (43). The definition formulated by the European Hernia Society is similar: “Any abdominal wall gap with or without a bulge in the area of a postoperative scar, palpable or perceptible by clinical examination or imaging” (44).

Incisional hernia is not only a cosmetic problem, but can also be a painful, discomforting, potentially life-threatening condition with risk for strangulation of intra-abdominal content. However, up to half of those who develop incisional hernia do not have symptoms (35) (43) (45) (46) (47). Although the symptoms from incisional hernias vary, they can have substantial impact on health-related quality-of-life for some patients (35).

There are no criteria that confirm the diagnosis of incisional hernia. Physical examination should be performed in the supine position in a relaxed state and during a Valsalva manoeuvre. Imaging diagnostics may be necessary, especially in obese patients (46). In a large trial, more than half of incisional hernias were only diagnosed after radiological examination (48) and the European Hernia Association recommends that future prospective studies on incisional hernia should integrate postoperative radiology in the follow-up (49).

The incidence of incisional hernia after open abdominal surgery varies in the literature from 5 to 70%, usually around 20 % (50) (51) (52). In a review and metanalysis from 2015, the mean cumulative incidence of incisional hernia after two years was 13% (53). The introduction of a new suturing technique, the small-stitch small-bite method (SSSB) recommended by hernia society groups around the world in 2014 (49), has reduced the incidence by 75% to around 6 % (51).

Most incisional hernias probably form during the early stage of wound healing, the most important factor being separation of the edge of the aponeurosis. Studies have shown that if the edges of the aponeurosis are more than 12 mm apart during the first postoperative month, an incisional hernia will develop (54), probably due to inability of the scar tissue to overbridge the defect. It is therefore important that sutures keep the edges of the aponeurosis in an optimal position during the first weeks of healing

Most studies regarding development and prevention of incisional hernia have been carried out on medial incisions. Other studies, however, have shown lower incisional hernia rates with other types of abdominal incision. There is no consensus on how to prevent incisional hernias or how to repair them.

The diagnosis of incisional hernia may be delayed years after the primary procedure due to patient delay or reluctance of the surgeon to recognise the incisional hernia. When the above-mentioned diagnostic procedures are applied, around 90 % of all incisional hernias are detected within the first 12 months after surgery (43).

The long-term cumulative incidence of incarceration in patients with incisional hernia has been estimated to be around 1% (45) (55). It has been reported that 49% of all patients with an incisional hernia have symptoms, and that 36% undergo surgery (53).

Surgery for incisional hernia repair is costly for the individual as well as for society (55) (56). Furthermore, incisional hernia repair has a recurrence rate of up to 45% (57), rendering prophylactic methods for preventing incisional hernia very cost-effective (55) (58) (59).

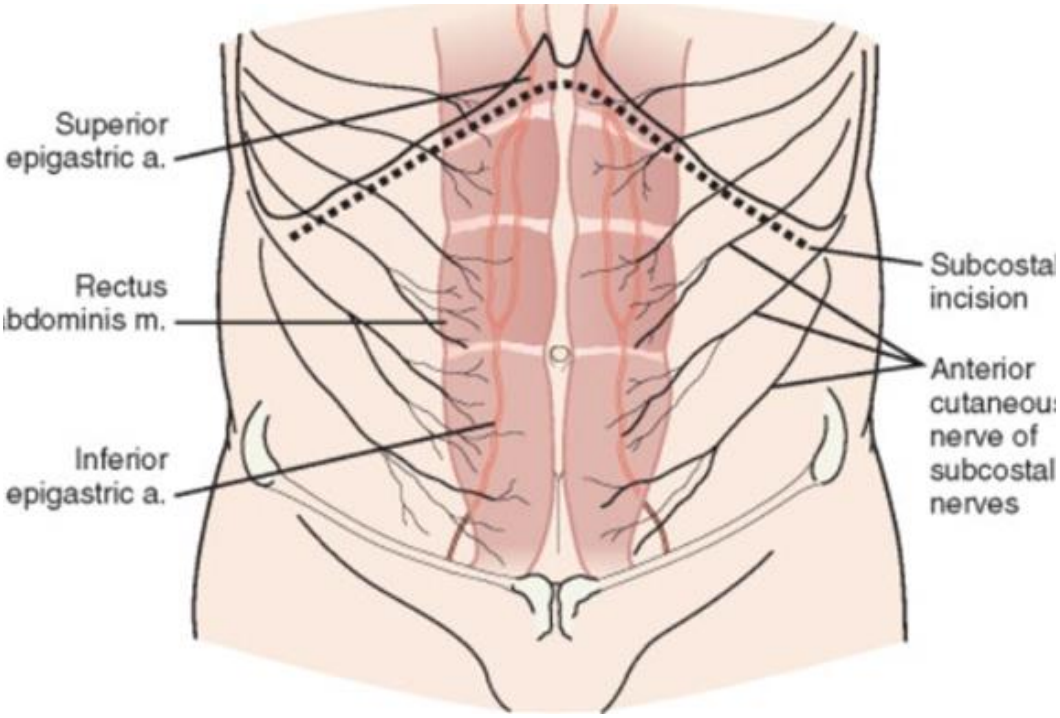

Figure 4. Placement of subcostal incision showing the vessels and nerves being divided by the incision. (60) *Used by permission from Elsevier for thesis non-profit university use*

Figure 5. Incisional hernia after left-sided nephrectomy for renal cell carcinoma through a subcostal incision (61) *Used by permission from Elsevier for thesis non-profit university use.*

1.7 BULGING

Another adverse effect of abdominal surgery is damage to the nerves, blood vessels, and muscles leading to abdominal wall muscle atrophy. Muscle atrophy often results in a permanent flank bulge that may be mistaken for an incisional hernia. The bulge however does not contain abdominal viscera and the fascia is intact. Even though flank bulging is a well-known postoperative phenomenon after open renal cell carcinoma surgery, very little is known about its impact on everyday life and the rate remains unknown. Most studies on postoperative flank bulging are done on patients after aortic surgery where the incision is somewhat different to those used for renal cell cancer surgery. In 2004, Chatterjee et al (62) published a study showing that 49% of all patients experienced a flank bulge one year after the surgery and 24% had persistent flank pain. No significant association between pain and bulging was found. They also found that flank bulging was more common after left-sided nephrectomy and that no difference in bulge incidence was seen between surgeons. The dominance of left-sided bulging is probably explained by the anatomical location of the kidney being more cranial on the left side than on the right side. These anatomical features may lead to a longer incision with greater trauma to muscles and nerves as well as higher tension in the cranially applied retractors causing pressure on the nerves, vessels, and nerves on the left side. Chatterjee et al (62) concluded that the high rate of flank bulge and its impact on QoL especially amongst younger patients should demand more attention when deciding surgical technique, in favor of minimally invasive techniques. This reasoning was taken up by Crouzet et al in a study from 2014 where change in flank muscle volume after partial nephrectomy was compared between open and minimally invasive techniques. (63) Loss of flank muscle volume was significantly greater after partial nephrectomy via a flank incision than after a minimally invasive technique ($p<0.005$). Patients with an open technique also had significantly greater flank bulging when measured with computer tomography. The patients who had open surgery also reported significantly ($p<0.005$) more symptoms in the form of paresthesia, numbness, and flank bulging. In two studies conducted on patients undergoing renal cell cancer surgery in northern Sweden, 20% had a bulge at the first clinical checkup and 28% had a bulge on the first CT scan. At the final follow-up (up to 24 months after surgery), 10% had a persistent bulge clinically and 19% on CT scan. No significant risk factors for bulging were found. This could indicate that the abdominal wall regains some of its function over time. On the other hand, 18% of patients reported pain and 31% a bulge at the five-year follow-up, suggesting that abdominal wall problems persist over time (64) (65).

Studies, first performed on cadavers, showed the nerve with the largest motor supply to the anterolateral abdominal wall arises from Th12, is located 1,5-2 cm medial to the tip of the 12th rib, and runs towards the suprapubic region (66) (67). In the study by Ozel et al (67), these anatomical findings were tested on forty people undergoing living donor nephrectomy who were followed up by ultrasound after one year. No significant difference in muscle atrophy was seen between the surgical and the non-surgical side.

A recent study published in 2021 by Kranz et al (68) was based on a questionnaire regarding postoperative morbidity and objective satisfaction with cosmetic appearance. The

questionnaire was sent out to patients that had undergone different types of retroperitoneal surgery through a flank incision. In all, 120 patients answered (50% of those invited) and of these 36% reported bulging. Patients reporting bulging were invited to attend a physical examination where it was established that 60% of those that had reported bulging actually had a bulge. Thirteen per cent of the patients were found to have both bulge and pain. A BMI >25 was the only significant risk factor for developing a bulge.

A few studies have been published on how to surgically treat flank bulging, either with mesh placement or plication of the rectus aponeurosis. Success rates close to 100% have been reported but these studies have poor statistical power due to few participants (69) (70).

Non-surgical attempts to the rehabilitate a flank bulge have been tried, but more research is needed.

2 CURRENT KNOWLEDGE

2.1 SMALL-STITICH-SMALL-BITES TECHNIQUE (SSSB)

The work that led to the recommendation of single layer closure of the incision with a continuous suture, was first conducted by Jenkins in 1976 (71). He suggested using continuous monofilament suture with a length of at least four times the incision, to prevent burst abdomen. Similar studies have been published since then, one of the most cited being that of the Sundsvall group led by Israelsson in 1993 (72) and repeated in a similar setting in the STITCH-trial by Deerenberg in 2015 (48). The STITCH trial showed that incisional hernia and wound dehiscence may be avoided by simply changing the way the aponeurosis is sutured.

The key feature of the small-stitch-small-bites (SSSB) technique is the use of a slowly absorbable suture for running small-bite stitches to the aponeurosis, striving to reach a wound:suture length ratio of at least 1:4. (48) (72)

In a randomized trial (73) on two groups (small-bite stiches vs large-bite stitches, but the same suture length and material), incisional hernia rate was found to be 6% in the small-bite group compared to 18.0% in the large-bite group. In the small-bite group, no correlation between potential risk factors and development of incisional hernia were found. In the large-bite group, duration of surgery more than 120 minutes and postoperative surgical site infection were associated with incisional hernia (73).

In another large randomized prospective study on small-bite versus large-bite suturing (STITCH-trial), the incisional hernia rate in the small-bite group was found to be 13% compared to 21% in the large-bite group (59). In that study, risk factors for incisional hernia development were not evaluated. The higher than normal rate of incisional hernias may be explained by the routine postoperative radiological examination, where more than half of the incisional hernia were discovered.

The SSSB technique uses slowly resorbable suture material that should withstand stresses on the wound for at least six weeks postoperatively (74) (75) (76). The use of non-absorbable suture has not improved the rate of incisional hernia (75) (76), but the presence of foreign material in the tissue for a longer period may impact the rates of infection and adhesions.

A monofilament suture material is recommended, so it is important to use a self-locking knot to avoid surgical site infection and slipping of the knot as well as to achieve higher tensile strength (Fig 4) (77). Conventional knots reduce the suture strength by up to 40%, but a self-locking knot reduces suture strength by approximately 10% (77). Millbourn et al and Israelsson et al recommend USP 2/0 monofilament suture which has been shown to have a zero rate of wound dehiscence in a study on over 350 midline incisions (39). The use of a continuous suture technique rather than interrupted has been shown to provide a stronger wound and is less time-consuming (21) (78).

The suture:incision length ratio of 1:4 was already shown to be advantageous in Jenkins´s study from 1976. (71) This may be accomplished either by using many small stitches or fewer large stitches with tension in the suture line. Several studies have shown that by limiting the distance between stitches to 5 mm, the risk for incisional hernia, surgical infection, and wound dehiscence is much less than with the large stitch technique even if the suture:incision length rate is the same. This is probably explained by more soft tissues being entrapped in the large stitches, leading to compression and even necrosis of the aponeurosis. This leads to slack sutures with the edges of the aponeurosis ending up more than 12 mm apart, resulting in an incisional hernia (79) (80). A suture:incision length ratio more than 1:4 has not shown any greater benefit (73).

It has been argued that separate closure of peritoneum prevents adherence of small bowels to the abdominal wall thereby limiting the development of incisional hernia (81). However, in animal studies, peritoneal closure caused more adhesions of small intestine to the abdominal wall, and in humans does not reduce the risk for incisional hernia (50) (82) (83).

Introduction of the small-stitch-small-bites (SSSB) technique has also been shown to be cost-effective (59).

Since 2014, the SSSB technique has been recommended by the European Hernia Society as the closing technique of choice for midline incisions. The SSSB technique is widely used for closing other incisions as well though more research is needed before a consensus can be reached regarding the use of the SSSB technique for incisions other than the midline. The benefits of this closing technique may be extrapolated to other incisions as well since the mechanisms behind wound healing, surgical site infection, and undermined suture line are the same regardless of the incision and despite differences in abdominal wall function.

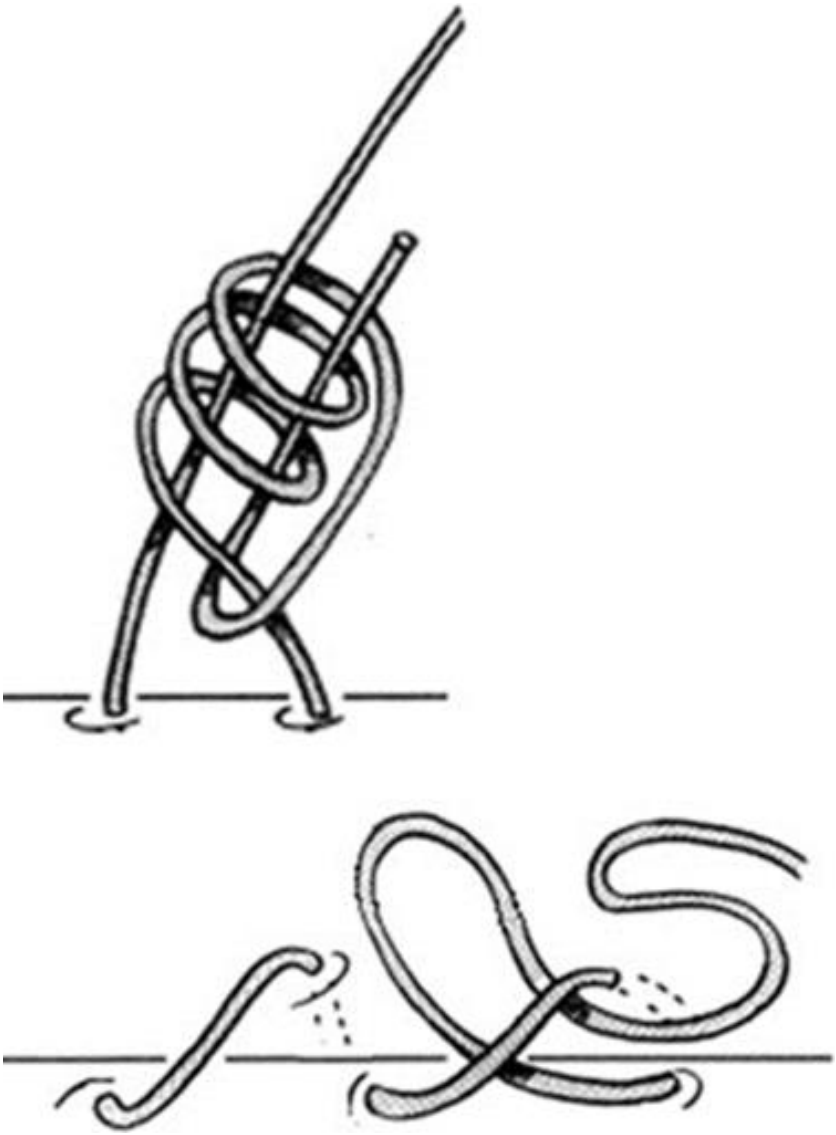

Figure 6. Suture starts with a self-locking knot and ends with an anchor knot. (84) *Used by permission from Elsevier for thesis non-profit university use*

2.2 RISK FACTORS FOR WOUND DEHISCENCE AND INCISIONAL HERNIA DEVELOPMENT

2.2.1 Surgical technique and postoperative-related risk factors

The principles of abdominal wall closure after midline incision have changed radically over the last two decades. In the guidelines on closure of abdominal wall incisions from the European Hernia Society 2015 (49), it is stated that suture technique and suture material are the most important risk factors for the development of an incisional hernia. The recommendation for midline closure was based on a meta-analysis from 2010 and a review from 2013. (84) (85) Recommendations are to use continuous monofilament suture material with closure of the aponeurosis in one layer only. The guidelines apply to midline incisions, but the technique has in most settings been applied to other incision locations (23) (49) (85). A recently published randomized multicenter study (86) compared single and multilayer flank incision closure, with bulging as outcome. A total of 177 patients undergoing different types of procedures at three different hospitals in Germany were included. The flank incisions were closed either in three layers or in one single superficial layer with running sutures one centimeter from the fascia edges and one centimeter apart. The study showed that closing the flank incision in three layers was superior to single layer closure regarding the bulge rate 6 months after surgery (34% vs 52%, OR 2.04 CI95% 1.11-3.73). There was no significant difference between the rates of incisional hernia and pain between the groups 6 months after surgery. QoL was reported to be higher among the patients where multilayer technique was used. This study supports the hypothesis that damage to nerves and muscles does not depend on the suturing technique but rather the incision and trauma inflicted during the procedure.

The second most important measure to reduce the risk for incisional hernia is to avoid surgical site infections, defined by the Center of Disease Control (CDC) as a purulent discharge from the wound, irrespective of the presence of a positive bacteriology culture. This depends on surgical technique to a great extent. Postoperative wound infection increases the risk for wound dehiscence and later incisional hernia (87) (88). After surgery through a midline incision, the surgical site infection rate is reported to be 15% (74) (84) (87) (89). Bacterial contamination during surgery is the factor most strongly associated with surgical site infection. Gastrointestinal and trauma surgery are associated with the highest risk for surgical site infection (90) (91). The use of monofilament suture material decreases the risk for surgical site infection by reducing to a minimum the surface area available for bacterial adherence (92). Bacterial overgrowth is prevented by limiting tissue necrosis in the wound during the aponeurosis incision and wound closure, minimizing the risk for surgical site infection (93). Application of appropriate tension during closure of the wound limits tissue necrosis (78). It is difficult to decide on the right suture tension since postoperative oedema and physical activity of the patient are unknown, but the current recommendation is to adjoin the wound edges but not compress them. Large stitches seem to increase the risk for surgical site infection probably due to more soft tissue necrosis, encouraging bacterial overgrowth and limiting the synthesis of collagen (78). Large-bite stitches (more than 10 mm from the wound

edges) give a surgical site infection rate of 10 % whereas small-bite stitches (5-8 mm from the wound edges) lowered the surgical site infection rate to 5 % (51).

The presence of a surgical site infection decreases the integrity of the aponeurosis and causes the suture to cut through supporting tissues (73) (90). Surgical site infections often develop in the immediate postoperative period when the tensile strength of the wound depends solely on the suture line. Tissue weakness due to infection allows the suture to cut through leading to wound dehiscence and subsequent incisional hernia.

Another way of decreasing the risk for incisional hernia is to use other approaches than midline incision whenever feasible. A systematic review by Bickenbach et al 2013 (94) and a Cochrane review by Brown et al 2005 (24) compared midline incisions to other incision locations. Both showed significantly lower incisional hernia rates when using incisions other than midline incisions to enter the abdominal cavity. There were no decreases in surgical site infection and burst abdomen rates. These two reviews are the basis of the EHS recommendation to use other incision locations than the midline whenever possible (49).

Apart from surgical technique and material, there are patient-related factors for surgical site infection. Diabetes mellitus is a well-known risk factor for all forms of wound complication including surgical site infection. Obesity and smoking also impair wound healing by delaying the immune response in the wound area (73) (91) (95) (96). In general, patient-related risk factors for surgical site infection are the same as those for incisional hernia development.

Facility- and procedure-related risk factors include inadequate ventilation in the operating theatre, poor sterilization of equipment, inadequate personal hand wash, duration of surgery, hypothermia, and blood transfusion (91) (96). By optimizing the manageable patient-related risk factors before surgery as well as maintaining a sterile facility during the procedure, surgical infection can be prevented (97)

The use of postoperative binders has not prevent burst abdomen or incisional hernia in a systematic review from 2014 that included both RCTs and surveys (98) A Swedish randomized study by Clay et al (99) showed significantly less pain on postoperative Day 5 if a binder was used.

The principle of restricted physical activity in the immediate postoperative period is widespread. There are no recommendations in current guidelines, about physical restriction to reduce incisional hernia development, due to lack of studies. Indeed, it is argued that limited postoperative physical activity may delay return to normal activity and work (49). A questionnaire-based survey including forty-one colorectal surgeons in Denmark and Sweden showed no consensus on how physical restriction should be advised during the first six postoperative weeks. The only agreement was that restriction was more usual after open surgery than minimally invasive surgery. The authors concluded that type of restriction is the personal preference of the surgeon since there is no evidence that physical restriction prevents incisional hernia. (100)

Altered tension in the wound	**Disturbance of wound healing**
Coughing Ascites Postoperative bowl obstruction Obesity Chronic obstructive pulmonary disease Postoperative coughing Postoperative bowel obstruction Previous abdominal surgery Previous hernia	High age Hypertension Cancer Hemodynamic instability Chronic obstructive pulmonary disease Ascites Anaemia Corticosteroid use Sepsis Surgical site infection Hypoalbuminemia Uraemia Chemotherapy Previous hernia Smoking Diabetes Radiotherapy Immunosuppression Connective tissue disorder Previous abdominal surgery Length of incision

Table 1 Factors affecting incisional hernia development

2.2.2 Patient-related risk factors

Even though most patient-related risk factors remain unrecognized, some correlate with development of incisional hernia, such as old age, cachexia, obesity, smoking, previous bariatric surgery, corticosteroid medication, previous abdominal surgery, and connective tissue disease. (46) (72) (78) (88) (101) (102) (103) (table 1) Few studies have been carried out since the recommendation of the small-stitch small-bites (SSSB) method was introduced in 2014 (49). The risk factors named above are therefore from before the introduction of SSSB, and therefore further research is needed to assess whether these risk factors are also relevant when the SSSB technique is used.

A general limitation of studies on risk factors for developing incisional hernia is that the surgical technique used when closing the incision is not described i.e., the most important risk factor has not been taken into consideration.

Many risk factors are hard to differentiate from each other as they are strongly associated. Risk factors may be divided into two groups, elevated postoperative abdominal pressure and disturbance of wound healing. (table 1) Many risk factors are found in both groups, and it seems reasonable to expect that the presence of several risk factors in one patient considerably elevates the risk for incisional hernia development.

As mentioned above, patient related risk factors for wound dehiscence and incisional hernia are similar. Obesity is widely considered to be a risk factor for incisional hernia, probably due to larger stiches being required with greater compression in soft tissue in each bite leading to tissue necrosis, suture cutting, and slack sutures creating a gap between the edges of the aponeurosis. Necrosis also serves as a ground for bacteria to thrive on (90) (95) (104). Obesity also increases the intra-abdominal pressure, thereby increasing tension in the suture line and aponeurosis. Visceral fat has been shown to be of particular importance for incisional hernia development. A study showed that perirenal fat, when used as a surrogate definition of visceral adiposity strongly predicted the risk for incisional hernia (105). Previous studies have reported an association between perirenal fat and postoperative complications (106) (107). Intra-abdominal adipose may also increase tension on the aponeurosis and suture line.

Diabetes is another well-known risk factor often seen together with obesity. It impairs the cellular mechanisms involved in wound healing by decreasing the activity of the cells responsible for formation of early stages of collagens. Diabetes is also a well-known risk factor for infection due to changes in the capillary system that disturb the immune response. Furthermore, poor glucose regulation provides nutrients for bacterial overgrowth. Another risk factor related to diabetes is insulin resistance, a common and well-known consequence of surgery not only present in diabetic patients. (108) Murine models have shown that insulin resistance affects wound healing (109). Forty per cent of diabetes patients are resistant to insulin which further explains why diabetes is a risk factor for incisional hernia. Postoperative insulin resistance can be limited by carbohydrate loading preoperatively or by nutrition drinks the night before elective surgery. Since insulin resistance is a well-known risk factor for

several surgical complications, it is one of the issues targeted in ERAS (enhanced recovery after surgery) regime. (110) Smoking is another risk factor that is targeted before elective surgery, not only because it is a risk factor for incisional hernia. (46) (111), but also because it impairs wound healing by decreasing oxygen supply to the tissues. This affects cells of the immune system and cells responsible for collagen synthesis during wound healing. (112) It has also been shown that perioperative administration of oxygen reduces the risk for surgical site complications (113) Postoperative coughing has also been shown to increase the risk for incisional hernia, probably due to rapid increases in abdominal pressure.

Another aspect of interest related to incisional hernia development is alterations in the connective tissues. Several studies have been carried out on patients where alterations in the collagen matrix are suspected. In a study comparing the risk for incisional hernia development in patients undergoing sigmoid colectomy for diverticulitis or sigmoid cancer, the group with diverticulitis had a cumulative incidence of 15.1% and cancer group 5.8% for incisional hernia. This difference may be due to alterations in the collagen matrix. (114) Several studies conducted on patients undergoing open surgery for abdominal aortic aneurysm have shown an elevated risk for incisional hernia suggesting alterations in the connective tissues in this patient group. However, more recent studies where modern closure techniques are used, have shown that this patient group does not have an increased incidence of incisional hernia (115) (116). This indicates that more research is needed that also incorporate biogenetic risk factors for incisional hernia.

There are some studies published after the small-stitch small-bites (SSSB) technique for wound closure was introduced. Millbourn et al 2004 (51) did not find any significant risk factors for incisional hernia after introducing the SSSB technique, nor when evaluating the technique several years later (51) (73). In a large retrospective study on patients undergoing surgery 2013-2016 when the SSSB technique gradually got recognized, the incidence of wound dehiscence (1.3%) was too low to find any specific risk factor. (117) A retrospective study where suture technique was documented and similar to SSSB, no risk factor for incisional hernia could be found. The proper application of the SSSB technique probably minimizes the impact of other risk factors for incisional hernia.

2.3 REPAIR OF INCISONAL HERNIA

The aim of incisional hernia repair is to restore the continuity of the abdominal wall, either by approximating the borders of the fascia or by replacing or elongating the fascia with a mesh.

There are no official guidelines, neither from European Hernia Society (EHS) nor Americas Hernia Society regarding repair of incisional hernia. Several authors have reviewed current knowledge as described below. (118) (119) (120) Most studies on incisional hernia repair concern midline incisions, but the same principles are used in other incisional hernia locations.

A primary defect less than two centimeters can be sutured with non-absorbable or slowly absorbable suture without mesh reinforcement (118) (119) (121).

For defects larger than two cm or recurrent incisional hernia a mesh should be applied (118). The mesh can be of synthetic (non-absorbable or slowly absorbable) or of biological material (119) (121).

The mesh can be placed ventral to the abdominal muscles (onlay) (Fig 7), between the borders of the hernia (inlay), behind the abdominal muscles but ventral to the dorsal fascia (retromuscular or sublay), ventral to the peritoneum (preperitoneal or sublay), or in the abdominal cavity adherent to the peritoneum (intraperitoneal).

Sublay placement, whether retromuscularly or preperitoneally, is often preferred since it limits the risk for infection, intestinal adhesion, and recurrence (118) (119). The mesh can be placed using either an open technique or a minimally invasive technique.

Over the last two years, it has been debated whether an open or minimally invasive technique should be used for the repair. There is presently a shift from Intraperitoneal Onlay Mesh (IPOM) using a minimally invasive technique towards an open sublay technique or modern minimally invasive techniques where the mesh is placed outside the abdominal cavity (118) (119).

The problem of all methods of repair is the risk for infection, with rates up to 30 % in a Cochrane report. (122) These infections are often complicated by the presence of suture or mesh. An infection may thus need months of antibiotics or, in the worst-case scenario, removal of the infected area as well as the mesh with a high risk for intra-abdominal complications such as fistulae and adhesions. The presence of a surgical site infection after incisional hernia repair is the most important risk factor for recurrence, with the risk for surgical site infection being even higher after repair of the recurrence (123). The infection risk is somewhat reduced using minimally invasive surgery and a biological mesh (89) (120).

Even though most studies have been performed on midline repairs. Techniques for midline hernia repair can be extrapolated to other incisional hernia locations. Placement of the mesh may, however, be more complicated since there is lower strength in the aponeurosis laterally than in the midline. Furthermore, different traction forces affect the abdominal wall and the proximity to bony structures makes the attachment of the mesh to the abdominal wall complicated. These circumstances may lead to even higher recurrence rates after incisional hernia repair on hernias outside the midline. (23) (27)

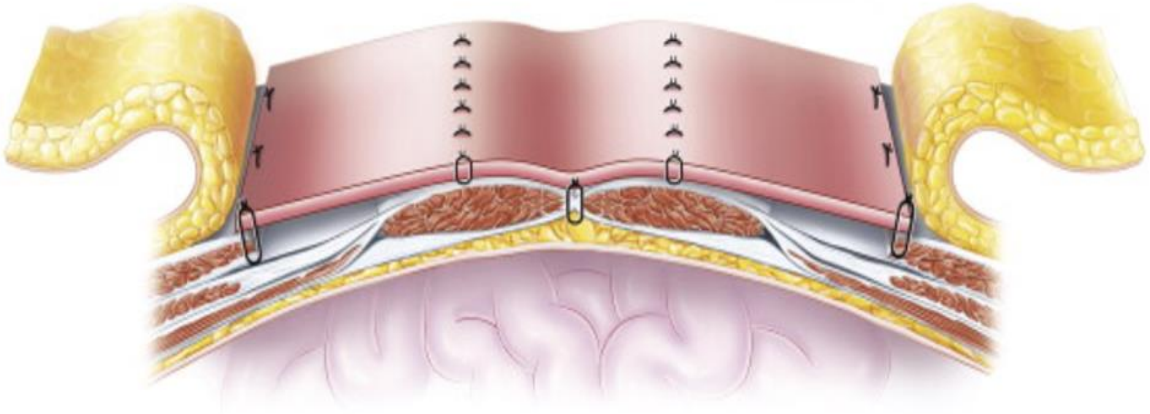

Figure 7. Onlay mesh placement superficial to the rectus muscle and the external oblique aponeurosis (101) *Used by permission from Elsevier for thesis non-profit university use*.

2.4 INGUINAL HERNIA

Inguinal hernia is a weakening or a defect in the abdominal wall in the inguinal region above the inguinal ligament. Fat or a sack formation of peritoneum, often with content of intra-abdominal fat or structures originating from the abdominal cavity, may protrude through the hernia. The content of the hernia sack is extruded through the defect, creating a palpable or visible bulge in the inguinal region. Inguinal hernias are divided into direct (medial) or indirect (lateral) depending on the anatomical position. In the case of indirect hernias, contents of the abdominal cavity protrude through the deep inguinal ring whereas in direct inguinal hernia the contents bulge through a weakened medial transverse fascia that forms the dorsal wall of the inguinal canal. The anatomical distinction of indirect or direct inguinal hernia are the epigastric vessels. (Fig 8) An inguinal hernia can be hard to distinguish from a femoral hernia since femoral hernias protrude through the femoral canal where the femoral vein exits just distal to the inguinal ligament.(124)

As the inguinal hernia extends, fat or any of the organs in the abdominal cavity may protrude through the externa inguinal ring and become visible as a bulge in the groin or palpable as a weakening in the abdominal wall.

Inguinal hernias are diagnosed from symptoms and a visible or palpable bulge in the groin area. If there are typical symptoms of inguinal hernia but no findings at physical examination, magnetic resonance tomography or herniography may help to diagnose a small inguinal hernia (124) (125)

Besides a bulge, symptoms of inguinal hernia are pain, feeling of heaviness, altered bowel habit, and discomfort during physical activity. Even though an inguinal hernia is considered benign, up to 3 % become life-threatening each year if the content of the hernia sack becomes incarcerated leading to strangulation and finally ischemia. Inguinal hernia is 10-15 times more common in males. (126)

Forty-eight per cent of all men over 75 years in Sweden, are diagnosed with inguinal hernia, making age the factor most associated with inguinal hernia besides male gender (124). Other factors associated with development of inguinal hernia are family history of inguinal hernia, abnormal collagen metabolism, radical prostatectomy (with open technique being more associated than minimally invasive), and underweight. (125) (127) (128)

Symptomatic inguinal hernia should be surgically treated. Asymptomatic or minimally symptomatic inguinal hernia could be treated with watchful waiting since the risk for emergency surgery due to incarceration is low. Most patients diagnosed with inguinal hernia will need surgical repair sooner or later, even after an initial decision to refrain from surgery (125) (125)

The only effective treatment of inguinal hernia is surgery. More than 15 million men worldwide undergo inguinal hernia repair each year (129), around 16 000 of them in Sweden (130), making inguinal hernia repair the most common general surgical procedure. The lifetime risk for inguinal hernia repair among men is above 25% (131).

There is no standard technique for inguinal hernia repair, but methods including mesh are strongly recommended regardless of open or minimally invasive surgical technique. (125) Mesh is used in more than 99% of all inguinal hernia repairs in Sweden (130) Mesh may be placed either above the muscles in the inguinal region or preperitoneally behind the muscles. Day surgery for inguinal hernia is recommended under general anesthesia in men above 65 years, and in Sweden about 80% of repairs are performed under general anesthesia. (130),

Complications after inguinal hernia repair are frequent (15-30%). Persistent pain is the most common with reports between 10-15%, as well as surgical site infection, seroma, hematoma and ischemic orchitis. (125) Recurrence requiring repair is reported in up to 20 % (126).

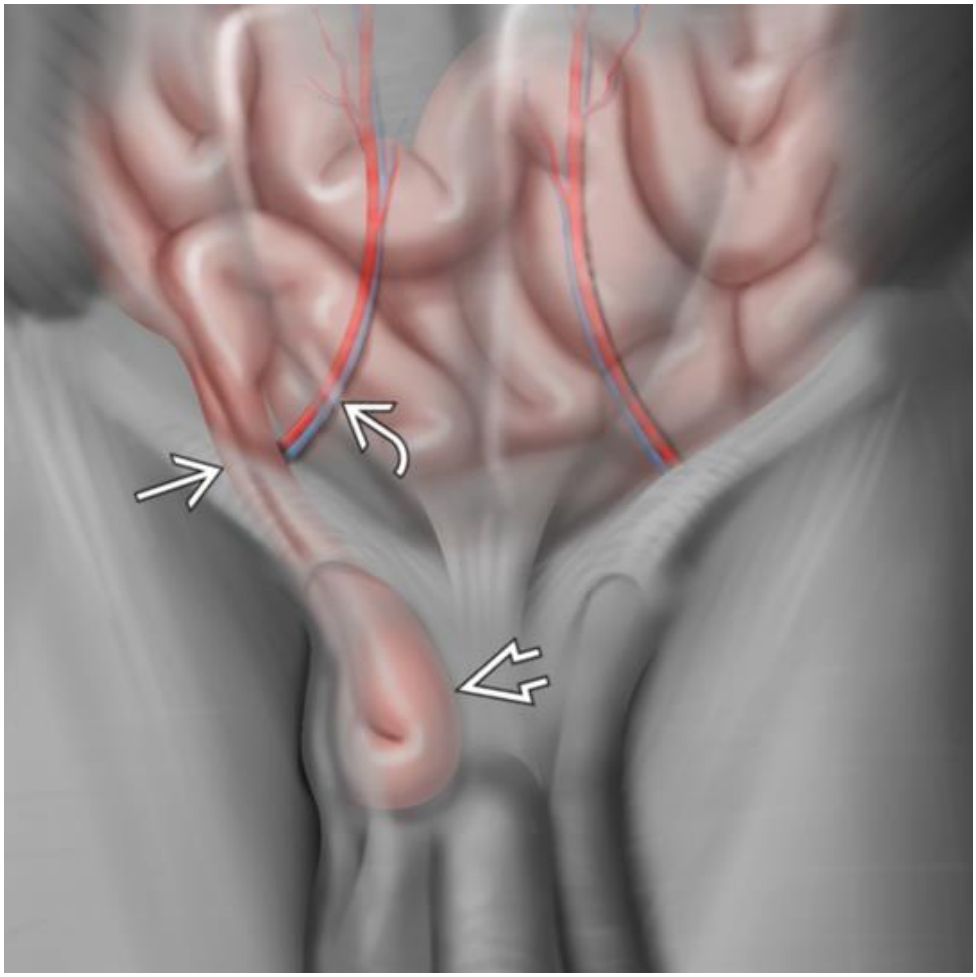

Figure 8. Indirect inguinal hernia with protruding small intestine lateral to the inferior epigastric vein and artery. *Used by permission from Elsevier for thesis non-profit university use.*

2.5 GONADAL STEROIDS – SEX HORMONES

Androgens such as testosterone and estrogens are both considered sex hormones and are present in both genders. In elderly males, testosterone levels decrease and in elderly females estrogen levels decrease. The decrease in sex hormones among aging people causes a lot of symptoms we associate with aging such as decreased muscle volume, dry vaginal mucosa, osteoporosis, and fatigue.

The sex hormones are all derived from cholesterol via different enzymes where progesterone is the precursor for formation of both estrogens and androgens. The most common androgen in males is testosterone formed by the Leydig cells in the testicles, whereas estrogens in women is formed in the ovaries. Smaller amounts are derived from dehydroepiandrosterone (DHEA) that is an inactive steroid formed in the adrenal glands. DHEA serves as a precursor for estrogen and testosterone in targeted cells, an intracellular action called intracrinology. (133) Testosterone and estrogen derived from DHEA are released to the circulation in very limited amounts and have only minor impact on other cells or organs than the cells that formed them. Intracrine sex hormones have a major effect in the cells and tissue where they are formed, both normal and hormone-sensitive neoplastic cells. This is important for treatment of prostate cancer, breast cancer, and gynecological cancer. (132) (133)

2.5.1 Sex hormone's role in wound healing and hernia formation

Androgens and estrogens are considered anabolic, and both play major roles in growth and maturation from childhood to adulthood. (134) They also seem to stimulate wound healing albeit in different ways. Less is known about their role in hernia formation though it has been suggested for many decades that sex hormones are important due to stimulation of muscle and vessel growth by testosterone (doping with anabolic steroids) and stimulation of fibroblasts responsible for development of certain collagens by estrogens. (135). Our findings in Study III supports the hypothesis that sex hormones are important for inguinal hernia formation. Alterations in balance between testosterone and estrogen may cause an imbalance in wound healing and hernia formation, but more research is needed.

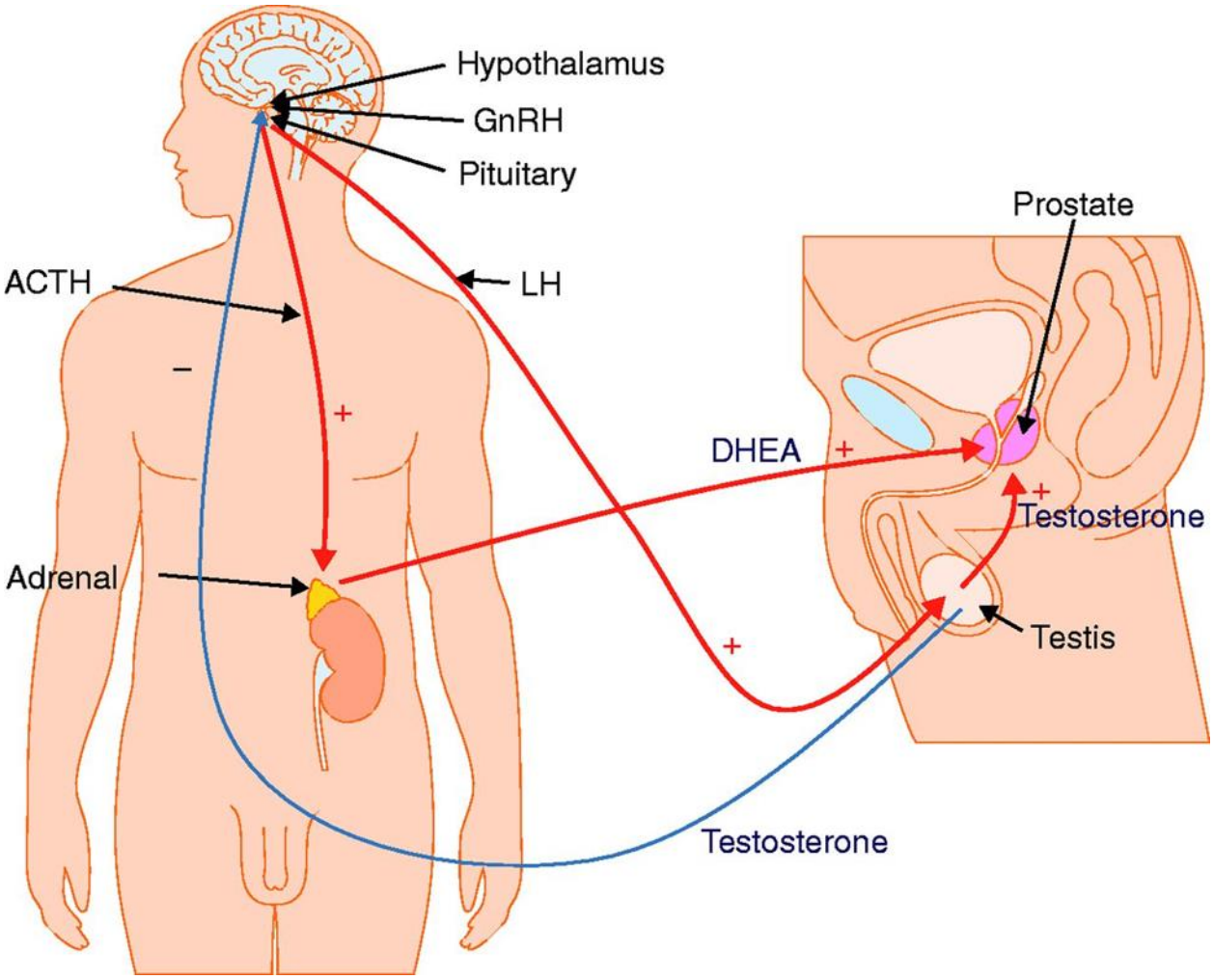

Figure 9. Sources of androgens in the male body. (132) *Used by permission from BioScientifica Limited for thesis non-profit university use*.

Abbreviations: ACTH, adrenocorticotropin; DHT, dihydrotestosterone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone, DHEA, dehydroepiandrosterone

2.6 UROLOGICAL CANCER

2.6.1 Introduction and surgical access

All urological organs are located outside the abdominal cavity i.e., retroperitoneally. To access the organs during cancer surgery, the surgeon may choose to pass through the abdominal cavity, thereby penetrating the peritoneum at one or two times. The last two decades have seen a rapid development of minimally invasive techniques for urological cancer surgery, fueled by the introduction of robot-assisted laparoscopy. The first condition to be targeted with a minimally invasive technique was prostate cancer. The surgical treatment of prostate cancer is associated with high expectation of not only oncological outcome but also of a good functional outcome regarding potency and continence. Since the prostate is situated in the cramped pelvic region, minimally invasive techniques are appropriate for radical prostatectomy. Minimally invasive techniques are also being developed for cystectomy and renal cancer surgery.

The urological cancers comprise around 25% of all cancers diagnosed in Sweden 2019 (136) and figures have been increasing the last 10-15 years due to the elderly population, more radiological techniques available, and opportunistic screening with PSA for prostate cancer.

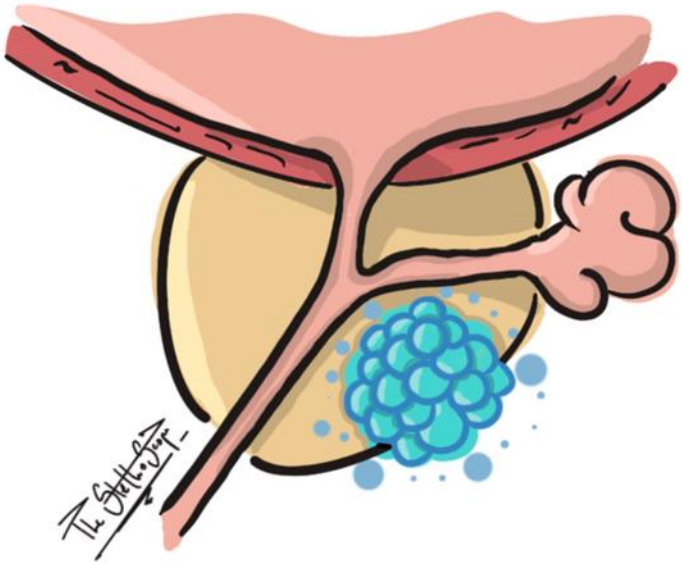

Figure 10 Prostate cancer ©Arad Hosseini

2.6.2 Prostate cancer

Prostate cancer is the most common type of cancer in Sweden. In 2019, the total number of new cases of prostate cancer was 10,984 (136). Altogether 2,313 men died of prostate cancer in Sweden in 2018. The annual incidence of prostate cancer has increased rapidly over the last few decades (age standardized, 1970 and 2019, 82 resp 179 per 100 000), but the mortality rate remains stable (136). Most prostate cancers are detected early due to opportunistic screening with PSA, and most of the men are expected to live many years with their cancer. In many cases men die with prostate cancer, not of it.

Treatment of prostate cancer may be divided into four groups (137)

1) expectancy

2) curative treatment, either with radiation or surgery

3) active surveillance

4) palliative medical treatment with various forms of hormonal and cytostatic treatment.

Hormonal therapy aims at castration since in the early stages, prostate cancer requires testosterone to develop. By decreasing testosterone levels, progress of the cancer may be slowed down.

2.6.2.1 Curative surgical treatment

Radical prostatectomy performed through a midline incision beneath the umbilicus without penetrating the abdominal cavity has been the gold standard for localized prostate cancer for decades. Recently, rapid development of minimally invasive radical prostatectomy has been driven by the availability and development of robot-assisted surgery and has now become the gold standard.

Both methods have the same oncological result and side-effects i.e., erectile dysfunction and incontinence, even though rates are decreasing as the techniques develop (138) (139) (140).

In 2019, 3,113 men underwent surgical treatment for prostate cancer in Sweden (136). Since the vast majority will not die of their prostate cancer, not only the oncological outcome but also the functional outcome is of great importance. The postoperative erectile function and continence have been thoroughly investigated and are recognized as major issues regarding outcome after prostate cancer surgery. Less is known about incisional hernia after radical prostatectomy, but it has been reported that the rate of inguinal hernia after radical prostatectomy is 5-15%. Others report the incidence to be higher after open radical prostatectomy than after minimally invasive procedures (127), whereas others report the other way around or no difference in incidence when comparing the two surgical techniques (138) (141). The cause of inguinal hernia is not known. It has been speculated that the nerve innervation of the inguinal region is compromised, thereby creating a weakness in the pelvic floor.

2.6.2.2 Hormonal treatment

For men with metastasizing prostate cancer and men with life expectancy less than 10-15 years, no curative treatment should be offered due to the side-effects of treatment. If the patient experiences symptoms or the prostate cancer is widespread, hormonal therapy is the first step of treatment. Hormonal treatment i.e., androgen deprivation therapy (ADT), aims to reduce the impact of testosterone on the prostate cancer. It is achieved either by blocking the gonadotropin-releasing hormone (GnRH) pathway, by blocking androgen receptors in the prostate with anti-androgens (AA), or by surgical removal of the testicles. Anti-androgens have less impact on other organs than drugs blocking the GnRH pathway. Blockage of the gonadotropin-releasing hormone (GnRH) pathway is achieved with a GnRH agonist or antagonist. GnRH agonists and antagonists have the same effect on serum testosterone after a couple of weeks, with a fall in level to <0.4 ng/dL and are considered as medical castration. (142). In healthy males, S-testosterone normally ranges from 270-1070 ng/dL (143). Blockage of androgen receptors with AA does not affect the level of testosterone in serum but prevents testosterone from stimulating the prostate cancer cells.

The third way of eliminating testosterone is surgical castration by bilateral orchidectomy, resulting in castration within hours. Orchidectomy is cost-effective and is good for the patient since no medical administration regarding prostate cancer is needed afterwards and therefor also limits the potential side effects.

Since small amounts of androgens are produced in other organs, a GnRH agonist or antagonist can be combined with an androgen receptor blocker (anti-androgens) to maximize the effect on the prostate cancer.

All three forms of hormonal treatment have side-effects including hot-flushes, dysthymia, muscle atrophy and weakness, sweating, and nausea. Breast enlargement and tenderness is a common side-effect of anti-androgens.

Figure 11. Robot-assisted minimally invasive surgery for renal cell carcinoma surgery performed at Karolinska University Hospital, Huddinge September 2021.

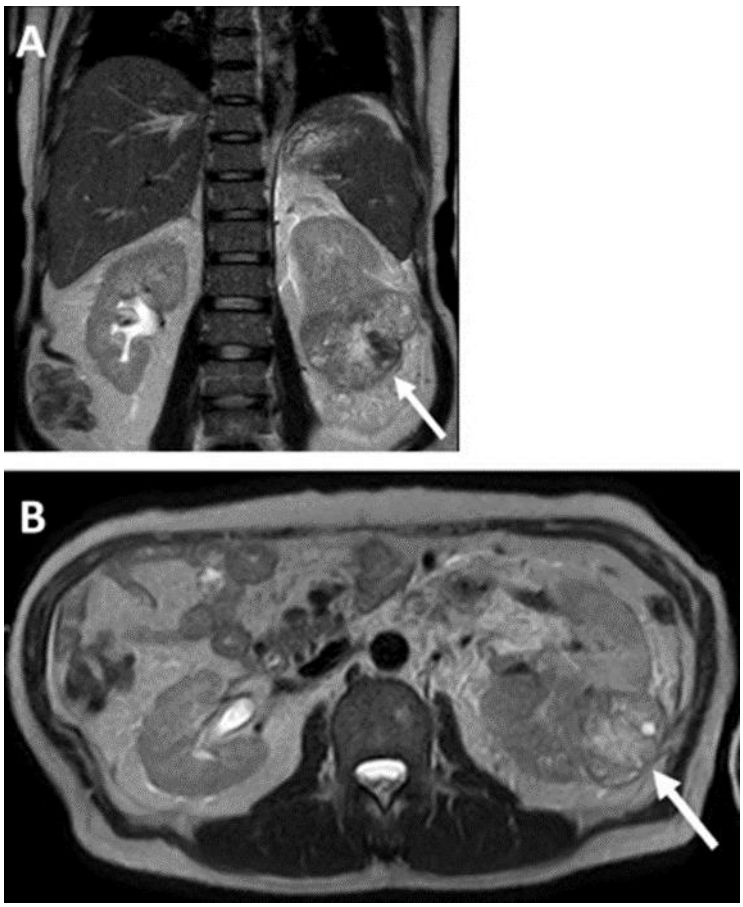

Figure 12 MRI of left-sided dorso-caudal renal cell carcinoma A axial, B sagittal

2.6.3 Renal cell carcinoma

In 2018, there were 1,300 new renal cell carcinomas diagnosed in Sweden (136). During the same year, 508 persons died of renal cell carcinoma. In 2018 the age-standardized incidence of renal cell carcinoma was 16 per 100 000 in men and 8 per 100 000 in women. Altogether 1,730 persons underwent surgery for suspected renal cell carcinoma in 2018. (136) Not all patients that undergo surgery for suspected renal cell carcinoma are finally diagnosed with renal cell carcinoma, resulting in more surgical procedures being performed than cases diagnosed. Examples of benign tumors are angiomyolipoma and oncocytoma. There are also other cancers such as urothelial carcinoma in the upper urinary tract and lymphoma in the kidneys at histopathology examination, that were deemed renal cell carcinoma at the preoperative investigation. Some patients also undergo more than one procedure for their cancer for various reasons. Renal cell carcinoma accounts for around 3 % of all diagnosed cancer each year in the European Union. (144) Approximately 65% of RCCs are diagnosed in men, usually between 60 and 80-years-of-age. It is a rare disease before 40 years. The incidence is increasing in both genders due to an aging population and a more widespread use of radiological examinations yielding more incidentally detected tumors. Of all renal cell carcinomas with a size less than four centimeters, 80% were incidentally diagnosed when radiological examinations were done for other reasons (145)

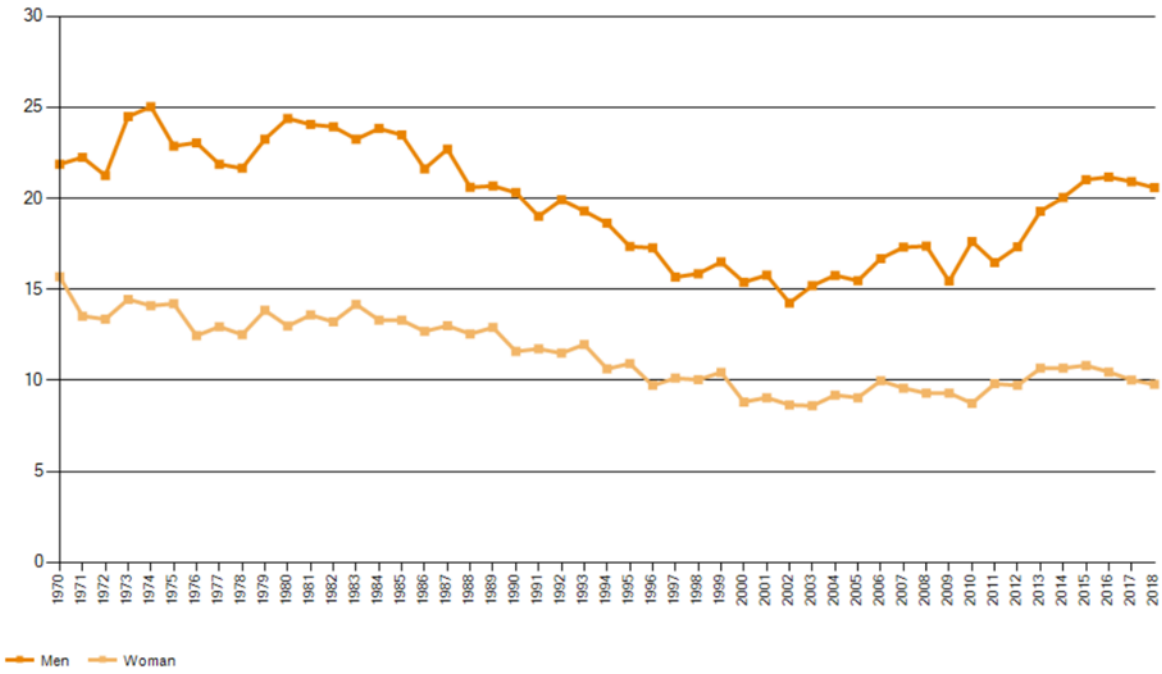

Figure 13. Age standardized (age 18-85+) incidence per 100 000 of the population in Sweden 1970-2018. (145)

Mortality rates have been the same for many years but have recently begun to decrease. Survival is related to the tumors stage at diagnosis. The estimated 5-year cancer-specific survival rate is 85% if the RCC is non-metastatic at diagnosis and 16% in patients with metastases at diagnosis. (146)

The most important risk factors for renal cell carcinoma development are smoking and morbid obesity. It is believed that smoking is the cause of 30% of all renal cell carcinomas. Other known risk factors for RCC are hypertension and renal cyst due to renal failure. Hereditary RCC accounts for 5-8% of all diagnosed renal cell carcinomas and is often associated with other cancer forms.

There is no way of differentiating a renal cell carcinoma from a benign renal tumor on radiological examination. Biopsies are not always trustworthy since there may be mixed benign and malignant cells. Common benign tumors of the kidney are angiomyolipoma and oncocytoma, and about 25% of all surgically treated radiologically suspected RCCs turn out to be benign on histopathology examination. Surgery is the only cure for RCC. The tumor is localized at diagnosis in 85% of cases, and treatment is aimed at radical removal of the tumor. Localized renal cell carcinomas are usually removed by radical nephrectomy or by nephron-sparing techniques such as partial nephrectomy. In frail patients, thermal ablation for small RCCs is an option. Surgery can be performed openly or with a minimally invasive technique such as laparoscopy, robot-assisted laparoscopy or hand-assisted laparoscopic surgery, as well as thermal ablation.

The kidney may be accessed through the abdominal cavity or through a retroperitoneal approach, with either an open or minimally invasive technique. Open surgery for renal cell carcinoma is usually performed through an incision below the 11th rib, providing wide exposure of the kidney for both retroperitoneal and transperitoneal techniques. A disadvantage of this incision is the trauma inflicted by the incision itself and the retractors applied during surgery on the sensory and motor nerves in the abdominal wall, which can lead to pain, paresthesia, and muscle weakness below the incision resulting in bulging (64) (62) (63). As mentioned above, transverse incisions are associated with less risk for incisional hernia, but once they develop, transverse incisional hernias cause more symptoms and are more difficult to repair. (23)

Since the introduction of minimally invasive surgical techniques and the introduction of robot-assisted minimally invasive surgical techniques, an increasing number of procedures are now carried out using minimally invasive surgery. The European Association of Urology (EAU) as well as the American Urological Association (AUA) recommend partial nephrectomy for stage T1 and T2 tumors (147) (148). Most recent Swedish guidelines regarding RCC state that at least 50% of all stage T2 tumors should undergo minimally invasive partial nephrectomy. (145) The combination of these recommendations, development of surgical techniques, and the ambition to spare nephrons have led to the increase in the number of partial nephrectomies performed in Sweden over the last ten years. Since most of the tumors diagnosed and treated are stages T1 or T2 with very low risk for metastasizing, cancer-specific survival rate is over 90%. It is thus important not just to consider the oncological outcome after different surgical methods but also the side-effects affecting quality-of-life. A Norwegian study (149) showed that patient that had undergone surgery for RCC with an open technique had a lower health related QoL (HRQoL) than the control population (4.9 years median follow-up). Patients operated with a minimally invasive technique reported no reduction in HRQoL. Even less is known about abdominal wall complications after minimally invasive RCC surgery compared to open surgery. In Study II, the rate and risk factors for incisional hernia after various surgical approaches were investigated. In Study IV, we investigated the abdominal wall pain and muscle atrophy after open surgery for suspected renal cell carcinoma.

2.7 SWEDISH POPULATION-BASED REGISTERS

Sweden is one of the countries with the most extensive registers regarding the entire population. The Swedish unique personal identity number enables the various registers to be cross-linked. Registers of interest to research may be divided into four categories: national public authority registers, quality records in healthcare, biobanks and researched generated data.

The national public authority registers and quality records in healthcare are managed by Statistics Sweden (SCB) and the National Board of Health and Welfare. These registers are used for official statistical publications by the government as well as for epidemiological research. All information in the registers is guarded by absolutely secrecy. Exceptions are made only for research purposes when data cannot be linked to the individual or cause suffering to the person or relatives. Once a year, Swedish citizens have the legal right obtains the information about themselves that has been stored in the registers.

The healthcare quality registers contain information about specific aspects of healthcare such as diagnoses, treatments, and outcomes. These registers are used to follow-up and improve healthcare and for epidemiological research.

Biobanks are not registers as such, but the other registers are linked with the various biobanks. Biobanks store specimens; mostly from clinical pathology or microbiology. Biobanks were not used in the studies in this thesis.

Research generated data registers are used to link several registers to a predefined cohort and cases matched by personal identity numbers. These registers can thus be used for special research projects. There is no complete list of all available research-generated data registers, but examples are Renal Cell Cancer Database Sweden (RCCBaSE) and Prostate Cancer Database Sweden (PcBaSE4) which were used in Study II and Study III respectively.

National public authority registers were used in Studies I, II, and III, including the Swedish Cause-of-Death Register (CDR), the Swedish National Cancer Register, and the National Patient Register (NPR) where all diagnoses and surgical treatments conducted within hospital settings as well as outpatient procedures are registered. Healthcare quality registers such as the National Swedish Kidney Cancer Register (NSKCR) were also used. These registers were mostly used together with RCCBaSE and PcBaSe4. In Study IV, we used data from a local trial.

2.7.1 Prostate Cancer Database Sweden (PcBaSe4)

PcBaSe4 is a research-generated population-based register where 98% of all diagnosed prostate cancers have been recorded since 1998. It was set up in 2008 when data from the National Prostate Cancer Register (NPCR) were linked with several other population-based registers. In the PcBaSe4 Sweden there is also a prostate cancer-free cohort matched by year of birth from the background population (150) (151).

2.7.2 Renal Cell Cancer Database Sweden (RCCBaSE)

RCCBaSE is a relatively new research-generated register set up in 2015. It is based on the National Swedish Kidney Cancer Register (NSKCR). NSKCR is linked with several population-based registers. A total of 9,416 cases of renal cell carcinoma were registered between 2005 and 2014 with a coverage rate between 2008 and 2017 of 99.5% when compared with the Swedish Cancer Register that is obligatory (152) (153). As a reference population, each case is matched with ten renal cell cancer-free controls matched for age, gender, and place of residence at time of diagnosis.

3 RESEARCH AIMS

I. To determine the rate of incisional hernia after surgery for prostate cancer or renal cell carcinoma and to compare rates after open versus minimally invasive surgery. To determine risk factors for developing incisional hernia.

II. To evaluate whether men on androgen deprivation therapy (ADT) for prostate cancer have a higher risk for developing inguinal hernia than men with prostate cancer but without ADT.

III. To expand our understanding of how the degree of muscle atrophy evolves over time after open renal cell carcinoma surgery and how it relates to pain from the abdominal wall.

4 MATERIALS AND METHODS

4.1 PATIENTS AND METHODS

Study I: The cohort comprised all men undergoing radical prostatectomy between 1st January 2004 and 31st December 2013 (n=19,743). They were grouped into open radical prostatectomy (ORP) and minimally invasive radical prostatectomy (MIRP) (n=11,485 resp. n=8,258). We used the Swedish National Prostate Cancer Register (NPCR) to identify the cohort. NPCR was linked with the National Patient Register (NPR), to identify relevant comorbidity prior to radical prostatectomy, and diagnosis or treatment for incisional hernia (ICD-10 codes K43.0-K43.9) and intervention codes JAD10-JAD87) after radical prostatectomy. NPCR was also linked to the Swedish Cause-of-Death Register (CDR).

Primary outcome was diagnosis or treatment for incisional hernia, and predictors of interest were the two surgical approaches. Clinical tumor stage, prostate volume, lymph node dissection, and year of surgery were covariates.

Time-to-event analysis was used to calculate the risk for incisional hernia, where time of radical prostatectomy applied as entry point to the cohort and endpoint was diagnosis or treatment for incisional hernia. Death or loss to follow-up were censoring events. Rate of inguinal hernia was calculated using Cox proportional hazard analysis. Multivariate cox proportional hazard regression analysis was used to analyze potential risk factors.

Study II: The RCCBaSE was used to identify the cohort consisting of all patients undergoing surgery for renal cell carcinoma (RCC) (n=6,417. Female n=2,415. Male n=4,002) between November 2005 and March 2015.

Diagnosis or treatment for incisional hernia after surgery for RCC was the primary outcome. Predictors of interest were open or minimally invasive approach. Covariates were radical or partial nephrectomy, tumor stage, affected side, gender, age, transperitoneal or extraperitoneal approach, and year of surgery. Death or loss to follow-up were censoring events.

To determine the impact of surgical approach on the risk for incisional hernia, a time-to-event analysis was used. Date of RCC surgery was used as entry point to the cohort. Diagnosis or treatment for incisional hernia was treated as endpoint. To calculate the cumulative rate Kaplan-Meier survival analysis was used. Multivariate Cox proportional hazard regression analysis was used for analysis of risk factors.

Risk categories	Definition
Localized prostate cancer	
Low risk	T1-2, Gleason score 2–6 and PSA <10 ng/ml
Intermediate risk	T1-2, Gleason score 7 and/or PSA 10 to <20 ng/ml
High risk	T3 and/or Gleason score 8–10 and/or PSA 20 to <50 ng/ml
Regional metastasis	T4 and/or N1 and/or PSA 50 to <100 ng/ml in the absence of distant metastases (M0 or Mx)
Distant metastases	M1 and/or PSA ≥100 ng/ml

Table 2. Prostate cancer risk categories from the Prostate Cancer Database Sweden (PcBaSe) based on a modification of the guidelines of the National Comprehensive Cancer Network (NCCN) (from Study III)

Study III. PCBaSE4 was used to identify all men in Sweden diagnosed with prostate cancer that had not been treated with curative intent between 1st January 2008 and 31st December 2016 (n=30,823). Out these, 1,324 men were found to have been diagnosed or treated for inguinal hernia (ICD-10 K40.0-K41.9 resp. intervention codes JAB00-JAB80, JAC10-JAC40) at least six months after prostate cancer diagnosis.

Nested case-control study design was used to estimate the odds ratios (OR) by using conditional multivariate logistic regression.

Exposure was defined as hormonal treatment for prostate cancer. Diagnosis or treatment for inguinal hernia was considered as endpoint. All odds ratios were adjusted for marital status, education level, prostate cancer risk category, Charlson Comorbidity Index (CCI), total time on hormone treatment, type of hormone treatment, time from prostate cancer diagnosis, and primary prostate cancer treatment. All men with inguinal hernia (cases) were matched with ten controls by year of birth only.

Study IV. Between 1st September 20016 and 30th October 2019, 50 patients planned to undergo open surgery for suspected renal cell carcinoma (RCC) performed at Karolinska University Hospital, Huddinge, were included in a prospective cohort study after informed consent. The patients were asked to fill in a questionnaire regarding general health prior surgery and three months after surgery with an extra question about pain from the abdominal wall. Forty-three patients had at least one postoperative Computer Tomography (CT) and were included in the final cohort. CT was used to measure the thickness of the abdominal wall on the surgical side as well as the non-surgical side prior to surgery, and at least once

after surgery. Dependent samples t-test was used to analyze differences between the surgical and non-surgical side of the abdominal wall regarding muscle thickness and attenuation values. Repeated measures ANOVA of the mean abdominal wall thickness on both the non-surgical side and the surgical side was used to assess change in thickness over time. Patient-reported abdominal wall pain was correlated to gender, age (<65 year and >65 year), and degree of postoperative decrease in muscle thickness (>30 % decrease or <30% decrease) with ordinal regression to calculate the odds ratio (OR).

4.2 STATISTICAL ANALYSES

4.2.1 Regression models

Different types of regression models were used to estimate how independent variables (also called factors, exposures, predictors, or covariates) were related to a dependent variable (outcome). Regression models were mainly used to predict an outcome depending on the included predictors or, in some cases, to reveal causal relationships between outcome and predictors.

That are several different types of regression model. The most commonly used as well as the most straightforward model is linear regression which is used to determine the linear relationship between two (or more) continuous variables, and to predict the outcome based on the predictors.

In mathematical terms this is stated as:

$$Y = \beta 0 + \beta 1X + \varepsilon$$

where Y, is the outcome; $\beta 0$ is the intercept; $\beta 1$ is the slope coefficient; X is the predictor, and ε is the sample error.

Other commonly used regression models are multiple logistic regression, Poisson-regression, logistic regression, and several more depending on the data available.

4.2.1.1 Conditional multivariate logistic regression

Conditional multivariate logistic regression is a modification of logistic regression where matching is taken into consideration to control for confounding (variables that influence both the dependent and independent variable) and where the outcome variable is dichotomous i.e., has only two possible outcomes such as “yes” or “no”, “disease” or “no disease”. Predictor variables can be of any form. An odds ratio (OR) is calculated from the conditional multivariate logistic regression. OR is the strength of association between an outcome and an exposure, implying that the odds of outcome occur in the presence of the exposure divided by the odds of outcome occurring in the absence of the exposure. OR = 1 means that the outcome and the exposure are independent of each other i.e., the odds of the outcome are the same regardless of exposure or not. An OR >1 means that there could be a correlation between the outcome and the exposure i.e., exposure increases the odds of the outcome occurring. Inversely OR<1 implies that exposure may prevent the outcome occurring.

Conditional multivariate logistic regression was used in Study III to calculate the OR between inguinal hernia and hormone treatment for prostate cancer.

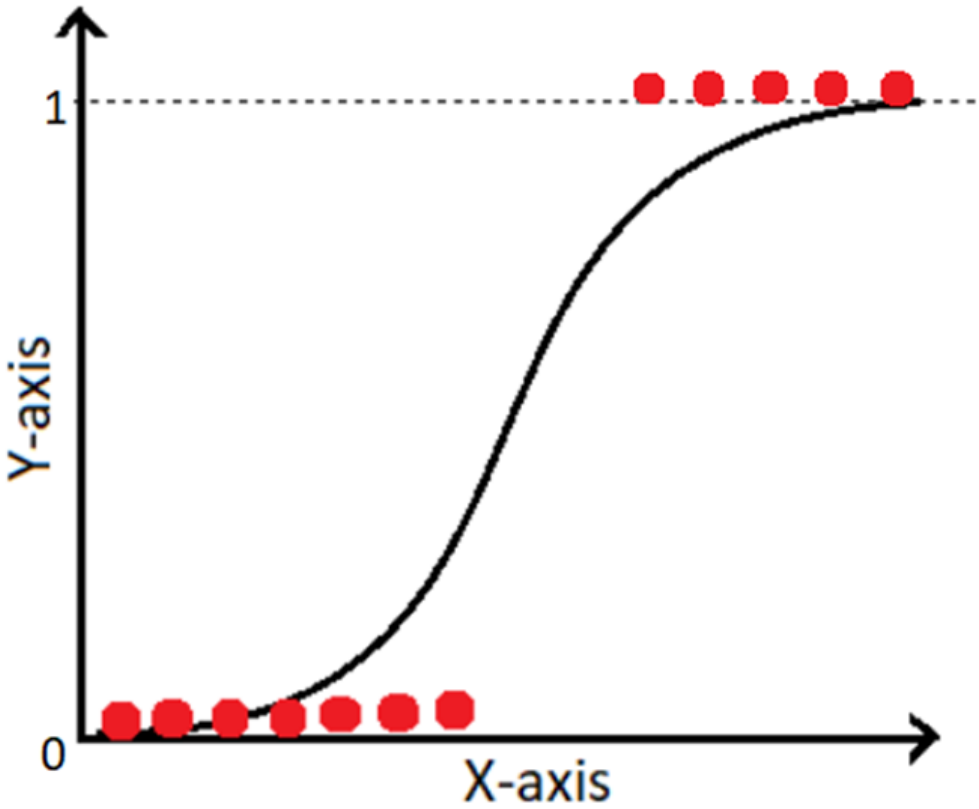

Figure 14. S-formed curve in logistic regression defined as P(Y=1|x)=1/((1+e^(-y))

4.2.1.2 Ordinal logistic regression

Ordinal logistic regression is a generalization of either multiple linear regression or binominal logistic regression and is used to determine which of the independent variables (if any) has a significant effect on the dependent variable e.g., outcome. The ordinal logistic regression model can also determine how well the model predicts the dependent variable.

In order to conduct ordinal logistic regression, four assumptions must be considered: 1) One dependent (outcome) variable that is measured at the ordinal level; 2) One or more independent variables (predictors) that are continuous, ordinal, or categorical. Ordinal independent variables should be distributed so that they can be treated as continuous; 3) There should be no multicollinearity. Multicollinearity occurs when there are two or more continuous independent variables that are strongly correlated to each other making it hard to see in which way each independent variable contributes to the outcome; and 4) Each independent variable must have the same impact on each incremental step of the outcome i.e., proportional odds. If all assumptions are met, ordinal regression can be used to calculate the odds and how well the model works to predict the outcome variable.

Ordinal logistic regression was used in Study IV. Outcome in that case was level of pain in the abdominal wall after open surgery for suspected renal cell carcinoma. As independent variables (predictors), we used age at surgery, gender, and change in abdominal wall thickness comparing preoperative thickness of the abdominal wall with thickness approximately six and eighteen months after surgery.

4.2.1.3 Cox regression

Cox regression is a statistical method for determining time-to-event data, using a survival function that predicts the probability of an event occurring given a time for the included predictors. To use this model, the variable should be independent, and the hazard should not vary over time. Cox regression was used in Studies I and II to determine the hazard ratios for each defined risk factor for developing incisional hernia after prostate cancer surgery or surgery for renal cell carcinoma.

4.3 SURVIVAL ANALYSIS

4.3.1 Kaplan-Meier method

The Kaplan-Meier method estimates the probability of the outcome over a defined time period; time-to-event. The Kaplan Meier method, often referred to as a survival analysis, estimates the probability of the outcome not occurring during a defined time period. To run a Kaplan Meier analysis: 1. The outcome should either be the event occurring or participant being censored. Each subject can only reach one outcome, either event occurring or censoring, not both; 2) The survival time (time to event or time to censorship) should be clearly defined and precisely measured; and 3) The event and censoring must be independent of each other and the censoring event must occur in a similar pattern in all groups tested.

We used the Kaplan-Meier method in Studies I and II to estimate the cumulative rate of incisional hernia after prostate cancer surgery and surgery for renal cell carcinoma.

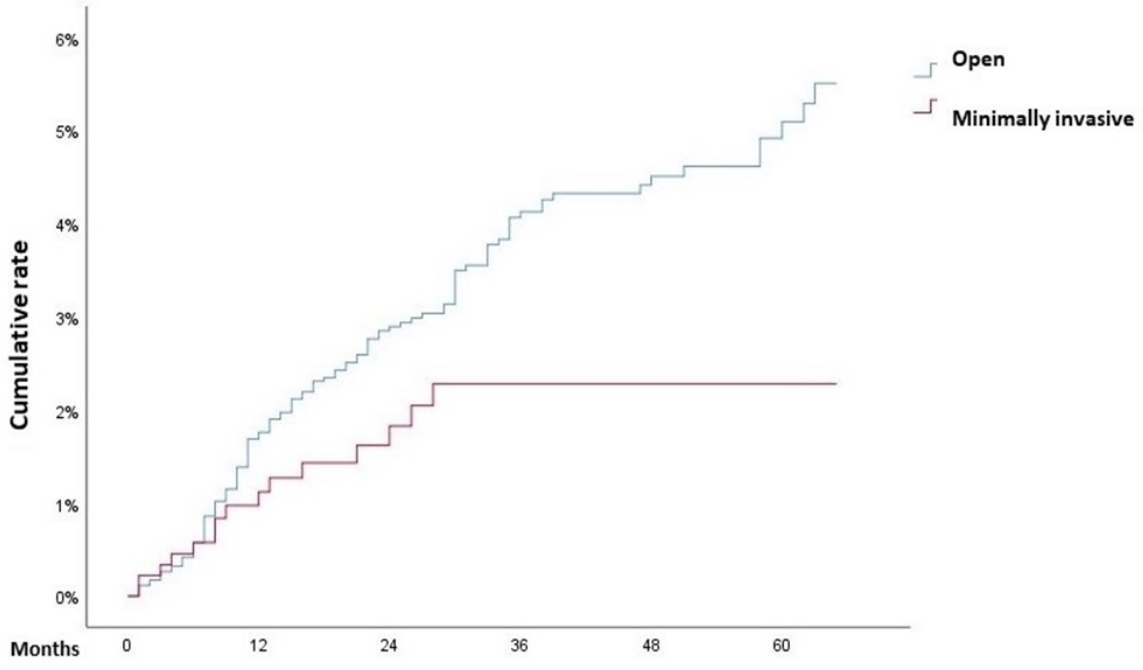

Figure 15. Kaplan-Meier survival analysis of probability of incisional hernia among patients operated with either open or minimally invasive technique for renal cell carcinoma. Figure from Study II.

4.4 DIFFERENCES BETWEEN GROUPS

4.4.1 T-test

T-test is a parametric test for expected mean difference between groups. It tests whether data follow students t-distribution under the null hypothesis. T-test can be used to see if the means from two data sets significantly differ from each other, reported as T-statistic and a p-value. The means of the two data sets should follow the normal distribution and the data sets should have the same variance. Data used in the t-test should be totally independently sampled or totally paired. If measurements are dependent, samples are tested repeatedly, samples are paired, or if samples are matched, dependent sample tests should be used instead.

4.4.1.1 Dependent samples t-test

The dependent samples t-test compare means of different measurement in one group, the measurement must be paired with measurements from another group which is why it is also called paired t-test. The null hypothesis of dependent samples t-test is that the population mean difference between the paired values is zero. The alternative hypothesis is that the population mean difference between the paired values is not zero. The results from the dependent samples t-test will state if the null hypothesis is rejected or not, and if the alternative hypothesis can be rejected or accepted. From a dependent samples t-test, point estimate and confidence interval of the mean difference between the two groups can be calculated. It will also give the significance of the difference and a measure of the effect size. We used the dependent sample t-test to analyze differences between the surgical and non-surgical side of the abdominal wall regarding thickness and attenuation values.

4.4.2 Analysis of Variance (ANOVA)

ANOVA analysis is used in the simplest way to determine whether there is a significant difference between the means of two or more independent groups.

4.4.2.1 Repeated measures ANOVA

The repeated measures ANOVA detects any difference between means of related observations, it must also include at least one independent variable. The measure of one observation must be directly linked with measures of all other observations. Repeated measures ANOVA can be used to investigate changes in means over three or more points in time or differences in means under three or more different conditions. Null hypothesis for repeated measures ANOVA states that the related means are equal at all observations and the alternative hypothesis states that there is a difference in related means in at least one observation. Repeated measures ANOVA evaluates the significance of the difference between related means reported as F-statistic and p-value. Repeated measures ANOVA is considered as an extension of the dependent t-test as it handles independent variables as well.

4.4.3 Shapiro-Wilk’s test

A Shapiro-Wilk´s test, is a normality test, that tests for normality i.e., does the data set have a normal distribution in frequentist statistics. The null hypothesis in Shapiro-Wilk´s test is normality. So, if the null hypothesis is not rejected the data are distributed close to normal and have no outliers. We used Shapiro-Wilk’s test together with boxplots and histograms to see the distribution of data in Study IV.

4.4.4 Levene's test

Lavene´s test handles the equality of variances for a variable calculated for two or more groups. The null hypothesis for Lavene´s test is that the population variances are equal (called homoscedasticity). If the p-value of the test is non-significant it concludes that there is a difference in the variance and the null hypothesis is rejected. T-test typically assumes homoscedasticity and Levene's test can be used to assure homoscedasticity, as in Study IV, before analyzing the results by repeated measures ANOVA analysis.

4.4.5 Mauchly's Test of Sphericity

Mauchly's Test of Sphericity tests the assumption of sphericity (that the variances of the differences between all combinations of related groups are equal). Null hypothesis is that the variances of the differences are equal. If the Mauchly's Test of Sphericity is significant ($p < .05$) it means that sphericity has been violated.

4.4.6 Greenhouse-Geisser correction

Greenhouse-Geisser correction adjusts for violated sphericity in repeated measure ANOVA by estimating the degree of sphericity that should be used for the calculations. We used it for correction of sphericity before analyzing the results with repeated measures ANOVA in Study IV.

4.4.7 Intra Class Correlation Coefficient (ICC)

Intra class correlation coefficient describes how well measures in the same group resemble each other. ICC was used in Study IV to calculate conformity between the two radiologists when measuring the thickness of the abdominal wall.

4.4.8 Bonferroni correction

The Bonferroni correction is used to decrease the risk for type I error when testing multiple hypotheses. It sets the significance level at a lower cut-off meaning that fewer of the hypotheses tested will fall out as significant when they are not significant. The correction is set by dividing the preferred p-value by the number of hypotheses tested. Bonferroni correction was used when comparing abdominal wall measurements in Study IV.

4.5 STUDY DESIGN

This thesis is written in the field of epidemiology. Epidemiology is briefly explained as “the study of anything that happens to people” or more scientifically “science concerned with the study of the factors determining and influencing the frequency and distribution of disease, injury, and other health-related events, and their causes, in a defined human population.“

In order to conduct epidemiological research, there are several types of study design that are used.

For Studies I and II in this thesis, we used a retrospective cohort study design, for Study III we used a nested case-control study design, and in Study IV we used a prospective cohort design.

4.5.1 Cohort study design

In a cohort study design, a defined group of people are followed over time for a certain outcome to occur in the presence of a certain exposure. The frequency of the outcome i.e., the rate of the outcome occurring over a defined time span is measured in relation to the exposure. In this way the relative risk can be calculated as the effect of the exposure on the outcome. The advantage of cohort studies is that it is possible to study several outcomes and exposures in the same cohort. In retrospective cohort studies, especially when using register data, the collection of data is already complete. Register studies are thus not as time consuming and expensive to conduct as studies with other designs. Cohort studies may suffer from selection bias as a confounding by indication. A major disadvantage is that a cohort study cannot prove casual effect since the exposure has not been randomly allocated and the outcome thus may be explained by other variables that may differ between exposed and non-exposed groups and have an association with the outcome, so called confounders. Confounders, if known, can be adjusted for in the analysis. Unknown confounders or bias can exert unknown effects on the results and conclusion of the study. We used a retrospective cohort study design in Studies I and II and a prospective in Study IV.

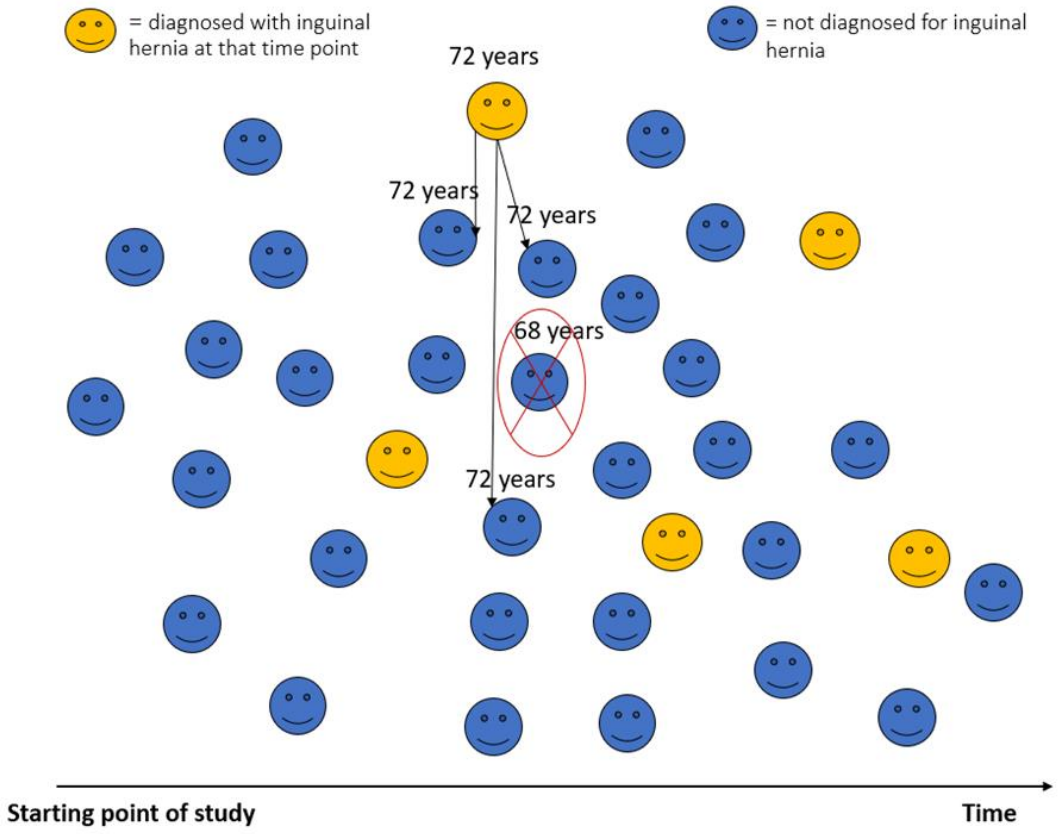

Figure 17. In a nested case-control study, cases are matched with controls when the outcome appears. This figure shows how the study group in Study III was assembled. The case could be matched with all men 72 years-of age that had not, at the time of the case's diagnosis of inguinal hernia, been diagnosed with inguinal hernia, as control

4.5.2 Nested case-control study design

A nested case-control study is a case-control study performed on a defined cohort, meaning that cases and controls are from the same cohort and the controls are chosen independently of the exposure.

By using a nested case-control study design, selection bias can potentially be reduced, since both cases and controls are from the same cohort. The design is suitable for studying rare outcomes but not rare exposures. If previously collected data are used, the nested case-control study is more time effective and cheaper to conduct. A possible disadvantage is reduced power due smaller sample sizes.

To analyze the data collected in a nested case-control study, the sample model must be taken into consideration to avoid biased estimates. Conditional logistic regression is one way to assess the sampling in a nested case-control study.

We used a nested case-control design in Study III

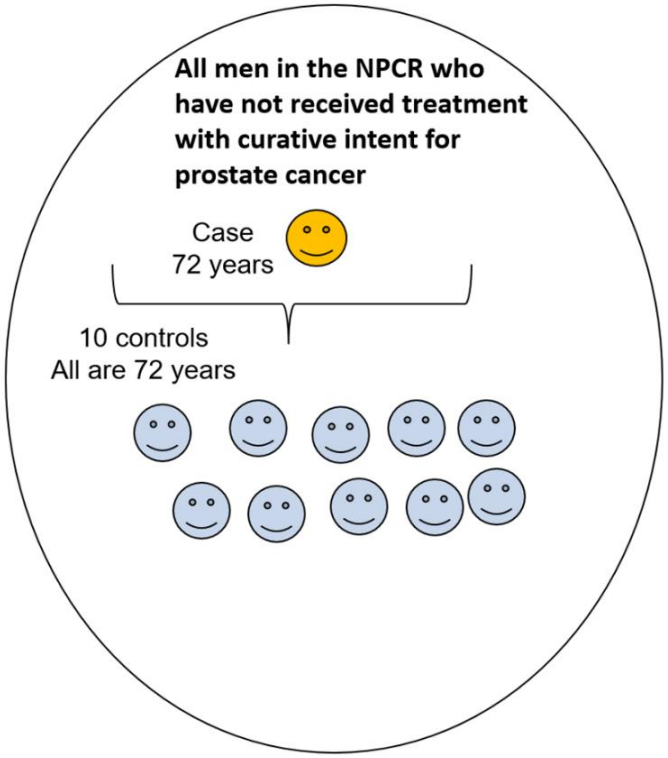

Figure 16. Nested case-control study design from Study III where cases and controls were chosen from the same cohort in the PvBaSe4 consisting of all men that had not received treatment with curative intent for prostate cancer i.e., no surgery, no radiation. Cases and controls were matched by age only when the outcome was analyzed, in this case inguinal hernia.

4.6 ETHICAL CONSIDERATIONS

In Study I, II, and III, we used large population-based registers in a retrospective study. Major ethical considerations when using registers are the integrity and autonomy of the patients. In Sweden, residence registration of all residents is regulated by the government. You cannot refuse being registered in a National authority register. Once a year, a person can demand to see where they are registered and what is registered. All data in national authority registers are stored on secured servers. Data extracted from the registers are routinely anonymized. To obtain consent from all patients in larges studies such as Study I, II, and III would be extremely time-consuming and practically impossible.

In Study IV, sampling was performed at Karolinska University Hospital Huddinge. All patients were asked to sign an informed consent form before inclusion. All patient data were anonymized and stored at the Region Stockholm server with the same security routines as all patient data at the hospital. Although the patients included gained no benefit from participating in the study, our intention was to improve management of future patients undergoing surgery via a flank incision, not only urological surgery but also in general, transplant, gynecological and cardiovascular surgery.

All studies had consent from the Swedish Ethics Review Authority before they were conducted.

5 RESULTS

Study I: During the study period 1st January 2004 to 31st December 2013, 19,743 men underwent radical prostatectomy in Sweden. Open radical prostatectomy (ORP) was performed in 11,485 (58%) and minimally invasive radical prostatectomy (MIRP) in 8,258 (42%). In all, 358 men were diagnosed with or had surgery for incisional hernia at the end of the study period. Five years after ORP resp MIRP the cumulative rate was 1.4% (CI 95% 1.2-1.7%) and 2.7% (CI 95% 2.3-3.2%) respectively. Risk factors for incisional hernia in the ORP group was age above 63 years (median, $p < 0.001$) and in the MIRP group age above 62 years (median), lymph node dissection and prostate volume above 38 ml (median, all $p < 0.05$) was associated with higher risk for incisional hernia development.

Study II. The final cohort comprised of 6,417 patients that had undergone renal cell cancer surgery between November 2005 and March 2015. Of those, 5,216 (81%) had undergone open surgery and 1,201 (19%) minimally invasive surgery. By the end of the study, 140 (2,2%) had been diagnosed with incisional hernia, including 124 (89%) in the open surgery group. Five years after surgery, the cumulative rate of incisional hernia for the full cohort was 4.5 % (CI 95% 3.6%-5.4%), 2.4% (CI 95% 1.0%-3.4%) after minimally invasive and 5.2% (CI 95% 4.0%-6.4%) after open surgery. Open or minimally invasive surgical approach had a significant impact on incisional hernia development with a HR 1.74 (CI 95% 1.02-2.98) but no other covariates had a statistically significant impact on the cohort. Univariate analysis showed an increased risk for incisional hernia for surgery performed on the left side HR 1.46 (CI 95% 1.02-2.09) and age above 55 years ($p = 0.04$) in the open surgery group. No risk factor for incisional hernia development was found in the minimally invasive group.

Study III. The cohort consisted of all men diagnosed with prostate cancer in Sweden between January 1st 2008 and December 31st 2016, that had not received treatment with curative intend for prostate cancer. In all, 1,324 men were identified that had been diagnosed with or treated for inguinal hernia before 31st December 2017. The cases were matched with ten controls from the same cohort. We used a conditional multivariate logistic regression model to calculate odds ratios (OR). Exposure was any prior hormone treatment for prostate cancer, endpoint was diagnosis or repair of inguinal hernia. We adjusted for marital status, education level, prostate cancer risk category, Charlson Comorbidity Index (CCI), total time on hormone treatment, type of hormone treatment, time from prostate cancer diagnosis, and primary prostate cancer treatment. After at least nine years of hormone treatment with GnRH, the OR for inguinal hernia was 3.32 (CI 95% 2.33-4.73) and hormone treatment with GnRH for less than seven years or monotherapy with antiandrogens were associated with decreased risk for diagnosis or treatment of inguinal hernia (table 3). Cases had lower prostate cancer risk, were more often under active surveillance as primary treatment, and had lower CCI than controls, indicating better general health than controls.

Study IV. Altogether 43 patients who had given informed consent were included in the final cohort. These patients were planned to undergo open renal cell carcinoma (RCC) surgery with a transverse incision below the costal arch between January 2016 and December 2019. They were found to have a statistically significant decrease in abdominal wall thickness at the first and the second computer tomography (CT) follow-up when using repeated measures ANOVA. Post hoc pairwise comparison showed significant differences between abdominal thicknesses measured on the preoperative CT (8.9 ± 2.2 mm), first postoperative CT (6.2 ± 2.3 mm, $P<0.001$), and second postoperative CT scans (5.2 ± 1.9 mm, $P<0.001$) (Fig 14). We used ordinal regression to analyze association between pain from the abdominal wall, age and gender, and degree of decrease in abdominal wall thickness. Age <65 years was associated with a statistically significant odds of perceiving more severe pain from the abdominal wall, OR 5.20 (CI95% 1.16 to 23.41). There was, however, no statistically significant association between the extent of muscular atrophy and pain intensity.

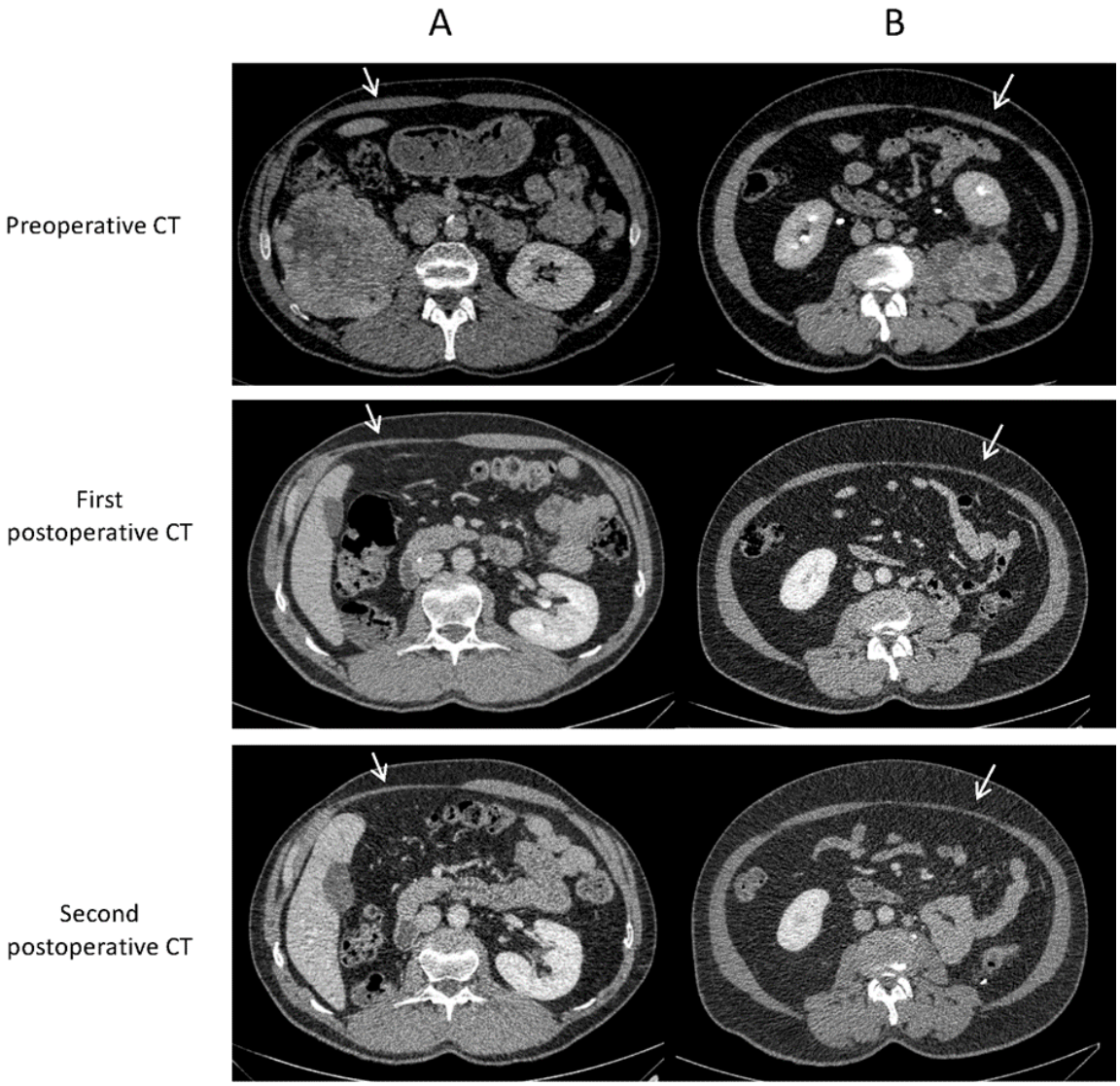

Figure 18. Development of the abdominal wall over time in two patients in Study IV. Arrows indicate surgical side.

6 DISCUSSION

6.1 GENERAL DISCUSSION

Abdominal wall complications after cancer surgery may seem a minor problem compared to the prospect of successful cancer treatment and prolonged survival. However, when incisional hernias or inguinal hernias develop, incarceration of contents can be life-threatening. Abdominal wall hernia may also have a considerably negative impact on quality-of-life. In Sweden, most patients diagnosed with cancer survive many years after surgical or medical treatment, either cured or with their cancer in remission. Preventable side-effects such as hernias may impair quality-of-life for the years in life remaining and attention must be paid to this issue. The oncology surgeon usually meets the patient the first months after surgery, focusing mainly on the oncological outcome. Subsequent follow-ups, according to national guidelines, are carried out by the same or other surgeon, or cancer nurses. The original surgeon may thus never be informed of an incisional hernia developing later. Awareness of incisional hernias among oncology surgeons may also be limited since surgeons that handle and repair these hernias usually work in other surgical units or even hospitals. The risk for postoperative abdominal complications and how to avoid them by using appropriate surgical techniques should be addressed prior to and during surgery in each individual case.

6.2 DICUSSION STUDY I, II, AND IV

Even though the incidence of incisional hernia in our cohorts was low compared to previous studies, much can be done to reduce it even more, aiming at zero abdominal wall complications. There is, unfortunately, a tendency for closure of an abdominal incision to be left in the hands of an inexperienced surgeon. More attention should be focused on teaching our younger colleagues' good surgical technique and the appropriate way to close an incision, as early as possible in their surgical training. It is my belief, though not yet confirmed by any study, that the SSSB technique should be used for closure of all abdominal incisions.

As minimally invasive techniques are becoming the gold standard for almost all urological cancer procedures, even less attention is paid to wound closure. In Study I, we showed that there was a 30% higher incidence of incisional hernia after minimally invasive radical prostatectomy (MIRP) than after open radical prostatectomy (ORP). Other studies have also reported up to three times the risk of incisional hernia after MIRP than ORP (138) (141). Fridriksson et al also reported a higher rate of incisional hernia repairs after MIRP. (138) Most men undergoing radical prostatectomy have more than ten years expected survival. (154) Any persisting complication may thus have a great impact on their life. We also showed that the volume of the prostate was a risk factor for incisional hernia development in the MIRP group. Surgeons attempt to limit harm to the abdominal wall by limiting the length of the skin and fascial incisions as much as possible. If the incision is not elongated enough to allow easy extraction of the specimen after MIRP, forceful traction of the specimen may cause a rift in the fascia making it difficult to suture the fascia edges. This may explain why

prostate volume was seen as a risk factor for incisional hernia development. One study showed that the incidence of incisional hernia could be reduced by 80% at the optic trocar site if a transverse incision was used instead of a longitudinal one (155). This agrees with the finding that transverse incisions in general have a lower incisional hernia rate than midline incisions (24). By accurately judging the length and direction of the incision, the rate of incisional hernia may be reduced. One study showed an association between the surgeon's surgical volume during the previous year and the risk for incisional hernia (141). Such information on surgeon experience is not available in our registers, where only the main surgeon was recorded for many years. Since the main surgeon rarely closes the incision, it is usually done by the first assistant or a younger colleague and therefore not registered. A systematic review of trocar site closure showed the importance of closing port incisions over 10 mm diameter to prevent an incisional hernia (156), this is also the recommendation in the European Hernia Society guidelines (49). Closing of port incisions less than 10 mm had no impact on the rate of incisional hernia in a literature review from 2020. (157). Apart from poor surgical technique, it is possible that difference in mechanical factors that affect the abdominal wall above and below the umbilicus, could affect incisional hernia development. Most minimally invasive surgeons performing MIRP prefer optic port placement at or above the umbilical level to gain access to and expose the deep pelvic area. (158) Transverse incision for the optical port has been recommended in a Cochrane review by Brown et al 2005 (24) as well as a study on transverse optic port incisions in MIRP where Beck (159) reported an 80% reduction in incisional hernia rate. The optic port site is often the preferred site of specimen extraction. By using a transverse incision for one of the lateral ports, extraction of the specimen there should have the same low risk for incisional hernia.

Shorter incisions cause less damage to the nerves, vessels, and muscles thus the risk of numbness and pain after minimally invasive surgery is less frequent than after open surgery. Studies have also shown that when the nerve bundle along the 12th rib is identified during surgery, lateral muscle atrophy and bulging may be avoided (66) (67). A recently published study reported that if a flank incision is closed in multiple layers instead of a single mass closure in one layer, the risk for bulging is reduced by one third. (86) If renal cell carcinoma surgery must be performed with an open technique, incision length must be kept to a minimum especially laterally and when on the left side. The nerve bundle along the 12th rib should be identified, and the incision angle should be as steep as possible to reduce the extent of muscles, vessels and nerves being transected. When closing the incision, the SSSB technique should be used in at least two layers to the restore the anatomy.

Little is known on how to treat postoperative muscle atrophy or flank bulging. There are no obvious surgical procedures to improve abdominal wall function, and once function is lost it is hard to restore regardless of physiotherapy and exercising the muscles in the abdominal wall since damage to the motor nerves is one of the main reasons for postoperative flank bulging, but further research is needed.

6.3 DISCUSSION STUDY III

For many years, hormone treatment for prostate cancer was associated with a relatively short survival expectancy. This resulted in a conservative approach to diagnosing and treating other diseases, especially benign conditions such as inguinal hernia. Over the last fifteen years, however, several new anti-androgen treatments have been introduced and the life expectancy of advanced prostate cancer may now be several decades after diagnosis, and most men die with their prostate cancer not of it. It is therefore of great importance to be aware of the rare side-effects that may occur after many years of hormone treatment for prostate cancer. One such is inguinal hernia, and in Study III we found an odds ratio (OR) of 3.32 after nine years on GnRH treatment. Our findings also partly support an old hypothesis that alterations in sex hormone levels in physiological aging in men may be one of the main reasons why the incidence of inguinal hernia increases with age. This has not been shown previously in humans and further research is needed.

Testosterone is anabolic and stimulates muscle growth. Long-term suppression of testosterone, as in GnRH analogue treatment, leads to general muscle atrophy. Estrogen stimulates fibroblasts responsible for fibrinisation of the muscles. This combination leads to a weaker abdominal wall in the groin.

Histopathology studies have reported alterations in the lower abdominal muscle around the protrusion of the hernia sack among men with inguinal hernia. (134) (135) (160) Already in the 1930´s it was reported that scrotal hernias were more common in male mice treated with estrogen and that castrated female mice had higher prevalence of inguinal hernia. (161) (162) Unfortunately I have not been able to retrieve the original articles. During the 50´s and 60´s, studies on female mice showed that injection of testosterone led to inguinal hernia development. Zhou et al 2018 (23) reported that the presence of locally produced estrogen in muscle increases the risk for inguinal hernia in mice treated with aromatase (the enzyme that converts testosterone to estrogen) in a manner similar to humans. In the same study they also reported a higher rate of expression of estrogen receptors in the lower abdominal wall muscles in men with inguinal hernia than in men without. The role of estrogen in the formation of inguinal hernia has been demonstrated in another study where male mice were given tamoxifen, an estrogen receptor blocker. (163) All male mice developed inguinal hernia and histology revealed altered ratios of collagen types in the groin area. A disturbed ratio between testosterone and estrogen could promote inguinal hernia development in men treated with GnRH due to increased muscle atrophy due to the lack of testosterone and elevated fibrinisation caused by the presence of estrogens, leading to a weakening of the lower abdominal wall.

One study showed that estrogen levels decrease more slowly than testosterone levels in aging men, leading to a higher estrogen: testosterone ratio for the first eight years of the study period. (164). The activity of aromatase has shown to be increased in aging men (165), causing locally higher production of estrogen in muscle and adipose tissue. Locally higher estrogen stimulates fibroblasts and thus muscle fibrinisation. In Study III, men treated with

anti-androgen monotherapy (AA) (a treatment that does not affect serum testosterone levels) did not have a higher incidence of inguinal hernia.

Even though estrogens are mostly derived from androgens, another precursor is dehydroepiandrosterone (DHEA). Some DHEA is formed in the testicles, but the adrenal glands (and to a limited extent the brain) produce 90-95% of the DHEA that serves as a precursor for locally produced testosterone and estrogens in the cells of targeted organs. These locally produced hormones only have an effect in the organs producing them and are released into the circulation in very limited amounts. DHEA levels are decreased during treatment with GnRH analogues but not to the same extent as serum testosterone. (166) Since aromatase levels and activity are increased in the muscles of aging men, the ratio of locally active estrogens is even higher in castrated men.

The physician that initiates treatment with GnRH-analogues is rarely the one that follows the patient after the prostate cancer becomes stable. Most prostate cancer treatment follow-ups are performed by blood-sampling followed by phone call or a letter from a cancer nurse. Most patients with GnRH analogue treatment and a bulge in the groin seek their general practitioner. As a result, oncologists and urologists often remain unaware of inguinal hernia development, and the patient may not even be offered treatment from which they would benefit because of their malignant “life-limiting” disease. Knowledge of the impressive improvement in prostate cancer treatment with improved survival prognosis should thus be spread to all healthcare providers.

6.4 LIMITATIONS

Study I and II. Both are retrospective register studies with incisional hernia as outcome measure. Outcome may be underestimated since there are patients with an incisional hernia where the decision not to perform surgery is taken and the ICD-code for incisional hernia never registered. However, the potential underdiagnosis of incisional hernia applies to all subgroups, and severe cases are usually diagnosed and treated. Even if minor asymptomatic incisional hernias remain undiagnosed, our endpoint should capture all clinically relevant incisional hernias. No information on incision or extraction site is kept in the registers. Furthermore, registers lack information about the surgeon's previous surgical volume; a factor that has been reported to be risk factor for incisional hernia development.

Study III. Even though it has been mandatory to register all inpatients and those attending outpatient clinics in the Swedish National Patient Register since 2001, primary healthcare is not covered. This could result in a falsely low estimate of the prevalence of inguinal hernia in the population, but again, this would apply uniformly to the whole study cohort. Although there were statistically significant associations between >9 years treatment with GnRH and a diagnosis of inguinal hernia, we cannot draw any conclusion regarding a causal relationship. There may be other mechanisms than those described above.

Study IV. The degree of pain prior to surgery was not evaluated and any persisting pain may have been caused by factors other than the incision. The questionnaires were not answered at the same time as when the CT was performed after surgery. The sample size was small, possibly explaining the lack of association between the degree of atrophy and pain. The study did not include assessment of bulging, instead we chose CT assessment of rectus abdominis atrophy believing this to be more robust and reliable. One can also consider bulging as a pseudo-marker or symptom of muscular wall atrophy and muscle innervation deficit.

7 CONCLUSIONS

Study I. Incisional hernia rate after radical prostatectomy during the study period was higher after minimally invasive surgical technique than after an open surgery. Incisional hernia is a preventable postoperative condition that needs further attention if we are to decrease postoperative morbidity, improve health-related quality-of-life and decrease healthcare costs.

Study II. In this population-based study on incisional hernia after surgery for renal cell carcinoma (RCC), the cumulative rate was found to be 4,5% five years after surgery. Even though rates were lower than after other procedures in the abdominal cavity, further attention is still needed since this is a preventable complication. The risk for incisional hernia was 1.74 (CI95% 1.02-2.98) times greater after open surgery than after minimally invasive surgery. Risk factors for incisional hernia development after open surgery were left-sided incision and age above 55 years. No risk factors were detected in the minimally invasive group.

Even though minimally invasive surgery for RCC is constantly increasing, open surgery will still be needed in the future and the risk for development of incisional hernia needs to be recognized in the urological community.

Study III. Treatment for more than nine years with GnRH is associated with an increased risk for inguinal hernia development. This finding supports the hypothesis that alterations in sex hormone levels increases the risk for inguinal hernia. To our knowledge, this is the first study investigating the effect of sex hormones on the development of inguinal hernia in humans.

Study IV. Despite the rapid increase in minimally invasive techniques, a significant proportion of renal cell carcinoma surgery will continue to be performed via a flank incision. This study demonstrates the development of postoperative abdominal muscle atrophy and pain which persists over time, though the study was too small to confirm an association between the two. Future studies on avoidance of muscle atrophy and how to treat it are needed.

8 POINTS OF PERSPECTIVE

8.1 FUTURE RESEARCH

Study I, II and IV in this thesis had large cohorts where the outcome measures had not been thoroughly investigated in these patient groups before, even though they are well-known complications. These studies may serve as a springboard for future research. One of the fields that needs further prospective investigation is how to close transverse incisions in the abdominal wall. It is often assumed that the small-stitch-small-bites (SSSB) technique is appropriate for closing transverse incisions and port site incisions. However, there is no research in this field evaluating if this is the case, and how this could impact incisional hernia rates. At present, there are no guideline recommendations (49) on how to close incisions than other midline incisions to prevent incisional hernia. A randomized study using the SSSB technique for incisions other than midline, would serve as a reference for future guidelines to lower the risk for incisional hernia, improve health-related quality-of-life, and lower costs for society.

Future studies should evaluate the long-term impact of flank incisional hernia repair on QoL.

The lack of studies on how physical activity impacts incisional hernia development makes it difficult to give adequate postoperative advice. Restricting physical activity for at least the first month after surgery is widely recommended, although evidence for this is weak. (100) More studies in this field are needed to give evidence-based recommendations to the patient. Physical activity may possibly benefit by reducing bulging of the flank. We know that motor nerves can regenerate, and early stimulation of the nerves may increase regeneration, promote blood flow and lymph drainage, and lower the risk for bulging. Apart from just limiting abdominal wall complications, physical activity during and after cancer treatment significantly improves clinical, functional, psychological, and in some population's even survival outcomes. (167) (168) (169) It is thus very important that the patient regains as much of his/her preoperative physical condition as possible in as short a time as possible. Advice regarding restricted physical activity after surgery should be based on evidence, and studies in this field should be conducted in the future.

Study III, to my knowledge, is the first to report the impact of sex hormones changes on the lower abdominal wall and on the development of inguinal hernia and will be hypothesis generating for further studies. Studies on mice have reported increased inguinal hernia formation if aromatase levels in lower abdominal wall muscles are elevated. Murine studies also report that estrogen receptors are more expressed in lower abdominal wall muscle in men with inguinal hernia than in men without (170). Amato et al 2012 found that men with inguinal hernia had a different tissue composition in the inguinal region compared to men without inguinal hernia, showing more fibrotic tissue and atrophic muscles. (135) Clinical studies on serum testosterone and aromatase levels in men with inguinal hernia, combined with biopsies from the inguinal area should be performed. Men with recurrent inguinal hernia and men with a family history of inguinal hernia are of special interest in future studies.

Prescription of testosterone to aging men has increased during the last decade (171) but is still controversial, and there are several ethical considerations to be addressed before routinely prescribing testosterone. A randomized study on testosterone treatment to decrease the risk for inguinal hernia, would require thorough safety and ethical considerations and will probably take many years before it can be executed.

8.2 CLINICAL IMPLICATIONS

General recognition of the risk for incisional hernia after open and minimally invasive surgery, as reported in **Study I and II,** and adaption of suitable surgical closure techniques to reduce that risk, will have a direct clinical impact on postoperative health-related quality-of-life and may also decrease the cost to society.

Study IV emphasizes the importance of awareness of the risk for muscle atrophy and flank bulging after open renal cell carcinoma surgery. By choosing minimally invasive surgery to reduce the risk for muscle atrophy and bulging, and by making incision angles as short and as steep as possible for adequate exposure during open surgery, the risk for incisional hernia will be reduced to a minimum. Limiting harm to vessels, muscles, and nerves in the area should reduce muscle atrophy and bulge formation and persisting pain from the abdominal wall after surgery.

Awareness that long-term GnRH treatment for prostate cancer has an increased risk for inguinal hernia that may reduce QoL, should be considered in decisions to repair the hernia or not in men with advanced or recurrent prostate cancer. Once inguinal hernia is diagnosed it should be repaired if the patient's general health is good enough. Further studies on sex hormones and inguinal hernia described in **Study III** may have pronounced clinical implications in the future both for the individual patient and for the cost to society. If sex hormones are found to be crucial for the stability of the aponeuroses and wound healing, detection of subclinical hypogonadism may turn out to be an important part of preoperative screening in patients undergoing elective abdominal surgery.

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- Still not giving me the right answer.

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