
Inguinal Hernia after Urologic Surgery in Males with Special Reference to Radical Retropubic Prostatectomy

A Clinical, Epidemiological and Methodological Study

by

Johan Stranne

Department of Urology
Institute of Clinical Sciences
The Sahlgrenska Academy at Göteborg University
Sahlgrenska University Hospital

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ABSTRACT

Inguinal Hernia after Urologic Surgery in Males with Special Reference to Radical Retropubic Prostatectomy

A Clinical, Epidemiological and Methodological Study

Johan Stranne, *Department of Urology, Institute of Clinical Sciences, the Sahlgrenska Academy at Göteborg University, Sahlgrenska University Hospital*

Background and aims: In 1996 the first report indicating that inguinal hernia (IH) was a complication to radical retropubic prostatectomy (RRP) was published. The main aims of this thesis were to further establish this relation, to establish the background incidence of IH in men not subjected to surgery, to identify risk factors for postoperative IH occurrence and to investigate whether postoperative IH is a complication also after other types of surgery performed through a lower midline incision. A further aim was to form a hypothesis regarding the etiology of this complication and explore which methodological considerations have to be addressed when postoperative IH incidence is investigated.

Materials and methods: A retrospective patient file survey (PFS) was used on 1039 patients subjected to RRP (n=375 [I] + 664 [III]) and pelvic lymph node dissection for staging of prostate cancer before radiotherapy (PLND) (n=184 [I]). The factors studied in the PFS were post-RRP IH incidence, age at RRP, preoperative IH morbidity, postoperative anastomotic stricture, influence of concurrent PLND at RRP and duration of surgery. From the ongoing Scandinavian Prostate Cancer Group (SPCG) 6 study a database search was used where the annual IH incidence for patients not subjected to surgery (n=953) and patients subjected to RRP (n=152) was investigated (II). Two patient administered questionnaires (PAQ) were also used. One prospective PAQ was sent to patients subjected to RRP (n=207) in whom the postoperative IH incidence was studied and preoperative IH morbidity (III). One retrospective PAQ was sent to patients subjected to PLND (n=88), open prostatectomy for benign prostatic hyperplasia (n=95) and cystectomy (n=76) where the postoperative IH incidence was explored (IV).

Results and conclusions: The results show that the incidence of IH within 2 years after RRP is increased at least fifteen-fold as compared to a non-surgical group of patients. The background incidence of clinically overt IHs in men with prostate cancer and a mean age of 69 years is less than 0.5% per year. Increased age and preoperative IH morbidity are risk factors, but postoperative anastomotic stricture, concurrent PLND at the time of RRP and duration of surgery do not seem to increase the risk of post-RRP IH development. The risk of postoperative IH development after other urological procedures in males performed through a lower midline incision seems to be of a similar magnitude as following RRP. The incision *per se* seems to be the cause of the lesion, probably resulting in a direct disruption of the "shutter mechanism" of the inguinal anulus internus. Constitutional factors predisposing for IH may add to the risk. In the methodological analysis PAQ was found to be superior to PFS to detect previous IH morbidity as well as postoperative IHs.

LIST OF PUBLICATIONS

This thesis is based on the following papers which in the text will be referred to either by direct reference, e.g. **paper I**, or by their respective Roman numerals, e.g. **(I)**.

- I. Inguinal Hernia after Radical Retropubic Prostatectomy for Prostate Cancer: A Study of Incidence and Risk Factors in Comparison to No Operation and Lymphadenectomy.**
P. Lodding, C. Bergdahl, M. Nyberg, E. Pileblad, J. Stranne and J. Hugosson
J Urol 166(3): 964-7, 2001
- II. Inguinal Hernia in Stage M₀ Prostate Cancer: A Comparison of Incidence in Men Treated With and Without Radical Retropubic Prostatectomy--An Analysis of 1105 Patients**
J. Stranne, J. Hugosson, P. Iversen, T. Morris and P. Lodding
Urology 65(5):847-51, 2005
- III. Post-Radical Retropubic Prostatectomy Inguinal Hernia: An Analysis of Risk Factors With Special Reference to Preoperative Inguinal Hernia Morbidity and Pelvic Lymph Node Dissection**
J. Stranne, J. Hugosson and P. Lodding
Accepted for publication J Urol, November 2006
- IV. Inguinal Hernia is a Common Postoperative Complication after Urological Lower Midline Incision Surgery in Males**
J. Stranne, J. Hugosson and P. Lodding
Submitted for publication

ABBREVIATIONS IN THE TEXT IN ALPHABETICAL ORDER

OP	-	Open prostatectomy
PAQ	-	Patient administered questionnaire
PFS	-	Patient file survey
PLND	-	Pelvic lymph node dissection
PSA	-	Prostate specific antigen
RRP	-	Radical retropubic prostatectomy
SPCG	-	Scandinavian Prostate Cancer Group

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INTRODUCTION

To start with a cliché: carcinoma of the prostate is a very common disease. It is today the leading cancer diagnosis for men in the USA and the fourth most common cancer in men worldwide (Reiter and deKernion 2002). In Sweden prostate cancer is the most common cause of cancer related death, accounting for 5.8% of all male deaths in 2003 (The Cancer Register 2005). However, incidence and mortality rates vary significantly between different countries throughout the world. Radical retropubic prostatectomy (RRP) is today considered the gold standard for treating localized prostate cancer (Pirtskhalaishvili et al. 2001; Aus et al. 2005) and its hitherto most well-known postoperative complications incontinence, impotence and stricture of the vesico-urethral anastomosis are all well described in the literature (Besarani et al. 2004). The priorities of the procedure are often described as “cancer control, continence and potency” in falling order of importance (Walsh 2002). Inguinal hernia was first reported as a suspect postoperative complication to RRP by Regan and co-workers (Regan et al. 1996). In this thesis, the existence of this complication is confirmed, potential mechanisms behind post-RRP inguinal hernia development are explored and the post-RRP inguinal hernia incidence is compared to the inguinal hernia incidence after other urological procedures performed through a lower midline incision in males.

Radical prostatectomy: historical background

The first historical description of prostate cancer dates from the Ebers papyrus of the ancient Egypt around 1500 BC (Braun 1977). The history of radical prostatectomy, however, is only a little more than a century old. In 1866 Kùchler suggested that a perineal approach, first described by the Greeks in 400 BC to remove bladder stones, could be used also for removal of prostatic carcinoma (Kùchler 1866). Although he only ever performed this procedure on a cadaver, his theories were applied on a living prostate cancer patient the following year by the famous surgeon

Theodor Billroth at the University of Zürich. He was also the first to describe the procedure in a medical journal (Billroth 1869). Unfortunately, Billroth's mortality rate for perineal prostatectomy was 100% (n=1) and during the rest of the century urologists concentrated their efforts mainly on describing the pathology and epidemiology of prostate cancer rather than developing its surgical management. However, in the beginning of the 20th century, Professor Hugh H. Young performed four radical perineal prostatectomies at Johns Hopkins University Hospital. He published his work in 1905 (Young 1905) and described the results as "a success". Per- and postoperative morbidity and mortality rates were still very high but after this publication the number of prostatectomies performed in the world slowly started to increase.

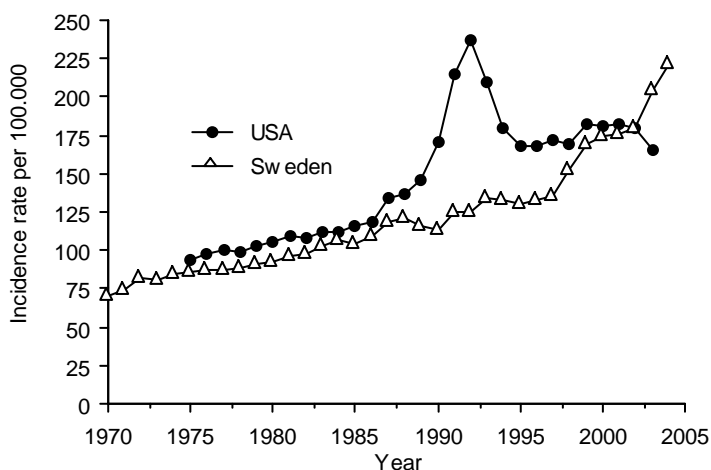
The next great leap for the surgical management of prostate cancer came with the development of the retropubic approach for the procedure. The first radical *retropubic* prostatectomy (RRP) was performed in London by the Irish professor Terence Millin and was described in *The Lancet* in 1945 (Millin 1945). The per- and postoperative mortality rates remained rather high but were gradually reduced with improved surgical and anesthesiological techniques over the years. The per- and postoperative morbidity following both perineal and retropubic prostatectomy, consisting of substantial blood loss, severe incontinence, erectile dysfunction and stricture of the vesico-urethral anastomosis, also remained very high.

The detection of prostate cancer was for a very long time dependant on the finding of a palpable nodule at digital rectal examination. Many of the detected tumors were, as a consequence, spread outside the prostate at the time of detection and consequently not curable. The low chance of cure, the high postoperative morbidity and the development of hormonal treatment after the 1940ies (Huggins and Hodges 1941) added up to a rather dubious reputation of prostate cancer surgery. The number of radical prostatectomies performed throughout the world therefore remained limited.

The discovery of prostate-specific antigen (PSA) in the 70ies (Ablin et al. 1970; Wang et al. 1979) changed this dramatically. The publication of a number of PSA screening materials resulted in an increasingly widespread use of PSA for early detection of

prostate cancer (Hernandez and Thompson 2004). This led to a huge increase in the prostate cancer incidence in the USA (SEER 2006). With a few years delay a similar increase could be noted in Sweden, from less than 75 new cases per 100.000 inhabitants in 1970 to approximately 225 new cases per 100.000 inhabitants in 2004, could be observed (Figure 1)(The Cancer Register 2005).

Figure 1



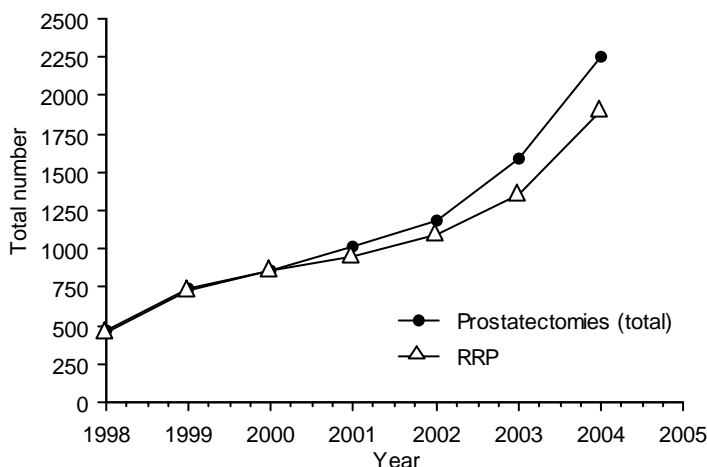
Annual incidence of prostate cancer in USA from 1975 to 2003 and in Sweden from 1970 to 2004 (data adapted from National Cancer Institute: SEER- Surveillance Epidemiology and End Results and the Swedish national board of health and welfare: The Cancer Register).

One consequence of this was a stage migration of the disease towards smaller, potentially curable, tumors which in turn led to a dramatic increase in the demand for curative treatment options with acceptable side effects. Also during the 70ies important work was initiated to decrease the per- and postoperative complications of RRP. In 1982 Walsh described the detailed anatomy of the prostate gland, its blood supply and especially the existence and function of the neuro-vascular bundles (Walsh and Donker 1982). He subsequently applied this newly acquired knowledge and performed the first nerve-sparing RRP (Walsh et al. 1983). This was the start of a dramatic development of surgical technique still

going on today, where peroperative blood loss has been minimized and the known postoperative complications of incontinence, erectile dysfunction and anastomotic stricture have been reduced to very low levels in expert hands (Walsh 1998). A potential cure with acceptable side effects thereby existed and RRP rapidly became the gold standard of treatment for localized prostate cancer (Pirtskhalaishvili et al. 2001; Aus et al. 2005).

The increased detection of early cases of prostate cancer and the improved reputation of RRP led to a veritable explosion of the number of prostatectomies performed all over the world. In 1998 the total number of prostatectomies performed in Sweden was 467. In 2004, the number had increased to 2258 of which 1904 were retropubic (Figure 2)(The Hospital Discharge Register 2005).

Figure 2



Total number of radical prostatectomies (retropubic, perineal and laparoscopic) and number of radical retropubic prostatectomies (RRP) performed in Sweden from 1998 to 2004 (data adapted from the Swedish national board of health and welfare: The Hospital Discharge Register).

The number of radical prostatectomies performed in 2003 in the USA was 167,000 (National Hospital Discharge Survey 2003). Thus, radical prostatectomy is today a very common procedure and the number performed each year is likely to increase even further

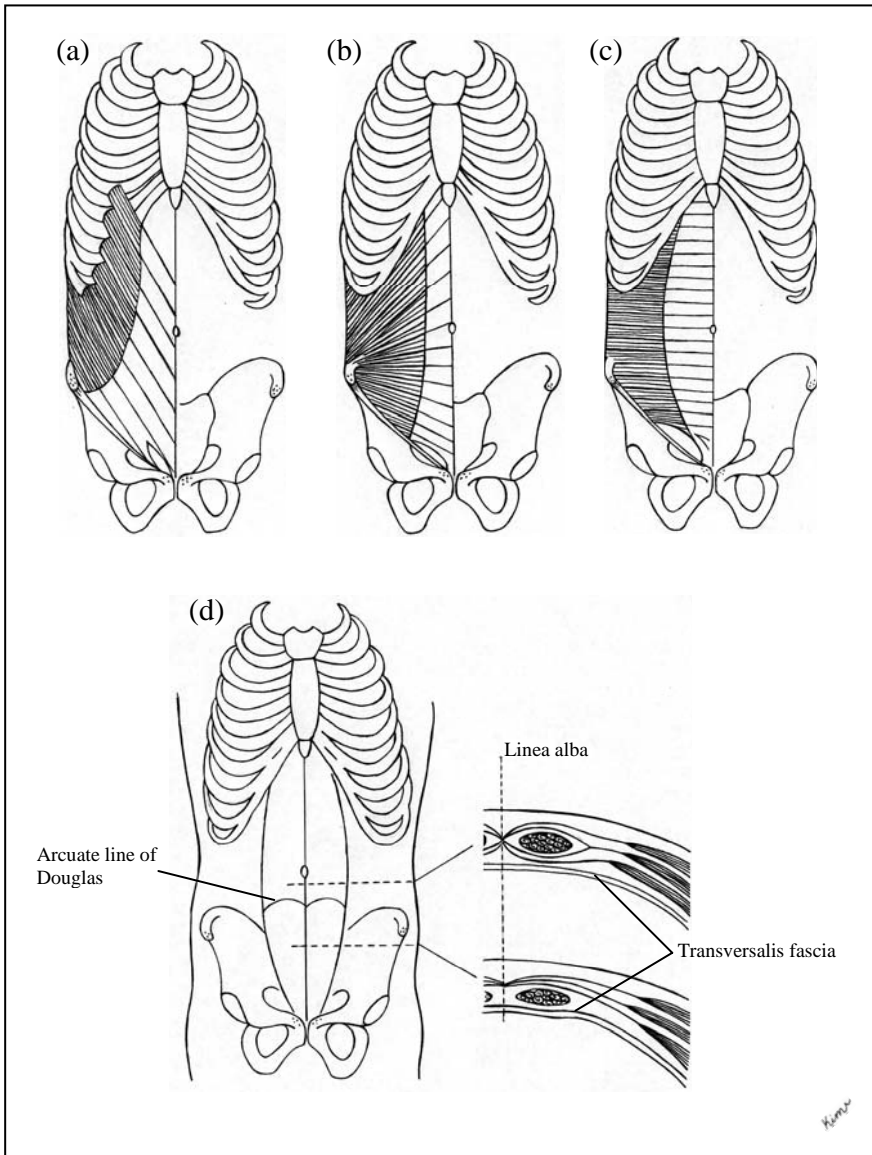
as screening with PSA and other markers becomes more frequently used throughout the world (Thompson et al. 2005; Constantinou and Feneley 2006)

Inguinal hernia – anatomy, etiology and epidemiological aspects

Inguinal hernia is approximately 10 times more common in men than in women (Rutkow 1998). The historical references to this condition predates even those of prostate cancer and can be traced as far back as to ancient Mesopotamia around 4000 B.C. where healers performed hernia repairs (Skandalakis et al. 2002).

The exact cause of inguinal hernia development in humans is still not entirely understood (McArdle 1997; Fitzgibbons et al. 2005). The abdominal muscles and aponeuroses are illustrated in Figure 3 a-d. The rectus muscle of the abdominal wall is reinforced with fasciae on both sides above the arcuate line of Douglas (linea semicircularis) but not below (Figure 3d). The arcuate line of Douglas is located 3-6 cm below the umbilicus (Malangoni and Gagliardi 2004). In quadrupeds this is functional since the inguinal canal is directed in an upwards slope and the weight of the intra-abdominal organs is on the cranial, reinforced part of the abdominal wall. In humans, walking on their hind legs, a rather weak transversalis fascia and the absence of the posterior rectus sheath in the lower abdominal wall constitutes a potential tenacity problem with the weight of the abdominal contents exerting pressure from the inside. The inguinal canal is defined superiorly by the arching fibers of the aponeurosis of the transverse abdominis and the internal oblique muscles. These are sometimes joined together in the so called conjoined tendon (falx inguinalis). Anteriorly it is defined by the external oblique muscle and its aponeurosis, inferiorly by the inguinal ligament and posteriorly by the transversalis fascia. The superficial opening of the canal, the anulus externus, is formed by a slit in the medial portion of the aponeurosis of the external oblique muscle and the deep opening, the anulus internus, by an opening in the transversalis fascia (Figure 4). The latter is reinforced by superior and inferior crurae

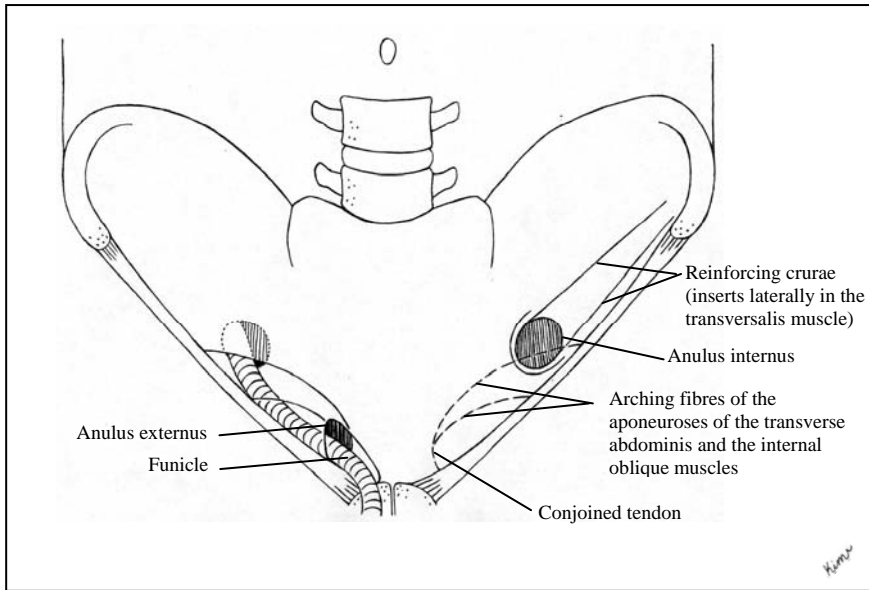
Figure 3



Muscular and aponeurosal layers of the abdominal wall: a) external oblique muscle b) internal oblique muscle c) transversalis muscle d) rectus muscle above and below arcuate line of Douglas. Note that linea alba is separate from the transversalis fascia at all levels.

forming a sling of the fascia attached laterally to the inside of the transversalis muscle.

Figure 4



Anulus externus of the inguinal canal in the external oblique aponeurosis (left) and conjoined tendon of the internal oblique and transversalis aponeurosis leading to the anulus internus in the transversalis fascia (aponeurosis of external oblique muscle removed) (right). The reinforcing crurae of the anulus internus in the transversalis fascia inserts in the transversalis muscle laterally.

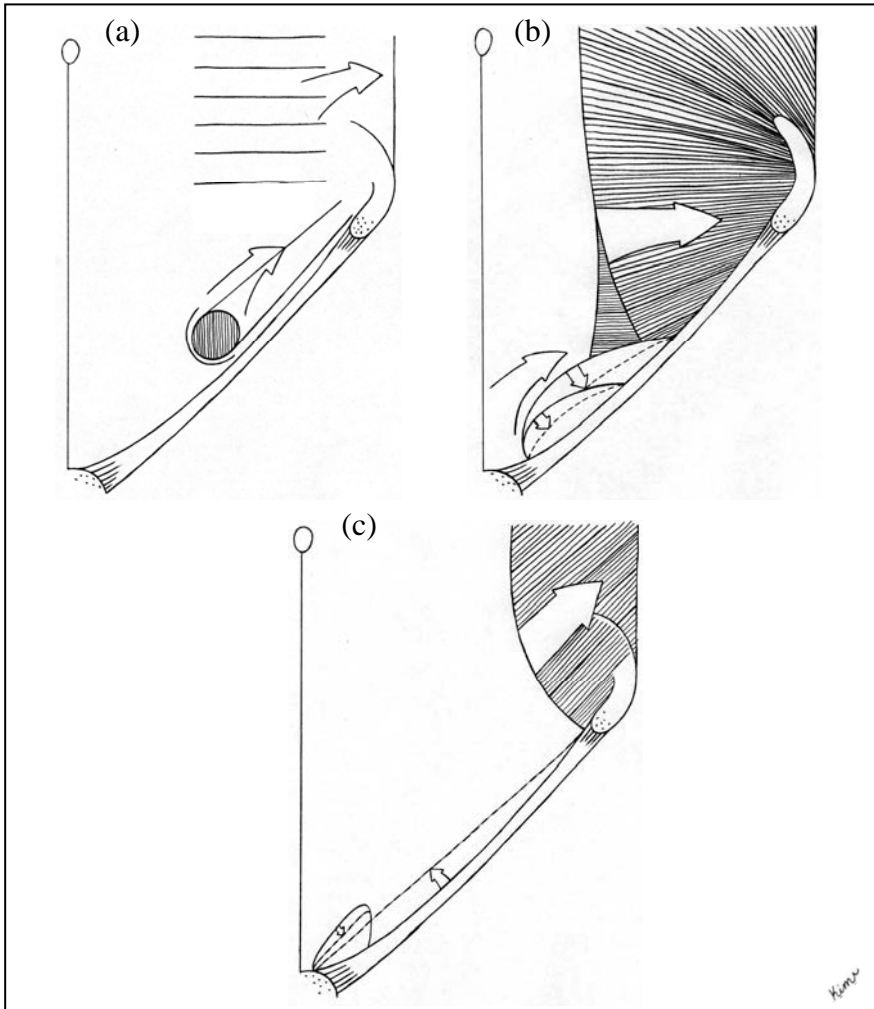
When the intra-abdominal pressure is increased, e.g. by coughing, heavy lifting etc, the integrity of the canal is maintained through a tensioning of the lateral abdominal muscles in a form of “shutter mechanism” (McArdle 1997; Abrahamson 1998; Kux 2002; Quinn 2002; Malangoni and Gagliardi 2004; Fitzgibbons et al. 2005). This is a complex action which involves all the muscle layers. From the inside, the transversalis muscle tenses the crurae of the fascia sling around the anulus internus, transposing the opening in craniolateral direction (Figure 5a). The tensioning of the transversalis muscle together with the internal oblique muscle also extends to the aponeurotic arc, the conjoined tendon, straightening and

descending the arc towards the inguinal ligament and closing the anulus internus from above (Figure 5b). The strong external oblique muscle, at the same time, lifts the inguinal ligament towards this flattened arc, further closing the shutter-like mechanism (Figure 5c). The combined actions of the muscles thereby support the pressure on both the anulus internus and on the relatively weak transversalis fascia medial to the anulus internus by this action.

There are two types of inguinal hernias, medial and lateral, also referred to as direct or indirect, distinguished by on which side of the inferior epigastric vessels the hernia originates. The etiology and pathogenesis of the two types are different, even though defects in connective tissues, congenital or acquired, seem to be a common denominator (Sorensen et al. 2002). Lateral hernias also have a higher risk of complication, e.g. incarceration, than medial hernias although the distinction between the two usually is difficult before any surgical intervention is made (Malangoni and Gagliardi 2004)

The medial, or direct, inguinal hernia is acquired and usually occurs late in life (McArdle 1997). The hernia protrudes directly through the transversalis fascia, medially to the epigastric vessels. The cause is traditionally believed to be a combination of raised intra-abdominal pressure and a relative weakness of the transversalis fascia of the posterior wall of the inguinal canal (McArdle 1997; Abrahamson 1998; Fitzgibbons et al. 2005). Kux, in the latest edition of “Nyhus and Condon’s hernia”, argues that an additional defect of the external oblique aponeurosis is present in males, causing a failure to support the transversalis fascia and the direct inguinal space, thereby predisposing for medial hernia formation (Kux 2002). The incidence of direct hernias increases with age as the connective tissue of the body degenerates (Ashcroft et al. 1997; Sorensen et al. 2002) and this type of hernia is also more common in patients with connective tissue disorders such as the Marfan syndrome, cutis laxa etc (Fitzgibbons et al. 2005).

Figure 5



Shutter mechanism: a) lateral tension of the crurae from transverse muscles moves anulus internus cranio-laterally b) tension of the transversalis and inner oblique muscles lowers the conjoint tendon towards inguinal ligament c) tension of external oblique muscles raises inguinal ligament.

In the lateral, or indirect, inguinal hernia, which is the most common type, the hernia sac runs together with the spermatic cord beginning in the anulus internus lateral to the inferior epigastrical vessels. The traditional explanation for these hernias is that they are congenital in origin and Russell proposed a model he called the “saccular theory” in 1906 (Russell 1906). Russell’s hypothesis was that the presence of a patent processus vaginalis, i.e. deficient closure of the peritoneum in the funicle after the descending of the testicles in foetal development, was “...*essential* in every case...”. Increased intra-abdominal pressure might then stretch the defective anulus internus further, finally allowing internal organs to protrude through the orifice. The notion of a mandatory existence of a congenital defect that develops into a clinical hernia later in life has been challenged (Fitzgibbons et al. 2005) and most likely the cause of indirect herniation is multifactorial. Patent processi vaginalis has a prevalence of approximately 20% in men without symptoms of inguinal hernia (Hughson 1925; van Wessem et al. 2003) and less than 50% of all patients with this congenital defect develop inguinal hernia later in life (Conner and Peacock 1973). A defect of the supportive tissues of the “shutter mechanism”, either by incrimination of the action of the lateral abdominal muscles e.g. by denervation (Arnbjornsson 1982), or by defects in the connective tissues mentioned earlier (Sorensen et al. 2002) are considered causative for this type of herniation as well.

Despite the long history of inguinal hernia as a disease and the vast number of inguinal hernias in the population, no reliable epidemiological data exist to our knowledge on the incidence or prevalence of this lesion (Rutkow 1998; Nielsen 2005; Rutkow 2005). Various attempts to define these epidemiological cornerstones have been made, from George Arnaud’s “A Dissertation on Hernias, or Ruptures in Two Parts” from 1748 (Arnaud 1748) to more modern materials as Abramson and colleagues’ material from 1978 (Abramson et al. 1978) and the RAND Corporation report by Rubenstein and co-workers on men in California from 1983 (Rubenstein et al. 1983), with highly variable results. The latter two are large studies attempting to establish the epidemiology of inguinal hernias. Despite the large size of these materials, there are huge differences in prevalence figures between them, for example a figure of 14.3% for men aged

55 to 64 years in the Abramson material (Abramson et al. 1978) as compared to 3.9% for the corresponding group in the Rubenstein material (Rubenstein et al. 1983). The methods used in the two studies are different, Abramson using clinical examination to identify all hernias whereas self-reporting from an insurance enrollment was used by Rubenstein. This illustrates the impact of what method of detection is used when conducting studies on incidence and prevalence of inguinal hernia. The detected hernias in the Abramson study were a mixture of clinically overt and subclinical hernias (i.e. noticed by the physician at examination but not by the patient). Subclinical inguinal hernias are common in the population. Various reports, in which the presence of subclinical inguinal hernias has been actively explored during surgery for other reasons (Schlegel and Walsh 1989; Watson et al. 1994; Lepor et al. 2001; Nielsen and Walsh 2005), at autopsy (Ajmani and Ajmani 1983) or by computed tomography (Fukuta et al. 2006), show a prevalence of between 5 and 33%. The different methods of hernia detection probably explain the variable results from existing studies. In the work of establishing incidence and prevalence figures for inguinal hernia it is therefore important to consider the way in which the hernias are detected in order to obtain comparable results. So far the figures from Abramson and his co-workers are probably the most accurate. For men aged 65-74 years he reports a total “life-time prevalence” of inguinal hernia including subclinical lesions (“palpable impulse at examination”) of 40% and a “life-time prevalence” of clinically significant inguinal hernias of 31% (Abramson et al. 1978).

Almost 800.000 inguinal hernia repairs were made annually in the USA in the late nineties (Rutkow 1998) and in Sweden over 17.000 were made in 2003 (The Hospital Discharge Register 2005). The incidence of inguinal hernia in the population is even higher since not all inguinal hernias need surgical repair. Inguinal hernia is a potentially serious condition with risk of incarceration, bowel strangulation and gangrene requiring emergency surgery. Even though most inguinal hernias are not that dramatic Nyhus, in the 14th edition of the Sabiston Textbook of Surgery, describes inguinal hernia and subsequent intestinal obstruction as one of the top 10 causes of death in the United States in the sixties (Nyhus et al. 1991). More recent data from the Swedish Hernia Registry shows

that 5% of inguinal hernia repairs between 1992 and 1999 were emergency procedures and bowel resection was a consequence of 5.4% of these cases (Sandblom et al. 1999), indicating that the lesion is far from harmless. In most cases though, the symptoms of inguinal hernia are restricted to a mass in the region of the groin, sometimes extending down to the scrotum, which may result in pain and discomfort. This condition also frequently causes decreased work capacity with significant economic consequences, both for the patient and for society as a whole (McArdle 1997).

A suspected association between RRP and inguinal hernia and the planning of this thesis

As we have seen, patients subjected to RRP increased steadily in number during the nineties. Today they constitute by far the largest urological patient group operated on through a lower midline incision. These patients, due to the malignant nature of their disease, are usually followed long-term postoperatively at regular intervals by the operating urologist. The urologists at centers where RRP is frequently performed thereby see a large number of patients in the postoperative phase of this relatively standardized surgical procedure. Patients that are considered for RRP are also in relatively good health (Aus et al. 2005). These factors in combination with a decreasing rate of other postoperative complications, have led to a unique opportunity to discover new, previously unknown, postoperative complications to the procedure. Accordingly, in 1996, the first report on a new postoperative complication of the RRP procedure was reported by Reagan and co-workers, who noted an overall incidence of postoperative inguinal hernia of 12% within 6 months after RRP (Regan et al. 1996). The following year two hernia surgeons in New York reported an unproportionally high number of patients who underwent to previous RRP in a retrospective case control study of male patients subjected to inguinal hernia surgery at their clinic (Fischer and Wantz 1997). However, after these initial reports the problem did not receive any attention in the literature until 2001, when our first report was published (**paper I**).

During the planning of this thesis it became obvious that several questions had to be addressed in order to explore the issue of inguinal hernia as a possible complication to RRP. The expected background incidence of this common lesion in male patients of this age group had to be established. Different potential risk factors such as preoperative inguinal hernia morbidity, concurrent pelvic lymph node dissection (PLND), duration of the procedure and postoperative anastomotic stricture development had to be explored. Furthermore, the incidence of postoperative inguinal hernia after other urological procedures performed through a lower midline incision needed to be addressed. During the course of the study significant differences in sensitivity between methods used to detect preoperative inguinal hernia morbidity and postoperative inguinal hernia development became evident. Methodological considerations thereby also became important.

AIMS OF THE STUDY

The objectives of this thesis were primarily to answer the following questions:

1. What is the incidence of postoperative inguinal hernia after RRP compared to the expected background incidence in men of a similar age group not subjected to surgery? (I, II & III)
2. Can risk factors for the development of inguinal hernia after RRP be identified? (I & III)
3. What is the impact of the varying degrees of sensitivity of the different methods for detection of preoperative inguinal hernia morbidity and postoperative inguinal hernia development used in the study and which methodological considerations thus need to be addressed? (II-IV)
4. Is postoperative inguinal hernia a common complication also after other types of surgical procedures performed through a lower midline incision in males? (I & IV)
5. Can a hypothesis be formed regarding the etiology of the complication based on the results of these studies? (I-IV)

MATERIALS AND METHODS

Patient materials

Paper I: 375 men who underwent RRP and 184 men who underwent pelvic lymph node dissection (PLND) for staging of prostate cancer before radiation therapy in Göteborg between 1988 and 1997 were identified from a retrospective patient file survey (PFS) of all men with prostate cancer treated with curative intent during this period. In addition, a control group of 65 men with non-metastatic prostate cancer, not previously subjected to RRP or PLND, was included for comparison. This non-surgical group consisted of patients included in the Scandinavian Prostate Cancer Group Study No. 6 (SPCG 6) at our clinic. SPCG 6 is a prospective randomized study (Iversen et al. 2002). In this study patients with stage M₀, T1b or higher and any N-stage prostate cancer were included to receive either the antiandrogen bicalutamide 150 mg daily or placebo in a 1:1 ratio; both given in addition to standard care. Mean age was 64 years (median 65, range 47-77) for the RRP group, 67 years (median 67, range 53-79) for the PLND group and 71 years (median 71, range 61-75) for the non-surgical group.

Paper II: From the entire database of the SPCG 6 study (n=1218) we excluded all men that had been subject to any other prostate cancer treatment than watchful waiting or RRP at the time of inclusion (radiotherapy [n=68], cryotherapy [n=3], radical perineal prostatectomy [n=1] and post-RRP radiotherapy [n=2]). We also excluded all patients with a follow-up of less than 3 months (n=39). Thus, all patients who had not received any treatment for their prostate cancer (non-surgical; n=953) or had previously been subjected to RRP (n=152) with a minimum follow-up of 3 months were included. Access to the database was made possible through the kind permission of the SPCG and of AstraZeneca.

Mean age at beginning of follow-up was 69 years (median 70, range 53-75) for the non-surgical group and 63 years (median 64, range 45-74) for the RRP-group.

Paper III: All patients who underwent RRP at the Urological Department at Sahlgrenska University Hospital during the period 1998 to 2002 and had a follow-up of more than 3 months were identified through the hospital surgical registry (n=664). 498 of these patients underwent a concurrent RRP and PLND. The remaining 166 had low-risk tumors with Gleason score ≤ 6 , PSA $< 10\text{ng/ml}$ and ≤ 2 positive biopsies and were considered to have such low risk of positive lymph nodes that staging by PLND was unnecessary. These patients therefore underwent RRP only, without a concurrent PLND.

All of the above patients who were operated on after January 1st 2001 (n=271) also received a prospective, patient administered questionnaire (PAQ) prior to the operation and at 3, 6, 12, 18, 24 and 36 months postoperatively. 207 patients completed the preoperative and at least one postoperative questionnaire and these were included in a sub-analysis.

Mean age at RRP for the entire group (n=664) was 63 years (median 64, range 43-75) and for the PAQ-group (n=207) 63 years (median 64, range 43-74).

Paper IV: Male patients operated on with various procedures performed through a lower midline incision at the Urological department at Sahlgrenska University Hospital during the period 1994 to 2003 were identified through the hospitals surgical registry (n=433). The procedures investigated were open prostatectomy for benign prostate hyperplasia (OP) (n=130), PLND as staging before planned radiation therapy for prostate cancer (n=119), and cystectomy for bladder cancer (n=184). 260 of these patients were identified to be alive at the time of our study (OP n=95; PLND n=89; cystectomy n=76) and these were sent questionnaires. 74 (78%), 71 (81%) and 56 (74%) responded from the respective groups. The mean age at surgery was 74 years (median 75, range 54-90) for the OP group, 64 years (median 65, range 47-77) for the PLND group and 67 years (median 68, range 26-86) for the cystectomy group. These patients were subsequently compared with the 953 non-surgical patients in **paper II** and the 207 RRP patients in **paper III** who had responded to the PAQ.

Methods for data collection

In this study three different methods have been used to collect data:

1. Retrospective patient file survey (PFS)
2. Database search
3. Patient administered questionnaire (PAQ)

Retrospective patient file survey (PFS)

PFS was used in **papers I & III**. Patient files for RRP and PLND patients for **paper I** and all patients for **paper III** were screened for references to inguinal hernias and anastomotic strictures that developed postoperatively. Inguinal hernia was defined as a newly developed inguinal hernia confirmed by any physician during follow-up and anastomotic stricture was defined as a stricture confirmed at endoscopy, requiring incision. Patients were not routinely examined for inguinal hernias or anastomotic strictures during their normal follow-up at the clinic. Consequently only clinically apparent hernias and strictures which had been noted in the files were registered. Subclinical inguinal hernias and strictures remained undetected.

For **paper I** the files of all the RRP-patients who developed a postoperative inguinal hernia and those of 95 RRP-patients who did not develop postoperative inguinal hernia were further reviewed with regards to pre-RRP inguinal hernia surgery. The sample of 95 patients was selected because their clinical files were easily available for PFS in a computer database, unlike the rest of the patients in this group. They were deemed to constitute a representative sample and did not differ from the overall RRP-group in any other sense. Mean follow-up time was 39 months (median 35, range 1-110) for the RRP-group and 47 months (median 40, range 1-121) for the PLND-group. In all cases where an inguinal hernia had been repaired surgically, the operation record was reviewed in an attempt to determine type and side of the hernia as well as whether the hernia was de novo or recurrent after previous inguinal hernia surgery. For **paper I** we also identified the 65 non-surgical patients at our clinic who were included in the SPCG 6 study. Since these patients were followed at our clinic at

12-weekly intervals we had files on all of them and could use PFS of the clinical file records from the SPCG 6 to screen for inguinal hernia events. All new medical conditions were recorded as adverse events at each visit. Mean follow-up time for the non-surgical group was 45 months (median 47, range 29-59).

For **paper III** the patient files were again screened for references to inguinal hernias and anastomotic strictures. Additional data on type of operation (RRP with or without concurrent PLND), preoperative inguinal hernia surgery, prevalent inguinal hernias at the time of RRP and the duration of surgery was also gathered from the patient files. The mean follow-up time was 40 months (median 37, range 3-85) for the whole group of patients (n=664).

Data-base search

The second method of data collection used in this study was a data-base search used for **paper II**. The protocol of the SPCG 6 study required a medical history to be obtained and a medical examination to be performed at the time of inclusion. All previously repaired or prevalent hernias should therefore, in principle, have been recorded at this point. The patients were then seen at 12 weekly intervals during follow-up until disease progression, withdrawal from the study or death. At each visit the patient was actively asked for any new medical conditions that had developed since their last visit and the protocol required each new condition to be recorded as an adverse event. No new physical examination was required in the absence of suspicious events. Thus, all newly developed symptomatic inguinal hernias mentioned by the patients were recorded, but subclinical hernias were not.

We approached the Scandinavian prostate cancer group and AstraZeneca and asked if we could use this very large material of prostate cancer patients of a similar, albeit slightly higher age, as the typical RRP patients, to establish the base-line epidemiological data on inguinal hernia we were looking for. We were kindly granted the permission to use the data by the SPCG and AstraZeneca. The database was searched for any adverse event including the word “hernia” by Dr Thomas Morris from AstraZeneca. We were provided with the extracted data for analysis

and each of these events was then reviewed. Of the included patients (n=1105) all hernia events except de novo inguinal hernias were disregarded (e.g. incisional hernia, abdominal hernia or “worsening” of an already existing hernia). Mean follow-up was 39 months (median 42, range 3-72) from inclusion in SPCG 6 for the non-surgical group and 50 months (median 47, range 5-155) from time of surgery for the RRP group. A mean time of 20 months (median 11, range 0.5-151) has been added to the follow-up time for the RRP group, being the time from surgery to the time of inclusion in SPCG 6.

Patient administered questionnaire (PAQ)

The third method of data collection used in this study was patient administered questionnaires (PAQ). A different PAQ was used for each of **papers III & IV**.

In **paper III** the PAQ on inguinal hernia was part of a larger quality control instrument which was distributed prospectively. The PAQ was given to the patient prior to the operation and was redistributed at 3, 6, 12, 18, 24 and 36 months postoperatively. The part of the questionnaire concerning inguinal hernia is shown in original and in English translation in appendix 1. It contains questions on previous inguinal hernia surgery, prevalent inguinal hernias at the time of RRP and any postoperative inguinal hernia development. Mean follow-up was 25 months (median 24, range 3-36) for the PAQ group (n=207). The data obtained from the PAQ for these patients was compared to the corresponding data obtained from the PFS on the same patients.

For **paper IV** a retrospective PAQ was constructed asking about preoperative inguinal hernia morbidity and about any de-novo inguinal hernia presenting after the patients’ respective urological surgery. The questions were made simple and straight forward and the questionnaire, exemplified by the one sent to cystectomy patients, can be seen in original and in English translation in appendix 2. The questionnaires for the other investigated diagnoses differ only in the introductory text. When analyzing the data a “Don’t know” answer was considered as a “no” answers. The mean follow-up time for the PAQ patients in

paper IV was 69 months (median 70, range 23-138) for the OP group, 71 months (69, 28-141) for the PLND group and 67 months (68, 23-132) for the cystectomy group.

Statistical methods

We have calculated Kaplan-Meier plots to present continuous incidence data in **papers I-IV**. A Life Table plot was employed for the PAQ data in **paper III** since this data was pooled during certain predetermined time intervals, rather than continuously. The log rank (Mantel Cox) test was used to test the significance of differences in **papers I-III**. In **paper IV** we compared the PAQ data from **paper III** and the base-line data on non-surgical men from **paper II** to the collected material. However, even though we believe that the data from the different groups in **paper IV** is comparable, it is collected with different methods. We therefore chose not to perform any statistical analysis of differences between the groups. For **paper III & IV** we used the Kaplan-Meier estimates to determine the cumulative inguinal hernia incidence at different times. In **paper IV** we estimated the cumulative inguinal hernia incidence at 24 months, including confidence intervals, for all five groups. This data was illustrated in a Forest plot. Furthermore we calculated the annual attributional morbidity for inguinal hernia for the first five postoperative years by considering the hernia morbidity for the non-surgical group from **paper II** as the background morbidity. The excess inguinal hernia morbidity attributable to each consecutive postoperative year was then calculated by subtracting the background morbidity from the inguinal hernia morbidity for each postoperative year and for each surgical group.

In **paper I & III** a multivariate Cox proportional hazards model was used to calculate the relative risks attributed to the studied potential risk factors. The Mann-Whitney U test was used in **paper I & II** for testing differences in age.

All statistics were made using the software StatView for Windows versions 4.0 to 5.0.1 and the SAS 9.1.3 software, SAS Institute Inc., Cary, NC. Consultations were made with statistician

Catrin Berqvist, PhD, for planning and executing statistical analyses of the study.

RESULTS

Paper I: 51 of the 375 RRP patients (13.6%) developed a postoperative inguinal hernia during the follow-up period, including 4 patients with bilateral hernias. Mean time to the hernia diagnosis was 14 months (median 10, range 1-58). The cumulative inguinal hernia free survival was significantly lower for the RRP group than for the non-surgical group (log rank [Mantel Cox] test $p=0.013$) (Fig 1, **I**). 14 of the 184 PLND patients (7.6%) developed inguinal hernia during follow-up. This number was not significantly different from that of either the non-surgical or the RRP group. The two risk factors for postoperative inguinal hernia development that were significant in the study were increased age (Mann-Whitney U test $p=0.05$) and postoperative anastomotic stricture (Cox proportional hazards ratio 8.6 [$p=0.007$]). There were too few patients and events regarding preoperative inguinal hernia morbidity in the study to perform any statistical evaluation of this factor. However, 9 of the 51 patients (18%) who developed a postoperative hernia had undergone previous hernia repair as compared to 5 of the 95 (5%) investigated RRP patients without postoperative hernia.

Paper II: 23 (2.4%) of the 953 patients in the non-surgical group developed an inguinal hernia during the follow-up. The corresponding figure in the RRP group was 13 (8.6%) of the 152 patients (log rank [Mantel Cox] test $p=0.010$) (Fig. 1, **II**). There were no significant difference in age between the patients who developed inguinal hernia and the ones that did not.

Paper III: Of the 664 patients in the PFS 89 (13%) developed postoperative inguinal hernias: 30 left sided, 37 right sided, 3 bilateral and 19 on unknown side. The mean time to hernia was 16 months (median 11, range 3-71). When data from the PFS was analyzed with Cox proportional hazards ratio regarding PLND, preoperative inguinal hernia morbidity, postoperative stricture, duration of surgery and age the only significant risk factor was age ($p=0.0220$) (Table 2, **III**).

Of the 207 patients in the PAQ 33 (16%) reported a postoperative inguinal hernia after a mean time of 13 months (median 12, range 3-36). When a Cox proportional hazards ratio

analysis was made on the PAQ-subgroup preoperative inguinal hernia morbidity turned out to be a significant risk factor for the development of postoperative inguinal hernia ($p=0.010$) (Table 4, **III**). This difference was also significant in a Life-Table survival analysis (log rank [Mantel Cox] $p=0.0103$) (Fig 2, **III**).

The cumulative postoperative inguinal hernia incidence detected by PFS was 7.6%, at 12 months, 11.6% at 24 months and 13.1% at 36 months postoperatively. The corresponding values from the PAQ were 10.8% at 12 months, 15.7% at 24 months and 19.5% at 36 months postoperatively (Table 1, **III**).

In a sub-analysis of the 207 patients who had answered the PAQ, the PFS data and the PAQ data could be compared regarding postoperative inguinal hernia development as well as preoperative inguinal hernia morbidity. The PAQ was clearly superior to PFS in detecting both postoperative inguinal hernia and preoperative inguinal hernia surgery (table 3, **III**). Obviously PFS, on the other hand, was an accurate tool for identifying patient age at the time of surgery, the type of surgical procedure performed, the duration of the procedure and the occurrence of postoperative anastomotic strictures.

Paper IV: The cumulative incidence of inguinal hernia at 24 months after surgery extracted from the respective Kaplan-Meier estimates (Fig 1, **IV**) was 8.1% for the OP group, 8.5% for the PLND group, 14.3% for the cystectomy group. The corresponding figures for the 207 RRP patients evaluated by PAQ from **paper III**, and from the non-surgical patients in **paper II** were 15.7% and 0.78% respectively. When illustrated in a Forest plot with 95% confidence intervals there was a distinct difference between the non-surgical group and the patients who underwent surgery (Fig 2, **IV**).

The annual attributional risk was high, 5-11%, the first postoperative year after the investigated surgical procedures. The attributional risk then subsequently approached the background morbidity of the non-surgical control group. After 3-4 years of the respective surgical procedures there seemed to be no increased risk of inguinal hernia development (Fig 3, **IV**).

DISCUSSION

Methodological considerations

In this study three fundamentally different methods of data collection have been used, patient file survey (PFS), data-base search and patient administered questionnaires (PAQ).

PFS, used for **paper I & III**, seemed the most obvious method of data collection in the beginning of this study. All previous reported data on post-RRP inguinal hernia development was based on PFS (Regan et al. 1996; Fischer and Wantz 1997) and the patient files were readily available at the clinic. It is a retrospective method and thereby suffers disadvantages. The method is obviously good at determining patient age at surgery as well as duration and type of the procedure since these are hard facts always recorded in the patient files. PFS is also accurate for finding post-RRP anastomotic strictures in the investigated patients since this is a complication detected and managed by urologists in all cases. On the other hand, PFS has a low sensitivity for detecting both preoperative inguinal hernia morbidity and postoperative inguinal hernia development. No direct question regarding inguinal hernia was asked by the urologist and no directed investigation of the groins was performed at admission for RRP. A previous hernia repair without recurrence usually leaves little residue and many years could have passed between the time of this procedure and the present RRP. The patient and the urologist have the present cancer operation as well as more imminent potential cancer recurrence and other complications on their minds both at the time of admittance for the RRP and at follow-up visits. A previous inguinal hernia repair many years ago may therefore not seem relevant in this context and may well not be commented in the clinical file. The knowledge of inguinal hernia in connection to RRP was not generally acknowledged at the time when the patients in our studies were admitted for surgery. Thus, an inguinal hernia developing during follow-up might not be connected to the previous RRP, either by the patient or the urologist. The patient may therefore choose to take a newly developed hernia to their general

practitioner for measures. All these factors probably contribute to the low sensitivity of PFS for detection of inguinal hernias. Thus, PFS, when not combined with active questioning and/or examination, is liable to substantially underestimate the incidence of pre- and postoperative inguinal hernia morbidity. The specificity for inguinal hernia detection by PFS, on the other hand, is likely to be high since all hernia events should be physician confirmed to be recorded in the patient file.

The second method of data collection was used in **paper II**. During the process of **paper I**, in which we investigated the subgroup of SPCG 6 patients at our hospital, we saw the possibility to investigate a much larger group of patients with non-metastatic prostate cancer not subjected to RRP, using the entire SPCG 6 database of more than 1000 patients. This would allow us to establish a very large control group. We could also identify a new group of RRP patients within the SPCG 6 database, and investigate the post-RRP inguinal hernia incidence. For **paper II** we therefore used the whole database of the SPCG 6 study and screened for inguinal hernia events. This method has its similarities to PFS. The database was not specifically designed for inguinal hernia detection. No specific questions on inguinal hernia were presented to the patients and no aimed physical examinations of the groin region were performed unless the patient complained of symptoms. However, a physical examination as well as a medical history was obtained from the patient at the time of inclusion in the SPCG 6 study and the patients were then followed at 12-weekly intervals until prostate cancer progression, death or withdrawal. At each visit, the patients were actively asked whether any *new medical conditions* had developed since the last visit. The protocol required each new condition to be recorded as an adverse event. Events could be orally reported by the patients, and/or detected or verified at physical examination by the urologist during the visit. The frequent and long lasting contacts between the patients and the investigating urologist often created a strong patient/physician relationship between the two, in which the investigating urologist sometimes ended up in the role of the patients' general practitioner. Thus, any newly developed symptomatic inguinal hernia would be recorded, but subclinical hernias would not. We believe that the risk of underreporting of inguinal hernia events from this database

search is less than after PFS. Any adverse event at the regular visits of the SPCG 6 study should have been reported in the clinical file record, whilst in the general practice, with perhaps yearly visits the presence of a condition such as an inguinal hernia, seemingly unrelated to prostate cancer, may be overlooked. We believe that the incidence from **paper II** reflects a baseline annual inguinal hernia incidence of men with prostate cancer of this age group, not subjected to surgery, which is accurate enough to be used as control to other materials. Furthermore, even though these patients belong to a selected group with a specific disease, prostate cancer, we have no reason to suspect any inguinal hernia protective qualities of this disease. To the contrary, an increased prevalence of bladder outlet obstruction is likely to be present in this patient group due to their prostate disease (Whitmore et al. 1991; Crain et al. 2004), and this is a known risk factor for inguinal hernia development (Abramson et al. 1978).

There could have been a long time period between possible previous hernia surgery and the inclusion of the SPCG 6 study increasing the risk of recall bias. Recall bias is a systematic error introduced due to differences in accuracy or completeness of recall to memory, by the patient, of past events or experiences (Stedman's 1995) and some of these hernias, seemingly unrelated and irrelevant to prostate cancer, may therefore easily have been overlooked by the patient at the time of inclusion. This uncertainty of the accuracy of previous medical history was the reason why we decided not to use the baseline data from the time of inclusion regarding previous inguinal hernia morbidity and abdominal surgery. Some men in SPCG 6 may also have developed inguinal hernia during the time between their RRP and the inclusion in the study (mean time 20 months [median 11]). We knew from previous studies that the mean time to hernia development after RRP is less than a year (Regan et al. 1996; **I**). Some of these hernias may well have been overlooked by the patient at the inclusion, deemed unrelated and irrelevant to the prostate cancer at hand. In **paper II** a significant increase in post-RRP inguinal hernia incidence was demonstratable, although somewhat lower than in our previous report. Notably, the cluster of inguinal hernias during the first year noted in other materials was less pronounced (Fig 1, **I** & Fig 1, **II**). We believe that the somewhat lower incidence of post-RRP

inguinal hernia in this material may be due to an underreporting of inguinal hernias in the previous medical history of the patients at the time of inclusion in SPCG 6. Thus, we consider the database search to have a high sensitivity for detecting inguinal hernia events occurring during the active phase of the study but a somewhat lower sensitivity for previously occurred events. The study, therefore, probably provides us with reliable incidence data on the non-surgical patients, but less so for the post-RRP patients.

The third method used for data collection in this work was two different PAQs, one prospectively administered PAQ in **paper III** and one retrospectively administered PAQ in **paper IV**. In the prospectively administered PAQ, the patients received a direct question on whether they ever had undergone inguinal hernia surgery, if they had a present inguinal hernia and, postoperatively, whether they had developed an inguinal hernia since the previous questionnaire (see appendix 1).

The higher sensitivity for postoperative inguinal hernia detection of the prospectively administered PAQ as compared to the PFS which emerged in **paper III** led to considerations as to what method to use for **paper IV**. The follow-up after RRP is rather standardized and the patients are, in most cases, monitored by the operating urologist for a long period of time. Most of these men are relatively healthy and physically active at the time of their RRP in order to be considered as candidates for the procedure (Aus et al. 2005). These factors increase the likelihood that an inguinal hernia will be noticed during the follow-up period, recorded in the patient file and detected in the PFS. Despite this, only about 2/3 of the hernias were detected by PFS (**III**). When planning **paper IV** we were expecting an even lower detection rate for PFS due to additional confounding factors. After open prostatectomy for benign prostate hyperplasia (OP), as this is a procedure for a benign condition, there are usually only one or two follow-up visits at three to six months postoperatively and many inguinal hernias may not present themselves this early. After pelvic lymph node dissection (PLND) for staging before radiotherapy against prostate cancer, the patients are monitored for a long period of time, but by a non-surgically schooled oncologist likely to concentrate on known postradiation complications (Pirtskhalaishvili et al. 2001; Peeters et al. 2006). Postoperative inguinal hernia development

may therefore be overlooked and would thus not be detectable by PFS. Despite this, we noted a clear tendency of an increased rate of post-PLND inguinal hernia development in **paper I** and Ichioka and co-workers could later confirm this suspicion (Ichioka et al. 2004). Patients subject to cystectomy are closely and regularly followed by the operating urologist. Due to the aggressive nature of the bladder cancer and the extensiveness of the cystectomy procedure they are suffering high per- and postoperative morbidity rates as well as a high postoperative mortality rate (Knap et al. 2004). A relatively benign lesion such as an inguinal hernia is therefore at risk of being overlooked during the postoperative period. Bearing these factors in mind, we designed a retrospective PAQ rather than using PFS for postoperative inguinal hernia detection in **paper IV**. The retrospective design of the PAQ for **paper IV** increased the risk for yet other confounders. For retrospective studies these could be that the study group may differ from other materials in ways that are not obvious and are not identified by the investigators, the study group may be incomplete since study patients could have died from the investigated condition and a possible recall bias by the patients may effect the results (Winter 1997). The questionnaires from **papers III & IV** are also non-validated instruments, a potential weakness of both studies. Despite that only 259 (60%) of the 432 identified patients in **paper IV** were alive at the time of the study (OP=95/130, PLND=88/118, cystectomy=76/184) we have no reason to believe that inguinal hernia morbidity influences the mortality in these groups in any significant way. The mortality rate of inguinal hernia is very low today (Fitzgibbons et al. 2006). Furthermore, the follow-up time for the three groups is also long (table 1, **IV**) and the mortality rate due to high age, especially in the OP-group, and to bladder cancer complications in the cystectomy group during the follow-up time can therefore be expected to be high. We therefore believe that the 60% remaining of the investigated patients constitutes a representative sample of the total group regarding inguinal hernia formation.

The response rate of the remaining patients was also generally high, further reducing the influence of confounding factors. To minimize the influence of possible recall bias and the lack of validation of the questionnaires we kept the design as simple as

possible with “yes/no/don’t know” answer alternatives (see appendix 2). In all cases when the patients displayed any uncertainty, e.g. answered “don’t know”, on their inguinal hernia status, they were considered as to have “no hernia”. The directed questions were likely to raise the patient’s awareness of his groins and any discomfort is thereby likely to have been noticed by the patient. Such discomfort may be of non-hernia origin and thereby result in a false high value. However, previous studies have shown that self-reporting of inguinal hernias rather underestimates the incidence as compared to clinical examination by a physician (Abramson et al. 1978; Rubenstein et al. 1983; Rutkow 1998). Only clinically overt hernias will be noticed by the patient and reported, while subclinical lesions remain unreported. A degree of under-reporting is therefore likely in both the prospectively and the retrospectively administered PAQ.

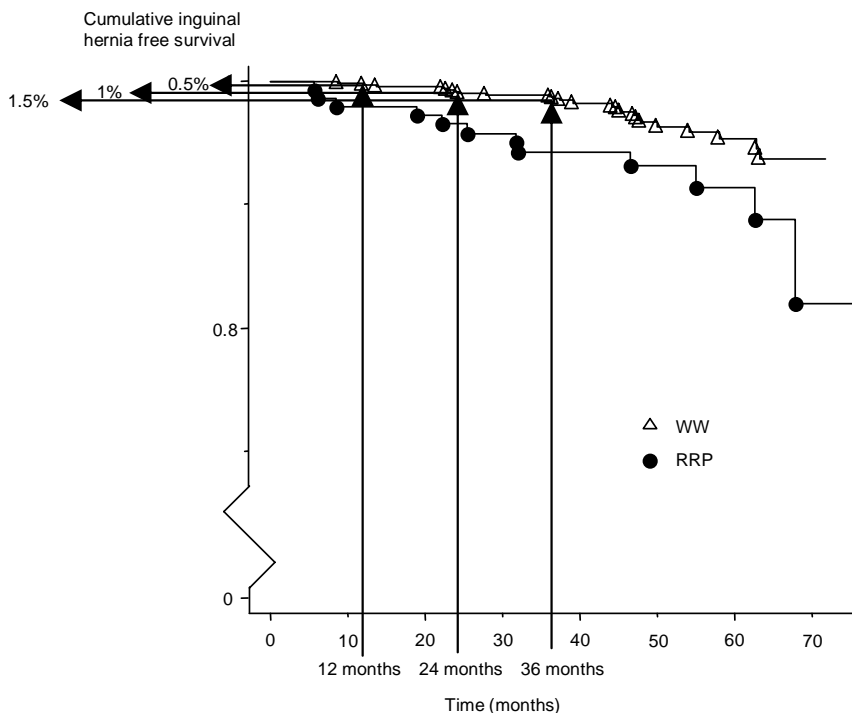
For **paper IV**, a PFS was also performed. As could be expected in the light of our findings in **paper III** and the discussion above, this proved to be a lot less sensitive for inguinal hernia detection than did the retrospectively administered PAQ. All but one of the inguinal hernias detected by the PFS was also reported in the PAQ. Although the PFS also revealed an increased rate of postoperative inguinal hernia we chose not to include this data in the manuscript, deeming the PAQ based data to be more valid.

Epidemiological considerations

Crude incidence, i.e. the total number of inguinal hernias divided by the total number of patients in the study, was presented by Regan (Regan et al. 1996) as well as in our first papers (**I & II**). However, these figures are dependant on the length of the follow-up time and the number of dropouts during the study and are thereby not readily comparable to figures from other studies. By comparing longitudinal Kaplan Meier estimates at specific times with censoring of patients with limited follow-up these differences are accounted for, making results from different studies more comparable. We had presented hernia-free survival data in both **paper I** and **paper II** graphically based on these calculations. The cumulative incidence of inguinal hernia development at various

times can be approximately extracted as illustrated in Figure 7. The annual incidence of inguinal hernia for men not subjected to surgery of the investigated age group could thereby be calculated to approximately 0.5%.

Figure 7



*Extraction of approximate cumulative incidence at 12, 24 and 36 months from Kaplan-Meier plot from **paper II**.*

In **paper III** we reported the cumulative incidence at 12, 24 and 36 months, obtained from the corresponding Kaplan-Meier estimates (Table 1, **III**). The cumulative incidence at 24 months seemed the most useful figure since most inguinal hernias develop in the first two postoperative years and this figure was used for further comparison between various groups in the study.

The lack of solid epidemiological data on such a common lesion and with such a long history as inguinal hernia is amazing. The study of Abramson and co-workers from 1978 (Abramson et

al. 1978) on the population in western Jerusalem probably provides the most accurate prevalence figures in the literature. However, we have not been able to identify any accurate incidence figures. There are references to an incidence in the general population of 3.5 to 5% in some papers (Regan et al. 1996; Nielsen and Walsh 2005; Hicks et al. 2006). There is no mentioning if this is the annual incidence or the life-time cumulative incidence in any of these references and there seems to be a slight confusion of concepts since most of these reports directly or indirectly refer to either Rutkow's very illustrative papers from 1998 (Rutkow 1998) and 2003 (Rutkow 2003) and/or the study by Abramson from 1978 (Abramson et al. 1978). Professor Rutkow, when specifically asked by this author, agrees that no such incidence data on the general population can be extracted from his articles (Rutkow 2005). Furthermore, for an annual incidence, a figure of 3.5% would be extremely high and would mean that the cumulative risk (probability) for a single person to develop an inguinal hernia would be 83% after 50 years ($1-[1-0.035]^{50}$) and 92% after 70 years ($1-[1-0.035]^{70}$). Thus, these incidence figures are clearly incorrect. An annual incidence of 0.5%, as we found in **paper II**, would by an analogous calculation lead to a cumulative risk for a person to develop an inguinal hernia of 22% after 50 years and 30% after 70 years. This figure seems more likely and is further supported by our data from **paper III** where we have found previous inguinal hernia surgery or a present inguinal hernia at the time of surgery in approximately 16% of the patients with a mean age of 63 years. Abramson also presents a life-time prevalence rate of inguinal hernias in men 65-74 years of age of 40%. A backwards probability calculation of this to estimate the annual incidence gives the following equation: $0.40=1-x^{70}$; $x=0.993$, leading to an annual incidence of $1-0.993$, or 0.7%.

Since increasing age is a known risk factor for inguinal hernia development (Abramson et al. 1978; Rutkow 1998) the incidence is likely to vary somewhat during life. However, we believe that the incidence from **paper II** does not only reflect a baseline annual inguinal hernia incidence of non-surgical men with prostate cancer of the investigated age group, but is also a good estimate of the annual incidence of all non-surgical men of this age group. We therefore used our data on non-surgical men from **paper II** as a

control group to all investigated groups in **paper IV** and could thereby illustrate a rather large increase in postoperative inguinal hernia after all investigated procedures.

General considerations

When we initiated this work six years ago very little was known about the occurrence of inguinal hernias following RRP. Only two reports had been published suggesting that the problem existed (Regan et al. 1996; Fischer and Wantz 1997) and virtually nothing was known about potential risk factors or underlying mechanisms. Furthermore, the underlying morbidity in inguinal hernia in this age group of males was unknown. **Paper I** constitutes the first large, well defined material where the postoperative incidence of inguinal hernia could be shown to be increased as compared to a non-surgical group of patients (13.6% vs. 2%). This study clearly established postoperative inguinal hernia as a true complication following RRP. The first aim of the present study, to establish the incidence of post-RRP inguinal hernia, was thereby achieved.

Paper I also showed a tendency, although not statistically significant, of increased incidence of postoperative inguinal hernia after PLND as compared to the non-surgical control group. However, the non-surgical group was small (n=65) and hernia events were very few. The PLND group, although large (n=184), was followed postoperatively mainly by oncologists who may not have been focusing on a complication of inguinal hernia type. With a larger control group the difference would probably have been statistically significant. The seemingly high incidence of inguinal hernia after PLND generated the hypothesis that the mobilization of the bladder medially to expose the iliac vein during PLND may render the anulus internus incompetent, thus increasing the risk of hernia formation. PLND might thus add to the risk of post-RRP inguinal hernia formation when performed concurrently. Our conclusions from this paper were furthermore that careful inquiry about previous hernias and a physical examination of the groins prior to the RRP was important.

Several questions arose during the completion of this work. The lack of epidemiological data on inguinal hernia was a major one. The epidemiological aspects on inguinal hernia have been discussed in further detail above but the varying prevalence figures and the general absence in the literature of solid incidence figures in the male population made it uncertain to which degree the incidence figures seen after RRP were indeed increased. The small control group of non-surgical men in **paper I** rendered the data obtained to be flawed by the shortcomings of wide confidence intervals and low power. Despite this we could show a difference between the RRP and the non-surgical patients. For future work we realized that the base-line inguinal hernia incidence needed to be better established in a larger group of men with prostate cancer of similar age.

In **paper II** we therefore studied a very large group of non-surgical men with prostate cancer. The patients were also of similar age to the investigated RRP patients. The most important result from this paper was the determination of a crude overall incidence of inguinal hernia in this non-surgical population of men with M₀ prostate cancer of similar age of 2.4% after a mean follow-up time of 39 months. This figure is substantially lower than after RRP. A baseline annual inguinal hernia incidence of less than 0.5% could also be extracted from this paper. We could also show a high post-RRP inguinal hernia incidence. Thus, the background incidence of inguinal hernia was now established and we had again shown that post-RRP inguinal hernia was a reality, using a different patient set. The establishment of the “normal” background incidence of inguinal hernia in men of a similar age group was thereby achieved and we could move on to explore the impact of potential risk factors and mechanisms of inguinal hernia development in **paper III**.

Starting from the year 2000, a number of patients with low-risk tumors at our clinic were not subjected to simultaneous PLND at the time of RRP. The inguinal hernia incidence after RRP with or without concurrent PLND could thus be compared, and the hypothesis that concurrent PLND might add to the risk of postoperative inguinal hernia raised in **paper I**, further discussed by Ichioka (Ichioka et al. 2004), could thereby be investigated. In addition to this, we investigated the influence of a number of other

potential risk factors. The patient administered quality control questionnaires (PAQ), which had been introduced at our clinic, including questions on pre- and postoperative inguinal hernia morbidity, also gave us the opportunity to evaluate the data obtained with the method of PFS we had used for postoperative inguinal hernia detection thus far, and compare it to data obtained through a prospectively administered PAQ.

In **paper III** a lot of time and effort was dedicated to methodological considerations. The results clearly showed that these were very important when investigating postoperative inguinal hernia development. Retrospective PFS, although providing reliable data concerning postoperative anastomotic strictures, patient age at surgery and duration and type of surgery, had a low sensitivity of detecting both preoperative inguinal hernia morbidity and postoperative inguinal hernia development as compared to a PAQ. The increase in cumulative incidence for the RRP patients in the PAQ group (n=207) was 15 fold as compared to non-surgical patients in **paper II** and the problem seemed even greater than previously anticipated. Furthermore, in order to obtain reliable data regarding postoperative anastomotic strictures, patient age at surgery and duration and type of surgery as well as preoperative inguinal hernia morbidity and postoperative inguinal hernia development, a combination of the PFS and the PAQ was essential.

We could also show that PLND did not increase the risk of inguinal hernia development, nor did increased duration of surgery or postoperative anastomotic stricture. Age was once again shown to be a risk factor, although with small influence.

The concept of preoperative inguinal hernia morbidity is highly complex and requires further clarification. The concept involves previous inguinal hernia surgery on either side as well as prevalent inguinal hernias at the time of the RRP. Patients with prevalent inguinal hernias which were repaired at the time of RRP were considered similar to those who had had previous inguinal hernia surgery. For the patients with prevalent inguinal hernias which were not repaired at the time of RRP, only the opposite side could be considered during the postoperative follow-up. A prevalent inguinal hernia not repaired at the time of RRP thereby reduces the “groins at risk” by 50% in our studies for that particular

patient, since he only has one groin left to develop a *de novo* post-RRP inguinal hernia. Previously repaired inguinal hernias, uni- or bilaterally, are generally associated with an overall cumulative risk of recurrence of 5% within 5 years (Nilsson et al. 1998). The risk of developing a recurrent inguinal hernia in a groin previously operated on after RRP is unknown, but is likely to differ from the risk in a groin not operated on. Thus, the individual risk of post-RRP inguinal hernia development varies for these patients depending on the number of “groins at risk” and previous inguinal hernia surgery. This will affect the overall risk of post-RRP inguinal hernia in the investigated population in a complex and unpredictable way. In **paper III** we therefore choose to add the previous and prevalent inguinal hernia groups together, forming the “preoperative inguinal hernia morbidity” group, in order to simplify calculations. We also choose to not adjust for any variation of “groins at risk” in the patient material. The prospectively administered PAQ achieved a higher detection rate of both post-RRP inguinal hernias and preoperative inguinal hernia morbidity than the PFS did. Based on the PAQ data preoperative inguinal hernia morbidity emerged as a significant risk factor for post-RRP inguinal hernia development, especially on the contralateral side of previous inguinal hernia repairs.

The findings in **paper III** indicated that no unique maneuver of the RRP seemed to cause the increased rate of postoperative inguinal hernia development. PLND also seemed to cause an increased rate of postoperative inguinal hernia development (Ichioka et al. 2004). However, the combination of RRP and concurrent PLND did not increase this rate further. Thus, postoperative inguinal hernia development ought not to be due to any unique maneuvers of either procedure, but rather to what they have in common. Our conclusion was therefore that the midline incision *per se* and the following disruption of the anatomic-physiologic balance in the abdominal wall was the triggering factor.

It has in the past been debated whether appendectomy and the “McBurney incision” could cause right sided inguinal hernias (Lichtenstein and Isoe 1951; Gue 1972; Leech et al. 1972; Arnbjornsson 1982; Malazgirt et al. 1992; Avsar et al. 2002) but apart from this no other reports on potential association between

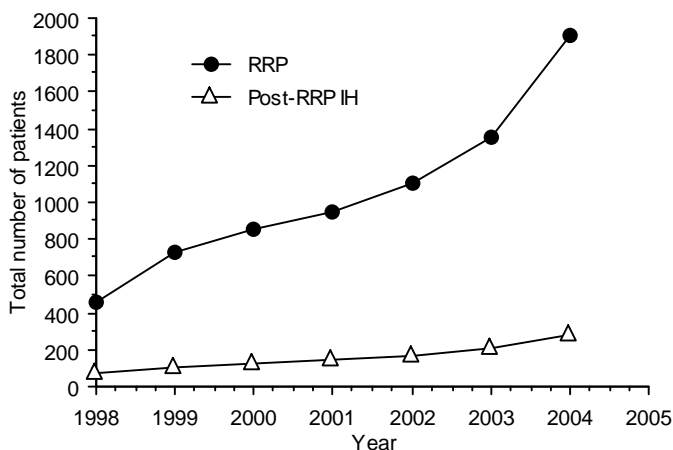
abdominal surgery and inguinal hernia development had appeared in the literature until Regan and co-workers published their findings 1996 (Regan et al. 1996).

Ichioka and co-workers could, using retrospective PFS, not show an increased rate of inguinal hernia after cystectomy in 56 patients (Ichioka et al. 2004). We suspected that this could be due to the very low sensitivity of PFS expected after this procedure and the small sample size. The higher sensitivity for postoperative inguinal hernia detection of the PAQ as compared to PFS in **paper III** gave us the idea to construct a new tool for postoperative inguinal hernia detection, a retrospectively administered PAQ. The use of this PAQ in **paper IV** confirmed our suspicion that the rate of postoperative inguinal hernia was increased after all these three urological operations. These procedures have the lower midline incision in common but are quite different in several other aspects such as duration, opening of the peritoneum, construction of urinary diversions etc. We also presented the attributable annual risk as a variable in this paper. This clearly illustrates that the increased incidence of inguinal hernia caused by the various procedures during the first two to three postoperative years, later approaches the background risk by year four or five. The unambiguous results from **paper IV** further support our hypothesis that, in men of this age group, a midline incision *per se* is causative for postoperative inguinal hernia development. We had now established that postoperative inguinal hernia is not a unique phenomenon following RRP, but that it also occurs following other types of surgery performed through lower midline incisions, and that the postoperative incidence after the investigated procedures seems to be similarly high.

Further studies on the incidence of postoperative inguinal hernia after various types of abdominal surgery will no doubt show the magnitude of this problem. Nevertheless, our results suggest that a considerable proportion of all inguinal hernias in the population may be due to previous surgery. Approximately 3500 lower midline incisions were made on males in urological surgery in Sweden in 2004 and almost the double in general surgery (The Hospital Discharge Register 2005). A cumulative incidence of inguinal hernia of 15% at 24 months (**paper III & IV**) and a requirement of surgical repair rate of 80%, as data from **paper I**

indicates (Table 3, I), would translate into more than 1000 inguinal hernias annually, or more than 5% of the 17000 inguinal hernia repairs performed annually in Sweden (The Hospital Discharge Register 2005). The number of lower midline incisions performed are also increasing, especially RRP, as can be seen in Figure 8. The problem of postoperative inguinal hernias is thereby further increased. Thus, apart from the implications for the individual patient, the magnitude of this previously unrecognized problem for society is considerable and increasing. The average cost of in- and outpatient hernia repairs is approximately 1000 Euro per patient (Saviano et al. 1996; Andersen et al. 2003). 1000 hernia repairs would consequently lead to a cost for the Swedish society of 1.000.000 Euro each year. In addition to this, the cost of sick leaves and the suffering and risk of complications for the individual patients must be considered.

Figure 8



Actual increase in number of RRP performed annually between 1998 and 2004 and projected increase in the number of inguinal hernias due to RRP if 15% of patients develop post-RRP inguinal hernia (data adapted from the Swedish national board of health and welfare: The Hospital Discharge Register).

Etiological considerations

The last aim of the present study was to form a hypothesis regarding the etiology of postoperative inguinal hernia formation. Based on data gathered from all four papers, such a hypothesis has been formed.

The vast majority of the postoperative inguinal hernias found after RRP were indirect, or lateral, as shown in **paper I**. The fact that most post-RRP inguinal hernias are indirect implies that the defect somehow affects the integrity of the anulus internus and its “shutter mechanism”. Various potential mechanisms could be the cause of this disruption.

Direct damage to the innervation of the abdominal muscles involved in the “shutter mechanism” has been reported after appendectomy (Arnbjornsson 1982; Avsar et al. 2002). The appendectomy incision can cause paralysis of the inferior fibers of the transversus abdominis muscle, thereby leading to a defective tension of the inner anulus of the inguinal canal. These findings are supported by electromyographic findings (Arnbjornsson 1982) and are suggested to cause an increased risk of right sided inguinal herniation after this kind of incision. However, the innervation of the lateral muscles of the abdominal wall is multiple and the nerves are extending dorsolaterally from the lower intercostal and upper lumbar nerves (Quinn 2002). While a lateral incision for appendectomy may well damage these nerves, a midline incision is very unlikely to cause a paralysis of the “shutter mechanism” by direct nerve injury.

An indirect damage to the nerves of the lateral abdominal muscle by the potential ischemia induced by the self-retaining retractor has been discussed as a contributing factor to post-RRP inguinal hernia formation in **paper I** and by others (Regan et al. 1996; Ichioka et al. 2004). The blood supply of the lateral muscles of the abdominal wall is primarily from the lower three intercostal arteries, the deep circumflex arteries, and the lumbar arteries (Quinn 2002) and is also not likely to be affected by a low midline incision, or by the retractor. Furthermore, if an indirect damage were caused by ischemia, it ought to be influenced by the duration of the procedure, i.e. the period of time during which traction-induced ischemia of the tissue may occur. This was measured in

paper III and the duration was not found to significantly influence the subsequent development of post-RRP inguinal hernia. The rate of postoperative inguinal hernia is high after PLND and OP as well, both being procedures of substantially shorter duration than the RRP. We therefore believe that damage to the innervation of the lateral abdominal muscles, direct or indirect, seems unlikely but to further clarify this aspect studies including electromyographic examination of the abdominal muscles before and after lower midline incisions could be of some interest.

Maneuvers associated with the RRP procedure such as mobilization of the bladder medially to expose the iliac vein before concurrent PLND was also suggested to contribute to post-RRP inguinal hernia development in **paper I** as well as in the paper by Ichioka (Ichioka et al. 2004). The postoperative inguinal hernia incidence after isolated PLND was high in these studies, even though it was lower than after RRP with concurrent PLND, suggesting a possible additive effect of PLND on the incidence following RRP. However, as discussed above, no such effect for RRP + PLND, as compared to RRP only could be seen in **paper III**. Postoperative inguinal hernia is also a common complication to several other quite varying procedures (**IV**) further speaking against any influence of maneuvers specific to RRP. These findings all indicate that the incision *per se* is of the greatest importance for this type of inguinal hernia development.

Postoperative stricture of the anastomotic region, which appeared to be a significant risk factor in **paper I**, did in **paper III** not affect the inguinal hernia incidence in any significant manner. Anastomotic stricture as a risk factor had also been debated after our first paper. Some authors have not found any relationship between postoperative anastomotic stricture and inguinal hernia in their materials (Andersen et al. 2003; Ichioka et al. 2004) while others had too small patient materials to draw any firm conclusions in this matter (Nomura et al. 2005; Twu et al. 2005). The frequency of stricture did not differ between **paper I** and **paper III**. We have no explanation for the discrepancy regarding the association between post-RRP inguinal hernia and anastomotic stricture in our material. However, since no significant influence could be shown in **paper III**, which constitutes a much larger material than **paper**

I., we interpret our data to indicate that any significant influence of anastomotic stricture is unlikely.

Increased age is a known risk factor for inguinal hernia development in general (Abramson et al. 1978; Rutkow 1998) and this relationship is further confirmed in both **paper I** and **III**. Degeneration of connective tissue in the body is known to increase the risk of inguinal hernia formation (Sorensen et al. 2002; Fitzgibbons et al. 2005) and connective tissue degeneration increases with age (Ashcroft et al. 1997; Sorensen et al. 2002). However, the influence of age is small, and the practical clinical consequence for the individual patient of this risk factor is therefore limited.

In **paper III** preoperative inguinal hernia morbidity was a risk factor for post-RRP inguinal hernia development. Furthermore, an increased post-RRP risk of recurrence of a previously repaired inguinal hernia on the same side was suggested. This indicates that a constitutional tendency for inguinal hernia development plays a role in these patients. Such constitutional predisposing factors could be degeneration of connective tissue, patent processus vaginalis or subclinical inguinal hernias, expressed as a preoperative history of inguinal hernia morbidity.

Subclinical inguinal hernias have been suggested to be a possible contributing factor to post-RRP inguinal hernia development (Fukuta et al. 2006). Various materials indicate that subclinical defects of the internal orifice occur in between 5 and 33% of patients (Ajmani and Ajmani 1983; Schlegel and Walsh 1989; Watson et al. 1994; Lepor et al. 2001; Nielsen and Walsh 2005; Fukuta et al. 2006). The Abramson material from Jerusalem reported a prevalence of 14.3% of inguinal hernia for men aged 55-64 years and included a number of subclinical inguinal hernias as the data was gathered by clinical examination and all lesions were included (Abramson et al. 1978). The RAND material did not include subclinical lesions, as the data was gathered by questionnaire, and reported a prevalence of 3.9% in men of the same age group (Rubenstein et al. 1983). The difference in prevalence between the materials may therefore indicate a prevalence of approximate 10% of subclinical hernias in the population. In **paper III** we found 7% clinical inguinal hernias at the time of surgery, but no specific screening was made to identify

subclinical lesions. The actual prevalence is therefore probably higher and subclinical lesions are also likely to be more frequent in patients with preoperative inguinal hernia morbidity. The midline incision and subsequent surgical procedure could be pushing these subclinical hernias into clinically significant inguinal hernias. This conception is further supported by the recent finding of Fukuta and co-workers who reported a prevalence of 20.4% of subclinical inguinal hernias detected by computed tomography scan before RRP (Fukuta et al. 2006). The risk of postoperative inguinal hernia was increased 7-fold among these patients.

Shorter incisions are reported to cause less postoperative inguinal hernias (Nomura et al. 2005; Walsh 2005). Nomura and co-workers perform what they call “minilap RRP”, i.e. a RRP performed through an 8-10 cm incision in the midline above the pubic bone. This observation is very interesting and is further supported by Walsh who has made the same observation using 8 cm incisions when performing RRP (Walsh 2005). The concept that the length of the incision affects the incidence of postoperative inguinal hernia development further supports our theory that the incision *per se* is of causal importance. The mechanism that Nomura and co-workers suggest is that damage to the posterior layer of the rectus sheath, above the arcuate line of Douglas, disrupts the superior attachment of the ligamentum interfoveolare (Hesselbach’s ligament). This, they argue, loosens the inferior end of this ligament, medially of the anulus internus, where it strengthens the transversalis fascia. Their argument is based on the writers’ dissections on cadavers where they found that “Hesselbach’s ligament extended to the posterior layer of the rectus sheath”. Nomura and his co-workers further argue that the “minilap” incision does not extend past the arcuate line, thus leaving the ligamentum interfoveolare intact to protect the anulus internus from indirect hernias. When examining our own procedures we find that the arcuate line is hardly ever included cranially in the incision of our conventional RRP. On the few occasions where the posterior fascia is incised above this line the integrity is usually resutured. The superior attachment of the ligamentum interfoveolare will thereby be re-constructed in the midline and no loosening of the ligament medially of the anulus internus ought to take place.

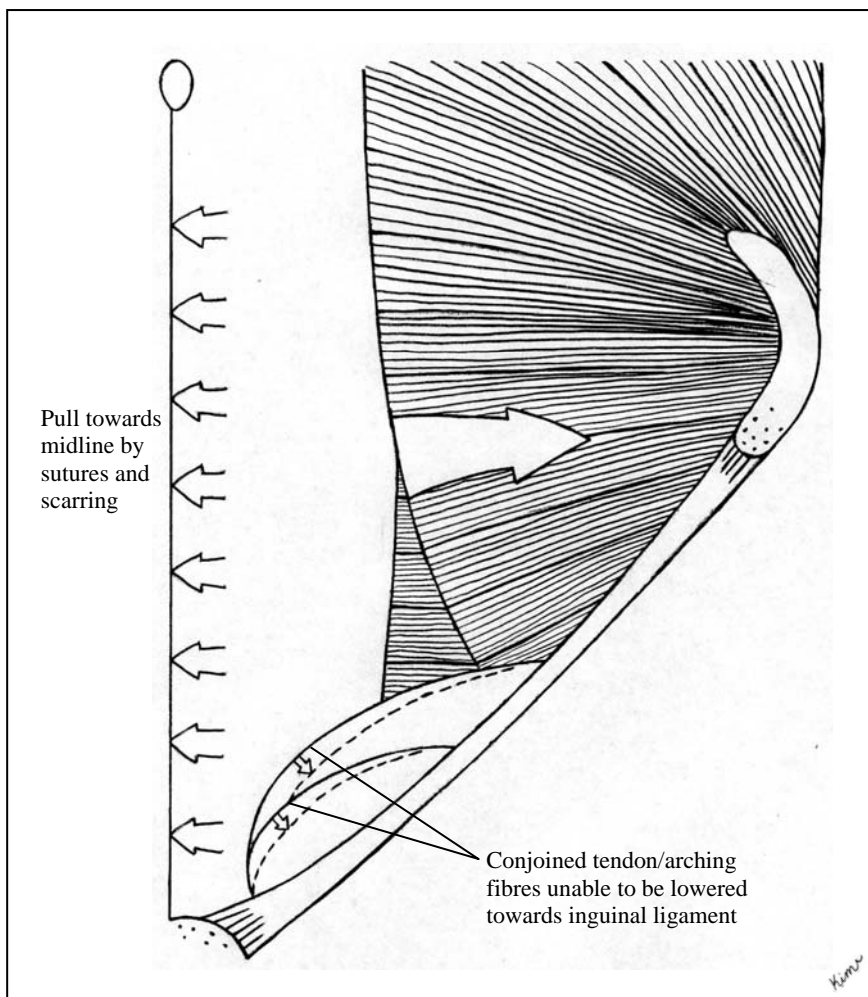
Nomura and co-workers further claim that the “transversalis fascia over the deep inguinal ring was disrupted by both conventional and minilap RRP procedures to a similar degree”, (Nomura et al. 2005). The transversalis fascia covers the rectus abdominis and transversal muscle on the inside but lies separately all the way and is not part of the linea alba of the midline below or above the arcuate line of Douglas (Gray 2000) (Figure 3d, page 14). The lower midline incision cuts through the medial attachment of all layers of the supporting tissues of the inguinal canal and the transversalis fascia is in most cases therefore left unsutured. In our view, various lengths of the midline incision will therefore most certainly lead to various degrees of disruption of the fascia in the midline, regardless whether the incision is extended above the linea arcuata or not.

In our view the resuturing of the lower midline incision will potentially lead to two things. Firstly, the midline attachment of the three lateral abdominal muscle layers will be shortened by the pull of the sutures and the subsequent tissue scaring. This will be the case both above and below the arcuate line of Douglas. The protective action of the shutter mechanism is thereby impaired by a horizontal counteracting force to the straightening of the arching fibers of the transverse and the internal oblique muscles. Thus, the conjoined tendon will be unable to be lowered towards the inguinal ligament as can be seen in Figure 9. Secondly, the lack of attachment of the transversalis fascia medially will do the opposite. By not reestablishing this medial attachment, the counteracting force in the transversalis fascia to the tension of the lateral abdominal muscles above the inguinal canal, will be deprived. The loss of this antagonistic force in the medial direction will redirect the tension of the transversalis fascia and subsequently cause a failure to move the anulus internus craniolaterally as illustrated in Figure 10.

The combined effect will then be that the “shutter” will not close and the anulus internus is left unprotected to the formation of an indirect inguinal hernia. A shorter incision would lead to both a reduced horizontal shortening of the abdominal muscle aponeurosis and a reduced loss of the counteracting force on the transversalis fascia. Thus, the impediment of the shutter mechanism would be

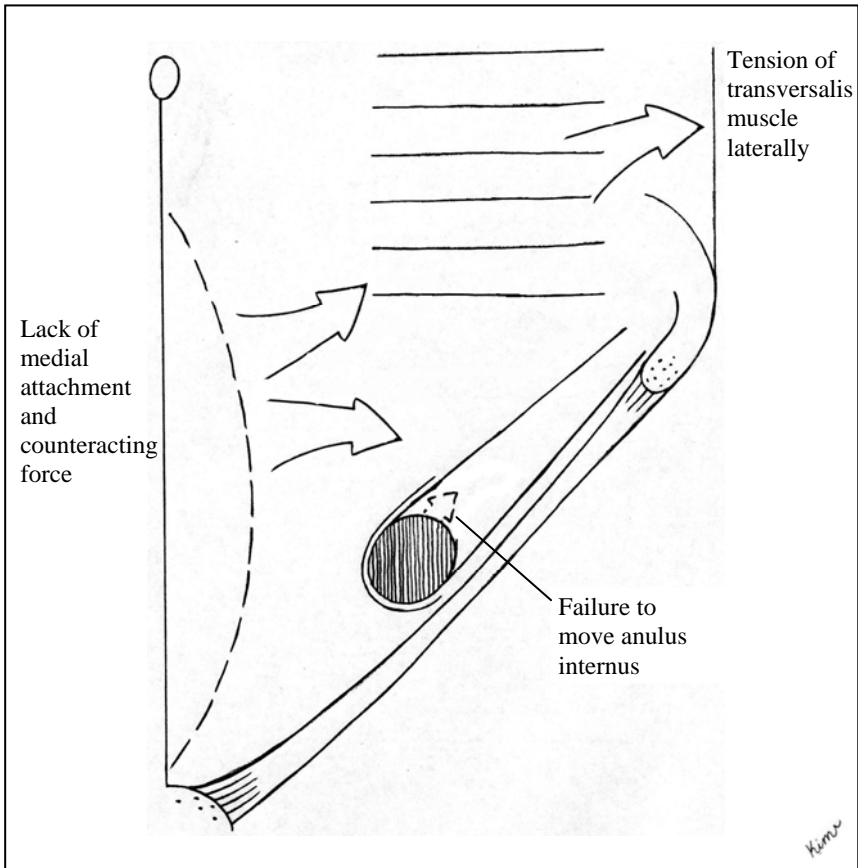
less pronounced if the incision was shorter and the risk of developing a postoperative inguinal hernia would be less.

Figure 9



The pull of the sutures and the subsequent tissue scarring after closing of the incision shortens the midline attachment in the horizontal plane of the three lateral abdominal muscle layers. This results in the failure of the conjoined tendon part of shutter mechanisms to close when internal oblique and transversalis muscles tense.

Figure 10



A midline incision results in the loss of the counteracting force in the transversalis fascia above the inguinal canal. This causes the tensing of the transversalis fascia to become inefficient which in turn causes failure to move the anulus internus craniolaterally.

Future studies

The identification of inguinal hernia as a common postoperative complication to surgery performed through lower midline incisions in males is merely a start. This study has aimed to increase the knowledge on the incidence and risk factors of this complication. However, further studies are needed to clarify many aspects of the problem. Both large epidemiological studies on clinical and subclinical inguinal hernia incidence and prevalence, to more specific studies such as electromyographic examination of the abdominal muscles before and after the incision or a simple study randomizing patients between one long and one short standardized incision would be interesting. Also studies aimed at further clarifying the importance of preoperative inguinal hernia morbidity are necessary. In order to easily perform such studies on inguinal hernia incidence pre- and postoperatively in large patient groups a validation of our PAQs would be of much use.

One thing is clear, lower midline incision does lead to postoperative inguinal hernias in 10-20% of the men operated on. The most pressing issue is therefore to find ways to avoid the complication. Studies on prophylactic measures are warranted. Such a study is also presently conducted at our clinic, and over 350 RRP patients have been included. On these patients a unilateral prophylactic narrowing of the internal inguinal anulus using a non-resorbable return suture lateral to the spermatic cord on a randomized side has been applied. It is too early to draw any firm conclusions from this study, but the preliminary results indicate that a prophylactic measure is both feasible and appealing. Our findings from **paper I & III** indicate that prophylactic measures may be especially interesting to study in the risk group of patients who have preoperative inguinal hernia morbidity of any sort.

Finally, it is also important to study the incidence of postoperative inguinal hernia development in the rapidly growing group of patients subjected to laparoscopic radical prostatectomy. If the risk in this patient group is unchanged following surgery, this would have a bearing on the choice of technique for prostate cancer surgery.

KEY RESULTS AND CONCLUSIONS

- The incidence of inguinal hernia after RRP is increased at least fifteen-fold compared to non-surgical patients of a similar age group with stage M₀ prostate cancer.
- The background incidence of clinically overt inguinal hernias in the male population aged 65-75 years is low, less than 0.5% per year.
- Increased age and preoperative inguinal hernia morbidity are risk factors for postoperative inguinal hernia development.
- Postoperative anastomotic stricture, concurrent PLND at the time of RRP and duration of surgery do not seem to increase the risk of post-RRP inguinal hernia development.
- The risk of postoperative inguinal hernia development after other procedures through lower midline incisions in men seems to be similar to that after RRP.
- Added together these results indicate that the incision itself is the cause of the lesion, causing a direct disruption of the “shutter mechanism” of the inguinal anulus internus. Constitutional factors such as defective supportive tissue and/or the presence of subclinical inguinal hernias probably contribute to varying degrees in the individual patient.
- The method of detection of inguinal hernias is important when planning future studies on incidence and prevalence since there is great variation between various methods. Patient administered questionnaires (PAQ) are superior to retrospective patient file survey (PFS) to detect clinically overt inguinal hernias and also to detect a history of previous inguinal hernia surgery.

To conclude this thesis: lower midline incision surgery in men aged 55-75 years causes inguinal hernia in 10 to 20%. This is of particular interest considering the rapidly increasing number of RRP's performed.

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APPENDICES

Appendix 1.

Prospectively administered PAQ in original (Swedish) and English translation (paper III).

Datum: _____

Namn: _____

Personnr: _____ - _____

Vi undersöker även om behandling mot prostatacancer (operation resp. strålning) kan leda till en ökad risk för ljumskbråck. Vi ber Dig därför att även besvara nedanstående frågor.

A. FRÅGORNA INOM DETTA AVSNITT BESVARAS ENDAST FÖRE DIN PROSTATACANCERBEHANDLING:

1. Har Du ljumskbråck i dagsläget?
 - a. Nej, inte vad jag vet
 - b. Ja, höger sida
 - c. Ja, vänster sida
 - d. Ja, båda sidor

2. Har Du opererats för ljumskbråck tidigare i livet, och i så fall ungefär när?
 - a. Nej
 - b. Ja, höger sida, år.....
 - c. Ja, vänster sida, år.....

B. DETTA AVSNITT BESVARAS ENDAST EFTER DIN PROSTATACANCERBEHANDLING:

1. Har Du utvecklat ljumskbråck på någondera sidan efter Din prostatacancerbehandling, och i så fall när?
 - a. Nej
 - b. Ja, höger sida, år.....
 - Ja, vänster sida, år.....

2. Hur har bråcket behandlats?
 - a. Ingen operation är planerad
 - b. Väntar på operation
 - c. Är opererad, var god ange sjukhus och tidpunkt:
.....

Date: _____ Name: _____
ID-number: _____ - _____

We also investigate whether treatment against prostate cancer (surgery or radiation) can lead to an increased risk of inguinal hernia development. We therefore ask you to answer the following questions.

C. THE QUESTIONS IN THIS SECTION SHOULD ONLY BE ANSWERED BEFORE YOUR PROSTATE CANCER TREATMENT:

1. Do you have an inguinal hernia at the moment?
 - a. No, not to my knowledge
 - b. Yes, right side
 - c. Yes, left side
 - d. Yes, on both sides

2. Have you had surgery for inguinal hernia previously in life, and in that case approximately when?
 - a. No
 - b. Yes, right side, year.....
 - c. Yes, left side, year.....

D. THIS SECTION SHOULD ONLY BE ANSWERED AFTER YOUR PROSTATE CANCER TREATMENT:

1. Have you developed inguinal hernia on either side after your prostate cancer treatment, and in that case when?
 - a. No
 - b. Yes, right side, year.....
 - c. Yes, left side, year.....

2. How has the inguinal hernia been treated?
 - a. No surgery is planned
 - b. Waiting for surgery
 - c. Surgery has been performed, please state hospital and time:.....

Appendix 2.

Retrospectively administered PAQ in original (Swedish) and English translation (paper IV).

**Enkät:
postoperativa ljumskbräck efter borttagande av urinblåsan**

Försök att tänka tillbaks till tiden för Er operation på urologiska kliniken, Sahlgrenska sjukhuset och besvara därefter följande frågor efter bästa förmåga. Sätt kryss i rutan som passar bäst. Vad gäller tidpunkt för eventuella ljumskbräck, försök gärna att minnas *ungefärlig* tidpunkt när det först upptäcktes.

Fråga 1.

Under tiden före Er operation på urologiska kliniken, Sahlgrenska sjukhuset:

1.1 Hade Ni ljumskbräck vid tiden för borttagandet av Er urinblåsa?	Ja	Nej	Vet ej
1.2 Om Ni hade ljumskbräck, i så fall vilken sida?	Höger	Vänster	Båda
1.3 Hade Ni opererats för ljumskbräck innan borttagandet av Er urinblåsa?	Ja	Nej	Vet ej
1.4 Om Ni hade opererats för ljumskbräck, i så fall på vilken sida?	Höger	Vänster	Båda

Fråga 2.

Under tiden efter Er operation på urologiska kliniken, Sahlgrenska sjukhuset, fram till idag:

2.1 Har Ni fått ljumskbräck efter borttagandet av Er urinblåsa?	Ja	Nej	Vet ej
2.2 Om Ni har fått ljumskbräck, i så fall när?	År? (Månad?)		
2.3 Om Ni har fått ljumskbräck, i så fall på vilken sida?	Höger	Vänster	Båda

Ev.kommentarer: _____

Om Du har några frågor angående enkäten kan Ni ringa på telefon 0709-55 88 65 under dagtid så ska vi försöka besvara dessa efter bästa förmåga.

Tack för Er medverkan,

Johan Stranne

Pär Lodding

**Questionnaire:
Postoperative inguinal hernia after removal of urinary bladder**

Try to think back to the time of your operation at the Urological Clinic, Sahlgrenska University Hospital, and try to answer the following questions. Tick the box that suits your answer best. When considering time of any inguinal hernias, try to remember the approximate date when it was first noticed.

Question 1.

During the time ***before*** your operation at the urological clinic, Sahlgrenska University Hospital:

1.1 Did you have an inguinal hernia at the time of removal of your urinary bladder?	Yes	No	Don't know
1.2 If you had an inguinal hernia, on which side was it located?	Right	Left	Both
1.3 Had you undergone surgery for inguinal hernia before the time of removal of your urinary bladder?	Yes	No	Don't know
1.4 If you had undergone surgery for inguinal hernia, on which side?	Right	Left	Both

Question 2.

During the time ***after*** your operation at the Urological Clinic, Sahlgrenska University Hospital, until today:

2.1 Have you developed an inguinal hernia after removal of your urinary bladder?	Yes	No	Don't know
2.2 If you have developed an inguinal hernia, at what date did it occur?	Year? (month?)		
2.3 If you have developed an inguinal hernia, on which side did it occur?	Right	Left	Both

Comments: _____

If you have any questions regarding the questionnaire you can call 0709-558865 during day time and we will do our best to answer.

Thank you for your cooperation,

Johan Stranne

Pär Lodding