
Carcinoma of the Urinary Bladder

Aspects of Treatment, Costs and Follow-up Routines

by

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To my family

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Abstract

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Aspects of treatment, costs and follow-up routines

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Aims: To determine costs and factors related to the total costs of cystectomy. To study the results of the radiological examinations performed 7-14 days after cystectomy. To investigate if a single instillation of epirubicin after transurethral resection (TUR) may influence the time to the first recurrence and its size. To elucidate if a routine with reduced numbers of follow-up cystoscopies in patients with stage Ta tumour is safe.

Patients and methods: The clinical records of 70 consecutive patients subjected to cystectomy were studied. Costs were determined for cystectomies and 22 different factors possibly related to total costs were analysed. The clinical records for a total number of 200 consecutive cystectomy patients were analysed for the results of the postoperative urography. A total number of 404 patients in 13 hospitals were randomised to either one instillation of 50 mg epirubicin or placebo within 6 hours after TUR. We included 138 patients with low-grade tumours who had a negative 4-month cystoscopy in a prospective observational study. The size and number of subsequent recurrences were determined.

Results and conclusions: The total costs (median) for cystectomy was 189,479 SEK. Room and Board was the most expensive single item. In the multivariate analysis high preoperative blood loss was the most important factor associated with high total hospital costs. Not a single patient out of 170 had urinary leakage or a significant stricture visualised at the postoperative urography. It can be concluded that a postoperative urography is unnecessary in patients with a normal postoperative course. Seventy-nine (51.0%) out of 155 evaluable patients in the epirubicin group had a recurrence as compared to 95 (62.5%) out of 152 patients in the placebo group. Half of the recurrences were small-sized and could be fulgurated at the time of the follow-up cystoscopy. The clinical benefit of single instillations thus seems questionable. Patients with low-grade stage Ta tumours who are tumour-free at 4 months can safely follow a routine with cystoscopy at month 12 and 24 and almost all recurrences can be fulgurated at follow-up.

Key words: bladder cancer, cystectomy, stents, economics, follow-up cystoscopy, single-instillation, epirubicin, recurrence size

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List of publications

The thesis is based on the following papers, which will be referred to in the text by their Roman numbers

- I. Costs of radical cystectomy. Berrum-Svennung I, Hedelin H and Holmäng S.
Scand J Urol Nephrol 2005;39(1):36-41

- II. Routine postoperative urography after cystectomy and urinary diversion is not necessary. Berrum-Svennung I and Holmäng S.
Scand J Urol Nephrol 2005;39(3):211-213

- III. A single instillation of Epirubicin after transurethral resection of bladder tumors prevents only small-sized recurrences (up to 5 millimeters). Berrum-Svennung I, Granfors T, Jahnsen S, Boman H and Holmäng S.
In press, J Urol

- IV. Noninvasive grade 1 tumors with a negative first cystoscopy: Single institution experience with reduced number of follow-up cystoscopies during the first two years. Berrum-Svennung I and Holmäng S.
In manuscript

Abbreviations

BCG	Bacillus Calmette- Guerin
CT	Computerised Tomography
MRI	Magnetic Resonance Imaging Scan
PUNLMP	Papillary Urothelial Neoplasm of Low Malignant Potential
Tis/CIS	Cancer in situ
TNM	Tumour Node Metastasis
TURB	Transurethral resection of bladder
WHO	World Health Organisation

TABLE OF CONTENTS

INTRODUCTION	9
CARCINOMA OF THE URINARY BLADDER	9
EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY.....	9
BIOLOGY	12
SYMPTOM AND SIGNS	13
PRIMARY INVESTIGATION.....	13
NORMAL URINARY BLADDER	13
TRANSURETHRAL RESECTION OF THE BLADDER	14
CLASSIFICATION - TUMOUR GRADING	14
STAGE AND INITIAL TREATMENT.....	17
<i>Flat tumours – carcinoma in situ</i>	17
<i>Stage Ta</i>	18
<i>Stage T1</i>	19
<i>Stage 2-4 and metastatic disease</i>	20
INTRAVESICAL CHEMO- AND IMMUNOTHERAPY – HISTORY AND MANAGEMENT.....	20
<i>BCG</i>	21
<i>Mitomycin C</i>	21
<i>Epirubicin</i>	22
<i>Single-shot instillation</i>	22
RECURRENCES.....	22
PROGNOSTIC FACTORS	23
STAGING TESTS.....	23
RADICAL CYSTECTOMY	24
POSTOPERATIVE MANAGEMENT AFTER CYSTECTOMY WITH URINARY DIVERSION	27
COSTS.....	28
FOLLOW-UP – BLADDER CANCER.....	28
<i>Follow-up Ta grade 1, low-grade tumours</i>	29
<i>Follow-up Ta grade 2-3 – high-grade tumours</i>	29
<i>Follow-up T 1 grade 1-3 and CIS</i>	29
<i>Follow-up after curative cystectomy</i>	30
AIMS OF THE STUDY	31
PAPER I.....	31
PAPER II.....	31
PAPER III	31

PAPER IV	31
PATIENTS AND METHODS.....	32
PAPER I.....	32
PAPER II.....	33
PAPER III	33
PAPER IV	34
RESULTS.....	36
PAPER I.....	36
PAPER II.....	36
PAPER III	36
PAPER IV	37
DISCUSSION.....	38
PAPER I.....	38
PAPER II.....	39
PAPER III	39
PAPER IV	40
CONCLUSIONS.....	42
PAPER I.....	42
PAPER II.....	42
PAPER III	42
PAPER IV	42
SWEDISH SUMMARY	43
ACKNOWLEDGEMENTS.....	45
REFERENCES	47

Visdom består i att inse hur lite vi vet
Sokrates

Introduction

Cancer of the urinary bladder is the ninth most common malignant disease worldwide with approximately 250,000 new cases each year (Cookson 2004). It is the fifth most common malignancy in Europe and the fourth in the United States (American Cancer Society, 2007). Bladder cancer is one of the most prevalent cancer diseases as a result of the long mean survival time among bladder cancer patients. Median age in Sweden at diagnosis is 72 years. More than 50% of all tumours are at diagnosis non-invasive (stage Ta), whereas approximately 40% of primary tumours are invasive, i.e invading sub-epithelial connective tissue or muscle (stage T1-T4) (Larsson 2003). Treatment is completely different for these groups. The management of each individual patient depends on many different factors, most important is the stage and grade of the disease but the physical condition and mental status as well as patients preferences are also important. The total cost per patient is the highest of all cancers due to the long average survival of the bladder cancer patient and the need for lifelong routine monitoring and treatment (Botteman 2003).

This thesis has its focus on bladder cancer follow-up routines, treatment and economic aspects of the disease.

Carcinoma of the urinary bladder

Epidemiology, aetiology and pathology

Cancer in the urinary bladder has a worldwide variation in incidence. The incidence rate of cancer is defined as the number of new cases diagnosed per 100,000 persons per year. The incidence rate of bladder cancer in the western world is 10-30 new cases/100,000 persons. Bladder cancer is uncommon in Asia, but has a very high incidence in for example Egypt. The highest incidence internationally is found in Italy for men and for women in New Orleans (Napalkov 1997). Incidence rates are generally higher in the

developed countries, with exception for earlier described countries with endemic schistosomiasis. In Sweden 2,000 new cases are diagnosed yearly. Urinary bladder cancer is the fifth most common malignancy disease in Sweden (Socialstyrelsen: Epidemiologiskt centrum). Bladder cancer is after prostate cancer the most common urologic cancer in Sweden. Bladder cancer has a great variation in incidence due to gender and race. The disease is between two to five times more common in men than in women. Race also influences the incidence rate with a factor of 1.5-2. It is most common in white men and unusual in black women.

Transitional cell carcinomas comprise more than 90% of bladder cancers in western countries. In Sweden, 97% of all urinary bladder cancers are transitional cell carcinomas (Nationellt kvalitetsregister för blåscancer – diagnosår 2005). A few per cent are squamous cell carcinomas and adenocarcinomas. Small cell carcinomas and lymphomas are occasionally seen while malignant melanomas are distinctly rare. The prevalence of squamous cell carcinomas is considerably higher in Egypt and the Middle East, where infection by *Schistosoma Haematobium* is endemic.

The mortality in Sweden in bladder cancer is approximately 600 cases a year. The number of bladder cancer deaths is unchanged despite an increase in the number of new bladder cancer cases in Sweden during the last decades.

Figure 1

Incidence 1961-2003
Bladder cancer

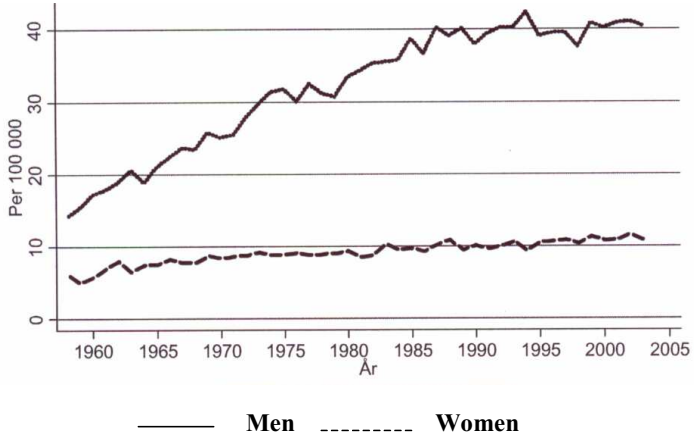
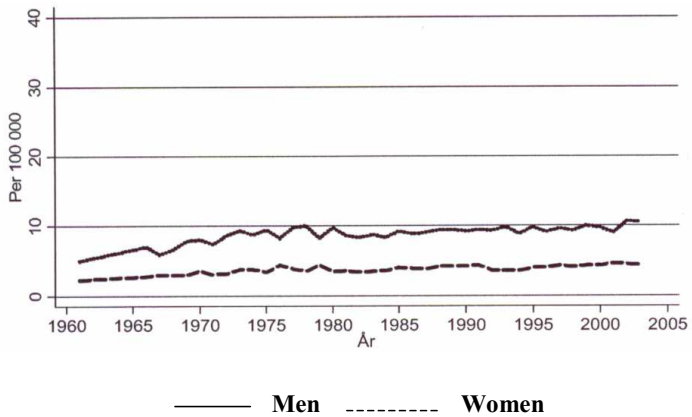


Figure 2

Mortality 1961-2003
Bladder cancer



Risk factors for bladder cancer are mostly exogenous. Smoking is a major, well-established and avoidable risk factor for bladder cancer. Smoking increases the risk fourfold compared to persons who have never smoked (Steineck 1970). The latency period is approximately 20-30 years. Smoking accounts for one-third to half of bladder cancers diagnosed among men and one-quarter of those among women. Smoking black tobacco appears to result in a higher risk than smoking blond tobacco. Other risk factors for bladder cancer are previous pelvic radiation, previous systemic chemotherapy, local long-term irritating factors such as cystolithiasis and chronic catheter. Workers in the rubber and chemical industry as well as in the steel, iron and aluminium industry also have an increased risk.

Biology

One theory is that carcinogens in urine cause bladder cancer due to damage of the DNA in the urothelium. The main change in grade 1 tumours seems to be in chromosome 9. These tumours have a high risk of recurrence but a low risk of progression.

Grade 2-3 tumours have a disturbance in the p53-synthesis, which is regulated from chromosome 17 (Malmström 2006). These theories support the clinical observation that bladder cancer is a number of different diseases with different grade and infiltrative properties.

The incidence of subsequent upper tract tumours is only 3-4% in patients with a primary bladder cancer. On the other hand, patients with primary tumours in the renal pelvis and ureter run a 40% risk of a subsequent bladder cancer. This is indirect evidence for the theory that urothelial cancer cells spread in a distal direction with the flow of urine.

Symptom and signs

The most common presenting symptom is painless haematuria episodes, which occurs in about 81% of bladder cancer patients. Other common symptoms are voiding problems, urinary tract infections and abdominal pain (Boman 2002). The patient can also have anaemia and sterile pyuria.

Primary investigation

The first step in the diagnosis is cystoscopy, often with urinary or bladder wash cytology. Cytology has a high specificity (97-100%) but varies considerably in sensitivity, which is high (90-95%) in large-sized high-grade tumours but low (20-30%) in small-sized low-grade tumours. Histopathological material from the tumour is obtained by means of a transurethral resection of the bladder (TURB). All patients with suspected bladder cancer undergo at least one TURB, with bimanual palpation, which provides important prognostic information (Wijkström 1984).

The purpose of TURB can be a complete removal of all visible tumour or just a way to get tissue for diagnosis, depending on how advanced the tumour is. It also gives information about the stage and grade. TURB should be in two fractions, superficial and deep to make it easier for the pathologist to determine the depth of infiltration.

A physical examination and a careful patient history are natural parts of the primary investigation for evaluation of the presence and degree of any comorbidity.

Normal urinary bladder

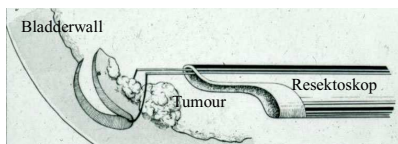
The normal urothelium is three to seven cell layers thick and has contact with urine at its surface. The urothelium rests on the basal membrane of the lamina propria. This membrane borders on the lamina propria, or the sub-epithelial connective tissue, which

includes some smooth muscle fibres. The detrusor muscle layer is organised in a criss-cross way, like a basket, so each fibre runs from the outer to the inner layer and back again. Outside this layer is abundant fat in which multiple plexa with large veins are found.

Transurethral resection of the bladder

This type of surgery is for the first time in almost all patients performed at the operation theatre since most primary tumours are larger than 10 mm in diameter. Patients are under general or spinal anaesthesia during surgery. TUR of smaller tumours can be performed as day-care surgery. A lubricating jelly with local anaesthesia in the urethra is always used before introducing the resectoscope into the urinary bladder. The resectoscope has a loop which is 6.5 millimeters wide (Fig. 3). The suspected tumour is cut away with the loop. Tumour tissue is removed and sent for histopathological examination in the Department of Pathology. Smaller recurrent tumours can be fulgurated and/or biopsied in the office under local anaesthesia.

Figure 3. TURB



Classification - tumour grading

The biological behaviour of a tumour differs from grade to grade. Consequently, it is of utmost importance to know the tumour grade since treatment and prognosis vary depending on the grade.

At the present time (2007) in Sweden the WHO classification from 1999 is used although there is a later version from 2004. This classification system (WHO 1999) consists of three different grades of cancer and papillary urothelial neoplasm of low malignant potential (PUNLMP). PUNLMP is not a cancer but has an inherent low potential for later development of a truly malignant disease. It corresponds to the most benign forms of grade 1 tumours in the WHO 1973 classification system (Busch 2002). Actually, the 1973 WHO system is still the most used grading system worldwide. It also has a three-tier grading system but only grades one and three are defined. Grade 2 was not clearly outlined which is the main critique against the WHO 1973 classification. Many pathologists were tempted to use grade 2 too often, which was a great problem for urologists, since some of these grade 2 tumours were almost grade 3 tumours and others were almost grade 1 tumours (Holmäng 2000). Another classification system was suggested by Bergkvist and Moberger (Bergkvist 1965). This system was modified by Malmström and co-workers in 1987 (Malmström 1987). Grade 2 tumours were divided in 2 subgroups (2A and 2B) between which there is a sharp limit which has clinical importance. WHO 1999 is similar to the modified Bergkvist system. WHO 2004 is the most recent grading system, which is recommended in the EAU guidelines, but not used in Sweden.

Table 1. Comparisons of different grading systems

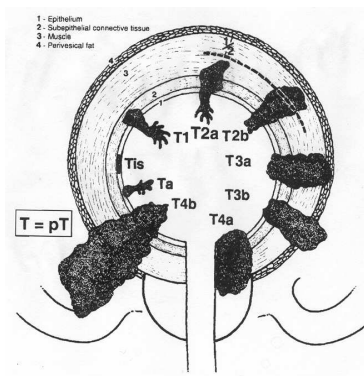
<u>WHO 1973</u>	<u>Modified.Bergkvist 1987</u>	<u>WHO/ISUP 1998</u>	<u>WHO 1999</u>
I	I	PUNLMP	LMP
II	IIA	Low-grade	I
II	IIB	High-grade	II
III	III	High-grade	III

Staging of bladder tumours is performed according to the TNM classification from 2002.

Table 2. TNM classification 2002

Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ (flat tumour)
T1	Tumour invades sub-epithelial connective tissue
T2	Tumour invades muscle T2a tumour invades superficial muscle (inner half) T2b tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue T3a microscopically T3b macroscopically (extra vesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall T4a Tumour invades prostate, uterus, or vagina T4b Tumour invades pelvic wall or abdominal wall

Figure 4. TNM 2002



The Tumour, Node, Metastases (TNM) 2002 is widely accepted, also in Sweden. The prefix T means clinical stage which is an assessment at the time of cystoscopy combined with results from radiological examinations. When information on the histopathological information is included it is termed “pT”. The majority of bladder cancers, over 50%, are Ta tumours. It is important to separate all infiltrative tumours from the Ta group, since it is a different type of disease. The term superficial bladder tumour includes Ta, Tis and T1 tumours but is no longer recommended. The reason is that it comprises tumours with widely varying biological potential (Murphy 2000, Soloway 2002). For planning the follow-up it is a must to know stage and grade of the tumour.

Stage and initial treatment

The prognosis of bladder cancer depends on both stage and grade. The goal with staging is to get more information about the tumour in order to give appropriate treatment leading to an optimal prognosis.

Flat tumours – carcinoma in situ

It is an invisible disease since most of the diseased areas in the bladder cannot be seen. Actually, carcinoma in situ cannot be seen at all. What we see are red oedematous areas that are the result of inflammation in the lamina propria underlying the carcinoma in situ. This disease is almost always multifocal and incurable with TUR only, since all involved areas cannot be identified. There are two different types of CIS. Primary, which is CIS without any earlier or coexistent tumour. This type comprises 1-2% of all newly diagnosed bladder carcinomas. Secondary Tis, which is CIS with a concomitant or earlier papillary tumour. This type is the most common kind of CIS.

CIS has a high progression rate and all patients with CIS should have BCG treatment as soon as possible. BCG treatment results in approximately 80% complete response determined at the first follow-up cystoscopy but after five years only approximately 50% are still tumour-free. Radical cystectomy is the preferred treatment when intravesical measures fail.

Stage Ta

Stage Ta is the most common form of bladder cancer. Ta bladder tumours grow in the mucosa in a papillary and non-invasive way. Such tumours comprise 49% of all newly diagnosed tumours in Sweden (Nationellt kvalitetsregister för blåscancer – diagnosår 2005). The recurrence rate for this group is high, 50-70%, but the progression rate is low, between 2 and 10%.

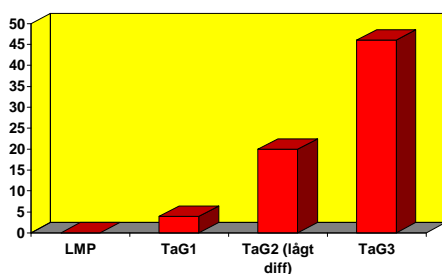
PUNLMP are always non-invasive and comprise approximately 10-15% of all newly diagnosed tumours. They have an excellent prognosis with minimal or no risk at all of progression. The risk of recurrence is 35% during the first five years (Holmäng 1999).

Approximately 33% of the patients have Stage Ta Grade 1 tumours at initial diagnosis. Stage progression occurs but no more than 5% during five years of follow-up. Solitary Ta grade 1 tumours require no adjuvant treatment apart from possibly a single instillation of a cytostatic agent.

Stage Ta Grade 2 constitutes 10-20% of all newly diagnosed tumours. Progression in this group of high-grade tumours is higher, up to 20% in one report (Holmäng 2001). Although other authors have found a much lower progression rate it seems appropriate to have respect for these tumours and have a different treatment regimen and follow-up routine than what is the case for grade 1 tumours. There are no studies which can guide us in this matter but the best way may be to treat multifocal and/or large-sized TaG2 tumours like TaG3 tumours. Taking into account the high recurrence rate and the progression rate it may well be the case that these tumours should be liberally treated with intravesical BCG or intravesical chemotherapy.

Stage Ta G3 is not so common and represents only 3% of all newly diagnosed tumours. The progression rate of grade 3 tumours varies from report to report ranging from 0% to 45%.

Figure 5. % progression in Ta tumours



Holmång et al J Urol 2001

Stage T1

Twenty per cent of all bladder carcinomas infiltrate the lamina propria but not deeper already at initial diagnosis. Thus, they penetrate the basal membrane and invade a subepithelial layer of connective tissue. Most of the T1 tumours are grade 3. Stage T1 can be sub-staged into three levels of invasion, T1a, T1b and T1c. T1a tumours are tumours which infiltrate into the superficial part of the lamina propria. T1b tumours infiltrate deeper into the layer where the large vessels and muscle bundles are located. T1c tumours infiltrate even deeper and almost reach the muscularis propria. T1b and T1c are sometimes combined and termed T1b. T1a is usually termed superficial and T1b deep lamina propria invasion. The depth of invasion is an important prognostic factor for progression. Re-resection is recommended for all T1 tumours to ascertain that the patient has been correctly staged and also to improve radicality.

BCG is recommended in T1 grade 2 and 3 without solid tumour pattern and vascular invasion. Immediate cystectomy is the choice of treatment in T1 grade 2 and 3 with solid tumour pattern and/or vascular invasion (Andius 2006).

Stage 2-4 and metastatic disease

T2 denotes an infiltration into the muscle layer and is substaged into two levels, A and B, depending on whether the depth of infiltration is superficial or deep into the muscle layer. Stage 3 is also subdivided into two levels, A and B, depending on micro- or macroinfiltration to the perivesical tissue. Approximately one third of the patients with newly diagnosed disease are in stages T2-3-4. Radical cystectomy is recommended in T2, T3, T4a, No-Nx, M0.

Sometimes a cystectomy can be performed in more advanced cases in order to get palliation from severe local symptoms such as recurrent bleeding.

Intravesical chemo- and immunotherapy – history and management

Intravesical instillations were first described as early as in 1903. Instillations of cytostatics have been used in the management of bladder cancer since the 1960s. A considerable number of substances have been tested (Table 3).

Table 3.

Instillation agent history

- 1903 Silver nitrate
- 1919 Triklorättiksyra
- 1948 Podofyllin
- 1961 Thiotepa
- 1965 Actinomycin C
- 1965 5-Fluorouracil
- 1966 Mannitol myleran
- 1966 Metotrexate
- 1967 Mitomycin C
- 1973 Epodyl
- 1976 BCG
- 1977 Adriamycin
- 1986 Epirubicin
- 1990 Interferon
- 1997 Valrubicin

At the present time (2007) the following substances are the most used: Thiotepa, Adriamycin, Epirubicin, Mitomycin C and BCG.

The majority of patients with stage Ta/T1 bladder tumours can be given instillations prophylactically and/or treated with instillation therapy. The duration time for instillation therapy is as a rule one to two hours. The optimal effect is achieved when the patient changes position every fifteen minutes so that all parts of the bladder can come into contact with the solution. Chemotherapy instillations can be given in two different ways, one single instillation immediately after TURB or additional courses of instillations during four to eight weeks. It is recommended that patients with no prior intravesical therapy are given a single instillation of a cytostatic drug after endoscopic removal of low-grade Ta bladder cancers. Intravesical instillation of BCG or mitomycin C is recommended for CIS and after endoscopic removal of T1 and high grade Ta tumours. On the other hand, chemotherapy may be helpful in BCG failures (Malmström 1998).

BCG

BCG immunotherapy is at present the most effective intravesical agent for treatment and prophylaxis of high-grade bladder cancer. The exact mechanism is unknown. The treatment can be given a couple of weeks after resection, depending on the size of the resection surface. Immunotherapy is the first-line treatment for CIS. BCG is the only drug with at least some effect against progression. Other treatment indications are T1 disease and multifocal or recurrent Ta tumours. The traditional treatment schedule is one instillation once every week for 6 weeks with additional instillations in many cases.

Mitomycin C

Mitomycin C is an antitumour antibiotic. It has a low molecular weight and is usually minimally absorbed when given intravesically. There is no standard dose, and it may vary from 20 to 60 mg per instillation. Chemical cystitis is the most common side-effect but it will disappear after cessation of therapy.

Epirubicin

Epirubicin is a cytotoxic antibiotic. It has an antitumoural effect by binding to DNA resulting in an inhibition of the enzyme system which is essential for the transcription and replication of DNA.

Epirubicin is usually administered in a dose of 30–80 mg diluted in saline.

The only significant side-effect of epirubicin appears to be drug-induced cystitis.

Single-shot instillation

An unwanted effect of TURB is that cancer cells are freed from the tumour, float around in the bladder and may implant in the TUR wound or other injured urothelial surfaces. Instilled cytotoxic agents will mostly exert their effect on tumour cells since the normal urothelium has a low mitosis activity. This will hopefully minimise implantation and further growth.

Popart et al. showed that a single instillation of epirubicin had a significant effect on marker lesions with acceptable toxicity (Popart 1985). A number of randomised studies have been performed which show that a single instillation of a cytotoxic drug, mainly epirubicin and mitomycin, will reduce the number of subsequent recurrences (Burnard 1976, Abrams 1981, Zincke 1993, Oosterlinck 1993, Bouffioux 1995, Tolley 1996, Ali-El-Dein 1997, Solsona 1999, Rajala 2002 and Okamura 2002). Single-shot instillation is recommended for all Ta and T1 tumours in the European Guidelines since 2002. It is known that a single postoperative instillation of epirubicin and mitomycin result in a lower recurrence rate, but there is a lack of knowledge in some aspects, for example the size of the recurrences and the costs for a single instillation treatment policy.

Recurrences

Up to 75% of all patients with Ta, Tis and T1 tumours will have recurrences during the first five years after the initial diagnosis if TUR was the only treatment. Different mechanisms have been suggested for the high recurrence rate. 1. Residual tumour, due to an incomplete resection. 2. Small-sized tumours, not visible at the time of the primary

resection. The tumour will be visible at follow-up. 3. Precancerous changes in the entire bladder urothelium “field change” result in a high recurrence rate for some tumours. 4. Cancer cell implantation at the site of resection.

The temporal risk for recurrences is biphasic and is highest around month 3 and 21 (Malmström 2003).

Prognostic factors

The most important prognostic factors for Ta and T1 tumours are the number of tumours, tumour size, prior recurrence rate, T category, presence of CIS, tumour grade and poor response to intravesical therapy.

Staging tests

TUR, bimanual palpation and intravenous pyelography are recommended in the EAU guidelines for T-staging. Ultrasonography, bone scan and CT or MRI are optional evaluations.

CT abdomen provides information about the presence or absence of pelvic and para-aortic lymphadenopathy and visceral metastases as well as bladder tumour infiltration depth and adherence to surrounding tissue and organs. CT should preferably be done before TURB for correct information. CT and MRI both have an inherent staging error, since their ability to identify small-sized lymph node metastases is poor. For N-staging the only method capable of excluding metastatic disease in lymph nodes is lymphadenectomy. For M-staging, chest radiographs are recommended in all patients. Bone scans are recommended in patients who have symptoms that suggest bone involvement. Ultrasound is an easy way to find out if a liver metastasis is present.

Radical cystectomy

Radical cystectomy including urinary diversion is the golden standard treatment for muscle-invasive bladder cancer and for stage Ta/T1/Tis bladder cancer when local therapies have failed.

Unfortunately, not all of these patients are in a good enough physical and mental condition to undergo such extensive surgery as cystectomy.

Radical cystectomy actually includes three surgical procedures: 1. Lymph node dissection, 2. Cystectomy and 3. Urinary diversion.

Lymph node dissection can be performed in many ways and different authors describe various types of dissection. Limited lymph node dissection is an extirpation of lymphatic tissue in the obturator fossa which provides just a few nodes. Limited dissection can be a bit more extensive and include the area between the genito-femoral nerve and internal iliac vessel, a so called conventional pelvic dissection. Extended dissection includes all lymphatic tissue up to the aortic bifurcation and sometimes even up to the inferior mesenteric artery. There is no consensus in the way the lymph node dissection should be performed due to the lack of randomised studies. Cystectomy in the male patient includes removal of the bladder as well as the distal part of the ureter, seminal vesicles and prostate. The uterus, adnexa and anterior wall of the vagina should be removed in the female patient.

Radical cystectomy with urinary diversion is associated with a high complication rate of about 20-30%. Common complications are ileus, wound rupture and infections (Rosario 2000, Malavaud 2002, Chang 2002). The postoperative mortality is the time up to 30 days after surgery and is mostly a result of treatment complications. The mortality is 1-5% but may be even higher in some hospitals (Schoenberg 2002, Malavaud 2002).

The mortality is usually not significantly increased due to high age, poor physical condition, co-morbidity or stage. The EAU guidelines recommend that a surgical procedure like cystectomy should be performed in centres with good experience of the major types of diversion techniques. Urinary diversion can be performed in three ways; incontinent urinary diversion, continent urinary diversion and orthotopic neobladder substitution. (Fig 6-8)

Ileal conduit, the incontinent alternative, is a surgical procedure which is not so technically difficult in comparison with the reservoirs. In the other two diversion types a reservoir is constructed. The orthotopic neobladder is sutured to the urethra and the continent pouch is connected to a stoma below the umbilicus. The Bricker conduit is the most common type of diversion in Sweden. Actually, it has gained increased popularity during recent years. In 1997, 55% of the diversions following cystectomy for bladder carcinoma were incontinent diversions compared to 72% in 2005 (Nationellt kvalitetsregister för blåscancer – diagnosår 2005). One possible explanation for this change is that more and more elderly patients have been operated on and a Bricker conduit is the preferred alternative in this group.

Radiation therapy is an alternative to radical cystectomy but results seem to be inferior. It is estimated that up to 50% of patients will get recurrences within the bladder. Curative radiotherapy is suggested as a treatment in elderly patients who are unfit for cystectomy but there are actually few, if any, studies performed in this patient category which show any benefit of the treatment.

The Different Reconstructive Techniques Illustrated
Conduit

Figure 6

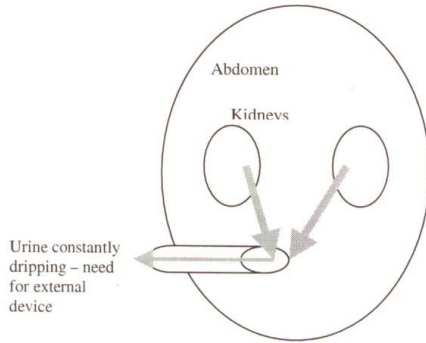


Figure 7

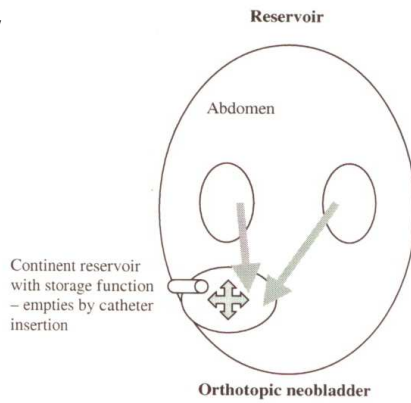
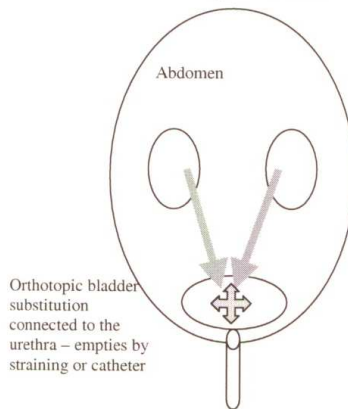


Figure 8



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Postoperative management after cystectomy with urinary diversion

Patients who have undergone a cystectomy with urinary diversion may need an abundance of resources postoperatively. Most patients are in the intensive care unit during the first period after surgery. Epidural anaesthesia is frequently used during the first days for lowering the postoperative pain.

At the present time (2007) many of the patients who undergo cystectomy are elderly and have one or more comorbidities and thus need more help. The length of hospital stay after cystectomy was reported by many authors and is at least partly related to the complexity of the urinary diversion. Mean postoperative hospital stay varies in different studies between 7 to 22.7 days (Bredin 1977, Malavaud 2002, Rosario 2000, Chang 2002).

During the first days after surgery the fluid balance is controlled. Serum electrolytes are checked periodically. Most patients can start drinking small amounts the day after surgery if they are in such a condition that the nasogastric tube can be removed. Enteral nutrition starts often after the third day, since many patients have a prolonged ileus. Ureteral stents are considered favourable and are routinely inserted during the operation. Most patients undergo some form of radiological evaluation before the removal of the ureteric stents. Guidelines and national recommendations do not include postoperative management explaining why it differs from hospital to hospital. There is a lack of scientific evidence and studies on ureteral stents and the possible value of radiological evaluations. The drainage tube is left in place for some days depending on the amount of the discharge. Women have their vaginal pack for about one day. Antibiotic prophylaxis is routine but varies from department to department; from a single per-operative dose to 3 days. Complications are common, as previously mentioned and may result in prolonged time in the ward. During the postoperative period specially trained nurses and stomal therapists help the patient to learn to care for the stoma and change the collection bags. Some patients need one to three weeks in a geriatric ward before returning home.

Costs

Bladder cancer is one of the 10 most common malignant diseases worldwide and treatment costs are substantial. From a clinical and economic aspect it is important to remember that bladder cancer is often a chronic disease.

The high incidence and long survival lead to a high prevalence of the disease. Lifelong routine monitoring and treatment are often necessary. The cost in bladder cancer, from diagnosis to death, is the highest of all cancers per patient. Only a few studies have focused on the economic aspects in this disease (Botteman 2003).

In one Swedish hospital the total cost for bladder cancer diagnosis, treatment and follow-up was nearly 7,000,000 SEK (2,800,000 SEK per 100,000 inhabitants per year) (Hedelin 2002). A number of authors have suggested a reduction in the number of cystoscopies among patients with low-grade bladder tumours. Follow-up cystoscopies only account for 13% of the total treatment costs. Thus, a reduction in cystoscopy controls would probably only lead to small financial savings. Radical cystectomies account for 34% of the total treatment costs, but there are few authors who have studied the economics of the procedure. Transurethral resections account for 40% of the total treatment costs (Hedelin 2002). The overall costs increase when a TURB is performed with the patient staying overnight in hospital (Hedelin 2002). Considerable economic gains are possible when small-sized tumours are treated under local anaesthesia at the time of the follow-up cystoscopy.

Follow-up – Bladder cancer

Even though all treatments for bladder cancer including TURB, endovesical chemotherapy, immunotherapy and cystectomy decrease the recurrence and progression rate, the persistent possibility of developing new tumours obliges the urologist to perform life-long follow-up. Follow-up consists of regular check-up cystoscopies. After every recurrence, the cystoscopy schedule restarts from the beginning.

Follow-up Ta grade 1, low-grade tumours

Stage Ta low-grade tumour is a benign kind of tumour. It has a low risk of progression and the recommended follow-up schedule is cystoscopy every 3 months during the first two years, every 6 months for another 1-2 years, followed by yearly controls. Retrospective studies show that patients with grade 1 tumours who are tumour-free at the first follow-up cystoscopy after TURB have few recurrences and progression is very uncommon (Fitzpatrick 1986, Parmar 1989, Morris 1993, Öge 2000). A number of authors have suggested a less intense follow-up regimen for patients with grade 1 tumours and the European Association of Urology recommends cystoscopy at month 9 and 21 for patients who are tumour-free at month 3 (Parmar 1989, Morgan 1991, Abel 1993, Morris 1993, Gulliford 1994, Hall 1994, Olsen 1995, Öge 2000, EAU Guidelines 2007). Follow-up cystoscopy should continue for at least 5 years. Still, many urologists control patients at the traditional intervals, which are the same for all bladder tumours, regardless of grade.

Follow-up Ta grade 2-3 – high-grade tumours

Cystoscopy is recommended every 3 months for the first 2 years, every 6 months for another 1-2 years followed by yearly controls lifelong. Patients with grade 3 tumours should receive adjuvant intravesical BCG treatment. Treatment of patients with grade 2 tumours is controversial. Most patients with grade 2 according to the 1973 WHO classification system have a low risk of progression and need no adjuvant therapy but the situation is quite different for patients with WHO 1999 grade 2 tumours. Such patients have high-grade tumours with a significant risk of progression and intravesical BCG seems logical. There are, however, no instillation studies which focus on patients with grade 2 WHO 1999 and the possible benefit of such adjuvant treatment is simply not studied.

Follow-up T 1 grade 1-3 and CIS

The prevailing opinion is that patients with stage Ta/T1/Tis grade 3 tumours should undergo a second resection to improve the number of tumour-free patients and obtain a

correct staging. An alternative to a second resection is as follows: Intravesical treatment 2-3 weeks after TURB. Follow-up cystoscopy 4-6 weeks after the last intravesical treatment. If a recurrence is seen it will be treated with TUR. Patients who have low-grade recurrences may be treated with more instillations. Radical cystectomy is recommended in case of a new invasive grade 3 tumour or recurrent CIS.

Follow-up after curative cystectomy

It seems appropriate with a physical examination about 2-3 months postoperatively. It may include a chest x-ray, urine analysis, sonography of liver, kidney and retroperitoneum. The follow-up is supposed to find disturbances in kidney function, urinary infection, reservoir stones, strictures or urothelial tumours in the upper urinary tract or urethra.

Cytology and cystoscopy are recommended in case of a retained urethra.

Aims of the study

Paper I

To determine the costs for a cystectomy, with and without complications and to study prognostic factors related to the total costs.

Paper II

To investigate the results of the intravenous pyelography which usually is performed 7-14 days after cystectomy.

Paper III

To study if a single instillation of epirubicin after transurethral resection may influence the time to the first recurrence and its size.

Paper IV

To study if a routine with reduced numbers of follow-up cystoscopies during the first two years in patients with low-grade stage Ta tumour is medically safe and clinically feasible.

Patients and methods

Paper I

We studied the clinical records and relevant economy files for 70 consecutive patients subjected to radical cystectomy between March 1994 and April 1998 in Sahlgrenska University Hospital. Twenty-two different variables were recorded for each patient. The total costs and costs for various services for each patient were retrieved in the records of the hospital administration. The itemised costs for “Room and board” were calculated each year based on actual costs for the urology department during the preceding year. Costs were included for all employees and for emergency service as well as for the hospital administration. The cost per day is thus an average cost for urology patients and not the true cost for a patient treated with cystectomy. All prices were corrected for inflation according to the health care consumer price index.

An uncomplicated case was arbitrarily defined as a patient with at most 2 days in the intensive care unit and no reoperation.

We have calculated mean, standard deviation, median and range with the StatView statistical computer program. For comparison between groups, Mann-Whitney’s U-test was used for ordered and continuous variables, and Fisher’s exact test for dichotomous variables. Spearman’s non-parametric correlation coefficient was used in all correlation analyses. Partial correlation analyses and logistic regression was used in order to evaluate if a variable (with significant relationship to cost) directly or indirectly affected cost, given another variable (covariate). Stepwise regression analysis was used after transforming the dependent variable to normal distribution by calculating normal score using Blom’s method (Blom 1958). All tests were two-tailed and conducted at 5% significance level. Statistician Gunnar Ekeröth performed the statistical analyses of the study.

Paper II

We identified a total number of 200 consecutive patients who were treated with radical cystectomy and urinary diversion between 1994 and 2002. The complete clinical records of all 200 patients were available in the archives of the hospital. The data concerning the postoperative period were scrutinized. We registered date of surgery, type of diversion, symptoms or signs of urinary leakage or obstruction and date and results of all postoperative radiological examinations. 178 patients were finally evaluated and we registered the frequency of significant findings at routine postoperative urography.

Paper III

A total number of 404 patients in 13 hospitals were randomised to either one instillation of 50 mg epirubicin or placebo within 6 hours after TUR of bladder tumours.

It was estimated that 60% of the patients in the epirubicin group and 40% of the patients in the placebo group were free of recurrences after 2 years. A minimum number of 130 patients in each arm were required when calculating with a power of 0.9 with a statistical significance of 5%. Inclusion criteria were 1-3 papillary tumours, a maximal tumour diameter of 30 mm and a tumour which looked like a grade 1-2 tumour. The randomisation was done by study nurses at each participating centre from lists with pre-determined treatment alternatives which were generated at random by a statistician. There were separate lists for patients with primary and recurrent tumours. Patients were randomly allocated to receive either 50 mg epirubicin in 50 ml saline or 50 ml saline which was instilled within 6 hours after TUR. Patients were evaluated with cystoscopy according to the routines at each participating centre and follow-up was terminated 24 months after inclusion.

We calculated the costs of a single instillation when the study started in 1998. All costs have been updated to the year 2006 using the consumer price index for the health and care sector (www.scb.se) and transformed from SEK to USD using an exchange rate of 6.65 SEK=1 USD. It was assumed that a nurse would have to spend an average of 45 minutes with the procedure. This included time to go to the pharmacy, time to go to the

recovery room, instillation and finally disposal of the toxic solution (54 USD). The epirubicin solution costs amounted to 210 USD and the total cost for one patient is 264 USD. The total cost for all 203 patients in the epirubicin group was 53,592 USD. Calculation of costs for operative procedures in Sahlgrenska University Hospital were performed in 1997. These data show that the cost of a TUR for bladder cancer with a hospitalised patient is 4,210 USD and a TUR in day surgery with the patient under spinal or general anaesthesia is 758 USD. A biopsy and fulguration under local anaesthesia at the time of follow-up cystoscopy amounted to 587 USD. For the purpose of this study, we assumed that costs in the other 13 hospitals were the same as in Sahlgrenska University Hospital.

The Mann-Whitney U-test was performed to test the difference between treatment groups for continuous variables and Fisher's exact test for dichotomous variables. The log-rank test was performed to test differences in survival functions between the two treatment groups. For descriptive purposes Kaplan-Meier estimates were presented. All tests were two-tailed and conducted at 5% significance level.

Statistician Anders Odlén, Gunnar Ekeröth and Aldina Pivodic, performed the statistical analyses of the study.

Paper IV

Patients who were tumour-free at the first follow-up cystoscopy 4 months after TUR of a low-grade tumour (pTaG1, WHO 1999) had their next cystoscopies at month 12 and month 24 omitting controls at months 8, 16 and 20. The clinical records were scrutinised in order to avoid inclusion of patients with earlier high-grade or invasive tumours. All urologists were given oral and written information about this new follow-up routine. Patients with stage Ta grade 2 tumours (WHO 1973) were also included if a histopathological review, some weeks later, showed a grade 1 (WHO 1999) tumour. The size of the tumour was determined by the urologist using an object with a known diameter such as the electrode, biopsy forceps or resection-loop for comparison. We registered the

date and results of the cystoscopy as well as the size of the recurrences and the way they were managed.

Results

Paper I

The total costs (median) of 53 uncomplicated and 17 complicated cystectomies were 181,096 SEK and 290,625 SEK, respectively. Room and Board was the most expensive single item and accounted for 33-36% of total costs in both groups. The preoperative variables had no or minimal prognostic significance for high total costs. The univariate analyses show only that (low) age is significantly related ($p<0.05$) to high total costs in the multivariate analysis. High peroperative blood loss was the most important factor associated with high total hospital costs for radical cystectomy.

Paper II

An intravenous urography was performed in 170 patients and bilateral retrograde pyelographies were performed in seven patients. One patient who had bilateral pyelostomies underwent an antegrade examination.

There was no leak identified in anyone out of 170 patients examined by urography. One patient with a Bricker conduit had a small leakage at the uretero-intestinal anastomosis diagnosed by a retrograde examination.

Paper III

Seventy-nine (51.0%) out of 155 evaluable patients in the epirubicin group had a recurrence as compared to 95 (62.5%) out of 152 patients in the placebo group ($p=0.04$). Most recurrences (63.3%) were small-sized (1-5 mm). The tumour size was unknown in 5 patients. Thirty-three (42.9%) out of 79 patients with recurrences in the epirubicin arm compared to 29 patients (31.5%) out of 95 in the placebo arm had larger (>5 mm) first recurrences ($p=0.12$). Roughly half of the patients with first recurrences were managed in

day surgery and the other half spent a total number of 145 days in hospital, with no difference between groups.

Paper IV

A total number of 196 patients were notified by the urologists in our institution and registered between June 2000 and June 2006. A total number of 138 patients were found to fulfill the inclusion criteria. Fifty-eight patients were not accepted for inclusion by the study coordinator for inclusion for the following reasons: The first cystoscopy was not performed at 4 months +/- 2 weeks, previous high-grade or invasive tumour or no tumour at all. Eighty-seven of 138 patients were examined at month 12 +/- 1 month. At month 12, 28 patients had recurrences and 59 had not. The recurrences were solitary in 21 patients and multiple in 7 patients. Twenty-four out of 28 recurrences (86%) were fulgurated with or without biopsy under local anaesthesia at the 12-month control and 4 patients (14%) were treated under general or spinal anaesthesia. Fifty-one other patients were examined more than one month before or after the 12-month date. During the first year only a few of these patients had recurrences consisting of small tumours which were fulgurated under local anaesthesia at the time of the follow-up cystoscopy. No tumour progression was registered.

Discussion

Paper I

It is obvious that there is much money to save if most of the complications after cystectomy could be avoided. Our study could not show that it is possible to predict who will develop complications among those patients selected for operation. We have only found one paper where cystectomy costs were determined and the greatest difference in costs was increasing costs for laboratory and pharmacy costs, which are 4-12 times higher today.

The duration of hospital stay has been reported to be from 21.5 days in Boston in 1969-1973 to 7 days in Nashville between 1995 and 2000. Complications are seen in 20-30% after radical cystectomy, even in institutions where many operations are performed each year. The definition of a complication varies from author to author but the high percentage can be explained by a complicated operation in a patient group with a high prevalence of cardiovascular and respiratory disease. The major finding in our study was that a high number of blood transfusions were associated with high total costs for cystectomy. Jahnsen and associates studied the extent of blood transfusion and cancer-related mortality in a cohort of 130 patients treated with cystectomy. No overall association between extent of blood transfusion and cancer-related mortality was found but a tendency towards an increased risk early in the follow-up period was observed (Jahnsen 1994).

The Nashville group reported that the mean blood loss was as low as 523 ml when a stapler device was used and 756 ml when the traditional technique was used. The data from Nashville regarding operating time, bleeding and hospital stay are impressive. Chang and associates adhere to a collaborative clinical care pathway for radical cystectomy and the surgeons each perform more than 30 cystectomies every year (Chang 2002).

Paper II

All patients who had signs and symptoms of urinary leakage or obstruction were identified before the time of the planned urography. This is the main explanation why we did not find one single patient with urine leak or stricture out of 170 examined by urography. It is unlikely that there is a leakage of clinical importance if there is no urine in the abdominal drains. We presume that it is of limited benefit to diagnose a leakage early if there is no urine in the drains and no signs or symptoms. The results after stentograms 5-8 days postoperatively in 73 patients were reported by Manion, who identified 3 ureteral leaks in 135 ureteroenteric anastomoses (Manion 1997). In another study the incidence of leaks and complications 13 days postoperatively in 51 patients who underwent routine stentograms was reported. They concluded that routine evaluation of the ureterointestinal anastomosis with stentograms before stent removal was unnecessary and may increase patient morbidity (Pantuck 1997). Both authors concluded that routine evaluation was unnecessary and Pantuck even suggested that it may increase patient morbidity. Pantuck and associates estimated the additional cost of detecting a single anastomotic leakage with routine stentograms to 58,000 USD in 1997. The cost in March 2004 for a urography in our radiology department is approximately 290 USD. The total cost for 170 patients amounts to 49,300 USD, which does not include transportation services for patients.

Paper III

Sylvester and associates performed a meta-analysis using 7 published studies and demonstrated a significant benefit of a single instillation over placebo (Sylvester 2004). The net benefit was estimated to be 12% or, in other words, the number of patients needed to treat to prevent one recurrence is 8.5. One should keep in mind that these calculations were based on the evaluable number of patients in the studies included in the meta-analysis. There was a high percentage of excluded patients in most studies since the randomisation procedure was performed before the true nature of the tumour was known.

As many as up to 28% of the patients in the larger studies were excluded mainly because the histopathological report demonstrated no tumour or a muscle-invasive tumour. In other words, in clinical practice, the number of patients needed to treat in order to prevent one recurrence is reasonably higher than 8.5 since patients cannot be excluded as they can in a study. The authors of single instillation studies did not report the size of the first recurrences (Burnand 1976, Abrams 1981, Zincke 1983, Oosterlinck 1993, Bouffieux 1995, Tolley, Ali-El-Dein 1997, Rajala 2002, Okamura 2002). One exception is Solsona et al. who stated that “early recurrences comprised in general a few small papillary tumours.” Unfortunately, exact data on the recurrence size cannot be found in their paper. The reason is that they categorised recurrences which were 1-9mm, as 1cm tumours. The resulting size range of the recurrences is 1-2 cm which, of course, is unintentionally very misleading.

A watchful waiting policy in small recurrent tumours was recently suggested by Soloway et al. Gofrit et al. studied recurrent TaG1 tumours and found a watchful waiting policy quite acceptable, in particular in patients with tumours less than 5 mm in diameter since their average monthly growth was much smaller than larger tumours (Gofrit 2006, Soloway 2003).

Most likely, almost all recurrences in the present study ought to have been possible to treat under either local anaesthesia or under full anaesthesia as a day-surgery procedure. If so, a single instillation policy would result in increased costs for the health care system.

One weakness with the present study is that the tumour size was estimated by the surgeon and not determined in a precise way. We believe that this should not have influenced the result of the study due to the high number of patients and since it was randomised. One might argue that another weakness was the short follow-up period.

Paper IV

The clinical message of our study is that patients with a negative cystoscopy at month 4 after TUR of a grade 1 tumour have a benign course of disease.

There are data that suggest that 40% of all costs for treatment of bladder cancer are attributable to TUR and only 13% to follow-up cystoscopies (Hedelin 2002). Consequently, the potential savings by treating small-sized recurrences under local anaesthesia are of course much higher than the savings from omittance of some cystoscopies.

Our results show that the new routine is safe or, in other words, patients with pTaG1 and a negative first cystoscopy are a selected group with extremely low risk of progression in stage. Outpatient treatment of low-grade recurrences has been done for more than 50 years at a cost which is only 10-20% of that for inpatient management (Klein 1981, Hedelin 2002). It can be assumed that fulguration under local anaesthesia is better tolerated using a flexible cystoscope and many authors have shown the feasibility and safety using such an instrument (German 1992, Wedderburn 1999).

A high proportion of small-sized lesions in patients with a history of bladder cancer are actually histologically non-malignant (Svatek 2005). It would have been an advantage in the present study if all tumours were biopsied. Patients with non-malignant changes could consequently have had their next follow-up visit after 12 months and not after 4 months, which would result in a lower percentage with recurrences at the 12-month visit.

A weakness with our study is that there were a high number of patients who did not follow the routines. These patients also had small-sized recurrences and no serious tumours. The timing of the first cystoscopy may also be questioned since it was performed at 4 months according to local routines. Intuitively, a negative first cystoscopy at 4 months must be a stronger sign of good prognosis than a negative cystoscopy at 3 months. It may, in our opinion, be a good idea to separate “good” grade 1 tumours from “bad” grade 2-3 tumours and have separate “tracks” with an initial 4-month cystoscopy for patients with grade 1 tumours and 3-month cystoscopy for patients with high-grade tumours (grade 2 and 3). Based on our experience we suggest that one interested urologist aided by a secretary is given the possibility to supervise the changing of follow-up routines in order to ensure that all patients who should follow the new routine also do it.

CONCLUSIONS

Paper I

Total costs may be very high for a cystectomy with complications. The peroperative blood loss was the most important factor associated with high total hospital costs for radical cystectomy due to bladder cancer. The bleeding can be influenced why substantial reductions in total costs for cystectomy seem possible.

Paper II

A routine postoperative urography is not necessary in patients who have a normal postoperative course after cystectomy and urinary diversion.

Paper III

We confirmed the results of previous studies which showed that 8.5 patients have to be treated with a single instillation to prevent one recurrence. Furthermore, our data may indicate that only small-sized recurrences are prevented such that could easily be fulgurated under local anaesthesia at the time of follow-up cystoscopy. The benefit of single instillations can be questioned if this finding can be confirmed by others.

Paper IV

Patients with low-grade stage Ta tumours who are tumour-free at 4 months can safely follow a routine with cystoscopy at month 12 and 24. One should be aware of the risk that true high-grade tumours are erroneously included and followed at too infrequent intervals.

Swedish summary

Syfte: Att fastställa kostnader för cystektomi och studera prognostiska faktorer relaterade till totalkostnaden. Att studera resultaten av de radiologiska undersökningarna som rutinmässigt utförs 7-14 dagar efter cystektomi. Att studera om en singeldos epirubicin efter transurethral resektion av en blåstumör påverkar tid till recidiv och storlek på det första recidivet. Att prospektivt studera om ett reducerat antal cystoskopikontroller hos patienter med lågradig blåstumör är kliniskt genomförbart.

Patienter och metoder: Journaler och relevanta ekonomiuppgifter för 70 patienter analyserades. Kostnader beräknades för varje cystektomi och olika faktorer som var relaterade till totalkostnaden analyserades. Resultatet av urografi studerades för 200 konsekutiva patienter som genomgått cystektomi. Totalt randomiserades 404 patienter på 13 sjukhus till endera 50 mg epirubicin eller placebo inom 6 timmar efter TUR av blåstumör.

Patienter med lågradig, Ta tumör utan recidiv vid första cystoskopikontrollen vid fyra månader(± 2 veckor) blev kontrollcystoskoperade vid 12 månader(± 1 månad) och därefter vid 24 månader(± 2 månad).

Resultat: Mediankostnaden för en cystektomi var 189.479 SEK. Kostnad för vård på avdelningen var den enskilt dyraste posten. Blodförlusten under operation var den mest betydelsefulla faktorn associerad till totalkostnad. Ingen patient av de 170 som genomgick en postoperativ urografi hade urinläckage eller striktur. Således är denna undersökning onödig så länge det postoperativa förloppet är normalt. Sjuttionio (51%) av 155 evaluerbara patienter i epirubicinarmen fick recidiv jämfört med 95 (62.5%) av 152 i placebo gruppen ($p=0.04$). De flesta recidiven (63.3%) var små (1-5mm). 33 (42.9%) av 79 patienter med recidiv i epirubicinarmen jämfört med 29 patienter (31.5%) av 95 i placeboarmen hade större(>5 mm) första recidiv. Resultat från tidigare studier konfirmerades, vilket visar att 8.5 patienter behöver behandlas med en singelinstillation för att förhindra ett recidiv. Vidare talar våra data för att det bara är små recidiv som förhindras, sådana som kirurgiskt enkelt kan åtgärdas på mottagningen i lokal anestesi i samband med uppföljningscystoskopin. Nyttan med engångsinstillation kan

ifrågasättas om våra fynd kan konfirmeras av andra.

Patienter med lågradig Ta tumör som är tumörfria vid 4-månaderskontrollen kan på ett säkert sätt vidare kontrolleras månad 12 och 24.

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