

## **Chapter 1:**

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### **General Introduction and Outline of the Thesis**



## **Introduction**

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In the Netherlands radical cystectomy is the gold standard treatment for therapy resistant superficial bladder cancer and muscle invasive bladder cancer. Although cystoprostatectomy has evolved in the past years, survival improved only slightly since the past decades. In addition to oncological outcome, quality of life issues gained increasing importance in the treatment of bladder cancer with new interest in bladder sparing strategies and operative techniques improving functional outcome.

After cystectomy three types of lower urinary tract reconstruction are presently considered; an ileal conduit, a continent heterotopic pouch, or bladder reconstruction with an orthotopic neobladder. Although there is no scientific prove of increased quality of life after any of the named urinary diversions, problems with the urinary diversion and sexual problems are identified as the most common inconveniences.<sup>1-3</sup> Although the effects of radical cystectomy changed somewhat by nerve sparing techniques and the construction of orthotopic bladders, the ideal therapy should both cure the patient of bladder cancer and preserve the (functioning) native bladder. External beam radiotherapy offers bladder preservation, but at the cost of a local recurrence rate of approximately 30% and possibly a decreased overall survival as compared to cystectomy.<sup>4</sup> Combined modality treatments may achieve equivalent oncological results with bladder preservation in selected bladder cancer patients, but only a selection of bladder cancers can be treated with preservation of the native bladder.

More recent findings on the anatomy, physiology, and nerve supply of the pelvis have resulted in modified nerve sparing cystectomy and prostatectomy techniques. These techniques made it feasible to restore the lower urinary tract with improved continence rates and maintained sexual function after cystectomy. Despite nerve sparing, the results with respect to preserving potency often do not meet the expectations. An alternative might be a prostate sparing cystectomy in suitable patients. The major critic on organ preserving approaches and prostate sparing cystectomy in muscle invasive bladder cancer is the fear of compromising oncological results, both in terms of local recurrence and mortality.

This thesis describes the results of the applied treatments for bladder cancer in the region of greater Amsterdam, and explores the oncological and functional results after dissimilar treatment strategies (cystectomy, prostate sparing cystectomy, and bladder sparing modalities) for different types and stages of bladder cancer.

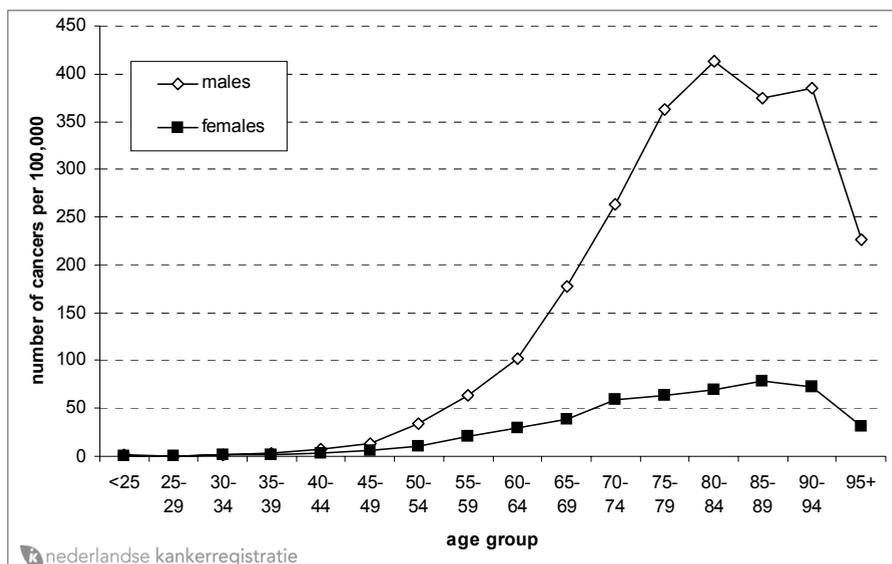
## **Epidemiology**

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At any point in time 2.7 million people worldwide are diagnosed or followed-up with bladder cancer.<sup>5</sup> Certain environmental carcinogens, such as benzidine, tobacco, nitrates and 2- and 4-naphtylamine predispose people to transitional cell tumours. As a consequence bladder tumours are more prevalent in men older than 50 and densely populated industrial areas. In the Netherlands 5269

new patients were diagnosed with bladder cancer in 2007. At that time it was the fifth most common malignancy in men, with a (age standardized) male to female ratio of 4.2 : 1. The incidence rises with increasing age (figure 1). 70% of these bladder cancers is not muscle invasive and can be treated with transurethral resections with or without additional intravesical installations. Of these superficial bladder cancers 15% is therapy resistant, while 30% of the bladder cancers is muscle invasive at first diagnosis.

**Figure 1:** Age specific incidence of bladder cancer in the Netherlands



## Presentation and Staging

Bladder cancers present in the majority of patients with painless haematuria. A subgroup of patients complains of urgency and increased frequency. Pelvic pain and urinary tract obstruction may be symptoms of more advanced tumours. The urothelial tissue in the complete urothelial tract may be involved, including renal pelvis, ureters, bladder, and urethra. This tissue is normally 3 to 7 layers thick, and contains no blood or lymphatic vessels. Urothelial cancers differ from normal urothelium by an increased number of epithelial cell layers with papillary folding of the mucosa, loss of cell polarity, abnormal cell maturation from basal to superficial layers, increased nuclear-cytoplasmic ratio, prominent nucleoli, or an increased number of mitoses.<sup>6</sup>

In the bladder the urothelial tissue rests on the lamina propria, a layer of connective tissue interlaced with the muscular coat. This layer contains blood vessels, lymphatic vessels and nerves. A tumour which invades this layer therefore has the ability to metastasize by lymphatic or hematogenic spread. The lamina propria rest on a muscular layer, which in its turn is surrounded by perivesical fat.

This anatomy is the base of the tumour, node and metastases (TNM) classification of the International Union against Cancer, which guides therapeutic options and has prognostic value. The diagnosis of bladder cancer depends on cystoscopic examination and subsequent transurethral resection (TUR). Pathological evaluation of the resected lesion should describe the depth of invasion according to the TNM classification, tumour grade according to the WHO/ISUP grading system, and the histological subtype (table 1 and 2, figure 2).<sup>7</sup>

**Table 1 & Figure 2:** Tumour, node and metastases (TNM) classification of the International Union against Cancer

T0	No evidence of primary tumour	
Ta	Non- invasive papillary carcinoma	
Tis	Carcinoma in situ	
T1	Tumour invades subepithelial connective tissue	
T2a	Tumour invades superficial muscle (inner half)	
T2b	Tumour invades deep muscle (outer half)	
T3a	Tumour invades perivesical fat microscopically	
T3b	Tumour invades perivesical fat macroscopically	
T4a	Tumour invades prostate, uterus or vagina	
T4b	Tumour invades pelvic or abdominal wall	
N0	No lymph node metastasis	
N1	Metastasis in a single lymph node < 2cm	
N2	Metastasis in a single lymph node > 2 cm but < 5 cm, or multiple lymph nodes < 5 cm	
N3	Metastasis in a lymph node > 5 cm	
M0	No distant metastasis	
M1	Distant metastasis	

**Table 2:** WHO grading in 1973 and 2004

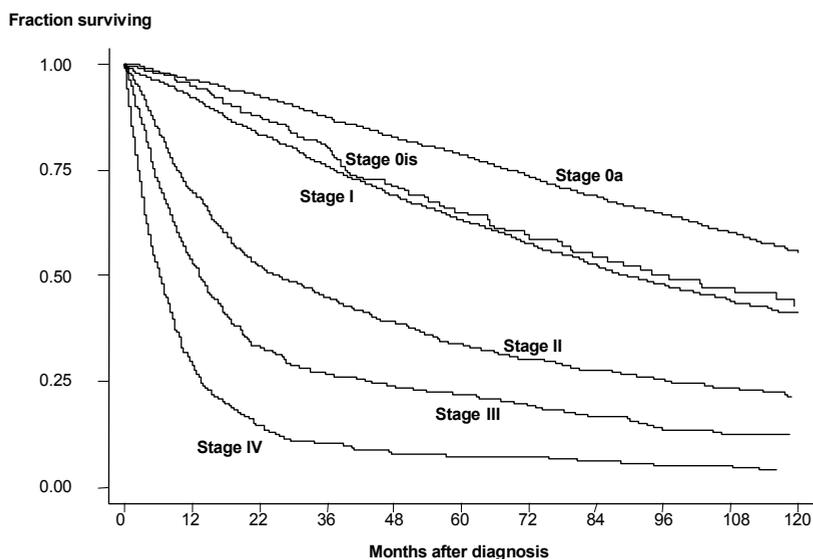
WHO grading 1973	WHO grading 2004
Urothelial papilloma	Urothelial papilloma
Grade 1: well differentiated	Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Grade 2: moderately differentiated	Low-grade papillary urothelial carcinoma
Grade 3: poorly differentiated	High-grade papillary urothelial carcinoma

The TNM classification changed during the time interval of the study population in this thesis. The 2002 TNM classification differs from the 1997 and 1992 TNM classification and includes now bladder wall infiltration of different depth (T2a inner half, T2b outer half). In 2004 a new classification system of non invasive urothelial tumours was published, although of less importance for patients in need of a cystectomy as muscle invasive bladder cancers are (almost) always high grade. This new WHO/ISUP classification differentiates papillary urothelial

neoplasms of low malignant potential (PUNLMP) from low- or high-grade urothelial carcinoma's, while the intermediate group of moderately differentiated has been removed.

Bladder cancers are regarded non muscle invasive (Ta, Tis or T1 tumours) or muscle invasive (T2, T3, or T4 tumours) based on physical examination, imaging, findings during cystoscopy and TUR, and histopathology. CT-scan is the most commonly used imaging modality, but can just roughly determine the extent of invasion, and detects large suspicious lymph nodes only. The only reliable way of staging lymph nodes at this moment is lymphadenectomy, although newer imaging techniques such as ultra small superparamagnetic particles of iron oxide (USPIO) and diffusion weighted magnetic resonance imaging (DW-MRI) or combinations of these are promising.<sup>8</sup> The clinical course reflects the wide range of tumour biology. Non-muscle invasive low grade tumours have a minor risk of leading to death, while invasive high grade tumours are often fatal, despite treatment (figure 3).<sup>22</sup>

**Figure 3:** Survival according to stage of bladder cancer in the region of greater Amsterdam.



Risk stratification is essential for optimal management of bladder cancer. Apart from staging and grading the bladder tumour, the histological subtype defines the most suitable therapeutic approach. More than 90% of all bladder cancers are urothelial cell cancers, also known as transitional cell cancers (TCC). Up to 5% of bladder tumours are squamous cell in origin, and 2% are adenocarcinomas. The rest consists of urothelial carcinoma with aberrant differentiation, e.g. squamous/glandular differentiation, sarcomatoid carcinoma, micropapillary carcinoma and small cell carcinomas. All the histological variances carry a worse prognosis than pure urothelial cell carcinoma. Apart

from urothelial cancer we also focus in this thesis on small cell carcinomas, which are thought to arise from neuroendocrine stem cells. At time of diagnosis, they are often metastasised, which makes cystectomy as sole therapy not an option.

## **Treatment**

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Stage, grade and subtype define the most suitable treatment and prognosis. Superficial tumours can be treated by (repeated) transurethral resections and additional adjuvant intravesical instillations. In patients in whom this treatment fails and in patients with muscle invasive bladder cancer radical cystectomy with subsequent urinary diversion is considered the gold standard treatment in the Netherlands, in the absence of distant metastases.

### **Cystectomy**

Standard radical cystectomy consists of a regional lymph node dissection and removal of the bladder, including prostate, seminal vesicles and vasa deferentia in man, and uterus, adnexa and anterior vaginal wall in woman. In this procedure the autonomic nerves, which are essential for a normal sexual response are often removed or damaged. Walsh described how the neurovascular bundles containing cavernous nerves can be preserved during prostatectomy for prostate cancer.<sup>9</sup> In a similar way the nerve sparing cystoprostatectomy was developed, to improve postoperative sexual functions and urinary continence.<sup>10-12</sup> At the same time interest in performing orthotopic urinary diversions emphasized the need to identify those men at high risk for urethral recurrences.<sup>13</sup> Urethral tumours occur in approximately 7% of men following cystectomy, so if the urethra may be spared in the majority of patients, why not the prostate?<sup>14</sup> The major critic on prostate sparing cystectomy is the fear of compromising oncological results in terms of urethral recurrences, pelvic and distant recurrences, and development of prostate cancer.<sup>15</sup> The need for removing the prostate is still debated, and various modified cystectomy techniques preserving (part of) the prostate have been described. Spitz et al described a cystectomy with partial prostatectomy while preserving vasa deferentia, seminal vesicles and posterior prostate (in patients without malignancy),<sup>16</sup> Muto et al combined cystectomy with an adenoma enucleation according to Millin<sup>17</sup>, and Colombo et al<sup>18</sup> and Vallancien et al<sup>19</sup> described extirpation of the bladder preceded by transurethral resection of prostatic tissue and prostatic urothelium with preservation of the prostatic capsule. This thesis describes oncological and functional results in a group of patients selected for prostate sparing cystectomy after extensive selection by sampling of the bladder neck, prostate and prostatic urethra without effort to remove all prostatic urothelium.

Total cystectomy should include dissection of the regional lymph nodes. This is the only reliable method of determining lymph node status, and might be of therapeutic value. The limits of lymph node dissection are still subject to debate, with an increasing number of studies reporting that an extended lymphadenectomy provides further diagnostic and therapeutic benefit.<sup>20,21</sup> An extended lymph node dissection should include all obturator, internal, external, common iliac and pre-sacral nodes, as well as the nodes at the aortic bifurcation.

### **Radiotherapy**

External beam radiotherapy offers the advantage of bladder preservation, but is considered insufficient as solitary treatment for bladder cancer. Radiotherapy leads to local recurrences in approximately 30% and possibly a decreased overall survival as compared to cystectomy.<sup>4</sup>

While cystectomy is considered therapy of choice in patients with stage 2 and 3 bladder cancer, more patients were treated by radiotherapy than by cystectomy between 1988 and 2001 in the region of greater Amsterdam.<sup>22</sup> Reasons may be that these patients have been offered primary radiotherapy as part of a bladder preserving strategy, with salvage cystectomy in case of persistent disease. Another reason may be that cystectomy was not considered a therapeutic option, either due to high age, major co-morbidity and/or decreased performance status, or patient's choice.

Combined modality treatments may achieve equivalent oncological results with bladder preservation in selected bladder cancer patients. Patients with small solitary organ confined muscle invasive bladder tumours can be treated with interstitial radiotherapy, in which implantation of radioactive Iridium<sup>192</sup> is combined with external radiotherapy and bladder preserving surgery. To become a reasonable alternative to cystectomy, a bladder sparing approach should not compromise survival. Additionally, the preserved native bladder should maintain good bladder function. Due to the different nature of both treatments randomized trials comparing surgery with brachytherapy are extremely difficult to conduct. At this time no prospective studies exist, but based on reported local control rates of 70-90% brachytherapy appears a reasonable alternative to cystectomy.<sup>23-25</sup> In this thesis we compare the outcome of both modalities.

Both forms of radiotherapy carry the risk of residual disease or new tumour growth in the bladder in which case a salvage cystectomy should be considered. Surgery after previous pelvic radiation can be technically challenging. Anatomical planes are more difficult to distinguish because of desmoplastic reaction. Tissue ischemia after radiation can lead to more vulnerable intestinal tissue, with higher risk of anastomotic leakage and delayed wound healing. After brachytherapy the previous surgical exposure to place the loops for afterloading of iridium can be an additional cause of obliterated anatomical planes. In this thesis the results of salvage cystectomy after brachytherapy and external radiotherapy are reviewed.

### **Chemotherapy**

Combination Cisplatin based chemotherapy is the only treatment strategy providing the potential of long-term survival in metastatic bladder cancer.<sup>26</sup> In addition, it appears to be more effective in patients with nodal metastases compared with visceral metastases.<sup>27</sup> In localized disease the role of chemotherapy before (neoadjuvant) or after (adjuvant) is less well defined. Neoadjuvant chemotherapy is intended for patients with operable stage 2-4a disease.

Chemotherapy is given prior definitive treatment to improve survival by treatment of micrometastases in an early stage. Although neoadjuvant chemotherapy results in a modest improvement of overall survival by 5-7%, it is not routinely incorporated in localized disease in the Netherlands.<sup>28</sup> Most patients studied in neoadjuvant trials had (clinically) tumour negative nodes or unknown lymph node status. The MRC meta-analysis comprised 2688 patients, of whom 4% had clinically node positive disease and 48% had an unknown lymph node status.<sup>29</sup> The treatment and timing of chemotherapy in patients with tumour positive nodes without distant metastases remains subject of debate. Although an extended resection of lymph nodes might be of curative value in itself, the exact role of surgery in lymphogenic metastasized bladder cancer still has to be defined.<sup>21,30,31</sup> In the Netherlands it was common practice not to perform cystectomy and to abort surgery in favour of neoadjuvant chemotherapy if confronted with positive nodes. Cystectomy with complementary lymph node dissection followed in case of a response to chemotherapy. In this thesis we evaluated the use of MVAC with subsequent cystectomy in patients with histological proof of tumour positive lymph nodes without distant metastases.

### ***Small cell bladder cancer***

Apart from grade and stage, the histological subtype defines the most suitable therapeutic approach. Primary small cell carcinoma (SCC) of the bladder is rare, accounting for less than 1% of all bladder malignancies. Metastases are often present at the time of diagnosis, prognosis is poor, and there is no established optimum treatment. Only Cisplatin-based chemotherapy has been predictive to influence survival, while local therapy alone is often insufficient for cure.<sup>32</sup> Cystectomy with adjuvant chemotherapy has been propagated as the treatment of choice.<sup>33</sup> Small cell lung cancer (SCLC) shares many clinicopathological features with SCC and a two-stage system of limited and extensive disease is widely used to determine prognosis and treatment.<sup>34-37</sup> In this thesis we evaluated the feasibility and efficacy of a therapeutic algorithm for the management of small cell carcinoma of the bladder based on a two-stage system of limited and extensive disease in analogy to the practiced staging and treatment for SCLC, in which chemotherapy and sequential radiation was applied for limited disease and chemotherapy alone for extensive disease.

### **Urinary diversions after cystectomy**

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After cystectomy several types of urinary diversions are offered to patients. Controversies exist on whether any type of diversion can be used in any patient.<sup>38,39</sup> Many considerations determine the final choice of urinary diversion in the individual patient; it should be oncologically safe, technically feasible and secure, provide good functional results, and comply with the patient's choice if possible. Increasing emphasis is placed on decreased hospital stay for patients who undergo various surgical procedures, underlining the need for technically

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safe procedures reflected in low peri-operative and late complication rates.<sup>40</sup> Continent urinary diversions may be of great psychological benefit to selected patients, but may be associated with different side effects. Hyperchloremic metabolic acidosis can occur because of re-absorption of ammonium chloride and secretion of sodium bicarbonate by ileal tissue of the neobladder.<sup>41,42</sup> Resection of part of the ileum for urinary diversion may also lead to vitamin B12 or folic acid deficiencies.<sup>43,44</sup> In this thesis we assessed early and late complication rates, functional results, and metabolic changes in the four different urinary diversions that were used between 1990 and 2005, and the association of tumour stage, ASA-score, age and previous received pelvic radiotherapy with these variables.

### Follow-up

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After cystectomy pelvic recurrence rates vary between 4-34%, while distant metastases occur in up to 50% of all patients, both highly dependent on stage.<sup>45-48</sup> Follow-up of these patients is recommended to detect pelvic recurrence and distant metastasis as early as possible to permit additional treatment if indicated. According to the 2007 EAU guidelines the oncological follow-up after cystectomy should be guided by prognostic factors, of which pT and pN-stage are the most important in determining the most efficient regimen. Three-monthly assessments postoperatively include physical examination, urine and blood analysis, ultrasonography of kidney, liver and retroperitoneum, and chest X-ray. In case of pN+ additional CT scans and bone scintigraphy are recommended.

The 2008 EAU guidelines state that follow-up should be dependent on stage of the initial tumour. Recent studies doubt the efficacy of standard follow-up schedules as many patients present with symptoms of a recurrence.<sup>49</sup> Combined with the poor prognosis of these patients despite subsequent therapy this leads to the question if similar results at lower costs can be achieved by symptom-guided follow-up. To evaluate this we analysed patterns of recurrence and relapse presentation in association with clinicopathological factors, and the tools used for diagnosis of recurrence in chapter nine of this thesis.

### Outline of the Thesis

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In **chapter 2** we describe a population based study of survival and the local recurrence rate after cystectomy of all patients diagnosed with bladder cancer between 1988 and 2001 in the region of greater Amsterdam, which covers a population of 2.84 million people. In **chapter 3** we describe the effect of neoadjuvant chemotherapy (MVAC) and subsequent surgery in bladder cancer patients with tumour-positive lymph nodes, in whom the response in both the primary tumour and lymph nodes, long-term clinical outcome, and clinicopathological features potentially predictive for survival are analysed. In **chapter 4** we evaluate the outcome of 25 patients with small cell bladder

cancer treated with chemotherapy with or without subsequent local therapy, analogous to protocols of small cell lung cancer which is based on a two-stage system of limited and extensive disease. In the **5th chapter** we compare the long-term survival after brachytherapy with cystectomy in patients with invasive bladder cancer. We describe the survival, the morbidity and functional results of the different urinary diversions used in patients in need of a salvage cystectomy after failure of interstitial radiotherapy and external beam radiotherapy in **chapter 6**. Our experience with the prostate sparing cystectomy is described in **chapter 7**, based on the articles "Clinical outcomes after sexuality preserving cystectomy and neobladder (prostate sparing cystectomy) in 44 patients" and "Prostate sparing cystectomy: long term oncological results". We present the association of clinical factors, complications and functional results of the four most widely used diversions in 281 patients in **chapter 8**. In **chapter 9** we describe the patterns of recurrence after cystectomy, relapse presentation and the tools used to diagnose recurrence of disease, based on the article "Follow-up after cystectomy: regularly scheduled, risk adjusted, or symptom guided? Patterns of recurrence, relapse presentation, and survival after cystectomy". In **chapter 10** we discuss the presented data and describe future perspectives of these subjects.

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