

Guidelines on **Muscle-invasive and Metastatic Bladder Cancer**

J.A. Witjes (chair), E. Compérat, N.C. Cowan, M. De Santis,
G. Gakis, T. Lebret, M.J. Ribal, A. Sherif

TABLE OF CONTENTS

PAGE

1.	INTRODUCTION	5
1.1	The guideline	5
1.2	Methodology	5
1.2.1	Data identification	5
1.2.2	Publication history	5
1.3	Summary of updated information	6
1.4	Potential conflict of interest statement	7
1.5	References	7
2.	EPIDEMIOLOGY AND RISK FACTORS	7
2.1	Epidemiology	7
2.2	Risk factors for bladder cancer	8
2.2.1	Tobacco smoking	8
2.2.2	Occupational exposure to chemicals	8
2.2.3	Radiotherapy	8
2.2.4	Dietary factors	8
2.2.5	Bladder schistosomiasis	9
2.2.6	Chronic urinary tract infection	9
2.2.7	Chemotherapy	9
2.2.8	Synchronous and metachronous upper urinary tract tumours	9
2.2.9	Gender	9
2.2.10	Ethnic and socioeconomic status	10
2.3	Conclusions and recommendations for epidemiology and risk factors	10
2.4	References	10
3.	CLASSIFICATION	13
3.1	Tumour, node, metastasis classification	13
3.2	Histological grading of non-muscle-invasive bladder tumours	13
3.2.1	WHO grading	13
3.3	Pathology	14
3.3.1	Handling of specimens by urologists	14
3.3.2	Handling of specimens by pathologists	14
3.3.3	Pathology of muscle-invasive bladder cancer	14
3.3.4	pT2 substaging in node-negative disease after cystectomy	15
3.3.5	Recommendations for assessing tumour specimens	15
3.4	Conclusions and recommendations for classification in MIBC	15
3.5	References	16
4.	DIAGNOSIS AND STAGING	17
4.1	Primary diagnosis	17
4.1.1	Symptoms	17
4.1.2	Physical examination	17
4.1.3	Bladder imaging	18
4.1.4	Urinary cytology and urinary markers	18
4.1.5	Cystoscopy	18
4.1.6	Transurethral resection (TUR) of invasive bladder tumours	18
4.1.7	Random bladder and prostatic urethral biopsy	18
4.1.8	Second resection	19
4.1.9	Concomitant prostate cancer	19
4.1.10	Specific recommendations for primary assessment of presumably invasive bladder tumours	19
4.2	Imaging for staging MIBC	19
4.2.1	Local staging of MIBC	19
4.2.1.1	MRI for local staging of invasive bladder cancer	19
4.2.1.2	CT imaging for local staging of MIBC	20
4.2.2	Imaging of lymph nodes in MIBC	20
4.2.3	Upper urinary tract urothelial carcinoma (UTUC)	20
4.2.4	Distant metastases other than lymph nodes	20

4.2.5	Future developments	20
4.2.6	Conclusions and recommendations for staging in MIBC	21
4.3	References	21
5.	TREATMENT FAILURE OF NON-MUSCLE INVASIVE BLADDER CANCER	25
5.1	High-risk non-muscle-invasive urothelial carcinoma	25
5.2	Carcinoma <i>in situ</i>	26
5.3	Recommendations for treatment failure of non-muscle-invasive bladder cancer	27
5.4	References	27
6.	NEOADJUVANT CHEMOTHERAPY	29
6.1	Introduction	29
6.2	The role of imaging to assess treatment response	29
6.2.1	Conclusions and recommendation	30
6.3	Disadvantages of neoadjuvant chemotherapy	30
6.4	Conclusions and recommendations for neoadjuvant chemotherapy	31
6.5	References	31
7.	RADICAL SURGERY AND URINARY DIVERSION	34
7.1	Removal of the tumour-bearing bladder	34
7.1.1	Background	34
7.1.2	Timing and delay of cystectomy	34
7.1.3	Indications	34
7.1.4	MIBC and comorbidity	34
7.1.4.1	Evaluation of comorbidity	35
7.1.4.2	Comorbidity scales	35
7.1.4.3	Conclusions and recommendations for comorbidity scales	37
7.1.5	References	37
7.1.6	Radical cystectomy - technique and extent	40
7.1.7	Laparoscopic/robotic-assisted laparoscopic cystectomy	41
7.2	Urinary diversion after radical cystectomy	41
7.2.1	Preparations for surgery	41
7.2.1.1	Patient selection for orthotopic diversion	42
7.2.2	Ureterocutaneostomy	42
7.2.3	Ileal conduit	42
7.2.4	Continent cutaneous urinary diversion	42
7.2.5	Ureterocolonic diversion	43
7.2.6	Orthotopic neobladder	43
7.3	Morbidity and mortality	43
7.4	Survival	43
7.5	Conclusions for radical cystectomy and urinary diversion	44
7.6	Recommendations for radical cystectomy and urinary diversion	44
7.7	References	45
8.	NON-RESECTABLE TUMOURS	51
8.1	Palliative cystectomy for muscle-invasive bladder carcinoma	51
8.2	Conclusions and recommendations for non-resectable tumours	52
8.3	Supportive care	52
8.4	References	52
9.	NEOADJUVANT / ADJUVANT RADIOTHERAPY IN MUSCLE-INVASIVE BLADDER CANCER	53
9.1	Pre-operative radiotherapy	53
9.1.1	Retrospective studies	53
9.1.2	Randomised studies	54
9.1.3	Effect of pre-treating patients with neoadjuvant radiotherapy before cystectomy	54
9.2	Conclusions and recommendations for pre-operative radiotherapy	55
9.3	References	55

10.	BLADDER-SPARING TREATMENTS FOR LOCALISED DISEASE	56
10.1	Transurethral resection of bladder tumour (TURB)	56
10.1.1	Conclusion and recommendation for TURB	57
10.1.2	References	57
10.2	External beam radiotherapy (EBRT)	57
10.2.1	Conclusions and recommendation for external beam radiotherapy	58
10.2.2	References	58
10.3	Chemotherapy	59
10.3.1	Conclusion and recommendation for chemotherapy for muscle-invasive bladder tumours	59
10.3.2	References	60
10.4	Multimodality bladder-preserving treatment	61
10.4.1	Conclusions and recommendations for multimodality treatment in muscle-invasive bladder cancer	62
10.4.2	References	62
11.	ADJUVANT CHEMOTHERAPY	63
11.1	Conclusion and recommendation for adjuvant chemotherapy	63
11.2	References	64
12.	METASTATIC DISEASE	64
12.1	Prognostic factors and treatment decisions	64
12.1.1	Comorbidity in metastatic disease	65
12.1.2	Not eligible for cisplatin (unfit)	65
12.2	Single-agent chemotherapy	65
12.3	Standard first-line chemotherapy for fit patients	65
12.4	Carboplatin-containing chemotherapy in fit patients	66
12.5	Non-platinum combination chemotherapy	66
12.6	Chemotherapy in patients unfit for cisplatin	66
12.7	Second-line treatment	66
12.8	Low-volume disease and post-chemotherapy surgery	67
12.9	Treatment of bone metastases	67
12.10	Conclusions and recommendations for metastatic disease	67
12.11	Biomarkers	68
12.12	References	69
13.	QUALITY OF LIFE	74
13.1	Introduction	74
13.2	Choice of urinary diversion	74
13.3	Non-curative or metastatic bladder cancer	75
13.4	Conclusions and recommendations for HRQoL	75
13.5	References	75
14.	FOLLOW-UP	77
14.1	Site of recurrence	77
14.1.1	Distant recurrences	77
14.1.2	Urothelial extravesical recurrences (see comment below)	78
14.1.3	Conclusions and recommendations for specific recurrence sites	78
14.1.4	Follow-up of functional outcomes and complications	79
14.2	References	79
15.	ABBREVIATIONS USED IN THE TEXT	81

1. INTRODUCTION

1.1 The guideline

The European Association of Urology (EAU) Guidelines Panel for Muscle-invasive and Metastatic Bladder Cancer (MIBC) has prepared these guidelines to help urologists assess the evidence-based management of MIBC and to incorporate guideline recommendations into their clinical practice. The EAU Guidelines Panel comprises an international multidisciplinary group of experts from the fields of urology, pathology, radiology and oncology.

It is evident that optimal treatment strategies for MIBC require the involvement of a specialist multidisciplinary team and a model of integrated care to avoid fragmentation of patient care.

The Muscle-invasive and Metastatic Bladder Cancer guidelines are one of four EAU guidelines documents addressing bladder cancer (EAU Guidelines on Non-muscle-invasive (TaT1 and CIS) Bladder Cancer, EAU Guidelines on Upper Urinary Tract Urothelial Cell Carcinomas and EAU Guidelines on Primary Urethral Carcinoma) which, together, present a comprehensive overview of the management of urothelial neoplasms (1-3).

1.2 Methodology

1.2.1 Data identification

Comprehensive literature searches were designed for each section of the MIBC guidelines with the help of an expert external consultant. Following detailed internal discussion, searches were carried out in the Cochrane Library database of Systematic Reviews, the Cochrane Library of Controlled Clinical Trials, and Medline & Embase on the Dialog-Datastar platform. The searches used the controlled terminology of the respective databases. Both Mesh and Emtree were analysed for relevant terms; urinary bladder neoplasms (Medline) and bladder cancer (Embase) were the narrowest single terms available.

Extensive use of free text ensured the sensitivity of the searches, although the subsequent concomitant workload for panel members having to assess the substantial body of literature greatly increased.

Search strategies covered the last 10 years for Medline and for Embase in most cases. Randomised controlled trial (RCT) strategies used were based on Scottish Intercollegiate Guidelines Network (SIGN) and Modified McMaster/Health Information Research Unit (HIRU) filters for RCTs, systematic reviews and practice guidelines on the OVID platform. Results of all searches were scan-read by panel members. In many cases there was a high 'numbers needed to read' due to the sensitivity of the search.

There is clearly a need for continuous re-evaluation of the information presented in the current guidelines by an expert panel. It must be emphasised that these guidelines contain information for the treatment of an individual patient according to a standardised approach.

The level of evidence (LE) and grade of recommendation (GR) provided in this guideline follow the listings in Tables 1 and 2 (4). The aim of grading the recommendations is to provide transparency between the underlying evidence and the recommendation given.

It should be noted, however, that when recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of RCTs may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Alternatively, absence of high level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences and cost when a grade is assigned (5-7).

The EAU Guidelines Office do not perform cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever this data is available, the expert panels will include the information.

1.2.2 Publication history

The EAU published the first guidelines on bladder cancer in 2000. This document covered both superficial

(non-muscle-invasive) bladder cancer and MIBC. As different treatment strategies are employed for these conditions it was decided to split these topics up, resulting in a first publication of the MIBC guidelines in 2004, with subsequent updates in 2007, 2009, 2010, 2011, 2012 and this 2013 update. A quick reference document presenting the main findings is also available alongside several scientific publications (8-10).

All texts can be viewed and downloaded for personal use at the EAU website:
<http://www.uroweb.org/guidelines/online-guidelines/>.

1.3 Summary of updated information

For this 2013 update, of note are the following changes:

Chapter 2 “Epidemiology and risk factors”;

- Section 2.2.8 Carcinoma *in situ* has been added.

Chapter 3 “Classification”;

- Sections 3.3, through 3.3.5 were revisited resulting in slightly adapted recommendations in section 3.3.4 (recommendations for the assessment of tumour specimens).
- Section 3.3.5 (pT2 substaging in node-negative disease after cystectomy) has been added.

Chapter 4 “Diagnosis and staging”;

- Sections 4.2.1.2 (CT imaging for local staging of MIBC), 4.2.2 (Imaging of lymph nodes in MIBC) and 4.2.3 Upper urinary tract urothelial carcinoma) have been added, as well as section 4.2.5 (Future developments).

Chapter 6 “Neoadjuvant Chemotherapy”;

- A new section 6.2 (The role of imaging to assess treatment response) has been included. The text has been updated with new literature resulting in amended conclusions and recommendations (section 6.4).

Chapter 7 “Radical Surgery and Urinary Diversion”

- A new section 7.1.4 (MIBC and comorbidity) on co-morbidities and patient selection for orthotopic diversion has been added.

Chapter 12 “Metastatic disease”;

- New data has been added, in particular to section 12.3 (Standard first-line chemotherapy for “fit” patients).

Chapter 14 “Follow-up”;

- Additional data included on recurrences and secondary urethral tumours.

For all updated sections, the literature has been assessed for currency.

Updates of chapters 5 - 8 - 9 - 10 - 11 and 13 are foreseen for publication in 2014.

Table 1: Level of evidence*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

*Modified from Sackett, et al. (4).

Table 2: Grade of recommendation*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

*Modified from Sackett, et al. (4).

1.4 Potential conflict of interest statement

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: <http://www.uroweb.org/guidelines/>.

1.5 References

1. Babjuk M, Oosterlinck W, Sylvester R, et al; members of the EAU Guidelines Panel on Non-muscle-invasive bladder cancer. Guidelines on Non-muscle-invasive bladder cancer (TaT1 and CIS). Edn. presented at the EAU Annual Congress 2013. ISBN 978-90-79754-71-7. Arnhem, The Netherlands. <http://www.uroweb.org/guidelines/online-guidelines/>
2. Rouprêt M, Zigeuner R, Palou J, et al; members of the EAU Guidelines Panel on Non-muscle-invasive bladder cancer. Guidelines on upper urinary tract urothelial cell carcinoma. Edn. presented at the EAU Annual Congress 2013. ISBN 978-90-79754-71-7. Arnhem, The Netherlands. <http://www.uroweb.org/guidelines/online-guidelines/>
3. Gakis G, Witjes JA, Compérat E, et al; members of the EAU Guidelines Panel on Muscle-invasive and Metastatic Bladder Cancer. Guidelines on Primary Urethral Carcinoma. Edn. presented at the EAU Annual Congress 2013. ISBN978-90-79754-71-7. Arnhem, The Netherlands. <http://www.uroweb.org/guidelines/online-guidelines/>
4. Modified from Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009. <http://www.cebm.net/index.aspx?o=1025> [access date January 2013]
5. Atkins D, Best D, Briss PA, et al; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004 Jun 19;328(7454):1490. <http://www.ncbi.nlm.nih.gov/pubmed/15205295>
6. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336(7650):924-6. <http://www.ncbi.nlm.nih.gov/pubmed/18436948>
7. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. Going from evidence to recommendations. *BMJ* 2008 May;336(7652):1049-51. <http://www.bmj.com/content/336/7652/1049.long>
8. Stenzl A, Cowan NC, De Santis M, et al.; European Association of Urology (EAU). Treatment of muscle-invasive and metastatic bladder cancer: update of the EAU guidelines. *Eur Urol* 2011 Jun;59(6):1009-18. <http://www.ncbi.nlm.nih.gov/pubmed/21454009>
9. Stenzl A, Cowan NC, De Santis M, et al.; European Association of Urology. [Update of the Clinical Guidelines of the European Association of Urology on muscle-invasive and metastatic bladder carcinoma]. *Actas Urol Esp* 2010 Jan;34(1):51-62. [Article in Spanish] <http://www.ncbi.nlm.nih.gov/pubmed/20223133>
10. Stenzl A, Cowan NC, De Santis M, et al. The updated EAU guidelines on muscle-invasive and metastatic bladder cancer. *Eur Urol* 2009 Apr;55(4):815-25. <http://www.ncbi.nlm.nih.gov/pubmed/19157687>

2. EPIDEMIOLOGY AND RISK FACTORS

2.1 Epidemiology

Bladder cancer is the ninth most common cancer diagnosis worldwide, with more than 330,000 new cases each year and more than 130,000 deaths per year, with an estimated male-female ratio of 3.8:1.0 (1). At any point in time, 2.7 million people have a history of urinary bladder cancer (1).

At the initial diagnosis of bladder cancer, 70% of cases are diagnosed as non-muscle-invasive bladder cancer (NMIBC) and approximately 30% as muscle-invasive bladder cancer (MIBC). Among patients treated with radical cystectomy because of MIBC, 57% had muscle invasion at presentation, while 43% were initially diagnosed with NMIBC that progressed despite organ-preserving treatment (2). Approximately one-third of patients diagnosed with MIBC have undetected metastases at the time of treatment for the primary tumour (3), while 25% of patients who undergo radical cystectomy present with lymph node involvement at the time of surgery.

2.2 Risk factors for bladder cancer

2.2.1 Tobacco smoking

Tobacco smoking is the most well-established risk factor for bladder cancer, causing 50-65% of male cases and 20-30% of female cases (4). A causal relationship has been established between exposure to tobacco and cancer in studies in which chance, bias, and confounding can be ruled out with reasonable confidence (5).

The incidence of bladder cancer is directly related to the duration of smoking and the number of cigarettes smoked per day (6). The risk of bladder cancer is also higher in those who start smoking at a young age or who are exposed to environmental tobacco smoke during childhood (7). A recent meta-analysis looked at 216 observational studies on cigarette smoking and cancer from 1961 to 2003, with reported estimates for current and/or former smokers. The pooled risk estimates for bladder cancer demonstrated a significant association for both current and former smokers. In an analysis of 21 studies, the overall relative risk calculated for current smokers was 2.77 (95% confidence interval [CI], 2.17 to 3.54), while an analysis of 15 studies showed that the overall relative risk calculated for former smokers was 1.72 (95% CI, 1.46 to 2.04) (8). An immediate decrease in the risk of bladder cancer was observed in those who stopped smoking. The reduction was about 40% within 1-4 years of quitting smoking and 60% after 25 years of cessation (6). Encouraging people to stop smoking would result in the incidence of bladder cancer decreasing equally in men and women.

2.2.2 Occupational exposure to chemicals

Occupational exposure is the second most important risk factor for bladder cancer. Work-related cases have accounted for 20-25% of all bladder cancer cases in several series. The substances involved in chemical exposure have been benzene derivatives and aryl amines (2-naphthylamine, 4-ABP, 4,4'-methylenedianiline, and o-toluidine), and it is likely to occur in occupations in which dyes, rubbers, textiles, paints, leathers, and chemicals are used (9). The risk of bladder cancer due to occupational exposure to carcinogenic aromatic amines is significantly greater after 10 years or more of exposure; the mean latency period usually exceeds 30 years (10,11). The chemicals involved have contributed minimally to the current incidence of bladder cancer in Western countries because of strict regulations. In fact, there has been a trend towards a decrease in bladder cancer due to occupational exposure, as indicated by a pooled analysis of 11 European case-control studies on bladder cancer between 1976 and 1996 (12).

An example of occupational exposure is that of aromatic amines. These are established carcinogens for urothelium and can be inactivated by a metabolic acetylation pathway. The presence of an NAT2 slow-acetylation genotype has been associated with a higher risk of bladder cancer (13), suggesting that patients who are slow acetylators may be more susceptible to bladder cancer than rapid acetylators.

Other risk factors include phenacetin, which the International Agency for Research on Cancer (IARC) included in 1987 among proven human carcinogens. Some studies have suggested that the risk of bladder cancer due to phenacetin is dose-dependent; however, the data concerning its metabolite acetaminophen are controversial (14).

2.2.3 Radiotherapy

Increased rates of secondary bladder malignancies have been reported after external-beam radiotherapy (EBRT) for gynaecological malignancies, with relative risks of 2-4 (15). A recent population cohort study identified 243,082 men treated for prostate cancer between 1988 and 2003 in the Surveillance, Epidemiology and End Results database (SEER) in the USA. The standardised incidence ratios for bladder cancer developing after radical prostatectomy (RP), EBRT, brachytherapy (BT), and EBRT-BT were 0.99, 1.42, 1.10, and 1.39, respectively, in comparison with the general U.S. population. The increased risk of bladder cancer in patients undergoing ERBT, BT, or ERBT-BT should be taken into account during follow-up, although the likelihood of mortality was described as very low in a recent study (16). It has recently been proposed that patients who have received radiotherapy for prostate cancer with modern modalities such as intensity-modulated radiotherapy (IMRT) may have lower rates of in-field bladder and rectal secondary malignancies (17). Nevertheless, since longer follow-up data are not yet available, and as bladder cancer requires a long period to develop, patients treated with radiation and with a long life-expectancy are at highest risk and should be followed up closely (17).

2.2.4 Dietary factors

Several dietary factors have been considered to be related to bladder cancer; however, the links remain controversial. Currently, there is limited evidence of a causal relationship between bladder cancer and dietary factors. A meta-analysis of 38 articles reporting data on diet and bladder cancer supported the hypothesis that vegetable and fruit intake reduces the risk of bladder cancer (18). For bladder cancer, there appears to be no association between dietary trans fatty acid (TFA) intake and an increased risk, as observed for prostate cancer (19).

2.2.5 **Bladder schistosomiasis**

Bladder schistosomiasis (bilharzia) is the second most common parasitic infection after malaria, with about 600 million people exposed to infection in Africa, Asia, South America, and the Caribbean (20). Although there is a well-established relationship between squamous cell carcinoma of the bladder and schistosomiasis, the trends are changing for bladder cancer in endemic zones such as Egypt. Data from the National Cancer Institute (NCI) in Cairo, the largest tertiary cancer hospital in Egypt, showed that patients diagnosed in 2005 had a six-fold higher chance of developing urothelial carcinoma in comparison with patients diagnosed in 1980 (21). This shift from squamous cell carcinoma to urothelial carcinoma is attributed to a decline in the detection of bilharzia eggs in urine samples, probably due to better control of the disease in rural populations (22,23).

2.2.6 **Chronic urinary tract infection**

Muscle-invasive bladder cancer, particularly invasive squamous cell carcinoma, has been linked to the presence of chronic urinary tract infection (UTI) distinct from schistosomiasis. A direct association between bladder cancer and UTIs has been observed in several case-control studies, which have reported a twofold increased risk of bladder cancer in patients with recurrent UTIs in some series. However, some of these results may be attributed to recall bias (24). Furthermore, to date, no clear relationship between any bacterial or viral infection and bladder cancer has been established in prospective studies (25). However, an increased risk of bladder cancer has been described in patients with long-term indwelling catheters (26).

2.2.7 **Chemotherapy**

The use of cyclophosphamide, an alkylating agent used to treat lymphoproliferative diseases and other nonneoplastic diseases, has been correlated with subsequent development of MIBC, with a latency period of 6-13 years. Acrolein is a metabolite of cyclophosphamide and is responsible for the increase in the incidence of bladder cancer. This effect occurs independently of the association of haemorrhagic cystitis with the same treatment (27,28) and was counteracted with concomitant application of mercapto-ethanesulfonate (MESNA) (29).

2.2.8 **Synchronous and metachronous upper urinary tract tumours**

In some cases, there is an association between upper tract urothelial carcinoma (UTUC) and bladder cancer. The incidence of UTUC after a diagnosis of NMIBC has been reported to be between 1.7% and 26%. Although synchronous UTUC and NMIBC are uncommon, 46% of UTUCs are invasive.

In a retrospective review of 1,529 patients with primary non-muscle-invasive bladder carcinoma who underwent initial examination of the upper urinary tract with excretory urography, those with a tumour in the bladder trigone were almost six times more likely to develop a synchronous tumour in the upper urinary tract (30). Examination of the upper urinary tract alone in patients with a tumour in the trigone or with multiple bladder tumours was capable of diagnosing 41% or 69% of UTUCs, respectively. In multiple and high-risk tumours, there is an increased risk of tumour recurrence in the upper urinary tract. Carcinoma in situ (CIS) in the bladder is an important risk factor for subsequent upper urinary tract recurrence (31). As well, it has been shown in various studies that tumour involvement of the distal ureter at RC is an independent risk factor for metachronous upper urinary tract (mUUT) recurrence (32,33), with an approximately 2.6-fold increase in the relative risk (33).

In addition, the overall incidence of bladder cancer developing after treatment for UTUC has been reported in the literature as 15-50%. Level 1 evidence from prospective randomised trials is not yet available. Intraluminal tumour seeding and pan-urothelial field change effects have both been proposed to explain intravesical recurrences. In most cases, bladder cancer arises in the first 2 years after UTUC management. However, the risk is lifelong, and repeat episodes are common. No variables can be used to predict future bladder cancer recurrence in UTUC patients reliably. A history of bladder cancer prior to UTUC management and upper tract tumour multifocality are the only commonly reported clinical risk factors in the current literature (34).

2.2.9 **Gender**

In a retrospective study of patients who had undergone radical cystectomy, it was found that women were more likely to be diagnosed with primary muscle-invasive disease than men (85% vs. 51%) (2). It has been suggested that women are more likely to be older than men when diagnosed, with a direct effect on their survival. In addition, delayed diagnosis is more likely in women after haematuria is observed, as the differential diagnosis in women includes diseases that are more prevalent than bladder cancer (35).

Differences in the gender prevalence of bladder cancer may be due to other factors besides tobacco and chemical exposure. In a large prospective cohort study, postmenopausal status was associated with an

increase in bladder cancer risk even after adjustment for smoking status. This result suggests that the differences in oestrogen and androgen levels between men and women may be responsible for some of the difference in the gender prevalence of bladder cancer (36-38). Recently, a study of Egyptian women found that younger age at menopause (< 45 y) was a factor associated with an increasing risk of bladder cancer, while multiple pregnancies and use of oral contraceptives were associated with decreased odds of having bladder cancer. The strength of the associations was greater in the urothelial carcinoma group (39). A recent publication mentions that female gender has a significant negative impact on cancer-specific survival in patients who are younger and have lymphovascular invasion, possibly suggesting different clinical phenotypes (40).

2.2.10 Ethnic and socioeconomic status

There are limited data on this topic, but a study based on 13,234 cases diagnosed in the SEER database in the period 1979-2003 showed that the survival time from diagnosis was significantly lower among cancer cases in patients with low socioeconomic status (SES) compared with those with higher SES. Hazard ratios for all causes and cancer-specific mortality among blacks in comparison with whites for eight of the most common types of cancer combined lost statistical significance after adjustment for SES factors and treatments. However, blacks still had unfavourable prognoses in comparison with whites even after adjustment for SES and treatment for tumours such as breast, colorectal, and urinary bladder cancer (41).

2.3 Conclusions and recommendations for epidemiology and risk factors

Conclusions	LE
The incidence of muscle-invasive disease has not changed for 5 years.	
Active and passive tobacco smoking continues to be the main risk factor, while the exposure-related incidence is decreasing.	2a
The increased risk of developing bladder cancer in patients undergoing external-beam radiotherapy (EBRT), brachytherapy, or a combination of EBRT and brachytherapy, must be taken into account during patient follow-up. As bladder cancer requires time to develop, patients treated with radiation at a young age are at the greatest risk and should be followed up closely.	3
The estimated male-to-female ratio for bladder cancer is 3.8 : 1.0. Women are more likely to be diagnosed with primary muscle-invasive disease than men.	3
Currently, treatment decisions cannot be based on molecular markers.	3

Recommendations	GR
The principal preventable risk factor for muscle-invasive bladder cancer is active and passive smoking.	B
Notwithstanding stricter regulations, workers should be informed about the potential carcinogenic effects of a number of recognised substances, duration of exposure, and latency periods. Protective measures should be recommended.	A

2.4 References

1. Ploeg M, Aben KK, Kiemeny LA. The present and future burden of urinary bladder cancer in the world. *World J Urol* 2009 Jun;27(3):289-93.
<http://www.ncbi.nlm.nih.gov/pubmed/19219610>
2. Vaidya A, Soloway MS, Hawke C, et al. De novo muscle invasive bladder cancer: is there a change in trend? *J Urol* 2001 Jan;165(1):47-50.
<http://www.ncbi.nlm.nih.gov/pubmed/11125361>
3. Prout GR Jr, Griffin PP, Shipley WU. Bladder carcinoma as a systemic disease. *Cancer* 1979 Jun;43(6):2532-9.
<http://www.ncbi.nlm.nih.gov/pubmed/455239>
4. Freedman ND, Silverman DT, Hollenbeck AR, et al. Association between smoking and risk of bladder cancer among men and women. *JAMA* 2011 Aug 17;306(7):737-45.
<http://www.ncbi.nlm.nih.gov/pubmed/21846855>
5. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco smoke and involuntary smoking. *IARC Monogr Eval Carcinog Risks Hum* 2004;83:1-1438.
<http://www.ncbi.nlm.nih.gov/pubmed/15285078>
6. Brennan P, Bogillot O, Cordier S, et al. Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. *Int J Cancer* 2000 Apr;86(2):289-94.
<http://www.ncbi.nlm.nih.gov/pubmed/10738259>

7. Bjerregaard BK, Raaschou-Nielsen O, Sørensen M, et al. Tobacco smoke and bladder cancer-in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2006 Nov;119(10):2412-6. <http://www.ncbi.nlm.nih.gov/pubmed/16894557>
8. Gandini S, Botteri E, Iodice S, et al. Tobacco smoking and cancer: a meta-analysis. *Int J Cancer* 2008Jan;122(1):155-64. <http://www.ncbi.nlm.nih.gov/pubmed/17893872>
9. Pashos CL, Botteman MF, Laskin BL, et al. Bladder cancer: epidemiology, diagnosis, and management. *Cancer Pract* 2002 Nov-Dec;10(6):311-22. <http://www.ncbi.nlm.nih.gov/pubmed/12406054>
10. Harling M, Schablon A, Schedlbauer G, et al. Bladder Cancer among hairdressers: a meta-analysis. *Occup Environ Med* 2010 May;67(5):351-8. <http://www.ncbi.nlm.nih.gov/pubmed/20447989>
11. Weistenhofer W, Blaszkewicz M, Bolt HM, et al. N-acetyltransferase-2 and medical history in bladder cancer cases with a suspected occupational disease (BK 1301) in Germany. *J Toxicol Environ Health A* 2008;71(13-14):906-10. <http://www.ncbi.nlm.nih.gov/pubmed/18569594>
12. Kogevinas M, t' Mannetje A, Cordier S, et al. Occupation and bladder cancer among men in Western Europe. *Cancer Causes and Control* 2003 Dec;14(10):907-14. <http://www.ncbi.nlm.nih.gov/pubmed/14750529>
13. García-Closas M, Malats N, Silverman D, et al. NAT2 slow acetylation, GSTM1 null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses. *Lancet* 2005Aug;366(9486):649-59. <http://www.ncbi.nlm.nih.gov/pubmed/16112301>
14. Castela JE, Yuan JM, Gago-Dominguez M, et al. Non-steroidal anti-inflammatory drugs and bladder cancer prevention. *Br J Cancer* 2000 Apr;82(7):1364-9. <http://www.ncbi.nlm.nih.gov/pubmed/10755416>
15. Chrouser K, Leibovich B, Bergstralh E, et al. Bladder cancer risk following primary and adjuvant external beam radiation for prostate cancer. *J Urol* 2006 Jul;174(1):107-10. <http://www.ncbi.nlm.nih.gov/pubmed/15947588>
16. Nieder AM, Porter MP, Soloway MS. Radiation therapy for prostate cancer increases subsequent risk of bladder and rectal cancer: a population based cohort study. *J Urol* 2008 Nov;180(5):2005-9; discussion 2009-10. <http://www.ncbi.nlm.nih.gov/pubmed/18801517>
17. Zelefsky MJ, Housman DM, Pei X, et al. Incidence of secondary cancer development after high-dose intensity-modulated radiotherapy and image-guided brachytherapy for the treatment of localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2012 Jul 1;83(3):953-9. <http://www.ncbi.nlm.nih.gov/pubmed/22172904>
18. Steinmaus CM, Nuñez S, Smith AH. Diet and bladder cancer: a meta-analysis of six dietary variables. *Am J Epidemiol* 2000 Apr;151(7):693-702. <http://www.ncbi.nlm.nih.gov/pubmed/10752797>
19. Hu J, La Vecchia C, de Groh M, et al; Canadian Cancer Registries Epidemiology Research Group. Dietary trans fatty acids and cancer risk. *Eur J Cancer Prev* 2011 Nov;20(6):530-8. <http://www.ncbi.nlm.nih.gov/pubmed/21701388>
20. [No authors listed.] Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June, 1994. *IARC Monogr Eval Carcinog Risks Hum* 1994;61:1-241. <http://www.ncbi.nlm.nih.gov/pubmed/7715068>
21. Felix AS, Soliman AS, Khaled H, et al. The changing patterns of bladder cancer in Egypt over the past 26 years. *Cancer Causes Control* 2008 May;19(4):421-9. <http://www.ncbi.nlm.nih.gov/pubmed/18188671>
22. Gouda I, Mokhtar N, Bilal D, et al. Bilharziasis and bladder cancer: a time trend analysis of 9843 patients. *J Egypt Natl Canc Inst* 2007 Jun;19(2):158-62. <http://www.ncbi.nlm.nih.gov/pubmed/19034337>
23. Salem HK, Mahfouz S. Changing Patterns (Age, Incidence, and Pathologic Types) of Schistosoma-associated Bladder Cancer in Egypt in the Past Decade. *Urology* 2012 Feb;79(2):379-83. <http://www.ncbi.nlm.nih.gov/pubmed/22112287>
24. Pelucchi C, Bosetti C, Negri E, et al. Mechanisms of disease: The epidemiology of bladder cancer. *Nat Clin Pract Urol* 2006 Jun;3(6):327-40. <http://www.ncbi.nlm.nih.gov/pubmed/16763645>

25. Abol-Enein H. Infection: is it a cause of bladder cancer? *Scand J Urol Nephrol Suppl* 2008 Sep;(218):79-84.
<http://www.ncbi.nlm.nih.gov/pubmed/18815920>
26. Locke JR, Hill DE, Walzer Y. Incidence of squamous cell carcinoma in patients with long-term catheter drainage. *J Urol* 1985 Jun;133(6):1034-5.
<http://www.ncbi.nlm.nih.gov/pubmed/3999203>
27. Kaldor JM, Day NE, Kittelmann B, et al. Bladder tumours following chemotherapy and radiotherapy for ovarian cancer: a case-control study. *Int J Cancer* 1995 Sept 27;63(1):1-6.
<http://www.ncbi.nlm.nih.gov/pubmed/7558434>
28. Travis LB, Curtis RE, Glimelius B, et al. Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. *J Natl Cancer Inst* 1995 Apr;87(7):524-30.
<http://www.ncbi.nlm.nih.gov/pubmed/7707439>
29. Monach PA, Arnold LM, Merkel PA. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: a data-driven review. *Arthritis Rheum* 2010 Jan;62(1):9-21.
<http://www.ncbi.nlm.nih.gov/pubmed/20039416>
30. Palou J, Rodríguez-Rubio F, Huguet J, et al. Multivariate analysis of clinical parameters of synchronous primary superficial bladder cancer and upper urinary tract tumor. *J Urol* 2005 Sep;174(3):859-61;discussion 861.
<http://www.ncbi.nlm.nih.gov/pubmed/16093970>
31. Babjuk M, Oosterlinck W, Sylvester R, et al. EAU Guidelines on TaT1 (Non-muscle-invasive Bladder Cancer). In: EAU Guidelines. Edition presented at the 24th EAU Congress, Stockholm, Sweden, 2012. ISBN-978-90-79754-09-0.
<http://www.uroweb.org/guidelines/online-guidelines/>
32. Tran W, Serio AM, Raj GV, et al. Longitudinal risk of upper tract recurrence following radical cystectomy for urothelial cancer and the potential implications for long-term surveillance. *J Urol* 2008 Jan;179(1):96-100.
<http://www.ncbi.nlm.nih.gov/pubmed/17997449>
33. Volkmer BG, Schnoeller T, Kuefer R, et al. Upper urinary tract recurrence after radical cystectomy for bladder cancer--who is at risk? *J Urol* 2009 Dec;182(6):2632-7.
<http://www.ncbi.nlm.nih.gov/pubmed/19836794>
34. Azémar MD, Comperat E, Richard F, et al. Bladder recurrence after surgery for upper urinary tract urothelial cell carcinoma: frequency, risk factors, and surveillance. *Urol Oncol* 2011 Mar-Apr;29(2):130-6.
<http://www.ncbi.nlm.nih.gov/pubmed/19762256>
35. Cárdenas-Turanzas M, Cooksley C, Pettaway CA, et al. Comparative outcomes of bladder cancer. *Obstet Gynecol* 2006 Jul;108(1):169-75.
<http://www.ncbi.nlm.nih.gov/pubmed/16816072>
36. McGrath M, Michaud DS, De Vivo I. Hormonal and reproductive factors and the risk of bladder cancer in women. *Am J Epidemiol* 2006 Feb;163(3):236-44.
<http://www.ncbi.nlm.nih.gov/pubmed/16319290>
37. Scosyrev E, Noyes K, Feng C, et al. Sex and racial differences in bladder cancer presentation and mortality in the US. *Cancer* 2009 Jan;115(1):68-74.
<http://www.ncbi.nlm.nih.gov/pubmed/19072984>
38. Stenzl A. Words of wisdom. Re: sex and racial differences in bladder cancer presentation and mortality in the US. *Eur Urol* 2010 Apr;57(4):729.
<http://www.ncbi.nlm.nih.gov/pubmed/20965044>
39. Wolpert BJ, Amr S, Ezzat S, et al. Estrogen exposure and bladder cancer risk in Egyptian women. *Maturitas* 2010 Dec;67(4):353-7.
<http://www.ncbi.nlm.nih.gov/pubmed/20813471>
40. May M, Stief C, Brookman-May S, et al. Gender-dependent cancer-specific survival following radical cystectomy. *World J Urol* 2012 Oct;30(5):707-13.
<http://www.ncbi.nlm.nih.gov/pubmed/21984471>
41. Du XL, Lin CC, Johnson NJ, et al. Effects of individual-level socioeconomic factors on racial disparities in cancer treatment and survival: Findings from the National Longitudinal Mortality Study, 1979-2003. *Cancer* 2011 Jul;117(14):3242-51.
<http://www.ncbi.nlm.nih.gov/pubmed/21264829>

3. CLASSIFICATION

3.1 Tumour, node, metastasis classification

The tumour, node, metastasis (TNM) classification of malignant tumours is the method most widely used to classify the extent of cancer spread. Recently, a seventh edition was published, effective as of 2010 (1 (Table 3). There are no significant modifications in it for bladder cancer in comparison with the previous edition (2002).

Table 3: TNM classification of urinary bladder cancer (2009)

T - Primary Tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumour"
T1	Tumour invades subepithelial 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 (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N - Regional Lymph Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph-node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M - Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis

3.2 Histological grading of non-muscle-invasive bladder tumours

A new classification of noninvasive urothelial tumours was proposed by the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) in 1998. It was published by the WHO in 2004 (2,3) (see table below). Its major contribution is a detailed histological description of the various grades using specific cytological and architectural criteria. A web site (<http://www.pathology.jhu.edu/bladder>) illustrating examples of various grades has been developed to improve accuracy in using the system.

World Health Organization (WHO) grading for urothelial papilloma in 1973 and 2004 (2,3)

<p>1973 WHO grading</p> <ul style="list-style-type: none"> • Grade 1: well differentiated • Grade 2: moderately differentiated • Grade 3: poorly differentiated <p>2004 WHO grading</p> <ul style="list-style-type: none"> • Papillary urothelial neoplasm of low malignant potential (PUNLMP) • Low-grade papillary urothelial carcinoma • High-grade papillary urothelial carcinoma

3.2.1 WHO grading

The 2004 WHO grading differentiates between papilloma, papillary urothelial neoplasms of low malignant potential (PUNLMP), and low-grade and high-grade urothelial carcinomas.

Papilloma is composed of a delicate fibrovascular core covered by normal urothelium. PUNLMP is defined as a papillary fibrovascular growth covered with proliferated urothelium, exceeding the normal thickness. Although PUNLMPs have a negligible risk of progression, they are not completely benign and have a tendency to recur (3b). The low-grade papillary urothelial carcinoma group includes the majority of former grade 1 (WHO 1973) cases and some former grade 2 cases (if there is variation in the architectural and cytological features at high magnification).

Use of the 2004 WHO classification is recommended, as this should result in a uniform diagnosis of tumours better classified according to their risk potential. However, until the 2004 WHO classification has been validated by further clinical trials, tumours should be graded using both the 1973 and the 2004 WHO classifications (4). Most clinical trials published so far on bladder tumours have been performed using the 1973 WHO classification, so this is used in the 2013 edition of the guidelines.

3.3 Pathology

3.3.1 Handling of specimens by urologists

In transurethral resection (TUR) specimens, the superficial and deep areas of the tumour must be sent to the pathology laboratory separately. If random biopsies of the flat mucosa have been carried out, each biopsy of the flat mucosa must also be sent separately.

In radical cystectomy, bladder fixation must be carried out as soon as possible. The pathologist must open the specimen from the urethra to the bladder dome and fix the specimen in formalin. In some circumstances, this procedure can also be performed by the urologist. In a female cystectomy specimen, the length of the urethral segment removed en bloc with the specimen should be checked, preferably by the urological surgeon (5).

3.3.2 Handling of specimens by pathologists

Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists (6,7). It must be stressed that it may be very difficult to confirm the presence of a neoplastic lesion using gross examination of the cystectomy specimen after TUR or chemotherapy, so the entire retracted or ulcerated area must be included.

It is mandatory to study the urethra, ureter, and prostate in men and the radial margins (8). In urethra-sparing cystectomy, the level of urethral dissection, the completeness of the prostate specifically at the apex (in men), and the inclusion of the entire bladder neck and amount of adjacent urethra (in women) should be documented. All lymph node specimens should be provided in their totality, in clearly labeled containers. In case of doubt, or if there is adipose differentiation of the lymph node, the entire specimen is to be included.

Lymph nodes should be counted and measured on slides, and capsular bursting and the percentage of lymph-node invasion should be reported, as well as vascular emboli. If there is metastatic spread into the perivesical fat without real lymph node structures (capsule, subcapsular sinus), this localisation should nevertheless be considered as N+.

Fresh frozen sections can be helpful in determining the treatment strategy. A recent study confirmed the reliability of fresh frozen sections of obturator lymph nodes, but similar studies are warranted to confirm these results (9). As yet, fresh frozen sections have mainly been used in the setting of clinical studies.

3.3.3 Pathology of muscle-invasive bladder cancer

In muscle-invasive bladder cancer, there are usually no cases of PUNLMP or low-grade carcinoma. All cases are high-grade urothelial carcinomas. For this reason, no further prognostic information can be provided by grading the lesions (10). However, some morphological subtypes can be helpful in assessing the prognosis and treatment options. The following differentiation is currently used:

1. Urothelial carcinoma (more than 90% of all cases).
2. Urothelial carcinomas with squamous and/or glandular partial differentiation (11,12).
3. Micropapillary urothelial carcinoma.
4. Nested carcinoma (13).
5. Urothelial carcinomas with trophoblastic differentiation.
6. Small cell carcinomas (14).
7. Spindle cell carcinomas.

For staging, TNM 2002/2010 (6th or 7th edition) is recommended (both editions are identical for bladder cancer). Blood vessel invasion and lymph node infiltration have an independent prognostic significance (15). It

appears that the pN category is closely related to the number of lymph nodes studied by the pathologist (16). For this reason, some authors have reported that more than nine lymph nodes have to be investigated in order to reflect pN0 appropriately (17).

3.3.4 **pT2 substaging in node-negative disease after cystectomy**

In 1997, the American Joint Committee on Cancer (AJCC) updated the TNM staging system and introduced substaging for the T2 tumour stage (18). The latest version was published in 2009, but without any changes from the previous 2002 version (1). This substratification was intended to provide better risk assessment for follow-up strategies and to improve counselling of patients for adjuvant treatment options (19). However, in patients with node-negative, pT2a-T2b bladder cancer, subsequent studies have challenged the prognostic importance of substratifying pT2 tumours into those involving the inner half of the detrusor muscle (T2a) or its outer half (T2b) and have suggested that the two substages should be consolidated into one (20-22). The limitations of these studies were that the extent of lymphadenectomy and the numbers of retrieved lymph nodes were not exactly reported, which may have biased the final survival analysis (22). In addition, patients with non-urothelial cell carcinoma and those who underwent neoadjuvant chemotherapy were not excluded from the analyses (20,21).

A recent multicentre series including 565 patients with pT2 urothelial carcinoma of the bladder therefore attempted to overcome these limitations and reported significant differences in survival between the two substages in node-negative pT2 disease (23). These findings have also been confirmed in a single-centre Egyptian cohort including 1,737 patients with pT2 bladder cancer, 54% of whom had squamous cell carcinomas (24). Furthermore, significant differences in the recurrence-free and cancer-specific survival have also been confirmed in a single-centre series of patients with pT2 urothelial carcinoma of the bladder who were treated with an extended pelvic lymphadenectomy approach (25). pT2 substaging has also recently been incorporated into prognostic models designed to predict upstaging and recurrence after radical cystectomy. A multicenter study has suggested using a weighted prognostic model for patients with node-negative pT2 bladder cancer. Among various independent risk factors (presence of high-grade disease or lymphovascular invasion), pT2 substaging was the strongest one for recurrence-free survival (26). This finding was also confirmed in a large single-centre series including 948 patients with cT2N0M0 bladder carcinoma, in which pT2 substaging was also found to be predictive of the risk of recurrence (27,28). In conclusion, the present data support the current approach using substratification of node-negative pT2 bladder cancer and can be used to tailor the need for adjuvant treatment.

New prognostic markers are under investigation (29). Currently, there is insufficient evidence to recommend the standard use of the prognostic marker p53 in high-risk muscle-invasive disease, as it does not yield sufficient data on which to base treatment in an individual patient.

3.3.5 **Recommendations for assessing tumour specimens**

<i>Mandatory evaluations</i>
Histological subtype
Depth of invasion
Resection margins, including CIS
Extensive lymph-node representation
<i>Optional evaluation</i>
Bladder wall blood vessel invasion
CIS, carcinoma <i>in situ</i> .

3.4 **Conclusions and recommendations for classification in MIBC**

Conclusions and recommendations	LE	GR
The AJCC substratification into node-negative pT2 bladder cancer is of prognostic value after radical cystectomy in patients but who have not undergone neoadjuvant chemotherapy.	3	B
Substaging into pT2a and b is not tenable in TURB specimens.		
The pathological depth of muscle invasion should be reported by the pathologist in patients with node-negative pT2 bladder cancer after cystectomy.	3	B

3.5 References

1. Sobin LH, Gospodariwicz M, Wittekind C (eds). TNM classification of malignant tumors. UICC International Union Against Cancer. 7th edn. Wiley-Blackwell, 2009 Dec; pp. 262-265.
<http://www.nicc.org/tnm/>
2. Epstein JI, Amin MB, Reuter VR, et al. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. *Am J Surg Pathol* 1998 Dec;22(12):1435-48.
<http://www.ncbi.nlm.nih.gov/pubmed/9850170>
3. Sauter G, Algaba F, Amin M, et al. Tumours of the urinary system: non-invasive urothelial neoplasias. In: Eble JN, Sauter G, Epstein JI, Sesterhenn I, eds. WHO classification of classification of tumors of the urinary system and male genital organs. Lyon: IARCC Press, 2004, pp. 29-34.
<http://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb7/index.php>
- 3b. Pan CC, Chang YH, Chen KK, et al. Prognostic significance of the 2004 WHO/ISUP classification for prediction of recurrence, progression, and cancer-specific mortality of non-muscle-invasive urothelial tumors of the urinary bladder: a clinicopathologic study of 1,515 cases. *Am J Clin Pathol* 2010 May;133(5):788-95.
<http://www.ncbi.nlm.nih.gov/pubmed/20395527>
4. Lopez-Beltran A, Montironi R. Non-invasive urothelial neoplasms: according to the most recent WHO classification. *Eur Urol* 2004 Aug;46(2):170-6.
<http://www.ncbi.nlm.nih.gov/pubmed/15245809>
5. Stenzl A. Current Concepts for Urinary Diversion in Women. *Eur Urol (EAU Update Series 1)*;2003: 91-9.
6. Varinot J, Camparo P, Roupert M, et al. Full analysis of the prostatic urethra at the time of radical cystoprostatectomy for bladder cancer: impact on final disease stage. *Virchows Arch*. 2009 Nov;455(5):449-53.
<http://www.ncbi.nlm.nih.gov/pubmed/19841937>
7. Hansel DE, Amin MB, Comperat E, et al. A Contemporary Update on Pathology Standards for Bladder Cancer: Transurethral Resection and Radical Cystectomy Specimens. *Eur Urol*. 2013 Feb;63(2):321-32.
<http://www.ncbi.nlm.nih.gov/pubmed/23088996>
8. Herr HW. Pathologic evaluation of radical cystectomy specimens. *Cancer* 2002 Aug;95(3):668-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12209761>
9. Baltaci S, Adsan O, Ugurlu O, et al. Reliability of frozen section examination of obturator lymph nodes and impact on lymph node dissection borders during radical cystectomy: results of a prospective multicentre study by the Turkish Society of Urooncology. *BJU Int* 2011 Feb;107(4):547-53.
<http://www.ncbi.nlm.nih.gov/pubmed/20633004>
10. Jimenez RE, Gheiler E, Oskanian P, et al. Grading the invasive component of urothelial carcinoma of the bladder and its relationship with progression free survival. *Am J Surg Pathol* 2000 Jul;24(7):980-7.
<http://www.ncbi.nlm.nih.gov/pubmed/10895820>
11. Kapur P, Lotan Y, King E, et al. Primary adenocarcinoma of the urinary bladder: value of cell cycle biomarkers. *Am J Clin Pathol* 2011 Jun;135(6):822-30.
<http://www.ncbi.nlm.nih.gov/pubmed/21571954>
12. Ploeg M, Aben KK, Hulsbergen-van de Kaa CA, et al. Clinical epidemiology of nonurothelial bladder cancer: analysis of the Netherlands Cancer Registry. *J Urol* 2010 Mar;183(3):915-20
<http://www.ncbi.nlm.nih.gov/pubmed/20083267>
13. Wasco MJ, Daignault S, Bradley D, et al. Nested variant of urothelial carcinoma: a clinicopathologic and immunohistochemical study of 30 pure and mixed cases. *Hum Pathol* 2010 Feb;41(2):163-71.
<http://www.ncbi.nlm.nih.gov/pubmed/19800100>
14. Mukesh M, Cook N, Hollingdale AE, et al. Small cell carcinoma of the urinary bladder: a 15-year retrospective review of treatment and survival in the Anglian Cancer Network. *BJU Int* 2009 Mar;103(6):747-52.
<http://www.ncbi.nlm.nih.gov/pubmed/19076139>
15. Leissner J, Koeppen C, Wolf HK. Prognostic significance of vascular and perineural invasion in urothelial bladder cancer treated with radical cystectomy. *J Urol* 2003 Mar;169:955-60.
<http://www.ncbi.nlm.nih.gov/pubmed/12576821>
16. Jensen JB, Høyer S, Jensen KM. Incidence of occult lymph-node metastasis missed by standard pathological examination in patients with bladder cancer undergoing radical cystectomy. *Scan J Urol Nephrol* 2011 Dec;45(6):419-24.
<http://informahealthcare.com/doi/abs/10.3109/00365599.2011.599336>

17. Shariat SF, Karam JA, Lerner SP. Molecular markers in bladder cancer. *Curr Opin Urol* 2008 Jan;18(1):1-8.
<http://www.ncbi.nlm.nih.gov/pubmed/18090481>
18. Sobin DH, Wittekind Ch. *TNM Classification of Malignant Tumours*. 6th Edn. New York: Wiley-Liss. pp.199-202.
<http://www.ncbi.nlm.nih.gov/nlmcatalog/101136037>
19. Greene FL, P. D., Fleming ID, Fritz A, Balch CM, Haller DG, et al. (2002) *AJCC Cancer Staging Manual*. pp. 335-337, Lippincott-Raven, Philadelphia
20. Boudreaux KJ Jr, Chang SS, Lowrance WT, et al. Comparison of American Joint Committee on Cancer pathologic stage T3a versus T3b urothelial carcinoma: analysis of patient outcomes. *Cancer* 2009 Feb 15;115(4):770-5.
<http://www.ncbi.nlm.nih.gov/pubmed/19152431>
21. Tokgoz H, Turkolmez K, Resorlu B, et al. Pathological staging of muscle invasive bladder cancer. Is substaging of pT2 tumors really necessary? *Int Braz J Urol* 2007 Nov-Dec;33(6):777-83; discussion 783-4.
<http://www.ncbi.nlm.nih.gov/pubmed/18199345>
22. Yu RJ, Stein JP, Cai J, et al. Superficial (pT2a) and deep (pT2b) muscle invasion in pathological staging of bladder cancer following radical cystectomy. *J Urol* 2006 Aug;176(2):493-8; discussion 498-9.
<http://www.ncbi.nlm.nih.gov/pubmed/16813876>
23. Tilki D, Reich O, Karakiewicz PI, et al. Validation of the AJCC TNM substaging of pT2 bladder cancer: deep muscle invasion is associated with significantly worse outcome. *Eur Urol* 2010 Jul;58(1):112-7. 20.
<http://www.ncbi.nlm.nih.gov/pubmed/20097469>
24. Ghoneim MA, Abdel-Latif M, el-Mekresh M, et al. Radical cystectomy for carcinoma of the bladder: 2,720 consecutive cases 5 years later. *J Urol* 2008 Jul;180(1):121-7.
<http://www.ncbi.nlm.nih.gov/pubmed/18485392>
25. Gakis G, Schilling D, Renninger M, et al. Comparison of the new American Joint Committee on Cancer substratification in node-negative pT2 urothelial carcinoma of the bladder: analysis of patient outcomes in a contemporary series. *BJU Int* 2011 Mar;107(6):919-23.
<http://www.ncbi.nlm.nih.gov/pubmed/21392208>
26. Sonpavde G, Khan MM, Svatek RS, et al. Prognostic risk stratification of pathological stage T2N0 bladder cancer after radical cystectomy. *BJU Int* 2011 Sep;108(5):687-92.
<http://www.ncbi.nlm.nih.gov/pubmed/21087453>
27. Mitra AP, Skinner EC, Miranda G, et al. A precystectomy decision model to predict pathological upstaging and oncological outcomes in clinical stage T2 bladder cancer. *BJU Int* 2013 Feb;111(2): 240-8.
<http://www.ncbi.nlm.nih.gov/pubmed/22928881>
28. Gakis G. A precystectomy decision model to predict pathological upstaging and oncological outcomes in clinical stage T2 bladder cancer. *BJU Int* 2013 Feb;111(2):186-7.
<http://www.ncbi.nlm.nih.gov/pubmed/22928948>
29. Tiguert R, Lessard A, So A, et al. Prognostic markers in muscle invasive bladder cancer. *World J Urol* 2002 Aug;20:190-5.
<http://www.ncbi.nlm.nih.gov/pubmed/12196903>

4. DIAGNOSIS AND STAGING

4.1 Primary diagnosis

4.1.1 Symptoms

Painless haematuria is the most common presenting complaint. Others include urgency, dysuria, increased frequency and, in more advanced tumours, pelvic pain and symptoms related to urinary tract obstruction.

4.1.2 Physical examination

Physical examination should include rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally advanced tumours. In addition, bimanual examination under anaesthesia should be carried out before and after TUR to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall (1,2). However, considering the discrepancy between bimanual examination and pT stage after cystectomy (11% clinical overstaging and 31% clinical understaging) some caution is suggested with the

interpretation of bimanual examination (3).

4.1.3 Bladder imaging

Patients with a bladder mass identified by any diagnostic imaging technique should undergo cystoscopy, biopsy and or resection for histopathological diagnosis and staging.

4.1.4 Urinary cytology and urinary markers

Examination of a voided urine or bladder-washings for exfoliated cancer cells has high sensitivity in high-grade tumours (LE: 3) and is useful indicator in cases of high-grade malignancy or CIS.

Positive urinary cytology may originate from a urothelial tumour located anywhere in the urinary tract. Evaluation of cytology specimens can be hampered by low cellular yield, UTIs, stones or intravesical instillations, but for experienced readers, specificity exceeds 90% (4,5) (LE: 2b). However, negative cytology does not exclude tumour. Cytology should be performed on fresh urine with adequate fixation. Early morning urine is not suitable as cytolysis may often be present. There is no known urinary marker specific for the diagnosis of invasive bladder cancer (6).

4.1.5 Cystoscopy

Ultimately, the diagnosis of bladder cancer is made by cystoscopy and histological evaluation of resected tissue. In general, cystoscopy is initially performed in the office using flexible instruments. If a bladder tumour has been visualised unequivocally in earlier imaging studies, such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US), a diagnostic cystoscopy may be omitted and the patient can proceed directly to TUR for a histological diagnosis.

A careful description of the cystoscopic findings is necessary. This should include documentation of the site, size, number, and appearance (papillary or solid) of the tumours, as well as a description of mucosal abnormalities. Use of a bladder diagram is recommended.

The use of photodynamic diagnosis could be considered, especially if a T1 high-grade tumour is present, to find associated CIS. The additional presence of CIS may lead to a modified treatment plan (see also Section 5.1). Photodynamic diagnosis is highly sensitive for the detection of CIS; with experience, the rate of false-positives may be similar to the technique of regular white light cystoscopy (7).

4.1.6 Transurethral resection (TUR) of invasive bladder tumours

The goal of TUR is to enable histopathological diagnosis and staging, which requires the inclusion of bladder muscle in the resection biopsies.

The strategy of resection depends on the size of the lesion. Small tumours (less than 1 cm) can be resected en bloc, where the specimen contains the complete tumour plus a part of the underlying bladder wall including bladder muscle. Larger tumours have to be resected separately in fractions, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle and the edges of the resection area. At least the deeper part of the resection specimen must be referred to the pathologist in a separate labelled container to enable him to make a correct diagnosis. Avoid cauterisation as much as possible during resection to prevent tissue destruction. In cases in which photodynamic diagnosis is used, fluorescing areas should be biopsied in order to detect primary or associated CIS lesions. Fluorescence endoscopy should not be used in the first 6 weeks after any instillation therapy due to a higher rate of false-positive results.

4.1.7 Random bladder and prostatic urethral biopsy

Bladder tumours are often multifocal and can be accompanied by CIS or dysplasia. These lesions may present themselves as velvet-like, reddish areas, indistinguishable from inflammation, or may not be visible at all.

The biopsies from normal-looking mucosa in patients with invasive bladder tumours, so-called random biopsies (R-biopsies) show a low yield (8). Fluorescence cystoscopy is performed using filtered blue light after intravesical instillation of a photosensitiser, which was experimentally 5-aminolevulinic acid (5-ALA), and more recently hexaminolaevulinate (HAL), following approval by the European Medicines Agency. It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures in detecting malignant tumours, particularly CIS (9-12) (LE: 2a). However, false-positive results may be induced by inflammation, recent TUR or intravesical instillation therapy. A recent multicentre, prospective, international trial showed that, in experienced hands, the rate of false-positives is not higher than seen in regular, white-light cystoscopy (7). Material obtained by random or directed biopsies must be sent for pathological assessment in separate containers.

The involvement of the prostatic urethra and ducts in male patients with bladder tumours is reported. The exact risk is not known, but it seems to be higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS and in multiple tumours (13,14) (LE: 3). Identification of involvement of the prostatic urethra can be determined either at the time of primary TUR or by frozen section during the cystoprostatectomy procedure. A frozen section has a higher negative predictive value and is more accurate (15-17).

4.1.8 **Second resection**

There is a significant risk of leaving residual tumour in the bladder after the initial TUR (18,19) (LE: 1). Residual disease is observed in 33-53% of patients (19-25). The tumour may be understaged by the initial resection. There is a 4-25% probability that tumours initially staged as non-muscle invasive are muscle-invasive (20,21). Correct staging is extremely important since it will directly affect the type of treatment. A second TUR should always be performed if the initial resection has been incomplete, e.g. when multiple and/or large tumours are present, or if the pathologist reports that the specimen contains no muscle tissue. A second TUR should be performed when a high-grade, non-muscle-invasive tumour or a T1 tumour is detected at the initial TUR. There is no consensus about the strategy and timing of a second TUR. Most authors recommend resection at 2-6 weeks after the initial TUR. The procedure should include a resection of the primary tumour site.

4.1.9 **Concomitant prostate cancer**

Ruling out prostate cancer is important since 25-46% of patients undergoing cystectomy for bladder cancer (26,27) have prostate cancer confirmed by histopathology analysis of the resected specimen.

4.1.10 **Specific recommendations for primary assessment of presumably invasive bladder tumours**

(For general information on the assessment of bladder tumours, see EAU Guidelines on Non-muscle-invasive Bladder cancer [28])

Recommendations	GR
Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended.	C
Biopsy of the prostatic urethra is recommended for cases of bladder neck tumour, when bladder carcinoma <i>in situ</i> is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	C
In women undergoing a subsequent orthotopic neobladder, procedure information is required (including a histological evaluation) of the bladder neck and urethral margin, either prior to, or at the time of cystoscopy.	C
The pathological report should specify the grade, the depth of tumour invasion and whether the lamina propria and muscle tissue are present in the specimen.	C

4.2 **Imaging for staging MIBC**

The treatment and prognosis for MIBC is determined by tumour stage and grade (29). In clinical practice, CT and MRI are the imaging techniques used.

The purpose of using imaging for staging MIBC is to determine prognosis and provide information to assist with treatment selection. Tumour staging must be accurate to ensure the correct choice of treatment is made.

Imaging parameters required for staging MIBC are:

- the extent of local tumour invasion;
- tumour spread to lymph nodes;
- tumour spread to the upper urinary tract and other distant organs (liver, lungs, bones, peritoneum, pleura, adrenal glands and others).

4.2.1 **Local staging of MIBC**

Both CT and MRI may be used for assessment of local invasion, but they are unable to diagnose accurately microscopic invasion of perivesical fat (T3a) (30). The principal aim of CT and MRI is therefore to detect T3b disease or higher.

4.2.1.1 **MRI for local staging of invasive bladder cancer**

Magnetic resonance imaging has superior soft tissue contrast resolution compared with CT, but poorer spatial resolution. In studies performed before the availability of multidetector CT, MRI was reported as more accurate in local assessment. The accuracy of MRI for primary tumour staging varies from 73% to 96% (mean 85%).

These values were 10-33% (mean 19%) higher than those obtained with CT (31). Dynamic contrast-enhanced MRI may help to differentiate bladder tumour from surrounding tissues or post-biopsy reaction, because enhancement of the tumour occurs earlier than the normal bladder wall due to neovascularisation (32-34)).

In 2006, a link was established between the use of gadolinium-based contrast agents and nephrogenic systemic fibrosis (NSF), which may result in a fatal or severely debilitating systemic fibrosis. Patients with impaired renal function are at risk of developing NSF and the non-ionic linear gadolinium-based contrast agents should be avoided (gadodiamide, gadopentetate dimeglumine and gadoversetamide). A stable macrocyclic contrast agent should be used (gadobutrol, gadoterate meglumine or gadoteridol). Alternatively, contrast-enhanced CT could be performed using iodinated contrast media (35) (LE: 4).

4.2.1.2 CT imaging for local staging of MIBC

The advantages of CT include high spatial resolution, shorter acquisition time, wider coverage in a single breath hold and lower susceptibility to variable patient factors. Computed tomography is unable to differentiate between stages Ta to T3a, but it is useful for detecting invasion into the perivesical fat (T3b) and adjacent organs. The accuracy of CT in determining extravesical tumour extension varies from 55% to 92% (36) and increases with more advanced disease (37).

4.2.2 Imaging of lymph nodes in MIBC

The assessment of metastases to lymph nodes based simply on size is limited by the inability of both CT and MRI to identify metastases in normal-sized or minimally enlarged nodes. The sensitivity for detection of lymph node metastases is low, ranging from 48-87%. Specificity is also low as nodal enlargement may be due to benign disease. Overall, CT and MRI show similar results in the detection of lymph node metastases in a variety of primary pelvic tumours (38-43). Pelvic nodes, measured on CT or MRI, greater than 8 mm and abdominal nodes greater than 10 mm in a maximum short-axis diameter, should be regarded as pathologically enlarged. (44,45).

Currently, there is no evidence supporting the routine use of positron emission tomography (PET), computed tomography (PET/CT) in the nodal staging of bladder cancer, although the method has been evaluated with varying results in small prospective trials (46-49).

4.2.3 Upper urinary tract urothelial carcinoma (UTUC)

Excretory-phase computed tomography urography is the imaging technique with the highest diagnostic accuracy for UTUC and has replaced conventional intravenous urography and ultrasonography as the first-line imaging test for investigating high-risk patients (50). The sensitivity of CT urography for UTUC is reported to range from 0.67 to 1.0 and specificity from 0.93 to 0.99 depending on the technique used (51-58). Attention to technique is therefore very important for optimum results.

For UTUC detected by CT urography, a biopsy for histopathological confirmation of diagnosis is recommended to eliminate false-positive results and to provide information regarding the grade of the tumour to aid in the choice of treatment. (52,53,59-61). This is usually performed ureteroscopically.

4.2.4 Distant metastases other than lymph nodes

Prior to any treatment aimed at cure, it is essential to evaluate the presence of distant metastases. Computed tomography and MRI are the diagnostic techniques of choice to detect metastases to lung and liver. Metastases to bones or brain at the presentation of invasive bladder cancer are rare. A bone scan and additional brain imaging are therefore not routinely indicated unless the patient has specific symptoms or signs to suggest bone or brain metastases (62,63). Magnetic resonance imaging is more sensitive and specific for diagnosing bone metastases than bone scintigraphy (64,65) (LE: 2b).

4.2.5 Future developments

Evidence is accruing in the literature suggesting that FDG-PET/CT might have potential clinical use for staging metastatic bladder cancer (66,67) but there is no consensus as yet. The results of further trials are awaited before a recommendation can be made.

Recently, the first study was published showing the feasibility of diffusion-weighted imaging (DWI) over T2W and DCE for assessing the therapeutic response to induction chemotherapy against MIBC (68). The high specificity of DWI indicates that DWI is useful for accurate prediction of a complete histopathological response, allowing better patient selection for bladder-sparing protocols. Results from prospective studies are awaited.

4.2.6 Conclusions and recommendations for staging in MIBC

Conclusions	LE
Imaging as part of staging in muscle-invasive bladder cancer (MIBC) provides information about prognosis and assists in selection of the most appropriate treatment.	2b
There is insufficient data on the use of DW MRI and FDG-PET/CT in MIBC currently to allow a recommendation to be made.	

DW MRI = diffusion-weighted magnetic resonance imaging; FDG-PET/CT = fluorodeoxyglucose-positron emission tomography

Recommendations	GR
In patients with confirmed muscle-invasive bladder cancer, CT of the chest, abdomen and pelvis is the optimal form of staging, including excretory-phase CT urography for complete examination of the upper urinary tracts.	B
Excretory-phase CT urography is preferred to MR urography for diagnosing UTUCs in terms of greater diagnostic accuracy, less cost, and greater patient acceptability. MR urography is used when CT urography is contra-indicated for reasons related to contrast administration or radiation dose.	C
Ureteroscopic-guided biopsy is recommended for histopathological confirmation of diagnosis in the pre-operative assessment of UTUC.	C
CT or MRI is recommended for staging locally advanced or metastatic disease in patients in whom radical treatment is being considered.	B
CT and MRI are generally equivalent in diagnosing local and distant abdominal metastases but CT is preferred to diagnose pulmonary metastases.	C

CT = computed tomography; MR = magnetic resonance; UTUC = upper urinary tract urothelial carcinoma

4.3 References

- Fossa SD, Ous S, Berner A. Clinical significance of the 'palpable mass' in patients with muscle-infiltrating bladder cancer undergoing cystectomy after pre-operative radiotherapy. *Br J Urol* 1991 Jan;67(1):54-60.
<http://www.ncbi.nlm.nih.gov/pubmed/1993277>
- Wijkström H, Norming U, Lagerkvist M, et al. Evaluation of clinical staging before cystectomy in transitional cell bladder carcinoma: a long-term follow-up of 276 consecutive patients. *Br J Urol* 1998 May;81(5):686-91.
<http://www.ncbi.nlm.nih.gov/pubmed/9634042>
- Ploeg M, Kiemeny LA, Smits GA, et al. Discrepancy between clinical staging through bimanual palpation and pathological staging after cystectomy. *Urol Oncol* 2012 May-Jun;30(3):247-51
<http://www.ncbi.nlm.nih.gov/pubmed/20451418>
- Raitanen M-P, Aine R, Rintala E, et al. FinnBladder Group. Differences between local and review urinary cytology and diagnosis of bladder cancer. An interobserver multicenter analysis. *Eur Urol* 2002 Mar;41(3):284-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12180229>
- Lokeshwar VB, Habuchi T, Grossman HB, et al. Bladder tumor markers beyond cytology: international consensus panel on bladder tumor markers. *Urology* 2005 Dec;66 (6 Suppl 1):35-63.
<http://www.ncbi.nlm.nih.gov/pubmed/16399415>
- Van Rhijn BW, van der Poel HG, van der Kwast Th. Urine Markers for bladder cancer surveillance: a systematic review. *Eur Urol* 2005 Jun;47(6):736-48.
<http://www.ncbi.nlm.nih.gov/pubmed/15925067>
- Stenzl A, Burger M, Fradet Y, et al. Hexaminolevulinic acid guided fluorescence cystoscopy reduces recurrence in patients with non-muscle invasive bladder cancer. *J Urol* 2010 Nov;184(5):1907-13
<http://www.ncbi.nlm.nih.gov/pubmed/20850152>
- May F, Treiber U, Hartung R, et al. Significance of random bladder biopsies in superficial bladder cancer. *Eur Urol* 2003 Jul;44(1):47-50.
<http://www.ncbi.nlm.nih.gov/pubmed/12814674>
- Fradet Y, Grossman HB, Gomella L, et al; PC B302/01 Study Group A comparison of hexaminolevulinic acid fluorescence cystoscopy and white light cystoscopy for the detection of carcinoma in situ in patients with bladder cancer: a phase III, multicenter study. *J Urol* 2007 Jul;178(1):68-73; discussion 73.
<http://www.ncbi.nlm.nih.gov/pubmed/17499291>

10. Grossman HB, Gomella L, Fradet Y, et al; PC B302/01 Study Group. A phase III, multicentre comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of superficial papillary lesions in patients with bladder cancer. *J Urol* 2007 Jul;178(1):62-7. <http://www.ncbi.nlm.nih.gov/pubmed/17499283>
11. Schmidbauer J, Witjes F, Schmeller N, et al. Hexvix PCB301/01 Study Group. Improved detection of urothelial carcinoma in situ with hexaminolevulinate fluorescence cystoscopy. *J Urol* 2004 Jan;171(1):135-8. <http://www.ncbi.nlm.nih.gov/pubmed/14665861>
12. Jichlinski P, Guillou L, Karlsen SJ, et al. Hexyl aminolevulinate fluorescence cystoscopy: new diagnostic tool for photodiagnosis of superficial bladder cancer-a multicenter study. *J Urol* 2003 Jul;170(1):226-9. <http://www.ncbi.nlm.nih.gov/pubmed/12796694>
13. Matzkin H, Soloway MS, Hardeman S. Transitional cell carcinoma of the prostate. *J Urol* 1991 Nov;146(5):1207-12. <http://www.ncbi.nlm.nih.gov/pubmed/1942262>
14. Mungan MU, Canda AE, Tuzel E, et al. Risk factors for mucosal prostatic urethral involvement in superficial transitional cell carcinoma of the bladder. *Eur Urol* 2005 Nov;48(5):760-3. <http://www.ncbi.nlm.nih.gov/pubmed/16005563>
15. Kassouf W, Spiess PE, Brown GA, et al Prostatic urethral biopsy has limited usefulness in counselling patients regarding final urethral margin status during orthotopic neobladder reconstruction. *J Urol* 2008 Jul;180(1):164-7; discussion 167. <http://www.ncbi.nlm.nih.gov/pubmed/18485384>
16. Walsh DL, Chang SS. Dilemmas in the treatment of urothelial cancers of the prostate. *Urol Oncol* 2009 Jul-Aug;27(4):352-7. <http://www.ncbi.nlm.nih.gov/pubmed/18439852>
17. Leuret T, Herve JM, Barre P, et al. Urethral recurrence of transitional cell carcinoma of the bladder. Predictive value of preoperative latero-montanal biopsies and urethral frozen sections during prostatectomy. *Eur Urol* 1998;33(2):170-4. <http://www.ncbi.nlm.nih.gov/pubmed/9519359>
18. Brausi M, Collette L, Kurth K, et al. EORTC Genito-Urinary Tract Cancer Collaborative Group. Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. *Eur Urol* 2002 May;41(5): 523-31. <http://www.ncbi.nlm.nih.gov/pubmed/12074794>
19. Miladi M, Peyromaure M, Zerbib M, et al. The value of a second transurethral resection in evaluating patients with bladder tumours. *Eur Urol* 2003 Mar;43(3):241-5. <http://www.ncbi.nlm.nih.gov/pubmed/12600426>
20. Jakse G, Algaba F, Malmström PU, et al. A second-look TUR in T1 transitional cell carcinoma: why? *Eur Urol* 2004 May;45(5):539-46. <http://www.ncbi.nlm.nih.gov/pubmed/15082193>
21. Brauers A, Buettner R, Jakse G. Second resection and prognosis of primary high risk superficial bladder cancer: is cystectomy often too early? *J Urol* 2001 Mar;165(3):808-10. <http://www.ncbi.nlm.nih.gov/pubmed/111176474>
22. Schips L, Augustin H, Zigeuner RE, et al. Is repeated transurethral resection justified in patients with newly diagnosed superficial bladder cancer? *Urology* 2002 Feb;59(2):220-3. <http://www.ncbi.nlm.nih.gov/pubmed/11834389>
23. Grimm MO, Steinhoff Ch, Simon X, et al. Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. *J Urol* 2003 Aug;170(2 Pt 1):433-7. <http://www.ncbi.nlm.nih.gov/pubmed/12853793>
24. Divrik RT, Yildirim Ü, Zorlu F, et al. The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesical mitomycin: a prospective, randomized clinical trial. *J Urol* 2006 May;175(5):1641-4. <http://www.ncbi.nlm.nih.gov/pubmed/16600720>
25. Jahnson S, Wiklund F, Duchek M, et al. Results of Second-look resection after primary resection of T1 tumour of the urinary bladder. *Scand J Urol Nephrol* 2005;39(3):206-10. <http://www.ncbi.nlm.nih.gov/pubmed/16127800>
26. Damiano R, Di Lorenzo G, Cantiello F, et al. Clinicopathologic features of prostate adenocarcinoma incidentally discovered at the time of radical cystectomy: an evidence-based analysis. *Eur Urol* 2007 Sep;52(3):648-57. <http://www.ncbi.nlm.nih.gov/pubmed/17600614>

27. Gakis G, Schilling D, Bedke J, et al. Incidental prostate cancer at radical cystoprostatectomy: implications for apex-sparing surgery. *BJU Int* 2010 Feb;105(4):468-71.
<http://www.ncbi.nlm.nih.gov/pubmed/20102366>
28. Babjuk M, Oosterlinck W, Sylvester R, et al; members of the EAU Guidelines Panel on Non-muscle-invasive bladder cancer. Guidelines on Non-muscle-invasive bladder cancer (TaT1 and CIS). Edn. presented at the EAU Annual Congress 2013. ISBN 978-90-79754-71-7. Arnhem, The Netherlands.
<http://www.uroweb.org/online/online-guidelines/>
29. Jewett HJ. Proceedings: Cancer of the bladder. Diagnosis and Staging. *Cancer* 1973 Nov;32(5):1072-4. [no abstract available]
<http://www.ncbi.nlm.nih.gov/pubmed/4757902>
30. Paik ML, Scolieri MJ, Brown SL, et al. Limitations of computerized tomography in staging invasive bladder cancer before radical cystectomy. *J Urol* 2000 Jun;163(6):1693-6.
<http://www.ncbi.nlm.nih.gov/pubmed/10799162>
31. Barentsz JO, Jager GJ, Witjes JA, et al. Primary staging of urinary bladder carcinoma: the role of MR imaging and a comparison with CT. *Eur Radiol* 1996;6(2):129-33.
<http://www.ncbi.nlm.nih.gov/pubmed/8797968>
32. Barentsz JO, Jager GJ, van Vierzen PB, et al. Staging urinary bladder cancer after transurethral biopsy: value of fast dynamic contrast-enhanced MR imaging. *Radiology* 1996 Oct;201(1):185-93.
<http://www.ncbi.nlm.nih.gov/pubmed/8816542>
33. Mallampati GK, Siegelman ES. MR imaging of the bladder. *Magn Reson Imaging Clin N Am* 2004 Aug;12(3):545-55.
<http://www.ncbi.nlm.nih.gov/pubmed/15271370>
34. Rajesh A, Sokhi HK, Fung R, et al. Bladder cancer: evaluation of staging accuracy using dynamic MRI. *Clin Radiol* 2011 Dec;66(12):1140-5.
<http://www.ncbi.nlm.nih.gov/pubmed/21924408>
35. Thomsen HS. Nephrogenic systemic fibrosis: history and epidemiology. *Radiol Clin North Am* 2009 Sep;47(5):827-31.
<http://www.ncbi.nlm.nih.gov/pubmed/19744597>
36. Kundra V, Silverman PM. Imaging in oncology from the University of Texas M. D. Anderson Cancer Center. Imaging in the diagnosis, staging, and follow-up of cancer of the urinary bladder. *AJR Am J Roentgenol* 2003 Apr 180(4):1045-54.
<http://www.ncbi.nlm.nih.gov/pubmed/12646453>
37. Kim B, Semelka RC, Ascher SM, et al. Bladder tumor staging: comparison of contrast-enhanced CT, T1- and T2-weighted MR imaging, dynamic gadolinium-enhanced imaging, and late gadolinium-enhanced imaging. *Radiology* 1994 Oct;193(1):239-45.
<http://www.ncbi.nlm.nih.gov/pubmed/8090898>
38. Kim JK, Park SY, Ahn HJ, et al. Bladder cancer: analysis of multi-detector row helical CT enhancement pattern and accuracy in tumor detection and perivesical staging. *Radiology* 2004 Jun;231(3):725-31.
<http://www.ncbi.nlm.nih.gov/pubmed/15118111>
39. Jager GJ, Barentsz JO, Oosterhof GO, et al. Pelvic adenopathy in prostatic and urinary bladder carcinoma: MR imaging with a three-dimensional T1-weighted magnetization-prepared-rapid gradient-echo sequence. *AJR Am J Roentgenol* 1996 Dec;167(6):1503-7.
<http://www.ncbi.nlm.nih.gov/pubmed/8956585>
40. Yang WT, Lam WW, Yu MY, et al. Comparison of dynamic helical CT and dynamic MR imaging in the evaluation of pelvic lymph nodes in cervical carcinoma. *AJR Am J Roentgenol* 2000 Sep;175(3):759-66.
<http://www.ncbi.nlm.nih.gov/pubmed/10954463>
41. Kim SH, Kim SC, Choi BI, et al. Uterine cervical carcinoma: evaluation of pelvic lymph node metastasis with MR imaging. *Radiology* 1994 Mar;190(3):807-11.
<http://www.ncbi.nlm.nih.gov/pubmed/8115631>
42. Kim SH, Choi BI, Lee HP, et al. Uterine cervical carcinoma: comparison of CT and MR findings. *Radiology* 1990 Apr;175(1):45-51.
<http://www.ncbi.nlm.nih.gov/pubmed/2315503>
43. Oyen RH, Van Poppel HP, Ameye FE, et al. Lymph node staging of localized prostatic carcinoma with CT and CT-guided fine-needle aspiration biopsy: prospective study of 285 patients. *Radiology* 1994 Feb;190(2):315-22.
<http://www.ncbi.nlm.nih.gov/pubmed/8284375>
44. Barentsz JO, Engelbrecht MR, Witjes JA, et al. MR imaging of the male pelvis. *Eur Radiol* 1999;9(9):1722-36.
<http://www.ncbi.nlm.nih.gov/pubmed/10602944>

45. Dorfman RE, Alpern MB, Gross BH, et al. Upper abdominal lymph nodes: criteria for normal size determined with CT. *Radiology* 1991 Aug;180(2):319-22.
<http://www.ncbi.nlm.nih.gov/pubmed/2068292>
46. Swinnen G, Maes A, Pottel H, et al. FDG-PET/CT for the Preoperative Lymph Node Staging of Invasive Bladder Cancer. *Eur Urol* 2010 Apr;57(4):641-7.
<http://www.ncbi.nlm.nih.gov/pubmed/19477579>
47. Kibel AS, Dehdashti F, Katz MD, et al. Prospective study of [18F]fluorodeoxyglucose positron emission tomography/computed tomography for staging of muscle-invasive bladder carcinoma. *J Clin Oncol* 2009 Sep 10;27(26):4314-20.
<http://www.ncbi.nlm.nih.gov/pubmed/19652070>
48. Lu YY, Chen JH, Liang JA, et al. Clinical value of FDG PET or PET/CT in urinary bladder cancer: a systemic review and meta-analysis. *Eur J Radiol* 2012 Sep;81(9):2411-6.
<http://www.ncbi.nlm.nih.gov/pubmed/21899971>
49. Vargas HA, Akin O, Schöder H, et al. Prospective evaluation of MRI, ¹¹C-acetate PET/CT and contrast-enhanced CT for staging of bladder cancer. *Eur J Radiol* 2012 Dec;81(12):4131-7.
<http://www.ncbi.nlm.nih.gov/pubmed/22858427>
50. Cowan NC. CT urography for hematuria. *Nat Rev Urol* 2012 Mar;9(4):218-26.
<http://www.ncbi.nlm.nih.gov/pubmed/22410682>
51. Chow LC, Kwan SW, Olcott EW, et al. Split-bolus MDCT urography with synchronous nephrographic and excretory phase enhancement. *AJR Am J Roentgenol* 2007 Aug;189(2):314-22.
<http://www.ncbi.nlm.nih.gov/pubmed/17646456>
52. Cowan NC, Turney BW, Taylor NJ, et al. Multidetector computed tomography urography for diagnosing upper urinary tract urothelial tumour. *BJU Int* 2007 Jun;99(6):1363-70.
<http://www.ncbi.nlm.nih.gov/pubmed/17428251>
53. Fritz GA, Schoellnast H, Deutschmann HA, et al. Multiphasic multidetector-row CT (MDCT) in detection and staging of transitional cell carcinomas of the upper urinary tract. *Eur Radiol* 2006 Jun;16(6):1244-52.
<http://www.ncbi.nlm.nih.gov/pubmed/16404565>
54. Maheshwari E, O'Malley ME, Ghai S, et al. Split-bolus MDCT urography: Upper tract opacification and performance for upper tract tumors in patients with hematuria. *AJR Am J Roentgenol* 2010 Feb;194(2):453-8.
<http://www.ncbi.nlm.nih.gov/pubmed/20093609>
55. Sudakoff GS, Dunn DP, Guralnick ML, et al. Multidetector computerized tomography urography as the primary imaging modality for detecting urinary tract neoplasms in patients with asymptomatic hematuria. *J Urol* 2008 Mar;179(3):862-7; discussion 867.
<http://www.ncbi.nlm.nih.gov/pubmed/18221955>
56. Wang LJ, Wong YC, Chuang CK, et al. Diagnostic accuracy of transitional cell carcinoma on multidetector computerized tomography urography in patients with gross hematuria. *J Urol* 2009 Feb;181(2):524-31; discussion 531.
<http://www.ncbi.nlm.nih.gov/pubmed/19100576>
57. Wang LJ, Wong YC, Huang CC, et al. Multidetector computerized tomography urography is more accurate than excretory urography for diagnosing transitional cell carcinoma of the upper urinary tract in adults with hematuria. *J Urol* 2010 Jan;183(1):48-55.
<http://www.ncbi.nlm.nih.gov/pubmed/19913253>
58. Jinzaki M, Matsumoto K, Kikuchi E, et al. Comparison of CT urography and excretory urography in the detection and localization of urothelial carcinoma of the upper urinary tract. *AJR Am J Roentgenol* 2011 May;196(5):1102-9.
<http://www.ncbi.nlm.nih.gov/pubmed/21512076>
59. Van Der Molen AJ, Cowan NC, Mueller-Lisse UG, et al. CT Urography Working Group of the European Society of Urogenital Radiology (ESUR). CT urography: definition, indications and techniques. A guideline for clinical practice. *Eur Radiol* 2008 Jan;18(1):4-17.
<http://www.ncbi.nlm.nih.gov/pubmed/17973110>
60. Albani JM, Ciaschini MW, Streem SB, et al. The role of computerized tomographic urography in the initial evaluation of hematuria. *J Urol* 2007 Feb;177(2):644-8.
<http://www.ncbi.nlm.nih.gov/pubmed/17222650>
61. Gray Sears C, Ward JF, Sears ST, et al. Prospective comparison of computerized tomography and excretory urography in the initial evaluation of asymptomatic microhematuria. *J Urol* 2002 Dec;168(6):2457-60.
<http://www.ncbi.nlm.nih.gov/pubmed/12441939>

62. Braendengen M, Winderen M, Fosså SD. Clinical significance of routine pre-cystectomy bone scans in patients with muscle-invasive bladder cancer. *Br J Urol* 1996 Jan;77(1):36-40.
<http://www.ncbi.nlm.nih.gov/pubmed/8653315>
63. Brismar J, Gustafson T. Bone scintigraphy in staging bladder carcinoma. *Acta Radiol* 1988 Mar-Apr;29(2):251-2.
<http://www.ncbi.nlm.nih.gov/pubmed/2965914>
64. Lauenstein TC, Goehde SC, Herborn CU, et al. Whole-body MR imaging: evaluation of patients for metastases. *Radiology* 2004 Oct;233(1):139-48.
<http://www.ncbi.nlm.nih.gov/pubmed/15317952>
65. Schmidt GP, Schoenberg SO, Reiser MF, et al. Whole-body MR imaging of bone marrow. *Eur J Radiol* 2005 Jul;55(1):33-40.
<http://www.ncbi.nlm.nih.gov/pubmed/15950099>
66. Yang Z, Cheng J, Pan L, et al. Is whole-body fluorine-18 fluorodeoxyglucose PET/CT plus additional pelvic images (oral hydration-voiding-refilling) useful for detecting recurrent bladder cancer. *Ann Nucl Med* 2012 Aug;26(7):571-7.
<http://www.ncbi.nlm.nih.gov/pubmed/22763630>
67. Maurer T, Souvatzoglou M, Kübler H, et al. Diagnostic efficacy of [11C]choline positron emission tomography/computed tomography compared with conventional computed tomography in lymph node staging of patients with bladder cancer prior to radical cystectomy. *Eur Urol* 2012 May;61(5):1031-8.
<http://www.ncbi.nlm.nih.gov/pubmed/22196847>
68. Yoshida S, Koga F, Kobayashi S, et al. Role of diffusion-weighted magnetic resonance imaging in predicting sensitivity to chemoradiotherapy in muscle-invasive bladder cancer. *Int J Radiat Oncol Biol Phys* 2012 May 1;83(1):e21-7.
<http://www.ncbi.nlm.nih.gov/pubmed/22414281>

5. TREATMENT FAILURE OF NON-MUSCLE INVASIVE BLADDER CANCER

5.1 High-risk non-muscle-invasive urothelial carcinoma

The recurrence and progression rate of NMIBC is strongly associated with tumour grade and invasion into the lamina propria. The progression to T2 tumours varies from 6% to 25% in Ta and from 27% to 48% in T1 tumours of all grades. Inter- and intra-observer varying abilities in grading and staging and the completeness of TUR are key variables that confound the results of present long-term studies of TUR, with or without intravesical therapy.

The understaging error in TaT1 tumours of 35-62% presented in large cystectomy series is due to the presence of recurrent tumours of largely unknown pre-cystectomy therapy and the lack of a second TUR (1-3) (LE: 3). The latter identifies 24-49% of T2 tumours that have been diagnosed initially as non-muscle-invasive tumours (4,5) (LE: 3). However, in spite of these disadvantages, recent meta-analyses have demonstrated that *Bacillus Calmette-Guérin* (BCG) therapy prevents the risk of tumour recurrence (6,7). Two other meta-analyses showed that BCG therapy decreases the risk of tumour progression (8,9).

So far, no significant overall- or disease-specific survival advantages have been shown, as compared to no intravesical therapy (8-10) (LE: 1).

The disease progression rate is low in patients with small tumours (< 3 cm) and without associated CIS. Twenty per cent of patients progress within 5 years, with approximately 90% of patients keeping their intact bladder during follow-up of up to 10 years (11) (LE: 2). However, in a recently published, prospective, multicentre trial, the progression rate was significantly lower than previously reported, even when the presence of concomitant CIS was considered. This was probably due to the combination of a second resection, prior to inclusion in the trial and maintenance treatment as part of the protocol (12) (LE: 1b).

Progression to MIBC significantly decreases cancer-specific survival (CSS). In a review of 19 trials and 3,088 patients, CSS after progression from NMIBC to MIBC was 35%, which is significantly worse compared to patients with MIBC without a history of NMIBC. This underlines the need to recommend early radical treatment in case of intravesical therapy failure (13,14).

According to the EAU NMIBC Guidelines, it is reasonable to propose immediate radical cystectomy to those patients with non-muscle-invasive tumour who are at highest risk of progression (14). These are:

- multiple and/ or large (> 3 cm) T1, high-grade (G3) tumours;
- T1, high-grade (G3) tumours with concurrent CIS;
- recurrent T1, high-grade (G3) tumours;
- T1G3 and CIS in prostatic urethra;
- micropapillary variant of urothelial carcinoma.

Although the percentage of patients with primary TaT1 tumours and the indication for cystectomy in TaT1 tumours is not specified in large cystectomy series, the 10-year recurrence-free survival is approximately 80% and similar to TUR and BCG maintenance therapy (1,3,15,16) (LE: 3). In the case of recurrent TaT1, mostly associated with CIS, the understaging at the time of cystectomy is 34%, but the 10-year survival is not significantly different for patients with pT1 and pT2 tumours (17) (LE: 3). This is in contrast to an earlier report, which indicates a significantly worse outcome for patients with previous TUR(s) (18) (LE: 3).

Undoubtedly, patients with muscle-invasive recurrence are best treated with radical cystectomy. However, the outcome in terms of the presence of lymph node metastases and cancer-free survival may be inferior to patients with the same tumour stage, but who receive radical cystectomy at first presentation (19) (LE: 3).

There is uncertainty about the treatment of patients who develop tumour recurrence in spite of BCG therapy because of different BCG therapy schedules and the absence of a uniform definition of BCG failure. It has been indicated that the recurrence (persistence) of tumour at 9 months in spite of BCG therapy is associated with a 30% chance of invasive tumours and death due to metastatic disease (20) (LE: 3). Solsona et al. demonstrated that 80% of patients who had persistent disease at 3 months progressed to muscle-invasive disease (21) (LE: 3). In addition, adequate tissue sampling from the prostatic urethra is an essential factor in considering the outcome of conservative treatment, since urethral tumours are associated with a significant decrease in tumour-free survival (22) (LE: 3). However, with careful selection and surveillance, a durable complete response can also be achieved in patients diagnosed with superficial bladder transitional cell carcinoma involving the prostatic urethra (23). Based on these findings, cystectomy should be performed in appropriate patients at least at 9 months, because additional BCG therapy yields a response rate of only 27-51% and of unknown duration (24,25) (GR: C). Salvage chemotherapy is associated with a limited response and should not be offered (26,27) (LE: 3).

Patients with disease recurring within 2 years of initial TUR plus BCG therapy have a better outcome than patients who already have muscle-invasive disease, indicating that cystectomy should be performed at first recurrence, even in non-muscle-invasive disease (19) (LE: 3; GR: C).

5.2 Carcinoma *in situ*

Primary CIS confined to the bladder is treated with intravesical BCG, yielding a complete response rate of 83-93% (28,29) (LE: 2). Carcinoma *in situ* associated with TaT1 is treated according to the overt tumour.

Approximately 50% of patients develop recurrent disease with muscle invasion or extravesical tumour (28,30) (LE: 2). Between 11% and 21% die of the disease within 5-7 years after an initial complete response (28,31) (LE: 2). Non-responders or incomplete responders have a significant risk of tumour progression of 33-67% (21,32) (LE: 2).

The current guidelines on non-muscle-invasive bladder cancer define BCG failure as:

- a. Whenever muscle-invasive tumour is detected during follow-up.
- b. If high-grade, non-muscle-invasive tumour is present at both 3 and 6 months.
- c. High-grade recurrence after BCG (more recurrences, Ta → T1 or upgrading, appearance of CIS).

In patients with tumour present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases, both in patients with papillary tumours and CIS but with increasing risk of progression.

There are now several bladder preservation strategies available that can be categorised as immunotherapy, chemotherapy, device-assisted therapy, and combination therapy (33). However, experience is limited and treatments other than radical cystectomy must be considered oncologically inferior at the present time (34-36).

5.3 Recommendations for treatment failure of non-muscle-invasive bladder cancer

Recommendations	GR
In all T1 tumours at high risk of progression (i.e. high grade, multifocality, carcinoma in situ, and tumour size, as outlined in the EAU guidelines for Non-muscle-invasive bladder cancer [14]), immediate radical treatment is an option.	C
In all T1 patients failing intravesical therapy, radical treatment should be offered.	B

5.4 References

- Hautmann RE, Gschwend JE, de Petriconi RC, et al. Cystectomy for transitional cell carcinoma of the bladder: results of a surgery only series in the neobladder era. *J Urol* 2006 Aug;176(2):486-92. <http://www.ncbi.nlm.nih.gov/pubmed/16813874>
- Madersbacher S, Hochreiter W, Burkhard F, et al. Radical cystectomy for bladder cancer today—a homogeneous series without neoadjuvant therapy. *J Clin Oncol* 2003 Feb;21(4):690-6. <http://www.ncbi.nlm.nih.gov/pubmed/12586807>
- Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001 Feb;19(3):666-75. <http://www.ncbi.nlm.nih.gov/pubmed/11157016>
- Brauers A, Buettner R, Jakse G. Second resection and prognosis of primary high risk superficial bladder cancer: is cystectomy often too early? *J Urol* 2001 Mar;165(3):808-10. <http://www.ncbi.nlm.nih.gov/pubmed/11176474>
- Herr WH. The value of second transurethral resection in evaluating patients with bladder tumors. *J Urol* 1999 Jul;162(1):74-6. <http://www.ncbi.nlm.nih.gov/pubmed/10379743>
- Shelley MD, Court JB, Kynaston H, et al. Intravesical bacillus Calmette-Guérin versus mitomycin C for Ta and T1 bladder cancer. *Cochrane Database Syst Rev* 2003;(3):CD003231. <http://www.ncbi.nlm.nih.gov/pubmed/12917955>
- Sylvester RJ, Brausi MA, Kirkels WJ, et al. EORTC Genito-Urinary Tract Cancer Group. Long-term efficacy results of EORTC Genito-Urinary Group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, Bacillus Calmette-Guérin, and Bacillus Calmette-Guérin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. *Eur Urol* 2010 May;57(5):766-73. <http://www.ncbi.nlm.nih.gov/pubmed/20034729>
- Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guérin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *J Urol* 2002 Nov;168(5):1964-70. <http://www.ncbi.nlm.nih.gov/pubmed/12394686>
- Böhle A, Bock PR. Intravesical bacille Calmette-Guérin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumour progression. *Urology* 2004 Apr;63(4):682-6. <http://www.ncbi.nlm.nih.gov/pubmed/15072879>
- Malmström PU, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the longterm outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette- Guérin for non-muscle-invasive bladder cancer. *Eur Urol* 2009 Aug;56(2):247-56. <http://www.ncbi.nlm.nih.gov/pubmed/19409692>
- Serretta V, Pavone C, Ingargiola GB, et al. TUR and adjuvant intravesical chemotherapy in T1G3 bladder tumors: recurrence, progression and survival in 137 selected patients followed up to 20 years. *Eur Urol* 2004 Jun;45(6):730-5. <http://www.ncbi.nlm.nih.gov/pubmed/15149744>
- Duchek M, Johansson R, Jahnson S, et al. Members of the Urothelial Cancer Group of the Nordic Association of Urology. Bacillus Calmette-Guérin is superior to a combination of epirubicin and interferon-alpha2b in the intravesical treatment of patients with stage T1 urinary bladder cancer. A prospective, randomized, Nordic study. *Eur Urol* 2010 Jan;57(1):25-31. <http://www.ncbi.nlm.nih.gov/pubmed/19819617>
- van den Bosch S, Alfred Witjes J. Long-term cancer-specific survival in patients with high-risk, non-muscle-invasive bladder cancer and tumour progression: a systematic review. *Eur Urol* 2011 Sep;60(3):493-500. <http://www.ncbi.nlm.nih.gov/pubmed/21664041>

14. Babjuk M, Oosterlinck W, Sylvester R, et al; members of the EAU Guidelines Panel on Non-muscle-invasive bladder cancer. Guidelines on Non-muscle-invasive bladder cancer (TaT1 and CIS). Edn. presented at the EAU Annual Congress 2013. ISBN 978-90-79754-71-7. Arnhem, The Netherlands. <http://www.uroweb.org/guidelines/online-guidelines/>
15. Pansadoro V, Emiliozzi P, de Paula F, et al. Long-term follow-up of G3T1 transitional cell carcinoma of the bladder treated with intravesical bacille Calmette-Guérin: 18-year experience. *Urology* 2002 Feb;59(2):227-31. <http://www.ncbi.nlm.nih.gov/pubmed/11834391>
16. Margel D, Tal R, Golan S, et al. Long-term follow-up of patients with Stage T1 high-grade transitional cell carcinoma managed by Bacille Calmette-Guérin immunotherapy. *Urology* 2007 Jan;69(1):78-82. <http://www.ncbi.nlm.nih.gov/pubmed/17270621>
17. Freeman JA, Esrig D, Stein JP, et al. Radical cystectomy for high risk patients with superficial bladder cancer in the era of orthotopic urinary reconstruction. *Cancer* 1995 Sep;76(5):833-9. <http://www.ncbi.nlm.nih.gov/pubmed/8625187>
18. Stöckle M, Alken P, Engelmann U, et al. Radical cystectomy-often too late? *Eur Urol* 1987;13(6):361-7. <http://www.ncbi.nlm.nih.gov/pubmed/3428318>
19. Herr HW, Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? *J Urol* 2001 Oct;166(4):1296-9. <http://www.ncbi.nlm.nih.gov/pubmed/11547061>
20. Merz VW, Marth D, Kraft R, et al. Analysis of early failures after intravesical instillation therapy with bacille Calmette-Guerin for carcinoma in situ of the bladder. *Br J Urol* 1995 Feb;75(2):180-4. <http://www.ncbi.nlm.nih.gov/pubmed/7850322>
21. Solsona E, Iborra I, Rubio J, et al. The optimum timing of radical cystectomy for patients with recurrent high-risk superficial bladder tumour. *BJU Int* 2004 Dec;94(9):1258-62. <http://www.ncbi.nlm.nih.gov/pubmed/15610101>
22. Huguet J, Crego M, Sabaté S, et al. Cystectomy in patients with high risk superficial bladder tumors who fail intravesical BCG therapy: pre-cystectomy prostate involvement as a prognostic factor. *Eur Urol* 2005 Jul;48(1):53-9. <http://www.ncbi.nlm.nih.gov/pubmed/15967252>
23. Taylor JH, Davis J, Schellhammer P. Long-term follow-up of intravesical bacillus Calmette-Guérin treatment for superficial transitional-cell carcinoma of the bladder involving the prostatic urethra. *Clin Genitourin Cancer* 2007 Sep;5(6):386-9. <http://www.ncbi.nlm.nih.gov/pubmed/17956711>
24. Brake M, Loertzer H, Horsch R, et al. Recurrence and progression of stage T1, grade 3 transitional cell carcinoma of the bladder following intravesical immunotherapy with bacillus Calmette-Guerin. *J Urol* 2000 Jun;163(6):1697-701. <http://www.ncbi.nlm.nih.gov/pubmed/10799163>
25. Pansadoro V, Emiliozzi P, Defidio L, et al. Bacillus Calmette-Guerin in the treatment of stage T1 grade 3 transitional cell carcinoma of the bladder: Long-term results. *J Urol* 1995 Dec;154(6):2054-8. <http://www.ncbi.nlm.nih.gov/pubmed/7500457>
26. Malmström PU, Wijkström H, Lundholm C, et al. 5-year followup of a randomized prospective study comparing mitomycin C and bacillus Calmette-Guerin in patients with superficial bladder carcinoma. Swedish-Norwegian Bladder Cancer Study Group. *J Urol* 1999 Apr;161(4):1124-7. <http://www.ncbi.nlm.nih.gov/pubmed/10081852>
27. Steinberg G, Bahnson R, Brosman S, et al. Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. The Valrubicin Study Group. *J Urol* 2000 Mar;163(3):761-7. <http://www.ncbi.nlm.nih.gov/pubmed/10687972>
28. Jakse G, Hall R, Bono A, et al. Intravesical BCG in patients with carcinoma in situ of the urinary bladder: long-term results of EORTC GU Group phase II protocol 30861. *Eur Urol* 2001 Aug;40(2):144-50. <http://www.ncbi.nlm.nih.gov/pubmed/11528191>
29. Losa A, Hurle R, Lembo A. Low dose bacillus Calmette-Guerin for carcinoma in situ of the bladder: long-term results. *J Urol* 2000 Jan;163(1):68-71. <http://www.ncbi.nlm.nih.gov/pubmed/10604316>
30. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J Urol* 2000 Apr;163(4):1124-9. <http://www.ncbi.nlm.nih.gov/pubmed/10737480>

31. de Reijke TM, Kurth KH, Sylvester RJ, et al. European Organization for the Research and Treatment of Cancer-Genito-Urinary Group. Bacillus Calmette-Guerin versus epirubicin for primary, secondary or concurrent carcinoma in situ of the bladder: results of a European Organization for the Research and Treatment of Cancer--Genito- Urinary Group Phase III Trial (30906). *J Urol* 2005 Feb;173(2):405-9. <http://www.ncbi.nlm.nih.gov/pubmed/15643181>
32. Hudson MA, Herr WH. Carcinoma in situ of the bladder. *J Urol* 1995 Mar;153(3 Pt 1):564-72. <http://www.ncbi.nlm.nih.gov/pubmed/7861485>
33. Yates DR, Brausi MA, Catto JW, et al. Treatment options available for bacillus Calmette-Guérin failure in non-muscle-invasive bladder cancer. *Eur Urol* 2012 Dec;62(6):1088-96. <http://www.ncbi.nlm.nih.gov/pubmed/22959049>
34. Solsona E, Iborra I, Dumont R, et al. The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer. *J Urol* 2000 Sep;164(3 Pt 1):685-9. <http://www.ncbi.nlm.nih.gov/pubmed/10953125>
35. Herr HW, Dalbagni G. Defining bacillus Calmette-Guerin refractory superficial bladder tumours. *J Urol* 2003 May;169(5):1706-8. <http://www.ncbi.nlm.nih.gov/pubmed/12686813>
36. Lerner SP, Tangen CM, Sucharew H, et al. Failure to achieve a complete response to induction BCG therapy is associated with increased risk of disease worsening and death in patients with high risk non muscle invasive bladder cancer. *Urol Oncol* 2009 Mar-Apr;27(2):155-9. <http://www.ncbi.nlm.nih.gov/pubmed/18367117>

6. NEOADJUVANT CHEMOTHERAPY

6.1 Introduction

The standard treatment for patients with muscle-invasive bladder cancer is radical cystectomy. However, this 'gold standard' only provides 5-year survival in about 50% of patients (1-5). In order to improve these unsatisfactory results, the use of peri-operative chemotherapy has been explored since the 1980s. There are many advantages of administering chemotherapy before planned definitive surgery (or radiation therapy) to patients with operable urothelial carcinoma of the urinary bladder, muscle-invasive, clinically negative nodes (cN0), including:

- Chemotherapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low.
- Potential reflection of in-vivo chemosensitivity.
- Tolerability of chemotherapy is expected to be better before cystectomy rather than after.
- Hypothetically patients with micrometastatic disease might respond to neoadjuvant therapy and reveal a favourable pathological status, determined mainly by negative lymph node status and negative surgical margins.

6.2 The role of imaging to assess treatment response

For patients who respond to neoadjuvant chemotherapy, known as responders, and especially those who show a complete response (pT0 N0), neoadjuvant chemotherapy has a major impact on overall survival (OS) (6). The overtreatment of non-responders and patients in the non-target population (i.e. patients without micrometastatic disease) are major drawbacks of neoadjuvant chemotherapy. The best option is early pre-operative identification of responders utilizing tumour molecular profiling in TUR-specimens, but there is still a lack of reliable methods for clinical use (7). Alternatively, some investigators are exploring imaging methods for the early identification of responders at the time of treatment cycles.

A small pilot study, using PET imaging to monitor response to chemotherapy, suggested that alterations in tumour metabolism occur long before visible changes appear on CT or MRI (8).

In a recent retrospective evaluation of 27 patients undergoing total or partial cystectomy after neoadjuvant chemotherapy (n = 8), neoadjuvant chemoradiation (n = 10), or no neoadjuvant therapy (n = 9), tumour stage assessed by MRI was only consistent with post-cystectomy pathology findings in 59.3 % of the patients (9).

Another study evaluated conventional vs. fast dynamic contrast-enhanced MRI before and after 2, 4 and 6 cycles of MVAC (10). Only 9 of 22 patients subsequently underwent cystectomy. After two MVAC cycles, the

accuracy, sensitivity, and specificity of conventional MRI in distinguishing responders from non-responders were 73%, 79%, and 63%, respectively. With the dynamic technique, these figures were 95%, 93%, and 100%, respectively. The differences were not significant. The authors concluded that after two cycles, dynamic MRI helped detect 13 of 14 responders and eight of eight non-responders.

Finally, the application of results from the imaging of treatment responses in the adjuvant (metastatic) setting to the neoadjuvant setting should be done with caution. Finding robust and reproducible methods of imaging, early in the selection process for neoadjuvant chemotherapy, remains challenging.

In the adjuvant setting, present metastatic marker lesions are evaluated that allow testing of different and new imaging response criteria (11), while in the neoadjuvant setting the only marker lesion is the primary tumour itself. Tumour size measurement prior to and during neoadjuvant chemotherapy should be done to identify responders and non-responders.

Attempts have been made in small published series to identify responders while monitoring patients undergoing neoadjuvant chemotherapy, suggesting that the response after two cycles of neoadjuvant chemotherapy is related to outcome, but firm conclusions cannot yet be made (8,9).

The meaning of stable disease after two cycles of neoadjuvant chemotherapy is unknown. To identify progression during neoadjuvant chemotherapy imaging is being used, notwithstanding the lack of published data to support its efficacy.

6.2.1 Conclusions and recommendation

Conclusions	LE
Overtreatment of non-responders and those in the non-target population (i.e. patients without micrometastatic disease) is a major drawback in using neoadjuvant chemotherapy.	
Neoadjuvant treatment of responders and especially patients who show complete response (pT0 N0) has a major impact on overall survival.	2

Recommendations
In case of progression under neoadjuvant chemotherapy, this treatment should be discontinued.

6.3 Disadvantages of neoadjuvant chemotherapy

The disadvantages of neoadjuvant chemotherapy are:

- Clinical staging using CT or MR imaging may often result in over- and understaging and has a staging accuracy of only 70% (12,13). Overtreatment is the possible negative consequence.
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy (14,15).

The side effects of neoadjuvant chemotherapy affecting the outcome of surgical morbidity need to be considered. In one randomised trial (16), the same distribution of post-operative complications grade 3-4 was seen in both trial arms (16). In the combined Nordic trials NCS1 + NCS2, (n = 620), neoadjuvant chemotherapy did not have any major adverse effect on the percentage of performable cystectomies. In the intention-to-treat analysis, the cystectomy-frequency was 86% in the experimental arm and 87% in the control arm, while 71% of patients received all three chemotherapy cycles (17).

Several randomised phase III trials investigated the question of whether or not neoadjuvant chemotherapy improved survival, with conflicting results (18-34).

Differences in trial design were mainly the type of chemotherapy (i.e. single-agent cisplatin or combination chemotherapy) and the number of cycles planned. From the statistical point of view, the studies differed in size, patient characteristics (e.g. clinical T-stages included) and the type of definitive treatment allowed (cystectomy and/or radiotherapy). Patients had to be fit for cisplatin. Because of the lack of clarity, even though a considerable number of randomised trials had been performed, three meta-analyses were undertaken to answer the very important question of whether or not neoadjuvant chemotherapy prolongs survival (35-37).

- The first meta-analysis, published in 2003 (35), included 10 randomised trials (except for results of the INT 0080-study [26]) and showed a 13% reduction in the risk of death, equivalent to 5% absolute benefit at 5 years (increased overall survival [OS] from 45% to 50%).

- The second meta-analysis, published in 2004 (36), included 11 of 16 randomised trials with OS data of 2605 patients. A statistically significant decrease in the risk of death (10%) was seen, corresponding to an absolute improvement in OS of 5% (from 50% to 55%).
- In the most recent meta-analysis, published in 2005 (38), with updated independent patient data of 11 randomised trials (3005 patients), a statistically significant survival benefit in favour of neoadjuvant chemotherapy was also seen. The results of this analysis confirmed the previously published data and showed 5% absolute improvement in survival at 5 years. The Nordic combined trial showed an absolute benefit of 8% in survival at 5 years and 11% in the clinical T3 subgroup, translating into nine patients needed to treat (17). Of note, only cisplatin combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful benefit (35,37); the regimens tested were MVA(E)C, CMV, CM, cisplatin/adriamycin, cisplatin/5-fluorouracil (5-FU), and CarboMV. To date, it is unknown if more modern chemotherapy regimens are as effective.

The updated analysis of the largest randomised phase III trial (24) with a median follow-up of 8 years confirmed the former results and provided some additional interesting findings:

- A 16% risk reduction of death.
- An improvement in 10-year survival from 30% to 36% with neoadjuvant CMV.
- No benefit for locoregional control and locoregional disease-free survival, with the addition of neoadjuvant CMV independent of the definitive treatment.

The presence of micrometastases is postulated to be lower in smaller tumours (T2) compared to more extensive tumours (T3b-T4b). T4 stage tumours are prone to a higher degree of clinical understaging because macrometastatic nodal deposits are detected more often in post-cystectomy specimens of these extensive tumours (38). Further data support the use of neoadjuvant chemotherapy in the subgroup of T2b-T3b tumours (former classification T3), which has been shown to provide a modest but substantial improvement in long-term survival and significant downstaging.

6.4 Conclusions and recommendations for neoadjuvant chemotherapy

Conclusions	LE
Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival.	1a
Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical technique, and current chemotherapy combinations.	
In current routine clinical practice, it is difficult to select patients who will respond to neoadjuvant chemotherapy due to the lack of a widely applicable test. In the future, genetic markers, in a 'personalised medicine' setting, will make it easier to select patients for treatment and to differentiate responders from non-responders.	

Recommendations	GR
Neoadjuvant chemotherapy is recommended for T2-T4a, cN0M0 bladder cancer and should always be cisplatin-based combination therapy.	A
Neoadjuvant chemotherapy is not recommended in patients with PS \geq 2 and/or impaired renal function.	B

6.5 References

1. Stein JP, Skinner DG. Radical cystectomy for invasive bladder cancer: long-term results of a standard procedure. *World J Urol* 2006 Aug;24(3):296-304.
<http://www.ncbi.nlm.nih.gov/pubmed/16518661>
2. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001 Sep;19(3):666-75.
<http://www.ncbi.nlm.nih.gov/pubmed/11157016>
3. Dalbagni G, Genega E, Hashibe M, et al. Cystectomy for bladder cancer: a contemporary series. *J Urol* 2001 Apr;165(4):1111-6.
<http://www.ncbi.nlm.nih.gov/pubmed/11257649>
4. Bassi P, Ferrante GD, Piazza N, et al. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. *J Urol* 1999 May;161(5):1494-7.
<http://www.ncbi.nlm.nih.gov/pubmed/10210380>

5. Ghoneim MA, el-Mekresh MM, el-Baz MA, et al. Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1,026 cases. *J Urol* 1997 Aug;158(2):393-9.
<http://www.ncbi.nlm.nih.gov/pubmed/9224310>
6. Rosenblatt R, Sherif A, Rintala E, et al. Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. *Eur Urol* 2012 Jun;61(6):1229-38.
<http://www.ncbi.nlm.nih.gov/pubmed/22189383>
7. Meeks JJ, Bellmunt J, Bochner BH, et al. A systematic review of neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer. *Eur Urol* 2012 Sep;62(3):523-33.
<http://www.ncbi.nlm.nih.gov/pubmed/22677572>
8. Letocha H, Ahlström H, Malmström PU, et al. Positron emission tomography with L-methyl-11C-methionine in the monitoring of therapy response in muscle-invasive transitional cell carcinoma of the urinary bladder. *Br J Urol* 1994 Dec;74(6):767-74.
<http://www.ncbi.nlm.nih.gov/pubmed/7827849>
9. Nishimura K, Fujiyama C, Nakashima K, et al. The effects of neoadjuvant chemotherapy and chemoradiation therapy on MRI staging in invasive bladder cancer: comparative study based on the pathological examination of whole layer bladder wall. *Int Urol Nephrol* 2009 Dec;41(4):869-75.
<http://www.ncbi.nlm.nih.gov/pubmed/19396568>
10. Barentsz JO, Berger-Hartog O, Witjes JA, et al. Evaluation of chemotherapy in advanced urinary bladder cancer with fast dynamic contrast-enhanced MR imaging. *Radiology* 1998 Jun;207(3):791-7.
<http://www.ncbi.nlm.nih.gov/pubmed/9609906>
11. Krajewski KM, Fougeray R, Bellmunt J, et al. Optimisation of the size variation threshold for imaging evaluation of response in patients with platinum-refractory advanced transitional cell carcinoma of the urothelium treated with vinflunine. *Eur J Cancer* 2012 Jul;48(10):1495-502.
<http://www.ncbi.nlm.nih.gov/pubmed/22176867>
12. Sternberg CN, Pansadoro V, Calabrò F, et al. Can patient selection for bladder preservation be based on response to chemotherapy? *Cancer* 2003 Apr;97(7):1644-52.
<http://www.ncbi.nlm.nih.gov/pubmed/12655521>
13. Herr HW, Scher HI. Surgery of invasive bladder cancer: is pathologic staging necessary? *Semin Oncol* 1990 Oct;17(5):590-7.
<http://www.ncbi.nlm.nih.gov/pubmed/2218571>
14. Sánchez-Ortiz RF, Huang WC, Mick R, et al. An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. *J Urol* 2003 Jan;169(1):110-5; discussion 115.
<http://www.ncbi.nlm.nih.gov/pubmed/12478115>
15. Stein JP. Contemporary concepts of radical cystectomy and the treatment of bladder cancer. *J Urol* 2003 Jan;169(1):116-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12478116>
16. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003 Aug;349(9):859-66.
<http://www.ncbi.nlm.nih.gov/pubmed/12944571>
17. Sherif A, Holmberg L, Rintala E, et al. Nordic Urothelial Cancer Group. Neoadjuvant cisplatin based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. *Eur Urol* 2004 Mar;45(3):297-303.
<http://www.ncbi.nlm.nih.gov/pubmed/15036674>
18. Wallace DM, Raghavan D, Kelly KA, et al. Neo-adjuvant (pre-emptive) cisplatin therapy in invasive transitional cell carcinoma of the bladder. *Br J Urol* 1991 Jun;67(6):608-15.
<http://www.ncbi.nlm.nih.gov/pubmed/2070206>
19. Font A, Saladie JM, Carles J, et al. Improved survival with induction chemotherapy in bladder cancer: preliminary results of a randomized trial. *Ann Oncol* 1994;5:71, abstr #355.
20. Martínez-Piñero JA, Gonzalez Martin M, Arocena F, et al. Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: a prospective randomized phase III study. *J Urol* 1995 Mar;153(3 Pt 2):964-73.
<http://www.ncbi.nlm.nih.gov/pubmed/7853584>
21. Rintala E, Hannisdahl E, Fosså SD, et al. Neoadjuvant chemotherapy in bladder cancer: a randomized study. Nordic Cystectomy Trial I. *Scand J Urol Nephrol* 1993;27(3):355-62.
<http://www.ncbi.nlm.nih.gov/pubmed/8290916>

22. Malmström PU, Rintala E, Wahlqvist R, et al. Five-year followup of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic Cystectomy Trial I. The Nordic Cooperative Bladder Cancer Study Group. *J Urol* 1996 Jun;155(6):1903-6.
<http://www.ncbi.nlm.nih.gov/pubmed/8618283>
23. [No authors listed] Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. *Lancet* 1999 Aug;354(9178):533-40.
<http://www.ncbi.nlm.nih.gov/pubmed/10470696>
24. International Collaboration of Trialists; Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group); European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group; Australian Bladder Cancer Study Group; National Cancer Institute of Canada Clinical Trials Group; Finnbladder; Norwegian Bladder Cancer Study Group; Club Urologico Espanol de Tratamiento Oncologico Group, Griffiths G, Hall R, Sylvester R, Raghavan D, Parmar MK. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *J Clin Oncol* 2011 Jun;29(16):2171-7.
<http://www.ncbi.nlm.nih.gov/pubmed/21502557>
25. Bassi P PG, Cosciani S, Lembo A, et al. Neoadjuvant M-VAC chemotherapy of invasive bladder cancer: The G.U.O.N.E. multicenter phase III trial. *Eur Urol* 1998 (Suppl);33:142,abstr 567.
26. Sherif A, Rintala E, Mestad O, et al. Nordic Urothelial Cancer Group. Neoadjuvant cisplatinmethotrexate chemotherapy for invasive bladder cancer-Nordic cystectomy trial 2. *Scand J Urol Nephrol* 2002;36(6):419-25.
<http://www.ncbi.nlm.nih.gov/pubmed/12623505>
27. Sengeløv L, von der Maase H, Lundbeck F, et al. Neoadjuvant chemotherapy with cisplatin and methotrexate in patients with muscle-invasive bladder tumours. *Acta Oncol* 2002;41(5):447-56.
<http://www.ncbi.nlm.nih.gov/pubmed/12442921>
28. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003 Aug;349(9):859-66.
<http://www.ncbi.nlm.nih.gov/pubmed/12944571>
29. Italian Bladder Cancer Study Group (GISTV). Neoadjuvant treatment for locally advanced bladder cancer: a randomized prospective clinical trial. *J Chemother* 1996;8(suppl 4):345-6.
30. Orsatti M, Curotto A, Canobbio L, et al. Alternating chemo-radiotherapy in bladder cancer: a conservative approach. *Int J Radiat Oncol Biol Phys* 1995 Aug;33(1):173-8.
<http://www.ncbi.nlm.nih.gov/pubmed/7642415>
31. Shipley WU, Winter KA, Kaufman DS, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *J Clin Oncol* 1998 Nov;16(11):3576-83.
<http://www.ncbi.nlm.nih.gov/pubmed/9817278>
32. Marcuello E TJ, Villavicencio H, Algaba F, et al. A phase III trial of neoadjuvant chemotherapy (NCT) in patients (PTS) with invasive bladder cancer (IBC). Preliminary results: NCT improves pathological complete response rate. *Eur J Cancer* 1995;31A:S241, abstr 1155.
33. Cannobio L CA, Boccardo F, Venturini M, et al. A randomized study between neoadjuvant chemoradiotherapy (CT-RT) before radical cystectomy and cystectomy alone in bladder cancer. A 6 year follow-up. *Proc Am Soc Clin Oncol* 1995;14:245, abstr 654.
34. Abol-Enein H E-MM, El Baz M, Ghoneim MA. Neo-adjuvant chemotherapy in the treatment of invasive transitional bladder cancer. A controlled prospective randomized study. *Br J Urol* 1997;79 (Suppl 4): 174.
35. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Lancet* 2003 Jun;361(9373):1927-34.
<http://www.ncbi.nlm.nih.gov/pubmed/12801735>
36. Winquist E, Kirchner TS, Segal R, et al. Genitourinary Cancer Disease Site Group, Cancer Care Ontario Program in Evidence-based Care Practice Guidelines Initiative. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. *J Urol* 2004 Feb;171(2 Pt 1):561-9.
<http://www.ncbi.nlm.nih.gov/pubmed/14713760>

37. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. *Eur Urol* 2005 Aug;48(2):202-205; discussion 205-6.
<http://www.ncbi.nlm.nih.gov/pubmed/15939524>
38. Sherif A HL, Rintala E, Mestad O, et al. Nordic Urothelial Cancer Group. Downstaging and pathoanatomical outcome following neoadjuvant cisplatin based combination chemotherapy for muscle-invasive bladder carcinoma: An analysis of selected patients from two combined randomized prospective Nordic trials. *Urology* 2006;68(Suppl 1):137, MP-1307.

7. RADICAL SURGERY AND URINARY DIVERSION

7.1 Removal of the tumour-bearing bladder

7.1.1 *Background*

Radical cystectomy is the standard treatment for localised MIBC in most countries of the Western world (1,2). Recent interest in patients' quality of life (QoL) has increased the trend toward bladder preservation treatment modalities, like radio- and/or chemotherapy (see Chapters 9 and 10). Performance status and age influence the choice of primary therapy, as well as the type of urinary diversion, with cystectomy being reserved for younger patients without concomitant disease and with a better performance status. The value of assessing overall health before recommending and proceeding with surgery was emphasised in a recent multivariate analysis (3). The analysis found an association between comorbid disease and adverse pathological and survival outcome following radical cystectomy (3). Performance status and comorbidity have a different impact on treatment outcome and must be evaluated independently (4).

Controversy remains about age, radical cystectomy and the type of urinary diversion. Cystectomy is associated with the greatest risk reduction in disease-related and non-disease-related death in patients older than 80 years (3). The largest, retrospective, single-institution study on cystectomy to date found that patients above 80 years had increased post-operative morbidity but not an increased mortality. Although some patients successfully underwent a neobladder procedure, most patients were treated with an ileal conduit diversion (5). It is particularly important to evaluate the function and QoL of elderly patients using a standardised geriatric assessment, as well as carrying out a standard medical evaluation (see Section 7.1.4) (6).

7.1.2 *Timing and delay of cystectomy*

A retrospective series of 153 patients, with a clear indication for radical surgery of locally advanced bladder cancer, found that patients treated more than 90 days after the primary diagnosis showed a significant increase in extravesical disease (81 vs 52%) (7).

The delay in cystectomy not only affects the outcome of treatment, but also the type of urinary diversion. In organ-confined urothelial cancer of the bladder, the average time from primary diagnosis to cystectomy was 12.2 months in patients who received a neobladder and 19.1 months in those who received an ileal conduit. This was even more noticeable with organ-confined invasive cancer; the average time to surgery was 3.1 months with a neobladder and 15.1 months with an ileal conduit (8). Similar results have been observed in a series of 247 patients: recurrence-free survival and OS were significantly better in patients treated before 90 days compared to others treated after 90 days (9).

7.1.3 *Indications*

Traditionally, radical cystectomy was recommended for patients with MIBC T2-T4a, N0-Nx, M0 (1). Other indications include high-risk and recurrent superficial tumours, BCG-resistant Tis, T1G3 (see Chapter 5), as well as extensive papillary disease that cannot be controlled with TUR and intravesical therapy alone.

Salvage cystectomy is indicated for non-responders to conservative therapy, recurrences after bladder-sparing treatments, non-urothelial carcinomas (these tumours respond poorly to chemo- and radiotherapy), and as a purely palliative intervention, including in fistula formation, pain or recurrent macrohaematuria (see Section 8.1 Palliative cystectomy).

7.1.4 *MIBC and comorbidity*

Complications related to radical cystectomy may be directly related to pre-existing patient comorbidities as well as the surgical procedure, the bowel anastomosis, or the urinary diversion. A significant body of literature

has evaluated the usefulness of age as a prognostic factor for radical cystectomy (10-12). Advanced age has been identified as a risk factor for complications due to radical cystectomy, although chronological age is less important than biological age. Other risk factors for morbidity include prior abdominal surgery, extravesical disease, and prior radiotherapy (13), while an increased body mass index is associated with a higher rate of wound dehiscence and hernia (14).

7.1.4.1 Evaluation of comorbidity

Rochon et al. showed that an evaluation of comorbidity provides a better indicator of life expectancy in MIBC than does the patient's age (15). The evaluation helps to identify the medical conditions likely to interfere with, or have an impact on, treatment and the evolution and prognosis of MIBC (16).

The value of assessing overall health before recommending and proceeding with surgery was emphasised by Zietman et al., who demonstrated an association between comorbidity and adverse pathological and survival outcome following radical cystectomy (17). Similar results were found for the impact of comorbidities on cancer-specific and other-cause mortalities in a population-based competing risk analysis of more than 11,260 patients from the SEER registries. Age carried the highest risk for other-cause mortality but not for increased cancer-specific death, while the stage of locally advanced tumour was the strongest predictor for decreased cancer-specific survival (18). Stratifying elderly patients according to their risk-benefit profile using a multidisciplinary approach will help to select patients most likely to benefit from radical surgery and to optimise treatment outcomes (19).

Unfortunately, most series evaluating radical cystectomy do not include indices of comorbidity in the patient evaluation.

7.1.4.2 Comorbidity scales

A range of comorbidity scales have been developed (20), six of which have been validated (LE: 3):

- CIRS (Cumulative Illness Rating Scale) (21);
- Kaplan-Feinstein index (22);
- Charlson Comorbidity Index (CCI) (23);
- ICD (Index of Coexistent Disease) (24);
- ACE-27 (25);
- Total Illness Burden Index (TIBI) (26).

The Charlson Comorbidity Index ranges from 0 to 30 according to the importance of comorbidities described in four levels and is calculated by the healthcare practitioner from the patient's medical record. The score was widely studied in patients with bladder cancer and found to be an independent prognostic factor for peri-operative mortality (27,28), overall mortality (29), and cancer-specific mortality (30-33). Only the age-adjusted version of the Charlson comorbidity index was correlated with both cancer-specific mortality and other cause-mortality (34).

The ICD evaluates 14 possible comorbidities and is also calculated from the patient's medical record.

The CIRS provides a quantification of the severity of organic disease in 14 systems and is calculated from the medical record. Nurses and doctors were shown to provide comparable calculations of CIRS (35). Although CIRS has been validated in elderly subjects (36,37), it has not been validated in bladder cancer treatment.

The Kaplan Feinstein index evaluated 12 comorbidities using a score from 0 to 3, with 0 indicating no problem, 1 indicating a light and non-chronic decompensated comorbidity, 2 indicating a significant decompensation, and 3 indicating severe decompensation. The final score of 0-3 is the highest rating given to a disease. The final score may be 3 if two or more pathologies have been given a score of 2. The healthcare practitioner calculates the Kaplan Feinstein index data from the medical record.

The TIBI evaluates the 16 diseases across 110 items. The TIBI questionnaire is completed by the patient himself. The TIBI was initially validated in a cohort of patients with type 2 diabetes. The TIBI was then correlated to the QoL, age, number of days spent in bed during the previous three months, and reduced mobility in a cohort of 1,638 men with a prostate cancer (38). None of the four last scales mentioned above (ICD, CIRS, Kaplan Feinstein index, TIBI) were not validated in the setting of bladder cancer treatments.

Performances of the Charlson Comorbidity Index and ACE-27 are approximately equivalent (LE: 3). The age-adjusted Charlson Comorbidity Index (Table 4) is the most widely used comorbidity index in cancer for estimating long-term survival and must be easily calculated using a specific calculator (39).

Table 4: Calculation of Charlson Comorbidity Index

Number of points	Conditions
1 point	50-60 years Myocardial infarction Heart failure Peripheral vascular insufficiency Cerebrovascular disease Dementia Chronic lung disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2 points	61-70 years Hemiplegia Moderate to severe kidney disease Diabetes with organ damage Tumours of all origins
3 points	71-80 years Moderate to severe liver disease
4 points	81-90 years
5 points	> 90 years
6 points	Metastatic solid tumours AIDS

Interpretation

1. Calculate Charlson Score or Index = i
 - a. Add comorbidity score to age score
 - b. Total denoted as 'i' in the Charlson Probability calculation (see below). i = sum of comorbidity score to age score.

2. Calculate Charlson Probability (10-year mortality)
 - a. Calculate $Y = 10^{(i \times 0.9)}$
 - b. Calculate $Z = 0.983^Y$ (where Z is the 10-year survival)

The assessment of the health of the oncology patient must be supplemented by measuring the activity level of the patient. Extermann et al. showed that there was no correlation between morbidity and competitive activity level of the patient (4). ECOG-PS scores and Karnofsky index have been validated to measure the activity level of the patient (LE: 3) (40). Performance status was correlated to patient overall survival after radical cystectomy (32,41) and palliative chemotherapies (42-44).

The ASA score has been validated to assess, prior to surgery, the risk of post-operative complications. In the bladder cancer setting, ASA scores equal to or greater than 3 were associated with major complications (45,46), particularly those related to the type of urinary diversion (Table 5) (47).

Table 5: ASA score (48).

ASA	
1.	No organic pathology or patients in whom the pathological process is localised and does not cause any systemic disturbance or abnormality.
2.	A moderate but definite systemic disturbance caused either by the condition that is to be treated or surgical intervention, or which is caused by other existing pathological processes, forms this group.
3.	Severe systemic disturbance from any cause or causes. It is not possible to state an absolute measure of severity, as this is a matter of clinical judgment.
4.	Extreme systemic disorders which have already become an imminent threat to life, regardless of the type of treatment. Because of their duration or nature, there has already been damage to the organism that is irreversible.
5.	Moribund patients not expected to survive 24 hours, with or without surgery.

According to a consensus conference of the National Institutes of Health, the aim of the Standardized Geriatric Assessment (SGA) is to discover, describe and explain the many problems of the elderly, to catalogue the resources and strengths of the elderly, to assess needs services to the individual and to develop a coordinated plan of care. The SGA is thus a medico-psycho-social index.

The SGA can be carried out by means of several protocols. These protocols differ in the completeness of diagnostic research. The protocol is the most complete Comprehensive Geriatric Assessment (CGA) (49). The CGA is suited to the care of cancer patients (50). In bladder cancer, the CGA was used to adapt gemcitabine chemotherapy in previously untreated elderly patients with advanced bladder carcinoma (51).

The Senior Adult Oncology Program proposed by Balducci et al. presents a less comprehensive evaluation than a SGA evaluation (52). Even though these protocols identified previously unrecognised geriatric medical and social problems, their usefulness is not clearly demonstrated yet. (53). Similarly, the CGA, when performed in patients in general medicine, does not alter the risk of hospitalisation or death within 2 years of the evaluation (54). To provide benefit to patients, the CGA should be associated with the management problems it identifies (55).

7.1.4.3 Conclusions and recommendations for comorbidity scales

Conclusions	LE
Chronological age is of limited relevance.	3
A comorbidity score developed in particular for assessment of patients diagnosed with bladder cancer would be most helpful.	3

Recommendations	GR
The decision regarding bladder sparing or radical cystectomy in the elderly/geriatric patient with invasive bladder cancer should be based on tumour stage and comorbidity best quantified by a validated score, such as the Charlson Comorbidity Index.	B
The ASA score does not address comorbidities and should not be used in this setting.	B

7.1.5 References

- World Health Organization (WHO) Consensus Conference in Bladder Cancer, Hautmann RE, Abol-Enein H, Hafez K, Haro I, Mansson W, Mills RD, Montie JD, Sagalowsky AI, Stein JP, Stenzl A, Studer UE, Volkmer BG. Urinary diversion. *Urology* 2007 Jan;69(1 Suppl):17-49.
<http://www.ncbi.nlm.nih.gov/pubmed/17280907>
- Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001 Feb;19(3):666-75.
<http://www.ncbi.nlm.nih.gov/pubmed/11157016>
- Miller DC, Taub DA, Dunn RL, et al. The impact of co-morbid disease on cancer control and survival following radical cystectomy. *J Urol* 2003 Jan;169(1):105-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12478114>
- Extermann M, Overcash J, Lyman GH, et al. Comorbidity and functional status are independent in older cancer patients. *J Clin Oncol* 1998 Apr;16(4):1582-7.
<http://www.ncbi.nlm.nih.gov/pubmed/9552069>
- Figueroa AJ, Stein JP, Dickinson M, et al. Radical cystectomy for elderly patients with bladder carcinoma: an updated experience with 404 patients. *Cancer* 1998 Jul;83(1):141-7.
<http://www.ncbi.nlm.nih.gov/pubmed/9655304>
- Geriatric Assessment Methods for Clinical Decision making. NIH Consens Statement Online 1987 Oct Online 19-21 [cited 2013 Feb, 6th];6(13):1-21.
<http://consensus.nih.gov/1987/1987GeriatricAssessment065html.htm>
- Chang SS, Hassan JM, Cookson MS, et al. Delaying radical cystectomy for muscle invasive bladder cancer results in worse pathological stage. *J Urol* 2003 Oct;170(4 Pt 1):1085-7.
<http://www.ncbi.nlm.nih.gov/pubmed/14501697>
- Hautmann RE, Paiss T. Does the option of the ileal neobladder stimulate patient and physician decision toward earlier cystectomy? *J Urol* 1998 Jun;159(6):1845-50.
<http://www.ncbi.nlm.nih.gov/pubmed/9598473>
- Sánchez-Ortiz RF, Huang WC, Mick R, et al. An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. *J Urol* 2003 Jan;169(1):110-5; discussion 115.
<http://www.ncbi.nlm.nih.gov/pubmed/12478115>

10. Gamé X, Soulié M, Seguin P, et al. Radical cystectomy in patients older than 75 years: assessment of morbidity and mortality. *Eur Urol* 2001 May;39(5):525-9.
<http://www.ncbi.nlm.nih.gov/pubmed/11464032>
11. Clark PE, Stein JP, Groshen SG, et al. Radical cystectomy in the elderly: comparison of clinical outcomes between younger and older patients. *Cancer* 2005 Jul 1;104(1):36-43.
<http://www.ncbi.nlm.nih.gov/pubmed/15912515>
12. May M, Fuhrer S, Braun KP, et al. Results from three municipal hospitals regarding radical cystectomy on elderly patients. *Int Braz J Urol* 2007 Nov-Dec;33(6):764-73; discussion 774-6.
<http://www.ncbi.nlm.nih.gov/pubmed/18199344>
13. Lawrentschuk N, Colombo R, Hakenberg OW, et al. Prevention and management of complications following radical cystectomy for bladder cancer. *Eur Urol* 2010 Jun;57(6):983-1001.
<http://www.ncbi.nlm.nih.gov/pubmed/20227172>
14. Novara G, De Marco V, Aragona M, et al. Complications and mortality after radical cystectomy for bladder transitional cell cancer. *J Urol* 2009 Sep;182(3):914-21.
<http://www.ncbi.nlm.nih.gov/pubmed/19616246>
15. Rochon PA, Katz JN, Morrow LA, et al. Comorbid illness is associated with survival and length of hospital stay in patients with chronic disability. A prospective comparison of three comorbidity indices. *Med Care* 1996 Nov;34(11):1093-101.
<http://www.ncbi.nlm.nih.gov/pubmed/8911426>
16. Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. *J Chronic Dis* 1970 Dec;23(7):455-468.
<http://www.sciencedirect.com/science/article/pii/0021968170900548>
17. Zietman AL, Shipley WU, Kaufman DS. Organ-conserving approaches to muscle-invasive bladder cancer: future alternatives to radical cystectomy. *Ann Med* 2000 Feb;32(1):34-42.
<http://www.ncbi.nlm.nih.gov/pubmed/10711576>
18. Lughezzani G, Sun M, Shariat SF, et al. A population-based competing-risks analysis of the survival of patients treated with radical cystectomy for bladder cancer. *Cancer* 2011 Jan 1;117(1):103-9.
<http://www.ncbi.nlm.nih.gov/pubmed/20803606>
19. Froehner M, Brausi MA, Herr HW, et al. Complications following radical cystectomy for bladder cancer in the elderly. *Eur Urol* 2009 Sep;56(3):443-54.
<http://www.ncbi.nlm.nih.gov/pubmed/19481861>
20. de Groot V, Beckerman H, Lankhorst GJ, et al. *J Clin Epidemiol* 2003 Mar;56(3):221-9. How to measure comorbidity. a critical review of available methods.
<http://www.ncbi.nlm.nih.gov/pubmed/12725876>
21. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc* 1968 May;16(5):622-6. [No abstract available].
<http://www.ncbi.nlm.nih.gov/pubmed/5646906>
22. Kaplan MH, Feinstein AR. The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. *J Chronic Dis* 1974 Sep;27(7-8):387-404. [No abstract available].
<http://www.ncbi.nlm.nih.gov/pubmed/4436428>
23. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83.
<http://www.ncbi.nlm.nih.gov/pubmed/3558716>
24. Greenfield S, Apolone G, McNeil BJ, et al. The importance of co-existent disease in the occurrence of postoperative complications and one-year recovery in patients undergoing total hip replacement. Comorbidity and outcomes after hip replacement. *Med Care* 1993 Feb;31(2):141-54.
<http://www.ncbi.nlm.nih.gov/pubmed/8433577>
25. Paleri V, Wight RG. Applicability of the adult comorbidity evaluation - 27 and the Charlson indexes to assess comorbidity by notes extraction in a cohort of United Kingdom patients with head and neck cancer: a retrospective study. *J Laryngol Otol* 2002 Mar;116(3):200-5.
<http://www.ncbi.nlm.nih.gov/pubmed/11893262>
26. Litwin MS, Greenfield S, Elkin EP, et al. Assessment of prognosis with the total illness burden index for prostate cancer: aiding clinicians in treatment choice. *Cancer* 2007 May 1;109(9):1777-83.
<http://www.ncbi.nlm.nih.gov/pubmed/17354226>
27. Mayr R, May M, Martini T, et al. Predictive capacity of four comorbidity indices estimating perioperative mortality after radical cystectomy for urothelial carcinoma of the bladder. *BJU Int* 2012 Sep;110(6 Pt B):E222-7.
<http://www.ncbi.nlm.nih.gov/pubmed/22314129>

28. Morgan TM, Keegan KA, Barocas DA, et al. Predicting the probability of 90-day survival of elderly patients with bladder cancer treated with radical cystectomy. *J Urol* 2011 Sep;186(3):829-34.
<http://www.ncbi.nlm.nih.gov/pubmed/21788035>
29. Abdollah F, Sun M, Schmitges J, et al. Development and validation of a reference table for prediction of postoperative mortality rate in patients treated with radical cystectomy: a population-based study. *Ann Surg Oncol* 2012 Jan;19(1):309-17.
<http://www.ncbi.nlm.nih.gov/pubmed/21701925>
30. Miller DC, Taub DA, Dunn RL, et al. The impact of co-morbid disease on cancer control and survival following radical cystectomy. *J Urol* 2003 Jan;169(1):105-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12478114>
31. Koppie TM, Serio AM, Vickers AJ, et al. Age-adjusted Charlson comorbidity score is associated with treatment decisions and clinical outcomes for patients undergoing radical cystectomy for bladder cancer. *Cancer* 2008 Jun;112(11):2384-92.
<http://www.ncbi.nlm.nih.gov/pubmed/18404699>
32. Bolenz C, Ho R, Nuss GR, et al. Management of elderly patients with urothelial carcinoma of the bladder: guideline concordance and predictors of overall survival. *BJU Int* 2010 Nov;106(9):1324-9.
<http://www.ncbi.nlm.nih.gov/pubmed/20500510>
33. Yoo S, You D, Jeong IG, et al. Does radical cystectomy improve overall survival in octogenarians with muscle-invasive bladder cancer? *Korean J Urol* 2011 Jul;52(7):446-51.
<http://www.ncbi.nlm.nih.gov/pubmed/21860763>
34. Mayr R, May M, Martini T, et al. Comorbidity and performance indices as predictors of cancer-independent mortality but not of cancer-specific mortality after radical cystectomy for urothelial carcinoma of the bladder. *Eur Urol* 2012 Oct;62(4):662-70.
<http://www.ncbi.nlm.nih.gov/pubmed/22534059>
35. Hudon C, Fortin M, Vanasse A. et al. Cumulative Illness Rating Scale was a reliable and valid index in a family practice context. *J Clin Epidemiol* 2005 Jun;58(6):603-8.
<http://www.ncbi.nlm.nih.gov/pubmed/15878474>
36. Nagarathnam N, Gayagay G Jr. Validation of the Cumulative Illness Rating Scale (CIRS) in hospitalized nonagenarians. *Arch Gerontol Geriatr* 2007 Jan-Feb;44(1):29-36.
<http://www.ncbi.nlm.nih.gov/pubmed/16621072>
37. Parmelee PA, Thuras PD, Katz IR, et al. Validation of the Cumulative Illness Rating Scale in a geriatric residential population. *J Am Geriatr Soc* 1995 Feb;43(2):130-7.
<http://www.ncbi.nlm.nih.gov/pubmed/7836636>
38. Stier DM, Greenfield S, Lubeck DP, et al. Quantifying comorbidity in a disease-specific cohort: adaptation of the total illness burden index to prostate cancer. *Urology* 1999 Sep;54(3):424-9.
<http://www.ncbi.nlm.nih.gov/pubmed/10475347>
39. Hall WH, Ramachandran R, Narayan S, et al. An electronic application for rapidly calculating Charlson comorbidity score. *BMC Cancer* 2004 Dec 20;4:94.
<http://www.ncbi.nlm.nih.gov/pubmed/15610554>
40. Blagden SP, Charman SC, Sharples LD, et al. Performance status score: do patients and their oncologists agree? *Br J Cancer* 2003 Sep 15;89(6):1022-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12966419>
41. Weizer AZ, Joshi D, Daignault S, et al. Performance status is a predictor of overall survival of elderly patients with muscle invasive bladder cancer. *J Urol* 2007 Apr;177(4):1287-93.
<http://www.ncbi.nlm.nih.gov/pubmed/17382715>
42. Logothetis CJ, Finn LD, Smith T, et al. Escalated MVAC with or without recombinant human granulocyte-macrophage colony-stimulating factor for the initial treatment of advanced malignant urothelial tumors: results of a randomized trial. *J Clin Oncol* 1995 Sep;13(9):2272-7.
<http://www.ncbi.nlm.nih.gov/pubmed/7666085>
43. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000 Sep;18(17):3068-77.
<http://www.ncbi.nlm.nih.gov/pubmed/11001674>
44. Niegisch G, Fimmers R, Siener R, et al. Prognostic factors in second-line treatment of urothelial cancers with gemcitabine and paclitaxel (German Association of Urological Oncology trial AB20/99). *Eur Urol* 2011 Nov;60(5):1087-96.
<http://www.ncbi.nlm.nih.gov/pubmed/21839579>
45. Boström PJ, Kössi J, Laato M, et al. Risk factors for mortality and morbidity related to radical cystectomy. *BJU Int* 2009 Jan;103(2):191-6.
<http://www.ncbi.nlm.nih.gov/pubmed/18671789>

46. de Vries RR, Kauer P, van Tinteren H, et al. Short-term outcome after cystectomy: comparison of two different perioperative protocols. *Urol Int* 2012;88(4):383-9.
<http://www.ncbi.nlm.nih.gov/pubmed/22433508>
47. Malavaud B, Vaessen C, Mouzin M, et al. Complications for radical cystectomy. Impact of the American Society of Anesthesiologists score. *Eur Urol* 2001 Jan;39(1):79-84.
<http://www.ncbi.nlm.nih.gov/pubmed/111173943>
48. Haynes SR, Lawler PG. An assessment of the consistency of ASA physical status classification allocation. *Anaesthesia* 1995 Mar;50(3):195-9.
<http://www.ncbi.nlm.nih.gov/pubmed/7717481>
49. Cohen HJ, Feussner JR, Weinberger M, et al. A controlled trial of inpatient and outpatient geriatric evaluation and management. *N Engl J Med* 2002 Mar 21;346(12):905-12.
<http://www.ncbi.nlm.nih.gov/pubmed/11907291>
50. Balducci L, Yates J. General guidelines for the management of older patients with cancer. *Oncology* 2000 Nov;14(11A):221-7.
<http://www.ncbi.nlm.nih.gov/pubmed/11195414>
51. Castagneto B, Zai S, Marengo D, et al. Single-agent gemcitabine in previously untreated elderly patients with advanced bladder carcinoma: response to treatment and correlation with the comprehensive geriatric assessment. *Oncology* 2004;67(1):27-32.
<http://www.ncbi.nlm.nih.gov/pubmed/15459492>
52. Balducci L, Cox CE, Greenberg H, et al. Management of Cancer in the Older Aged Person. *Cancer Control* 1994 Mar;1(2):132-137.
<http://www.ncbi.nlm.nih.gov/pubmed/10886961>
53. Miller DK, Lewis LM, Nork MJ, et al. Controlled trial of a geriatric case-finding and liaison service in an emergency department. *J Am Geriatr Soc* 1996 May;44(5):513-20.
<http://www.ncbi.nlm.nih.gov/pubmed/8617898>
54. Fletcher AE, Price GM, Ng ES, et al. Population-based multidimensional assessment of older people in UK general practice: a cluster-randomised factorial trial. *Lancet* 2004 Nov 6-12;364(9446):1667-77.
<http://www.ncbi.nlm.nih.gov/pubmed/15530627>
55. Stuck AE, Egger M, Hammer A, et al. Home visits to prevent nursing home admission and functional decline in elderly people: systematic review and meta-regression analysis. *JAMA* 2002 Feb 27;287(8):1022-8.
<http://www.ncbi.nlm.nih.gov/pubmed/11866651>

7.1.6 **Radical cystectomy - technique and extent**

Radical cystectomy also includes the dissection of regional lymph nodes. There is substantial data on the extent of lymphadenectomy. Controversies in evaluating the clinical significance of lymphadenectomy are related to two main aspects of nodal dissection: therapeutic procedure and/or staging instrument.

In the only autopsy investigation performed so far, it was shown that in 215 patients with MIBC and nodal dissemination, the frequency of metastasis was 92% in regional (perivesical or pelvic), 72% in retroperitoneal, and 35% in abdominal lymph nodes. There was also a significant correlation between nodal metastases and concomitant distant metastases ($p < 0.0001$). Approximately 47% of the patients had both nodal metastases and distant dissemination and only 12% of the patients had nodal dissemination as the sole metastatic manifestation (1).

Several localisation studies of lymphadenectomy (2-7) have demonstrated both retrospectively and prospectively that metastatic lymph nodes in bladder cancer patients are not found outside the pelvis if the pelvic lymph nodes are free of tumour.

An attempt has been made to categorise the extent of lymphadenectomy. A standard lymphadenectomy in bladder cancer patients involves the removal of all nodal tissue cranially up to, and including, the common iliac bifurcation, with the ureter being the medial border, and including the internal iliac, presacral, obturator fossa and external iliac nodes (8). An extended lymphadenectomy includes all lymph nodes in the region of the aortic bifurcation and common iliac vessels medially to the crossing ureters. The lateral borders are the genitofemoral nerves, caudally the circumflex iliac vein, the ligamentum lacunare and the lymph node of Cloquet, as well as the area described in the standard lymphadenectomy (9-11). A superextended lymphadenectomy extends cephalad to the level of the inferior mesenteric artery (12).

In order to assess how and if cancer outcomes are influenced by the different extents of lymphadenectomy for patients with clinical N0M0 MIBC, a systematic review of the literature was undertaken for comparative studies. The systematic review methodology is outlined in detail elsewhere (13). In brief, a systematic review of the literature was conducted in accordance with the PRISMA guidelines (14). Two independent reviewers

performed abstract and full text screening, data abstraction and risk of bias assessment. The results were tabulated in baseline characteristics and summary of findings tables. A narrative synthesis of the evidence was performed. Out of 1,696 abstracts retrieved and assessed, 18 studies fulfilled the review criteria and were included (15-31,31b). Of the nine studies comparing extended lymphadenectomy with standard or limited lymphadenectomy, six studies reported a survival benefit in favour of extended lymphadenectomy. Two studies compared the results of a high-volume centre performing extended lymphadenectomy vs. another high-volume centre performing a superextended lymph node dissection in patients undergoing radical cystectomy. Both studies reported no difference in regard to overall survival and cancer recurrence (31,32).

Two other reviews reported similar findings. Karl et. al. (33) concluded that a more limited field of lymph node dissection (LND) in the pelvis was associated with suboptimal staging as well as poorer outcomes compared with a standard or extended lymphadenectomy, both in patients with node-positive and node-negative disease. Svatek and colleagues (34) concluded that extended lymph node dissection (LND) with complete skeletonisation of all pelvic structures up to the mid-upper third of the common iliac vessels was superior to limited LND. However, all of these identified studies suffer from significant methodological limitations and are prone to biases, thereby compromising the quality and reliability of the evidence. Further data from ongoing randomised trials on the therapeutic impact of extent of lymphadenectomy are awaited.

It has been suggested that progression-free survival as well as OS might be correlated with the amount of lymph nodes removed during surgery, although there are no reliable data on the minimum number of lymph nodes which must be removed. Nevertheless, the probability of survival increases with the number of dissected lymph nodes (35). Removal of more than 10-15 lymph nodes has been postulated as sufficient for the evaluation of the lymph node status as well as being beneficial for OS in retrospective studies (7,36,37). The number of lymph nodes removed does, however, not appear to correlate well with the anatomic template of lymphadenectomy. Suggested explanations include variability between patients, difficulties in accurate anatomical assignment of removed lymph nodes, inter-surgeon variability, and differences in method of lymph node submission and processing (38-41).

7.1.7 Laparoscopic/robotic-assisted laparoscopic cystectomy

Laparoscopic cystectomy and robotic-assisted laparoscopic cystectomy (RALC) have been shown to be feasible both in male and female patients (42,43). Both cystectomy and lymphadenectomy have been done in small series, according to the same principles used in cystectomy and anterior exenteration for several decades now (44). However, these techniques are still experimental because of the limited number of cases reported, an absence of long-term oncological and functional outcome data, and a possible selection bias (45,46).

Laparoscopic intracorporeal construction of urinary diversion (with or without robotic assistance) has been tested in small series only (45,47,48). It is a challenging and lengthy procedure with the current technical equipment available and must therefore be regarded as experimental. Laparoscopic cystectomy and pelvic lymphadenectomy (with or without robotic assistance), with extracorporeal construction of urinary diversion, is an option for surgical treatment (LE: 3).

Laparoscopic and robot-assisted radical cystectomy data suffer from selection bias including younger patients, lower stage, and minimal comorbidities compared to most contemporary open series (49-51). This selection bias makes interpretation of peri-operative outcomes difficult.

7.2 Urinary diversion after radical cystectomy

From an anatomical standpoint, three alternatives are presently used after cystectomy:

- Abdominal diversion, such as an urethrocuteaneostomy, ileal or colonic conduit, and various forms of a continent pouch.
- Urethral diversion, which includes various forms of gastrointestinal pouches attached to the urethra as a continent, orthotopic urinary diversion (neobladder, orthotopic bladder substitution).
- Rectosigmoid diversions, such as uretero (ileo-) rectostomy.

Different types of segments of the intestinal tract have been used to reconstruct the urinary tract, including the stomach, ileum, colon, and the appendix (52). Several studies have compared certain aspects of health-related QoL, such as sexual function, urinary continence and body image, in patient cohorts with different types of urinary diversion. However, further research is needed on pre-operative tumour stage and functional situation, socioeconomic status, time interval to primary surgery, etc.

7.2.1 Preparations for surgery

For cystectomy, general preparations are necessary as for any other major pelvic and abdominal surgery. If the

urinary diversion is constructed from gastrointestinal segments, the length or size of the respective segments and their pathophysiology when storing urine must be considered (53). Despite the necessary interruption and re-anastomosis of bowel, a formal bowel preparation may not be necessary (54). Furthermore, bowel recovery time has been reduced by the use of early mobilisation, early oralisation and gastrointestinal stimulation with metoclopramide and chewing gum (55).

Patients undergoing continent urinary diversion have to be motivated both to learn about their diversion and to be manually skilful in manipulating their diversion. Contraindications to more complex forms of urinary diversion include:

- debilitating neurological and psychiatric illnesses;
- limited life expectancy;
- impaired liver or renal function;
- transitional cell carcinoma of the urethral margin or other surgical margins.

Relative contraindications specific for an orthotopic neobladder are high-dose pre-operative radiation therapy, complex urethral stricture disease, and severe urethral sphincter-related incontinence (56-58).

7.2.1.1 Patient selection for orthotopic diversion

Radical cystectomy and urinary diversion are the two steps of one operation. However, the literature uniformly reports the complications of radical cystectomy, while ignoring the fact that most complications are diversion-related (59). Age alone is not a criterion for offering continent diversion (60,61). Medical comorbidities, cardiac and pulmonary function and cognitive function are all important factors that should be considered, along with the patient's social support and patient preference.

7.2.2 Ureterocutaneostomy

Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. It is considered as a safe procedure. It is therefore preferred in older, or otherwise compromised, patients, who need a supravescical diversion (62,63). However, others have demonstrated that, in carefully selected elderly patients, all other forms of wet and dry urinary diversions, including orthotopic bladder substitutions, are possible (64).

Technically, either one ureter, to which the other shorter one is attached end-to-side, is connected to the skin (transuretero-ureterocutaneostomy) or both ureters are directly anastomosed to the skin. Due to the smaller diameter of the ureters, stoma stenosis has been observed more often than in intestinal stomas (62).

In a recent retrospective comparison with short or median follow-up of 16 months, the diversion-related complication rate was considerably lower for ureterocutaneostomy compared to an ileal or colon conduit (65). Despite the limited comparative data available, however, it has to be taken into consideration that older data and clinical experience suggest stricturing on skin level and ascending UTI are more frequent complications in comparison to an ileal conduit diversion. In a retrospective study comparing various forms of intestinal diversion, ileal conduits had fewer late complications than continent abdominal pouches or orthotopic neobladders (66).

7.2.3 Ileal conduit

The ileal conduit is still an established option with well-known/predictable results. However, up to 48% of patients develop early complications including UTIs, pyelonephritis, uretero-ileal leakage and stenosis (66). The main complications in long-term follow-up studies are stomal complications in up to 24% of cases and functional and/or morphological changes of the upper urinary tract in up to 30% (67-69). An increase in complications was seen with increased follow-up in the Berne series of 131 patients followed for a minimum of 5 years (median follow-up 98 months) (67): the rate of complications increased from 45% at 5 years to 94% in those surviving longer than 15 years. In the latter group, 50% of patients developed upper urinary tract changes and 38% developed urolithiasis.

7.2.4 Continent cutaneous urinary diversion

A low-pressure detubularised ileal reservoir can be used as a continent cutaneous urinary diversion for self-catheterisation; gastric, ileocecal and sigma pouches have also been described (70-72). Different antireflux techniques can be used (73). Most patients have a well-functioning reservoir with day-time and night-time continence approaching 93% (74). A stomal stenosis in 23.5% of patients with an appendix stoma and 15% with an efferent intussuscepted ileal nipple was observed in a study, reviewing retrospectively the results of more than 800 patients. Stone formation in the pouch occurred in 10% of patients (74-76). In a small series of previously irradiated female patients, incontinence and stomal stenosis was 18% (8/44 patients) (77).

7.2.5 **Ureterocolonic diversion**

The oldest and most common form was primarily a refluxive and later an antirefluxive connection of ureters into the intact rectosigmoideum (uretero [recto] sigmoidostomy) (78,79). Most indications for this procedure have become obsolete due to a high incidence of upper urinary tract infections and the long-term risk of developing colon cancer (80,81). Bowel frequency and urge incontinence were additional side-effects of this type of urinary diversion. However, it may be possible to circumvent the above-mentioned problems by interposing a segment of ileum between ureters and rectum or sigmoid in order to augment capacity and to avoid direct contact between the urothelium and colonic mucosa as well as faeces and urine (82).

7.2.6 **Orthotopic neobladder**

An orthotopic bladder substitution to the urethra is now commonly used both in men and women. Contemporary reports document the safety and long-term reliability of this procedure. In several large centres, this has become the diversion of choice for most patients undergoing cystectomy (58,83,84). In elderly patients (> 80 years), however, it is very rarely performed, even in high-volume expert centres (85,86).

The terminal ileum is the gastrointestinal segment most often used for bladder substitution and there is less experience with ascending colon, including caecum, and the sigmoid (83). The emptying of the reservoir anastomosed to the urethra requires abdominal straining, intestinal peristalsis and sphincter relaxation. Early and late morbidity in up to 22% of the patients is reported (87,88). Long-term complications include diurnal (8-10%) and nocturnal incontinence (20-30%), ureterointestinal stenosis (3-18%), urinary retention (4-12%) both in males and female patients, metabolic disorders and vitamin B12 deficiency in series with 1054 and more than 1300 patients (58,89). In a recent study, which compared cancer control and the patterns of disease recurrence in neobladder and conduit patients, no cancer-specific survival difference could be identified between the two groups when adjusting for pathological stage (90). Urethral recurrence in neobladder patients seems rare (1.5-7% for both male and female patients) (58,91). These results indicate that the choice of a neobladder both in male and female patients does not compromise the oncological outcome of cystectomy. It remains debatable whether a neobladder is better for QoL compared to a non-continent urinary diversion (92-94).

Various forms of upper tract reflux protection, including a simple isoperistaltic tunnel, an ileal intussusception, a tapered ileal prolongation implanted subserosally, and a direct (sub)mucosal or subserosal ureteral implantation, have been described (76,88). According to the reported long-term results, the upper urinary tract is protected sufficiently by either method.

In conclusion, standard radical cystectomy in male patients with bladder neoplasms includes removal of the entire bladder, prostate, seminal vesicles, distal ureters (length of the segment undefined), and corresponding lymph nodes (extent undefined) (LE: 2b). Currently, it is not possible to recommend a particular type of urinary diversion. However, most institutions will prefer ileal orthotopic neobladders and ileal conduits based on clinical experience (95,96). In selected patients, ureterocutaneostomy is surgically the least burdensome type of diversion (LE: 3). Recommendations related to radical cystectomy and urinary diversions are listed in section 7.6.2.

7.3 **Morbidity and mortality**

In a recent comprehensive long-term study (n = 1054), peri-operative mortality was reported in 3% of cases, and early complications, defined as any complication within 3 months of surgery, in 28% (84,89). Late morbidity is usually due to the type of urinary diversion (see above). Early morbidity associated with radical cystectomy for NMIBC (at high risk for disease progression) is similar and not less than that associated with muscle-invasive tumours (97). In general, a lower morbidity and mortality has been observed by surgeons and by hospitals with a higher case load and therefore more experience (98).

7.4 **Survival**

Research findings have demonstrated good survival outcomes:

- According to a multi-institutional database of 888 consecutive patients undergoing cystectomy and lymphadenectomy for bladder cancer, the outcome at 5 years was 58% for a mean recurrence-free survival and 66% for bladder cancer-specific survival (99).
- The recurrence-free and OS in a large single centre study of 1054 male and female patients was 68% and 66% at 5 years and 60% and 43%, at 10 years, respectively (100).
- In node-positive patients, another study reported that 10-year disease-specific and OS rates were 27.7% and 20.9%, respectively (148). In this cohort, 10-year disease-specific and OS rates were 72.9% vs. 49.1% for organ-confined disease (defined as \leq pT3a), and 33.3% vs. 22.8% for non-organ-confined disease (101).
- In another study, 5-year recurrence-free survival was 76% in patients with pT1 tumours, 74% for

pT2, 52% in pT3, and 36% in pT4 tumours (102). Tumour stage and nodal involvement are the only independent predictors of survival (103).

7.5 Conclusions for radical cystectomy and urinary diversion

Conclusions	LE
For MIBC radical cystectomy is the curative treatment of choice.	3
A higher case load reduces morbidity and mortality of cystectomy.	3
Radical cystectomy includes removal of regional lymph nodes.	3
There are data to support that an extended LND (vs. a standard or limited LND) improves survival after radical cystectomy.	3
Radical cystectomy in both sexes must not include the removal of the entire urethra in all cases, which may then serve as outlet for an orthotopic bladder substitution. The terminal ileum and colon are the intestinal segments of choice for urinary diversion.	3
The type of urinary diversion does not affect oncological outcome.	3
Laparoscopic and robotic-assisted laparoscopic cystectomy is feasible but still investigational.	3
In patients older than 80 years with MIBC, cystectomy is an option.	3
Surgical outcome is influenced by comorbidity, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volumes of cystectomy, and type of urinary diversion.	2
Surgical complications of cystectomy and urinary diversion should be reported in a uniform grading system. Currently, the best-adapted, graded system for cystectomy is the Clavien grading system.	2

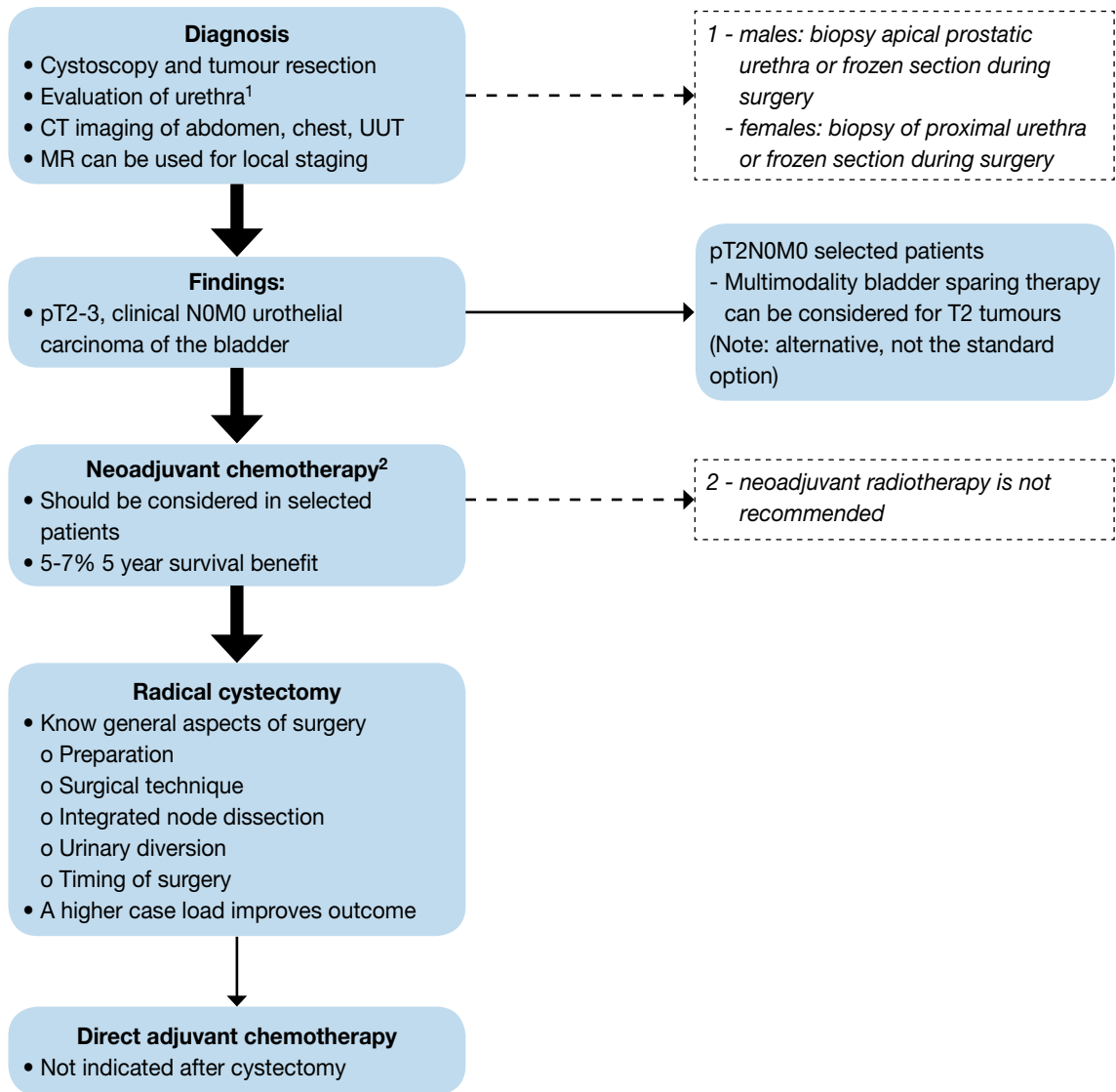
7.6 Recommendations for radical cystectomy and urinary diversion

Recommendations	GR
Radical cystectomy is recommended in T2-T4a, N0 M0, and high-risk non-muscle-invasive bladder cancer (as outlined above).	A*
Do not delay cystectomy more than 3 months since it increases the risk of progression and cancer-specific death.	B
Pre-operative radiotherapy is not recommended in subsequent cystectomy with urinary diversion.	A
Lymph node dissection should be an integral part of cystectomy. An extended LND is recommended.	B
The urethra can be preserved if margins are negative. If no bladder substitution is attached, the urethra must be checked regularly.	B
Laparoscopic and robot-assisted laparoscopic cystectomy are both management options. However, current data have not sufficiently proven the advantages or disadvantages for both oncological and functional outcomes of laparoscopic and robotic-assisted laparoscopic cystectomy.	C
Before cystectomy, the patient should be fully informed about the benefits and potential risks of all possible alternatives, and the final decision should be based on a balanced discussion between patient and surgeon.	B
Pre-operative bowel preparation is not mandatory. 'Fast track' measurements may reduce the time of bowel recovery.	C
An orthotopic bladder substitute should be offered to male and female patients lacking any contraindications and who have no tumour in the urethra and at the level of urethral dissection.	B

LND = lymph node dissection.

*Upgraded following EAU Working Panel consensus.

Figure 1: Flowchart for the management for T2-T4a N0M0 urothelial bladder cancer



7.7 References

1. Wallmeroth A, Wagner U, Moch H, et al. Patterns of metastasis in muscle-invasive bladder cancer (pT2-4): An autopsy study on 367 patients. *Urol Int* 1999;62(2):69-75. <http://www.ncbi.nlm.nih.gov/pubmed/10461106>
2. Jensen JB, Uihøi BP, Jensen KM. Lymph node mapping in patients with bladder cancer undergoing radical cystectomy and lymph node dissection to the level of the inferior mesenteric artery. *BJU Int* 2010 Jul;106(2):199-205. <http://www.ncbi.nlm.nih.gov/pubmed/20002670>
3. Vazina A, Dugi D, Shariat SF, et al. Stage specific lymph node metastasis mapping in radical cystectomy specimens. *J Urol* 2004 May;171(5):1830-4. <http://www.ncbi.nlm.nih.gov/pubmed/15076287>
4. Leissner J, Ghoneim MA, Abol-Enein H, et al. Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. *J Urol* 2004 Jan;171(1):139-44. <http://www.ncbi.nlm.nih.gov/pubmed/14665862>
5. Roth B, Wissmeyer MP, Zehnder P, et al. A new multimodality technique accurately maps the primary lymphatic landing sites of the bladder. *Eur Urol* 2010 Feb;57(2):205-11. <http://www.ncbi.nlm.nih.gov/pubmed/19879039>
6. Ghoneim MA, Abol-Enein H. Lymphadenectomy with cystectomy: is it necessary and what is its extent? *Eur Urol* 2004 Oct;46(4):457-61. <http://www.ncbi.nlm.nih.gov/pubmed/15363560>

7. Fleischmann A, Thalmann GN, Markwalder R, et al. Extracapsular extension of pelvic lymph node metastases from urothelial carcinoma of the bladder is an independent prognostic factor. *J Clin Oncol* 2005 Apr;23(10):2358-65.
<http://www.ncbi.nlm.nih.gov/pubmed/15800327>
8. Mills RD, Fleischmann A, Studer UE. Radical cystectomy with an extended pelvic lymphadenectomy: rationale and results. *Surg Oncol Clin N Am* 2007 Jan;16(1):233-45.
<http://www.ncbi.nlm.nih.gov/pubmed/17336246>
9. Stein JP. The role of lymphadenectomy in patients undergoing radical cystectomy for bladder cancer. *Curr Oncol Rep* 2007 May;9(3):213-21.
<http://www.ncbi.nlm.nih.gov/pubmed/17430693>
10. Schilling D, Horstmann M, Nagele U, et al. Cystectomy in women. *BJU Int* 2008 Nov;102(9 Pt B):1289-95
<http://www.ncbi.nlm.nih.gov/pubmed/19035894>
11. Abol-Enein H, El-Baz M, Abd El-Hameed MA, et al. Lymph node involvement in patients with bladder cancer treated with radical cystectomy: a patho-anatomical study--a single center experience. *J Urol* 2004 Nov;172(5 Pt 1):1818-21.
<http://www.ncbi.nlm.nih.gov/pubmed/15540728>
12. Zlotta AR. Limited, extended, superextended, megaextended pelvic lymph node dissection at the time of radical cystectomy: what should we perform? *Eur Urol* 2012 Feb;61(2):243-4.
<http://www.ncbi.nlm.nih.gov/pubmed/22119158>
13. Bruins M, Veskimaie E, Hernandez V, Imamura M, Stewart F, Lam T, Neuberger M, Dahm P, Witjes F, N'Dow J. Systematic review of role and extent of lymphadenectomy during radical cystectomy for cN0M0 muscle invasive bladder cancer: Methods protocol (EAU MIBC Guideline 2013 update).
http://www.uroweb.org/gls/refs/Systematic_methodology_Bladder_Cancer_2013_update.pdf
14. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(6): e1000097.
doi:10.1371/journal.pmed1000097
15. Brössner C, Pycha A, Toth A, et al. Does extended lymphadenectomy increase the morbidity of radical cystectomy? *BJU Int* 2004 Jan;93(1):64-6.
<http://www.ncbi.nlm.nih.gov/pubmed/14678370>
16. Dhar NB, Klein EA, Reuther AM, et al. Outcome after radical cystectomy with limited or extended pelvic lymph node dissection. *J Urol* 2008 Mar;179(3):873-78.
<http://www.ncbi.nlm.nih.gov/pubmed/18221953>
17. Finelli A, Gill IS, Desai MM, et al. Laparoscopic extended pelvic lymphadenectomy for bladder cancer: technique and initial outcomes. *J Urol* 2004 Nov;172(5 Pt 1):1809-12.
<http://www.ncbi.nlm.nih.gov/pubmed/15540725>
18. Holmer M, Bendahl PO, Davidsson T, et al. Extended lymph node dissection in patients with urothelial cell carcinoma of the bladder: can it make a difference? *World J Urol* 2009 Aug;27(4):521-6.
<http://www.ncbi.nlm.nih.gov/pubmed/19145436>
19. Poulsen AL, Horn T, Steven K. Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. *J Urol* 1998 Dec;160(6 Pt 1):215-9.
<http://www.ncbi.nlm.nih.gov/pubmed/9817313>
20. Jensen JB, Ulhøi BP, Jensen K. Extended versus limited lymph node dissection in radical cystectomy: Impact on recurrence pattern and survival. *Int J Urol* 2012 Jan;19(1):39-47.
<http://www.ncbi.nlm.nih.gov/pubmed/22050425>
21. Abd El-Latif A, Miocinovic R, Stephenson AJ. Impact of extended (E) versus standard lymph node dissection (SLND) on post-cystectomy survival (PCS) among patients with LN-negative urothelial bladder cancer (UBC). *J Urol* 2011;(185, No. 4S, Suppl):abstract #1896.
22. Abd El-Latif A, Miocinovic R, Stephenson AJ. Impact of extended versus standard lymph node dissection on overall survival among patients with urothelial cancer of bladder. *J Urol* 2012 May;187 S4 Suppl, abstract # 1752.
23. Abol-Enein H, Tilki D, Mosbah A. Does the extent of lymphadenectomy in radical cystectomy for bladder cancer influence disease-free survival? A Prospective Single-Center Study. *Eur Urol* 2011 Sep;60(3):572-7.
<http://www.ncbi.nlm.nih.gov/pubmed/21684070>
24. Dharaskar A, Kumar V, Kapoor R, et al. Does extended lymph node dissection affect the lymph node density and survival after radical cystectomy? *Indian J Cancer* 2011 April-June; 48,(2):230-3.
<http://www.ncbi.nlm.nih.gov/pubmed/21768672>

25. Simone G, Papalia R, Ferriero M, et al. Stage-specific impact of extended versus standard pelvic lymph node dissection in radical cystectomy. *Int J Urol* 2012 Sep 12. doi: 10.1111/j.1442-2042.2012.03148.x. [Epub ahead of print]
<http://www.ncbi.nlm.nih.gov/pubmed/22970939>
26. Zehnder P, Studer UE, Skinner EC, et al. Super Extended Versus Extended Pelvic Lymph Node Dissection in Patients Undergoing Radical Cystectomy for Bladder Cancer: A Comparative Study. *J Urol* 2011 Oct;186(4):1261-8.
<http://www.ncbi.nlm.nih.gov/pubmed/21849183>
27. Abdollah F, Sun M, Schmitges J, et al. Stage-specific impact of pelvic lymph node dissection on survival in patients with non-metastatic bladder cancer treated with radical cystectomy. *BJU Int* 2012 Apr;109(8):1147-54.
<http://www.ncbi.nlm.nih.gov/pubmed/21883849>
28. Liu JJ, Leppert J, Shinghal R. Practice patterns of pelvic lymph node dissection for radical cystectomy from the veterans affairs central cancer registry (VACCR). *J Urol* 2011 May; 185 (4S, Suppl), abstract #1404.
29. Isaka S, Okano T, Sato N, et al. [Pelvic lymph node dissection for invasive bladder cancer]. *Nihon Hinyokika Gakkai Zasshi* 1989 Mar;80(3):402-6. [Article in Japanese].
<http://www.ncbi.nlm.nih.gov/pubmed/2733302>
30. Miyakawa M, Oishi K, Okada Y, et al. [Results of the multidisciplinary treatment of invasive bladder cancer]. *Kinyokika Kiyō* 1986 Dec;32(12):1931-9. [Article in Japanese]
<http://www.ncbi.nlm.nih.gov/pubmed/3825830>
31. Simone G, Eneim HA, Ferreiro M, et al. Extended versus super-extended PLND during radical cystectomy: comparison of two prospective series. *J Urol* 2012 May;(187 4S Suppl):e708, abstract #1755.
- 31b. Bostrom PJ, Mirtti T, Nurmi M, et al. Extended lymphadenectomy and chemotherapy offer survival advantage in muscle-invasive bladder cancer. Abstracts of the 2011 AUA Annual meeting. *J Urol* 2011.
32. Zehnder P, Studer UE, Skinner EC, et al. Super extended versus extended pelvic lymph node dissection in patients undergoing radical cystectomy for bladder cancer: a comparative study. *J Urol* 2011 Oct;186(4):1261-8.
<http://www.ncbi.nlm.nih.gov/pubmed/21849183>
33. Karl A, Carroll PR, Gschwend JE, et al. The impact of lymphadenectomy and lymph node metastasis on the outcomes of radical cystectomy for bladder cancer. *Eur Urol* 2009 Apr;55(4):826-35.
<http://www.ncbi.nlm.nih.gov/pubmed/19150582>
34. Svatek R, Zehnder P. Role and extent of lymphadenectomy during radical cystectomy for invasive bladder cancer. *Curr Urol Rep* 2012 Apr;13(2):115-21.
<http://www.ncbi.nlm.nih.gov/pubmed/22328190>
35. Koppie TM, Vickers AJ, Vora K, Dalbagni G, Bochner BH: Standardization of pelvic lymphadenectomy performed at radical cystectomy: can we establish a minimum number of lymph nodes that should be removed? *Cancer* 2006 Nov;107(10):2368-74.
<http://www.ncbi.nlm.nih.gov/pubmed/17041887>
36. Wright JL, Lin DW, Porter MP. The association between extent of lymphadenectomy and survival among patients with lymph node metastases undergoing radical cystectomy. *Cancer* 2008 Jun;112(11):2401-8.
<http://www.ncbi.nlm.nih.gov/pubmed/18383515>
37. Studer UE, Collette L. Morbidity from pelvic lymphadenectomy in men undergoing radical prostatectomy. *Eur Urol* 2006 Nov;50(5):887-9; discussion 889-92.
<http://www.ncbi.nlm.nih.gov/pubmed/16956714>
38. Davies JD, Simons CM, Ruhotina N, et al. Anatomic basis for lymph node counts as measure of lymph node dissection extent: a cadaveric study. *Urology* 2013 Feb;81(2):358-63.
<http://www.ncbi.nlm.nih.gov/pubmed/23374802>
39. Parkash V, Bifulco C, Feinn R, et al. To count and how to count, that is the question: interobserver and intraobserver variability among pathologists in lymph node counting. *Am J Clin Pathol* 2010 Jul;134(1):42-9.
<http://www.ncbi.nlm.nih.gov/pubmed/20551265>
40. Pagano F, Bassi P, Galetti TP, et al. Results of contemporary radical cystectomy for invasive bladder cancer: a clinicopathological study with an emphasis on the inadequacy of the tumor, nodes and metastases classification. *J Urol* 1991 Jan;145(1):45-50.
<http://www.ncbi.nlm.nih.gov/pubmed/1984097>

41. Stein JP, Penson DF, Cai J, et al. Radical cystectomy with extended lymphadenectomy: evaluating separate package versus en bloc submission for node positive bladder cancer. *J Urol* 2007 Mar;177(3):876-81
<http://www.ncbi.nlm.nih.gov/pubmed/17296365>
42. Chade DC, Laudone VP, Bochner BH, et al. Oncological outcomes after radical cystectomy for bladder cancer: open versus minimally invasive approaches. *J Urol* 2010 Mar;183(3):862-69.
<http://www.ncbi.nlm.nih.gov/pubmed/20083269>
43. Kasraeian A, Barret E, Cathelineau X, et al. Robot-assisted laparoscopic cystoprostatectomy with extended pelvic lymphadenectomy, extracorporeal enterocystoplasty, and intracorporeal enterourethral anastomosis: Initial Montsouris experience. *J Endourol* 2010 Mar;24(3):409-13.
<http://www.ncbi.nlm.nih.gov/pubmed/20218885>
44. Schumacher MC, Jonsson MN, Wiklund NP. Does extended lymphadenectomy preclude laparoscopic or robot-assisted radical cystectomy in advanced bladder cancer? *Curr Opin Urol* 2009 Sep;19(5):527-32.
<http://www.ncbi.nlm.nih.gov/pubmed/19553823>
45. Hautmann RE. The oncologic results of laparoscopic radical cystectomy are not (yet) equivalent to open cystectomy. *Curr Opin Urol* 2009 Sep;19(5):522-6.
<http://www.ncbi.nlm.nih.gov/pubmed/19550335>
46. Ng CK, Kauffman EC, Lee MM, et al. A comparison of postoperative complications in open versus robotic cystectomy. *Eur Urol* 2010 Feb;57(2):274-81.
<http://www.ncbi.nlm.nih.gov/pubmed/19560255>
47. Pruthi RS, Nix J, McRackan D, et al. Robotic-assisted laparoscopic intracorporeal urinary diversion. *Eur Urol* 2010;57:1013-21.
<http://www.ncbi.nlm.nih.gov/pubmed/20079567>
48. Haber GP, Campbell SC, Colombo JR, et al. Perioperative outcomes with laparoscopic radical cystectomy: "pure laparoscopic" and "open-assisted laparoscopic" approaches. *Urology* 2007 Nov;70(5):910-5.
<http://www.ncbi.nlm.nih.gov/pubmed/18068447>
49. Hautmann RE. The oncologic results of laparoscopic radical cystectomy are not (yet) equivalent to open cystectomy. *Curr Opin Urol* 2009 Sep;19(5):522-6.
<http://www.ncbi.nlm.nih.gov/pubmed/19550335>
50. Pruthi RS, Nielsen ME, Nix J, et al. Robotic radical cystectomy for bladder cancer: surgical and pathological outcomes in 100 consecutive cases. *J Urol* 2010 Feb;183(2):510-4.
<http://www.ncbi.nlm.nih.gov/pubmed/20006884>
51. Cha EK, Wiklund NP, Scherr DS. Recent advances in robot-assisted radical cystectomy. *Curr Opin Urol* 2011 Jan;21(1):65-70.
<http://www.ncbi.nlm.nih.gov/pubmed/21171200>
52. Stenzl A. Bladder substitution. *Curr Opin Urol* 1999 May;9(3):241-5.
<http://www.ncbi.nlm.nih.gov/pubmed/10726098>
53. Madersbacher S, Studer UE. Contemporary cystectomy and urinary diversion. *World J Urol* 2002 Aug;20(3):151-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12196898>
54. Pruthi RS, Nielsen M, Smith A, et al. Fast track program in patients undergoing radical cystectomy: results in 362 consecutive patients. *J Am Coll Surg* 2010 Jan;210(1):93-9.
<http://www.ncbi.nlm.nih.gov/pubmed/20123338>
55. Kouba EJ, Wallen EM, Pruthi RS. Gum chewing stimulates bowel motility in patients undergoing radical cystectomy with urinary diversion. *Urology* 2007 Dec;70(6):1053-6.
<http://www.ncbi.nlm.nih.gov/pubmed/18158012>
56. Tanrikut C, McDougal WS. Acid-base and electrolyte disorders after urinary diversion. *World J Urol* 2004 Sep;22(3):168-71.
<http://www.ncbi.nlm.nih.gov/pubmed/15290206>
57. Farnham SB, Cookson MS. Surgical complications of urinary diversion. *World J Urol* 2004 Sep;22(3):157-67.
<http://www.ncbi.nlm.nih.gov/pubmed/15316737>
58. Hautmann RE, Volkmer BG, Schumacher MC, et al. Long-term results of standard procedures in urology: the ileal neobladder. *World J Urol* 2006 Aug;24(3):305-14.
<http://www.ncbi.nlm.nih.gov/pubmed/16830152>
59. Hautmann RE, de Petriconi RC, Volkmer BG. Lessons learned from 1,000 neobladders: the 90-day complication rate. *J Urol* 2010 Sep;184(3):990-4; quiz 1235.
<http://www.ncbi.nlm.nih.gov/pubmed/20643429>

60. Hautmann RE, Volkmer BG, Schumacher MC, et al. Long-term results of standard procedures in urology: the ileal neobladder. *World J Urol* 2006 Aug;24(3):305-14.
<http://www.ncbi.nlm.nih.gov/pubmed/16830152>
61. Stein JP, Ginsberg DA, Skinner DG. Indications and technique of the orthotopic neobladder in women. *Urol Clin North Am* 2002 Aug;29(3):725-34.
<http://www.ncbi.nlm.nih.gov/pubmed/12476536>
62. Deliveliotis C, Papatsoris A, Chrisofos M, et al. Urinary diversion in high-risk elderly patients: modified cutaneous ureterostomy or ileal conduit? *Urology* 2005 Aug;66(2):299-304.
<http://www.ncbi.nlm.nih.gov/pubmed/16040096>
63. Kilciler M, Bedir S, Erdemir F, et al. Comparison of ileal conduit and transureteroureterostomy with ureterocutaneostomy urinary diversion. *Urol Int* 2006;77(3):245-50.
<http://www.ncbi.nlm.nih.gov/pubmed/17033213>
64. Figueroa AJ, Stein JP, Dickinson M, et al. Radical cystectomy for elderly patients with bladder carcinoma: an updated experience with 404 patients. *Cancer* 1998 Jul;83(1):141-7.
<http://www.ncbi.nlm.nih.gov/pubmed/9655304>
65. Pycha A, Compoj E, Martini T, et al. Comparison of complications in three incontinent urinary diversions. *Eur Urol* 2008 Oct;54:825-32.
<http://www.ncbi.nlm.nih.gov/pubmed/18502026>
66. Nieuwenhuijzen JA, de Vries RR, Bex A, et al. Urinary diversions after cystectomy: the association of clinical factors, complications and functional results of four different diversions. *Eur Urol* 2008 Apr;53: 834-42; discussion 842-4.
<http://www.ncbi.nlm.nih.gov/pubmed/17904276>
67. Madersbacher S, Schmidt J, Eberle JM, et al. Long-term outcome of ileal conduit diversion. *J Urol* 2003 Mar;169(3):985-90.
<http://www.ncbi.nlm.nih.gov/pubmed/12576827>
68. Wood DN, Allen SE, Hussain M, et al. Stomal complications of ileal conduits are significantly higher when formed in women with intractable urinary incontinence. *J Urol* 2004 Dec;172(6 Pt 1):2300-3.
<http://www.ncbi.nlm.nih.gov/pubmed/15538253>
69. Neal DE. Complications of ileal conduit diversion in adults with cancer followed up for at least five years. *Br Med J (Clin Res Ed)* 1985 Jun;290(6483):1695-7.
<http://www.ncbi.nlm.nih.gov/pubmed/3924218>
70. Benson MC, Olsson CA. Continent urinary diversion. *Urol Clin North Am* 1999 Feb;26(1):125-47, ix.
<http://www.ncbi.nlm.nih.gov/pubmed/10086055>
71. Gerharz EW, Köhl UN, Melekos MD, et al. Ten years' experience with the submucosally embedded in situ appendix in continent cutaneous diversion. *Eur Urol* 2001 Dec;40(6):625-31.
<http://www.ncbi.nlm.nih.gov/pubmed/11805408>
72. Jonsson O, Olofsson G, Lindholm E, et al. Long-time experience with the Kock ileal reservoir for continent urinary diversion. *Eur Urol* 2001 Dec;40(6):632-40.
<http://www.ncbi.nlm.nih.gov/pubmed/11805409>
73. Stenzl A, Nagele U, Kuczuk M, et al. Cystectomy - Technical Considerations in Male and Female Patients. *EAU Update Series* 2005 Sep; 3(3):138-146.
<http://www.journals.elsevierhealth.com/periodicals/euus/article/PIIS1570912405000310/abstract>
74. Wiesner C, Bonfig R, Stein R, et al. Continent cutaneous urinary diversion: long-term follow-up of more than 800 patients with ileocecal reservoirs. *World J Urol* 2006 Aug;24(3):315-8.
<http://www.ncbi.nlm.nih.gov/pubmed/16676186>
75. Wiesner C, Stein R, Pahernik S, et al. Long-term followup of the intussuscepted ileal nipple and the in situ, submucosally embedded appendix as continence mechanisms of continent urinary diversion with the cutaneous ileocecal pouch (Mainz pouch I). *J Urol* 2006 Jul;176(1):155-9; discussion 159-60.
<http://www.ncbi.nlm.nih.gov/pubmed/16753391>
76. Thoeny HC, Sonnenschein MJ, Madersbacher S, et al. Is ileal orthotopic bladder substitution with an afferent tubular segment detrimental to the upper urinary tract in the long term? *J Urol* 2002 Nov;168(5):2030-4; discussion 2034.
<http://www.ncbi.nlm.nih.gov/pubmed/12394702>
77. Leissner J, Black P, Fisch M, et al. Colon pouch (Mainz pouch III) for continent urinary diversion after pelvic irradiation. *Urology* 2000 Nov;56(5):798-802.
<http://www.ncbi.nlm.nih.gov/pubmed/11068305>
78. Simon J. Ectopia Vesicae (Absence of the anterior walls of the Bladder and the pubic abdominal parietes) Operation for directing the orifices of the ureteres into the rectum, temporary success. *JAMA* 1911;56:398.

79. Coffey R. Physiologic implantation of the severed ureter or common bile duct into the intestine. *JAMA* 1911;LVI(6):397-403.
<http://jama.jamanetwork.com/article.aspx?articleid=435854>
80. Azimuddin K, Khubchandani IT, Stasik JJ, et al. Neoplasia after reterosigmoidostomy. *Dis Colon Rectum* 1999 Dec;42(12):1632-8.
<http://www.ncbi.nlm.nih.gov/pubmed/10613486>
81. Gerharz EW, Turner WH, Kälble T, et al. Metabolic and functional consequences of urinary reconstruction with bowel. *BJU Int* 2003 Jan;91(2):143-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12519116>
82. Kälble T, Busse K, Amelung F, et al. Tumor induction and prophylaxis following different forms of intestinal urinary diversion in a rat model. *Urol Res* 1995;23(6):365-70.
<http://www.ncbi.nlm.nih.gov/pubmed/8788273>
83. World Health Organization (WHO) Consensus Conference in Bladder Cancer, Hautmann RE, Abol-Enein H, Hafez K, Haro I, Mansson W, Mills RD, Montie JD, Sagalowsky AI, Stein JP, Stenzl A, Studer UE, Volkmer BG. Urinary diversion. *Urology* 2007 Jan;69(1 Suppl):17-49.
<http://www.ncbi.nlm.nih.gov/pubmed/17280907>
84. Stein JP, Skinner DG. Radical cystectomy for invasive bladder cancer: long-term results of a standard procedure. *World J Urol* 2006 Aug;24(3):296-304.
<http://www.ncbi.nlm.nih.gov/pubmed/16518661>
85. Donat SM, Siegrist T, Cronin A, et al. Radical cystectomy in octogenarians—does morbidity outweigh the potential survival benefits? *J Urol* 2010 Jun;183(6):2171-7.
<http://www.ncbi.nlm.nih.gov/pubmed/20399461>
86. Hautmann RE, de Petriconi RC, Volkmer BG. 25 years of experience with 1,000 neobladders: longterm complications. *J Urol* 2011 Jun;185(6): 2207-12.
<http://www.ncbi.nlm.nih.gov/pubmed/21497841>
87. Stein JP, Dunn MD, Quek ML, et al. The orthotopic T pouch ileal neobladder: experience with 209 patients. *J Urol* 2004 Aug;172(2):584-7.
<http://www.ncbi.nlm.nih.gov/pubmed/15247737>
88. Abol-Enein H, Ghoneim MA. Functional results of orthotopic ileal neobladder with serous-lined extramural ureteral reimplantation: experience with 450 patients. *J Urol* 2001 May;165(5):1427-32.
<http://www.ncbi.nlm.nih.gov/pubmed/11342891>
89. Stein JP, Skinner DG. Results with radical cystectomy for treating bladder cancer: a 'reference standard' for high-grade, invasive bladder cancer. *BJU Int* 2003 Jul;92(1):12-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12823375>
90. Yossepowitch O, Dalbagni G, Golijanin D, et al. Orthotopic urinary diversion after cystectomy for bladder cancer: implications for cancer control and patterns of disease recurrence. *J Urol* 2003 Jan;169(1):177-81.
<http://www.ncbi.nlm.nih.gov/pubmed/12478130>
91. Stein JP, Clark P, Miranda G, et al. Urethral tumor recurrence following cystectomy and urinary diversion: clinical and pathological characteristics in 768 male patients. *J Urol* 2005 Apr;173(4):1163-8.
<http://www.ncbi.nlm.nih.gov/pubmed/15758728>
92. Gerharz EW, Månsson A, Hunt S, et al. Quality of life after cystectomy and urinary diversion: an evidence based analysis. *J Urol* 2005 Nov;174(5):1729-36.
<http://www.ncbi.nlm.nih.gov/pubmed/16217273>
93. Hobisch A, Tosun K, Kinzl J, et al. Life after cystectomy and orthotopic neobladder versus ileal conduit urinary diversion. *Semin Urol Oncol* 2001 Feb;19(1):18-23.
<http://www.ncbi.nlm.nih.gov/pubmed/11246729>
94. Porter MP, Penson DF. Health related quality of life after radical cystectomy and urinary diversion for bladder cancer: a systematic review and critical analysis of the literature. *J Urol* 2005 Apr;173(4): 1318-22.
<http://www.ncbi.nlm.nih.gov/pubmed/15758789>
95. Vallancien G, Abou El Fettouh H, Cathelineau X, et al. Cystectomy with prostate sparing for bladder cancer in 100 patients: 10-year experience. *J Urol* 2002 Dec;168(6):2413-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12441929>
96. Stenzl A, Sherif H, Kuczyk M. Radical cystectomy with orthotopic neobladder for invasive bladder cancer: a critical analysis of long term oncological, functional and quality of life results. *Int Braz J Urol* 2010 Sep-Oct;36(5):537-47.
<http://www.ncbi.nlm.nih.gov/pubmed/21044370>

97. Cookson MS, Chang SS, Wells N, et al. Complications of radical cystectomy for nonmuscle invasive disease: comparison with muscle invasive disease. *J Urol* 2003 Jun;169(1):101-4.
<http://www.ncbi.nlm.nih.gov/pubmed/12478113>
98. Eastham JA. Do high-volume hospitals and surgeons provide better care in urologic oncology? *Urol Oncol* 2009 Jul-Aug;27(4):417-21.
<http://www.ncbi.nlm.nih.gov/pubmed/19573772>
99. Shariat SF, Karakiewicz PI, Palapattu GS, et al. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. *J Urol* 2006 Dec;176(6 Pt 1):2414-22; discussion 2422.
<http://www.ncbi.nlm.nih.gov/pubmed/17085118>
100. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001 Feb;19(3):666-75.
<http://www.ncbi.nlm.nih.gov/pubmed/11157016>
101. Gschwend JE, Dahm P, Fair WR. Disease specific survival as endpoint of outcome for bladder cancer patients following radical cystectomy. *Eur Urol* 2002 Apr;41(4):440-8.
<http://www.ncbi.nlm.nih.gov/pubmed/12074817>
102. Madersbacher S, Hochreiter W, Burkhard F, et al. Radical cystectomy for bladder cancer today—a homogeneous series without neoadjuvant therapy. *J Clin Oncol* 2003 Feb;21(4):690-6.
<http://www.ncbi.nlm.nih.gov/pubmed/12586807>
103. Bassi P, Ferrante GD, Piazza N, et al. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. *J Urol* 1999 May;161(5):1494-7.
<http://www.ncbi.nlm.nih.gov/pubmed/10210380>

8. NON-RESECTABLE TUMOURS

8.1 Palliative cystectomy for muscle-invasive bladder carcinoma

For patients with inoperable locally advanced tumours (T4b, invading the pelvic or abdominal wall), radical cystectomy is not usually a therapeutic option (1). Treatment of these patients remains a clinical challenge. These patients are candidates for palliative treatments, such as palliative radiotherapy.

Inoperable locally advanced tumours may be accompanied by several debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction. There are several treatment options for patients with these symptoms. In advanced bladder cancer complicated by bleeding, cystectomy with urinary diversion is the most invasive treatment. It carries the greatest morbidity and should be considered only if there are no other options (1).

In patients with locally advanced pelvic cancer and urinary bladder involvement, palliative radical cystectomy with urinary diversion using intestinal segments is usually performed for the relief of symptoms such as pain, recurrent bleeding, urgency and fistula formation (2).

Zebic, et al. (2005) (3) retrospectively analysed patients aged ≥ 75 years, who had received radical cystectomies with either curative or palliative intent. The indications for palliative cystectomy were advanced pelvic malignancy with severe irritating voiding symptoms, severe pain and recurrent macrohaematuria requiring blood transfusions (3). Zebic, et al. (2005) concluded that elderly people have a greater risk of peri-operative morbidity and mortality, especially those with very advanced pelvic malignancies, who have undergone palliative cystectomy (3).

Advanced MIBC can be associated with ureteral obstruction. In invasive tumours, the mechanism of ureteral obstruction is probably caused by a combination of mechanical blockage by the tumour and invasion of ureteral orifices by tumour cells interfering with ureteral peristalsis. Bilateral ureteral obstruction, or unilateral obstruction to a solitary functioning kidney, can result in uraemia. Treatment of such patients is still a dilemma. El-Tabey et al. retrospectively reviewed the records of patients who presented with bladder cancer and obstructive uraemia (4). Patients with inoperable locally advanced bladder tumours (23 patients, 37.7%) were treated with permanent nephrostomy tubes to relieve obstruction; radical cystectomy was not an option. Ten patients underwent surgery (26.3%); palliative cystectomy without lymphadenectomy was carried out for advanced nodal involvement in four patients and for locally advanced disease infiltrating the pelvic wall in six patients. In all 10 patients, local pelvic recurrence was reported within the first year of follow-up (4).

In another study, post-operative outcome was reported for primary radical cystectomy in 20 T4 bladder cancer patients (of which seven cases were T4b). The authors concluded that primary cystectomy for T4 bladder cancer was technically feasible and had a very tolerable therapy-related morbidity and mortality (5).

8.2 Conclusions and recommendations for non-resectable tumours

Conclusions
Primary radical cystectomy in T4b bladder cancer is not a curative option.
If there are symptoms, radical cystectomy may be a therapeutic/palliative option.
Intestinal or non-intestinal forms of urinary diversion can be used with or without palliative cystectomy.

Recommendations	LE	GR
In patients with inoperable locally advanced tumours (T4b), primary radical cystectomy is a palliative option and cannot be offered as curative treatment.		B
In patients with symptoms palliative cystectomy may be offered.		
Prior to any further interventions, surgery-related morbidity and quality-of-life should be fully discussed with the patient.	3	B

8.3 Supportive care

Severe, localised problems can occur in patients with invasive, non-operable bladder cancer and those in whom cystectomy has not been performed because of metastatic disease. These problems include pain, bleeding, voiding problems and obstruction of the upper urinary tract (UUT).

Obstruction of the UUT

Unilateral (best kidney) or bilateral nephrostomy tubes provide the easiest solution for UUT obstruction, but patients find the tubes are inconvenient and prefer ureteral stenting. However, stenting can be difficult to achieve and stents must be regularly replaced. There is also the risk of stent obstruction or displacement. Another possible solution is the possibility of a urinary diversion with, or without, a palliative cystectomy.

Bleeding and pain

In the case of bleeding, first screen the patient for coagulation disorders or review the patient's use of anticoagulant drugs. Transurethral (laser) coagulation may be difficult in a bladder full of tumour or with a bleeding tumour. Intravesical rinsing of the bladder with 1% silver nitrate or 1-2% alum can be effective (12), and can usually be done without any form of anaesthesia. The instillation of formalin (2.5-4% during 30 minutes) is a more aggressive and more painful procedure, requiring general or regional anaesthesia. Formalin instillation also has a higher risk of side effects, e.g. bladder fibrosis, but is more likely to control the bleeding (13). Vesicoureteral reflux should be excluded to prevent renal complications.

Radiation therapy is another common strategy for control of bleeding, which is also used to control pain. In an older report, haematuria and pain control were 59% and 73%, respectively (14). Irritative bladder and bowel complaints due to irradiation are possible but are usually mild. Non-conservative options are embolisation of specific arteries in the small pelvis, with success rates as high as 90% (15). Radical surgery is a last resort and includes cystectomy and diversion.

8.4 References

- Ok JH, Meyers FJ, Evans CP. Medical and surgical palliative care of patients with urological malignancies. *J Urol* 2005 Oct;174(4 Pt 1):1177-82.
<http://www.ncbi.nlm.nih.gov/pubmed/16145365>
- Ubrig B, Lazica M, Waldner M, et al. Extraperitoneal bilateral cutaneous ureterostomy with midline stoma for palliation of pelvic cancer. *Urology* 2004 May;63(5):973-5.
<http://www.ncbi.nlm.nih.gov/pubmed/15134993>
- Zebic N, Weinknecht S, Kroepfl D. Radical cystectomy in patients aged > or = 75 years: an updated review of patients treated with curative and palliative intent. *BJU Int* 2005 Jun;95(9):1211-4.
<http://www.ncbi.nlm.nih.gov/pubmed/15892803>
- El-Tabey NA, Osman Y, Mosbah A, et al. Bladder cancer with obstructive uremia: oncologic outcome after definitive surgical management. *Urology* 2005 Sep;66(3):531-5.
<http://www.ncbi.nlm.nih.gov/pubmed/16140072>
- Nagele U, Anastasiadis AG, Merseburger AS, et al. The rationale for radical cystectomy as primary therapy for T4 bladder cancer. *World J Urol* 2007 Aug;25(4):401-5.
<http://www.ncbi.nlm.nih.gov/pubmed/17525849>
- von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000 Sep;18(17):3068-77.
<http://www.ncbi.nlm.nih.gov/pubmed/11001674>

7. Sternberg CN, de Mulder P, Schornagel JH, et al. EORTC Genito- Urinary Cancer Group. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. *Eur J Cancer* 2006 Jan;42(1):50-4. <http://www.ncbi.nlm.nih.gov/pubmed/16330205>
8. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/ carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. *J Clin Oncol* 2009 Nov 20;27(33):5634-9. <http://www.ncbi.nlm.nih.gov/pubmed/19786668>
9. Cara S, Tannock IF. Retreatment of patients with the same chemotherapy: implications for clinical mechanisms of drug resistance. *Ann Oncol* 2001 Jan;12(1):23-7. <http://www.ncbi.nlm.nih.gov/pubmed/11249045>
10. Han KS, Joung JY, Kim TS, et al. Methotrexate, vinblastine, doxorubicin and cisplatin combination regimen as salvage chemotherapy for patients with advanced or metastatic transitional cell carcinoma after failure of gemcitabine and cisplatin chemotherapy. *Br J Cancer* 2008 Jan 15;98(1):86-90. <http://www.ncbi.nlm.nih.gov/pubmed/18087289>
11. Bellmunt J, Théodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009 Sep 20;27(27):4454-61. <http://www.ncbi.nlm.nih.gov/pubmed/19687335>
12. Goel AK, Rao MS, Bhagwat AG, et al. Intravesical irrigation with alum for the control of massive bladder hemorrhage. *J Urol* 1985 Jun;133(6):956-7. <http://www.ncbi.nlm.nih.gov/pubmed/3999219>
13. Donahue LA, Frank IN. Intravesical formalin for hemorrhagic cystitis: analysis of therapy. *J Urol* 1989 Apr;141(4):809-12. <http://www.ncbi.nlm.nih.gov/pubmed/2648027>
14. Srinivasan V, Brown CH, Turner AG. A comparison of two radiotherapy regimens for the treatment of symptoms from advanced bladder cancer. *Clin Oncol (R Coll Radiol)* 1994;6(1):11-3. <http://www.ncbi.nlm.nih.gov/pubmed/7513538>
15. Ghahestani SM, Shakhssalim N. Palliative treatment of intractable hematuria in context of advanced bladder cancer: a systematic review. *Urol J* 2009 Summer;6(3):149-56. <http://www.ncbi.nlm.nih.gov/pubmed/19711266>

9. NEOADJUVANT / ADJUVANT RADIOTHERAPY IN MUSCLE-INVASIVE BLADDER CANCER

Contrary to literature addressing radiotherapy prior to surgical intervention for muscle-invasive bladder cancer, data discussing findings for adjuvant radiotherapy after radical cystectomy are extremely scarce and outdated and relate mostly to non-urothelial cancer only (1). Possibly also due to late gastero-intestinal complications, post-operative radiotherapy has never been widely used. With the availability of equipment allowing for more precise targeting resulting in less damage to surrounding tissue, there may be reason to revisit this option in the future (2,3).

9.1 Pre-operative radiotherapy

9.1.1 Retrospective studies

Several retrospective studies have looked at the effect of pre-operative radiotherapy in patients with bladder cancer.

- The largest retrospective series (n = 526) showed that pre-operative radiotherapy at a dose of 50 Gy resulted in downstaging in 73% of cT3 patients versus 29% of patients who were not given pre-operative radiotherapy (4,5). Local control improved from 72% to 91% in pT3b patients (n = 91), but not in pT2 or pT3a patients, while overall survival improved from 40% to 52%.
- The results of a non-randomised study comparing 40 Gy vs. 5-20 Gy vs. no radiotherapy showed that only 40 Gy pre-operative radiotherapy reduced the risk of local recurrence from 27% to 11% and improved survival from 21% to 63% (6).
- Overall, nearly all retrospective studies of pre-operative radiotherapy at doses of 40-50 Gy, followed after 4-6 weeks by cystectomy, showed (4-12):

- downstaging of the tumour stage (40-65% of patients);
- lower risk of local recurrence (10-42%);
- improved survival (11-12%).
- Some studies showed that an improvement in local control was highest for T3b tumours (5-7).
- Other studies showed that achievement of a pathological complete remission (pCR) was a prognostic factor for survival (6-8).
- One retrospective study (8) found no significant increase in toxicity due to pre-operative radiotherapy (10% vs. 3%).

9.1.2 **Randomised studies**

There have been six published randomised studies investigating pre-operative radiotherapy.

- The largest randomised trial (n = 234 evaluable patients) administered pre-operative radiotherapy at a dose of 45 Gy in fractions of 1.8-2.2 Gy in muscle-invasive tumours. The results showed a significant increase in pCR (9% to 34%) in favour of pre-operative radiotherapy and no significant increase in 5-year survival of 33% to 45% (13). In patients not given adjuvant chemotherapy, survival was significantly better than in patients given pre-operative radiotherapy (25-52%). Pathological complete remission was a prognostic factor for better survival. A major limitation was the exclusion from the analysis of almost 50% of patients because they did not receive the planned treatment.
- The Southwest Oncology Group (SWOG) trial (n = 124), which used a pre-operative dose of 5 x 4 Gy, did not show a survival advantage (14).
- An Egyptian study in patients with bladder cancer caused by bilharzia (predominantly squamous cell carcinoma, n = 92) showed a significant survival advantage for > T3 tumours, but a marginal and nonsignificant difference for the whole group (15).
- A small, randomised study of 44 patients (16) showed a significant increase in pCR (18-55%) and a small increase in 5-year survival (61-72%, not significant), but the results were limited by a small patient population and differing radiotherapy schedules (32-54 Gy).
- In another small, three-armed study (n = 72), patients were randomised between surgery, surgery with pre-operative radiotherapy (45 Gy in 4-5 weeks) and radiotherapy alone (50-60 Gy in 4-6 weeks) (17). Pre-operative radiotherapy resulted in 24% of patients achieving pCR. There were no significant differences in survival or toxicity between the three arms.
- There was no reported increase in toxicity due to pre-operative radiotherapy in any of the above-mentioned studies.
- The effect on the local recurrence rate was not specifically documented in any of the studies.
- Three of the randomised studies looked at downstaging and found an increase in pCR following pre-operative radiotherapy from 9% to 34% (10), 0% to 24% (14) and from 18% to 55% (16).
- Local recurrences were not reported (13,17), nor were they similar in any of the randomised studies (16).
- All five randomised studies looked at survival. The largest study found a significant survival advantage from 25% to 52% in those patients who did not receive adjuvant chemotherapy (13). The Egyptian study found a survival advantage only for T3 patients or higher (15). No study found a significant survival advantage for the whole group.
- A meta-analysis of the randomised trials on the value of pre-operative radiotherapy showed an odds ratio for the difference in 5-year survival of 0.71 (95% CI: 0.48-1.06). However, the meta-analysis was potentially biased by the many patients in the largest trial, who did not receive the planned treatment. When the results of the largest trial were excluded, the odds ratio became 0.95 (95% CI: 0.57-1.55), indicating that improved survival with pre-operative radiotherapy had not been proven (18,19).
- The sixth RCT was not included in the meta-analysis (18) since its findings deviated from all the others. Furthermore, the follow-up period was only two years (20).

9.1.3 **Effect of pre-treating patients with neoadjuvant radiotherapy before cystectomy**

A recent study compared the long-term outcome of pre-treating patients before cystectomy with neoadjuvant radiotherapy (n = 90) vs. not pre-treating with radiotherapy (n = 97). The clinical stage of tumours was T1-3. Downstaging to T0 after cystectomy occurred in 7% (7/97) without radiotherapy vs. 57% (51/90) with radiotherapy. In cT3 tumours, these results were 0% (0/16) vs. 59% (19/34), respectively. Downstaging resulted in a longer PFS. In cT3 tumours, there was also a significant longer disease-specific survival. However, the results are limited by the small patient numbers and the retrospective nature of the study.

Another recent retrospective study on neoadjuvant radiotherapy also found a survival advantage, though the results were also limited (21).

9.2 Conclusions and recommendations for pre-operative radiotherapy

Conclusions	LE
No data exist to support that pre-operative radiotherapy for operable muscle-invasive bladder cancer increases survival.	2
Pre-operative radiotherapy for operable muscle-invasive bladder cancer, using a dose of 45-50 Gy in fractions of 1.8-2 Gy results in downstaging after 4-6 weeks.	2
Pre-operative radiotherapy with a dose of 45-50 Gy in fractions of 1.8-2 Gy does not significantly increase toxicity after surgery.	3
There are suggestions in older literature that pre-operative radiotherapy decreases local recurrence of muscle-invasive bladder cancer.	3

Recommendations	GR
Pre-operative radiotherapy is not recommended to improve survival.	B
Pre-operative radiotherapy for operable muscle-invasive bladder cancer results in tumour downstaging after 4-6 weeks.	C

9.3 References

- Zaghloul MS, Awwad HK, Akoush HH, Omar S, et al. Postoperative radiotherapy of carcinoma in bilharzial bladder: improved disease free survival through improving local control. *Int J Radiat Oncol Biol Phys* 1992;23(3):511-7.
<http://www.ncbi.nlm.nih.gov/pubmed/1612951>
- Zaghloul MS. The need to revisit adjuvant and neoadjuvant radiotherapy in bladder cancer. *Expert Rev Anticancer Ther* 2010 Oct;10(10):895-901.
<http://www.ncbi.nlm.nih.gov/pubmed/20942623>
- El-Monim HA, El-Baradie MM, Younis A, et al. A prospective randomized trial for postoperative vs. preoperative adjuvant radiotherapy for muscle-invasive bladder cancer. *Urol Oncol* 2011 Feb 24.
<http://www.ncbi.nlm.nih.gov/pubmed/21353794>
- Pollack A, Zagars GK, Dinney CP, et al. Preoperative radiotherapy for muscle-invasive bladder carcinoma. Long term follow-up and prognostic factors for 338 patients. *Cancer* 1994 Nov;74(10):2819-27.
<http://www.ncbi.nlm.nih.gov/pubmed/7954243>
- Cole CJ, Pollack A, Zagars GK, et al. Local control of muscle-invasive bladder cancer: preoperative radiotherapy and cystectomy versus cystectomy alone. *Int J Radiat Oncol Biol Phys* 1995 May;32(2):331-40.
<http://www.ncbi.nlm.nih.gov/pubmed/7751174>
- Spera JA, Whittington R, Littman P, et al. A comparison of preoperative radiotherapy regimens for bladder carcinoma. The University of Pennsylvania experience. *Cancer* 1988 Jan;61(2):255-62.
<http://www.ncbi.nlm.nih.gov/pubmed/3334959>
- Pollack A, Zagars GK, Cole CJ, et al. Significance of downstaging in muscle-invasive bladder cancer treated with preoperative radiotherapy. *Int J Radiat Oncol Biol Phys* 1997 Jan;37(1):41-9.
<http://www.ncbi.nlm.nih.gov/pubmed/9054875>
- Chougule P, Aygun C, Salazar O, et al. Radiation therapy for transitional cell bladder carcinoma. A ten-year experience. *Urology* 1988 Aug;32(2):91-5.
<http://www.ncbi.nlm.nih.gov/pubmed/3135646>
- Batata MA, Chu FC, Hilaris BS, et al. Bladder cancer in men and women treated by radiation therapy and/or radical cystectomy. *Urology* 1981 Jul;18(1):15-20.
<http://www.ncbi.nlm.nih.gov/pubmed/6789529>
- Fosså SD, Ous S, Berner A. Clinical significance of the 'palpable mass' in patients with muscle-infiltrating bladder cancer undergoing cystectomy after pre-operative radiotherapy. *Br J Urol* 1991 Jan;67(1):54-60.
<http://www.ncbi.nlm.nih.gov/pubmed/1993277>
- Gilloz A, Hérítier P. Comparative study of actuarial survival rates in P3 P4 (N+ Mo) transitional cell carcinoma of bladder managed by total cystectomy alone or associated with preoperative radiotherapy and pelvic lymphadenectomy. *Prog Clin Biol Res* 1984;162B:15-9.
<http://www.ncbi.nlm.nih.gov/pubmed/6504893>
- Smith JA, Batata M, Grabstald H, et al. Preoperative irradiation and cystectomy for bladder cancer. *Cancer* 1982 Mar;49(5):869-973.
<http://www.ncbi.nlm.nih.gov/pubmed/6800628>

13. Slack NH, Bross ID, Prout GR. Five-year follow-up results of a collaborative study of therapies for carcinoma of the bladder. *J Surg Oncol* 1977;9(4):393-405.
<http://www.ncbi.nlm.nih.gov/pubmed/330958>
14. Smith JA, Crawford ED, Paradelo JC, et al. Treatment of advanced bladder cancer with combined preoperative irradiation and radical cystectomy versus radical cystectomy alone: a phase III intergroup study. *J Urol* 1997 Mar;157(3):805-7; discussion 807-8.
<http://www.ncbi.nlm.nih.gov/pubmed/9072571>
15. Ghoneim MA, Ashamalla AK, Awaad HK, et al. Randomized trial of cystectomy with or without preoperative radiotherapy for carcinoma of the bilharzial bladder. *J Urol* 1985 Aug;134(2):266-8.
<http://www.ncbi.nlm.nih.gov/pubmed/3894693>
16. Anderström C, Johanson S, Nilsson S, et al. A prospective randomized study of preoperative irradiation with cystectomy or cystectomy alone for invasive bladder carcinoma. *Eur Urol* 1983;9(3):142-7.
<http://www.ncbi.nlm.nih.gov/pubmed/6861819>
17. Blackard CE, Byar DP. Results of a clinical trial of surgery and radiation in stages II and III carcinoma of the bladder. *J Urol* 1972 Dec;108(6):875-8.
<http://www.ncbi.nlm.nih.gov/pubmed/5082739>
8. Huncharek M, Muscat J, Geschwind JF. Planned preoperative radiation therapy in muscle invasive bladder cancer; results of a meta-analysis. *Anticancer Res* 1998 May;18(3b):1931-4.
<http://www.ncbi.nlm.nih.gov/pubmed/9677446>
19. Awwad HK, Baki HA, El Bolkainy, et al. Preoperative irradiation of T3 carcinoma in Bilharzial bladder. *Int J Radiat Oncol Biol Phys* 1070 Jun;5(6):787-94.
<http://www.ncbi.nlm.nih.gov/pubmed/500410>
16. Widmark A, Flodgren P, Damber JE, et al. A systematic overview of radiation therapy effects in urinary bladder cancer. *Acta Oncol* 2003;42(5-6):567-81.
<http://www.ncbi.nlm.nih.gov/pubmed/14596515>
17. Granfors T, Tomic R, Ljungberg B. Downstaging and survival benefits of neoadjuvant radiotherapy before cystectomy for patients with invasive bladder carcinoma. *Scand J Urol Nephrol* 2009;43(4):293-9.
<http://www.ncbi.nlm.nih.gov/pubmed/19363744>

10. BLADDER-SPARING TREATMENTS FOR LOCALISED DISEASE

10.1 Transurethral resection of bladder tumour (TURB)

When patients with an initially invasive bladder cancer, presenting with pT0 or pT1 status at second resection, are selected for transurethral resection of bladder tumour (TURB) alone, about half of them will have to undergo radical cystectomy for recurrent muscle-invasive cancer, with a disease-specific death rate ranging up to 47% within this group (1,2).

A disease-free status at re-staging TUR appears to be crucial in making the decision not to perform radical cystectomy (3,4). A prospective study by Solsona et al. (3) included 133 patients with a radical TUR and negative biopsies, and recently reported 15 year follow-up (5). Patients had regular cystoscopy and biopsies, and were treated additionally according to their findings. In all, only 6.7% were understaged during the initial TURB, 30% had recurrent NMIBC and went on to intravesical therapy, and 30% (n=40) progressed, of which 27 died of bladder cancer. This results in a cancer-specific survival (CSS) of 81.9%, 79.5% and 76.7%, and a progression-free survival (PFS) with intact bladder of 75.5%, 64.9%, 57.8%, after 5, 10 and 15 years respectively.

TUR alone is only possible as a therapeutic option if tumour growth is limited to the superficial muscle layer and if re-staging biopsies are negative for residual tumour (6). TUR alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach, or refuses open surgery (7).

10.1.1 Conclusion and recommendation for TURB

Conclusion and recommendation	LE	GR
Transurethral resection of bladder tumour (TURB) alone is not a curative treatment option in most patients.	2a	B

10.1.2 References

1. Barnes RW, Dick AL, Hadley HL, et al. Survival following transurethral resection of bladder carcinoma. *Cancer Res* 1977 Aug;37(8 Pt 2):2895-7.
<http://www.ncbi.nlm.nih.gov/pubmed/872119>
2. Herr HW. Transurethral resection of muscle-invasive bladder cancer: 10-year outcome. *J Clin Oncol* 2001 Jan;19(1):89-93.
<http://www.ncbi.nlm.nih.gov/pubmed/11134199>
3. Solsona E, Iborra I, Ricós JV, et al. Feasibility of transurethral resection for muscle infiltrating carcinoma of the bladder: long-term follow-up of a prospective study. *J Urol* 1998 Jan;159(1):95-8; discussion 98-9.
<http://www.ncbi.nlm.nih.gov/pubmed/9400445>
4. Holmäng S, Hedelin H, Anderström C, et al. Long-term follow-up of all patients with muscle invasive (stages T2, T3 and T4) bladder carcinoma in a geographical region. *J Urol* 1997 Aug;158(2):389-92.
<http://www.ncbi.nlm.nih.gov/pubmed/9224309>
5. Solsona E, Iborra I, Collado A, et al. Feasibility of radical transurethral resection as monotherapy for selected patients with muscle invasive bladder cancer. *J Urol* 2010 Aug;184(2):475-80
<http://www.ncbi.nlm.nih.gov/pubmed/20620402>
6. Herr HW. Conservative management of muscle-infiltrating bladder cancer: prospective experience. *J Urol* 1987 Nov;138(5):1162-3.
<http://www.ncbi.nlm.nih.gov/pubmed/3669160>
7. Whitmore WF Jr, Batata MA, Ghoneim MA, et al. Radical cystectomy with or without prior irradiation in the treatment of bladder cancer. *J Urol* 1977 Jul;118(1 Pt 2):184-7. [no abstract available]
<http://www.ncbi.nlm.nih.gov/pubmed/875217>

10.2 External beam radiotherapy (EBRT)

The target field usually comprises the bladder only, with a safety margin of 1.5-2 cm to allow for unavoidable organ movements (1-4). Any beneficial effect with larger pelvic fields has not been demonstrated. The target dose for curative radiotherapy for bladder cancer is 60-66 Gy, with a subsequent boost using external radiotherapy or interstitial brachytherapy. The daily dose is usually 1.8-2 Gy, and the course of radiotherapy should not extend beyond 6-7 weeks to minimise the repopulation of cancer cells. The use of modern standard radiotherapy techniques results in major, related, late morbidity of the urinary bladder or bowel in less than 5% of tumour-free patients (5-9). As well as the response to radiotherapy, important prognostic factors for outcome include:

- tumour size;
- hydronephrosis;
- completeness of the initial TURB.

Overall, 5-year survival rates in patients with MIBC range between 30% and 60%, depending on whether they have a complete response (CR) following radiotherapy. Cancer-specific survival rates are between 20% and 50% (10-14).

Prognostic factors for success were investigated in an Italian single institution series of 459 irradiated patients, including approximately 30% of unfit T1 patients, with 4.4 years average follow-up. Significant factors were found in a multivariate survival analysis to be:

- age;
- T category (for all end points);
- tumour dose (only for failure-free survival) (15).

Based on available trials, a Cochrane analysis has demonstrated that radical cystectomy has an overall survival benefit compared to radiotherapy (16).

External radiotherapy can be an alternative treatment in patients unfit for radical surgery, as demonstrated in a group of 92 elderly or disabled patients with T2-4 N0-1 M0 bladder cancer and a median age of 79 years. The

total dose given was 55 Gy in 4 weeks. The cystoscopic complete remission rate at 3 months was 78%, 3-year local control rate 56%, and 3-year overall survival 36%. Pre-treatment bladder capacity was demonstrated in 81% of patients (17).

Similar long-term results were reported by Chung et al (18). Threehundred and forty patients with MIBC were treated with EBRT alone, EBRT with concurrent chemotherapy, or neoadjuvant chemotherapy followed by EBRT. The overall CR was 55% and the 10 year DSS and OS were 35% and 19% respectively. Complete response was 64%, 79%, and 52% after EBRT alone, concurrent chemotherapy (n=36), and neoadjuvant chemotherapy (n=57) respectively, although in this last group most patients had T3 and T4 tumours. Younger age, lower tumour stage and absence of CIS were associated with a significant improvement in survival. For example, in the T2 group, 5 year OS was 44% and DSS was 58%. A relapse within 2 to 3 years was a bad prognostic sign. The authors concluded that EBRT monotherapy was an option only in highly selected patients.

10.2.1 Conclusions and recommendation for external beam radiotherapy

Conclusions	LE
External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach.	3
Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation because of extensive local tumour growth.	3

Recommendation	GR
Surgical intervention or multimodality treatment are the preferred curative therapeutic approaches since they are more effective than radiotherapy alone.	B

10.2.2 References

- Gospodarowicz MK, Blandy JP. Radiation therapy for organ-conservation for invasive bladder carcinoma. In: Vogelzang NJ, Scardino PT, Shipley WU, Coffey DS, eds. Comprehensive Textbook of Genitourinary Oncology. Lippincott: Williams and Wilkins, 2000; pp. 487-496.
- Duncan W, Quilty PM. The results of a series of 963 patients with transitional cell carcinoma of the urinary bladder primarily treated by radical megavoltage X-ray therapy. *Radiother Oncol* 1986 Dec;7(4):299-310.
<http://www.ncbi.nlm.nih.gov/pubmed/3101140>
- Gospodarowicz MK, Hawkins NV, Rawlings GA, et al. Radical radiotherapy for muscle invasive transitional cell carcinoma of the bladder: failure analysis. *J Urol* 1989 Dec;142(6):1448-53; discussion 1453-4.
<http://www.ncbi.nlm.nih.gov/pubmed/2585617>
- Gospodarowicz MK, Quilty PM, Scalliet P, et al. The place of radiation therapy as definitive treatment of bladder cancer. *Int J Urol* 1995 Jun;2(Suppl 2):41-8.
<http://www.ncbi.nlm.nih.gov/pubmed/7553304>
- Shipley WU, Zietman AL, Kaufman DS, et al. Invasive bladder cancer: treatment strategies using transurethral surgery, chemotherapy and radiation therapy with selection for bladder conservation. *Int J Radiat Oncol Biol Phys* 1997 Nov;39(4):937-43.
<http://www.ncbi.nlm.nih.gov/pubmed/9369144>
- Maciejewski B, Majewski S. Dose fractionation and tumor repopulation in radiotherapy for bladder cancer. *Radiother Oncol* 1991 Jul;21(3):163-70.
<http://www.ncbi.nlm.nih.gov/pubmed/1924851>
- De Neve W, Lybeert ML, Goor C, et al. Radiotherapy for T2 and T3 carcinoma of the bladder: the influence of overall treatment time. *Radiother Oncol* 1995 Sep;36(3):183-8.
<http://www.ncbi.nlm.nih.gov/pubmed/8532904>
- Milosevic M, Gospodarowicz M, Zietman A, et al. Radiotherapy for bladder cancer. *Urology* 2007 Jan;69(1 Suppl):80-92.
<http://www.ncbi.nlm.nih.gov/pubmed/17280910>
- Whitmore WF Jr, Batata MA, Ghoneim MA, et al. Radical cystectomy with or without prior irradiation in the treatment of bladder cancer. *J Urol* 1977 Jul;118(1 Pt 2):184-7.
<http://www.ncbi.nlm.nih.gov/pubmed/875217>
- Pollack A, Zagars GZ. Radiotherapy for stage T3b transitional cell carcinoma of the bladder. *Semin Urol Oncol* 1996 May;14(2):86-95.
<http://www.ncbi.nlm.nih.gov/pubmed/8734736>

11. De Neve W, Lybeert ML, Goor C, et al, Ribot JG. Radiotherapy for T2 and T3 carcinoma of the bladder: the influence of overall treatment time. *Radiother Oncol* 1995 Sep;36(3):183-8. <http://www.ncbi.nlm.nih.gov/pubmed/8532904>
12. Mameghan H, Fisher R, Mameghan J, et al. Analysis of failure following definitive radiotherapy for invasive transitional cell carcinoma of the bladder. *Int J Radiat Oncol Biol Phys* 1995 Jan;31(2):247-54. <http://www.ncbi.nlm.nih.gov/pubmed/7836076>
13. Herskovic A, Martz K, Al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992 Jun;326(24):1593-8. <http://www.ncbi.nlm.nih.gov/pubmed/1584260>
14. Näslund I, Nilsson B, Littbrand B. Hyperfractionated radiotherapy of bladder cancer. A ten-year followup of a randomized clinical trial. *Acta Oncol* 1994;33(4):397-402. <http://www.ncbi.nlm.nih.gov/pubmed/8018372>
15. Tonoli S, Bertoni F, De Stefani A, et al. Radical radiotherapy for bladder cancer: retrospective analysis of a series of 459 patients treated in an Italian institution. *Clin Oncol (R Coll Radiol)* 2006 Feb;18(1): 52-9. <http://www.ncbi.nlm.nih.gov/pubmed/16477920>
16. Shelley MD, Barber J, Wilt T, et al. Surgery versus radiotherapy for muscle invasive bladder cancer. *Cochrane Database Syst Rev* 2002;(1):CD002079. <http://www.ncbi.nlm.nih.gov/pubmed/11869621>
17. Piet AH, Hulshof MC, Pieters BR, et al. Clinical Results of a concomitant boost radiotherapy technique for muscle-invasive bladder cancer. *Strahlenther Onkol* 2008 Jun;184(6):313-8. <http://www.ncbi.nlm.nih.gov/pubmed/18535807>
18. Chung PW, Bristow RG, Milosevic MF, et al. Long-term outcome of radiation-based conservation therapy for invasive bladder cancer. *Urol Oncol* 2007 Jul-Aug;25(4):303-9. <http://www.ncbi.nlm.nih.gov/pubmed/17628296>

10.3 Chemotherapy

Chemotherapy alone rarely produces durable CRs. In general, a clinical complete response rate of up to 56%, as reported in some series, must be weighed against a staging error of > 60% (1-2). Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival (3), though it may be confounded by patient selection.

Several groups have reported the effect of chemotherapy on resectable tumours (neoadjuvant approach), as well as unresectable primary tumours (4-7). Neoadjuvant chemotherapy with 2-3 cycles of methotrexate, vinblastine, adriamycin plus cisplatin (MVAC) or cisplatin, methotrexate plus vinblastine (CMV) has led to a downstaging of the primary tumour in different prospective series (4-6). Pathological complete responses of bladder primary tumours were reached in 12-50% of patients after MVAC and in 12-22% of patients after gemcitabine/cisplatin (GC) in phase II and phase III trials (4-6,8-16). Contemporary series with GC followed by radical cystectomy reported inferior pT0 rates, which may have been related to a lack of dose density and inappropriate delay of surgery (17). As for bladder preservation, response is evaluated by cystoscopy and CT-imaging only, followed by close surveillance. This approach is prone to an imminent staging error, which can put the patient at risk for local recurrence and/or consecutive metastatic disease.

For very selected patients, a bladder-conserving strategy with TUR of the bladder and systemic cisplatin-based chemotherapy, preferably with MVAC, may allow long-term survival with intact bladder (18). However, this approach cannot be recommended for routine use.

10.3.1 Conclusion and recommendation for chemotherapy for muscle-invasive bladder tumours

Conclusion	LE
With cisplatin-based chemotherapy as primary therapy for locally advanced tumours in highly selected patients, complete and partial local responses have been reported.	2b
Recommendation	GR
Chemotherapy alone is not recommended as primary therapy for localised bladder cancer.	A

10.3.2 References

1. Scher HI, Yagoda A, Herr HW, et al. Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) effect on the primary bladder lesion. *J Urol* 1988 Mar;139(3):470-4.
<http://www.ncbi.nlm.nih.gov/pubmed/3343728>
2. Herr HW, Bajorin DF, Scher HI. Neoadjuvant chemotherapy and bladder-sparing surgery for invasive bladder cancer: ten-year outcome. *J Clin Oncol* 1998 Apr;16(4):1298-301.
<http://www.ncbi.nlm.nih.gov/pubmed/9552029>
3. Sternberg CN, Pansadoro V, Calabrò F, et al. Can patient selection for bladder preservation be based on response to chemotherapy? *Cancer* 2003 Apr 1;97(7):1644-52.
<http://www.ncbi.nlm.nih.gov/pubmed/12655521>
4. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003 Aug 28;349(9):859-66.
<http://www.ncbi.nlm.nih.gov/pubmed/12944571>
5. [No authors listed] Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. *Lancet* 1999 Aug 14;354(9178):533-40.
<http://www.ncbi.nlm.nih.gov/pubmed/10470696>
6. Kachnic LA, Kaufman DS, Heney NM, et al. Bladder preservation by combined modality therapy for invasive bladder cancer. *J Clin Oncol* 1997 Mar;15(3):1022-9.
<http://www.ncbi.nlm.nih.gov/pubmed/9060542>
7. Als AB, Sengelov L, von der Maase H. Long-term survival after gemcitabine and cisplatin in patients with locally advanced transitional cell carcinoma of the bladder: focus on supplementary treatment strategies. *Eur Urol* 2007 Aug;52(2):478-86.
<http://www.ncbi.nlm.nih.gov/pubmed/17383078>
8. Sternberg CN, Yagoda A, Scher HI, et al. M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. *J Urol* 1988 Mar;139(3):461-9.
<http://www.ncbi.nlm.nih.gov/pubmed/3343727>
9. Logothetis CJ, Dexeus FH, Finn L, et al. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. *J Clin Oncol* 1990 Jun;8(6):1050-5.
<http://www.ncbi.nlm.nih.gov/pubmed/2189954>
10. Loehrer PJ Sr, Einhorn LH, Elson PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1992 Jul;10(7):1066-73.
<http://www.ncbi.nlm.nih.gov/pubmed/1607913>
11. Kaufman D, Raghavan D, Carducci M, et al. Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. *J Clin Oncol* 2000 May;18(9):1921-7.
<http://www.ncbi.nlm.nih.gov/pubmed/10784633>
12. Stadler WM, Hayden A, von der Maase H, et al. Long-term survival in phase II trials of gemcitabine plus cisplatin for advanced transitional cell cancer. *Urol Oncol* 2002 Jul-Aug;7(4):153-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12474531>
13. Moore MJ, Winquist EW, Murray N, et al. Gemcitabine plus cisplatin, an active regimen in advanced urothelial cancer: a phase II trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1999 Sep;17(9):2876-81.
<http://www.ncbi.nlm.nih.gov/pubmed/10561365>
14. Bajorin DF, Dodd PM, Mazumdar M, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. *J Clin Oncol* 1999 Oct;17(10):3173-81.
<http://www.ncbi.nlm.nih.gov/pubmed/10506615>
15. Herr HW, Donat SM, Bajorin DF. Post-chemotherapy surgery in patients with unresectable or regionally metastatic bladder cancer. *J Urol* 2001 Mar;165(3):811-4.
<http://www.ncbi.nlm.nih.gov/pubmed/11176475>
16. von der Maase H, Andersen L, Crinò L, et al. Weekly gemcitabine and cisplatin combination therapy in patients with transitional cell carcinoma of the urothelium: a phase II clinical trial. *Ann Oncol* 1999 Dec;10(12):1461-5.
<http://www.ncbi.nlm.nih.gov/pubmed/10643537>
17. Weight CJ, Garcia JA, Hansel DE, et al. Lack of pathologic down-staging with neoadjuvant chemotherapy for muscle-invasive urothelial carcinoma of the bladder: a contemporary series. *Cancer* 2009 Feb 15;115(4):792-9.
<http://www.ncbi.nlm.nih.gov/pubmed/19127557>

18. Sternberg CN, Pansadoro V, Calabrò F, et al. Can patient selection for bladder preservation be based on response to chemotherapy? *Cancer* 2003 Apr;97(7):1644-52.
<http://www.ncbi.nlm.nih.gov/pubmed/12655521>

10.4 Multimodality bladder-preserving treatment

Recent organ-preservation strategies combine TURB, chemotherapy and radiation (1,2). The rationale for performing TURB and radiation is to achieve local tumour control. Application of systemic chemotherapy, most commonly as methotrexate, cisplatin and vinblastine (MCV), aims at the eradication of micrometastasis. Many protocols use cisplatin and/or 5-FU and, recently, gemcitabine with radiation, because of their established role as radiosensitisers. Cisplatin-based chemotherapy in combination with radiotherapy, following TURB, results in a complete response rate of 60-80%.

In a recent, small, phase 1-2 study the value of gemcitabine in multimodality treatment was emphasised, with a 5 year OS of 70.1% and DSS of 78.9% (3).

Another recent study with a mean follow-up of 42 months compared TURB + radiochemotherapy (n=331) with TURB + radiotherapy (n=142) (4). The overall CR was high (70.4%). However, the radiochemotherapy group had a clear survival advantage (median survival 70 months) compared to the radiotherapy group (median survival 28.5 months). Long-term results were dependent on stage, lymphatic invasion (LVI), residual tumour status and initial response at restaging TUR.

The importance of the radicality of the initial TUR was also confirmed in a recent Japanese study with 82 patients treated with TURB and chemoradiotherapy (5). Initial pCR rate was relatively low (39%) in the absence of a radical initial TURB. Still, clinical CR (84%) and survival data were high (5 year OS 77.7%, 5 year PFS 64.5%), although this included salvage treatment. Primary cT2 patients showed a significant improvement in survival compared to cT3-4 and recurrent cases.

Several other smaller recent series confirm the potential of multimodality protocols (6-9). Five year OS rates around 70% are reported. However, protocols differ for each study, as does patient selection. Recurring patients usually do badly, and so do patients with tumours progressing from NMIBC to MIBC. Low stage and complete TUR remain important prognostic variables.

It is recommended that early cystectomy is performed in individuals who do not achieve a complete response following combination therapy. About 40-45% of these patients may survive with an intact bladder at 4-5 years (2).

A comparable long-term survival rate of 50-60% at 5 year follow-up is reported by both multimodality bladder-preserving trials and cystectomy series. However, these therapeutic approaches have never been directly compared and patients in multimodality series are highly selected (2,10-12).

A bladder-preserving multimodality strategy requires very close multidisciplinary co-operation and a high level of patient compliance. Even if a patient has shown a complete response to a multimodality bladder-preserving strategy, the bladder remains a potential source of recurrence. About half of patients can be expected to survive with their native bladder intact. A T0 status at repeat TUR after the initial transurethral resection of the primary tumour, followed by chemotherapy in combination with radiotherapy, was identified as a prognostically important variable. However, even the latter patients are at a life-long risk of developing intravesical tumour recurrences and need meticulous surveillance and multiple invasive procedures. It has been postulated that a delay in radical cystectomy due to an initial bladder-preserving approach increases the risk of lymph node metastases to a lymph node positive rate of 26% when cystectomy becomes necessary due to treatment failure.

10.4.1 **Conclusions and recommendations for multimodality treatment in muscle-invasive bladder cancer**

Conclusions	LE
In a highly selected patient population, long-term survival rates of multimodality treatment are comparable to those of early cystectomy.	3
Delay in surgical therapy can compromise survival rates.	2b

Recommendations	GR
Transurethral resection of bladder tumour alone cannot be offered as a standard curative treatment option in most patients.	B
Radiotherapy alone is less effective than surgery and is only recommended as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach.	B
Chemotherapy alone is not recommended as primary therapy for muscle-invasive bladder cancer.	A
Surgical intervention or multimodality treatment are the preferred curative therapeutic approaches since they are more effective than radiotherapy alone.	B
Multimodality treatment could be offered as an alternative in selected, well-informed, well selected and compliant patients, especially for whom cystectomy is not an option.	B

10.4.2 **References**

- Weiss C, Wolze C, Engehausen DG, et al. Radiochemotherapy after transurethral resection for high-risk T1 bladder cancer: an alternative to intravesical therapy or early cystectomy? *J Clin Oncol* 2006 May;24(15):2318-24.
<http://www.ncbi.nlm.nih.gov/pubmed/16710030>
- Rödel C, Grabenbauer GG, Kühn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. *J Clin Oncol* 2002 Jul;20(14):3061-71.
<http://www.ncbi.nlm.nih.gov/pubmed/12118019>
- Caffo O, Fellin G, Graffer U, et al. Gemcitabine and radiotherapy plus cisplatin after transurethral resection as conservative treatment for infiltrating bladder cancer: Long-term cumulative results of 2 prospective single-institution studies. *Cancer* 2011 Mar 15;117(6):1190-6.
<http://www.ncbi.nlm.nih.gov/pubmed/20960501>
- Krause FS, Walter B, Ott OJ, et al. 15-year survival rates after transurethral resection and radiochemotherapy or radiation in bladder cancer treatment. *Anticancer Res* 2011 Mar;31(3):985-90.
<http://www.ncbi.nlm.nih.gov/pubmed/21498726>
- Hara T, Nishijima J, Miyachika Y, et al. Primary cT2 bladder cancer: a good candidate for radiotherapy combined with cisplatin for bladder preservation. *Jpn J Clin Oncol* 2011 Jul;41(7):902-7.
<http://www.ncbi.nlm.nih.gov/pubmed/21616918>
- Zapatero A, Martin de Vidales C, Arellano R, et al. Updated results of bladder-sparing trimodality approach for invasive bladder cancer. *Urol Oncol* 2010 Jul-Aug;28(4):368-74.
<http://www.ncbi.nlm.nih.gov/pubmed/19362865>
- Maarouf AM, Khalil S, Salem EA, et al. Bladder preservation multimodality therapy as an alternative to radical cystectomy for treatment of muscle invasive bladder cancer. *BJU Int* 2011 May;107(10):1605-10.
<http://www.ncbi.nlm.nih.gov/pubmed/20825396>
- Villavicencio H, Rodriguez Faba O, Palou J, et al. Bladder preservation strategy based on combined therapy in patients with muscle-invasive bladder cancer: management and results at long-term followup. *Urol Int* 2010;85(3):281-6.
<http://www.ncbi.nlm.nih.gov/pubmed/20689253>
- Aboziada MA, Hamza HM, AbdIbrahim AM. Initial results of bladder preserving approach by chemoradiotherapy in patients with muscle invading transitional cell carcinoma. *J Egypt Natl Canc Inst* 2009 Jun;21(2):167-74.
<http://www.ncbi.nlm.nih.gov/pubmed/21057568>
- Zietman AL, Grocela J, Zehr E, et al. Selective bladder conservation using transurethral resection, chemotherapy, and radiation: management and consequences of Ta, T1, and Tis recurrence within the retained bladder. *Urology* 2001 Sep;58(3):380-5.
<http://www.ncbi.nlm.nih.gov/pubmed/11549485>

11. Shipley WU, Kaufman DS, Zehr E, et al. Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. *Urology* 2002 Jul;60(1):62-7; discussion 67-8.
<http://www.ncbi.nlm.nih.gov/pubmed/12100923>
12. Wittlinger M, Rödel CM, Weiss C, et al. Quadrimodal treatment of high-risk T1 and T2 bladder cancer: transurethral tumor resection followed by concurrent radiochemotherapy and regional deep hyperthermia. *Radiother Oncol* 2009 Nov;93(2):358-63.
<http://www.ncbi.nlm.nih.gov/pubmed/19837472>

11. ADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy for patients after radical cystectomy with pT3/4 and/or lymph node positive (N+) disease without clinically detectable metastases (M0) is under debate (1,2). The benefits of chemotherapy in the adjuvant setting include:

- Chemotherapy is administered after accurate pathological staging.
- Overtreatment in patients at low risk for micrometastases is avoided.
- No delay in definitive surgical treatment, especially in patients not sensitive to chemotherapy.

The drawbacks of adjuvant chemotherapy are:

- Assessment of in vivo chemosensitivity of the tumour is not possible.
- Delay or intolerability of chemotherapy, due to post-operative morbidity.

There is not enough evidence in favour of the routine use of adjuvant chemotherapy (2,8). To date, there have been only five published randomised trials of adjuvant chemotherapy (3-7) and one meta-analysis (8), with updated individual patient data from six trials and a total of only 491 patients for survival analysis. Furthermore, all these trials were suboptimal with serious deficiencies, including low sample size (underpowered), substandard chemotherapy, early stopping of patient entry, and flaws in design and statistical analysis, including irrelevant endpoints or a lack of recommendations concerning salvage chemotherapy for relapse or metastases (2). The data are not convincing enough to give an unequivocal recommendation for the use of adjuvant chemotherapy.

From the evidence so far available, it is unclear whether immediate adjuvant chemotherapy or chemotherapy at the time of relapse is superior or if the two approaches are equivalent with respect to the endpoint overall survival. In recent trial updates, cisplatin-based combination chemotherapy was able to produce long-term disease-free survival, even in metastatic disease, albeit mainly in patients with lymph node metastases only, and with a good performance status (9-11).

Patients with extravesical and/or node positive disease following cystectomy should be enrolled in clinical trials whenever possible. In non-protocol-eligible patients, adjuvant cisplatin-based chemotherapy is an option provided the patient is well informed about the scarce data available.

Published trials of randomised adjuvant chemotherapy have used three to four cycles of CMV (cisplatin, methotrexate, vinblastine), CISCA (cisplatin, cyclophosphamide, and adriamycin), MVA(E)C (methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin) and CM (cisplatin, methotrexate) (12). There is no evidence that more modern or carboplatin-containing chemotherapy combinations are as effective. Patients ineligible for cisplatin should not receive adjuvant chemotherapy.

11.1 Conclusion and recommendation for adjuvant chemotherapy

Conclusion	LE
Adjuvant chemotherapy is under debate. Neither randomised trials nor a meta-analysis have provided sufficient data to support the routine use of adjuvant chemotherapy.	1a

Recommendation	GR
Adjuvant chemotherapy is advised within clinical trials, but not as a routine therapeutic option.	A

11.2 References

1. Cohen SM, Goel A, Phillips J, et al. The role of perioperative chemotherapy in the treatment of urothelial cancer. *Oncologist* 2006 Jun;11(6):630-40.
<http://www.ncbi.nlm.nih.gov/pubmed/16794242>
2. Sylvester R, Sternberg C. The role of adjuvant combination chemotherapy after cystectomy in locally advanced bladder cancer: what we do not know and why. *Ann Oncol* 2000 Jul;11(7):851-6.
<http://www.ncbi.nlm.nih.gov/pubmed/10997813>
3. Bono A, Benvenuti C, Gibba A, et al. Adjuvant chemotherapy in locally advanced bladder cancer. Final analysis of a controlled multicentre study. *Acta Urol Ital* 1997;11(1):5-8.
4. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. *J Urol* 1996 Feb;155(2):495-9; discussion 499-500.
<http://www.ncbi.nlm.nih.gov/pubmed/8558644>
5. Stöckle M, Meyenburg W, Wellek S, et al. Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long-term results of a controlled prospective study and further clinical experience. *J Urol* 1995 Jan;153(1):47-52.
<http://www.ncbi.nlm.nih.gov/pubmed/7966789>
6. Studer UE, Bacchi M, Biedermann C, et al. Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. *J Urol* 1994 Jul;152(1):81-4.
<http://www.ncbi.nlm.nih.gov/pubmed/8201695>
7. Skinner DG, Daniels JR, Russell CA, et al. Adjuvant chemotherapy following cystectomy benefits patients with deeply invasive bladder cancer. *Semin Urol* 1990 Nov;8(4):279-84.
<http://www.ncbi.nlm.nih.gov/pubmed/2284533>
8. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data. *Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol* 2005 Aug;48(2):189-199; discussion 199-201.
<http://www.ncbi.nlm.nih.gov/pubmed/15939530>
9. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005 Jul;23(21):4602-8.
<http://www.ncbi.nlm.nih.gov/pubmed/16034041>
10. Sternberg CN. Perioperative chemotherapy in muscle-invasive bladder cancer to enhance survival and/or as a strategy for bladder preservation. *Semin Oncol* 2007 Apr;34(2):122-8.
<http://www.ncbi.nlm.nih.gov/pubmed/17382795>
11. Stadler WM, Hayden A, von der Maase H, et al. Long-term survival in phase II trials of gemcitabine plus cisplatin for advanced transitional cell cancer. *Urol Oncol* 2002 Jul-Aug;7(4):153-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12474531>
12. Lehmann J, Retz M, Wiemers C, et al; AUO-AB 05/95. Adjuvant cisplatin plus methotrexate versus methotrexate, vinblastine, epirubicin, and cisplatin in locally advanced bladder cancer: results of a randomized, multicenter, phase III trial (AUO-AB 05/95). *J Clin Oncol* 2005 Aug;23(22):4963-74.
<http://www.ncbi.nlm.nih.gov/pubmed/15939920>

12. METASTATIC DISEASE

Approximately 30% of patients with urothelial cancer present with muscle-invasive disease, and about half relapse after radical cystectomy, depending on the pathological stage of the primary tumour and the nodal status. Local recurrence accounts for ~30% of relapses, whereas distant metastases are more common. About 10-15% of patients are already metastatic at diagnosis (1). Before the development of effective chemotherapy, patients with metastatic urothelial cancer rarely had a median survival that exceeded 3-6 months (2).

12.1 Prognostic factors and treatment decisions

Outcome of chemotherapy depends on patient-related factors and pre-treatment disease. Prognostic factors for response and survival have been established. In a multivariate analysis, Karnofsky performance status (PS) of $\leq 80\%$ and presence of visceral metastases were independent prognostic factors of poor survival after treatment with MVAC (methotrexate, vinblastine, adriamycin and cisplatin). These so-called Bajorin prognostic factors (3) have also been validated for newer combination chemotherapy regimens (4,5) and carboplatin combinations (6). These prognostic factors are crucial for assessing phase II study results and stratifying phase

III trials (7,8). Additional data on the prognostic value of elevated alkaline phosphatase and the number of disease sites (more or less than three) have been generated prospectively (9). A retrospective analysis showed that, in elderly patients, Eastern Cooperative Oncology Group (ECOG) PS 2-3 and haemoglobin < 10 mg/dL were independent predictors of poor survival (9). Age itself has no impact on response or toxic events (10).

For patients refractory to or progressing shortly after platinum-based combination chemotherapy, four prognostic groups have been established, based on three adverse factors that developed in patients treated with vinflunine and validated in an independent data set: Hb < 10 g/dL; presence of liver metastases; and ECOG PS \geq 1 (11).

12.1.1 Comorbidity in metastatic disease

Comorbidity is defined as “the presence of one or more diseases in addition to an index disease” (see Chapter 7). Patients with a history of cancer have an average of three co-morbid conditions and comorbidity is the rule rather than the exception. Incidence and prevalence of comorbidity increase with age. Comorbidity is an important predictor of clinical outcome (12). However, patients with comorbidity are mostly excluded from clinical trials (13).

In several studies, comorbidity was predictive of 1-5-year mortality rates, which was only partly true for age and sex.

Source	N	Comorbidity	Predictive capacity
Charlson ¹³	218	+	5-year mortality
Inouye ¹⁴	318	+	2-year mortality
Lee ¹⁵	8009	+	4-year mortality
Walter ¹⁶	1427	+	1-year mortality

Comorbidity increases with age. However, chronological age does not necessarily correlate with functional impairment. Physiological impairment varies substantially between individuals. There are several definitions by which patients can be selected as potentially fit or unfit for chemotherapy, but age is not among them.

12.1.2 Not eligible for cisplatin (unfit)

The European Organisation for Research and Treatment of Cancer (EORTC) conducted the first randomised phase II/III trial for urothelial carcinoma patients who were unfit for cisplatin chemotherapy (14). Their definitions are:

- fit: GFR \geq 60 mL/min and PS 0-1
- unfit: GFR < 60 mL/min and/or PS 2

A further survey of patients with metastatic urothelial cancer classified patients unfit for cisplatin-based chemotherapy who had: PS > 1; GFR \geq 60 mL/min; grade \geq 2 audiometric loss and peripheral neuropathy; and New York Heart Association (NYHA) class III heart failure (15).

More than 50% of patients with urothelial cancer are not eligible for cisplatin-based chemotherapy (16-19).

Renal function assessment is of utmost importance in the urothelial cancer population. Calculation of creatinine clearance (CrCl) (24-h urine collection) with current formulae tends to underestimate clearance in patients aged > 65 years compared to measured CrCl (16,21).

12.2 Single-agent chemotherapy

Response rates to single-agent, first-line chemotherapy have varied. The most robust data have shown a response rate of about 25% for first- and second-line gemcitabine in several large phase II trials (32-39).

Responses with single agents are usually short-lived and complete responses are rare. Of note, no long-term disease-free survival has been reported with single-agent chemotherapy. The median survival in such patients is only 6-9 months. Patients with WHO PS 3-4, with or without additional negative prognostic factors, are not expected to benefit from combination chemotherapy. The most appropriate approach for this patient group is best supportive care (BSC) or, at most, single-agent chemotherapy.

12.3 Standard first-line chemotherapy for fit patients

Cisplatin-containing combination chemotherapy has been the standard of care since the late 1980s. MVAC has been proven superior to cisplatin monotherapy and CISCA (cisplatin, cyclophosphamide and adriamycin)

(8,30) and, more recently, to cisplatin/docetaxel (31). MVAC and gemcitabine/cisplatin (GC) have prolonged survival up to 14.8 and 13.8 months, respectively compared to cisplatin monotherapy and CISCA (32-34). Neither of the two combinations is superior to the other, but equivalence has not been tested. Response rates were 46% and 49% for MVAC and GC, respectively. The long-term survival results have confirmed the anticipated equivalence of the two regimens (9). The major difference between the above-mentioned combinations is toxicity. The lower toxicity of GC (34) has resulted in it becoming a new standard regimen (35). MVAC is better tolerated when combined with granulocyte colony stimulating factor (G-CSF) (31,35).

High-dose intensity MVAC (HD-MVAC) with G-CSF is less toxic and more efficacious than standard MVAC in terms of dose density, complete response, and 2-year survival rate. However, there is no significant difference in median survival between the two regimens (36,37).

All disease sites have been shown to respond to cisplatin-based combination chemotherapy, but responses have been reported most often in lymph nodes. A response rate of 66% and 77% with MVAC and HD-MVAC, respectively, has been reported in retroperitoneal lymph nodes vs. 29% and 33% at extranodal sites (36). The disease sites also have an impact on long-term survival. In lymph-node-only disease, 20.9% of patients were alive at 5 years compared to only 6.8% of patients with visceral metastases (9).

Further intensification of treatment using the new PCG triple regimen (paclitaxel, cisplatin and gemcitabine) did not result in a significant improvement in OS in the intent-to-treat (ITT) population of a large randomised phase III trial, comparing PCG triple regimen to gemcitabine/cisplatin (38). However, the overall response rate (ORR) was higher with the triple regimen (56% vs. 44%; $P=0.0031$), the trend for OS improvement in the ITT population (15.8 vs. 12.7 months; $HR=0.85$, $P=0.075$) became significant in the eligible population and in the post-hoc analysis of patients who had primary bladder tumour. PCG is one new option for first-line treatment of UC.

Adding paclitaxel to GC did not induce major additional side effects. G4 neutropenia was more common (35.8% vs. 20% for GC), as was febrile neutropenia (13.2% vs. 4.3%), and the need for G-CSF was higher (17% vs. 11%). GC alone caused more G4 thrombocytopenia and thrombocytopenia-induced bleeding (11.4% vs. 6.8%).

12.4 Carboplatin-containing chemotherapy in fit patients

Carboplatin-containing chemotherapy is not equivalent to cisplatin combinations, and should not be considered interchangeable or standard.

Several randomised phase II trials of carboplatin vs. cisplatin combination chemotherapy have produced lower CR rates and shorter OS for the carboplatin arms (49-52).

12.5 Non-platinum combination chemotherapy

Different combinations of gemcitabine and paclitaxel have been studied as first- and second-line treatments. Apart from severe pulmonary toxicity with a weekly schedule of both drugs, this combination is well tolerated and produces response rates between 38% and 60% in both lines. Non-platinum combination chemotherapy has not been compared to standard cisplatin chemotherapy in randomised trials, therefore, it is not recommended for first-line use in patients who are fit enough (29,43-49).

12.6 Chemotherapy in patients unfit for cisplatin

Up to 50% of patients are ineligible for cisplatin-containing chemotherapy, either because of poor PS and/or impaired renal function, or because of comorbidity that prevents high-volume hydration (50,51). The first randomised phase II/III trial in this setting was conducted by EORTC and compared methotrexate/carboplatin/vinblastine (M-CAVI) and carboplatin/gemcitabine (GemCarbo) in patients unfit for cisplatin. Both regimens were active. Severe acute toxicity (SAT) was 13.6% in patients treated with GemCarbo vs. 23% with M-CAVI, while the ORR was 42% for GemCarbo and 30% for M-CAVI. Further analysis showed that in patients with PS 2 and impaired renal function, combination chemotherapy provided limited benefit (52). The ORR and SAT were both 26% for the former group, and 20% and 24%, respectively, for the latter group (52). Recent phase III data have confirmed these results (53).

12.7 Second-line treatment

Second-line chemotherapy data are highly variable and prognostic factors have been established only recently (see 12.1, [11]).

A reasonable strategy may be to re-challenge former cisplatin-sensitive patients if progression occurs at least

6-12 months after first-line cisplatin-based combination chemotherapy.

Second-line response rates of paclitaxel (weekly), docetaxel, oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% in small phase II trials (64-72). Although gemcitabine has also shown excellent response rates in second-line use (22,26-29,63,64), most patients already receive this drug as part of their front-line treatment.

Paclitaxel/gemcitabine have shown response rates of 38-60%, depending on patient selection. No adequate randomised phase III trial has been conducted to assess the true value of this second-line combination (2,44,48).

Vinflunine, a novel third-generation vinca alkaloid, has shown objective response rates of 18% and disease control in 67% of patients (65). A recent randomised phase III trial has compared vinflunine plus best supportive care against BSC alone in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease (66). The results showed a modest ORR (8.6%), a clinical benefit with a favourable safety profile and, most importantly, a survival benefit in favour of vinflunine, which was statistically significant in the eligible patient population (not in the ITT population). For second-line treatment of advanced or metastatic urothelial cancer, this trial reached the highest level of evidence ever reported. Currently, vinflunine is the only approved second-line treatment; any other treatment should take place in the context of clinical trials.

12.8 Low-volume disease and post-chemotherapy surgery

With cisplatin-containing combination chemotherapy, excellent response rates may be obtained in patients with lymph node but not other metastases, good PS, and adequate renal function, including a high degree of CRs, with up to 20% of patients achieving long-term disease-free survival (9,37,67,68). Stage migration may play a role in this positive prognostic development. A retrospective study of post-chemotherapy surgery after a partial or complete response has indicated that surgery may contribute to long-term disease-free survival in selected patients (69-71).

12.9 Treatment of bone metastases

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic urothelial cancer is 30-40% (72). Skeletal complications due to MBD have a detrimental effect on pain and quality of life and are also associated with increased mortality (73). Bisphosphonates reduce and delay skeletal-related events (SREs) due to bone metastases by inhibiting bone resorption. In a small pilot study in patients with bladder cancer, SREs caused by bone metastases were delayed (74). Denosumab is a fully human monoclonal antibody that binds to and neutralises RANKL (receptor activator of nuclear factor- κ B ligand), thereby inhibiting osteoclast function and preventing generalised bone resorption and local bone destruction. Denosumab is not inferior to zoledronic acid (ZA) in preventing or delaying SREs in patients with advanced MBD, including patients with urothelial carcinoma (75). Denosumab has recently been approved by the European Medicines Agency (EMA) for treatment of patients with bone metastases from solid tumours. Patients with MBD, irrespective of the cancer type, should be considered for bone-targeted treatment (73).

Patients treated with ZA or denosumab should be informed about possible side effects and receive prophylactic treatment for jaw osteonecrosis and hypocalcaemia, which is more common with denosumab. Aggressive calcium and vitamin D supplementation is recommended. Dosing regimens of ZA should follow regulatory recommendations and should be adjusted according to pre-existing medical conditions (86). For denosumab, no dose adjustments are required for variations in renal function.

12.10 Conclusions and recommendations for metastatic disease

Conclusions	LE
In a first-line setting, PS and the presence or absence of visceral metastases are independent prognostic factors for survival.	1b
In a second-line setting, prognostic factors are: liver metastasis, PS and haemoglobin < 10 g/dL)	2
Cisplatin-containing combination chemotherapy can achieve median survival of up to 14 months, with long-term disease-free survival reported in ~15% of patients with nodal disease and good PS.	1b
Single-agent chemotherapy provides low response rates of usually short duration.	2a
Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.	2a

Non-platinum combination chemotherapy produced substantial responses in first- and second-line settings, but has not been tested against standard chemotherapy in patients who are fit or unfit for treatment.	2a
There is no defined standard chemotherapy for unfit patients with advanced or metastatic urothelial cancer.	2b
Vinflunine reached the highest level of evidence ever reported for second-line use.	1b
Post-chemotherapy surgery after partial or complete response may contribute to long-term disease-free survival.	3
ZA and denosumab have been approved for all cancer types including urothelial cancer, because they reduce and delay SREs in MBD.	1

Recommendations	GR
<i>First-line treatment for fit patients:</i>	
Use cisplatin-containing combination chemotherapy with GC, PCG, MVAC, preferably with G-CSF, or HD-MVAC with G-CSF.	A
Carboplatin and non-platinum combination chemotherapy is not recommended.	B
<i>First-line treatment in patients ineligible (unfit) for cisplatin:</i>	
Use carboplatin combination chemotherapy or single agents.	C
For cisplatin-ineligible (unfit) patients, with PS2 or impaired renal function, as well as those with 0-1 poor Bajorin prognostic factors and impaired renal function, treatment with carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin is indicated.	A
<i>Second-line treatment:</i>	
In patients progressing after platinum-based combination chemotherapy for metastatic disease, vinflunine should be offered. Alternatively, treatment within a clinical trial setting may be offered.	A*
Zoledronic acid or denosumab is recommended for treatment of bone metastases.	B

* Grade A recommendation is weakened by a problem of statistical significance.

BSC = best supportive care; GC = gemcitabine plus cisplatin; G-CSF = granulocyte colony stimulating factor; GFR = glomerular filtration rate; MVAC = methotrexate, vinblastine, adriamycin plus cisplatin; HD MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PS = performance status; ZA = zoledronic acid

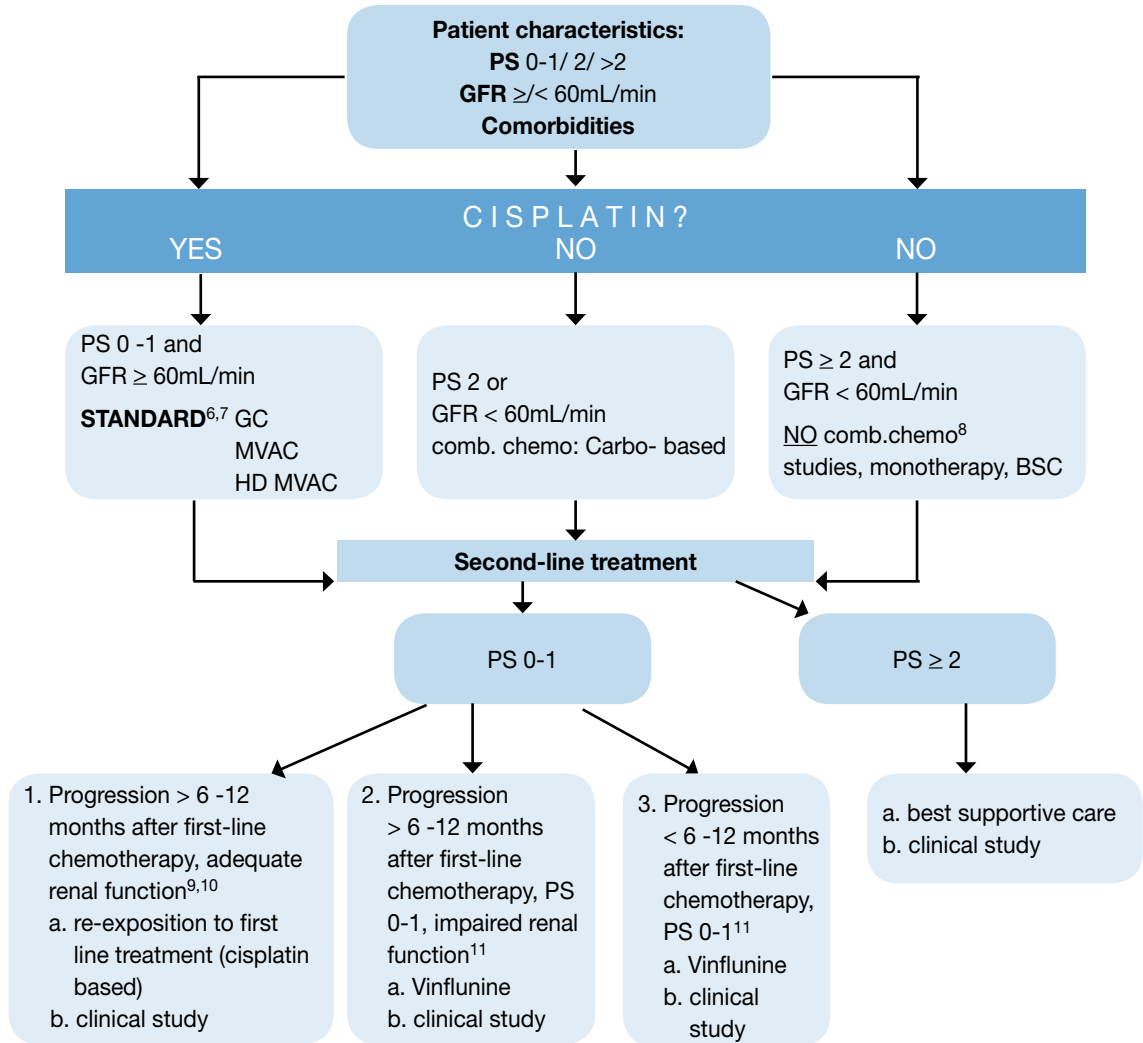
12.11 Biomarkers

Modest disease control rates, with sporadic marked responses, in some patients with urothelial bladder cancer have led to the investigation of biomarkers for assessment of post-operative prognosis and the potential value of peri-operative chemotherapy, and as predictors of response to chemotherapy or its monitoring. Most of the biomarkers are associated with tumour angiogenesis. Small studies, usually retrospective, have investigated microvessel density, altered p53 tumour expression (87), serum vascular endothelial growth factor (88), urinary and tissue basic fibroblast growth factor (89), urinary (wild-type and mutant) and tissue fibroblast growth factor receptor-3 (90), and more recently, thrombospondin-1 (91), circulating tumour cells (92,93), and multidrug resistance gene expression (94). Although a few biomarkers have shown potential, none has sufficient evidence to support its routine clinical use (LE: 3).

Recommendation on the use of biomarkers	GR
Currently, no biomarkers can be recommended in daily clinical practice because they have no impact on predicting outcome, treatment decisions or monitoring therapy in muscle-invasive bladder cancer.	A*

*Upgraded following panel consensus.

Figure 2: Flowchart for the management of metastatic urothelial cancer



BSC = best supportive care; GC = gemcitabine plus cisplatin; GFR = glomerular filtration rate; MVAC = methotrexate, vinblastine, adriamycin plus cisplatin; HD MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PS = performance status

12.12 References

- Rosenberg JE, Carroll PR, Small EJ. Update on chemotherapy for advanced bladder cancer. J Urol 2005 Jul;174(1):14-20. <http://www.ncbi.nlm.nih.gov/pubmed/15947569>
- Sternberg CN, Vogelzang NJ. Gemcitabine, paclitaxel, pemetrexed and other newer agents in urothelial and kidney cancers. Crit Rev Oncol Hematol 2003 Jun;46(Suppl):S105-S15. <http://www.ncbi.nlm.nih.gov/pubmed/12850531>
- Bajorin DF, Dodd PM, Mazumdar M, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 1999 Oct;17(10):3173-81. <http://www.ncbi.nlm.nih.gov/pubmed/10506615>
- Bellmunt J, Albanell J, Paz-Ares L, et al; Spanish Oncology Genitourinary Group. Pretreatment prognostic factors for survival in patients with advanced urothelial tumors treated in a phase I/II trial with paclitaxel, cisplatin, and gemcitabine. Cancer 2002 Aug;95(4):751-7. <http://www.ncbi.nlm.nih.gov/pubmed/12209718>
- Sengeløv L, Kamby C, von der Maase H. Metastatic urothelial cancer: evaluation of prognostic factors and change in prognosis during the last twenty years. Eur Urol 2001 Jun;39(6):634-42. <http://www.ncbi.nlm.nih.gov/pubmed/11464051>

6. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol* 2012 Jan 10;30(2): 191-9.
<http://www.ncbi.nlm.nih.gov/pubmed/22162575>
7. Bajorin D. The phase III candidate: can we improve the science of selection? *J Clin Oncol* 2004 Jan;22(2):211-3.
<http://www.ncbi.nlm.nih.gov/pubmed/14665614>
8. Loehrer PJ Sr, Einhorn LH, Elson PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1992 Jul;10(7):1066-73.
<http://www.ncbi.nlm.nih.gov/pubmed/1607913>
9. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005 Jul;23(21):4602-8.
<http://www.ncbi.nlm.nih.gov/pubmed/16034041>
10. Bamias A, Efstathiou E, Mouloupoulos LA, et al. The outcome of elderly patients with advanced urothelial carcinoma after platinum-based combination chemotherapy. *Ann Oncol* 2005 Feb;16(2): 307-13.
<http://www.ncbi.nlm.nih.gov/pubmed/15668289>
11. Bellmunt J, Choueiri TK, Fougeray R, et al. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. *J Clin Oncol* 2010 Apr 10;28(11):1850-5.
<http://www.ncbi.nlm.nih.gov/pubmed/20231682>
12. Pal SK, Hurria A. Impact of age, sex, and comorbidity on cancer therapy and disease progression. *J Clin Oncol* 2010 Sep 10;28(26):4086-93.
<http://www.ncbi.nlm.nih.gov/pubmed/20644100>
13. Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. *J Chronic Dis* 1970;23:455-69.
<http://www.sciencedirect.com/science/article/pii/0021968170900548>
14. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. *J Clin Oncol* 2009 Nov 20;27(33):5634-9.
<http://www.ncbi.nlm.nih.gov/pubmed/19786668>
15. Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. *J Clin Oncol* 2011 Jun 10;29(17):2432-8.
<http://www.ncbi.nlm.nih.gov/pubmed/21555688>
16. Dash A, Galsky MD, Vickers AJ, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. *Cancer* 2006 Aug;107(3): 506-13.
<http://www.ncbi.nlm.nih.gov/pubmed/16773629>
17. Nogue-Aliguer M, Carles J, Arrivi A, et al. Gemcitabine and carboplatin in advanced transitional cell carcinoma of the urinary tract: an alternative therapy. *Cancer* 2003 May 1;97(9):2180-6.
<http://www.ncbi.nlm.nih.gov/pubmed/12712469>
18. Balducci L, Extermann M. Management of cancer in the older person: a practical approach. *Oncologist* 2000;5(3):224-37.
<http://www.ncbi.nlm.nih.gov/pubmed/10884501>
19. De Santis, Bachner M. New developments in first- and second-line chemotherapy for transitional cell, squamous cell and adenocarcinoma of the bladder. *Curr Opin Urol* 2007 Sep;17(5):363-8.
<http://www.ncbi.nlm.nih.gov/pubmed/17762632>
20. Wedding U, Kodding D, Pientka L. Physicians' judgement and comprehensive geriatric assessment (CGA) select different patients as fit for chemotherapy. *Crit Rev Oncol Hematol* 2007 Oct;64(1):1-9.
<http://www.ncbi.nlm.nih.gov/pubmed/17613243>
21. Raj GV, Iasonos A, Herr H, et al. Formulas calculating creatinine clearance are inadequate for determining eligibility for Cisplatin-based chemotherapy in bladder cancer. *J Clin Oncol* 2006 Jul;24(19):3095-100.
<http://www.ncbi.nlm.nih.gov/pubmed/16809735>

22. von der Maase H. Gemcitabine in transitional cell carcinoma of the urothelium. *Expert Rev Anticancer Ther* 2003 Feb;3(1):11-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12597345>
23. Moore MJ, Tannock IF, Ernst DS, et al. Gemcitabine: a promising new agent in the treatment of advanced urothelial cancer. *J Clin Oncol* 1997 Dec;15(12):3441-5.
<http://www.ncbi.nlm.nih.gov/pubmed/9396395>
24. Stadler WM, Kuzel T, Roth B, et al. Phase II study of single-agent gemcitabine in previously untreated patients with metastatic urothelial cancer. *J Clin Oncol* 1997 Nov;15(11):3394-8.
<http://www.ncbi.nlm.nih.gov/pubmed/9363871>
25. Marengo D, Castagneto B, Zai S. Gemcitabine monochemotherapy in the elderly patient with advanced bladder cancer. *Proc Am Soc Clin Oncol* 2002;21:150b (abstr 2414).
26. Pollera CF, Ceribelli A, Crecco M, et al. Weekly gemcitabine in advanced bladder cancer: a preliminary report from a phase I study. *Ann Oncol* 1994 Feb;5(2):182-4.
<http://www.ncbi.nlm.nih.gov/pubmed/8186164>
27. Lorusso V, Pollera CF, Antimi M, et al. A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treated with platinum. Italian Co-operative Group on Bladder Cancer. *Eur J Cancer* 1998 Jul;34(8):1208-12.
<http://www.ncbi.nlm.nih.gov/pubmed/9849481>
28. Gebbia V, Testa A, Borsellino N, et al. Single agent 2',2'-difluorodeoxycytidine in the treatment of metastatic urothelial carcinoma: a phase II study. *Clin Ter* 1999 Jan-Feb;150(1):11-5.
<http://www.ncbi.nlm.nih.gov/pubmed/10367539>
29. Albers P, Siener R, Härtlein M, et al; German TCC Study Group of the German Association of Urologic Oncology. Gemcitabine monotherapy as second-line treatment in cisplatin-refractory transitional cell carcinoma - prognostic factors for response and improvement of quality of life. *Onkologie* 2002 Feb;25(1):47-52.
<http://www.ncbi.nlm.nih.gov/pubmed/11893883>
30. Logothetis CJ, Dexeus FH, Finn L, et al. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. *J Clin Oncol* 1990 Jun;8(6):1050-5.
<http://www.ncbi.nlm.nih.gov/pubmed/2189954>
31. Bamias A, Aravantinos G, Deliveliotis C, et al; Hellenic Cooperative Oncology Group. Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. *J Clin Oncol* 2004 Jan;22(2):220-8.
<http://www.ncbi.nlm.nih.gov/pubmed/14665607>
32. Sternberg CN, Yagoda A, Scher HI, et al. Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. *Cancer* 1989 Dec;64(12):2448-58.
<http://www.ncbi.nlm.nih.gov/pubmed/2819654>
33. Sternberg CN, Yagoda A, Scher HI, et al. M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. *J Urol* 1988 Mar;139(3):461-9.
<http://www.ncbi.nlm.nih.gov/pubmed/3343727>
34. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000 Sep;18(17):3068-77.
<http://www.ncbi.nlm.nih.gov/pubmed/11001674>
35. Gabrilove JL, Jakubowski A, Scher H, et al. Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. *N Engl J Med* 1988 Jun;318(22):1414-22.
<http://www.ncbi.nlm.nih.gov/pubmed/2452983>
36. Sternberg CN, de Mulder PH, Schornagel JH, et al; European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. *J Clin Oncol* 2001 May;19(10):2638-46.
<http://www.ncbi.nlm.nih.gov/pubmed/11352955>
37. Sternberg CN, de Mulder P, Schornagel JH, et al; EORTC Genito-Urinary Cancer Group. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. *Eur J Cancer* 2006 Jan;42(1):50-4.
<http://www.ncbi.nlm.nih.gov/pubmed/16330205>

38. Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/ cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. *J Clin Oncol* 2012 Apr 1;30(10):1107-13.
<http://www.ncbi.nlm.nih.gov/pubmed/22370319>
39. Dreicer R, Manola J, Roth BJ, et al. Phase III trial of methotrexate, vinblastine, doxorubicin, and cisplatin versus carboplatin and paclitaxel in patients with advanced carcinoma of the urothelium. *Cancer* 2004 Apr;100(8):1639-45.
<http://www.ncbi.nlm.nih.gov/pubmed/15073851>
40. Petrioli R, Frediani B, Manganeli A, et al. Comparison between a cisplatin-containing regimen and a carboplatin-containing regimen for recurrent or metastatic bladder cancer patients. A randomized phase II study. *Cancer* 1996 Jan;77(2):344-51.
<http://www.ncbi.nlm.nih.gov/pubmed/8625244>
41. Carteni G, Dogliotti L, Crucitta E, et al. Phase II randomised trial of gemcitabine plus cisplatin (GP) and gemcitabine plus carboplatin (GC) in patients (pts) with advanced or metastatic transitional cell carcinoma of the urothelium (TCCU). *Proc Am Soc Clin Oncol* 2003;22: abstr 1543.
http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=23&abstractID=102093
42. Bellmunt J, Ribas A, Eres N, et al. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. *Cancer* 1997 Nov;80(10):1966-72.
<http://www.ncbi.nlm.nih.gov/pubmed/9366300>
43. Sternberg CN, Calabrò F, Pizzocaro G, et al. Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. *Cancer* 2001 Dec;92(12):2993-8.
<http://www.ncbi.nlm.nih.gov/pubmed/11753976>
44. Meluch AA, Greco FA, Burris HA 3rd, et al. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie pearl cancer research network. *J Clin Oncol* 2001 Jun;19(12):3018-24.
<http://www.ncbi.nlm.nih.gov/pubmed/11408496>
45. Parameswaran R, Fisch MJ, Ansari RH, et al. A Hoosier Oncology Group phase II study of weekly paclitaxel and gemcitabine in advanced transitional cell (TCC) carcinoma of the bladder. *Proc Am Soc Clin Oncol* 2001;200:abstr 798.
http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=10&abstractID=798
46. Guardino AE, Srinivas S. Gemcitabine and paclitaxel as second line chemotherapy for advanced urothelial malignancies. *Proc Am Soc Clin Oncol* 2002;21: abstr 2413.
http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=16&abstractID=2413
47. Fechner G, Siener R, Reimann M, et al. Randomised phase II trial of gemcitabine and paclitaxel second-line chemotherapy in patients with transitional cell carcinoma (AUO Trial AB 20/99). *Int J Clin Pract* 2006 Jan;60(1):27-31.
<http://www.ncbi.nlm.nih.gov/pubmed/16409425>
48. Kaufman DS, Carducci MA, Kuzel T, et al. Gemcitabine (G) and paclitaxel (P) every two weeks (GP2w): a completed multicenter phase II trial in locally advanced or metastatic urothelial cancer (UC). *Proc Am Soc Clin Oncol* 2002;21: abstr 767.
http://www.asco.org/ASCO/Abstracts+&+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=16&abstractID=767
49. Calabrò F, Lorusso V, Rosati G, et al. Gemcitabine and paclitaxel every 2 weeks in patients with previously untreated urothelial carcinoma. *Cancer* 2009 Jun 15;115(12):2652-9.
<http://www.ncbi.nlm.nih.gov/pubmed/19396817>
50. Nogué-Aliguer M, Carles J, Arrivi A, et al; Spanish Cooperative Group. Gemcitabine and carboplatin in advanced transitional cell carcinoma of the urinary tract: an alternative therapy. *Cancer* 2003 May;97(9):2180-6.
<http://www.ncbi.nlm.nih.gov/pubmed/12712469>
51. Balducci L. Evidence-based management of cancer in the elderly. *Cancer Control* 2000 Jul-Aug;7(4):368-76.
<http://www.ncbi.nlm.nih.gov/pubmed/10895132>

52. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer “unfit” for cisplatin-based chemotherapy: phase II—results of EORTC study 30986. *J Clin Oncol* 2009 Nov 20;27(33):5634-9.
<http://www.ncbi.nlm.nih.gov/pubmed/19786668>
53. De Santis M, Bellmunt J, Mead G, et al. Randomized Phase II/III Trial Assessing Gemcitabine/ Carboplatin and Methotrexate/Carboplatin/Vinblastine in Patients With Advanced Urothelial Cancer Who Are Unfit for Cisplatin-Based Chemotherapy: EORTC Study 30986. *J Clin Oncol* 2012 Jan 10;30(2):191-9.
<http://www.ncbi.nlm.nih.gov/pubmed/22162575>
54. Vaughn DJ, Broome CM, Hussain M, et al. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. *J Clin Oncol* 2002 Feb;20(4):937-40.
<http://www.ncbi.nlm.nih.gov/pubmed/11844814>
55. Papamichael D, Gallagher CJ, Oliver RT, et al. Phase II study of paclitaxel in pretreated patients with locally advanced/metastatic cancer of the bladder and ureter. *Br J Cancer* 1997;75(4):606-7.
<http://www.ncbi.nlm.nih.gov/pubmed/9052419>
56. McCaffrey JA, Hilton S, Mazumdar M, et al. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. *J Clin Oncol* 1997 May;15(5):1853-7.
<http://www.ncbi.nlm.nih.gov/pubmed/9164195>
57. Moore M, Winquist E, Vokes E, et al. Phase II study of oxaliplatin in patients with inoperable, locally advanced or metastatic transitional cell carcinoma of the urothelial tract (TCC) who have received prior chemotherapy. *Proc Am Soc Clin Oncol* 2003;22: abstr 1638.
http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=23&abstractID=100319
58. Witte RS, Manola J, Burch PA, et al. Topotecan in previously treated advanced urothelial carcinoma: an ECOG phase II trial. *Invest New Drugs* 1998;16(2):191-5.
<http://www.ncbi.nlm.nih.gov/pubmed/9848585>
59. Petrylak D, Faulkner J, Van Veldhuizen P, et al. Evaluation of ZD1839 for advanced transitional cell carcinoma (TCC) of the urothelium: a Southwest Oncology Group Trial. *Proc Am Soc Clin Oncol* 2003;22: abstr 1619.
http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=23&abstractID=104215
60. Sridhar S, Stadler W, Le L, et al. Phase II study of bortezomib in advanced or metastatic urothelial cancer. A trial of the Princess Margaret Hospital [PMH] Phase II Consortium. *J Clin Oncol*, 2005 ASCO Annual Meeting Proceedings, Vol 23, No 16S Part I of II (June 1 Suppl), 2005:4677.
http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=34&abstractID=33648
61. Wulfing C, Machiels J, Richiels D, et al. A single arm, multicenter, open-label, phase II study of lapatinib as 2L treatment of pts with locally advanced/metastatic transitional cell carcinoma (TCC) of the urothelial tract. *J Clin Oncol*, 2005 ASCO Annual Meeting Proceedings, Vol 23, No 16S, Part I of II (June 1 Suppl) 2005:4594.
http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=34&abstractID=31739
62. Witte RS, Elson P, Bono B, et al. Eastern Cooperative Oncology Group phase II trial of ifosfamide in the treatment of previously treated advanced urothelial carcinoma. *J Clin Oncol* 1997 Feb;15(2): 589-93.
<http://www.ncbi.nlm.nih.gov/pubmed/9053481>
63. Sweeney CJ, Roth BJ, Kabbavar FF, et al. Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. *J Clin Oncol* 2006 Jul;24(21):3451-7.
<http://www.ncbi.nlm.nih.gov/pubmed/16849761>
64. Galsky MD, Mironov S, Iasonos A, et al. Phase II trial of pemetrexed as second-line therapy in patients with metastatic urothelial carcinoma. *Invest New Drugs* 2007 Jun;25(3):265-70.
<http://www.ncbi.nlm.nih.gov/pubmed/17146733>
65. Culine S, Theodore C, De Santis M, et al. A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen. *Br J Cancer* 2006 May;94(10):1395-401.
<http://www.ncbi.nlm.nih.gov/pubmed/16622447>
66. Bellmunt J, Théodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009 Sep 20;27(27):4454-61
<http://www.ncbi.nlm.nih.gov/pubmed/19687335>

67. Stadler WM. Gemcitabine doublets in advanced urothelial cancer. *Semin Oncol* 2002 Feb;29(1 Suppl3):15-9.
<http://www.ncbi.nlm.nih.gov/pubmed/11894003>
68. Hussain M, Vaishampayan U, Du W, et al. Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. *J Clin Oncol* 2001 May;19(9):2527-33.
<http://www.ncbi.nlm.nih.gov/pubmed/11331332>
69. Herr HW, Donat SM, Bajorin DF. Post-chemotherapy surgery in patients with unresectable or regionally metastatic bladder cancer. *J Urol* 2001 Mar;165(3):811-4.
<http://www.ncbi.nlm.nih.gov/pubmed/11176475>
70. Sweeney P, Millikan R, Donat M, et al. Is there a therapeutic role for post-chemotherapy retroperitoneal lymph node dissection in metastatic transitional cell carcinoma of the bladder? *J Urol* 2003 Jun;169(6):2113-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12771730>
71. Siefker-Radtke AO, Walsh GL, Pisters LL, et al. Is there a role for surgery in the management of metastatic urothelial cancer? The M.D. Anderson experience. *J Urol* 2004 Jan;171(1):145-8.
<http://www.ncbi.nlm.nih.gov/pubmed/14665863>
72. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev* 2001 Jun;27(3):165-76. Review.
<http://www.ncbi.nlm.nih.gov/pubmed/11417967>
73. Aapro M, Abrahamsson PA, Body JJ, et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. *Ann Oncol* 2008 Mar;19(3):420-32.
<http://www.ncbi.nlm.nih.gov/pubmed/17906299>
74. Zaghoul MS, Boutrus R, El-Hossieny H, et al. A prospective, randomized, placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer. *Int J Clin Oncol* 2010 Aug;15(4):382-9.
<http://www.ncbi.nlm.nih.gov/pubmed/20354750>
75. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol* 2011 Mar;29(9):1125-32.
<http://www.ncbi.nlm.nih.gov/pubmed/21343556>

13. QUALITY OF LIFE

13.1 Introduction

The evaluation of health-related quality of life (HRQoL) considers physical, psychological, emotional and social functioning.

Several questionnaires have been validated for assessing HRQoL in patients with bladder cancer, including FACT (Functional Assessment of Cancer Therapy)-G (1), EORTC QLQ-C30 (2), EORTC QLQ-BLM (muscle invasive bladder cancer module) (3), and SF (Short Form)-36 (4,5) and recently the BCI questionnaire specifically designed and validated for bladder cancer patients (6).

A psychometric test, such as the FACT-BL, should be used for recording bladder cancer morbidity. New intensive interviewing techniques have added valuable information to our knowledge of HRQoL, which greatly depends on patients' individual preferences in life (7).

Unfortunately, most retrospective studies do not evaluate the association between HRQoL and bladder cancer-specific issues after cystectomy, such as day-time and night-time incontinence or potency. Furthermore, important co-variables, such as a patient's age, mental status, coping ability and gender, have rarely been considered (8,9). It remains difficult to predict the impact of post-therapeutic symptoms because of individual differences in symptom tolerance.

13.2 Choice of urinary diversion

There is controversy about which type of urinary diversion is best for a patient's HRQoL (10). Some studies have not demonstrated any difference in HRQoL (9,11,12). Nevertheless, most patients stated that, given a choice, they would still opt for an orthotopic diversion rather than an ileal conduit (13). Another study reported that, although urinary function is better in conduit patients, the urinary bother is the same in both diversion groups, resulting in the same HRQoL evaluation (14).

Due to improved surgical techniques in orthotopic bladder substitution, some recent studies are supportive of continent bladder substitutes (3,15-18). Two studies have shown a statistically significant difference in HRQoL in favour of neobladders (18,19). Patients with an orthotopic substitution had significantly better physical function and a more active lifestyle compared to patients with an ileal conduit. It is important to note that HRQoL parameters are independent prognostic factors for overall survival (20). Patients with a continent bladder-substitute generally scored more favourably than those with an incontinent diversion, as judged by body image, social activity and physical function (14,15,21).

13.3 Non-curative or metastatic bladder cancer

In non-curative or metastatic bladder cancer, HRQoL is reduced because of associated micturition problems, bleeding, pain and therefore disturbance of social and sexual life (22). There is limited literature describing HRQoL in bladder cancer patients receiving palliative care (23), but there are reports of bladder-related symptoms relieved by palliative surgery (24), radiotherapy (25), and/or chemotherapy (26).

Alternative definitive treatments of MIBC, e.g. trimodality bladder-sparing procedures, have shown similar survival times compared to cystectomy. However, the impact on HRQoL has been controversial (26-31).

13.4 Conclusions and recommendations for HRQoL

Conclusions	LE
No randomised, prospective HRQoL study has evaluated the different forms of definitive treatment for MIBC.	
In most patient groups studied, the overall HRQoL after cystectomy remains good, irrespective of the type of urinary diversion used. The suggestion that continent diversions are associated with a higher HRQoL, has not been sufficiently substantiated.	2b
Important determinants of (subjective) QoL are a patient's personality, coping style and social support.	

Recommendations	GR
The use of validated questionnaires is recommended to assess HRQoL in patients with MIBC.	B
Unless a patient's comorbidities, tumour variables and coping abilities present clear contraindications, a continent urinary diversion should be offered.	C
Pre-operative patient information, patient selection, surgical techniques, and careful post-operative follow-up are the cornerstones for achieving good long-term results.	C
Patients should be encouraged to take active part in the decision-making process. Clear and exhaustive information on all potential benefits and side-effects should be provided, allowing them to make informed decisions.	C

HRQoL = health-related quality of life; MIBC = muscle-invasive bladder cancer

13.5 References

1. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993 Mar;11(3):570-9.
<http://www.ncbi.nlm.nih.gov/pubmed/8445433>
2. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993 Mar;85(5):365-76.
<http://www.ncbi.nlm.nih.gov/pubmed/8433390>
3. Sogni F, Brausi M, Frea B, et al. Morbidity and quality of life in elderly patients receiving ileal conduit or orthotopic neobladder after radical cystectomy for invasive bladder cancer. *Urology* 2008 May;71(5):919-23.
<http://www.ncbi.nlm.nih.gov/pubmed/18355900>
4. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992 Jun;30(6):473-83.
<http://www.ncbi.nlm.nih.gov/pubmed/1593914>
5. Ware JE Jr, Keller SD, Gandek B, et al. Evaluating translations of health status questionnaires. Methods from the IQOLA project. International Quality of Life Assessment. *Int J Technol Assess Health Care* 1995 Summer;11(3):525-51.
<http://www.ncbi.nlm.nih.gov/pubmed/7591551>

6. Gilbert SM, Dunn RL, Hollenbeck BK, et al. Development and validation of the Bladder Cancer Index: a comprehensive, disease specific measure of health related quality of life in patients with localized bladder cancer. *J Urol* 2010 May;183(5):1764-9.
<http://www.ncbi.nlm.nih.gov/pubmed/20299056>
7. Ramirez A, Perrotte P, Valiquette L, et al. Exploration of health-related quality of life areas that may distinguish between continent diversion and ileal conduit patients. *Can J Urol* 2005 Feb;12(1):2537-42.
<http://www.ncbi.nlm.nih.gov/pubmed/15777491>
8. Månsson A, Caruso A, Capovilla E, et al. Quality of life after radical cystectomy and orthotopic bladder substitution: a comparison between Italian and Swedish men. *BJU Int* 2000 Jan;85(1):26-31.
<http://www.ncbi.nlm.nih.gov/pubmed/10619940>
9. Autorino R, Quarto G, Di Lorenzo G, et al. Health related quality of life after radical cystectomy: comparison of ileal conduit to continent orthotopic neobladder. *Eur J Surg Oncol* 2009 Aug;35(8): 858-64.
<http://www.ncbi.nlm.nih.gov/pubmed/18824319>
10. World Health Organization (WHO) Consensus Conference on Bladder Cancer, Hautmann RE, Abol-Enein H, Hafez K, et al. Urinary diversion. *Urology* 2007 Jan;69(1 Suppl):17-49.
<http://www.ncbi.nlm.nih.gov/pubmed/17280907>
11. Månsson A, Davidsson T, Hunt S, et al. The quality of life in men after radical cystectomy with a continent cutaneous diversion or orthotopic bladder substitution: is there a difference? *BJU Int* 2002 Sep;90(4):386-90.
<http://www.ncbi.nlm.nih.gov/pubmed/12175394>
12. Wright JL, Porter MP. Quality-of-life assessment in patients with bladder cancer. *Nat Clin Pract Urol* 2007 Mar;4(3):147-54.
<http://www.ncbi.nlm.nih.gov/pubmed/17347659>
13. Saika T, Arata R, Tsushima T, et al; Okayama Urological Research Group. Health-related quality of life after radical cystectomy for bladder cancer in elderly patients with an ileal conduit, ureterocutaneostomy, or orthotopic urinary reservoir: a comparative questionnaire survey. *Acta Med Okayama* 2007 Aug;61(4):199-203.
<http://www.ncbi.nlm.nih.gov/pubmed/17853939>
14. Hedgepeth RC, Gilbert SM, He C, et al. Body image and bladder cancer specific quality of life in patients with ileal conduit and neobladder urinary diversions. *Urology* 2010 Sep;76(3):671-5.
<http://www.ncbi.nlm.nih.gov/pubmed/20451964>
15. Dutta SC, Chang SC, Coffey CS, et al. Health related quality of life assessment after radical cystectomy: comparison of ileal conduit with continent orthotopic neobladder. *J Urol* 2002 Jul;168(1):164-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12050514>
16. Hara I, Miyake H, Hara S, et al. Health-related quality of life after radical cystectomy for bladder cancer: a comparison of ileal conduit and orthotopic bladder replacement. *BJU Int* 2002 Jan;89(1): 10-13.
<http://www.ncbi.nlm.nih.gov/pubmed/11849152>
17. Stenzl A, Sherif H, Kuczyk M. Radical cystectomy with orthotopic neobladder for invasive bladder cancer: a critical analysis of long term oncological, functional and quality of life results. *Int Braz J Urol* 2010 Sep-Oct;36(5):537-47.
<http://www.ncbi.nlm.nih.gov/pubmed/21044370>
18. Philip J, Manikandan R, Venugopal S, et al. Orthotopic neobladder versus ileal conduit urinary diversion after cystectomy - a quality-of-life based comparison. *Ann R Coll Surg Engl* 2009 Oct;91(7):565-9.
<http://www.ncbi.nlm.nih.gov/pubmed/19558757>
19. Hobisch A, Tosun K, Kinzl J, et al. Life after cystectomy and orthotopic neobladder versus ileal conduit urinary diversion. *Semin Urol Oncol* 2001 Feb;19(1):18-23.
<http://www.ncbi.nlm.nih.gov/pubmed/11246729>
20. Roychowdhury DF, Hayden A, Liepa AM. Health-related quality-of-life parameters as independent prognostic factors in advanced or metastatic bladder cancer. *J Clin Oncol* 2003 Feb;21(4):673-8.
<http://www.ncbi.nlm.nih.gov/pubmed/12586805>
21. Hardt J, Filipas D, Hohenfellner R, et al. Quality of life in patients with bladder carcinoma after cystectomy: first results of a prospective study. *Qual Life Res* 2000 Feb;9(1):1-12.
<http://www.ncbi.nlm.nih.gov/pubmed/10981202>
22. Fosså SD, Aaronson N, Calais da Silva F, et al. Quality of life in patients with muscle-infiltrating bladder cancer and hormone-resistant prostatic cancer. *Eur Urol* 1989;16(5):335-9.
<http://www.ncbi.nlm.nih.gov/pubmed/2476317>

23. Mommsen S, Jakobsen A, Sell A. Quality of life in patients with advanced bladder cancer. A randomized study comparing cystectomy and irradiation-the Danish Bladder Cancer Study Group (DAVECA protocol 8201). *Scand J Urol Nephrol Suppl* 1989;125:115-20.
<http://www.ncbi.nlm.nih.gov/pubmed/2699072>
24. Nagele U, Anastasiadis AG, Merseburger AS, et al. The rationale for radical cystectomy as primary therapy for T4 bladder cancer. *World J Urol* 2007 Aug;25(4):401-5.
<http://www.ncbi.nlm.nih.gov/pubmed/17525849>
25. Fokdal L, Høyer M, von der Maase H. Radical radiotherapy for urinary bladder cancer: treatment outcomes. *Expert Rev Anticancer Ther* 2006 Feb;6(2):269-79.
<http://www.ncbi.nlm.nih.gov/pubmed/16445379>
26. Rödel C, Weiss C, Sauer R. Organ preservation by combined modality treatment in bladder cancer: the European perspective. *Semin Radiat Oncol* 2005 Jan;15(1):28-35.
<http://www.ncbi.nlm.nih.gov/pubmed/15662604>
27. Rödel C, Grabenbauer GG, Kühn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. *J Clin Oncol* 2002 Jul;20(14):3061-71.
<http://www.ncbi.nlm.nih.gov/pubmed/12118019>
28. Merseburger AS, Kuczyk MA. The value of bladder-conserving strategies in muscle-invasive bladder carcinoma compared with radical surgery. *Curr Opin Urol* 2007 Sep;17(5):358-62.
<http://www.ncbi.nlm.nih.gov/pubmed/17762631>
29. Milosevic M, Gospodarowicz M, Zietman A, et al. Radiotherapy for bladder cancer. *Urology* 2007 Jan;69(1 Suppl):80-92.
<http://www.ncbi.nlm.nih.gov/pubmed/17280910>
30. Rödel C, Weiss C, Sauer R. Trimodality treatment and selective organ preservation for bladder cancer. *J Clin Oncol* 2006;24(35):5536-44.
<http://www.ncbi.nlm.nih.gov/pubmed/17158539>
31. Zietman AL, Shipley WU, Kaufman DS. Organ-conserving approaches to muscle-invasive bladder cancer: future alternatives to radical cystectomy. *Ann Med* 2000 Feb;32(1):34-42.
<http://www.ncbi.nlm.nih.gov/pubmed/10711576>
32. Lodde M, Palermo S, Compj E, et al. Four years experience in bladder preserving management for muscle invasive bladder cancer. *Eur Urol* 2005 Jun;47(6):773-8; discussion 778-9.
<http://www.ncbi.nlm.nih.gov/pubmed/15925072>

14. FOLLOW-UP

An appropriate schedule for disease monitoring should be based on:

- natural timing of recurrence;
- probability of disease recurrence;
- functional deterioration at particular sites;
- possibilities of treatment of a recurrence (1).

Nomograms on cancer-specific survival following radical cystectomy have been developed and externally validated. However, their wider use cannot be recommended prior to further data (2-4).

Contemporary cystectomy series have demonstrated 5-15% probability of pelvic recurrence. Most recurrences manifest during the first 24 months, often within 6-18 months after surgery. However, late recurrences have occurred up to 5 years after cystectomy. Again, pTN and pN were predictive of the development of pelvic recurrence.

Patients have a poor prognosis after pelvic recurrence. Even with treatment, the median survival ranges from 4-8 months following diagnosis. Definitive therapy can sometimes provide prolonged survival, but in most cases provides significant palliation of symptoms. Treatment is with systemic chemotherapy, local surgery or radiotherapy.

14.1 Site of recurrence

14.1.1 Distant recurrences

Distant recurrences are seen in up to 50% of patients treated with cystectomy. Most recurrences occur in the first 24 months, although progression has been observed after more than 10 years (5). Again, pTN and pN were risk factors (6).

The most likely sites for distant recurrences are the lungs, liver and bones (7). Upper urinary tract recurrence is rarely seen (1.8-6.0%). However, when it develops, it usually does so within 28-49 months after cystectomy (8). Surveillance regimens often fail to detect tumours before symptoms develop. Radical nephro-ureterectomy can provide prolonged survival (9).

14.1.2 Urothelial extravesical recurrences (see comment below)

The incidence of secondary urethral tumours after radical cystectomy is 1.5-6.0% in males, with a mean recurrence-free interval of 13.5-39 months and a median survival of 28-38 months, of which > 50% died because of systemic disease.

Secondary urethral tumours are particularly likely to occur at 1-3 years after surgery. Prophylactic urethrectomy at the time of cystectomy is no longer justified in most patients. Independent predictors for urethral recurrence are: cystectomy for NMIBC, prostate involvement, and a history of previously recurrent NMIBC (8).

In women, the main risk factor is disease at the bladder neck (10). Many studies have demonstrated that the risk of urethral recurrence after orthotopic diversion (0.9-4%) (11-14) is significantly less than after non-orthotopic diversion (6.4-11.1%) (11,13).

There is little data and agreement about urethral follow-up, with some authors recommending routine surveillance with urethral wash cytology and urine cytology (14), and others doubting the need for routine urethral surveillance (12,15-17). Urethral washes and urine cytology do not appear to have any effect on survival (15,18,19). However, there is a significant survival advantage in males with urethral recurrence diagnosed asymptotically versus symptomatically, so follow-up of the male urethra is indicated in those patients at risk of urethral recurrence (8).

Treatment is influenced by the local stage and grade of a urethral occurrence:

- In CIS of the urethra, BCG instillations have shown success rates of 83% (14).
- In invasive disease, urethrectomy should be performed if the urethra is the only site of disease.
- In distant disease, systemic chemotherapy is indicated (7).

14.1.3 Conclusions and recommendations for specific recurrence sites

Site of recurrence	Conclusion	LE	Recommendation	GR
Pelvic recurrence	Poor prognosis			
	Treatment should be individualized depending on the local extent of tumour	2b	Radiotherapy, chemotherapy and possibly surgery are options for treatment, either alone or in combination	C
Upper urinary tract			See EAU guidelines on Upper Urinary Tract Carcinomas (20)	

UUTTs occur in 1.8-6% of cases in contemporary series and represent the most common sites of late recurrence (3 years of disease-free survival following radical cystectomy). The median OS is 10-55 months, and 60-67% of patients will die of metastatic disease (8).

A recent meta-analysis found that 38% of UUT recurrence was diagnosed by follow-up investigation, whereas in the remaining 62% diagnosis was based on symptoms. When urine cytology was used in surveillance, the rate of primary detection was 7% and with UUT imaging it was 29.6% (22).

The meta-analysis made the following useful conclusions:

- Patients with superficial cancer have a probability of a UUT-TCC lesion twice as high as those with invasive disease.
- Multifocality increases the risk of recurrence by 3-fold and recurrence from 2 to 4-fold.
- Positive ureteral or urethral margins increase the risk by 7-fold.

Table 6 Follow-up of invasive TCC with or without cystectomy*

Radiological procedure	Rating scale ¹	Comments	Relative radiation level*
X-ray chest	9		Minimum
CT urography	8		High
X-ray abdomen loopogram	8	In patients with an ideal loop post-cystectomy	Medium
X-ray intravenous urography	5	Utilisation of intravenous urography has continued to decline with the increasingly widespread use of CT urography	Medium
MR imaging abdomen and pelvis without and with contrast	5	See ESUR guidelines on contrast media version 7.0 (21)	None
CT abdomen and pelvis with contrast	5	Appropriate if CT urography is not available. Visceral/nodal status evaluated during CT urography	High
CT chest with contrast	3	Performed if chest X-ray is equivocal	Medium
US pelvis (bladder)	3		None
FDG-PET whole body indicated for suspected or nodal metastasis	2	Indicated for suspected nodal or distant metastasis	High
After 5 years of follow-up, oncological surveillance can be stopped and surveillance continued with functional surveillance			

¹ 1 is least appropriate; 9 is most appropriate.

* Adapted from: American College of Radiology. *Follow-up Imaging of Bladder Carcinoma*. Date of origin: 1996; Last review date: 2000.

14.1.4 Follow-up of functional outcomes and complications

Urinary-diversion related complications are detected in 45% of patients during the first 5 years of follow-up. This rate increases with time being more than 54% after 15 years of follow-up. Long-term follow-up of functional outcomes are desirable (8) (LE:3). Follow-up may stop after 15 years.

14.2 References

- Malkowicz SB, van Poppel H, Mickisch G, et al. Muscle-invasive urothelial carcinoma of the bladder. *Urology* 2007 Jan;69(1 Suppl):3-16.
<http://www.ncbi.nlm.nih.gov/pubmed/17280906>
- Karakiewicz PI, Shariat SF, Palapattu GS, et al. Nomogram for predicting disease recurrence after radical cystectomy for transitional cell carcinoma of the bladder. *J Urol* 2006 Oct;176(4 Pt 1):1354-61; discussion 1361-2.
<http://www.ncbi.nlm.nih.gov/pubmed/16952631>
- Shariat SF, Karakiewicz PI, Palapattu GS, et al. Nomograms provide improved accuracy for predicting survival after radical cystectomy. *Clin Cancer Res* 2006 Nov 15;12(22):6663-76.;
<http://www.ncbi.nlm.nih.gov/pubmed/17121885>
- Zaak D, Burger M, Otto W, et al. Predicting individual outcomes after radical cystectomy: an external validation of current nomograms. *BJU Int* 2010 Aug;106(3):342-8.
<http://www.ncbi.nlm.nih.gov/pubmed/20002664>
- Mathers MJ, Zumbo J, Wyler S, et al. Is there evidence for a multidisciplinary follow-up after urological cancer? An evaluation of subsequent cancers. *World J Urol* 2008 Jun;26(3):251-6.
<http://www.ncbi.nlm.nih.gov/pubmed/18421461>
- Ghoneim MA, Abdel-Latif M, el-Mekresh M, et al. Radical cystectomy for carcinoma of the bladder: 2,720 consecutive cases 5 years later. *J Urol* 2008 Jul;180(1):121-7.
<http://www.ncbi.nlm.nih.gov/pubmed/18485392>
- Bochner BH, Montie JE, Lee CT. Follow-up strategies and management of recurrence in urologic oncology bladder cancer: invasive bladder cancer. *Urol Clin North Am* 2003 Nov;30(4):777-89.
<http://www.ncbi.nlm.nih.gov/pubmed/14680314>

8. Soukup V, Babjuk M, Bellmunt J et al. Follow-up after surgical treatment of bladder cancer: A critical analysis of the literature. *Eur Urol* 2012 Aug 62(2): 290-302.
<http://www.ncbi.nlm.nih.gov/pubmed/22609313>
9. Sanderson KM, Cai J, Miranda G, et al. Upper tract urothelial recurrence following radical cystectomy for transitional cell carcinoma of the bladder: an analysis of 1,069 patients with 10-year followup. *J Urol* 2007 Jun;177:2088-94.
<http://www.ncbi.nlm.nih.gov/pubmed/17509294>
10. Stenzl A, Draxl H, Posch B, et al. The risk of urethral tumors in female bladder cancer: can the urethra be used for orthotopic reconstruction of the lower urinary tract? *J Urol* 1995 Mar;153(3 Pt 2):950-5.
<http://www.ncbi.nlm.nih.gov/pubmed/7853581>
11. Freeman JA, Tarter TA, Esrig D, et al. Urethral recurrence in patients with orthotopic ileal neobladders. *J Urol* 1996 Nov;156(5):1615-9.
<http://www.ncbi.nlm.nih.gov/pubmed/8863551>
12. Huguet J, Palou J, Serrallach M, et al. Management of urethral recurrence in patients with Studer ileal neobladder. *Eur Urol* 2003 May;43(5):495-8.
<http://www.ncbi.nlm.nih.gov/pubmed/12705993>
13. Nieder AM, Sved PD, Gomez P, et al. Urethral recurrence after cystoprostatectomy: implications for urinary diversion and monitoring. *Urology* 2004 Nov;64(5):950-4.
<http://www.ncbi.nlm.nih.gov/pubmed/15533484>
14. Varol C, Thalmann GN, Burkhard FC, et al. Treatment of urethral recurrence following radical cystectomy and ileal bladder substitution. *J Urol* 2004 Sep;172(3):937-42.
<http://www.ncbi.nlm.nih.gov/pubmed/15311003>
15. Lin DW, Herr HW, Dalbagni G. Value of urethral wash cytology in the retained male urethra after radical cystoprostatectomy. *J Urol* 2003 Mar;169(3):961-3.
<http://www.ncbi.nlm.nih.gov/pubmed/12576822>
16. Sherwood JB, Sagalowsky AI. The diagnosis and treatment of urethral recurrence after radical cystectomy. *Urol Oncol* 2006 Jul-Aug;24(4):356-61.
<http://www.ncbi.nlm.nih.gov/pubmed/16818191>
17. Slaton JW, Swanson DA, Grossman HB, et al. A stage specific approach to tumor surveillance after radical cystectomy for transitional cell carcinoma of the bladder. *J Urol* 1999 Sep;162(3 Pt 1):710-4.
<http://www.ncbi.nlm.nih.gov/pubmed/10458349>
18. Erckert M, Stenzl A, Falk M, et al. Incidence of urethral tumor involvement in 910 men with bladder cancer. *World J Urol* 1996;14(1):3-8.
<http://www.ncbi.nlm.nih.gov/pubmed/8646239>
19. Clark PE, Stein JP, Groshen SG, et al. The management of urethral transitional cell carcinoma after radical cystectomy for invasive bladder cancer. *J Urol* 2004 Oct;172(4 Pt 1):1342-7.
<http://www.ncbi.nlm.nih.gov/pubmed/15371837>
20. Roupôt M, Babjuk M, Compérat E, et al. EAU Guidelines on Urothelial Carcinomas of the Upper Urinary Tract. Edn. presented at the EAU Annual meeting, Milan 2013. ISBN978-90-79754-71-7.
<http://www.uroweb.org/guidelines/online-guidelines/>
21. Picozzi S, Ricci C, Gaeta M, et al. Upper urinary tract recurrence following radical cystectomy for bladder cancer: a meta-analysis on 13,185 patients. *J Urol* 2012 Dec;188(6):2046-54.
<http://www.ncbi.nlm.nih.gov/pubmed/23083867>

15. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

AJCC	American Joint Committee on Cancer
5-ALA	5-aminolevulinic acid
ASA (score)	American Society of Anesthesiologists
BC	bladder cancer
BCG	Bacillus Calmette-Guérin
BSC	best supportive care
BT	brachytherapy
CCI	Charlson Comorbidity Index
CGA	Comprehensive Geriatric Assessment
CI	confidence interval
CISCA	cisplatin, cyclophosphamide and adriamycine
CIRS	Cumulative Illness Rating Scale
CIS	carcinoma in situ
CM	cisplatin, methotrexate
CMV	cytomegalovirus
CR	complete response
CrCl	calculation of creatinine clearance
CSS	cancer-specific survival
CT	computed tomography
DCE	dynamic contrast enhanced
DSS	disease-specific survival
DWI	diffusion-weighted imaging
DW MRI	diffusion-weighted magnetic resonance imaging
ECOG	Eastern Cooperative Oncology Group
EAU	European Association of Urology
EBRT	external-beam radiotherapy
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
ESUR	European Society of Urogenital Radiology
FACT	Functional Assessment of Cancer Therapy
FDG-PET/CT	fluorodeoxyglucose-positron emission computed tomography
G-CSF	granulocyte colony stimulating factor
GC	gemcitabine, cisplatin
GFR	glomerular filtration rate
GR	grade of recommendation
HAL	hexaminolaevulinate
HRQoL	health-related quality of life
ICD	Index of Coexistent Disease
IMRT	intensity-modulated radiotherapy
ISUP	International Society of Urological Pathology
ITT	intention-to-treat
IVU	intravenous urography
LE	level of evidence
LND	lymph node dissection
M-CAVI	methotrexate, carboplatin, vinblastine
MCV	methotrexate, cisplatin and vinblastine
MBD	metastatic bone disease
MD CT	multidetector computed tomography
MDCTU	multidetector computed tomography urography
MESNA	mercapto-ethanesulfonate
MIBC	muscle-invasive bladder cancer
MRI	magnetic resonance imaging
mUUT	metachronous upper urinary tract
MVAC	methotrexate, vinblastine, adriamycine and cisplatin
NCI	National Cancer Institute
NMIBC	non-muscle-invasive bladder cancer
NSF	nephrogenic systemic fibrosis

NYHA	New York Heart Association Functional Classification
ORR	overall response rate
OS	overall survival
PCR	pathological complete remission
PET	positron emission tomography
PET/CT	positron emission tomography, computed tomography
PFS	progression-free survival
PS	performance status
PUNLMP	papillary urothelial neoplasm of low malignant potential
QoL	quality-of-life
RALC	robotic-assisted laparoscopic cystectomy
RANKL	receptor activator of nuclear factor- κ B ligand
RC	radical cystectomy
SAT	severe acute toxicity
SEER	Surveillance, Epidemiology and End Results database
SES	socioeconomic status
SREs	skeletal-related events
SWOG	Southwest Oncology Group
TFA	transfatty acid
TIBI	Total Illness Burden Index
TNM	Tumour, Node, Metastasis (classification)
TUR	transurethral resection
TURB	transurethral resection of bladder tumour
UC	urothelial carcinoma
US	ultrasound
UTI	urinary tract infection
UTUC	upper tract urothelial carcinoma
UUT	upper urinary tract
WHO	World Health Organisation
ZA	zoledronic acid

Conflict of interest

All members of the Muscle-invasive and Metastatic Bladder Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.