

Guidelines on Bladder Cancer

Muscle-invasive and Metastatic

A. Stenzl, N.C. Cowan, M. De Santis, G. Jakse, M. Kuczyk,
A.S. Merseburger, M.J. Ribal, A. Sherif, J.A. Witjes

TABLE OF CONTENTS

PAGE

1	INTRODUCTION	5
2	EPIDEMIOLOGY AND RISK FACTORS	5
2.1	Epidemiology	5
2.2	Risk factors for bladder cancer	6
2.3	Conclusions	7
2.4	Recommendation	7
2.5	References	7
3	CLASSIFICATION	8
3.1	Tumour, Nodes, Metastases Classification (TNM)	8
3.2	Histological grading of non-muscle-invasive bladder tumours	9
3.2.1	WHO/ISUP grading	9
3.3	References	9
3.4	Pathology	9
3.4.1	Urologist handling of the specimens	9
3.4.2	Pathologist handling of the specimens	10
3.4.3	Pathology of muscle-invasive bladder cancer	10
3.4.4	Guidelines on assessment of tumour specimens	10
3.5	References	10
4	DIAGNOSIS AND STAGING	11
4.1	Diagnosis	11
4.1.1	Symptoms	11
4.1.2	Physical examination	11
4.1.3	Imaging	11
4.1.3.1	Intravenous urography and CT scan	11
4.1.3.2	Ultrasonography	11
4.1.4	Urinary cytology and urinary markers	11
4.1.5	Cystoscopy	12
4.1.6	Transurethral resection of invasive bladder tumours	12
4.1.7	Bladder and prostatic urethral biopsy	12
4.1.8	Fluorescence cystoscopy	12
4.1.9	Second resection	12
4.1.10	Concomitant prostate cancer	13
4.1.11	Recommendations for primary assessment of presumably invasive bladder tumours	13
4.1.12	References	13
4.2	Imaging for staging in verified bladder tumours	14
4.2.1	Local staging of invasive bladder cancer	15
4.2.1.1	MR imaging for local staging of invasive bladder cancer	15
4.2.1.2	CT for local staging of invasive bladder cancer	15
4.2.2	Imaging of nodal involvement	15
4.2.3	Extravesical urothelial carcinoma	15
4.2.4	Distant metastases other than lymph nodes	15
4.2.5	Conclusions	15
4.2.6	Recommendations for staging	16
4.3	References	16
5	TREATMENT FAILURE OF NON-MUSCLE INVASIVE BLADDER TUMOURS	17
5.1	High-risk non-muscle-invasive urothelial carcinoma	17
5.2	Carcinoma in situ	18
5.3	Recommendations	18
5.4	References	18

6	NEOADJUVANT CHEMOTHERAPY	20
6.1	Conclusions	21
6.2	Recommendations	21
6.3	References	21
7	RADICAL SURGERY AND URINARY DIVERSION	23
7.1	Removal of the tumour bearing bladder	23
7.1.1	Background	23
7.1.2	Timing and delay of cystectomy	24
7.1.3	Indications	24
7.1.4	Technique and extent	24
7.1.5	Laparoscopic cystectomy	25
7.2	Urinary diversion after radical cystectomy	25
7.2.1	Ureterocutaneostomy	25
7.2.2	Ileal conduit	25
7.2.3	Continent cutaneous urinary diversion	25
7.2.4	Ureterocolonic diversion	26
7.2.5	Orthotopic neobladders	26
7.3	Morbidity and mortality	26
7.4	Survival	26
7.5	Conclusions	26
7.6	Recommendations	27
7.6.1	Recommendations for radical surgery	27
7.6.2	Recommendations for urinary diversion	27
7.7	References	27
8	NON-RESECTABLE TUMOURS	31
8.1	Palliative cystectomy for muscle-invasive bladder carcinoma	31
8.2	Conclusions	31
8.3	Recommendations	32
8.4	References	32
9	NEOADJUVANT RADIOACTIVITY IN MUSCLE-INVASIVE BLADDER CANCER	32
9.1	Pre-operative radiotherapy	32
9.1.1	Retrospective studies	32
9.1.2	Randomized studies	32
9.2	Conclusions	33
9.3	Recommendations	33
9.4	References	33
10	BLADDER-SPARING TREATMENTS	34
10.1	Transurethral resection of bladder tumour (TURBT)	34
10.1.1	Conclusion and recommendation	35
10.1.2	References	35
10.2	External beam radiotherapy	35
10.2.1	Conclusions	35
10.2.2	Recommendation	35
10.2.3	References	35
10.3	Chemotherapy	36
10.3.1	Conclusion	36
10.3.2	Recommendation	36
10.3.3	References	37
10.4	Multimodality treatment	37
10.4.1	Conclusions	37
10.4.2	Recommendations	38
10.4.3	References	38

11	ADJUVANT CHEMOTHERAPY	38
	11.1 Conclusion	39
	11.2 Recommendation	39
	11.3 References	39
12	METASTATIC DISEASE	40
	12.1 Prognostic factors and treatment decisions	40
	12.2 Single-agent chemotherapy	40
	12.3 Standard first-line chemotherapy for 'fit' patients	41
	12.4 Carboplatin-containing chemotherapy in 'fit' patients	41
	12.5 Non-platinum combination chemotherapy	41
	12.6 Chemotherapy in patients 'unfit' for cisplatin	41
	12.7 Second-line treatment	41
	12.8 Low-volume disease and post-chemotherapy surgery	42
	12.9 Conclusions	42
	12.10 Recommendations	42
	12.11 References	42
13.	QUALITY OF LIFE	47
	13.1 Conclusions	48
	13.2 Recommendations	48
	13.3 References	48
14	FOLLOW-UP	50
	14.1 Conclusions and recommendations according to condition	50
	14.2 General recommendations for follow-up	51
	14.3 References	51
15	ABBREVIATIONS USED IN THE TEXT	53

1. INTRODUCTION

The EAU guideline group for muscle-invasive and metastatic bladder cancer (MiM-BC) have prepared this guideline to help urologists assess the evidence-based management of muscle-invasive and metastatic bladder cancer and to incorporate the guideline recommendations into their clinical practice. Publications concerning muscle-invasive and metastatic bladder cancer are mostly based on retrospective analysis, including some larger multicentre studies and well-designed controlled studies. Only a few randomized studies are available, so that it is difficult to obtain high-level evidence-based data. The recommendations provided in the current guidelines are based on a systemic literature search using Medline, the Cochrane Central Register of Systematic Reviews, and reference lists in publications and review articles.

There is clearly a need for continuous re-evaluation of the information presented in the current guideline by an expert panel. It has to be emphasized that the current guideline contains information for the treatment of an individual patient according to a standardized approach. The information should be considered as providing recommendations without legal implications.

The level of evidence and grade of recommendation provided in this guideline follow the listings in Table 1. The aim of grading the recommendations is to provide transparency between the underlying evidence and the recommendation given.

Table 1: Levels of evidence and grade of guideline recommendations as used by EAU (1)

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomized trials
1b	Evidence obtained from at least one randomized trial
2a	Evidence obtained from one well-designed controlled study without randomization
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

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

1.1 REFERENCE

1. Modified from Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. <http://www.cebm.net/index.aspx?o=1025> [access date February 2009].

2. EPIDEMIOLOGY AND RISK FACTORS

2.1 Epidemiology

In 2006, in Europe, an estimated 104,400 incident cases of bladder cancer were diagnosed, of which 82,800 were diagnosed in men and 21,600 in women. This represents 6.6% of the total cancers in men and 2.1% in women, with an estimated male-to-female ratio of 3.8:1. In men, bladder cancer was the fourth most common cancer. Bladder cancer resulted in 4.1% of total deaths for cancer in men and 1.8% of total deaths in women (1).

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

2.2 Risk factors for bladder cancer

Tobacco smoking. Tobacco smoking is the most well-established risk factor for bladder cancer, causing about 50-65% of male cases and 20-30% of female cases. A casual relationship has been established between an exposure to tobacco and cancer in studies in which chance, bias and confounding can be ruled out with reasonable confidence (4). The alleged carcinogenic constituents of tobacco smoke include arylamines, particularly the potent carcinogen 4-aminobiphenyl, polycyclic aromatic hydrocarbons (PAHs), N-nitroso compounds, heterocyclic amines and various epoxides.

The incidence of bladder cancer is directly related to the duration of smoking and number of cigarettes smoked per day (5). There is also a higher risk of bladder cancer in those who start smoking at a young age and for those exposed to environmental tobacco smoke during childhood (6). An immediate decrease in the risk of bladder cancer has been observed in those who quit smoking. This reduction was about 40% within 1 to 4 years of quitting smoking and reached 60% after 25 years of cessation (5). The promotion of cessation of smoking would result in the incidence of bladder cancer decreasing equally in men and women.

Occupational exposure to chemicals. Occupational exposure is the second most important risk factor for bladder cancer. Work-related cases account for 20-25% of all bladder cancer cases in several series. The substances involved in chemical exposure have been benzene derivatives and arylamines (2-naphthylamine, 4-ABP, 4,4'-methylenedianiline and o-toluidine). Professions in which this exposure occurs include those that use dyes, rubbers, textiles, paints, leathers and chemicals (7). Because of strict regulations, these chemicals have contributed minimally to the current incidence of bladder cancer in Western countries. In fact, a trend towards a decrease in bladder cancer due to occupational exposure has been reported in a pooled analysis of 11 case-control studies on bladder cancer conducted in European countries between 1976 and 1996 (8). An example of occupational exposure is aromatic amines, which are established carcinogens for urothelium and which can be inactivated by a metabolic acetylation pathway. It has been postulated that patients with slow acetylation capability were more susceptible to bladder cancer than rapid acetylators. NAT1 and NAT-2 are N-acetyltransferase genes located on the short arm of human chromosome 8 and involved in amine inactivation. The presence of an NAT2 slow acetylation genotype has been related to a higher risk of bladder cancer (9).

Other risk factors include phenacetin, which was included in 1987 among proven human carcinogens by the International Agency for Research on Cancer (IARC). Some studies have suggested that the risk of bladder cancer due to phenacetin is dose-dependent; however, the data is controversial concerning its metabolite acetaminophen (10).

External beam radiation therapy. Increased rates of secondary bladder malignancies have been reported after external beam radiation therapy (EBRT) for gynaecological malignancies with relative risks of 2 to 4 (11). In patients treated for prostate cancer, the incidence of bladder cancer was significantly lower in patients treated with radical prostatectomy than in patients who underwent EBRT (12).

Dietary factors. Several dietary factors had been related to bladder cancer, but the results of different studies have been 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 reduced the risk of bladder cancer (13).

Chronic urinary tract infection. Muscle-invasive bladder cancer, particularly invasive squamous cell carcinoma, is directly related to the presence of chronic urinary tract infection. Bladder schistosomiasis has been considered a definitive cause of urinary bladder cancer with an associated five-fold risk. Schistosomiasis 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 (14). In the same way as cyclophosphamide, an alkylating agent used for treatment of lymphoproliferative diseases and other non-neoplastic diseases, it has been correlated with posterior development of muscle-invasive bladder cancer with a period of latency of 6-13 years. Acrolein is a metabolite of cyclophosphamide and is responsible for an increase in the incidence of bladder cancer, which is independent of the occurrence of haemorrhagic cystitis related to the same treatment (15, 16).

Gender. Finally, differences in bladder cancer incidence by gender have been studied. In a retrospective study of patients submitted to radical cystectomy, it was demonstrated that women are more likely to be diagnosed with primary muscle-invasive disease than men (85% vs 51%) (2). It has been proposed 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 because the differential diagnosis in women includes diseases more prevalent than bladder cancer (17).

Differences in the gender prevalence of bladder cancer may also be due to other factors than tobacco and chemical exposure. In a large prospective cohort study, post-menopausal status was associated with

an increase in bladder cancer risk even after adjusting for smoking status. Thus, the differences in oestrogen and androgen levels between men and women could be responsible for some of the difference in gender prevalence of bladder cancer (18).

2.3 Conclusions

- The incidence of muscle invasive disease has not changed for a period of 5 years.
- Active and passive tobacco smoking continues to be the major risk factor while exposure-related incidence is decreasing (Level of evidence: 2a).
- The estimated male to female ratio was 3.8:1, with women more likely to be diagnosed with primary muscle invasive disease than men.
- Currently, treatment decisions cannot be based on molecular markers.

2.4 Recommendation

- The most important primary prevention for muscle-invasive bladder cancer is to eliminate active and passive smoking (Grade of recommendation: B).

2.5 REFERENCES

1. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007;18(3):581-92.
<http://www.ncbi.nlm.nih.gov/pubmed/17287242>
2. Vaidya A, Soloway MS, Hawke C, Tiguert R, Civantos F. De novo muscle invasive bladder cancer: is there a change in trend?. *J Urol* 2001;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;43(6):2532-9.
<http://www.ncbi.nlm.nih.gov/pubmed/455239>
4. 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>
5. Brennan P, Bogillot O, Cordier S, Greiser E, Schill W, Vineis P, Lopez-Abente G, Tzonou A, Chang-Claude J, Bolm-Audorff U, Jöckel KH, Donato F, Serra C, Wahrendorf J, Hours M, T'Mannetje A, Kogevinas M, Boffetta P. Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. *Int J Cancer* 2000;86(2):289-94.
<http://www.ncbi.nlm.nih.gov/pubmed/10738259>
6. Bjerregaard BK, Raaschou-Nielsen O, Sørensen M, Frederiksen K, Christensen J, Tjønneland A, Overvad K, Chapelon FC, Nagel G, Chang-Claude J, Bergmann MM, Boeing H, Trichopoulos D, Trichopoulou A, Oikonomou E, Berrino F, Palli D, Tumino R, Vineis P, Panico S, Peeters PH, Bueno-de-Mesquita HB, Kiemeneij L, Gram IT, Braaten T, Lund E, Gonzalez CA, Berglund G, Allen N, Roddam A, Bingham S, Riboli E. Tobacco smoke and bladder cancer—in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2006;119(10):2412-6.
<http://www.ncbi.nlm.nih.gov/pubmed/16894557>
7. Pashos CL, Botteman MF, Laskin BL, Redaelli A. Bladder cancer: epidemiology, diagnosis, and management. *Cancer Pract* 2002;10(6):311-22.
<http://www.ncbi.nlm.nih.gov/pubmed/15285078>
8. Kogevinas M, T'Mannetje A, Cordier S, Ranft U, González CA, Vineis P, Chang-Claude J, Lynge E, Wahrendorf J, Tzonou A, Jöckel KH, Serra C, Porru S, Hours M, Greiser E, Boffetta P. Occupation and bladder cancer among men in Western Europe. *Cancer Causes and Control* 2003;14(10):907-14.
<http://www.ncbi.nlm.nih.gov/pubmed/14750529>
9. García-Closas M, Malats N, Silverman D, Dosemeci M, Kogevinas M, Hein DW, Tardón A, Serra C, Carrato A, García-Closas R, Lloreta J, Castañó-Vinyals G, Yeager M, Welch R, Chanock S, Chatterjee N, Wacholder S, Samanic C, Torà M, Fernández F, Real FX, Rothman N. NAT2 slow acetylation, GSTM1 null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses. *Lancet* 2005;366(9486):649-59.
<http://www.ncbi.nlm.nih.gov/pubmed/16112301>
10. Castela JE, Yuan JM, Gago-Dominguez M, Yu MC, Ross RK. Non-steroidal anti-inflammatory drugs and bladder cancer prevention. *Br J Cancer* 2000;82(7):1364-9.
<http://www.ncbi.nlm.nih.gov/pubmed/10755416>
11. Chrouser K, Leibovich B, Bergstralh E, Zincke H, Blute M. Bladder cancer risk following primary and adjuvant external beam radiation for prostate cancer. *J Urol* 2006;174(1):107-10.
<http://www.ncbi.nlm.nih.gov/pubmed/15947588>

12. Boorjian S, Cowan JE, Konety BR, DuChane J, Tewari A, Carroll PR, Kane CJ; Cancer of the Prostate Strategic Urologic Research Endeavor Investigators. Bladder cancer incidence and risk factors in men with prostate cancer: results from Cancer of the Prostate Strategic Urologic Research Endeavor. *J Urol* 2007;177(3):883-7.
<http://www.ncbi.nlm.nih.gov/pubmed/17296367>
13. Steinmaus CM, Nuñez S, Smith AH. Diet and bladder cancer: a meta-analysis of six dietary variables. *Am J Epidemiol* 2000;151(7):693-702.
<http://www.ncbi.nlm.nih.gov/pubmed/10752797>
14. [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>
15. Kaldor JM, Day NE, Kittelmann B, Pettersson F, Langmark F, Pedersen D, Prior P, Neal F, Karjalainen S, Bell J et al. Bladder tumours following chemotherapy and radiotherapy for ovarian cancer: a casecontrol study. *Int J Cancer* 1995;63(1):1-6.
<http://www.ncbi.nlm.nih.gov/pubmed/7558434>
16. Travis LB, Curtis RE, Glimelius B, Holowaty EJ, Van Leeuwen FE, Lynch CF, Hagenbeek A, Stovall M, Banks PM, Adami J et al. Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. *J Natl Cancer Inst* 1995;87(7):524-30.
<http://www.ncbi.nlm.nih.gov/pubmed/7707439>
17. Cárdenas-Turanzas M, Cooksley C, Pettaway CA, Sabichi A, Grossman HB, Elting L. Comparative outcomes of bladder cancer. *Obstet Gynecol* 2006;108(1):169-75.
<http://www.ncbi.nlm.nih.gov/pubmed/16816072>
18. McGrath M, Michaud DS, De Vivo I. Hormonal and reproductive factors and the risk of bladder cancer in women. *Am J Epidemiol* 2006;163(3):236-44.
<http://www.ncbi.nlm.nih.gov/pubmed/16319290>

3. CLASSIFICATION

3.1 Tumour, Nodes, Metastases Classification (TNM)

The 2002 TNM classification approved by the Union International Contre le Cancer (UICC) has been widely accepted (Table 2) (1). It differs from the previous versions in the definition of stage T2 and T3 tumours.

Table 2: 2002 TNM classification of urinary bladder cancer

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, uterus, vagina, pelvic wall, abdominal wall
	T4a Tumour invades prostate, uterus or vagina
	T4b Tumour invades pelvic wall or abdominal wall

N - Lymph nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension

M - Distant metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

3.2 Histological grading of non-muscle-invasive bladder tumours

In 1998, the new classification of non-invasive urothelial tumours was proposed by the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) (1998 WHO/ISUP classification). It was published by the WHO in 2004 (2, 3) (Table 3). Its major contribution is a detailed histological description of the various grades using specific cytological and architectural criteria. A website (www.pathology.jhu.edu/bladder) illustrating examples of various grades was developed to improve accuracy further in using the system.

Table 3: WHO grading in 1973 and in 2004 (2, 3)**1973 WHO grading**

- Urothelial papilloma
- Grade 1: well differentiated
- Grade 2: moderately differentiated
- Grade 3: poorly differentiated

2004 WHO grading

- Urothelial papilloma
- Papillary urothelial neoplasm of low malignant potential (PUNLMP)
- Low-grade papillary urothelial carcinoma
- High-grade papillary urothelial carcinoma

3.2.1 WHO/ISUP grading

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

The PUNLMP are defined as lesions that do not have cytological features of malignancy but show normal urothelial cells in a papillary configuration. Although they have a negligible risk for progression, they are not completely benign and still have a tendency to recur. The intermediate grade (grade 2), which was controversial in the 1973 WHO classification, has been eliminated.

The use of the 2004 WHO classification is advocated, as this should result in a uniform diagnosis of tumours, which will be better classified according to risk potential. However, until the 2004 WHO classification has been validated by more 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 and this edition of the guidelines therefore uses the 1973 WHO grade classification.

3.3 REFERENCES

1. Sobin DH, Wittekind Ch, eds. In: *TNM Classification of Malignant Tumours*. 6th edn. New York: Wiley-Liss, 2002; pp. 199-202.
2. Epstein JI, Amin MB, Reuter VR, Mostofi FK. 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;22(12):1435-48.
<http://www.ncbi.nlm.nih.gov/pubmed/9850170>
3. Sauter G, Algaba F, Amin M, Busch C, Chevillet J, Gasser T, Grignon DJ, Hofstadter F, Lopez-Beltran A, Epstein JI. 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.
4. Lopez-Beltran A, Montironi R. Non-invasive urothelial neoplasms: according to the most recent WHO classification. *Eur Urol* 2004;46(2):170-6.
<http://www.ncbi.nlm.nih.gov/pubmed/15245809>

3.4 Pathology**3.4.1 Urologist handling of the specimens**

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

In radical cystectomy, bladder fixation must be performed 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 (1).

3.4.2 Pathologist handling of the specimens

Handling of specimens should follow the general rules as published by a collaborative group of pathologists and urologists (2).

It must be stressed that it can be very difficult to certify the presence of a neoplastic lesion using gross examination of the cystectomy specimen after TUR or chemotherapy, and it is therefore necessary to include the entire retracted or ulcerated area.

Of the margins, it is mandatory to study the urethra, ureter, the prostate in men, and radial margins (3). 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 the amount of adjacent urethra (in women) should be documented.

3.4.3 Pathology of muscle-invasive bladder cancer

At this stage, there are no cases of papillary urothelial neoplasms of low malignant potential and low-grade carcinoma. All cases are high-grade urothelial carcinomas (grade II or grade III in WHO 1973). For this reason, no more prognostic information can be provided by grading muscle-invasive bladder cancer (4).

However, some morphological subtypes can be most important for prognosis and treatment decisions, as in:

- Small-cell carcinomas
- Urothelial carcinomas with squamous and/or glandular partial differentiation
- Spindle cell carcinomas
- Some urothelial carcinomas with trophoblastic differentiation.

For staging, TNM 2002 is recommended. The pattern of muscular invasion can provide some prognostic information. Most cases show nodular or cordonal growth, but about 44% of cases show an infiltrative pattern. According to some authors (4), the median survival time of a patient with an infiltrative pattern is lower than with other pattern types ($p = 0.06$). Blood vessel invasion and lymph node infiltration have an independent prognostic significance (5). It seems that the pN category is closely associated with the number of lymph nodes studied by the pathologist. For this reason, some authors have observed that more than nine lymph nodes have to be investigated to reflect pN0 appropriately (6).

New prognostic markers are under study (7). Currently, insufficient evidence exists to recommend the standard use of p53 as a prognostic marker in high-risk muscle-invasive disease, since it will not yield sufficient data upon which to base treatment in an individual patient.

3.4.4 GUIDELINES ON ASSESSMENT OF TUMOUR SPECIMENS

Mandatory evaluations

- Depth of invasion (categories pT2 vs pT3a, pT3b or pT4)
- Margins with special attention paid to the radial margin
- Histological subtype, if it has clinical implications
- Extensive lymph node representation (more than eight)

Optional evaluations

- Bladder wall blood vessel invasion
- Pattern of muscle invasion

3.5 REFERENCES

1. Stenzl A. Current Concepts for Urinary Diversion in Women. *Eur Urol*(EAU Update Series 1);2003:91-9.
2. Lopez-Beltran A, Bassi PF, Pavone-Macaluso M, Montironi R, European Society of Urology; Urology Working Group. Handling and pathology reporting of specimens with carcinoma of the urinary bladder, ureter, and renal pelvis. A joint proposal of the European Society of Urology and the Urology Working Group. *Vichows Arch* 2004;445(2):103-10.
<http://www.ncbi.nlm.nih.gov/pubmed/15185074>
3. Herr HW. Pathologic evaluation of radical cystectomy specimens. *Cancer* 2002;95(3):668-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12209761>

4. Jimenez RE, Gheiler E, Oskanian P, Tiguert R, Sakr W, Wood DP Jr, Pontes JE, Grignon DJ. Grading the invasive component of urothelial carcinoma of the bladder and its relationship with progression-free survival. *Am J Surg Pathol* 2000;24(7):980-7.
<http://www.ncbi.nlm.nih.gov/pubmed/10895820>
5. Leissner J, Koeppen C, Wolf HK. Prognostic significance of vascular and perineural invasion in urothelial bladder cancer treated with radical cystectomy. *J Urol* 2003;169:955-60.
<http://www.ncbi.nlm.nih.gov/pubmed/12576821>
6. Shariat SF, Karam JA, Lerner SP. Molecular markers in bladder cancer. *Curr Opin Urol* 2008;18(1):1-8.
<http://www.ncbi.nlm.nih.gov/pubmed/18090481>
7. Tiguert R, Lessard A, So A, Fradet Y. Prognostic markers in muscle invasive bladder cancer. *World J Urol* 2002;20:190-5.
<http://www.ncbi.nlm.nih.gov/pubmed/12196903>

4. DIAGNOSIS AND STAGING

4.1 Diagnosis

4.1.1 Symptoms

Painless haematuria is a common finding. In addition, there is a group of patients who complain of urgency, dysuria, increased frequency and pelvic pain. Pelvic pain and all the symptoms related to urinary tract obstruction are found in more advanced tumours.

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 should be carried out before and after TUR to assess whether there is a palpable mass or the tumour fixed to the pelvic wall (1,2).

4.1.3 Imaging

4.1.3.1 Intravenous urography and CT scan

Large tumours may be seen as filling defects in the bladder. Intravenous urography (IVU) is also used to detect filling defects in the calices, renal pelvis and ureters, and hydronephrosis, which may indicate the presence of a ureteral tumour. The necessity to perform routine intravenous pyelography once a bladder tumour has been detected is now questioned because of the low incidence of significant findings obtained with this method (3-5) (Level of evidence: 3). The incidence of upper urinary tract tumours is low (1.8%), but increases to 7.5% in tumours located in the trigone (4).

In many centres, computed tomography (CT) urography is used as an alternative to conventional IVU (6). CT tomography gives more information than IVU, especially in invasive tumours of the upper tract (Level of evidence: 2a).

4.1.3.2 Ultrasonography

Ultrasonography (US) is increasingly used as the initial tool to assess the urinary tract. This is not only because it avoids the use of contrast agents, but also because sensitive transducers have improved imaging of the upper urinary tract and bladder.

Transabdominal US permits characterization of renal masses, detection of hydronephrosis and visualization of intraluminal filling defects in the bladder. Combined with plain abdominal film, it can be as accurate as IVU in diagnosing the cause of haematuria (1, 2) (Level of evidence: 3).

4.1.4 Urinary cytology and urinary markers

Examination of a voided urine or bladder-washing specimen for exfoliated cancer cells has high sensitivity in high-grade tumours (Level of evidence: 3). It is therefore useful when a high-grade malignancy or carcinoma in situ (CIS) is present.

Positive urinary cytology may indicate urothelial tumour anywhere in the urinary tract from the calix, through the ureters, into the bladder and proximal urethra. Cytological interpretation is user-dependent (7). The evaluation can be hampered by low cellular yield, urinary tract infections, stones or intravesical instillations. In experienced hands, however, specificity exceeds 90% (8) (Level of evidence: 2b). Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable as cytolysis may be often present. There is no urinary marker registered specifically for the diagnosis of invasive bladder cancer. However, since most invasive tumours are high-grade, the positive predictive value of markers may be higher.

4.1.5 Cystoscopy

The diagnosis of bladder cancer ultimately depends on cystoscopic examination of the bladder and histological evaluation of the resected tissue. In general, cystoscopy is initially performed in the office, using flexible instruments. If a bladder tumour has been visualized in earlier imaging studies, such as 3D ultrasonography, multidetector row CT or MRI a diagnostic cystoscopy can be omitted since the patient will undergo TUR for a histological diagnosis.

A careful description of the finding is necessary. It should include 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.

4.1.6 Transurethral resection of invasive bladder tumours

The goal of TUR is to make the correct diagnosis, which means including bladder muscle in the resection biopsies.

The strategy of resection depends from 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. The specimens from different fractions must be referred to the pathologist in separate containers to enable him to make a correct diagnosis. Cauterization has to be avoided as much as possible during the resection to prevent tissue destruction.

4.1.7 Bladder and prostatic urethral biopsy

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

The biopsies from normal-looking mucosa in patients with bladder tumours, so called random biopsies (R-biopsies) or selected site mucosal biopsies, are only recommended if fluorescent areas are seen with photodynamic diagnosis (PDD). Cold cup biopsies from normal-looking mucosa should be performed when cytology is positive, when exophytic tumour is of non-papillary appearance, or when fluorescent areas are seen with PDD. When abnormal areas of urothelium are seen, it is advised to take 'cold cup' biopsies or biopsies with a resection loop. 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 has been reported. Although the exact risk is not known, it seems to be higher if tumour is located on the trigone or bladder neck, in the presence of bladder CIS and in multiple tumours (9, 10) (Level of evidence: 3). In these cases and when cytology is positive or when abnormalities of prostatic urethra are visible, biopsies of the prostatic urethra are recommended. The biopsy is taken using resection loop from the precolicular area.

Special care must be taken with tumours at the bladder neck and trigone in female patients where urethral preservation in subsequent orthotopic neobladder is planned. Tumour bladder neck biopsies are advisable but not mandatory, provided frozen section at the urethral margin is taken at the time of surgery (Level of evidence 4).

4.1.8 Fluorescence cystoscopy

As a standard procedure, cystoscopy and TUR are performed using white light. However, the use of white light may lead to missing lesions that are present but not visible.

Fluorescence cystoscopy is performed using filtered blue light after intravesical instillation of a photosensitizer, usually (5-ALA) or hexaminolaevulinate (HAL). It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures in detecting malignant tumour, particularly CIS (11-13) (Level of evidence: 2a). However, false-positive results can be induced by inflammation, a recent TUR, or intravesical instillation therapy.

4.1.9 Second resection

There is a significant risk of residual tumour after the initial TUR (14, 15) (Level of evidence: 1). Persistent disease was observed in 33-53% of patients (15-21). Moreover, the tumour may be understaged by the initial resection. There is a 10% probability that tumours initially staged as being of a lower stage are in fact muscle-invasive (16, 17). Correct staging is extremely important since it will directly affect the treatment modality. A second TUR should always be performed when the initial resection has been incomplete, e.g. when multiple and/or large tumours are present, or when the pathologist has reported that the specimen contained no muscle tissue. Furthermore, a second TUR should be performed when a high-grade, non-muscle-invasive tumour or a T1 tumour has been 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.

4.1.10 Concomitant prostate cancer

Ruling out progressive prostate cancer should be considered since 25-46% of patients submitted to cystectomy for bladder cancer (22) appear to have prostate cancer on final pathology. Unless the entire prostate is to be removed during cystectomy, any type of prostate cancer should be excluded.

4.1.11 Recommendations for primary assessment of presumably invasive bladder tumours

- Renal and bladder ultrasonography, IVU or CT prior to TUR (Grade of recommendation: B).
- Cystoscopy with description of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended (Grade of recommendation: C).
- TUR in one piece for small tumours (less than 1 cm), including a part from the underlying bladder muscle wall (Grade of recommendation: B).
- TUR in fractions (including muscle tissue) for larger tumours (Grade of recommendation: B).
- Biopsies of abnormal-looking urothelium, biopsies from normal-looking mucosa when cytology is positive or when exophytic tumour is of non-papillary appearance or in case of fluorescence if PDD is used (Grade of recommendation: C).
- Biopsy of the prostatic urethra in the case of bladder neck tumour, when bladder CIS is present or suspected or when abnormalities of prostatic urethra are visible (Grade of recommendation: C).
- Careful inspection with histological evaluation of the bladder neck and urethral margin, either prior to or at the time of cystoscopy in women undergoing a subsequent orthotopic neobladder (Grade of recommendation: C).
- A second TUR at 2-6 weeks after the initial resection when it was incomplete or when a high-grade or T1 tumour was detected (Grade of recommendation: B).
- The pathological report should specify the grade, the depth of tumour invasion and whether the lamina propria and muscle are present in the specimen (Grade of recommendation: C).

4.1.12 References

1. 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;67(1):54-60.
<http://www.ncbi.nlm.nih.gov/pubmed/1993277>
2. Wijkstrom H, Norming U, Lagerkvist M, Nilsson B, Naslund I, Wiklund P. Evaluation of clinical staging before cystectomy in transitional cell bladder carcinoma: a long-term follow-up of 276 consecutive patients. *Br J Urol* 1998;81(5):686-91.
<http://www.ncbi.nlm.nih.gov/pubmed/9634042>
3. Goessel C, Knispel HH, Millar K, Klan R. Is routine excretory urography necessary at first diagnosis of bladder cancer? *J Urol* 1997;157(2):480-1.
<http://www.ncbi.nlm.nih.gov/pubmed/8996338>
4. Palou J, Rodriguez-Rubio F, Huguet J, Segarra J, Ribal MJ, Alcaraz A, Villavicencio H. Multivariate analysis of clinical parameters of synchronous primary superficial bladder cancer and upper urinary tract tumors. *J Urol* 2005;174(3):859-61.
<http://www.ncbi.nlm.nih.gov/pubmed/16093970>
5. Holmang S, Hedelin H, Anderstrom C, Holmberg E, Johansson SL. Long-term follow-up of a bladder carcinoma cohort: routine followup urography is not necessary. *J Urol* 1998;160(1):45-8.
<http://www.ncbi.nlm.nih.gov/pubmed/9628602>
6. Nolte-Ernsting C, Cowan N. Understanding multislice CT urography techniques: many roads lead to Rome. *Eur Radiol* 2006;16(12):1670-86.
<http://www.ncbi.nlm.nih.gov/pubmed/16953373>
7. Raitanen M-P, Aine R, Rintala E, Kallio J, Rajala P, Juusela H, Tammela TL; FinnBladder Group. Differences between local and review urinary cytology and diagnosis of bladder cancer. An interobserver multicenter analysis. *Eur Urol* 2002;41(3):284-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12180229>
8. Lokeshwar VB, Habuchi T, Grossman HB, Murphy WM, Hautmann SH, Hemstreet GP 3rd, Bono AV, Getzenberg RH, Goebell P, Schmitz-Dräger BJ, Schalken JA, Fradet Y, Marberger M, Messing E, Droller MJ. Bladder tumor markers beyond cytology: international consensus panel on bladder tumor markers. *Urology* 2005;66 (6 Suppl 1):35-63.
<http://www.ncbi.nlm.nih.gov/pubmed/16399415>

9. Matzkin H, Soloway MS, Hardeman S. Transitional cell carcinoma of the prostate. *J Urol* 1991;146(5):1207-12.
<http://www.ncbi.nlm.nih.gov/pubmed/1942262>
10. Mungan MU, Canda AE, Tuzel E, Yorukoglu K, Kirkali Z. Risk factors for mucosal prostatic urethral involvement in superficial transitional cell carcinoma of the bladder. *Eur Urol* 2005;48(5):760-3.
<http://www.ncbi.nlm.nih.gov/pubmed/16005563>
11. Schmidbauer J, Witjes F, Schmeller N, Donat R, Susani M, Marberger M; Hexvix PCB301/01 Study Group. Improved detection of urothelial carcinoma in situ with hexaminolevulinate fluorescence cystoscopy. *J Urol* 2004;171(1):135-8.
<http://www.ncbi.nlm.nih.gov/pubmed/14665861>
12. Jichlinski P, Guillou L, Karlsen SJ, Malmstrom PU, Jocham D, Brennhovd B, Johansson E, Gartner T, Lange N, van den Bergh H, Leisinger HJ. Hexyl aminolevulinate fluorescence cystoscopy: a new diagnostic tool for photodiagnosis of superficial bladder cancer –a multicenter study. *J Urol* 2003;170(1):226-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12796694>
13. Hungerhuber E, Stepp H, Kriegmair M, Stief Ch, Hofstetter A, Hartmann A, Knuechel R, Karl A, Tritschler S, Zaak D. Seven years' experience with 5-aminolevulinic acid in detection of transitional cell carcinoma of the bladder. *Urology* 2007;69(2):260-4.
<http://www.ncbi.nlm.nih.gov/pubmed/17320660>
14. Brausi M, Collette L, Kurth K, van der Meijden A, Oosterlinck W, Witjes JA, Newling D, Bouffieux C, Sylvester R; 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;41(5):523-31.
<http://www.ncbi.nlm.nih.gov/pubmed/12074794>
15. Miladi M, Peyromaure M, Zerbib M, Saighi D, Debre B. The value of a second transurethral resection in evaluating patients with bladder tumours. *Eur Urol* 2003;43(3):241-5.
<http://www.ncbi.nlm.nih.gov/pubmed/12600426>
16. Jakse G, Algaba F, Malmstrom PU, Oosterlinck W. A second-look TUR in T1 transitional cell carcinoma: why? *Eur Urol* 2004;45(5):539-46.
<http://www.ncbi.nlm.nih.gov/pubmed/15082193>
16. 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;165(3):808-10.
<http://www.ncbi.nlm.nih.gov/pubmed/11176474>
18. Schips L, Augustin H, Zigeuner RE, Gallé G, Habermann H, Trummer H, Pummer K, Hubner G. Is repeated transurethral resection justified in patients with newly diagnosed superficial bladder cancer? *Urology* 2002;59(2):220-3.
<http://www.ncbi.nlm.nih.gov/pubmed/11834389>
19. Grimm MO, Steinhoff Ch, Simon X, Spiegelhalder P, Ackermann R, Vögeli, TA. Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. *J Urol* 2003;170(2 Pt 1):433-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12853793>
20. Divrik RT, Yildirim Ü, Zorlu F, Özen H. 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;175(5):1641-4.
<http://www.ncbi.nlm.nih.gov/pubmed/16600720>
21. Jahnsen S, Wiklund F, Duchek M, Mestad O, Rintala E, Hellsten S, Malmström PU. Results of secondlook 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>
22. Damiano R, Di Lorenzo G, Cantiello F, De Sio M, Perdona S, D'Armiento M, Autorino R. Clinicopathologic features of prostate adenocarcinoma incidentally discovered at the time of radical cystectomy: an evidence-based analysis. *Eur Urol* 2007;52(3):648-57.
<http://www.ncbi.nlm.nih.gov/pubmed/17600614>

4.2 Imaging for staging in verified bladder tumours

Imaging is indicated only if there is a clinical consequence. The treatment and prognosis for invasive bladder cancer is determined by tumour stage and grade (1). Tumour staging must be accurate for selecting the correct treatment in clinical practice. The use of CT scan and magnetic resonance imaging (MRI) has largely replaced other imaging modalities for staging of invasive bladder cancer.

The purpose of imaging for staging invasive bladder cancer is to:

- Assess the extent of local tumour invasion
- Detect tumour spread to lymph nodes
- Detect tumour spread to other distant organs, (liver, lung, bones, peritoneum, pleura, kidney, adrenal gland and others).

4.2.1 *Local staging of invasive bladder cancer*

Both CT and MRI may be used for assessment of local invasion (2) but they are unable to detect microscopic invasion of perivesical fat (T3a) (3). The 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*

MRI has superior soft tissue contrast resolution compared with CT, but poorer spatial resolution.

In studies performed before the availability of multidetector-row CT (MDCT), MRI was reported to be more accurate for 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 (4).

Fast dynamic contrast-enhanced MRI helps to differentiate bladder tumour from surrounding tissues because enhancement of the tumour occurs earlier than the normal bladder wall due to neovascularization (5, 6). Fast dynamic MRI with images acquired at one image per second helps to distinguish tumour from post-biopsy reaction (5).

4.2.1.2 *CT for local staging of invasive bladder cancer*

The advantages of CT include shorter acquisition time, wider coverage in a single breath hold, and lower susceptibility to various patient factors.

CT scan is unable to differentiate between stages Ta to T3a, but it is useful clinically 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% (7) and increases with more advanced disease (8).

A study by Kim et al. to determine the accuracy of MDCT for detection and staging of bladder cancer showed that CT had lower sensitivity (89%) and higher specificity (95%) compared to MRI for diagnosis of perivesical invasion, while the cancer detection rate and overall accuracy for perivesical invasion were similar (9). These findings are explained by better visualization of perivesical fat invasion on MRI, but because only mild inflammation around bladder cancers mimics perivesical invasion, this results in overstaging with MRI.

4.2.2 *Imaging of nodal involvement*

The assessment of nodal status based simply on size is limited by the inability of both CT and MRI to identify metastases in normal sized or minimally enlarged nodes. Sensitivities for detection of lymph node metastases are low, ranging from 48% to 87%. Specificities are also low as nodal enlargement may be due to benign pathology. Overall, the results of CT and MRI for detection of lymph node metastases in a variety of primary pelvic tumours are similar (10-14). Pelvic nodes greater than 8 mm and abdominal nodes greater than 10 mm in maximum short axis diameter (MSAD) should be regarded as enlarged on CT and MRI (15, 17).

4.2.3 *Extravesical urothelial carcinoma*

MDCT urography is the technique of choice for diagnosing upper urinary tract urothelial cancer (18, 19). MDCT urography should be incorporated into the CT staging protocol to rule out extravesical carcinoma.

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. MDCT and MRI are the diagnostic tools of choice to detect metastases to lung and liver. Metastases to bones or brain at presentation of invasive bladder cancer are rare. 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 (20, 21). MRI is more sensitive and specific for diagnosing bone metastases than bone scintigraphy (22, 23) (Level of evidence: 2b).

4.2.5 *Conclusions*

- Diagnosis of invasive bladder cancer is made by cystoscopy and biopsy.
- Imaging is used for formal staging only if it will make a difference to the selection of treatment options.
- In all T1 tumours considered for conservative treatment, a second TUR is recommended before deciding on definite treatment (Grade of recommendation: B).
- MRI is still the preferred modality if the patient is considered for radical treatment. MDCT due to its higher specificity may be equivalent to MRI regarding local staging.

- CT is recommended if there is suspicion of locally advanced or metastatic disease precluding radical treatment (Level of evidence: 2b-3).

4.2.6 Recommendations for staging

- For optimal local staging, either MRI with fast dynamic contrast-enhancement or MDCT with contrast enhancement are recommended for patients considered suitable for radical treatment (Grade of Recommendation: B).
- For patients with confirmed muscle-invasive bladder cancer, MDCT of the chest, abdomen and pelvis is the optimal form of staging, including MDCT urography for complete examination of the upper urinary tracts. If MDCT is not available, lesser alternatives are excretory urography and a chest X-ray (Grade of Recommendation: B).

4.3 REFERENCES

1. Jewett HJ. Proceedings: Cancer of the bladder. *Cancer* 1973;32(5):1072-4.
<http://www.ncbi.nlm.nih.gov/pubmed/4757902>
2. Husband JE, Olliff JF, Williams MP, Heron CW, Cherryman GR. Bladder cancer: staging with CT and MR imaging. *Radiology* 1989;173(2):435-40.
<http://www.ncbi.nlm.nih.gov/pubmed/2798874>
3. Paik ML, Scolieri MJ, Brown SI, Spirnak JP, Resnick MI. Limitations of computerized tomography in staging invasive bladder cancer before radical cystectomy. *J Urol* 2000;163(6):1693-6.
<http://www.ncbi.nlm.nih.gov/pubmed/10799162>
4. Barentsz JO, Jager GJ, Witjes JA, Ruijs JH. 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>
5. Barentsz JO, Jager GJ, van Vierzen PB, Witjes JA, Strijk SP, Peters H, Karssemeijer N, Ruijs SH. Staging urinary bladder cancer after transurethral biopsy: value of fast dynamic contrast-enhanced MR imaging. *Radiology* 1996;201(1):185-93.
<http://www.ncbi.nlm.nih.gov/pubmed/8816542>
6. Mallampati GK, Siegelman ES. MR imaging of the bladder. *Magn Reson Imaging Clin N Am* 2004;12(3):545-55.
<http://www.ncbi.nlm.nih.gov/pubmed/15271370>
7. 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 180(4):1045-54.
<http://www.ncbi.nlm.nih.gov/pubmed/12646453>
8. Kim B, Semelka RC, Ascher SM, Chalpin DB, Carroll PR, Hricak H. 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;193(1):239-45.
<http://www.ncbi.nlm.nih.gov/pubmed/8090898>
9. Kim JK, Park S-Y, Ahn HJ, Kim CS, Cho KS. Bladder cancer: analysis of multidetector row helical CT enhancement pattern and accuracy in tumor detection and perivesical staging. *Radiology* 2004;231(3):725-31.
<http://www.ncbi.nlm.nih.gov/pubmed/15118111>
10. Jager GJ, Barentsz JO, Oosterhof GO, Witjes JA, Ruijs SJ. 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;167(6):1503-7.
<http://www.ncbi.nlm.nih.gov/pubmed/8956585>
11. Yang WT, Lam WW, Yu MY, Cheung TH, Metreweli C. Comparison of dynamic helical CT and dynamic MR imaging in the evaluation of pelvic lymph nodes in cervical carcinoma. *AJR Am J Roentgenol* 2000;175(3):759-66.
<http://www.ncbi.nlm.nih.gov/pubmed/10954463>
12. Kim SH, Kim SC, Choi BI, Han MC. Uterine cervical carcinoma: evaluation of pelvic lymph node metastasis with MR imaging. *Radiology* 1994;190(3):807-11.
<http://www.ncbi.nlm.nih.gov/pubmed/8115631>
13. Kim SH, Choi BI, Lee HP, Kang SB, Choi YM, Han MC, Kim CW. Uterine cervical carcinoma: comparison of CT and MR findings. *Radiology* 1990;175(1):45-51.
<http://www.ncbi.nlm.nih.gov/pubmed/2315503>

14. Oyen RH, Van Poppel HP, Ameye FE, Van de Voorde WA, Baert AL, Baert LV. Lymph node staging of localized prostatic carcinoma with CT and CT-guided fine-needle aspiration biopsy: prospective study of 285 patients. *Radiology* 1994;190(2):315-22.
<http://www.ncbi.nlm.nih.gov/pubmed/8284375>
15. Barentsz JO, Engelbrecht MR, Witjes JA, de la Rosette JJ, van der Graaf M. MR imaging of the male pelvis. *Eur Radiol* 1999;9(9):1722-36.
<http://www.ncbi.nlm.nih.gov/pubmed/10602944>
16. Vinnicombe SJ, Norman AR, Nicolson V, Husband JE. Normal pelvic lymph nodes: evaluation with CT after bipedal lymphangiography [published erratum appears in *Radiology* 1995 Sep;196(3):800]. *Radiology* 1995;194(2):349-55.
<http://www.ncbi.nlm.nih.gov/pubmed/7824709>
17. Dorfman RE, Alpern MB, Gross BH, Sandler MA. Upper abdominal lymph nodes: criteria for normal size determined with CT. *Radiology* 1991;180(2):319-22.
<http://www.ncbi.nlm.nih.gov/pubmed/2068292>
18. Cowan NC, Turney BW, Taylor NJ, McCarthy CL, Crew JP. Multidetector computed tomography urography (MDCTU) for diagnosing upper urinary tract tumour. *BJU Int* 2007;99(6):1363-70.
<http://www.ncbi.nlm.nih.gov/pubmed/17428251>
19. Van Der Molen AJ, Cowan NC, Mueller-Lisse UG, Nolte-Ernsting CC, Takahashi S, Cohan RH; 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;18(1):4-17.
<http://www.ncbi.nlm.nih.gov/pubmed/17973110>
20. 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;77(1):36-40.
<http://www.ncbi.nlm.nih.gov/pubmed/8653315>
21. Brismar J, Gustafson T. Bone scintigraphy in staging bladder carcinoma. *Acta Radiol* 1988;29(2):251-2.
<http://www.ncbi.nlm.nih.gov/pubmed/2965914>
22. Lauenstein TC, Goehde SC, Herborn CU, Goyen M, Oberhoff C, Debatin JF, Ruehm SG, Barkhausen J. Whole-body MR imaging: evaluation of patients for metastases. *Radiology* 2004;233(1):139-48.
<http://www.ncbi.nlm.nih.gov/pubmed/15317952>
23. Schmidt GP, Schoenberg SO, Reiser MF, Baur-Melnyk A. Whole-body MR imaging of bone marrow. *Eur J Radiol* 2005;55(1):33-40.
<http://www.ncbi.nlm.nih.gov/pubmed/15950099>

5. TREATMENT FAILURE OF NON-MUSCLE-INVASIVE BLADDER TUMOURS

5.1 High-risk non-muscle-invasive urothelial carcinoma

The recurrence and progression rate of non-muscle-invasive bladder cancer 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 as well as staging and completeness of TUR are key variables confounding the results of present long-term studies of TUR, with or without intravesical therapy.

The understaging error in TaT1 tumours of 35% to 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) (Level of evidence: 3). The latter identifies 24% to 49% T2 tumours diagnosed initially as non-muscle-invasive tumours (4, 5) (Level of evidence: 3). However, in spite of these disadvantages, recent meta-analyses have shown that intravesical therapy with *Bacillus Calmette-Guerin* (BCG) maintenance therapy prevents recurrence (6) and progression (7) - but not significantly overall- or disease specific survival - compared to no therapy, intravesical chemotherapy or a BCG induction course only (7, 8) (Level of evidence: 1). Especially in patients with small tumours (< 3 cm) and without associated CIS, the progression rate is low (20% within 5 years), with approximately 90% of patients keeping their intact bladder during follow-up of up to 10 years (9) (Level of evidence: 2). The EAU guidelines therefore recommend a complete TUR and intravesical therapy in patients with high-grade TaT1-tumours (10) (Grade of recommendation: C).

Initial cystectomy can be considered based on tumour multiplicity, size, concomitant in situ cancer and

urothelial tumour of the prostatic urethra (10) (Grade of recommendation: C). 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, 11, 12) (Level of evidence: 3). In case of recurrent Ta/T1, mostly associated with carcinoma in situ, the understaging at time of cystectomy is 34%, but the 10-year survival is not significantly different for patients with pT1 and pT2 tumours (13) (Level of evidence: 3). This is in contrast to an earlier report indicating a significant worse outcome for patients with previous TUR(s) (14) (Level of evidence: 3).

Undoubtedly, patients with muscle-invasive recurrence are best treated with radical cystectomy. However, the outcome in terms of 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 (15) (Level of evidence: 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 (16) (Level of evidence: 3). Solsona et al. demonstrated that 80% of patients who had persistent disease at 3 months progressed to muscle invasive disease (17) (Level of evidence: 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 (18) (Level of evidence: 3). However, with careful selection and surveillance a durable complete response can be achieved also in patients diagnosed with superficial bladder transitional cell carcinoma involving the prostatic urethra (19). 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% to 51% and of unknown duration (20, 21) (Grade of recommendation: C). Salvage chemotherapy is associated with minor responses and should not be offered (22, 23) (Level of evidence: 3).

Patients with superficial 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 case of superficial disease (Level of evidence: 3; Grade of recommendation: C) (15).

5.2 Carcinoma *in situ*

Primary CIS confined to the bladder is treated with intravesical BCG, yielding a complete response rate of 83-93% (24, 25) (Level of evidence: 2). CIS associated with Ta/T1 is treated according to the overt tumour. Approximately 50% of patients develop recurrent disease with muscle invasion or extravesical tumour (24, 26) (Level of evidence: 2). Between 11% and 21% die of the disease within 5-7 years after an initial complete response (24, 27) (Level of evidence: 2). Non-responders or incomplete responders have a significant risk of tumour progression of 33% to 67% (17, 28) (Level of evidence: 2). Cystectomy should be performed in patients with an incomplete response at 9 months, tumour recurrence within the bladder, or extravesical recurrence (Grade of recommendation: B).

5.3 Recommendations

- In all T1 tumours at high risk of progression (such as high grade, multifocality, CIS present, and tumour size, as outlined in the non-muscle-invasive bladder cancer EAU guideline), immediate radical cystectomy is an option (Grade of recommendation: B).
- In all T1 patients failing intravesical therapy, cystectomy is an option. A delay in cystectomy increases the risk of progression and cancer-specific death (Grade of recommendation: B).

5.4 REFERENCES

1. Hautmann RE, Gschwend JE, de Petriconi RC, Kron M, Volkmer BG. Cystectomy for transitional cell carcinoma of the bladder: results of a surgery only series in the neobladder era. *J Urol* 2006;176(2):486-92.
<http://www.ncbi.nlm.nih.gov/pubmed/16813874>
2. Madersbacher S, Hochreiter W, Burkhard F, Thalmann GN, Danuser H, Markwalder R, Studer UE. Radical cystectomy for bladder cancer today—a homogeneous series without neoadjuvant therapy. *J Clin Oncol* 2003;21(4):690-6.
<http://www.ncbi.nlm.nih.gov/pubmed/12586807>
3. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, Skinner E, Bochner B, Thangathurai D, Mikhail M, Raghavan D, Skinner DG. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001;19(3):666-75.
<http://www.ncbi.nlm.nih.gov/pubmed/11157016>

4. 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;165(3):808-10.
<http://www.ncbi.nlm.nih.gov/pubmed/11176474>
5. Herr WH. The value of second transurethral resection in evaluating patients with bladder tumors. *J Urol* 1999;162(1):74-6.
<http://www.ncbi.nlm.nih.gov/pubmed/10379743>
6. Shelley MD, Court JB, Kynaston H, Wilt TJ, Coles B, Mason M. Intravesical bacillus Calmette-Guerin versus mitomycin C for Ta and T1 bladder cancer. *Cochrane Database Syst Rev.* 2003;(3):CD003231.
<http://www.ncbi.nlm.nih.gov/pubmed/12917955>
7. Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guerin 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;168(5):1964-70.
<http://www.ncbi.nlm.nih.gov/pubmed/12394686>
8. Böhle A, Bock PR. Intravesical BCG versus mitomycin C in superficial bladder cancer: formal metaanalysis of comparative studies on tumour progression. *Urology* 2004;63(4):682-6.
<http://www.ncbi.nlm.nih.gov/pubmed/15072879>
9. Serretta V, Pavone C, Ingargiola GB, Daricello G, Allegro R, Pavone-Macaluso M. 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;45(6):730-5.
<http://www.ncbi.nlm.nih.gov/pubmed/15149744>
10. Oosterlinck W, Lobel B, Jakse G, Malmström PU, Stöckle M, Sternberg C; European Association of Urology (EAU) Working Group on Oncological Urology. Guidelines on bladder cancer. *Eur Urol* 2002;41(2):105-12.
<http://www.ncbi.nlm.nih.gov/pubmed/12074395>
11. Pansadoro V, Emiliozzi P, de Paula F, Scarpone P, Pansadoro A, Sternberg CN. Long-term follow-up of G3T1 transitional cell carcinoma of the bladder treated with intravesical bacille Calmette-Guérin: 18-year experience. *Urology* 2002;59(2):227-31.
<http://www.ncbi.nlm.nih.gov/pubmed/11834391>
12. Margel D, Tal R, Golan S, Kedar D, Engelstein D, Baniel J. Long-term follow-up of patients with Stage T1 high-grade transitional cell carcinoma managed by Bacille Calmette-Guérin immunotherapy. *Urology* 2007;69(1):78-82.
<http://www.ncbi.nlm.nih.gov/pubmed/17270621>
13. Freeman JA, Esrig D, Stein JP, Simoneau AR, Skinner EC, Chen SC, Groshen S, Lieskovsky G, Boyd SD, Skinner DG. Radical cystectomy for high risk patients with superficial bladder cancer in the era of orthotopic urinary reconstruction. *Cancer* 1995;76(5):833-9.
<http://www.ncbi.nlm.nih.gov/pubmed/8625187>
14. Stöckle M, Alken P, Engelmann U, Jacobi GH, Riedmiller H, Hohenfellner R. Radical cystectomy - often too late?. *Eur Urol* 1987;13(6):361-7.
<http://www.ncbi.nlm.nih.gov/pubmed/3428318>
15. Herr HW, Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors?. *J Urol* 2001;166(4):1296-9.
<http://www.ncbi.nlm.nih.gov/pubmed/11547061>
16. Merz VW, Marth D, Kraft R, Ackermann DK, Zingg EJ, Studer U.E. Analysis of early failures after intravesical instillation therapy with bacille Calmette-Guerin for carcinoma in situ of the bladder. *Br J Urol* 1995;75(2):180-4.
<http://www.ncbi.nlm.nih.gov/pubmed/7850322>
17. Solsona E, Iborra I, Rubio J, Casanova J, Almenar S. The optimum timing of radical cystectomy for patients with recurrent high-risk superficial bladder tumour. *BJU Int* 2004;94(9):1258-62.
<http://www.ncbi.nlm.nih.gov/pubmed/15610101>
18. Huguet J, Crego M, Sabaté S, Salvador J, Palou J, Villavicencio H. 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;48(1):53-9.
<http://www.ncbi.nlm.nih.gov/pubmed/15967252>
19. 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;5(6):386-9.
<http://www.ncbi.nlm.nih.gov/pubmed/17956711>

20. Brake M, Loertzer H, Horsch R, Keller H. Recurrence and progression of stage T1, grade 3 transitional cell carcinoma of the bladder following intravesical immunotherapy with bacillus Calmette-Guerin. *J Urol* 2000;163(6):1697-701.
<http://www.ncbi.nlm.nih.gov/pubmed/10799163>
21. Pansadoro V, Emiliozzi P, Defidio L, Donadio D, Florio A, Maurelli S, Lauretti S, Sternberg CN. Bacillus Calmette-Guerin in the treatment of stage T1 grade 3 transitional cell carcinoma of the bladder: longterm results. *J Urol* 1995;154(6):2054-8.
<http://www.ncbi.nlm.nih.gov/pubmed/7500457>
22. Malmström PU, Wijkström H, Lundholm C, Wester K, Busch C, Norlén BJ. 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;161(4):1124-7.
<http://www.ncbi.nlm.nih.gov/pubmed/10081852>
23. Steinberg G, Bahnson R, Brosman S, Middleton R, Wajsman Z, Wehle M. 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;163(3):761-7.
<http://www.ncbi.nlm.nih.gov/pubmed/10687972>
24. Jakse G, Hall R, Bono A, Höftl W, Carpentier P, Spaander JP, van der Meijden AP, Sylvester R. 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;40(2):144-50
<http://www.ncbi.nlm.nih.gov/pubmed/11528191>
25. Losa A, Hurle R, Lembo A. Low dose bacillus Calmette-Guerin for carcinoma in situ of the bladder: long-term results. *J Urol* 2000;163(1):68-71.
<http://www.ncbi.nlm.nih.gov/pubmed/10604316>
26. Lamm DL, Blumenstein BA, Crissman JD, Montie JE, Gottesman JE, Lowe BA, Sarosdy MF, Bohl RD, Grossman HB, Beck TM, Leimert JT, Crawford ED. 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;163(4):1124-9.
<http://www.ncbi.nlm.nih.gov/pubmed/10737480>
27. de Reijke TM, Kurth KH, Sylvester RJ, Hall RR, Brausi M, van de Beek K, Landsoght KE, Carpentier P; 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;173(2):405-9.
<http://www.ncbi.nlm.nih.gov/pubmed/15643181>
28. Hudson MA, Herr WH. Carcinoma in situ of the bladder. *J Urol* 1995;53(3 Pt 1):564-72.
<http://www.ncbi.nlm.nih.gov/pubmed/7861485>

6. NEOADJUVANT CHEMOTHERAPY

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 neoadjuvant chemotherapy, i.e. administering chemotherapy to patients with operable urothelial carcinoma of the urinary bladder before the planned definitive surgery (or radiation). These advantages include:

- Chemotherapy is delivered at the earliest time point, when the burden of micrometastatic disease is expected to be low
- In vivo chemosensitivity is tested
- The tolerability of chemotherapy is expected to be better before than after cystectomy.

The disadvantages of neoadjuvant chemotherapy include:

- For clinical staging with CT or MRI, over- and under-staging is likely to happen with a staging accuracy of only 70% (6, 7). Overtreatment is the possible negative consequence
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy (8, 9)
- Side effects of chemotherapy might affect outcome of surgery and type of urinary diversion.

Several randomized phase III trials investigated the question of whether or not neoadjuvant chemotherapy improved survival, with conflicting results (10-27). Most patients were \leq 70 years old, had a performance status (PS) of 0-1 and a creatinine clearance of $>$ 50-60 mL/minute, due to the kind of chemotherapy (single-agent cisplatin or cisplatin combination chemotherapy) scheduled.

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 kind of definitive treatment allowed (cystectomy or radiotherapy or both).

Because of the lack of clarity, even though a considerable number of randomized trials had been performed, three meta-analyses were undertaken to answer the very important question of whether or not neoadjuvant chemotherapy prolongs survival (28-30).

The first meta-analysis, published in 2003 (28), included 10 randomized trials (except for results of the INT 0080-study [20]) and showed a 13% reduction in the risk of death, equivalent to 5% absolute benefit at 5 years (increased overall survival from 45% to 50%).

The second meta-analysis, published in 2004 (29), included 11 of 16 randomized trials with overall survival data of 2605 patients. A statistically significant decrease in the risk of death (10%) was seen, corresponding to an absolute improvement in overall survival of 5% (from 50% to 55%).

In the most recent meta-analysis, published in 2005 (30), with updated independent patient data (IPD) of 11 randomized trials (3,005 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 in the subgroup clinical T3, 11%, translating into 9 patients needed to treat (26). Of note, only cisplatin combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful benefit (28, 30); 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 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 (31). Further data is in support 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.

6.1 Conclusions

- Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival by 5-7% at 5 years (Level of evidence: 1a), irrespective of the type of definitive treatment used.
- Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical technique, and current chemotherapy combinations.

6.2 Recommendations

- Neoadjuvant cisplatin-containing combination chemotherapy should be considered in muscle-invasive bladder cancer, irrespective of definitive treatment (Grade of recommendation: A).
- Neoadjuvant chemotherapy is not recommended in patients with PS \geq 2 and impaired renal function (Grade of recommendation: B).

6.3 REFERENCES

1. Stein JP, Skinner DG. Radical cystectomy for invasive bladder cancer: long-term results of a standard procedure. *World J Urol* 2006;24(3):296-304.
<http://www.ncbi.nlm.nih.gov/pubmed/16518661>
2. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, Skinner E, Bochner B, Thangathurai D, Mikhail M, Raghavan D, Skinner DG. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001;19(3):666-75.
<http://www.ncbi.nlm.nih.gov/pubmed/11157016>
3. Dalbagni G, Genega E, Hashibe M, Zhang ZF, Russo P, Herr H, Reuter V. Cystectomy for bladder cancer: a contemporary series. *J Urol* 2001;165(4):1111-6.
<http://www.ncbi.nlm.nih.gov/pubmed/11257649>
4. Bassi P, Ferrante GD, Piazza N, Spinadin R, Carando R, Pappagallo G, Pagano F. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. *J Urol* 1999;161(5):1494-7.
<http://www.ncbi.nlm.nih.gov/pubmed/10210380>

5. Ghoneim MA, el-Mekresh MM, el-Baz MA, el-Attar IA, Ashamalla A. Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1,026 cases. *J Urol* 1997;158(2):393-9. <http://www.ncbi.nlm.nih.gov/pubmed/9224310>
6. Sternberg CN, Pansadoro V, Calabro F, Schnetzer S, Giannarelli D, Emiliozzi P, De Paula F, Scarpone P, De Carli P, Pizzo M, Platania A, Amini M. Can patient selection for bladder preservation be based on response to chemotherapy? *Cancer* 2003;97(7):1644-52. <http://www.ncbi.nlm.nih.gov/pubmed/12655521>
7. Herr HW, Scher HI. Surgery of invasive bladder cancer: is pathologic staging necessary? *Semin Oncol* 1990;17(5):590-7. <http://www.ncbi.nlm.nih.gov/pubmed/2218571>
8. Sanchez-Ortiz RF, Huang WC, Mick R, Van Arsdalen KN, Wein AJ, Malkowicz SB. 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;169(1):110-5; discussion 115. <http://www.ncbi.nlm.nih.gov/pubmed/12478115>
9. Stein JP. Contemporary concepts of radical cystectomy and the treatment of bladder cancer. *J Urol* 2003;169(1):116-7. <http://www.ncbi.nlm.nih.gov/pubmed/12478116>
10. Wallace DM, Raghavan D, Kelly KA, Sandeman TF, Conn IG, Teriana N, Dunn J, Boulas J, Latief T. Neo-adjuvant (pre-emptive) cisplatin therapy in invasive transitional cell carcinoma of the bladder. *Br J Urol* 1991;67(6):608-15. <http://www.ncbi.nlm.nih.gov/pubmed/2070206>
11. Font A, Saladie JM, Carles J, Pinsach L, Barnardas A, et al. Improved survival with induction chemotherapy in bladder cancer: preliminary results of a randomized trial. *Ann Oncol* 1994;5:71, abstr 355.
12. Martinez-Pineiro JA, Gonzalez Martin M, Arocena F, Flores N, Roncero CR, Portillo JA, Escudero A, Jimenez Cruz F, Isorna S. Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: a prospective randomized phase III study. *J Urol* 1995;153(3 Pt 2):964-73. <http://www.ncbi.nlm.nih.gov/pubmed/7853584>
13. Rintala E, Hannisdahl E, Fossa SD, Hellsten S, Sander S. 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>
14. Malmstrom PU, Rintala E, Wahlqvist R, Hellstrom P, Hellsten S, Hannisdahl E. 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;155(6):1903-6. <http://www.ncbi.nlm.nih.gov/pubmed/8618283>
15. [No authors listed] Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. *International collaboration of trialists. Lancet* 1999;354(9178):533-40. <http://www.ncbi.nlm.nih.gov/pubmed/10470696>
16. Hall R. Updated results of a randomised controlled trial of neoadjuvant cisplatin (C), methotrexate (m) and vinblastin (V) chemotherapy for muscle-invasive bladder cancer. *Proc Am Soc Clin Oncol* 2002;21:178A, abstr 710.
17. Bassi P PG, Cosciani S, Lembo A, Anselmo G, Sperandio P, 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.
18. Sherif A, Rintala E, Mestad O, Nilsson J, Holmberg L, Nilsson S, Malmström PU; Nordic Urothelial Cancer Group. Neoadjuvant cisplatin-methotrexate 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>
19. Sengelov L, von der Maase H, Lundbeck F, Barlebo H, Colstrup H, Engelholm SA, Krarup T, Madsen EL, Meyhoff HH, Mommsen S, Nielsen OS, Pedersen D, Steven K, Sørensen B. 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>
20. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, deVere White RW, Sarosdy MF, Wood DP Jr, Raghavan D, Crawford ED. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003;349(9):859-66. <http://www.ncbi.nlm.nih.gov/pubmed/12944571>

21. 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.
22. Orsatti M, Curotto A, Canobbio L, Guarneri D, Scarpati D, Venturini M, Franzone P, Giudici S, Martorana G, Boccardo F, et al. Alternating chemo-radiotherapy in bladder cancer: a conservative approach. *Int J Radiat Oncol Biol Phys* 1995;33(1):173-8.
<http://www.ncbi.nlm.nih.gov/pubmed/7642415>
23. Shipley WU, Winter KA, Kaufman DS, Lee WR, Heney NM, Tester WR, Donnelly BJ, Venner PM, Perez CA, Murray KJ, Doggett RS, True LD. 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;16(11):3576-83.
<http://www.ncbi.nlm.nih.gov/pubmed/9817278>
24. Marcuello E TJ, Villavicencio H, Algaba F, Maroto P, Huidobro G, 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.
25. Cannobio L CA, Boccardo F, Venturini M, Orsatti M, Vitale V, 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.
26. Sherif A, Holmberg L, Rintala E, Mestad O, Nilsson J, Nilsson S, Malmström PU; 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;45(3):297-303.
<http://www.ncbi.nlm.nih.gov/pubmed/15036674>
27. Abol-Enein H E-MM, El Baz M, Ghoneim MA. Neo-adjvant chemotherapy in the treatment of invasive transitional bladder cancer. A controlled prospective randomized study. *Br J Urol* 1997;79(Suppl 4):174.
28. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Lancet* 2003;361(9373):1927-34.
<http://www.ncbi.nlm.nih.gov/pubmed/12801735>
29. Winquist E, Kirchner TS, Segal R, Chin J, Lukka H; 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;171(2 Pt 1):561-9.
<http://www.ncbi.nlm.nih.gov/pubmed/14713760>
30. 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;48(2):202-205; discussion 205-6.
<http://www.ncbi.nlm.nih.gov/pubmed/15939524>
31. Sherif A HL, Rintala E, Mestad O, Nilsson J, Nilsson S, Malmstrom PU, Wijkström H; 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 randomised 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 localized muscle invasive bladder cancer in most countries of the Western Hemisphere (1, 2). New interest in quality-of-life issues 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 type of urinary diversion with cystectomy being reserved for younger patients without concomitant disease and better performance status. The value of assessing overall health before recommending and proceeding with surgery was emphasized in a recent multivariate analysis, which demonstrated an association between co-morbid disease and adverse pathological and survival outcome following radical cystectomy (3).

There is still controversy 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 demonstrated that patients above 80 years did have an increased postoperative morbidity but not an increased mortality. Some patients even successfully underwent a neobladder procedure in this group, but the majority of patients were treated with an ileal conduit diversion (4).

7.1.2 *Timing and delay of cystectomy*

In a retrospective series of 153 patients with a clear indication for radical surgery of locally advanced bladder cancer, a delay of treatment beyond 90 days of primary diagnosis caused a significant increase in extravescical disease (81 vs. 52%) (5).

The delay of cystectomy not only affects the outcome but also the type of urinary diversion. In organ-confined urothelial cancer of the bladder the average time from the primary diagnosis to cystectomy was 12.2 months in neobladder and 19.1 months in ileal conduit patients. It was even more striking for those patients who had an organ confined invasive cancer diagnosed; in neobladder patients the average time to surgery was 3.1 and in ileal conduit patients 15.1 months (6). Similar results have been observed in a series of 247 patients where superior recurrence-free survival and overall survival was significantly better in those treated within the 90 day period compared to others who were treated after a longer period (7).

7.1.3 *Indications*

Traditionally radical cystectomy is recommended for patients with muscle-invasive bladder cancer 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 for e.g. fistula formation, pain or recurrent macrohematuria (see section 8.1: palliative cystectomy).

7.1.4 *Technique and extent*

Radical cystectomy includes the removal of the bladder and adjacent organs, that is prostate and seminal vesicles in men, and uterus and adnexa in women (8). The inclusion of the entire prostate in male patients, and the extent of urethrectomy and vaginal resection in female patients, however, has recently been questioned (9, 10).

Various techniques of partial prostate- sparing cystoprostatectomy in male patients with localized tumours have been proposed and results of series with a longer follow-up have been published (11, 12). A randomized study comparing patients with and without remnant portions of the prostate is lacking and will be difficult to perform. Autopsy studies as well as studies looking at the unsuspected incidence of prostate cancer in cystoprostatectomy specimens suggest that in approximately 23-54% of patients a prostate cancer is found in the cystoprostatectomy specimen. Up to twenty-nine percent of these cancers may be clinically significant, locally recurrent or even metastatic in patients with prostatic tissue preserving radical cystectomy (13-15).

Furthermore urothelial cancer in the prostate was detected in 32 and 33% (69/240 cases and 77/235 cases, resp.) of patients undergoing radical cystoprostatectomy (14, 16). In another study 50/121 of the cystoprostatectomy specimens (41%) removed for urothelial cancer had unsuspected prostate cancer. Twenty-four of these 50 tumours (48%) were clinically significant. In the same study 58/121 patients (48%) had urothelial carcinoma in the prostate of which 19 (33%) had apical involvement (17). Overall in the above mentioned series only 26 to 33% of the patients undergoing cystoprostatectomy for bladder cancer had neither prostate cancer nor prostatic urothelial cancer in the specimen.

Radical cystectomy also includes the dissection of regional lymph nodes. There is a substantial amount of literature about the extent of lymphadenectomy. Yet, data regarding its clinical significance are controversial. In retrospective studies extended lymphadenectomy (removal of the obturator, internal, external, common iliac and presacral nodes as well as nodes at the aortic bifurcation) has been reported to improve survival in patients with muscle invasive bladder cancer. The curative value of lymph node dissection, however, is still unknown and a standardized lymph node dissection has yet to be defined (18-20).

There are several localization studies with regards to lymphadenectomy (21, 22) which demonstrated both retrospectively and prospectively that lymph nodes in bladder cancer patients are not found outside the pelvis if the pelvic lymph nodes are free of tumour. Furthermore progression free survival as well as overall survival might be correlated with the amount of lymph nodes removed during surgery. Removal of more than 15 lymph nodes has been postulated to be both sufficient for the evaluation of the lymph node status as well as beneficial for overall survival in retrospective studies (19, 22, 23). Interindividual differences in the number of pelvic and retroperitoneal lymph nodes and difficulties in processing of the removed tissue by pathologists

were not taken into account in these studies (18).

A distal ureteral segment (length not specified) should be resected and in case of CIS a frozen section for evaluation of the surgical margins should be performed (8, 24). Urethrectomy is recommended if there are positive margins at the level of urethral dissection, positive margins anywhere on the bladder specimen (in both sexes), if the primary tumour is located at the bladder neck or in the urethra (in women), or if tumour extensively infiltrates the prostate (1, 25, 26).

7.1.5 *Laparoscopic cystectomy*

Laparoscopic cystectomy has been shown to be feasible both in male and female patients (27, 28). The cystectomy itself and the subsequent urinary diversion can be done hand-assisted, robot-assisted or unaided (29). With the currently available technology and when using intestinal segments for the urinary diversion, to date a majority of authors favour an extracorporeal approach (28). There are no data confirming or declining benefits of laparoscopic cystectomy for the patients' quality of life, tumour specific and overall survival.

7.2 **Urinary Diversion after radical cystectomy**

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

- abdominal diversion such as ureterocutaneostomy, ileal or colonic conduit, and various forms of a cutaneous 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 for reconstruction of the urinary tract, including stomach, ileum, colon, and the appendix (30). Although several studies have compared certain aspects of health-related quality of life, like sexual function, urinary continence and body image in patient cohorts with different types of urinary diversion, more work is necessary in this field with regards to preoperative tumour stage and functional situation, socioeconomic status, time interval to primary surgery etc.

Patients undergoing continent urinary diversion have to be both motivated to learn and manually skilful to deal with their diversion. Debilitating neurological and psychiatric illnesses, limited life expectancy, and impaired liver or renal function as well as TCC of the urethral margin or other surgical margins are contraindications to more complex forms of urinary diversion. Relative contraindications specific for an orthotopic neobladder are high-dose preoperative radiation therapy, complex urethral stricture disease and severe urethral sphincter related incontinence (31-33).

7.2.1 *Ureterocutaneostomy*

Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. It is considered as a safe procedure and therefore preferred in older or otherwise compromised patients in need of a supravescical diversion (34, 35). Others have demonstrated, however, that in carefully selected elderly patients all other forms of wet and dry urinary diversions including orthotopic bladder substitutions are possible (4).

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 seems to be more frequent than with intestinal stomas (34).

7.2.2 *Ileal conduit*

The ileal conduit is still an established option with well-known/predictable results. However, up to 48% of the patients develop early complications including urinary tract infections, pyelonephritis, uretero-ileal leakage and stenosis (36). Stomal complications in up to 24% and functional and/or morphological changes of the upper urinary tract in up to 30% are the main complications in long-term follow-up studies (37-39). An increase in complications was seen with increasing follow-up in the Berne series of 131 patients followed for a minimum of 5 years (median follow-up 98 months) (37): the rate of complications increased from 45% at 5 years to 94% in those surviving longer than 15 years. In the latter group 50% and 38% of the patients had upper urinary tract changes and urolithiasis, respectively.

7.2.3 *Continent cutaneous urinary diversion*

A low-pressure detubularized ileal reservoir can be used as a continent cutaneous urinary diversion for self-catheterization; gastric, ileocecal and sigma pouches have also been described (40-42). Different anti-reflux techniques can be used [8e]. Most patients have a well functioning reservoir with daytime and night time continence approaching 93% (43). A stomal stenosis in 23.5% of patients with 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 (43-45). In a small series of previously irradiated female patients incontinence and stomal stenosis was 18% (8/44 patients) (46).

7.2.4 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) (47, 48). Most of the indications for this procedure have become obsolete due to a high incidence of upper urinary tract infections and a long term risk of developing colon cancer (49, 50). Bowel frequency and urge incontinence were additional side effects of this type of urinary diversion. A possibility to circumvent the above mentioned problems is to interpose a segment of ileum between ureters and rectum or sigmoid in order to augment capacity and to avoid a direct interaction between urothelium, colonic mucosa, together with faeces and urine (51).

7.2.5 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 a majority of patients undergoing cystectomy (33, 52). The gastrointestinal segment most frequently used for bladder substitution is the terminal ileum whereas there is less experience with ascending colon, including caecum, and the sigmoid (1). 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 (53, 54). Long-term complications include diurnal and nocturnal incontinence (8-10 and 20 to 30%, resp.), ureterointestinal stenosis (3-18%), urinary retention (4-12%) both in males and female patients, metabolic disorders and vitamin B12 deficiency in series with 1,054 and more than 1,300 patients (33, 55). In a recent study, which compared cancer control and 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 (56). Urethral recurrence in neobladder patients seems rare (1.5-7% both for male and female patients) (33, 57). These results indicate that the choice of a neobladder both in male and female patients does not compromise the oncological outcome of cystectomy.

The advantage in the quality of life compared to a non-continent diversion remains a matter of debate (58-60).

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 (45, 53, 54). According to the reported long term results the upper urinary tract is protected sufficiently by either method.

7.3 Morbidity and mortality

In a recent comprehensive study regarding long-term results in 1,054 patients, perioperative mortality was 3%, and early complications, defined as any complication within 3 months of surgery, were reported in 28% (52, 55). Late morbidity is usually due to the type of urinary diversion (see above). Early morbidity associated with radical cystectomy for non-muscle invasive disease (at high risk for disease progression) is similar and not less than that associated with muscle invasive tumours (61).

7.4 Survival

The outcome according to a multiinstitutional database of 888 consecutive patients undergoing cystectomy and lymphadenectomy for bladder cancer revealed a mean recurrence-free and bladder cancer specific survival of 58% and 66%, resp. at 5 years (62). The recurrence-free and overall survival in a large single centre study of 1,054 male and female patients was 68% and 66% at 5 years and 60% and 43%, at 10 years, respectively (2). In node positive patients, 10-year disease-specific and overall survival rates in another study have been reported to be 27.7% and 20.9% respectively (63). In this cohort, 10-year disease-specific and overall survival rates were 72.9% vs. 49.1% for organ confined (defined as \leq pT3a), and 33.3% vs. 22.8% for non-organ confined disease (63). 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 (64). Tumour stage and nodal involvement are the only independent predictors of survival (65).

7.5 Conclusions

- Cystectomy is the preferred curative treatment for localised bladder neoplasm (Level of evidence: 3)
- Radical cystectomy includes removal of regional lymph nodes, the extent of which has not been sufficiently defined (Level of evidence: 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 (Level of evidence: 3)

- Terminal ileum and colon are the intestinal segments of choice for urinary diversion (Level of evidence: 3)
- The type of urinary diversion does not affect oncological outcome (Level of evidence: 3)

7.6 Recommendations

7.6.1 Recommendations for radical cystectomy

- Radical cystectomy in T2-T4a, N0-NX, M0, and high risk non-muscle invasive BC as outlined above (Grade of recommendation: B)
- No preoperative radiotherapy (Grade of recommendation: A)
- Lymph node dissection should be an integral part of cystectomy, extent not established (Grade of recommendation: B)
- Preservation of the urethra is reasonable if margins are negative. If no bladder substitution is attached the urethra must be checked regularly (Grade of recommendation: B)
- Laparoscopic and robot assisted laparoscopic cystectomy may be an option. Current data, however, have not sufficiently proven its advantages or disadvantages (Grade of recommendation: C).

7.6.2 Recommendations for urinary diversion

- Treatment is recommended at centers experienced in major types of diversion techniques and postoperative care (Grade of recommendation: B)
- Before cystectomy, the patient should be counselled adequately regarding all possible alternatives, and the final decision should be based on a consensus between patient and surgeon (Grade of recommendation: B).
- 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 (Grade of recommendation: B)

7.7 REFERENCES

1. 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;69(1 Suppl):17-49.
<http://www.ncbi.nlm.nih.gov/pubmed/17280907>
2. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, Skinner E, Bochner B, Thangathurai D, Mikhail M, Raghavan D, Skinner DG. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001;19(3):666-75.
<http://www.ncbi.nlm.nih.gov/pubmed/11157016>
3. Miller DC, Taub DA, Dunn RL, Montie JE, Wei JT. The impact of co-morbid disease on cancer control and survival following radical cystectomy. *J Urol* 2003;169(1):105-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12478114>
4. Figueroa AJ, Stein JP, Dickinson M, Skinner EC, Thangathurai D, Mikhail MS, Boyd SD, Lieskovsky G, Skinner DG. Radical cystectomy for elderly patients with bladder carcinoma: an updated experience with 404 patients. *Cancer* 1998;83(1):141-7.
<http://www.ncbi.nlm.nih.gov/pubmed/9655304>
5. Chang SS, Hassan JM, Cookson MS, Wells N, Smith JA. Delaying radical cystectomy for muscle invasive bladder cancer results in worse pathological stage. *J Urol* 2003;170(4 Pt 1):1085-7.
<http://www.ncbi.nlm.nih.gov/pubmed/14501697>
6. Hautmann RE, Paiss T. Does the option of the ileal neobladder stimulate patient and physician decision toward earlier cystectomy?. *J Urol* 1998;159(6):1845-50.
<http://www.ncbi.nlm.nih.gov/pubmed/9598473>
7. Sanchez-Ortiz RF, Huang WC, Mick R, Van Arsdalen KN, Wein AJ, Malkowicz SB. 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;169(1):110-5; discussion 115.
<http://www.ncbi.nlm.nih.gov/pubmed/12478115>
8. Stenzl A, Nagele U, Kuczyk M, Sievert K, Anastasiadis A, Seibold J, Corvin S. Cystectomy – Technical Considerations in Male and Female Patients. *EAU Update Series* 2005;3:138-46.
9. Vallancien G, Abou El Fettouh H, Cathelineau X, Baumert H, Fromont G, Guillonneau B. Cystectomy with prostate sparing for bladder cancer in 100 patients: 10-year experience. *J Urol* 2002;168(6):2413-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12441929>
10. Muto G, Bardari F, D'Urso L, Giona C. Seminal sparing cystectomy and ileocapsuloplasty: long-term followup results. *J Urol* 2004;172(1):76-80.
<http://www.ncbi.nlm.nih.gov/pubmed/15201741>

11. Botto H, Sebe P, Molinie V, Herve JM, Yonneau L, Leuret T. Prostatic capsule- and seminal-sparing cystectomy for bladder carcinoma: initial results for selected patients. *BJU Int* 2004;94(7):1021-5. <http://www.ncbi.nlm.nih.gov/pubmed/15541120>
12. Colombo R, Bertini R, Salonia A, Da Pozzo LF, Montorsi F, Brausi M, Roscigno M, Rigatti P. Nerve and seminal sparing radical cystectomy with orthotopic urinary diversion for select patients with superficial bladder cancer: an innovative surgical approach. *J Urol* 2001;165(1):51-5; discussion 55. <http://www.ncbi.nlm.nih.gov/pubmed/11125362>
13. Abdelhady M, Abusamra A, Pautler SW, Chin JL, Izawa JI. Clinically significant prostate cancer found incidentally in radical cystoprostatectomy specimens. *BJU Int* 2007;99(2):326-9. <http://www.ncbi.nlm.nih.gov/pubmed/17026595>
14. Pettus JA, Al-Ahmadie H, Barocas DA, Koppie TM, Herr H, Donat SM, Dalbagni G, Reuter VE, Olgac S, Bochner BH. Risk assessment of prostatic pathology in patients undergoing radical cystoprostatectomy. *Eur Urol* 2008;53(2):370-5. <http://www.ncbi.nlm.nih.gov/pubmed/17689003>
15. Weizer AZ, Shah RB, Lee CT, Gilbert SM, Daignault S, Montie JE, Wood DP Jr. Evaluation of the prostate peripheral zone/capsule in patients undergoing radical cystoprostatectomy: defining risk with prostate capsule sparing cystectomy. *Urol Oncol* 2007;25(6):460-4. <http://www.ncbi.nlm.nih.gov/pubmed/18047952>
16. Shen SS, Lerner SP, Muezzinoglu B, Truong LD, Amiel G, Wheeler TM. Prostatic involvement by transitional cell carcinoma in patients with bladder cancer and its prognostic significance. *Hum Pathol* 2006;37(6):726-34. <http://www.ncbi.nlm.nih.gov/pubmed/16733214>
17. Revelo MP, Cookson MS, Chang SS, Shook MF, Smith JA Jr., Shappell SB. Incidence and location of prostate and urothelial carcinoma in prostates from cystoprostatectomies: implications for possible apical sparing surgery. *J Urol* 2004;171(2 Pt 1):646-51. <http://www.ncbi.nlm.nih.gov/pubmed/14713778>
18. Herr HW, Bochner BH, Dalbagni G, Donat SM, Reuter VE, Bajorin DF. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. *J Urol* 2002;167(3):1295-8. <http://www.ncbi.nlm.nih.gov/pubmed/11832716>
19. Leissner J, Hohenfellner R, Thuroff JW, Wolf HK. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. *BJU Int* 2000;85(7):817-23. <http://www.ncbi.nlm.nih.gov/pubmed/10792159>
20. 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;160(6 Pt 1):2015-9; discussion 2020. <http://www.ncbi.nlm.nih.gov/pubmed/9817313>
21. Ghoneim MA, Abol-Enein H. Lymphadenectomy with cystectomy: is it necessary and what is its extent? *Eur Urol* 2004;46(4):457-61. <http://www.ncbi.nlm.nih.gov/pubmed/15363560>
22. Fleischmann A, Thalmann GN, Markwalder R, Studer UE. Extracapsular extension of pelvic lymph node metastases from urothelial carcinoma of the bladder is an independent prognostic factor. *J Clin Oncol* 2005;23(10):2358-65. <http://www.ncbi.nlm.nih.gov/pubmed/15800327>
23. Studer UE, Collette L. Morbidity from pelvic lymphadenectomy in men undergoing radical prostatectomy. *Eur Urol* 2006;50(5):887-9; discussion 889-92. <http://www.ncbi.nlm.nih.gov/pubmed/16956714>
24. Stenzl A, Bartsch G, Rogatsch H. The remnant urothelium after reconstructive bladder surgery. *Eur Urol* 2002;41(2):124-31. <http://www.ncbi.nlm.nih.gov/pubmed/12074398>
25. Stenzl A, Colleselli K, Bartsch G. Update of urethra-sparing approaches in cystectomy in women. *World J Urol* 1997;15(2):134-8. <http://www.ncbi.nlm.nih.gov/pubmed/9144904>
26. Nagele U, Kuczyk M, Anastasiadis AG, Sievert KD, Seibold J, Stenzl A. Radical cystectomy and orthotopic bladder replacement in females. *Eur Urol* 2006;50(2):249-57. <http://www.ncbi.nlm.nih.gov/pubmed/16806663>
27. Vallancien G, Cathelineau X, Barret E, Rozet F. [Laparoscopy in the treatment of urologic cancers]. *Bull Cancer* 2007;94(12):1072-4. <http://www.ncbi.nlm.nih.gov/pubmed/18156115>

28. Haber GP, Campbell SC, Colombo JR, Jr, Fergany AF, Aron M, Kaouk J, Gill IS. Perioperative outcomes with laparoscopic radical cystectomy: "pure laparoscopic" and "open-assisted laparoscopic" approaches. *Urology* 2007;70(5):910-5.
<http://www.ncbi.nlm.nih.gov/pubmed/18068447>
29. Cathelineau X, Jaffe J. Laparoscopic radical cystectomy with urinary diversion: what is the optimal technique? *Curr Opin Urol* 2007;17(2):93-7.
<http://www.ncbi.nlm.nih.gov/pubmed/17285017>
30. Stenzl A. Bladder substitution. *Curr Opin Urol* 1999;9(3):241-5.
<http://www.ncbi.nlm.nih.gov/pubmed/10726098>
31. Tanrikut C, McDougal WS. Acid-base and electrolyte disorders after urinary diversion. *World J Urol* 2004;22(3):168-71.
<http://www.ncbi.nlm.nih.gov/pubmed/15290206>
32. Farnham SB, Cookson MS. Surgical complications of urinary diversion. *World J Urol* 2004;22(3):157-67.
<http://www.ncbi.nlm.nih.gov/pubmed/15316737>
33. Hautmann RE, Volkmer BG, Schumacher MC, Gschwend JE, Studer UE. Long-term results of standard procedures in urology: the ileal neobladder. *World J Urol* 2006;24(3):305-14.
<http://www.ncbi.nlm.nih.gov/pubmed/16830152>
34. Deliveliotis C, Papatsoris A, Chrisofos M, Dellis A, Liakouras C, Skolarikos A. Urinary diversion in highrisk elderly patients: modified cutaneous ureterostomy or ileal conduit?. *Urology* 2005;66(2):299-304.
<http://www.ncbi.nlm.nih.gov/pubmed/16040096>
35. Kilciler M, Bedir S, Erdemir F, Zeybek N, Erten K, Ozgok Y. 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>
36. Nieuwenhuijzen JA, de Vries RR, Bex A, van der Poel HG, Meinhardt W, Antonini N, Horenblas S. Urinary diversions after cystectomy: the association of clinical factors, complications and functional results of four different diversions. *Eur Urol*, 2008;53(4):834-44.
<http://www.ncbi.nlm.nih.gov/pubmed/17904276>
37. Madersbacher S, Schmidt J, Eberle JM, Thoeny HC, Burkhard F, Hochreiter W, Studer UE. Long-term outcome of ileal conduit diversion. *J Urol* 2003;169(3):985-90.
<http://www.ncbi.nlm.nih.gov/pubmed/12576827>
38. Wood DN, Allen SE, Hussain M, Greenwell TJ, Shah P.J. Stomal complications of ileal conduits are significantly higher when formed in women with intractable urinary incontinence. *J Urol* 2004;172(6 Pt 1):2300-3.
<http://www.ncbi.nlm.nih.gov/pubmed/15538253>
39. 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;290(6483):1695-7.
<http://www.ncbi.nlm.nih.gov/pubmed/3924218>
40. Benson MC, Olsson CA. Continent urinary diversion. *Urol Clin North Am* 1999;26(1):125-47, ix.
<http://www.ncbi.nlm.nih.gov/pubmed/10086055>
41. Gerharz EW, Kohl UN, Melekos MD, Bonfig R, Weingartner K, Riedmiller H. Ten years' experience with the submucosally embedded in situ appendix in continent cutaneous diversion. *Eur Urol* 2001;40(6):625-31.
<http://www.ncbi.nlm.nih.gov/pubmed/11805408>
42. Jonsson O, Olofsson G, Lindholm E, Tornqvist H. Long-time experience with the Kock ileal reservoir for continent urinary diversion. *Eur Urol* 2001;40(6):632-40.
<http://www.ncbi.nlm.nih.gov/pubmed/11805409>
43. Wiesner C, Bonfig R, Stein R, Gerharz EW, Pahernik S, Riedmiller H, Thuroff J.W. Continent cutaneous urinary diversion: long-term follow-up of more than 800 patients with ileocecal reservoirs. *World J Urol* 2006;24(3):315-8.
<http://www.ncbi.nlm.nih.gov/pubmed/16676186>
44. Wiesner C, Stein R, Pahernik S, Hahn K, Melchior SW, Thuroff JW. 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;176(1):155-9; discussion 159-60.
<http://www.ncbi.nlm.nih.gov/pubmed/16753391>

45. Thoeny HC, Sonnenschein MJ, Madersbacher S, Vock P, Studer U.E. Is ileal orthotopic bladder substitution with an afferent tubular segment detrimental to the upper urinary tract in the long term? *J Urol* 2002;168(5):2030-4; discussion 2034.
<http://www.ncbi.nlm.nih.gov/pubmed/12394702>
46. Leissner J, Black P, Fisch M, Hockel M, Hohenfellner R. Colon pouch (Mainz pouch III) for continent urinary diversion after pelvic irradiation. *Urology* 2000;56(5):798-802.
<http://www.ncbi.nlm.nih.gov/pubmed/11068305>
47. 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.
48. Coffey R. Physiologic implantation of the severed ureter or common bile duct into the intestine. *JAMA* 1911;56:397.
49. Azimuddin K, Khubchandani IT, Stasik JJ, Rosen L, Riether RD. Neoplasia after ureterosigmoidostomy. *Dis Colon Rectum* 1999;42(12):1632-8.
<http://www.ncbi.nlm.nih.gov/pubmed/10613486>
50. Gerharz EW, Turner WH, Kalble T, Woodhouse CR. Metabolic and functional consequences of urinary reconstruction with bowel. *BJU Int* 2003;91(2):143-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12519116>
51. Kalble T, Busse K, Amelung F, Waldherr R, Berger MR, Edler L, Riedmiller H. 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>
52. Stein JP, Skinner DG. Radical cystectomy for invasive bladder cancer: long-term results of a standard procedure. *World J Urol* 2006;24(3):296-304.
<http://www.ncbi.nlm.nih.gov/pubmed/16518661>
53. Stein J., Dunn MD, Quek ML, Miranda G, Skinner DG. The orthotopic T pouch ileal neobladder: experience with 209 patients. *J Urol* 2004;172(2):584-7.
<http://www.ncbi.nlm.nih.gov/pubmed/15247737>
54. Abol-Enein H, Ghoneim M.A. Functional results of orthotopic ileal neobladder with serous-lined extramural ureteral reimplantation: experience with 450 patients. *J Urol* 2001;165(5):1427-32.
<http://www.ncbi.nlm.nih.gov/pubmed/11342891>
55. Stein JP, Skinner DG. Results with radical cystectomy for treating bladder cancer: a 'reference standard' for high-grade, invasive bladder cancer. *BJU Int* 2003;92(1):12-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12823375>
56. Yossepowitch O, Dalbagni G, Golijanin D, Donat SM, Bochner BH, Herr HW, Fair WR, Russo P. Orthotopic urinary diversion after cystectomy for bladder cancer: implications for cancer control and patterns of disease recurrence. *J Urol* 2003;169(1):177-81.
<http://www.ncbi.nlm.nih.gov/pubmed/12478130>
57. Stein JP, Clark P, Miranda G, Cai J, Groshen S, Skinner D.G. Urethral tumor recurrence following cystectomy and urinary diversion: clinical and pathological characteristics in 768 male patients. *J Urol* 2005;173(4):1163-8.
<http://www.ncbi.nlm.nih.gov/pubmed/15758728>
58. Gerharz EW, Mansson A, Hunt S, Skinner EC, Mansson W. Quality of life after cystectomy and urinary diversion: an evidence based analysis. *J Urol* 2005;174(5):1729-36.
<http://www.ncbi.nlm.nih.gov/pubmed/16217273>
59. Hobisch A, Tosun K, Kinzl J, Kemmler G, Bartsch G, Holtl L, Stenzl A. Life after cystectomy and orthotopic neobladder versus ileal conduit urinary diversion. *Semin Urol Oncol* 2001;19(1):18-23.
<http://www.ncbi.nlm.nih.gov/pubmed/11246729>
60. 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;173(4):1318-22.
<http://www.ncbi.nlm.nih.gov/pubmed/15758789>
61. Cookson MS, Chang SS, Wells N, Parekh DJ, Smith JA Jr. Complications of radical cystectomy for nonmuscle invasive disease: comparison with muscle invasive disease. *J Urol* 2003;169(1):101-4.
<http://www.ncbi.nlm.nih.gov/pubmed/12478113>
62. Shariat SF, Karakiewicz PI, Palapattu GS, Lotan Y, Rogers CG, Amiel GE, Vazina A, Gupta A, Bastian PJ, Sagalowsky AI, Schoenberg MP, Lerner S.P. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. *J Urol* 2006;176(6 Pt 1):2414-22; discussion 2422.
<http://www.ncbi.nlm.nih.gov/pubmed/17085118>

63. Gschwend JE, Dahm P, Fair W.R. Disease specific survival as endpoint of outcome for bladder cancer patients following radical cystectomy. *Eur Urol* 2002;41(4):440-8.
<http://www.ncbi.nlm.nih.gov/pubmed/12074817>
64. Madersbacher S, Hochreiter W, Burkhard F, Thalmann GN, Danuser H, Markwalder R, Studer UE. Radical cystectomy for bladder cancer today--a homogeneous series without neoadjuvant therapy. *J Clin Oncol* 2003;21(4):690-6.
<http://www.ncbi.nlm.nih.gov/pubmed/12586807>
65. Bassi P, Ferrante GD, Piazza N, Spinadin R, Carando R, Pappagallo G, Pagano F. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. *J Urol* 1999;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 usually is not 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 cases 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.(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. concluded that elderly people have a greater risk of perioperative morbidity and mortality, especially those with very advanced pelvic malignancies, who have undergone palliative cystectomy (3).

Advanced muscle-invasive bladder cancer 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.(4) retrospectively reviewed the records of patients who presented with bladder cancer and obstructive uraemia. 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. In 10 patients (26.3%), who underwent surgery, palliative cystectomy without lymphadenectomy was carried out for advanced nodal involvement in four patients and locally advanced disease infiltrating the pelvic wall in six patients. In all patients, local pelvic recurrence was reported within the first year of follow-up (4).

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

8.2 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.

8.3 Recommendations

- For patients with inoperable locally advanced tumours (T4b), primary radical cystectomy is not a curative option (Grade of recommendation: B).
- The indication for performing a palliative cystectomy is symptom relief.
- Morbidity of surgery and quality of life should be weighed against other options (Level of evidence: 3; Grade of recommendation: B/C).

8.4 REFERENCES

1. Ok JH, Meyers FJ, Evans CP. Medical and surgical palliative care of patients with urological malignancies. *J Urol* 2005;174(4 Pt 1):1177-82.
<http://www.ncbi.nlm.nih.gov/pubmed/16145365>
2. Ubrig B, Lazica M, Waldner M, Roth S. Extraperitoneal bilateral cutaneous ureterostomy with midline stoma for palliation of pelvic cancer. *Urology* 2004;63(5):973-5.
<http://www.ncbi.nlm.nih.gov/pubmed/15134993>
3. 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;95(9):1211-4.
<http://www.ncbi.nlm.nih.gov/pubmed/15892803>
4. El-Tabey NA, Osman Y, Mosbah A, Mohsen T, Abol-Enein H. Bladder cancer with obstructive uremia: oncologic outcome after definitive surgical management. *Urology* 2005;66(3):531-5.
<http://www.ncbi.nlm.nih.gov/pubmed/16140072>
5. Nagele U, Anastasiadis AG, Merseburger AS, Corvin S, Hennenlotter J, Adam M, Sievert KD, Stenzl A, Kuczyk MA. The rationale for radical cystectomy as primary therapy for T4 bladder cancer. *World J Urol* 2007;25(4):401-5.
<http://www.ncbi.nlm.nih.gov/pubmed/17525849>

9. NEO-ADJUVANT RADIOTHERAPY IN MUSCLE-INVASIVE BLADDER CANCER

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 was from the MD Anderson Cancer Center in the USA (n = 526). It showed that 50 Gy pre-operative radiotherapy resulted in down-staging in 73% of cT3 patients versus 29% of patients who did not receive pre-operative radiotherapy (1, 2). Local control was also improved from 72% to 91% in pT3b patients (n = 91), but not in pT2 or pT3a patients. The improvement in survival in this retrospective series was from 40% to 52%. The results of a non-randomized study comparing 40 Gy, 5-20 Gy and no radiotherapy showed that only 40 Gy pre-operative radiotherapy improved the percentage of local recurrence from 27% to 11% and survival from 21% to 63% (3).

Overall, nearly all the retrospective studies investigating the effect of pre-operative radiotherapy with doses of 40-50 Gy, followed after 4-6 weeks by cystectomy, showed (1-9):

- down-staging of the tumour stage (40-65% of patients)
- lower risk of local recurrence (10-42%)
- improved survival (11-12%).

Some studies found that the improvement in local control was highest for T3b tumours (2-4). Other studies found that achievement of a pathological complete remission (pCR) is a prognostic factor for survival (3-5). One retrospective study (5) found no significant increase in toxicity due to pre-operative radiotherapy (10% versus 3%).

9.1.2 Randomized studies

There are five randomized studies investigating pre-operative radiotherapy. The largest randomized trial (234 evaluable patients), using pre-operative radiotherapy 45 Gy/1.8-2.2 Gy in muscle-invasive tumours, 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% (10). In patients who were not given adjuvant chemotherapy, survival was significantly better in those who received pre-operative radiotherapy (25-52%). pCR was a prognostic factor for better survival. A major drawback of this study is that almost 50% of patients did not receive the planned treatment and were excluded from the analysis. 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 (11).

A study from Egypt, dealing with patients with bladder cancer caused by bilharzia (predominantly squamous cell carcinoma, n = 92) also showed a significant survival advantage for \geq T3 tumours, but a marginal and non-significant difference for the whole group (12). A small, randomized study of 44 patients (13) also showed a significant increase in pCR (18–55%) and a small increase in 5-year survival (61–72%, not significant), but the disadvantages of this study were a small patient population and differing radiotherapy schedules (32–54 Gy).

Finally, in another small, three-armed study (n = 72), patients were randomized between surgery, surgery with pre-operative radiotherapy (45 Gy in 4–5 weeks) and radiotherapy alone (50–60 Gy in 4–6 weeks) (14). 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 randomized studies looked at down-staging and found an increase in pCR following pre-operative radiotherapy from 9% to 34% (10), 0% to 24% (14) and from 18% to 55% (13). Local recurrences were not reported (10, 14) nor were they similar (13).

All six randomized 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 (10). The Egyptian study found a survival advantage only for T3 patients or higher (12). No study found a significant survival advantage for the whole group. A meta-analysis of the randomized trials on the value of pre-operative radiotherapy showed an odds ratio for the difference in 5-year survival of 0.71 (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 (CI: 0.57–1.55), indicating that improved survival with pre-operative radiotherapy had not been proven (15, 16).

9.2 Conclusions

- It is not proven that pre-operative radiotherapy for operable muscle-invasive bladder cancer increases survival (Level of evidence: 2).
- It is shown that 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 down-staging after 4–6 weeks (Level of evidence: 2).
- Pre-operative radiotherapy with a dose of 45–50 Gy/1.8–2 Gy does not seem to significantly increase toxicity after surgery (Level of evidence: 3).
- There are suggestions in older literature that pre-operative radiotherapy will result in a decrease in local recurrence of muscle-invasive bladder cancer (Level of evidence: 3).

9.3 Recommendations

- Pre-operative radiotherapy is not recommended to improve survival (Grade of recommendation: B).
- Pre-operative radiotherapy for operable muscle-invasive bladder cancer results in tumour down-staging after 4–6 weeks (Grade of recommendation: A–C).

9.4 REFERENCES

1. Pollack A, Zagars GK, Dinney CP, Swanson DA, von Eschenbach AC. Preoperative radiotherapy for muscle-invasive bladder carcinoma. Long term follow-up and prognostic factors for 338 patients. *Cancer* 1994;74(10):2819–27.
<http://www.ncbi.nlm.nih.gov/pubmed/7954243>
2. Cole CJ, Pollack A, Zagars GK, Dinney CP, Swanson DA, von-Eschenbach AC. Local control of muscle-invasive bladder cancer: preoperative radiotherapy and cystectomy versus cystectomy alone. *Int J Radiat Oncol Biol Phys* 1995;32(2):331–40.
<http://www.ncbi.nlm.nih.gov/pubmed/7751174>
3. Spera JA, Whittington R, Littman P, Solin LJ, Wein AJ. A comparison of preoperative radiotherapy regimens for bladder carcinoma. The University of Pennsylvania experience. *Cancer* 1988;61(2):255–62.
<http://www.ncbi.nlm.nih.gov/pubmed/3334959>
4. Pollack A, Zagars GK, Cole CJ, Dinney CP, Swanson DA, Grossman HB. Significance of downstaging in muscle-invasive bladder cancer treated with preoperative radiotherapy. *Int J Radiat Oncol Biol Phys* 1997;37(1):41–9.
<http://www.ncbi.nlm.nih.gov/pubmed/9054875>

5. Chougule P, Aygun C, Salazar O, Young JJ Jr, Prempre T, Amin P. Radiation therapy for transitional cell bladder carcinoma. A ten-year experience. *Urology* 1988;32(2):91-5.
<http://www.ncbi.nlm.nih.gov/pubmed/3135646>
6. Batata MA, Chu FC, Hilaris BS, Whitmore WF, Kim YS, Lee MZ. Bladder cancer in men and women treated by radiation therapy and/or radical cystectomy. *Urology* 1981;18(1):15-20.
<http://www.ncbi.nlm.nih.gov/pubmed/6789529>
7. 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;67(1):54-60.
<http://www.ncbi.nlm.nih.gov/pubmed/1993277>
8. Gilloz A, Heritier 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>
9. Smith JA, Batata M, Grabstald H, Sogani PC, Herr H, Whitmore WF Jr. Preoperative irradiation and cystectomy for bladder cancer. *Cancer* 1982;49:869-973.
<http://www.ncbi.nlm.nih.gov/pubmed/6800628>
10. 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;9:393-405.
<http://www.ncbi.nlm.nih.gov/pubmed/330958>
11. 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;157:805-7; discussion 807-8.
<http://www.ncbi.nlm.nih.gov/pubmed/9072571>
12. Ghoneim MA, Ashamalla AK, Awaad HK, Whitmore WF Jr. Randomized trial of cystectomy with or without preoperative radiotherapy for carcinoma of the bilharzial bladder. *J Urol* 1985;134(2):266-8.
<http://www.ncbi.nlm.nih.gov/pubmed/3894693>
13. Anderstrom C, Johanson S, Nilsson S, Unsgaard B, Wahlqvist L. 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>
14. 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;108(6):875-8.
<http://www.ncbi.nlm.nih.gov/pubmed/5082739>
15. Huncharek M, Muscat J, Geschwind JF. Planned preoperative radiation therapy in muscle-invasive bladder cancer; results of a meta-analysis. *Anticancer Res* 1998;18(3b):1931-4.
<http://www.ncbi.nlm.nih.gov/pubmed/9677446>
16. Widmark A, Flodgren P, Damber JE, Hellsten S, Cavallin-Stahl E. 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>

10. BLADDER-SPARING TREATMENTS

10.1 Transurethral resection of bladder tumour

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 (TURBT) 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 restaging TUR appears to be crucial in making the decision not to perform radical cystectomy (3, 4). It is only possible to consider TUR alone as a therapeutic option if tumour growth is limited to the superficial muscle layer and if restaging biopsies are negative for residual tumour (5). 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 (6).

10.1.1 Conclusion and recommendation

- TUR alone is not a curative treatment option in most patients (Level of evidence: 2a; Grade of recommendation: B).

10.1.2 References

1. Barnes RW, Dick AL, Hadley HL, Johnston OL. Survival following transurethral resection of bladder carcinoma. *Cancer Res* 1977;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;19(1):89-93.
<http://www.ncbi.nlm.nih.gov/pubmed/11134199>
3. Solsona E, Iborra I, Ricos JV, Monros JL, Casanova J, Calabuig C. Feasibility of transurethral resection for muscle infiltrating carcinoma of the bladder: long-term follow-up of a prospective study. *J Urol* 1998;159:95-98; discussion 98-99.
<http://www.ncbi.nlm.nih.gov/pubmed/9400445>
4. Holmang S, Hedelin H, Anderstrom C, Johansson SL. Long-term follow-up of all patients with muscle invasive (stages T2, T3 and T4) bladder carcinoma in a geographical region. *J Urol* 1997;158(2):389-92.
<http://www.ncbi.nlm.nih.gov/pubmed/9224309>
5. Herr HW. Conservative management of muscle-infiltrating bladder cancer: prospective experience. *J Urol* 1987;138(5):1162-3.
<http://www.ncbi.nlm.nih.gov/pubmed/3669160>
6. Whitmore WF Jr, Batata MA, Ghoneim MA, Grabstald H, Unal A. Radical cystectomy with or without prior irradiation in the treatment of bladder cancer. *J Urol* 1977;118(1 Pt 2):184-7.
<http://www.ncbi.nlm.nih.gov/pubmed/875217>

10.2 External beam radiotherapy

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 minimize 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). Besides the response to radiotherapy, important prognostic factors for outcome include tumour size, hydronephrosis and the completeness of the initial TURBT.

Overall 5-year survival rates in patients with muscle-invasive bladder cancer range between 30% and 60%, with a cancer-specific survival rate of 20% and 50%, with or without a complete response following radiotherapy, respectively (10-14). Based on available trials, a Cochrane analysis has demonstrated that radical cystectomy has an overall survival benefit compared to radiotherapy (15).

10.2.1 Conclusions

- 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 (Level of evidence: 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 (Level of evidence: 3).

10.2.2 Recommendation

- There is evidence that radiotherapy alone is less effective than curative therapy (surgery or trimodality treatment) (Grade or recommendation: B).

10.2.3 References

1. 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.
2. 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;7(4): 299-310.
<http://www.ncbi.nlm.nih.gov/pubmed/3101140>

3. Gospodarowicz MK, Hawkins NV, Rawlings GA, Connolly JG, Jewett MA, Thomas GM, Herman JG, Garrett PG, Chua T, Duncan W et al. Radical radiotherapy for muscle invasive transitional cell carcinoma of the bladder: failure analysis. *J Urol* 1989;142(6):1448-53; discussion 1453-4.
<http://www.ncbi.nlm.nih.gov/pubmed/2585617>
4. Gospodarowicz MK, Quilty PM, Scalliet P, Tsujii H, Fossa SD, Horenblas S, Isaka S, Prout R, Shipley WU, Wijnmaalen AJ et al. The place of radiation therapy as definitive treatment of bladder cancer. *Int J Urol* 1995;2(Suppl 2):41-8.
<http://www.ncbi.nlm.nih.gov/pubmed/7553304>
5. Shipley WU, Zietman AL, Kaufman DS, Althausen AF, Heney NM. Invasive bladder cancer: treatment strategies using transurethral surgery, chemotherapy and radiation therapy with selection for bladder conservation. *Int J Radiat Oncol Biol Phys* 1997;39(4):937-43.
<http://www.ncbi.nlm.nih.gov/pubmed/9369144>
6. Maciejewski B, Majewski S. Dose fractionation and tumor repopulation in radiotherapy for bladder cancer. *Radiother Oncol* 1991;21(3):163-70.
<http://www.ncbi.nlm.nih.gov/pubmed/1924851>
7. De Neve W, Lybeert MLM, Goor C, Crommelin NA, Ribot JG. Radiotherapy for T2 and T3 carcinoma of the bladder: the influence of overall treatment time. *Radiother Oncol* 1995;36(3):183-8.
<http://www.ncbi.nlm.nih.gov/pubmed/8532904>
8. Milosevic M, Gospodarowicz M, Zietman A, Abbas F, Haustermans K, Moonen L, Rodel C, Schoenberg M, Shipley W. Radiotherapy for bladder cancer. *Urology* 2007;69(1 Suppl):80-92.
<http://www.ncbi.nlm.nih.gov/pubmed/17280910>
9. Whitmore WF Jr, Batata MA, Ghoneim MA, Grabstald H, Unal A. Radical cystectomy with or without prior irradiation in the treatment of bladder cancer. *J Urol* 1977;118(1 Pt 2):184-7.
<http://www.ncbi.nlm.nih.gov/pubmed/875217>
10. Pollack A, Zagars GZ. Radiotherapy for stage T3b transitional cell carcinoma of the bladder. *Semin Urol Oncol* 1996;14(2):86-95.
<http://www.ncbi.nlm.nih.gov/pubmed/8734736>
11. De Neve W, Lybeert ML, Goor C, Crommelin MA, Ribot JG. Radiotherapy for T2 and T3 carcinoma of the bladder: the influence of overall treatment time. *Radiother Oncol* 1995;36(3):183-8.
<http://www.ncbi.nlm.nih.gov/pubmed/8532904>
12. Mameghan H, Fisher R, Mameghan J, Brook S. Analysis of failure following definitive radiotherapy for invasive transitional cell carcinoma of the bladder. *Int J Radiat Oncol Biol Phys* 1995;31(2):247-54.
<http://www.ncbi.nlm.nih.gov/pubmed/7836076>
13. Herskovic A, Martz K, Al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, Cooper J, Byhardt R, Davis L, Emami B. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992;326(24):1593-8.
<http://www.ncbi.nlm.nih.gov/pubmed/1584260>
14. Naslund I, Nilsson B, Littbrand B. Hyperfractionated radiotherapy of bladder cancer. A ten-year follow-up of a randomized clinical trial. *Acta Oncol* 1994;33(4):397-402.
<http://www.ncbi.nlm.nih.gov/pubmed/8018372>
15. Shelley MD, Barber J, Wilt T, Mason MD. Surgery versus radiotherapy for muscle invasive bladder cancer. *Cochrane Database Syst Rev* 2002;(1):CD002079.
<http://www.ncbi.nlm.nih.gov/pubmed/11869621>

10.3 Chemotherapy

Chemotherapy alone rarely produces durable complete responses. 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). In the case of an initially incomplete TUR, a pathological complete response rate of 8-26% can be expected following an additional cisplatin-based systemic therapy (3-5). The use of cisplatin-based chemotherapy as the primary therapy for locally advanced (T3/T4) tumours has resulted in complete and partial local responses in 11% and 34% of cases, respectively (6-7).

10.3.1 Conclusion

With cisplatin-based chemotherapy as primary therapy for locally advanced tumours in highly selected patients, complete and partial local responses have been reported (Level of evidence: 2b).

10.3.2 Recommendation

Chemotherapy alone is not recommended as primary therapy for localized bladder cancer (Grade of recommendation: A).

10.3.3 References

1. Scher HI, Yagoda A, Herr HW, Sternberg CN, Bosl G, Morse MJ, Sogani PC, Watson RC, Dershaw DD, Reuter V et al. Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) effect on the primary bladder lesion. *J Urol* 1988;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;16(4):1298-301.
<http://www.ncbi.nlm.nih.gov/pubmed/9552029>
3. Scattoni V, Da Pozzo L, Nava L, Brogna L, Galli L, Torelli T, Campo B, Maffezzini M, Rigatti P. Five-year results of neoadjuvant cisplatin, methotrexate and vinblastine chemotherapy plus radical cystectomy in locally advanced bladder cancer. *Eur Urol* 1995;28(2):102-7.
<http://www.ncbi.nlm.nih.gov/pubmed/8529731>
4. Igawa M, Ohkuchi T, Ueki T, Ueda M, Okada K, Usui T. Usefulness and limitations of methotrexate, vinblastine, doxorubicin and cisplatin for the treatment of advanced urothelial cancer. *J Urol* 1990;144(3):662-5.
<http://www.ncbi.nlm.nih.gov/pubmed/2388322>
5. Angulo JC, Sanchez-Chapado M, Lopez JI, Flores N. Primary cisplatin, methotrexate and vinblastine aiming at bladder preservation in invasive bladder cancer: multivariate analysis on prognostic factors. *J Urol* 1996;155(6):1897-902.
<http://www.ncbi.nlm.nih.gov/pubmed/8618282>
6. Roberts JT, Fossa SD, Richards B, Kaye SB, White EF, Robinson MC, Uscinska B, Parmar MK. Results of Medical Research Council phase II study of low dose cisplatin and methotrexate in the primary treatment of locally advanced (T3 and T4) transitional cell carcinoma of the bladder. *Br J Urol* 1991;68(2):162-8.
<http://www.ncbi.nlm.nih.gov/pubmed/1884143>
7. Martinez-Piñero JA, Gonzalez Martin M, Arocena F, Flores N, Roncero CR, Portillo JA, Escudero A, Jimenez Cruz F, Isorna S. Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: a prospective randomized phase III study. *J Urol* 1995;153(3 Pt 2):964-73.
<http://www.ncbi.nlm.nih.gov/pubmed/7853584>

10.4 Multimodality treatment

Recent organ-preservation strategies combine TURBT, chemotherapy and radiation (1-5). The rationale for performing TURBT 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 radiosensitizers. Cisplatin-based chemotherapy in combination with radiotherapy, following TURBT, results in a complete response rate of 60-80%.

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

A comparable long-term survival rate of 50-60% at 5 years' follow-up is reported by both multimodality bladder-preserving trials and cystectomy series. However, both therapeutic approaches have never been directly compared and patients in multimodality series are highly selected (5-7).

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 tumor, 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 tumor recurrences with the need for 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

- There are comparable long-term survival rates in cases of multimodality treatment success (Level of evidence: 3).
- Delay in surgical therapy can compromise survival rates. (Level of evidence: 2b).

10.4.2 Recommendations

- TUR alone is not a curative treatment option in most patients (grade of recommendation: B).
- Radiotherapy alone is less effective than surgery (grade of recommendation: B).
- Chemotherapy alone is not recommended as primary therapy for localized bladder cancer (grade of recommendation: B).
- Multimodality treatment is an alternative in selected, well-informed and compliant patients where cystectomy is not considered for clinical or personal reasons (Grade of recommendation: B).

10.4.3 References

1. Shipley WU, Kaufman DS, Zietman AL, Griffin PP, Heney NM, Althausen AF. Selective bladder preservation by combined modality therapy for invasive bladder cancer. *Eur J Cancer* 1995;31A(Suppl 5):S239.
2. Shipley WU, Kaufman DS, Heney NM, Althausen AF, Zietman AL. An update of selective bladder preservation by combined modality therapy for invasive bladder cancer. *Eur Urol* 1998;33 Suppl 4:32-4.
<http://www.ncbi.nlm.nih.gov/pubmed/9615208>
3. Housset M, Dufour E, Maulard-Durtux C. Concomitant 5-fluouracil (5-FU)-cisplatin (CDDP) and bifractionated split course radiation therapy (BSCRT) for invasive bladder cancer. *Proc Am Soc Clin Oncol* 1997;16:1139A (abstr).
http://www.asco.org/ASCO/Abstracts+&+Virtual+Meeting/Abstracts?&vmview=abst_search_results_vie&selectedConfs=17,31,30,29,28&SearchFilter1=Title&SearchTerm1=cisplatin&SearchFilter2=Author&SearchTerm2=&SearchFilter3=Author&SearchTerm3=Housset
4. Weiss C, Wolze C, Engehausen DG, Ott OJ, Krause FS, Schrott KM, Dunst J, Sauer R, Rodel C. Radiochemotherapy after transurethral resection for high-risk T1 bladder cancer: an alternative to intravesical therapy or early cystectomy? *J Clin Oncol* 24(15):2318-24.
<http://www.ncbi.nlm.nih.gov/pubmed/16710030>
5. Rodel C, Grabenbauer GG, Kuhn R, Papadopoulos T, Dunst J, Meyer M, Schrott KM, Sauer R. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. *J Clin Oncol* 2002;20(14):3061-71.
<http://www.ncbi.nlm.nih.gov/pubmed/12118019>
6. Zietman AL, Grocela J, Zehr E, Kaufman DS, Young RH, Althausen AF, Heney NM, Shipley WU. Selective bladder conservation using transurethral resection, chemotherapy, and radiation: management and consequences of Ta, T1, and Tis recurrence within the retained bladder. *Urology* 2001;58(3):380-5.
<http://www.ncbi.nlm.nih.gov/pubmed/11549485>
7. Shipley WU, Kaufman DS, Zehr E, Heney NM, Lane SC, Thakral HK, Althausen AF, Zietman AL. Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. *Urology* 2002;60(1):62-7; discussion 67-8.
<http://www.ncbi.nlm.nih.gov/pubmed/12100923>

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 randomized 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 are sub-optimal with serious deficiencies, such as low sample size (underpowered), use of 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 end-point 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 in good PS (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 randomized adjuvant chemotherapy have used 3-4 cycles of CMV (cisplatin, methotrexate, vinblastine), CISCA (cisplatin, cyclophosphamide, and adriamycine), MVA(E)C (methotrexate, vinblastine, adriamycine or epirubicine, 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

- Adjuvant chemotherapy is under debate. Neither randomized trials nor a meta-analysis have provided sufficient data to support the routine use of adjuvant chemotherapy (Level of evidence: 1a).

11.2 Recommendation

- Adjuvant chemotherapy is advised within clinical trials, but not for routine use because it has not been studied sufficiently (Grade of recommendation: A).

11.3 REFERENCES

1. Cohen SM, Goel A, Phillips J, Ennis RD, Grossbard ML. The role of perioperative chemotherapy in the treatment of urothelial cancer. *Oncologist* 2006;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;11(7):851-6.
<http://www.ncbi.nlm.nih.gov/pubmed/10997813>
3. Bono A, Benvenuti C, Gibba A, Guazzeri S, Cosciani-Cunico S, Anselmo G. 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;155(2):495-9; discussion 499-500.
<http://www.ncbi.nlm.nih.gov/pubmed/8558644>
5. Stockle M, Meyenburg W, Wellek S, Voges GE, Rossmann M, Gertenbach U, Thuroff JW, Huber C, Hohenfellner R. 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;153(1):47-52.
<http://www.ncbi.nlm.nih.gov/pubmed/7966789>
6. Studer UE, Bacchi M, Biedermann C, Jaeger P, Kraft R, Mazzucchelli L, Markwalder R, Senn E, Sonntag RW. Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. *J Urol* 1994;152(1):81-4.
<http://www.ncbi.nlm.nih.gov/pubmed/8201695>
7. Skinner DG, Daniels JR, Russell CA, Lieskovsky G, Boyd SD, Krailo M, Groshen S. Adjuvant chemotherapy following cystectomy benefits patients with deeply invasive bladder cancer. *Semin Urol* 1990;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;48(2):189-199; discussion 99-201.
<http://www.ncbi.nlm.nih.gov/pubmed/15939530>

9. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, Moore MJ, Zimmermann A, Arning M. 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;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;34(2):122-8.
<http://www.ncbi.nlm.nih.gov/pubmed/17382795>
11. Stadler WM, Hayden A, von der Maase H, Roychowdhur D, Dogliotti L, Seymour L, Kaufmann D, Moore M. Long-term survival in phase II trials of gemcitabine plus cisplatin for advanced transitional cell cancer. *Urol Oncol* 2002;7(4):153-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12474531>
12. Lehmann J, Retz M, Wiemers C, Beck J, Thuroff J, Weining C, Albers P, Frohneberg D, Becker T, Funke PJ, Walz P, Langbein S, Reiher F, Schiller M, Miller K, Roth S, Kalbe T, Sternberg D, Wellek S, Stockle M; AJO-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 (AJO-AB 05/95). *J Clin Oncol* 2005;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; about half will relapse after radical cystectomy depending on the pathological stage of the primary tumour and the nodal status. Local recurrence accounts for about 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 exceeded the median survival of 3-6 months (2).

12.1 Prognostic factors and treatment decisions

Bladder cancer is a chemosensitive tumour. Response rates differ with respect to patient-related factors and pre-treatment disease. Prognostic factors for response and survival have been established. In a multivariate analysis, Karnofsky PS of 80% or less and the presence of visceral metastases were independently prognostic 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 chemotherapies (4, 5) and are crucial for assessing phase II study results and stratifying phase III trials (6, 7). Additional data on the prognostic value of elevated alkaline phosphatase and the number of disease sites (> or ≤ three) were generated prospectively (8). A retrospective analysis showed that, in elderly patients, an ECOG (Eastern Cooperative Oncology Group) PS 2-3 and a haemoglobin level of <10 mg/dl were independent predictors of poor survival (9). Age itself has no impact on response or toxic events (9).

Besides these prognostic factors, treatment decisions should also be based on a patient's renal function to decide whether a patient is 'fit' enough to receive a cisplatin-containing combination regimen (creatinine clearance ≥ 60 mL/min, PS, co-morbidity) (10-14). So far, there is no generally accepted definition for 'fit' or 'unfit' patients (15).

12.2 Single-agent chemotherapy

Varying response rates of single-agent first-line chemotherapy have been reported with only 12% for cisplatin compared to MVAC (7), 12% for carboplatin (10), 42% for paclitaxel (16), 31% for docetaxel (17), 29% for methotrexate, 19% for adriamycin, 15% for epirubicin, 13% for mitomycin C, 35% for 5-FU, 14% for vinblastine, 29% for ifosfamide and 8% for cyclophosphamide (18, 19). The most robust single-agent data is a response rate of about 25% for gemcitabine for first- and second-line use in several, larger-sized, phase II trials (20-27).

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 about 6-9 months. Patients with PS WHO 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 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 superior to cisplatin monotherapy and CISCA (cisplatin, cyclophosphamide and adriamycin) (7, 28) and, more recently, to cisplatin/docetaxel (29). MVAC and gemcitabine/cisplatin (GC) have prolonged survival up to 14.8 and 13.8 months, respectively (30-32). Neither of the two combinations was proven to be superior over the other, but equivalence was not tested, with response rates of 46% and 49% for MVAC and GC, respectively. The long-term survival results confirmed the anticipated equivalence of the two regimens (8). The major difference between the above-mentioned combinations was toxicity, with GC being less toxic (32). MVAC is better tolerated with the use of GCSF (29, 33).

High-dose intensity MVAC (HD-MVAC) with GCSF 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 (34, 35).

Further intensification of treatment using new triplets, dose-dense schedules or adding targeted therapies is still being investigated. These approaches should be reserved for clinical trials and are not considered suitable for routine use.

12.4 Carboplatin-containing chemotherapy in 'fit' patients

Carboplatin-containing chemotherapy is not proven to be equivalent to cisplatin combinations. However, it is probably inferior and therefore should not be considered interchangeable or standard. The only randomized phase III study of carboplatin-containing chemotherapy had a disappointing response rate of only 28.2% in the investigational arm (paclitaxel/carboplatin) compared to MVAC and had to be closed down early because of a low accrual rate. There is therefore no evidence that this doublet might have adequate efficacy for first-line use (36).

Various carboplatin versus cisplatin combination chemotherapies in randomized phase II trials have produced lower complete response rates and a shorter overall survival for the carboplatin arms (37-39).

12.5 Non-platinum combination chemotherapy

Gemcitabine and paclitaxel combinations in different schedules have been studied as both first- and second-line treatments. Apart from severe pulmonary toxicity with a weekly schedule of both drugs, this combination has been well tolerated and produced response rates between 38% and 60% in both lines. Because there has not been a randomized comparison. Because there has not been a randomized comparison to standard cisplatin chemotherapy, non-platinum combination-chemotherapy is not recommended for first-line use in patients who are fit enough (27, 40-45).

12.6 Chemotherapy in patients 'unfit' for cisplatin

Up to 50% of patients are unfit for cisplatin-containing chemotherapy, either due to a poor PS and/or impaired renal function, or due to co-morbidity that forbids high-volume hydration (46, 47). In such cases, carboplatin combination or single-agent chemotherapy is reasonable (10, 11). Non-platinum combinations, as front-line chemotherapy in patients with two adverse prognostic factors (GFR < 50-60 mL/min and PS \geq 2) should be reserved for investigational use because they have not been tested in purely 'unfit' patients and might be too toxic. Trials with clearly defined 'unfit' patients or patients with multiple adverse prognostic factors are rare. However, the first randomized phase II/III trial in this setting is currently being conducted by the EORTC. It compares carboplatin/vinblastin/methotrexate and carboplatin/gemcitabine in patients unfit for cisplatin (www.eortc.be).

12.7 Second-line treatment

Second-line chemotherapy data are highly variable and prognostic factors are unclear in this setting. Suggested prognostic factors include the choice of front-line chemotherapy (adjuvant/neoadjuvant), prior chemosensitivity, PS and the 'Bajorin'-prognostic factors. There is not yet enough data to define a chemotherapy standard in this setting. Re-exposition 12 months or more after response to a prior chemotherapeutic regimen is a reasonable strategy.

Second-line response rates of paclitaxel (weekly), docetaxel, oxaliplatin, topotecan, lapatinib, gefitinib and bortezomib range between 0% and 13% in small phase II trials (48-55).

Gemcitabine has been studied with excellent response rates also for second-line use (20, 24-27). However, most patients already receive this drug as part of their front-line treatment.

Vinflunine, a new third-generation vinca-alcaloid, has shown objective response rates of 18% and disease control in 67% (56). Publication of a phase III trial of vinflunine randomized against best supportive care is awaited.

In a phase II trial, pemetrexed 500 mg/m², given every 3 weeks, showed a promising response rate of 28% and manageable toxicity with the addition of vitamin B12 and folic acid supplementation and

dexamethasone prophylaxis (57). The excellent response rate could not be confirmed by a second, smaller-sized trial; however, this may have been due to patient selection (58).

Ifosfamide had a response rate of 20% but is prone to considerable toxicity (59).

Paclitaxel/gemcitabine showed response rates of 38-60%, depending on pre-treatment response and indication of prior chemotherapy. Unfortunately, no randomized trial has been conducted to assess the true value of this second-line combination (2, 41, 45).

12.8 Low-volume disease and post-chemotherapy surgery

With cisplatin-containing combination chemotherapy, patients with lymph node metastases only, good PS and an adequate renal function may achieve excellent response rates, including a high degree of complete responses, with up to 20% of patients achieving long-term disease-free survival (8, 35, 60, 61). Stage migration may play a role in this positive prognostic development.

A retrospective study of post-chemotherapy surgery after a partial or complete response indicated that post-chemotherapy surgery may contribute to long-term disease-free survival in selected patients (62-64).

12.9 Conclusions

- Urothelial carcinoma is a chemosensitive tumour.
- Performance status and the presence or absence of visceral metastases are independent prognostic factors for survival. These factors are at least as important as the type of chemotherapy administered (Level of evidence: 3).
- Cisplatin-containing combination chemotherapy is able to achieve a median survival of up to 14 months, with long-term disease-free survival reported in about 15% of patients with nodal disease and good PS (Level of evidence: 1b).
- Single-agent chemotherapy provides low response rates of usually short duration (Level of evidence: 2a).
- Carboplatin-combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of CR and survival (Level of evidence: 2a).
- Non-platinum combination chemotherapy has produced substantial responses in first- and second-line use, but has not been tested against standard chemotherapy in fit patients or in a purely unfit patient group (Level of evidence: 2a).
- To date, there is no defined standard chemotherapy for 'unfit' patients with advanced or metastatic urothelial cancer (Level of evidence: 2b).
- Small-sized phase II trials provide evidence of moderate response rates for single agents or non-platinum combinations at second-line use (Level of evidence: 2a).
- Post-chemotherapy surgery after a partial or complete response may contribute to long-term disease-free survival (Level of evidence: 3).

12.10 Recommendations

- Prognostic factors guide treatment selection (Grade of recommendation: B).
- First-line treatment for fit patients: use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with GCSF, or HD-MVAC with GCSF (Grade of recommendation: A).
- Carboplatin and non-platinum combination chemotherapy as first-line treatment in patients fit for cisplatin is not recommended (Grade of recommendation: B).
- First-line treatment in patients unfit for cisplatin: use carboplatin combination chemotherapy or single agents (Grade of recommendation: C).
- Second-line treatment: consider single agents or paclitaxel/gemcitabine if the patient has a good PS (Grade of recommendation: C).

12.11 REFERENCES

1. Rosenberg JE, Carroll PR, Small EJ. Update on chemotherapy for advanced bladder cancer. *J Urol* 2005;174(1):14-20.
<http://www.ncbi.nlm.nih.gov/pubmed/15947569>
2. Sternberg CN, Vogelzang NJ. Gemcitabine, paclitaxel, pemetrexed and other newer agents in urothelial and kidney cancers. *Crit Rev Oncol Hematol* 2003;46(Suppl):S105-S115.
<http://www.ncbi.nlm.nih.gov/pubmed/12850531>
3. Bajorin DF, Dodd PM, Mazumdar M, Fazzari M, McCaffrey JA, Scher HI, Herr H, Higgins G, Boyle MG. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. *J Clin Oncol* 1999;17(10):3173-81.
<http://www.ncbi.nlm.nih.gov/pubmed/10506615>

4. Bellmunt J, Albanell J, Paz-Ares L, Climent MA, Gonzalez-Larriba JL, Carles J, de la Cruz JJ, Guillem V, Diaz-Rubio E, Cortes-Funes H, Baselga J; 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;95(4):751-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12209718>
5. Sengelov 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;39(6):634-42.
<http://www.ncbi.nlm.nih.gov/pubmed/11464051>
6. Bajorin D. The phase III candidate: can we improve the science of selection? *J Clin Oncol* 2004;22(2):211-3.
<http://www.ncbi.nlm.nih.gov/pubmed/14665614>
7. Loehrer PJ Sr, Einhorn LH, Elson PJ, Crawford ED, Kuebler P, Tannock I, Raghavan D, Stuart-Harris R, Sarosdy MF, Lowe BA 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;10(7):1066-73.
<http://www.ncbi.nlm.nih.gov/pubmed/1607913>
8. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, Moore MJ, Zimmermann A, Arning M. 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;23(21):4602-8.
<http://www.ncbi.nlm.nih.gov/pubmed/16034041>
9. Bamias A, Efstathiou E, Mouloupoulos LA, Gika D, Hamilos G, Zorzou MP, Kakoyiannis C, Kastiris E, Bozas G, Papadimitriou C, Dimopoulos MA. The outcome of elderly patients with advanced urothelial carcinoma after platinum-based combination chemotherapy. *Ann Oncol* 2005;16(2):307-13.
<http://www.ncbi.nlm.nih.gov/pubmed/15668289>
10. Bellmunt J, Albanell J, Gallego OS, Ribas A, Vicente P, Carulla J, De Torres J, Morote J, Lopez M, Sole LA. Carboplatin, methotrexate, and vinblastine in patients with bladder cancer who were ineligible for cisplatin-based chemotherapy. *Cancer* 1992;70(7):1974-9.
<http://www.ncbi.nlm.nih.gov/pubmed/1525774>
11. Bellmunt J, de Wit R, Albanell J, Baselga J. A feasibility study of carboplatin with fixed dose of gemcitabine in "unfit" patients with advanced bladder cancer. *Eur J Cancer* 2001;37(17):2212-5.
<http://www.ncbi.nlm.nih.gov/pubmed/11677109>
12. Yagoda A. Chemotherapy of metastatic bladder cancer. *Cancer* 1980;45(7 Suppl):1879-88.
<http://www.ncbi.nlm.nih.gov/pubmed/7189443>
13. Raj GV, Iasonos A, Herr H, Donat SM. Formulas calculating creatinine clearance are inadequate for determining eligibility for cisplatin-based chemotherapy in bladder cancer. *J Clin Oncol* 2006;24(19):3095-100.
<http://www.ncbi.nlm.nih.gov/pubmed/16809735>
14. Carles J, Nogue M, Domenech M, Perez C, Saigi E, Villadiego K, Guasch I, Ibeas R. Carboplatin-gemcitabine treatment of patients with transitional cell carcinoma of the bladder and impaired renal function. *Oncology* 2000;59(1):24-7.
<http://www.ncbi.nlm.nih.gov/pubmed/10895062>
15. Sternberg CN, Donat SM, Bellmunt J, Millikan RE, Stadler W, De Mulder P, Sherif A, von der Maase H, Tsukamoto T, Soloway MS. Chemotherapy for bladder cancer: treatment guidelines for neoadjuvant chemotherapy, bladder preservation, adjuvant chemotherapy, and metastatic cancer. *Urology* 2007;69(1 Suppl):62-79.
<http://www.ncbi.nlm.nih.gov/pubmed/17280909>
16. Roth BJ, Dreicer R, Einhorn LH, Neuberger D, Johnson DH, Smith JL, Hudes GR, Schultz SM, Loehrer PJ. Significant activity of paclitaxel in advanced transitional-cell carcinoma of the urothelium: a phase II trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1994;12(11):2264-70.
<http://www.ncbi.nlm.nih.gov/pubmed/7525883>
17. de Wit R, Kruit WH, Stoter G, de Boer M, Kerger J, Verweij J. Docetaxel (Taxotere): an active agent in metastatic urothelial cancer; results of a phase II study in non-chemotherapy-pretreated patients. *Br J Cancer* 1998;78(10):1342-5.
<http://www.ncbi.nlm.nih.gov/pubmed/9823976>
18. Yagoda A. Chemotherapy of urothelial tract tumors. *Cancer* 1987;60(3 Suppl):574-85.
<http://www.ncbi.nlm.nih.gov/pubmed/3297286>
19. Roth BJ, Bajorin DF. Advanced bladder cancer: the need to identify new agents in the post-M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) world. *J Urol* 1995;153(3 Pt 2):894-900.
<http://www.ncbi.nlm.nih.gov/pubmed/7853569>

20. von der Maase H. Gemcitabine in transitional cell carcinoma of the urothelium. *Expert Rev Anticancer Ther* 2003;3(1):11-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12597345>
21. Moore MJ, Tannock IF, Ernst DS, Huan S, Murray N. Gemcitabine: a promising new agent in the treatment of advanced urothelial cancer. *J Clin Oncol* 1997;15(12):3441-5.
<http://www.ncbi.nlm.nih.gov/pubmed/9396395>
22. Stadler WM, Kuzel T, Roth B, Raghavan D, Dorr FA. Phase II study of single-agent gemcitabine in previously untreated patients with metastatic urothelial cancer. *J Clin Oncol* 1997;15(11):3394-8.
<http://www.ncbi.nlm.nih.gov/pubmed/9363871>
23. 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).
24. Pollera CF, Ceribelli A, Crecco M, Calabresi F. Weekly gemcitabine in advanced bladder cancer: a preliminary report from a phase I study. *Ann Oncol* 1994;5(2):182-4.
<http://www.ncbi.nlm.nih.gov/pubmed/8186164>
25. Lorusso V, Pollera CF, Antimi M, Luporini G, Gridelli C, Frassinetti GL, Oliva C, Pacini M, De Lena M. 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;34(8):1208-12.
<http://www.ncbi.nlm.nih.gov/pubmed/9849481>
26. 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;150(1):11-5.
<http://www.ncbi.nlm.nih.gov/pubmed/10367539>
27. Albers P, Siener R, Hartlein M, Fallahi M, Haeutle D, Perabo FG, Steiner G, Blatter J, Muller SC; 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;25(1):47-52.
<http://www.ncbi.nlm.nih.gov/pubmed/11893883>
28. Logothetis CJ, Dexeus FH, Finn L, Sella A, Amato RJ, Ayala AG, Kilbourn RG. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. *J Clin Oncol* 1990;8(6):1050-5.
<http://www.ncbi.nlm.nih.gov/pubmed/2189954>
29. Bamias A, Aravantinos G, Deliveliotis C, Bafaloukos D, Kalofonos C, Xiros N, Zervas A, Mitropoulos D, Samantas E, Pectasides D, Papakostas P, Gika D, Kourousis C, Koutras A, Papadimitriou C, Bamias C, Kosmidis P, Dimopoulos MA; 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;22(2):220-8.
<http://www.ncbi.nlm.nih.gov/pubmed/14665607>
30. Sternberg CN, Yagoda A, Scher HI, Watson RC, Geller N, Herr HW, Morse MJ, Sogani PC, Vaughan ED, Bander N et al. Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. *Cancer* 1989;64(12):2448-58.
<http://www.ncbi.nlm.nih.gov/pubmed/2819654>
31. 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;139(3):461-9.
<http://www.ncbi.nlm.nih.gov/pubmed/3343727>
32. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, Bodrogi I, Albers P, Knuth A, Lippert CM, Kerbrat P, Sanchez Rovira P, Wersall P, Cleall SP, Roychowdhury DF, Tomlin I, Visseren-Grul CM, Conte PF. 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;18(17):3068-77.
<http://www.ncbi.nlm.nih.gov/pubmed/11001674>
33. Gabrilove JL, Jakubowski A, Scher H, Sternberg C, Wong G, Grous J, Yagoda A, Fain K, Moore MA, Clarkson B 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;318(22):1414-22.
<http://www.ncbi.nlm.nih.gov/pubmed/2452983>

34. Sternberg CN, de Mulder PH, Schornagel JH, Theodore C, Fossa SD, van Oosterom AT, Witjes F, Spina M, van Groeningen CJ, de Balincourt C, Collette L; 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;19(10):2638-46.
<http://www.ncbi.nlm.nih.gov/pubmed/11352955>
35. Sternberg CN, de Mulder P, Schornagel JH, Theodore C, Fossa SD, van Oosterom AT, Witjes JA, Spina M, van Groeningen CJ, Duclos B, Roberts JT, de Balincourt C, Collette L; 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;42(1):50-4.
<http://www.ncbi.nlm.nih.gov/pubmed/16330205>
36. Dreicer R, Manola J, Roth BJ, See WA, Kuross S, Edelman MJ, Hudes GR, Wilding G. Phase III trial of methotrexate, vinblastine, doxorubicin, and cisplatin versus carboplatin and paclitaxel in patients with advanced carcinoma of the urothelium. *Cancer* 2004;100(8):1639-45.
<http://www.ncbi.nlm.nih.gov/pubmed/15073851>
37. Petrioli R, Frediani B, Manganelli A, Barbanti G, De Capua B, De Lauretis A, Salvestrini F, Mondillo S, Francini G. 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;77(2):344-51.
<http://www.ncbi.nlm.nih.gov/pubmed/8625244>
38. Carteni G, Dogliotti L, Crucitta E, Martoni A, Siena S, Onat H, Bertetto O, Bono A, Amadori D, Marini L. 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/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_detail_view&confID=23&abstractID=102093
39. Bellmunt J, Ribas A, Eres N, Albanell J, Almanza C, Bermejo B, Sole LA, Baselga J. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. *Cancer* 1997;80(10):1966-72.
<http://www.ncbi.nlm.nih.gov/pubmed/9366300>
40. Sternberg CN, Calabro F, Pizzocaro G, Marini L, Schnetzer S, Sella A. 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;92(12):2993-8.
<http://www.ncbi.nlm.nih.gov/pubmed/11753976>
41. Meluch AA, Greco FA, Burris HA 3rd, O'Rourke T, Ortega G, Steis RG, Morrissey LH, Johnson V, Hainsworth JD. 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;19(12):3018-24.
<http://www.ncbi.nlm.nih.gov/pubmed/11408496>
42. Parameswaran R, Fisch MJ, Ansari RH, Fox EP, Sweeney CJ, Einhorn LH. 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/ASCO/Abstracts+&+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=10&abstractID=798
43. 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/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?abstractID=2413&confID=16&index=y&vmview=abst_detail_view
44. Fechner GH, Siener R, Reimann M et al. Randomized phase II trial of gemcitabine and paclitaxel with or without maintenance treatment in patients with cisplatin refractory transitional cell carcinoma. *J Urol* 2002;167(Suppl 4):abstr 284.

45. Kaufman DS, Carducci MA, Kuzel T, Todd MB, Raghavan D, Oh WK, Smith MR, Nicol SJ, Stadler WW. 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
46. Nogue-Aliguer M, Carles J, Arrivi A, Juan O, Alonso L, Font A, Mellado B, Garrido P, Saenz A; Spanish Cooperative Group. Gemcitabine and carboplatin in advanced transitional cell carcinoma of the urinary tract: an alternative therapy. *Cancer* 2003;97(9):2180-6.
<http://www.ncbi.nlm.nih.gov/pubmed/12712469>
47. Balducci L. Evidence-based management of cancer in the elderly. *Cancer Control* 2000;7(4):368-76.
<http://www.ncbi.nlm.nih.gov/pubmed/10895132>
48. Vaughn DJ, Broome CM, Hussain M, Gutheil JC, Markowitz AB. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. *J Clin Oncol* 2002;20(4):937-40.
<http://www.ncbi.nlm.nih.gov/pubmed/11844814>
49. Papamichael D, Gallagher CJ, Oliver RT, Johnson PW, Waxman J. 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>
50. McCaffrey JA, Hilton S, Mazumdar M, Sadan S, Kelly WK, Scher HI, Bajorin DF. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. *J Clin Oncol* 1997;15(5):1853-7.
<http://www.ncbi.nlm.nih.gov/pubmed/9164195>
51. Moore M, Winqvist E, Vokes E, Hirte H, Hoving K, Stadler W. 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/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=23&abstractID=100319
52. Witte RS, Manola J, Burch PA, Kuzel T, Weinshel EL, Loehrer PJ Sr. 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>
53. Petrylak D, Faulkner J, Van Veldhuizen P, Mansukhani M, Crawford E. 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/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=23&abstractID=104215
54. Sridhar S, Stadler W, Le L, Hedley D, Pond G, Wright J, Vokes E, Thomas S, Moore M. 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://prostateca.asco.org/ASCO/Abstracts+&+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=34&abstractID=33648
55. Wulfing C, Machiels J, Richiels D, Grimm M, Treiber U, de Groot M, Beuzebec P, Farrel J, Stone NL, Leopold L, El-Hariry I. A single arm, multicenter, open-label, ph 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://prostateca.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_detail_view&confID=34&abstractID=31739
56. Culine S, Theodore C, De Santis M, Bui B, Demkow T, Lorenz J, Rolland F, Delgado FM, Longerey B, James N. A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen. *Br J Cancer* 2006;94(10):1395-401.
<http://www.ncbi.nlm.nih.gov/pubmed/16622447>
57. Sweeney CJ, Roth BJ, Kabbavar FF, Vaughn DJ, Arning M, Curiel RE, Obasaju CK, Wang Y, Nicol SJ, Kaufman DS. Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. *J Clin Oncol* 2006;24(21):3451-7.
<http://www.ncbi.nlm.nih.gov/pubmed/16849761>

58. Galsky MD, Mironov S, Iasonos A, Scattergood J, Boyle MG, Bajorin DF. Phase II trial of pemetrexed as second-line therapy in patients with metastatic urothelial carcinoma. *Invest New Drugs* 2007;25(3):265-70.
<http://www.ncbi.nlm.nih.gov/pubmed/17146733>
59. Witte RS, Elson P, Bono B, Knop R, Richardson RR, Dreicer R, Loehrer PJ Sr. Eastern Cooperative Oncology Group phase II trial of ifosfamide in the treatment of previously treated advanced urothelial carcinoma. *J Clin Oncol* 1997;15(2):589-93.
<http://www.ncbi.nlm.nih.gov/pubmed/9053481>
60. Stadler WM. Gemcitabine doublets in advanced urothelial cancer. *Semin Oncol* 2002;29(1 Suppl 3):15-9.
<http://www.ncbi.nlm.nih.gov/pubmed/11894003>
61. Hussain M, Vaishampayan U, Du W, Redman B, Smith DC. Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. *J Clin Oncol* 2001;19(9):2527-33.
<http://www.ncbi.nlm.nih.gov/pubmed/11331332>
62. Herr HW, Donat SM, Bajorin DF. Post-chemotherapy surgery in patients with unresectable or regionally metastatic bladder cancer. *J Urol* 2001;165(3):811-4.
<http://www.ncbi.nlm.nih.gov/pubmed/1117647>
63. Sweeney P, Millikan R, Donat M, Wood CG, Radtke AS, Pettaway CA, Grossman HB, Dinney CP, Swanson DA, Pisters LL. Is there a therapeutic role for post-chemotherapy retroperitoneal lymph node dissection in metastatic transitional cell carcinoma of the bladder? *J Urol* 2003;169(6):2113-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12771730>
64. Siefker-Radtke AO, Walsh GL, Pisters LL, Shen Y, Swanson DA, Logothetis CJ, Millikan RE. Is there a role for surgery in the management of metastatic urothelial cancer? The M. D. Anderson experience. *J Urol* 2004;171(1):145-8.
<http://www.ncbi.nlm.nih.gov/pubmed/14665863>

13. QUALITY OF LIFE

The evaluation of health-related quality of life (HRQL) considers physical, emotional and social functioning. Several questionnaires, e.g. FACT (Functional Assessment of Cancer Therapy)-G (1), EORTC QLQ-C30 (1) and SF (Short Form)-36 (3, 4), have been validated for assessing HRQL in patients with bladder cancer. A psychometrical test such as the FACT-BL should be used for recording bladder cancer morbidity. Recently, new intensive interviewing techniques add valuable information to our knowledge of HRQL, which greatly depends on patients' individual preferences in life (5).

Unfortunately, most retrospective studies do not evaluate the association between HRQL and bladder cancer-specific issues after cystectomy, such as incontinence or potency. Furthermore, important co-variables, such as a patient's age, mental status, coping ability and gender, have only rarely been considered (6). It remains difficult to predict the impact of post-therapeutic symptoms because of individual differences in symptom tolerance.

There is controversy about which type of urinary diversion is best for a patient's quality of life (7). Some studies have not demonstrated any difference (8, 9). As a result of improvement in surgical techniques and orthotopic bladder substitution, some more recent studies are in favour of the continent bladder substitutes (10-17). In one study (17), a statistically significant difference in HRQL in favour of neobladders was observed. Notably, HRQL parameters have been shown to represent an independent prognostic parameter for overall survival (18). Patients with a continent bladder-substitute generally score more favourably than those with an incontinent diversion, as judged by body image, social activity and physical function (11, 16).

In non-curative or metastatic bladder cancer, HRQL is reduced because of associated micturition problems, bleeding, pain and therefore disturbance of social and sexual life (19). Relief of bladder-related symptoms can be obtained by palliative surgery (20), radiotherapy (21) and/or chemotherapy (22), though there is limited literature describing HRQL in palliatively treated bladder cancer patients (23).

Alternative definitive treatments of muscle-invasive bladder cancer, e.g. trimodality bladder-sparing procedures, have shown similar survival times compared to cystectomy. However, the impact on HRQL has been controversial (24-29).

13.1 Conclusions

- There is no randomized prospective HRQL study evaluating different forms of definitive treatment for invasive bladder cancer.
- The overall HRQL after cystectomy remains good in most patients, whichever type of urinary diversion is used. Some data suggests that continent diversions produce a better HRQL (Level of evidence: 2b).

13.2 Recommendations

- HRQL in patients with muscle-invasive bladder cancer should be assessed using validated questionnaires (Grade of recommendation: A).
- Continent urinary diversions should be offered for reasons of HRQL, whenever a patient's age, personality, coping ability and tumour variables are suitable (Grade of recommendation: C).

13.3 REFERENCES

1. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;11(3):570-9.
<http://www.ncbi.nlm.nih.gov/pubmed/8445433>
2. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC 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;85(5):365-76.
<http://www.ncbi.nlm.nih.gov/pubmed/8433390>
3. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30(6):473-83.
<http://www.ncbi.nlm.nih.gov/pubmed/1593914>
4. Ware JE Jr, Keller SD, Gandek B, Brazier JE, Sullivan M. Evaluating translations of health status questionnaires. Methods from the IQOLA project. International Quality of Life Assessment. *Int J Technol Assess Health Care* 1995;11(3):525-51.
<http://www.ncbi.nlm.nih.gov/pubmed/7591553>
5. Ramirez A, Perrotte P, Valiquette L, Benard F, McCormack M, Saad F, Fournier C, Shariat S, Karakiewicz PI. Exploration of health-related quality of life areas that may distinguish between continent diversion and ileal conduit patients. *Can J Urol* 2005;12(1):2537-42.
<http://www.ncbi.nlm.nih.gov/pubmed/15777491>
6. Mansson A, Caruso A, Capovilla E, Colleen S, Bassi P, Pagano F, Mansson W. Quality of life after radical cystectomy and orthotopic bladder substitution: a comparison between Italian and Swedish men. *BJU Int* 2000;85(1):26-31.
<http://www.ncbi.nlm.nih.gov/pubmed/10619940>
7. World Health Organization (WHO) Consensus Conference on 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;69(1 Suppl):17-49.
<http://www.ncbi.nlm.nih.gov/pubmed/17280907>
8. Mansson A, Davidsson T, Hunt S, Mansson W. 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;90(4):386-90.
<http://www.ncbi.nlm.nih.gov/pubmed/12175394>
9. Wright JL, Porter MP. Quality-of-life assessment in patients with bladder cancer. *Nat Clin Pract Urol* 2007;4(3):147-54.
<http://www.ncbi.nlm.nih.gov/pubmed/17347659>
10. van der Veen JH, van Andel G, Kurth KH. Quality-of-life assessment in bladder cancer. *World J Urol* 1999;17(4):219-24.
<http://www.ncbi.nlm.nih.gov/pubmed/10460404>
11. Dutta SC, Chang SC, Coffey CS, Smith JA Jr, Jack G, Cookson MS. Health related quality of life assessment after radical cystectomy: comparison of ileal conduit with continent orthotopic neobladder. *J Urol* 2002;168(1):164-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12050514>
12. Okada Y, Oishi K, Shichiri Y, Kakehi Y, Hamaguchi A, Tomoyoshi T, Yoshida O. Quality of life survey of urinary diversion patients: comparison of continent urinary diversion versus ileal conduit. *Int J Urol* 1997;4(1):26-31.
<http://www.ncbi.nlm.nih.gov/pubmed/9179663>

13. Gerharz EW, Weingartner K, Dopatka T, Kohl UN, Basler HD, Riedmiller HN. Quality of life after cystectomy and urinary diversion: results of a retrospective interdisciplinary study. *J Urol* 1997;158(3 Pt 1):778-85.
<http://www.ncbi.nlm.nih.gov/pubmed/9258080>
14. Hart S, Skinner EC, Meyerowitz BE, Boyd S, Lieskovsky G, Skinner DG. Quality of life after radical cystectomy for bladder cancer in patients with an ileal conduit, cutaneous or urethral kock pouch. *J Urol* 1999;162(1):77-81.
<http://www.ncbi.nlm.nih.gov/pubmed/10379744>
15. Hara I, Miyake H, Hara S, Gotoh A, Nakamura I, Okada H, Arakawa S, Kamidono S. Health-related quality of life after radical cystectomy for bladder cancer: a comparison of ileal conduit and orthotopic bladder replacement. *BJU Int* 2002;89(1):10-13.
<http://www.ncbi.nlm.nih.gov/pubmed/11849152>
16. Hardt J, Filipas D, Hohenfellner R, Egle UT. Quality of life in patients with bladder carcinoma after cystectomy: first results of a prospective study. *Qual Life Res* 2000;9(1):1-12.
<http://www.ncbi.nlm.nih.gov/pubmed/10981202>
17. Hobisch A, Tosun K, Kinzl J, Kemmler G, Bartsch G, Holtl L, Stenzl A. Life after cystectomy and orthotopic neobladder versus ileal conduit urinary diversion. *Semin Urol Oncol* 2001;19(1):18-23.
<http://www.ncbi.nlm.nih.gov/pubmed/11246729>
18. 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;21(4):673-8.
<http://www.ncbi.nlm.nih.gov/pubmed/12586805>
19. Fossa SD, Aaronson N, Calais da Silva F, Denis L, Newling D, Hosbach G, Kaalhus O. 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>
20. Nagele U, Anastasiadis AG, Merseburger AS, Corvin S, Hennenlotter J, Adam M, Sievert KD, Stenzl A, Kuczyk MA. The rationale for radical cystectomy as primary therapy for T4 bladder cancer. *World J Urol* 2007;25(4):401-5.
<http://www.ncbi.nlm.nih.gov/pubmed/17525849>
21. Fokdal L, Hoyer M, von der Maase H. Radical radiotherapy for urinary bladder cancer: treatment outcomes. *Expert Rev Anticancer Ther* 2006;6(2):269-79.
<http://www.ncbi.nlm.nih.gov/pubmed/17525849>
22. Rodel C, Weiss C and Sauer R. Organ preservation by combined modality treatment in bladder cancer: the European perspective. *Semin Radiat Oncol* 2005;15(1):28-35.
<http://www.ncbi.nlm.nih.gov/pubmed/15662604>
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. Rodel C, Grabenbauer GG, Kuhn R, Papadopoulos T, Dunst J, Meyer M, Schrott KM, Sauer R. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. *J Clin Oncol* 2002;20:3061-71.
<http://www.ncbi.nlm.nih.gov/pubmed/12118019>
25. Merseburger AS, Kuczyk MA. The value of bladder-conserving strategies in muscle-invasive bladder carcinoma compared with radical surgery. *Curr Opin Urol* 2007;17(5):358-62.
<http://www.ncbi.nlm.nih.gov/pubmed/17762631>
26. Milosevic M, Gospodarowicz M, Zietman A, Abbas F, Haustermans K, Moonen L, Rodel C, Schoenberg M, Shipley W. Radiotherapy for bladder cancer. *Urology* 2007;69(1 Suppl):80-92.
<http://www.ncbi.nlm.nih.gov/pubmed/17280910>
27. Rodel 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>
28. Zietman AL, Shipley WU, Kaufman DS. Organ-conserving approaches to muscle-invasive bladder cancer: future alternatives to radical cystectomy. *Ann Med* 2000;32(1):34-42.
<http://www.ncbi.nlm.nih.gov/pubmed/10711576>
29. Lodde M, Palermo S, Comploj E, Signorello D, Mian C, Lusuardi L, Longhi E, Zanon P, Mian M, Pycha A. Four years experience in bladder preserving management for muscle invasive bladder cancer. *Eur Urol* 2005;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).

Contemporary cystectomy series demonstrate a 5-15% chance of pelvic recurrence. Most recurrences manifest during the first 24 months, with many occurring within 6-18 months after surgery. However, there have been late recurrences up to 5 years after cystectomy.

Variables associated with the development of a pelvic recurrence include the pathological stage (of the primary tumour) and lymph node status.

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

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. Again, pathological stage of the primary tumour and nodal status are risk factors. The most likely sites for distant recurrences are the lungs, liver and bones (2).

Upper urinary tract recurrence is rarely seen (2-7%), but when it develops, it usually does so within 22-40 months after cystectomy (1-4). Surveillance regimens often fail to detect tumours before symptoms develop. However, radical nephroureterectomy can provide prolonged survival (3).

The incidence of secondary urethral tumour is 5-17% and is particularly likely to occur at 1-3 years after surgery. Prophylactic urethrectomy at the time of cystectomy is no longer justified in most patients. In men, the most important risk factor for the development of urethral recurrence is prostatic stromal invasion (21-64%) (5-7). In women, the risk factor is disease at the bladder neck (8). Multiple studies demonstrate that the risk of urethral recurrence after orthotopic diversion (0.9-4%) (5, 9-11) is significantly less than after non-orthotopic diversion (6.4-11.1%) (5,10). There is little data and agreement about the follow-up of the urethra. Some authors recommend routine surveillance urethral wash cytology and UCS (9), while others question the need for routine urethral surveillance (9, 12-14). Urethral washes and urine cytology do not appear to have any effect on survival (12, 15, 16).

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

- In CIS in the urethra, BCG instillations have shown success rates of 83% (11).
- In invasive disease, urethrectomy should be performed if the urethra is the only site of disease.
- In distant disease, systemic chemotherapy is indicated (2).

14.1 Conclusions and recommendations according to condition

Condition	Conclusion or recommendation	Level of evidence or grade of recommendation
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour	3
	For non-invasive tumour, local organ conservative treatment is advised	C
	In isolated invasive disease, a urethrectomy should be performed	B
	Urethral washes and cytology are not recommended for follow-up	A
Pelvic recurrence	The prognosis is poor Treatment should be individualized depending on the local extent and symptoms	2b
	Radiotherapy, chemotherapy and possibly surgery are options for treatment, either alone or in combination	C
Upper urinary tract recurrence	Specific upper urinary tract imaging is only indicated in case of clinical symptoms; radical nephroureterectomy can provide prolonged survival	B

14.2 General recommendations for follow-up

This advice for follow-up is entirely based on expert opinion. General remarks are that follow up should be dependent on the stage of the initial tumour after cystectomy. This means that the higher the initial tumour stage, the larger the chance for subsequent tumour recurrence. A higher follow-up frequency will therefore result in identifying more recurrences. Non-oncological follow-up, for example monitoring of kidney function, seems indicated life long. After 5 years of follow-up, oncological surveillance may be stopped to be continued by functional surveillance.

At every visit, the following should be performed:

- History
- Physical examination
- Bone scan only when indicated.

14.3 REFERENCES

1. Malkowicz SB, van Poppel H, Mickisch G, Pansadoro V, Thuroff J, Soloway MS, Chang S, Benson M, Fukui I. Muscle-invasive urothelial carcinoma of the bladder. *Urology* 2007;69(1 Suppl):3-16.
<http://www.ncbi.nlm.nih.gov/pubmed/17280906>
2. 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;30(4):777-89.
<http://www.ncbi.nlm.nih.gov/pubmed/14680314>
3. Sanderson KM, Cai J, Miranda G, Skinner DG, Stein JP. 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;177:2088-94.
<http://www.ncbi.nlm.nih.gov/pubmed/17509294>
4. Stenzl A, Bartsch G, Rogatsch H. The remnant urothelium after reconstructive bladder surgery. *Eur Urol* 2002;41(2):124-31.
<http://www.ncbi.nlm.nih.gov/pubmed/12074398>
5. Freeman JA, Tarter TA, Esrig D, Stein JP, Elmajian DA, Chen SC, Groshen S, Lieskovsky G, Skinner DG. Urethral recurrence in patients with orthotopic ileal neobladders. *J Urol* 1996;156(5):1615-9.
<http://www.ncbi.nlm.nih.gov/pubmed/8863551>
6. Hardeman SW, Soloway MS. Urethral recurrence following radical cystectomy. *J Urol* 1990;144(3):666-9.
<http://www.ncbi.nlm.nih.gov/pubmed/2388323>
7. Levinson AK, Johnson DE, Wishnow KI. Indications for urethrectomy in an era of continent urinary diversion. *J Urol* 1990;144(1):73-5.
<http://www.ncbi.nlm.nih.gov/pubmed/2359182>
8. Stenzl A, Draxl H, Posch B, Colleselli K, Falk M, Bartsch G. 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;153(3 Pt 2):950-5.
<http://www.ncbi.nlm.nih.gov/pubmed/7853581>
9. Huguet J, Palou J, Serrallach M, Sole Balcells FJ, Salvador J, Villavicencio H. Management of urethral recurrence in patients with Studer ileal neobladder. *Eur Urol* 2003;43(5):495-8.
<http://www.ncbi.nlm.nih.gov/pubmed/12705993>
10. Nieder AM, Sved PD, Gomez P, Kim SS, Manoharan M, Soloway MS. Urethral recurrence after cystoprostatectomy: implications for urinary diversion and monitoring. *Urology* 2004;64(5):950-4.
<http://www.ncbi.nlm.nih.gov/pubmed/15533484>
11. Varol C, Thalmann GN, Burkhard FC, Studer UE. Treatment of urethral recurrence following radical cystectomy and ileal bladder substitution. *J Urol* 2004;172(3):937-42.
<http://www.ncbi.nlm.nih.gov/pubmed/15311003>
12. Lin DW, Herr HW, Dalbagni G. Value of urethral wash cytology in the retained male urethra after radical cystoprostatectomy. *J Urol* 2003;169(3):961-3.
<http://www.ncbi.nlm.nih.gov/pubmed/12576822>
13. Sherwood JB, Sagalowsky AI. The diagnosis and treatment of urethral recurrence after radical cystectomy. *Urol Oncol* 2006;24(4):356-61.
<http://www.ncbi.nlm.nih.gov/pubmed/16818191>
14. Slaton JW, Swanson DA, Grossman HB, Dinney CP. A stage specific approach to tumor surveillance after radical cystectomy for transitional cell carcinoma of the bladder. *J Urol* 1999;162(3 Pt 1):710-4.
<http://www.ncbi.nlm.nih.gov/pubmed/10458349>

15. Erckert M, Stenzl A, Falk M, Bartsch G. 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>
16. Clark PE, Stein JP, Groshen SG, Miranda G, Cai J, Lieskovsky G, Skinner DG. The management of urethral transitional cell carcinoma after radical cystectomy for invasive bladder cancer. *J Urol* 2004;172(4 Pt 1):1342-7.
<http://www.ncbi.nlm.nih.gov/pubmed/15371837>

15. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

ARCO	accelerated radiotherapy with carbogen
ARCON	accelerated radiotherapy with carbogen nicotinamide
ASCO	American Society of Clinical Oncology
5-ALA	5-aminolaevulinic acid
BC	bladder cancer
BCG	Bacille Calmette-Guérin
CI	confidence interval
CIS	carcinoma in situ
CISCA	cisplatin, cyclophosphamide plus adriamycin
CM	cisplatin, methotrexate
CMV	cisplatin, methotrexate plus vinblastine
CT	computed tomography
EAU	European Association of Urology
EBRT	external beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FACT	Functional Assessment of Cancer Therapy
5-FU	5-Fluorouracil
GC	gemcitabine plus cisplatin
GFR	glomerular filtration rate
GCSF	granulocyte colony stimulating factor
HAL	hexaminolaevulinate
HD-MVAC	high-dose methotrexate, vinblastine, adriamycin plus cisplatin
HRQL	health-related quality of life
IARC	International Agency for Research on Cancer
IPD	independent patient data
ISUP	International Society of Urological Pathology
IVU	Intravenous urography
MCV	methotrexate, cisplatin and vinblastine
MDCT	multidetector-row CT
MiM-BC	Muscle-invasive and metastatic bladder cancer
MRC	Medical Research Council (UK)
MR(I)	magnetic resonance (imaging)
MVAC	methotrexate, vinblastine, adriamycin plus cisplatin
MVA(E)C	methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin
NAT	N-acetyltransferase
OS	overall survival
PAHs	polycyclic aromatic hydrocarbons
PCR	pathological complete remission
PET	positron emission tomography
PS	performance status
PUNLMP	papillary urothelial neoplasms of low malignant potential
R-biopsies	random biopsies
SF-36	Short Form-36
SWOG	Southwest Oncology Group
TCC	transitional cell carcinoma
TNM	Tumour, Node, Metastases
TUR	transurethral resection
TURBT	transurethral resection of bladder tumour
UICC	Union International Contre le Cancer
UC	urethrocystoscopy
US	ultrasonography
UUT	upper urinary tract
WHO	World Health Organization

Conflict of interest

All members of the Muscle-Invasive and Metastatic Bladder Cancer guidelines writing panel have provided disclosure statements of all relationships which they have and which may be perceived as a potential source of conflict of interest. This information is kept on file in the European Association of Urology Central Office database. 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.