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New Italian guidelines on bladder cancer, based on the World Health Organization 2004 classification

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OBJECTIVE

To provide evidence-based recommendations on bladder cancer management

METHODS

A multidisciplinary guideline panel composed of urologists, medical oncologists, radiotherapists, general practitioners, radiologists, epidemiologists and methodologists conducted a structured review of previous reports, searching the Medline database from 1 January 2004 to 31 December 2008. The milestone papers published before January 2004 were accepted for analysis. The level of evidence and the grade of the recommendations were established using the GRADE system.

RESULTS

In all, 15 806 references were identified, 1940 retrieved, 1712 eliminated (specifying the reason for their elimination) and 971 included in the analysis, as well as 241 milestone reports. A consensus conference held to discuss the discrepancies between the scientific evidence and the clinical practice was then attended by 122 delegates of various specialities.

CONCLUSION

Recommendations on bladder cancer management are provided.

KEYWORDS

urinary bladder neoplasms, health planning guidelines, consensus development conference

INTRODUCTION

At present the treatment for urothelial bladder cancer (UBC) is mostly based on the 1973 WHO classification. For non-muscle-invasive BC (NMIBC), the most important predictor of progression is the grade, although it is also one of the main predictors of recurrence. Indeed, controversy still surrounds the prognostic meaning of the intermediate grade, G2, which accounts for half of the diagnoses. Consequently, many issues on the management of NMIBC are still being discussed. The rationale of the WHO 2004 classification is to make a step toward the creation of two distinct entities, low- and high-grade UBC. The clinical consequences are consistent. The most relevant clinical issue of low-grade cancer is recurrence, while for high-grade cancer it is progression. The main objective of the management of low-grade NMIBC should therefore be to prevent recurrence (to minimize the patient's burden), whereas the main objective for high-grade disease is to anticipate or prevent whenever possible progression to muscle invasive (MI) or metastatic BC (eventually affecting survival). In the production of the present guideline we followed the 2004 WHO rationale and abandoned definitively the criteria of 1973.

METHODS

The guidelines are based on scientific evidence, to develop an evidence-based clinical guideline, and were drafted conforming to explicit and rigorous methods, as well as the indications of the Center for Reviews and Dissemination of the University of York (for systematic reviews) [1] and the Conference on Guideline Standardization [2]. The Level of Evidence and the Grade of the

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recommendations were established using the GRADE system [3–8].

The multidisciplinary Guideline Panel was composed of urologists, medical oncologists, radiotherapists, GPs, radiologists, epidemiologists and methodologists. The panel approved a review protocol, the review questions, the facets (populations, interventions, outcomes and acceptable study designs) and the key words. A structured review of the literature was conducted, searching the Medline database from 1 January 2004 to 31 December 2008. The milestone papers published before January 2004 were accepted for analysis. In all, 15 806 references were identified, 1940 retrieved, 1712 eliminated (specifying the reason for their elimination) and 971 included in the analysis, as well as 241 milestone reports. The searching and selection processes were documented and retained. No formal quality measures were used, but every panellist assessed the internal and external validity of the retrieved studies and the methodologists supervised the analysis on request. An extraction form was developed for every scientific question. Data were synthesized by combining the results of hierarchically equal studies.

The GRADE system keeps strictly separated the quality (i.e. the level) of evidence and the grade of recommendation, giving an explicit and complete description of the judgement when there is a discrepancy between the quality of evidence and the given grade. The quality of evidence is classified in four grades, as high, moderate, low and very low. The algorithm to identify the grade level was previously described [3–8]. The grade of recommendation can be strong or weak according to the quality of evidence, and to the uncertainty of the balance between the desirable and undesirable effects, patient's preference and the wise use of resources. A Consensus Conference held in Fiuggi on 8–9 May 2009, to discuss the discrepancies between the scientific evidence and the clinical practice, was attended by 122 delegates of various specialities (urologists, medical oncologists, radiotherapists, GPs, radiologists, epidemiologists and methodologists).

RECOMMENDATIONS AND DISCUSSION

Recommendations are presented in the sequence which follows the steps of the clinicians approach to the disease.

PRIMARY PREVENTION

It is recommended not to smoke, do not try to smoke and in any case stop smoking as soon as possible. There is strong evidence that cigarette smoking can increase the risk of bladder cancer. Cigarette smoking has been estimated to be responsible for about a third of bladder tumours in men and a quarter in women [8–11].

There is no evidence of a link between the consumption of alcohol and risk of BC. There is no evidence of a link between the consumption of coffee and risk of BC; although there is a case for some connection, there is no evidence of any dose-risk relationship. There is no evidence of a link between the consumption of tea and risk of BC [12,13].

It is advisable to eat three or four helpings of vegetables every day. There is convincing evidence that the risk of bladder tumour is decreased by consuming large amounts of vegetables. There is weak evidence that high plasma selenium levels decrease the risk. There is weak evidence that the risk is decreased by consuming large amounts of fruits. There is no evidence that vitamins (A, C, carotenoids) can decrease the risk, despite their biological role. (antioxidant, inhibitors of carcinogenesis) [14,15].

Phenacetin should not be used in clinical practice. There is strong evidence that long-term treatments with analgesics containing phenacetin increase the risk of BC [16].

It is recommended not to use aromatic amines, aromatic polycyclic hydrocarbons, 4-amino-diphenile, tetrachloro-ethylene and benzopyrene, except in properly protected environments. There is evidence that 5–10% of bladder tumours in Europe are a consequence of the working environment. There is strong evidence of an increased risk of bladder tumours after exposure to the compounds listed above [17,18].

For the risk of a bladder tumour in patients who are treated by chemo- and/or radiotherapy for previous tumours, bladder tumour screening cannot be recommended because of lack of evidence. There is a slight increase in the risk of a second tumour in the bladder in men treated with radiotherapy for prostate tumour after 10–15 years of follow-up. There is evidence of a risk of bladder tumour in women treated with radiotherapy for cervical tumour after 15–20 years of follow-up. There is evidence of risk of a bladder tumour in patients treated with chemotherapy for Hodgkin and non-Hodgkin lymphomas, lymphoblastic leukaemia after 10 years of follow-up. There is strong evidence of bladder tumour risk in men treated with chemotherapy for testis tumour after 10–15 years of follow-up [19–23].

DIAGNOSIS

In cases of macroscopic haematuria a diagnostic investigation is recommended. In cases of microscopic haematuria a diagnostic investigation is recommended only for individuals in risk categories. Macroscopic haematuria is the most frequent symptom of urothelial tumours. The prevalence of malignancies among individuals with microscopic haematuria is 4.8%, which progressively increases with age, regardless of gender [24,25].

Ultrasonography (US) of the abdomen is suggested as the first level investigation if a bladder tumour is suspected. When a second level investigation is needed, multidetector CT urography (CTU) is suggested. Despite the lack of evidence of which should be the first-level investigation in cases of macroscopic haematuria, the prevalent opinion (91%) of the Consensus Conference was to use US of the abdomen as the first level of investigation because of its specificity and sensitivity, ≈95% and with no radiation risk. The CTU is the imaging investigation with the greatest specificity and sensitivity. The major limitation of CTU is its inability to detect flat non-invasive tumours. IVU has been replaced in clinical practice by the CTU [26–30].

When a bladder tumour is detected by US of the abdomen, there is no need for outpatient cystoscopy; with a flexible instrument, this is recommended in cases with negative findings on US. The routine use of either local anaesthesia or antibiotic prophylaxis is not advisable. Given the absence of evidence on this topic, the prevalent opinion (94%) of the Consensus Conference was to avoid unnecessary outpatient cystoscopy before transurethral resection (TUR) when a bladder tumour was already detected by abdominal US. Flexible cystoscopy should replace rigid cystoscopy,

having the same sensitivity but causing less discomfort. Flexible cystoscopy does not require anaesthesia. If the urine is not septic, antibiotic prophylaxis can be omitted [27,31–33].

Urinary cytology is advisable when US of the abdomen is negative. Indeed, biomolecular markers are not recommended for the diagnosis of bladder tumours. The prevalent opinion (97%) of the Consensus Conference agreed on the use of urinary cytology when a urothelial neoplasm is suspected and the US of the abdomen is negative; 45% of the Consensus Conference proposed the use of urinary cytology also if findings were positive at US, to detect the presence of high-grade tumour cells [34,35]

FIRST ENDOSCOPIC TREATMENT

Separate specimens should be collected at TUR; random bladder biopsies are advisable in cases of either multifocal neoplasm or positive cytology. If random bladder biopsies are to be taken it is advisable to take them under fluorescent cystoscopy. The TUR technique (particularly the separate resection of the tumour, base and margins, respectively) should ensure an evaluation of the histological type, stage and grade of the tumour.

In cases of multifocal neoplasia and/or positive cytology the prevalent opinion (82%) agreed on taking random bladder biopsies together with TUR, despite the lack of evidence on this topic. Fluorescent cystoscopy is superior to standard white-light cystoscopy for detecting both flat tumours and carcinoma *in situ* (CIS) [36–42].

PATHOLOGICAL CHARACTERIZATION

The use of Association of Directors of Anatomic and Surgical Pathology protocol is recommended; this protocol states that the presence of smooth muscle of the muscularis mucosae (i.e. lamina propria) should be described when found in specimens from either TUR or bladder biopsies.

When a lymphadenectomy has been carried out together with cystectomy, the lymph node status should be described [43–45].

The sole use of the WHO 2004 classification of bladder tumours is recommended. Clinical evidence suggests that the 2004 WHO classification is more reliable than the 1973 WHO classification, mainly due to the elimination of the ambiguity of the intermediate grade. Clinical evidence shows that the WHO 1973 and 2004 classifications are not interchangeable because they apply different morphological criteria. Moreover, inter- and intra-observer reproducibility of WHO 2004 is slightly superior to that of WHO 1973 [46–54]. Despite the lack of strong evidence, the Consensus Conference decided (71%) to use only the WHO 2004 classification of bladder tumours.

Biological markers are not recommended to be used for prognostic purposes. Analysis of the published data from 2004 until the present showed that none of the studies on biological markers had enough evidence to suggest the use of these tools in clinical practice [34–36].

CLINICAL CONSEQUENCES OF USING ONLY THE 2004 WHO CLASSIFICATION IN CLINICAL PRACTICE

Low-grade BC and papillary urothelial neoplasm of low malignant potential (PUNLMP) have a similar prognosis under the 2004 WHO classification [46]. All G1 tumours of the 1973 WHO classification belong to the low-grade BC or PUNLMP entity, whereas all G3 urothelial cancers belong to the high-grade entity [55]. The morphological criteria of the WHO 2004 reallocate the G2 cancers to low- or high-grade cancer. The WHO 2004 classification enlarges the group of patients at high risk of progression.

The meta-analysis of the European Organisation for the Research and Treatment of Cancer showed that ≈11% of NMIBCs progress to invasive or metastatic cancer. Grade is the most important pathological feature for progression, whereas it is not a strong predictor of recurrence. Excluding G2 BC, low-grade BCs belonging to the old G1 group are characterized by a risk of progression of ≈5% and of recurrence of ≈40%. However, high-grade BCs, the former G3, carry a risk of progression of ≈30% and of recurrence of ≈70% [55]. Therefore low-grade NMIBCs are characterized by a very low risk of progression, whereas cases at low or high risk of recurrence can be identified [55].

As a consequence of the extensive application of the WHO 2004 classification, different risk categories can be identified: low grade NMIBC at low risk of recurrence (single and first occurrence and <3 cm); low-grade NMIBC at high risk of recurrence (multiple or recurrent or >3 cm); and high-grade BCs. Treatment must be modulated on the basis of these risk categories.

TREATMENT OF LOW-GRADE NMIBC AT LOW RISK OF RECURRENCE AFTER TUR

The use of one immediate instillation of intravesical agents is not advisable after TUR. This treatment reduces the risk of recurrence risk by ≈12%, but only in patients with low-grade BC and a low risk of recurrence [56–59]. Given the biological, organizational and economic burden of the procedure, it is the general opinion of the Consensus Conference (90%) that it is not to be recommended.

TREATMENT OF LOW-GRADE NMIBC AT HIGH RISK OF RECURRENCE AFTER TUR

Despite the lack of strong evidence, it is the main opinion (80%) of the Consensus Conference that recurrences should not be treated only by TUR.

The use of one immediate instillation is not advisable; this reduces the recurrence risk by ≈12% only in cases with low-grade BC with a low risk of recurrence. High- and moderate-quality evidence shows that one perioperative instillation is not effective in cases of low-grade BC at high risk of recurrence [56–59].

The use of an induction treatment with intravesical agents to prevent recurrence is advisable. The use of a chemotherapeutic agent for the induction is advisable. The use of a maintenance schedule of ≥12 months after the induction is advisable.

Controversial evidence shows the superiority of BCG in preventing recurrence, although BCG treatment is significantly more toxic, according to high-quality studies. It is the main opinion of the Consensus Conference (88%) that a chemotherapeutic agent should be used instead of BCG. Moderate-quality evidence shows that a maintenance schedule of ≥12 months is more effective than short-term regimens (≤6 months) to prevent recurrences in patients with low-grade BC at high risk of recurrence [60–71].

The use of TUR, office fulguration or active surveillance for the management of the recurrence is advisable. There is a role also for office fulguration or active surveillance in cases with low-grade BC at high risk of recurrence [72–76].

FOLLOW-UP OF LOW-GRADE NMIBC

Cystoscopy at 3 months after the last TUR or therapeutic procedure is recommended. Moderate-quality evidence shows that the presence of recurrent/residual disease at cystoscopy 3 months after TUR is an important prognostic factor [56,77].

If the 3-month cystoscopy is negative, the first follow-up cystoscopy is recommended after 1 year in patients with low-grade BC at low risk of recurrence. If the 3-month cystoscopy is negative, the follow-up cystoscopy is recommended every 6 months in patients with low-grade BC at high risk of recurrence. Because of the less intensive follow up of low grade BCs, the periodic use of urinary cytology is advisable. Low- or moderate-quality evidence shows that annual cystoscopy for 5 years of follow-up is safe in patients with a low grade BC at low risk of recurrence, and with a negative 3-month cystoscopy. The main opinion of the Consensus Conference (65%) was concordant. Despite the lack of evidence, it is the main opinion of the Consensus Conference (72%) to use follow up cystoscopy every 6 months. Notwithstanding the lack of evidence, it is the main opinion of the Consensus Conference (85%) that urinary cytology should be used regularly in cases of a less intensive follow-up schedule. Half of the members of the Consensus Conference suggest cytology before cystoscopy [62,73–76,78–87].

TREATMENT OF HIGH-GRADE NMIBC

A second TUR followed by random biopsies of healthy bladder mucosa (i.e. a re-staging TUR) is recommended for newly diagnosed high-grade NMIBC. Moderate- or low-quality evidence shows a high likelihood of finding residual/recurrent cancer at the time of the re-staging TUR, even if the first TUR was complete and correct. At the time of TUR re-staging of NMIBC, the probability of finding MI disease is ≥4%. Low-quality evidence shows that the re-staging TUR might influence positively the response to BCG, the recurrence rate and the rate of progression.

The main opinion of the Consensus Conference was concordant for a second TUR (87%) and to add bladder mapping to the procedure (92%). There is no evidence on the timing of the re-staging TUR. Most authors suggested performing it 4–8 weeks after the first TUR [40,88–91].

An induction treatment with intravesical BCG to prevent recurrence if the re-staging TUR is negative is recommended. If the re-staging TUR is positive (NMIBC), a radical cystectomy (RC) is suggested as an option. A second topical treatment is advised if the first fails. If the topical treatment fails and there is a high-grade recurrence, a RC is recommended. An induction treatment with intravesical BCG or chemotherapeutic agent can reduce the likelihood of a recurrence in patients with high-grade NMIBC. BCG is probably better than chemotherapeutic agents for reducing the risk of recurrence.

It seems that a maintenance schedule is necessary to effectively reduce the risk of recurrence (especially for BCG). The progression, specific survival and overall survival rates are probably not influenced by the intravesical therapy. If the re-staging TUR detects recurrent/residual T1 cancer or involvement of prostatic urethra or multifocal CIS, the prognosis worsens significantly in some retrospective series. Despite the lack of evidence, it is the main opinion of the Consensus Conference (72%) that another topical treatment is an option after BCG failure. Low-quality evidence, based on retrospective series, shows excellent long-term oncological results in patients treated with RC for clinical NMIBC.

Very low-quality evidence shows that high-grade NMIBC treated by RC has a better oncological outcome than invasive BC, even if the pathological stage is the same. Very low-quality evidence shows that high-grade NMIBC treated by RC has a better oncological outcome if performed at the first T1 recurrence [55,69,92–104].

FOLLOW-UP OF HIGH-GRADE NMIBC TREATED CONSERVATIVELY

After induction treatment with BCG, a cystoscopy and, if negative, random bladder biopsies of healthy mucosa, are suggested. Thereafter (in cases with negative cystoscopy and biopsies) it is suggested to perform urinary cytology and cystoscopy every 3 months in the first 2 years, every 6 months in the subsequent 2 years and then yearly. Notwithstanding the lack of evidence, it is the opinion of the board to take random bladder biopsies at the end of an induction treatment with BCG in patients with high-grade NMIBC because outpatient cystoscopy and urinary cytology are at risk of false-negative results. Low-quality evidence shows that the 3-month cystoscopy has a major effect on the prognosis. Observational and retrospective studies show that recurrence and progression can also occur after many years in patients with high-grade NMIBC, but most of the events occur within 3 years [61,72–77,79–83,86,92–104].

The use of CTU to exclude a concomitant neoplasm of the upper urinary tract after diagnosis of a high-grade BC is suggested. Multidetector CT is suggested to obtain a comprehensive staging. The likelihood of a concomitant or subsequent neoplasm of the upper urinary tract is 5–10% in patients with high-grade NMIBC. CT is the standard technique for the diagnosis of distant metastasis. Moreover, it has an adequate accuracy for T and N staging, respectively, of 50–90% and 70–90% [26–30,84,85]. **Annual multidetector CTU is suggested.** The likelihood of a concomitant or subsequent neoplasm of the upper urinary tract is 5–10% in patients with high-grade bladder cancer [26–30,84,85].

TREATMENT OF MIBC, NON-METASTATIC

Treating MIBC with RC is recommended; a lymphadenectomy is also recommended. In patients at risk of progression an extension of the lymph node excision up to the aortic bifurcation cranially and to the whole pelvis caudally is recommended. Partial cystectomy is not recommended for MIBC. It is suggested to evaluate the distal urethral margin of the specimen with frozen-section analysis before constructing a neobladder. Before RC the use of CTU to exclude a concomitant neoplasm of the upper urinary tract after the diagnosis of a high-grade BC is suggested. Multidetector CT is suggested to obtain comprehensive staging. Historical series show a benefit of RC in terms of survival in cases with MIBC. Although the quality of the evidence is very low, RC is deemed to be the standard

treatment because the series are very large, the effect of the procedure in terms of survival is positive and the follow-up is very long [105–113]. The 10-year recurrence-free survival rate reaches 50% in the most recent series. Moreover RC is the most effective treatment to relieve symptoms and signs secondary to MIBC [105–113]. The likelihood of finding positive nodes is 16–24% in six recent series of >1000 RCs [114]. Lymphadenectomy is necessary to obtain proper staging and might improve survival in patients with a limited nodal burden [115–120]. The odds of metastasis at the presacral, common iliac, peri-aortic, paracaval and interartocaval nodal (up to the emergence of the inferior mesenteric artery) regions is ≈20% in cases with nodal metastasis recorded in the pathological report [115–120]. Therefore, lymph node excision should be extended to those regions. When nodal metastases of the internal, external iliac, obturator and perivesical regions can be excluded, the benefit of extending the dissection is controversial because the further spread of metastases is anecdotal [115–120]. Very low-quality evidence, based on series of limited size, shows that partial cystectomy is an option in cases with one MIBC tumour, distant from the trigone, with no concomitant CIS and the absence of residual/recurrent disease at the re-staging TUR [121–123]. The odds of maintaining the bladder without cancer is ≈50%. Indeed, very low-quality evidence shows that similarly selected cases, treated with only TUR and re-staging TUR, have the same outcome [121–123]. The main opinion of the Consensus Conference was concordant (78%).

To exclude the presence of cancer before proceeding to construct a neobladder, it is suggested by the main opinion of the Consensus Conference (69%), corroborated by low-quality evidence [124–127], that frozen sections of the distal urethral margin of the specimen should be analysed. The likelihood of a concomitant or subsequent neoplasm of the upper urinary tract is 5–10% in patients with high-grade BC. CT is the standard technique for the diagnosis of distant metastasis [26–30,84,85].

It is suggested to limit the use of ureterocutaneostomy to patients in a poor general condition, to avoid the risks connected with intestinal anastomosis. It is suggested to choose the urinary diversion after discussion with the patient. If the patient agrees, the orthotopic neobladder should be the first choice. Reports of complications related to urinary diversion should be standardized according to the Memorial Sloan-Kettering Cancer Center (MSKCC) complication grade system. It is recommended to extend the functional follow-up of the urinary diversion to lifelong It is not suggested to assess urine cultures in asymptomatic patients. Ureterocutaneostomy is a diversion with a high risk of UTI and stricture at the site of the skin anastomosis. Therefore it needs almost always to be protected by inserting a ureteric catheter, whereas urinary diversions with bowel interposition do not need the routine use of a ureteric catheter [128–133].

It is not yet possible to assess which urinary diversion with bowel interposition is the best in terms of complication rates or quality of life. Particularly, the pouch is indicated in patients with contraindication to urethral anastomosis (especially cases which need urethrectomy) and who prefer a continent diversion [131–141]. The board agrees on the need to standardize the system for reporting complications of urinary diversions. The most common is the MSKCC complication grade system [142].

It is recommended to use radical radiochemotherapy only in selected patients within clinical studies. Despite the lack of prospective randomized comparative studies between RC and radical radiotherapy, reports show long-term oncological local and distant control in many series of patients treated by TUR and radio-chemotherapy, with a high percentage of bladder preservation. Suitable patients should have MIBC (cT2 or cT3a) with no involvement of the high urinary tract and without CIS. The TUR should be complete and the re-staging TUR negative [143–147]. The main opinion of the Consensus Conference (75%) is to limit radical radiotherapy only to clinical studies.

It is suggested to discuss the opportunity of neoadjuvant chemotherapy with the patient underling the cost/benefit ratio. It is suggested not to use adjuvant chemotherapy. High-quality clinical evidence shows that neoadjuvant cisplatin-based chemotherapy has acceptable toxicity and increases the survival rate by 5–6.5% in patients with T2-T2/N0-N2/M0 clinical stage disease [148–152]. Adjuvant chemotherapy is feasible but a related survival benefit has not yet been ultimately confirmed by moderate- and high-quality studies [153,154]. There are no prospective randomized comparative studies of neoadjuvant vs adjuvant chemotherapy. The equivalence of methotrexate, vinblastine, adriamycin and cisplatin (MVAC), or gemcitabine, in the setting of neoadjuvant or adjuvant chemotherapy has never been assessed (only one retrospective very low-quality study is reported). The number of chemotherapy cycles for neoadjuvant or adjuvant chemotherapy has not been standardized [155,156].

FOLLOW-UP OF HIGH-GRADE MIBC AFTER RC

Very low-quality evidence shows that functional and oncological follow-up examinations should be carried out more frequently in the first 3 years. Thereafter, assessment intervals can be extended, although the patient should be followed lifelong. Case-series studies suggest that most functional complications occur within the first 2 years after RC [157–162]. Functional complications can be cured by active interventions. Therefore the board suggests a 3-monthly functional follow-up by a physical examination, laboratory assays (pH, HCO_{3-}, creatinine, haemoglobin serum assay) and US of the abdomen in the first year, 6-monthly in the next 2 years and yearly thereafter.

For the oncological follow-up there is no evidence for any clinical benefit [163–166]. However, while waiting for conclusive trials, the board agreed to a 6-monthly oncological surveillance using multidetector CTU, urinary cytology and urethral washing (in patients with a heterotopic urinary diversion). The board feels that surveillance schemes should be adapted on the basis of the individual risk to the patient [1,25–30,84,85,105–113,125,127,162–165]. The likelihood of asymptomatic bacteriuria is 66–80%, and therefore it does not seem necessary to treat asymptomatic patients with a positive urine culture [167].

TREATMENT OF METASTATIC MIBC

It is recommended to use chemotherapy in patients with metastasis (including those with clinically detected lymph node metastases). The most effective first-line chemotherapy scheme for metastatic bladder cancer is based on cisplatine. The standard

schemes are MVAC and gemcitabine, the toxicity of the latter being consistently less [148,168,169]. Despite very low-quality evidence, patients who fail the first line of treatment might be treated with a taxane-based scheme of chemotherapy [170].

It is suggested to indicate the excision of sub-diaphragmatic nodal metastasis only if a partial or complete response to chemotherapy has been ascertained, and after a comprehensive discussion with the patient of the cost/benefit ratio.

Notwithstanding the very low-quality evidence, a few studies show that surgical treatment of metastasis after chemotherapy might prolong survival [171–174]. The main opinion of the Consensus Conference (78%) is that surgery should be used in all feasible cases (48%) or in selected patients (30%). For morbidity, the surgery of metastasis seems feasible.

CONCLUSION

The 2004 WHO classification establishes a change in the treatments for managing NMIBC. The main objective is to overcome the controversies surrounding the prognostic value of the intermediate grade of the 1973 WHO classification. The clinical recommendations of our guidelines are based mostly on the new 2004 WHO classification, while definitively abandoning that of 1973.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Khan KS, ter Riet G, Glanville J, Sowden AJ, Kleijnen J.** Undertaking systematic reviews of research on effectiveness CRD's. Guidance for those carrying out or commissioning reviews. *CRD Report Number 4*, 2nd edn. University of York: NHS Centre for Reviews and Dissemination, 2001

2 **Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM.** Standardized reporting of clinical practice guidelines: a proposal from the conference on guideline standardization. *Ann Intern Med* 2003; **139**: 493–8

3 **Guyatt GH, Oxman AD, Vist GE *et al.*** Grade: an emerging consensus on rating quality of evidence and strengths of recommendations. *BMJ* 2008; **336**: 924–6

4 **Guyatt GH, Oxman AD, Vist GE *et al.*** What is 'quality of evidence' and why is it important for the clinicians. *BMJ* 2008; **336**: 995–8

5 **Guyatt GH, Oxman AD, Vist GE *et al.*** Going from evidence to recommendations. *BMJ* 2008; **336**: 1049–51

6 **Schünemann HJ, Oxman AD, Brozek J *et al.*** Grading quality of evidence and strengths of recommendations for diagnostic tests and strategies. *BMJ* 2008; **336**: 1106–10

7 **Guyatt GH, Oxman AD, Kunx R *et al.*** Incorporating considerations of resources use into grading recommendations. *BMJ* 2008; **336**: 1170–3

8 **Jaeschke R, Guyatt GH, Dellinger P *et al.*** Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. *BMJ* 2008; **337**: a744

9 **Bjerregaard BK, Raaschou-Nielsen O, Sørensen M *et al.*** Tobacco smoke and bladder cancer in The European Prospective Investigation Into Cancer and Nutrition. *Int J Cancer* 2006; **119**: 2412–6

10 **Doll R, Peto R, Boreham J, Sutherland I.** Mortality from cancer in relation to smoking: 50 years observations on British doctors. *Br J Cancer* 2005; **92**: 426–9

11 **Puente D, Hartge P, Greiser E *et al.*** A pooled analysis of bladder cancer case-control studies evaluating smoking in men and women. *Cancer Causes Control* 2006; **17**: 71–9

12 **Jiang X, Castelao JE, Groshen S *et al.*** Alcohol consumption and risk of bladder cancer in Los Angeles County. *Int J Cancer -B* 2007; **121**: 839–45

13 **Djoussé L, Arnett DK, Eckfeldt JH, Province MA, Singer MR, Ellison RC.** Alcohol consumption and metabolic syndrome: does the type of beverage matter? *Obes Res* 2004; **12**: 1375–85

14 **Schabath MB, Spitz MR, Lerner SP *et al.*** Case-control analysis of dietary folate and risk of bladder cancer. *Nutr Cancer* 2005; **53**: 144–51

15 **Holick CN, De Vivo I, Feskanich D, Giovannucci E, Stampfer M, Michaud DS.** Intake of fruits and vegetables, carotenoids, folate, and vitamins A, C, E and risk of bladder cancer among women (United States). *Cancer Causes Control* 2005; **16**: 1135–45

16 **Mccredie M, Stewart JH, Ford JM, Maclennan RA.** Phenacetin-containing analgesics and cancer of the bladder or renal pelvis in women. *Br J Urol* 1983; **55**: 220–4

17 **son E, Mannetje A, Walls C *et al.*** Case-control study of high risk occupations for bladder cancer in New Zealand. *Int J Cancer* 2008; **122**: 1340–6

18 **Colt JS, Baris D, Stewart P *et al.*** Occupation and bladder cancer risk in a population-based case-control study in New Hampshire. *Cancer Causes Control* 2004; **15**: 759–69

19 **Neugut AI, Ahsan H, Robinson E, Ennis RD.** Bladder carcinoma and other second malignancies after radiotherapy for prostate carcinoma. *Cancer* 1997; **79**: 1600–4

20 **Liauw SL, Sylvester JE, Morris CG, Blasko JC, Grimm PD.** Second malignancies after prostate brachytherapy: incidence of bladder and colorectal cancers in patients with 15 years of potential follow-up. *Int J Radiat Oncol Biol Phys* 2006; **66**: 669–73

21 **Moser EC, Noordijk EM, van Leeuwen FE *et al.*** Risk of second cancer after treatment of aggressive non-Hodgkin's lymphoma; an EORTC cohort study. *Haematologica* 2006; **91**: 1481–8

22 **Travis LB, Fosså SD, Schonfeld SJ *et al.*** Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. *J Natl Cancer Inst* 2005; **97**: 1354–65

23 **Chaturvedi AK, Engels EA, Gilbert ES *et al.*** Second cancers among 104,760 survivors of cervical cancer: evaluation of long-term risk. *J Natl Cancer Inst* 2007; **99**: 1634–43

24 **Edwards TJ, Dickinson AJ, Natale S, Gosling J, Mcgrath JS.** A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at

a protocol-driven haematuria clinic. *BJU Int* 2006; **97**: 301–5

25 **Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE.** A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. *J Urol* 2000; **163**: 524–7

26 **Kocakoc E, Kiris A, Orhan I, Poyraz AK, Artas H, Firdolas F.** Detection of bladder tumors with 3-dimensional sonography and virtual sonographic cystoscopy. *J Ultrasound Med* 2008; **27**: 45–53

27 **Francica G, Bellini SA, Scarano F, Miragliuolo A, De Marino FA, Maniscalco M.** Correlation of transabdominal sonographic and cystoscopic findings in the diagnosis of focal abnormalities of the urinary bladder wall: a prospective study. *J Ultrasound Med* 2008; **27**: 887–94

28 **Kim JK, Park SY, 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**: 725–31

29 **Tekes A, Kamel I, Imam K *et al.*** Dynamic MRI of bladder cancer: evaluation of staging accuracy. *AJR Am J Roentgenol* 2005; **184**: 121–7

30 **Browne RF, Meehan CP, Colville J, Power R, Torreggiani WC.** Transitional cell carcinoma of the upper urinary tract: spectrum of imaging findings. *Radiographics* 2005; **25**: 1609–27

31 **Bootsma AM, Laguna Pes MP, Geerlings SE, Goossens A.** Antibiotic prophylaxis in urologic procedures: a systematic review. *Eur Urol* 2008; **54**: 1270–86

32 **Chen YT, Hsiao PJ, Wong WY, Wang CC, Yang SSD, Hsieh CH.** Randomized double-blind comparison of lidocaine gel and plain lubricating gel in relieving pain during flexible cystoscopy. *J Endourol* 2005; **19**: 163–6

33 **van der Aa MN, Steyerberg EW, Sen EF *et al.*** Patients' perceived burden of cystoscopic and urinary surveillance of bladder cancer: a randomized comparison. *BJU Int* 2008; **101**: 1106–10

34 **Karakiewicz PI, Benayoun S, Zippe C *et al.*** Institutional variability in the accuracy of urinary cytology for predicting recurrence of transitional cell carcinoma of the bladder. *BJU Int* 2006; **97**: 997–1001

35 **Lokeshavar VB, Selzer MG.** Urinary bladder tumor markers. *Urol Oncol* 2006; **24**: 528–37

36 **Lopez-Beltran A, Bassi P, Pavone-Macaluso M, Montironi R.** Handling and pathology reporting of specimens with carcinoma of the urinary bladder, ureter, and renal pelvis. *Eur Urol* 2004; **45**: 257–66

37 **Maruniak NA, Takezawa K, Murphy WM.** Accurate pathological staging of urothelial neoplasms requires better cystoscopic sampling. *J Urol* 2002; **167**: 2404–7

38 **Van der Meijden A, Oosterlinck W, Brausi M, Kurth KH, Sylvester R, de Balincourt C.** Significance of bladder biopsies in Ta,T1 bladder tumors: a report of the EORTC Genito-Urinary Tract Cancer Cooperative Group. EORTC-GU Group Superficial Bladder Committee. *Eur Urol* 1999; **35**: 267–71

39 **Hara T, Takahashi M, Gondo T *et al.*** Risk of concomitant carcinoma in situ determining biopsy candidates among primary non-muscle-invasive bladder cancer patients: Retrospective analysis of 173 Japanese cases. *Int J Urol* 2009; **16**: 293–8

40 **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**: 760–3

41 **Schmidbauer J, Witjes F, Schmeller N *et al.*** Improved detection of urothelial carcinoma in situ with hexaminolevulinate fluorescence cystoscopy. *J Urol* 2004; **171**: 135–8

42 **Hungerhuber E, Stepp H, Kriegmair M *et al.*** Seven years' experience with 5-aminolevulinic acid in detection of transitional cell carcinoma of the bladder. *Urology* 2007; **69**: 260–4

43 **Amin MB, Srigley JR, Grignon DJ *et al.*** Updated protocol for the examination of specimens from patients with carcinoma of the urinary bladder, ureter, and renal pelvis. *Arch Pathol Laboratory Med* 2003; **127**: 1263–79

44 **Paner GP, Ro JY, Wojcik EM, Venkataraman G, Datta MW, Amin MB.** Further characterization of the muscle layers and lamina propria of the urinary bladder by systematic histologic mapping: implications for pathologic staging of invasive urothelial carcinoma. *Am J Surg Pathol* 2007; **31**: 1420–9

45 **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**: 726–34

46 **Pich A, Chiusa L, Formiconi A, Galliano D, Bortolin P, Navone R.** Biologic differences between noninvasive papillary urothelial neoplasms of low malignant potential and low-grade (grade 1) papillary carcinomas of the bladder. *Am J Surg Pathol* 2001; **25**: 1528–34

47 **Oosterhuis JW, Schapers RF, Janssen-Heijnen ML, Pauwels RP, Newling DW, ten Kate F.** Histological grading of papillary urothelial carcinoma of the bladder: prognostic value of the 1998 WHO/ISUP classification system and comparison with conventional grading systems. *J Clin Pathol* 2002; **55**: 900–1005

48 **Maclennan GT, Kirkali Z, Cheng L.** Histologic grading of noninvasive papillary urothelial neoplasms. *Eur Urol* 2007; **51**: 889–97

49 **Bircan S, Candir O, Serel TA.** Comparison of WHO 1973 WHO/ISUP 1998, WHO 1999 grade and combined scoring systems in evaluation of bladder carcinoma. *Urol Int* 2004; **73**: 201–8

50 **Campbell PA, Conrad RJ, Campbell CM, Nicol DL, Mactaggart P.** Papillary urothelial neoplasm of low malignant potential: reliability of diagnosis and outcome. *BJU Int* 2004; **93**: 1228–31

51 **Schned AR, Andrew AS, Marsit CJ, Zens MS, Kelsey KT, Karagas MR.** Survival following the diagnosis of noninvasive bladder cancer: WHO/International Society of Urological Pathology versus WHO classification systems. *J Urol* 2007; **178**: 1196–200

52 **Murphy WM, Takezawa K, Maruniak NA.** Inter observer discrepancy using the 1998 WHO/ISUP classification of urothelial neoplasms: practical choices for patient care. *J Urol* 2002; **168**: 968–72

53 **Gonul II, Poyraz A, Unsal C, Acar C, Alkibay T.** Comparison of 1998 WHO/ISUP and 1973 WHO classifications for interobserver variability in grading of papillary urothelial neoplasms of the bladder. Pathological evaluation of 258 cases. *Urol Int* 2007; **78**: 338–44

54 **Yin H, Leong AS.** Histologic grading of noninvasive papillary urothelial tumors:

validation of the 1998 WHO/ISUP system by immunophenotyping and follow-up. *Am J Clin Pathol* 2004; **121**: 679–87

55 **Sylvester RJ, van der Meijden AP, Oosterlinck W *et al.*** Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006; **49**: 466–5

56 **Sylvester RJ, Oosterlinck W, van der Meijden AP.** A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol* 2004; **171**: 2186–90

57 **Gudjónssona S, Adell L, Merdasa F *et al.*** Should all patients with non-muscle invasive bladder cancer receive early intravesical chemotherapy after transurethral resection? The results of a prospective randomized multicentre study. *Eur Urol* 2009; **55**: 773–80

58 **Solsona E, Iborra I, Ricós JV, Monrós JL, Casanova J, Dumont R.** Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: short and long-term follow up. *J Urol* 1999; **161**: 1120–3

59 **Oddens JR, van der Meijden AP, Sylvester R.** One immediate postoperative instillation of chemotherapy in low risk Ta, T1 bladder cancer patients. Is it always safe? *Eur Urol* 2004; **46**: 336–68

60 **van der Heijden AG, Kiemeney LA, Gofrit ON *et al.*** Preliminary European results of local microwave hyperthermia and chemotherapy treatment in intermediate or high risk superficial transitional cell carcinoma of the bladder. *Eur Urol* 2004; **46**: 65–71

61 **Sakai I, Miyake H, Harada K, Hara I, Inoue TA, Fujisawa M.** Analysis of factors predicting intravesical recurrence of superficial transitional cell carcinoma of the bladder without concomitant carcinoma in situ. *Int J Urol* 2006; **13**: 1389–92

62 **Pawinski A, Sylvester R, Kurth KH *et al.*** A combined analysis of European Organization for Research and Treatment of Cancer, and Medical Research Council randomized clinical trials for the prophylactic treatment of stage TaT1 bladder cancer. European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council Working Party on Superficial Bladder Cancer. *J Urol* 1996; **156**: 1934–40

63 **Sylvester RJ, Oosterlinck W, Witjes JA.** The schedule and duration of intravesical chemotherapy in patients with non-muscle-invasive bladder cancer: a systematic review of the published results of randomized clinical trials. *Eur Urol* 2008; **53**: 709–19

64 **Koga H, Kuroiwa K, Yamaguchi A, Osada Y, Tsuneyoshi M, Naito S.** A randomized controlled trial of short-term versus long-term prophylactic intravesical instillation chemotherapy for recurrence after transurethral resection of Ta/T1 transitional cell carcinoma of the bladder. *J Urol* 2004; **171**: 153–7

65 **Nomata K, Noguchi M, Kanetake H *et al.*** Intravesical adjuvant chemotherapy for superficial transitional cell bladder carcinoma: results of a randomized trial with epirubicin comparing short-term versus long-term maintenance treatment. *Cancer Chemother Pharmacol* 2002; **50**: 266–70

66 **Hendricksen K, Witjes WP, Idema JG *et al.*** Comparison of three schedules of intravesical epirubicin in patients with non-muscle-invasive bladder cancer. *Eur Urol* 2008; **53**: 984–91

67 **Shelley MD, Wilt TJ, Court J, Coles B, Kynaston H, Mason MD.** Intravesical bacillus Calmette-Guérin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. *BJU Int* 2004; **93**: 485–90

68 **Isbarn H, Budäus L, Pichlmeier U, Conrad S, Huland H, Friedrich MG.** Comparison of the effectiveness between long-term instillation of mitomycin C and short-term prophylaxis with MMC or bacille Calmette-Guérin. Study of patients with non-muscle-invasive urothelial cancer of the urinary bladder. *Urologe A* 2008; **47**: 608–15

69 **Friedrich MG, Pichlmeier U, Schwaibold H, Conrad S, Huland H.** Long-term intravesical adjuvant chemotherapy further reduces recurrence rate compared with short-term intravesical chemotherapy and short-term therapy with Bacillus Calmette-Guérin (BCG) in patients with non-muscle-invasive bladder carcinoma. *Eur Urol* 2007; **52**: 1123–9

70 **van der Meijden AP, Brausi M, Zambon V *et al.*** Papillary carcinoma of the bladder. A European Organization for Research and Treatment of Cancer genito-urinary group randomized phase III trial. *J Urol* 2001; **166**: 476–81

71 **Ojea A, Nogueira JL, Solsona E *et al.*** A multicentre, randomised prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: low-dose bacillus Calmette-Guerin (27 mg) versus very low-dose bacillus Calmette-Guerin (13.5 mg) versus mitomycin C. *Eur Urol* 2007; **52**: 1398–406

72 **Pruthi RS, Baldwin N, Bhalani V, Wallen EM.** Conservative management of low risk superficial bladder tumors. *J Urol* 2008; **179**: 87–90

73 **Donat SM, North A, Dalbagni G, Herr HW.** Efficacy of office fulguration for recurrent low grade papillary bladder tumors less than 0.5 cm. *J Urol* 2004; **171**: 636–9

74 **Soler-Martínez J, Vozmediano-Chicharro R, Morales-Jiménez P *et al.*** Holmium laser treatment for low grade, low stage, noninvasive bladder cancer with local anesthesia and early instillation of mitomycin C. *J Urol* 2007; **178**: 2337–9

75 **Herr HW.** Does cystoscopy correlate with the histology of recurrent papillary tumours of the bladder? *BJU Int* 2001; **88**: 683–5

76 **Cina SJ, Epstein JI, Endrizzi JM, Harmon WJ, Seay TM, Schoenberg MP.** Correlation of cystoscopic impression with histologic diagnosis of biopsy specimens of the bladder. *Hum Pathol* 2001; **3**: 630–7

77 **Guney S, Guney N, Canogullari Z, Ergenekon E.** Ta T1 low and intermediate transitional cell carcinoma of the bladder: recurrence rates and the timing of check cystoscopies within the first year. *Urol Int* 2008; **80**: 124–8

78 **Brausi M, Collette L, Kurth K *et al.*** 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**: 523–31

79 **Fujii Y, Kawakami S, Koga F, Nemoto T, Kihara K.** Long-term outcome of

bladder papillary urothelial neoplasms of low malignant potential. *BJU Int* 2003; **92**: 559–62

80 **Holmang S, Johansson SL.** Stage Ta-T1 bladder cancer: the relationship between findings at first followup cystoscopy and subsequent recurrence and progression. *J Urol* 2002; **167**: 1634–7

81 **Mariappan P, Smith G.** A surveillance schedule for G1Ta bladder cancer allowing efficient use of check cystoscopy and safe discharge at 5 years based on a 25-year prospective database. *J Urol* 2005; **173**: 1108–11

82 **Burger M, Denzinger S, Wieland WF, Stief CG, Hartmann A, Zaak D.** Does the current World Health Organization classification predict the outcome better in patients with noninvasive bladder cancer of early or regular onset? *BJU Int* 2008; **102**: 194–7

83 **Harada K, Igari D, Tanahashi Y, Watanabe H, Saltoh M, Mishina T.** Staging of bladder tumors by means of transrectal ultrasonography. *J Clin Ultrasound* 1977; **5**: 388–9

84 **Bajaj A, Sokhi H, Rajesh A.** Intravenous urography for diagnosing synchronous upper-tract tumours in patients with newly diagnosed bladder carcinoma can be restricted to patients with high-risk superficial disease. *Clin Radiol* 2007; **62**: 854–7

85 **Miyake H, Hara I, Yamanaka K, Inoue TA, Fujisawa M.** Limited significance of routine excretory urography in the follow-up of patients with superficial bladder cancer after transurethral resection. *BJU Int* 2006; **97**: 720–3

86 **Moonen PM, Merkx GF, Peelen P, Karthaus HF, Smeets DF, Witjes JA.** UroVysion compared with cytology and quantitative cytology in the surveillance of non-muscle-invasive bladder cancer. *Eur Urol* 2007; **51**: 1275–80

87 **Denzinger S, Wieland WF, Otto W, Filbeck T, Knuechel R, Burger M.** Does photodynamic transurethral resection of bladder tumour improve the outcome of initial T1 high-grade bladder cancer? A long-term follow-up of a randomized study. *BJU Int* 2008; **101**: 566–9

88 **Herr HW, Donat SM.** A re-staging transurethral resection predicts early progression of superficial bladder cancer. *BJU Int* 2006; **97**: 1194–8

89 **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**: 53–9

90 **Grimm MO, Steinhoff C, Simon X, Spiegelhalder P, Ackermann R, Vogeli TA.** Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. *J Urol* 2003; **170**: 433–7

91 **Divrik RT, Yildirim U, Zorlu F, Ozen 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**: 1641–4

92 **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**: 1964–70

93 **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

94 **Shelley MD, Court JB, Kynaston H, Wilt TJ, Fish RG, Mason M.** Intravesical Bacillus Calmette-Guerin in Ta and T1 Bladder Cancer. *Cochrane Database Syst Rev* 2000; **4**: CD001986

95 **Böhle A, Bock PR.** Intravesical bacille Calmette-Guérin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. *Urology* 2004; **63**: 682–6

96 **Raj GV, Herr H, Serio AM *et al.*** Treatment paradigm shift may improve survival of patients with high risk superficial bladder cancer. *J Urol* 2007; **177**: 1283–6

97 **Shariat SF, Palapattu GS, Karakiewicz PI *et al.*** Concomitant carcinoma in situ is a feature of aggressive disease in patients with organ-confined TCC at radical cystectomy. *Eur Urol* 2007; **51**: 152–60

98 **Akagashi K, Tanda H, Kato S *et al.*** Recurrence pattern for superficial bladder cancer. *Int J Urol* 2006; **13**: 686–91

99 **Wiesner C, Pfitzenmaier J, Faldum A, Gillitzer R, Melchior SW, Thüroff JW.** Lymph node metastases in non-muscle invasive bladder cancer are correlated with the number of transurethral resections and tumour upstaging at radical cystectomy. *BJU Int* 2005; **95**: 301–5

100 **Shariat SF, Palapattu GS, Karakiewicz PI *et al.*** Discrepancy between clinical and pathologic stage: impact on prognosis after radical cystectomy. *Eur Urol* 2007; **51**: 137–49

101 **Cai T, Nesi G, Tinacci G *et al.*** Can early single dose instillation of epirubicin improve bacillus Calmette-Guerin efficacy in patients with nonmuscle invasive high risk bladder cancer? Results from a prospective, randomized, double-blind controlled study. *J Urol* 2008; **180**: 110–5

102 **Lambert EH, Pierorazio PM, Olsson CA, Benson MC, Mckiernan JM, Poon S.** The increasing use of intravesical therapies for stage T1 bladder cancer coincides with decreasing survival after cystectomy. *BJU Int* 2007; **100**: 33–6

103 **Gårdmark T, Jahnson S, Wahlquist R, Wijkström H, Malmström PU.** Analysis of progression and survival after 10 years of a randomized prospective study comparing mitomycin-C and bacillus Calmette-Guérin in patients with high-risk bladder cancer. *BJU Int* 2007; **99**: 817–20

104 **de Reijke TM, Kurth KH, Sylvester RJ *et al.*** 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**: 405–9

105 **Prout GR, Marshall VF.** The prognosis with untreated bladder tumors. *Cancer* 1956; **9**: 551–8

106 **Stein JP, Lieskovsky G, Cote R *et al.*** Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001; **19**: 666–75

107 **Nishiyama H, Habuchi T, Watanabe J *et al.*** Clinical outcome of a large-scale multi-institutional retrospective study for locally advanced bladder cancer: a survey including 1131 patients treated during 1990–2000 in Japan. *Eur Urol* 2004; **45**: 176–81

108 **Herr H, Lee C, Chang S, Lerner S, Bladder Cancer Collaborative Group.**

Standardization of radical cystectomy and pelvic lymph node dissection for bladder cancer: a collaborative group report. *J Urol* 2004; **171**: 1823–8

109 **Cheng L, Weaver AL, Leibovich BC *et al.*** Predicting the survival of bladder carcinoma patients treated with radical cystectomy. *Cancer* 2000; **88**: 2326–32

110 **Ghoneim MA, Abdel-Latif M, el-Mekresh M *et al.*** Radical cystectomy for carcinoma of the bladder: 2,720 consecutive cases 5 years later. *J Urol* 2008; **180**: 121–7

111 **Shariat SF, Karakiewicz PI, Palapattu GS *et al.*** Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. *J Urol* 2006; **176**: 2414–22

112 **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**: 486–92

113 **International Bladder Cancer Nomogram Consortium, Bochner BH, Kattan MW, Vora KC.** Postoperative nomogram predicting risk of recurrence after radical cystectomy for bladder cancer. *J Clin Oncol* 2006; **24**: 3967–72

114 **Wright JL, Lin DW, Porter MP.** The association between extent of lymphadenectomy and survival among patients with lymph node metastases undergoing radical cystectomy. *Cancer* 2008; **112**: 2401–8

115 **Steven K, Poulsen AL.** Radical cystectomy and extended pelvic lymphadenectomy: survival of patients with lymph node metastasis above the bifurcation of the common iliac vessels treated with surgery only. *J Urol* 2007; **178**: 1218–23

116 **Capitanio U, Suardi N, Shariat SF *et al.*** Assessing the minimum number of lymph nodes needed at radical cystectomy in patients with bladder cancer. *BJU Int* 2009; **103**: 1359–62

117 **Honma I, Masumori N, Sato E *et al.*** Removal of more lymph nodes may provide better outcome, as well as more accurate pathologic findings, in patients with bladder cancer – analysis of role of pelvic lymph node dissection. *Urology* 2006; **68**: 543–8

118 **Leissner J, Ghoneim MA, Abol-Enein H *et al.*** Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. *J Urol* 2004; **171**: 139–44

119 **Vazina A, Dugi D, Shariat SF, Evans J, Link R, Lerner SP.** Stage specific lymph node metastasis mapping in radical cystectomy specimens. *J Urol* 2004; **171**: 1830–4

120 **Abol-Enein H, El-Baz M, Abd El-Hameed MA, Abdel-Latif M, Ghoneim MA.** Lymph node involvement in patients with bladder cancer treated with radical cystectomy: a patho-anatomical study – a single center experience. *J Urol* 2004; **172**: 1818–21

121 **Kassouf W, Swanson D, Kamat AM *et al.*** Partial cystectomy for muscle invasive urothelial carcinoma of the bladder: a contemporary review of the MD Anderson Cancer Center experience. *J Urol* 2006; **175**: 2058–62

122 **Leibovici D, Kassouf W, Pisters LL *et al.*** Organ preservation for muscle-invasive bladder cancer by transurethral resection. *Urology* 2007; **70**: 473–6

123 **Holzbeierlein JM, Lopez-Corona E, Bochner BH *et al.*** Partial cystectomy: a contemporary review of the Memorial Sloan-Kettering Cancer Center experience and recommendations for patient selection. *J Urol* 2004; **172**: 878–81

124 **Lebret T, Hervé JM, Barré P *et al.*** Urethral recurrence of transitional cell carcinoma of the bladder. Predictive value of preoperative latero-montanal biopsies and urethral frozen sections during prostatocystectomy. *Eur Urol* 1998; **34**: 67–72

125 **Ali-el-Dein B, Abdel-Latif M, Ashamallah A, Abdel-Rahim M, Ghoneim M.** Local urethral recurrence after radical cystectomy and orthotopic bladder substitution in women: a prospective study. *J Urol* 2004; **171**: 275–8

126 **Spiess PE, Kassouf W, Brown G *et al.*** Immediate versus staged urethrectomy in patients at high risk of urethral recurrence: is there a benefit to either approach? *Urology* 2006; **67**: 466–71

127 **Nelles JL, Konety BR, Saigal C, Pace J, Lai J.** Urologic Diseases in America Project. Urethrectomy following cystectomy for bladder cancer in men: practice patterns and impact on survival. *J Urol* 2008; **180**: 1933–6

128 **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**: 245–50

129 **Yang WJ, Cho KS, Rha KH *et al.*** Long-term effects of ileal conduit urinary diversion on upper urinary tract in bladder cancer. *Urology* 2006; **68**: 324–7

130 **Samuel JD, Bhatt RI, Montague RJ, Clarke NW, Ramani VA.** The natural history of postoperative renal function in patients undergoing ileal conduit diversion for cancer measured using serial isotopic glomerular filtration rate and 99m technetium-mercaptoacetyltriglycine renography. *J Urol* 2006; **176**: 2518–22

131 **Pahernik S, Beetz R, Schede J, Stein R, Thueroff JW.** Rectosigmoid pouch (Mainz pouch II) in children. *J Urol* 2006; **175**: 284–7

132 **Kouba E, Sands M, Lentz A, Wallen E, Pruthi RS.** A comparison of the Bricker versus Wallace ureteroileal anastomosis in patients undergoing urinary diversion for bladder cancer. *J Urol* 2007; **178**: 945–8

133 **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**: 305–14

134 **Song C, Kang T, Hong JH, Kim CS, Ahn H.** Changes in the upper urinary tract after radical cystectomy and urinary diversion: a comparison of antirefluxing and refluxing orthotopic bladdersubstitutes and the ileal conduit. *J Urol* 2006; **175**: 185–9

135 **Wiesner C, Bonfig R, Stein R *et al.*** Continent cutaneous urinary diversion: long-term follow-up of more than 800 patients with ileocecal reservoirs. *World J Urol* 2006; **24**: 315–8

136 **Hautmann S, Chun KHF, Currlin E, Braun P, Huland H, Juenemann KP.** Refluxing chimney versus nonrefluxing LeDuc ureteroileal anastomosis for orthotopic ileal neobladder: a comparative analysis for patients with bladder cancer. *J Urol* 2006; **175**: 1389–94

137 **Protogerou V, Moschou M, Antoniou N, Varkarakis J, Baias A, Deliveliotis C.** Modified S-pouch neobladder vs ileal conduit and a matched control

population: a quality-of-life survey. *BJU Int* 2004; **94**: 350–4

138 **Sogni F, Brausi M, Frea B *et al.*** Morbidity and quality of life in elderly patients receiving ileal conduit or orthotopic neobladder ater radicale cystectomy for invasive bladder cancer. *Urology* 2008; **71**: 919–23

139 **Wiesner C, Stein R, Pahernik S, Haehn K, Melchior SW, Thueroff JW.** Long-term follow-up 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**: 155–60

140 **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**: 1729–36

141 **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**: 1318–22

142 **Shabsigh A, Korets R, Vora KC *et al.*** Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. *Eur Urol* 2009; **55**: 164–74

143 **Zietman AL, Sacco D, Skowronski U *et al.*** Organ conservation in invasive bladder cancer by transurethral resection, chemotherapy and radiation: results of a urodynamic and quality of life study on long term survivors. *J Urol* 2003; **170**: 1772–6

144 **Danesi DT, Arcangeli G, Cruciani E *et al.*** Conservative treatment of invasive bladder carcinoma by transurethral resection, protracted intravenous infusion chemotherapy, and hyperfractionated radioadiotherapy. *Cancer* 2004; **101**: 2540–7

145 **Hussain SA, Stocken DD, Peake DR *et al.*** Long term results of a phase II study of synchronous chemo-radiotherapy in advanced muscle invasive bladder cancer. *Br J Cancer* 2004; **90**: 2106–11

146 **Kaufman DS, Winter KA, Shipley WU *et al.*** Phase I, –II RTOG study (99–06) of patients with muscle-invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, and twice-daily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. *Urology* 2009; **73**: 833–7

147 **Gogna KN, Matthews JH, Turner SL *et al.*** Efficacy and tolerability of concurrent weekly low dose cisplatin during radiation treatment of localized muscle invasive bladder transitional cell carcinoma: a report of two sequential phase II studies from the Trans Tasman Radiation Oncology Group. *Radiother Oncol* 2006; **81**: 9–17

148 **International Collaboration of Trialists.** Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. *Lancet* 1999; **354**: 533–40

149 **Sherif A, Holmberg L, Rintala E *et al.*** Neoadjuvant cisplatinum based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. *Eur Urol* 2004; **45**: 297–303

150 **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**: 561–9

151 **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**: 202–5

152 **Advanced Bladder Cancer Meta-analysis Collaboration.** Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Lancet* 2003; **361**: 1927–34

153 **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**: 189–99

154 **Ruggeri EM, Giannarelli D, Bria E *et al.*** Adjuvant chemotherapy in muscle-invasive bladder carcinoma: a pooled analysis from phase III studies. *Cancer* 2006; **106**: 783–8

155 **Dash A, Pettus JA, Herr HW *et al.*** A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. *Cancer* 2008; **113**: 2471–7

156 **Matsui Y, Nishiyama H, Watanabe J *et al.*** The current status of perioperative chemotherapy for invasive bladder cancer: a multiinstitutional retrospective study in Japan. *Int J Clin Oncol* 2005; **10**: 133–8

157 **Farnham SB, Cookson MS.** Surgical complications of urinary diversion. *World J Urol* 2004; **22**: 157–67

158 **Studer UE, Burkhard FC, Schumacher M *et al.*** Twenty years experience with an ileal orthotopic low pressure bladder substitute-lesson to be learned. *J Urol* 2006; **176**: 161–6

159 **Thorstenson A, Jacobsson H, Onelov E, Holst JJ, Hellstrom PM, Kinn AC.** Gastrointestinal function and metabolic control after construction of an orthotopic ileal neobladder in bladder cancer. *Scand J Urol Nephrol* 2007; **41**: 14–9

160 **Tal R, Sivan B, Kedar D, Baniel J.** Management of benign ureteral strictures following radical cystectomy and urinary diversion for bladder cancer. *J Urol* 2007; **178**: 538–42

161 **Wood DN, Allen SE, Hussain M, Greenwell TJ, Shah PJR.** Stomal complications of ileal conduits are significantly higher when formed in women with intractable urinary incontinence. *J Urol* 2004; **172**: 2300–3

162 **Ali-el-Dein B, Shaaban A *et al.*** Surgical complications following radical cystectomy and orthotopic neobladders in women. *J Urol* 2008; **180**: 206–10

163 **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**: 950–4

164 **Stein JP, Clark P, Miranda G, Cal J, Groshen S, Skinner DG.** Urethral tumor recurrence following cystectomy and urinary diversion: clinical and pathological characteristics in 768 male patients. *J Urol* 2005; **173**: 1163–8

165 **Austen M, Kaelble T.** Secondary malignancies in different forms of urinary diversion using isolated gut. *J Urol* 2004; **172**: 831–8

166 **Meissner C, Giannarini G, Schumacher MG, Thoeny H, Studer UE, Burkhard**

FC. The efficacy of excretory urography to detect upper urinary tract tumors after cystectomy for urothelial cancer. *J Urol* 2007; **178**: 2287–90

167 **Wood DP, Bianco FJ, Pontes JE, Heath MA, Dajusta D.** Incidence and significance of positive urine cultures in patients with an orthotopic neobladder. *J Urol* 2003; **169**: 2196–9

168 **Sternberg CN, De Mulder PHM, Schornagel JH *et al.*** 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, 30924. *J Clin Oncol* 2001; **19**: 2638–46

169 **von der Maase H, Hansen SW, Roberts JT *et al.*** Gemcitabine, 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**: 3068–77

170 **Bamias A, Aravantinos G, Deliveliotis C *et al.*** Docetaxel and cisplatin with granulocyte colony-stimulating factor (GCSF) versus MVAC with GCSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. *J Clin Oncol* 2004; **22**: 220–8

171 **Herr HW, Donat SM, Bajorin DF.** Post chemotherapy surgery in patients with unresectable or regionally metastatic bladder cancer. *J Urol* 2001; **165**: 811–4

172 **Sweeney P, Millikan R, Donat MS *et al.*** Is there a therapeutic role for post chemotherapy retroperitoneal lymph node dissection in metastatic transitional cell carcinoma? *J Urol* 2003; **169**: 2113–7

173 **Siefker-Radkte Walsh GL, Pisters LL *et al.*** Is there a therapeutic role for surgery in the management of metastatic urothelial cancer? MD Anderson experience. *J Urol* 2004; **171**: 145–8

174 **Kim CJ, Wakabayashi Y, Kushima R, Sakano Y, Yoshiki T, Okada Y.** Retroperitoneal lymph node dissection in patients with interaortocaval lymph node metastases of transitional cell carcinoma of the urinary tract. *Int J Urol* 2004; **11**: 243–7

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Abbreviations: **(U)(N)(MI)BC**, (urothelial) (non-) (muscle-invasive) bladder cancer; **US**, ultrasonography; **CTU**, CT urography; **TUR**, transurethral resection; **CIS**, carcinoma *in situ*; **PUNLMP**, papillary urothelial neoplasm of low malignant potential; **RC**, radical cystectomy; **MVAC**, methotrexate, vinblastine, adriamycin and cisplatin; **MSKCC**, Memorial Sloan-Kettering Cancer Center.