21. Raghavan D, Wallace DMA, Sandeman T, *et al.* First randomized trials of pre-emptive (neoadjuvant) intravenous (IV cisplatin (CDDP) for invasive transitional cell carcinoma of bladder. *Proc Am Soc Clin Oncol* 1989, **8**, 133.
22. Early Breast Cancer Trialist Collaborative Group: The effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: an overview of 61 randomised trials among 28.896 women. *N Engl J Med* 1988, **319**, 1681–1692.
23. Laurie JA, Moertel CF, Fleming TR, *et al.* Surgical adjuvant therapy of large-bowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil. *J Clin Oncol* 1989, **7**, 1447–1456.
24. Logothetis CJ, Johnson DE, Chong C, *et al.* Adjuvant cyclophosphamide, doxorubicin, and cisplatin chemotherapy for bladder cancer: an update. *J Clin Oncol* 1988, **6**, 1590–1596.
25 Einstein A, Coombs J, Pearse H, *et al.* Cisplatin adjuvant therapy following pre-operative radiotherapy plus radical cystectomy for invasive bladder carcinoma: a randomized trial of the National Bladder Cancer group. *Am Urol Assoc* 1985, **133**, 222.
26. Richards B, Bastable JRG, Freedman L, *et al.* Adjuvant chemotherapy with doxorubicin (adriamycin) and 5-fluorouracil in T3.NX.MO bladder cancer treated with radiotherapy. *Br J Urol* 1983, **55**, 386–391.
27. Daniels JR, Skinner DG, Russel CA, *et al.* The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: prospective comparative trial. *Proc Am Soc Clin Oncol* 1990, **131**, 1990.
28. Miller LS: Bladder cancer: superiority of preoperative irradiation therapy and cystectomy in clinical stage B2 and C. *Cancer* 1977, **39**, 973–980.
29. Bloom HJG, Hendry WF, Wallace DM, *et al.* Treatment of T3 bladder cancer: controlled trial of pre-operative radiotherapy and radical cystectomy versus radical radiotherapy. *Br J Urol* 1982, **54**, 136–151.
30. Shipley WU, Prout GR, Einstein AB, *et al.* Treatment of invasive bladder cancer by cisplatin and radiation in patients unsuited for surgery. *JAMA* 1987, **258**, 931–935.
31. Coppin C, Gospodarowicz: The NCI-Canada trial of concurrent cisplatin and radiotherapy for muscle invasive bladder cancer. In: Splinter TAW, Scher HI, eds. *Neoadjuvant Chemotherapy in Invasive Bladder Cancer*. New York, Wiley-Liss, 1990, 75–83.
32. Shipley WU, Kaufman DS, Heney NM, *et al.* The integration of chemotherapy, radiotherapy and transurethral surgery in bladder-sparing approaches for patients with invasive tumors. In: Splinter TAW, Scher H, eds. *Neoadjuvant Chemotherapy in Invasive Bladder Cancer*. New York, Wiley-Liss, 1990, 85–94.

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Optimal Management of Superficial Bladder Cancer

J.A. Witjes and F.M.J. Debruyne

INTRODUCTION

OPTIMAL MANAGEMENT of superficial bladder cancer is based on a knowledge of epidemiology, presenting symptoms and natural course.

Bladder cancer is, after prostatic cancer, the most frequent urological cancer. It is 3–4 times more frequent in men. As in all epithelial tumours, the incidence rises with age, with the highest incidence in the sixth and seventh decade. Several risk factors have been identified, of which smoking is the most important. More than 90% of bladder tumours are of the transitional cell type. Less than 10% of the tumours are adenocarcinomas and squamous cell carcinomas.

The key symptom is haematuria, whether macroscopic or microscopic. This should always raise suspicion of the diagnosis of a malignancy, until proven otherwise. In the diagnostic work, history (irritative bladder symptoms, recurrent infections) and physical examination should be followed by urine investigations, especially urine cytology. Together with intravenous urography (IVU) and urethrocystoscopy (UCS) the initial diagnosis of a (superficial) bladder cancer can be made.

The treatment of choice is an adequate transurethral resection of the tumour (TURT) together with random biopsies from the bladder and the prostatic urethra, unless there are major contraindications for surgery and/or anaesthesia. Together with a bimanual examination before and after operation the tumour category and grading can be assessed [1]. In case of contraindications against the TURT, initial therapy could be intravesical instillations of chemotherapeutic or immunotherapeutic agents, which are discussed below. If there is any doubt as to whether the initial TURT has been complete, a new UCS with TURT has to be planned after 4–6 weeks.

Further treatment depends on the pathological classification in which two major categories can be identified. Approximately 75% of the primary bladder tumours are superficial, invading as far as the lamina propria, and not infiltrating the muscle of the bladder wall (pTa, pT1, pTis). The other group of tumours are the muscle infiltrating bladder tumours (pT2-pT4b).

In the case of an infiltrating transitional cell carcinoma (TCC) further investigations to determine the presence or absence of

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lymph node involvement (N-status) or metastatic disease (M-status) are necessary. Surgery, (neoadjuvant) chemotherapy or radiotherapy are possible therapeutic options, depending on the final TNM classification.

In the case of a superficial TCC, which has been apparently completely resected, up to 70% of these tumours will recur, usually in the first year after TURT [2], and usually in the same stage and grade. These tumours could be true recurrences (regrowth after incomplete resection, or as a result of implant of tumour cells during TURT), or new occurrences. In a minority of cases (overall, less than 15%) progress to a higher pT stage and/or the development of metastases may occur. To prevent or delay recurrent tumour and eventual progression TURT should be followed by some form of intravesical therapy.

An exception to the high recurrence rate are patients with a small primary, solitary pTa grade 1 tumour. The chance for recurrence or progression in these cases is less than 5%, and these patients do not have to be treated after the TURT. Cystoscopic and cytologic follow up is sufficient [3].

All other superficial tumours should be treated with intravesical therapy, particularly in those cases with established high risk factors for recurrence (high stage and grade, multifocality, size, previous bladder tumours, positive biopsies). Similarly, patients with carcinoma *in situ* (CIS) represent a high-risk group.

CIS is a highly anaplastic preinvasive malignancy, which is difficult to control with transurethral resection. Radiotherapy is not effective. CIS will progress to invasive cancer, although this might take up to 77 months [4]. Intravesical therapy therefore is one of the only effective treatment modalities.

Another high risk group are pT1 grade III tumours, which are almost always seen with concomitant CIS. Recurrence rate for this group might be as high as 90% for multiple tumours, and the risk of progression to invasive cancer and/or metastases is 25–30% [5]. In these tumours radical surgery might be considered.

INTRAVESICAL PROPHYLAXIS AND THERAPY

The aim of intravesical prophylaxis is to prevent or delay superficial tumour recurrence or progression. In the case of therapy for residual tumour or CIS, treatment is given on similar lines. A drug is dissolved and instilled into the bladder with the use of a transurethral catheter. The catheter is taken out and the drug is left in the bladder for 1 to 2 hours. The patient has to change position to allow the drug to reach all parts of the bladder. The main advantage of this method is that no or little systemic uptake of the drug occurs while optimal contact between the tumour or tissue at risk and the drug is obtained. Disadvantages are the local side-effects in the bladder because of the high local drug concentration, and the need for transurethral manipulation. Usually a course consists of a number of weekly intravesical instillations. Three months after the initial TURT a further control UCS should be performed.

Several drugs have been used in the past and are listed below. They can be divided into chemotherapeutic agents (thiotepa, doxorubicin, ethoglucid, mitomycin) and immunotherapeutic agents (interferon, Bacillus Calmette-Guerin (BCG)).

Thiotepa

Thiotepa has a low molecular weight of 189, so absorption and systemic toxicity (myelosuppression) can occur, although this is rare and usually mild [10]. Full blood counts should be measured before and during treatment, and treatment should be delayed if necessary. The complete response rates for thiotepa are between 35% and 45% [6]. Patients with grade I tumours respond particularly well [11].

Table 1. Results of three studies dealing with intravesical treatment of superficial bladder cancer

Ref.	Agent	Tumour	No. of patients	Follow-up (months)	Success rate
7	Thiotepa	–	19	24	60%
	BCG Tice	–	39	24	100%
8	BCG Past.	pTa/1	67	34 (3–92)	87%
	Doxorubicin	pTa/1	53	40 (5–97)	57%
	Thiotepa	pTa/1	56	34 (6–78)	64%
9	BCG Connaught	CIS	52	–	72%
	Doxorubicin	CIS	57	–	47%

Doxorubicin

Doxorubicin has a relatively high molecular weight of 580, thus absorption and systemic toxicity are rare. Its side-effects are chemical cystitis in 25% and, infrequently, allergic reactions [12]. The long term success rates are not clear. Doxorubicin and thiotepa are both significantly inferior to BCG (Table 1) [13].

Ethoglucid

Ethoglucid has also been used for intravesical instillations. It is hardly absorbed at all and systemic side-effects are rare. In an EORTC study Kurth found both chemical cystitis and mild systemic reactions in only 3% of 96 patients treated with ethoglucid [14]. Only one case of serious toxicity was seen. No difference was found in this study between doxorubicin and ethoglucid regarding efficacy. Both drugs, however, prolonged the mean interval between recurrences, compared with transurethral resection alone.

Mitomycin

Mitomycin has a molecular weight of 329, and absorption is minimal. Myelosuppression is rare. The most frequent side-effects are chemical cystitis and allergic reactions (skin rash). Soloway treated 80 patients with persistent superficial bladder cancer, which had in most cases recurred following prior therapy with other agents [14]. His initial responses at twelve weeks were 37% for pTa, 44% for pT1, and 33% for CIS. Failure at twelve weeks was considered to be an important negative prognostic sign.

We carried out a comparative study between mitomycin and BCG, in 338 patients with superficial TCC [15]. Frequency of side-effects were not significantly different for both groups, nor were the recurrence rates. Chemical and bacterial cystitis were noted in 40%–50% in both groups. The recurrence rate for the BCG group was 0.28, for the mitomycin group 0.24 ($P = 0.400$). In our current study mitomycin is being compared with two different BCG strains.

Huland compared mitomycin to no intravesical therapy in a randomised trial after complete TURT [16]. The percentage of recurrences was 10% in the mitomycin group compared to 51% in the control group. A prospective multicentre trial confimed these results, although the recurrence rate was slightly higher (15.3%) with the same method of prophylaxis [17]. Future studies have to identify the exact value of these different chemotherapeutic intravesical agents.

Interferon

Limited clinical trials with interferon in bladder cancer suggest potential success after intravesical instillation, but further investigations are necessary [18,19]. Chodak compared high and low dose interferon in the intravesical treatment of patients with CIS. After at least 6 months 9 of 19 patients in the high dose group remained without recurrence. Both 5 patients in the high and low dose group underwent cystectomy, although the median time to surgery was longer in the high dose group. Glashan also compared two dosages in patients with CIS. 87 patients were treated for a maximum of 1 year. 20 patients in the high dose group (43%) and 2 patients in the low dose group (5%) achieved a complete response.

BCG

The antitumour effect of tuberculosis has been known since 1929, when autopsy studies of tuberculosis patients showed significantly fewer malignant tumours than in a control group. After several decades these findings were the basis for the use of BCG in cancer treatment. Results of animal studies led to its use in man (initially in the management of leukaemia). Morales was the first to use dissolved BCG in the human bladder in 1976 [20].

The mechanisms by which BCG exerts its antitumour activity remain unclear. There are non-immunological responses (inflammation), non-specific and specific immunological responses (humoral and cellular), but the activities and interactions of BCG with tumour cells are still not understood.

The efficacy of the BCG vaccine depends on several factors. The two most important are: (1) the ability of the organisms to multiply *in vivo* the so-called viability which differs in the available strains, and (2) the number of bacilli used in each vial (the dose). The dose is the number of colony-forming units (CFU), which is approximately 5×10^8 CFU in each ampoule. Although the antitumour effect increases with the dose, there seems to be an optimal dose, of 5×10^8 to 5×10^9 CFU.

Intravesical instillation of BCG is accepted as the best route of administration. A combination of the intravesical administration with intradermal administration does not seem to improve the results.

The clinical schedule is a course of six weekly instillations after a complete endoscopic resection of a superficial bladder tumour. In the case of a recurrence after BCG therapy, a second course of six instillations or maintenance therapy (e.g. monthly instillations for one year) can be given. Both regimens can improve the success rates, but the maintenance therapy has more local and systemic toxicity [13].

Side-effects after intravesical instillations with BCG are local or systemic. Lamm reviewed the data of 1278 patients treated with 5 different strains of BCG [22]. The local side-effects are cystitis-like in nature in over 90% of the patients. These complaints increase with the number of instillations, but are easily treated with non-steroidal anti-inflammatory drugs. Haematuria is seen in 43% of patients, but is seldom severe. Systemic side-effects such as fever (28%), malaise (24%) and nausea (8%) generally subside spontaneously. Severe side-effects (Table 2) are seen in about 5% of all patients [21]. It is important that the urologist working with BCG is familiar with antituberculous drugs (isoniazid, rifampicin, ethambutol). Only few fatal complications have been encountered, and traumatic catheterisation seems to play an important role in these severe problems. Therefore it is strongly recommended that if trauma during catheterisation occurs, the treatment is postponed for one week.

Table 2. Severe complications of intravesical BCG instillations in 2602 patients with superficial bladder cancer [21]

Side-effects	%
Fever > 39.5°C	2.9
Haematuria	1.0
Granulomatous prostatitis	0.9
BCG pneumonia/hepatitis	0.7
Arthritis/arthralgia	0.5
Epididymo-orchitis	0.4
BCG sepsis	0.4
Skin rash	0.3
Ureteral obstruction	0.3
Contracted bladder	0.2
Cytopenia	0.1
Renal abscess	0.1

The clinical results of BCG are good. Without treatment, overall after endoscopic resection more than 60% of the superficial bladder tumours recur, usually within the first year. With BCG the recurrence rates decrease to 35% or less with a minimal follow-up of one year [13]. BCG is superior to thiotepa and doxorubicin. After an incomplete endoscopic resection BCG can be used to eliminate residual tumour with success rates of 60–70%.

For CIS several chemotherapeutic agents have been investigated, with success rates between 29 and 48%. With BCG success rates between 42 and 83% are found (patients at least 1 year free of recurrences as seen on cystoscopy of cytology, after a complete endoscopic resection of tumour) which is very encouraging. BCG has also been used successfully in the treatment of ureteral CIS [23], and TCC in the prostatic urethra [24, 25].

Although at this moment BCG seems to be the drug of choice for several forms of superficial TCC, many questions remain unanswered, especially about the mechanisms of action, the optimal dose and clinical schedule. Future and ongoing investigations and clinical trials will hopefully give the answers.

SUMMARY AND CONCLUSIONS

Superficial transitional cell carcinoma of the bladder is a heterogeneous group of tumours. On the one hand there are small primary solitary pTa grade I tumours, which are very likely to progress after they have been treated by TURT, and on the other there are very aggressive forms, such as pT1 grade III with CIS, which have a high recurrence and progression rate. This makes it important for the treating urologist to be aware of the different aspects of superficial bladder cancer. There is also a possibility to choose between several intravesical drugs and schedules. It is important to know the advantages and disadvantages of these treatment modalities, to be able to individualise treatment as much as possible. Ongoing clinical trials will give us some answers with regard to efficacy and toxicity of several drugs. What has not changed is the need for regular follow-up with endoscopy and urine cytology. The natural preference for conservative treatment on the part of the patient should not prevent a urologist from using more aggressive forms of therapy when needed.

1. Hermanek P, Sobin LH. *TNM Classification of Malignant Tumours*, International Union Against Cancer, 4th ed. Heidelberg, Springer, 1987.
2. Soloway MS. Selecting initial therapy for bladder cancer. *Cancer 60* (Suppl.), 1987, 502–513.
3. Morrison DA, Murphy WM, Ford KS, Soloway MS. Surveillance of stage 0, grade I bladder cancer by cytology alone: is it acceptable? *J Urol* 1984, **132**, 672–674.
4. Jakse G, Hofstater F, Leitner G, *et al.* Karzinoma *in situ* der Harnblase: eine diagnostische und therapeutische Herausforderung. *Urologe* 1980, **19**, 93–99.
5. Anderstrom C, Johansson S, Nilsson S. The significance of lamina propria invasion on the prognosis of patients with bladder tumours. *J Urol* 1980, **124**, 23–26.
6. Lutzeyer W, Rubben H, Dahm H. Prognostic parameters in superficial bladder cancer: an analysis of 315 cases. *J Urol* 1982, **127**, 250–253.
10. Soloway MS, Ford KS. Thiotepa induced myelosuppression: review of 670 bladder instillations. *J Urol* 1983, **130**, 889–891.
11. Prout GR, *et al.* Long term fate of 90 patients with superficial bladder cancer randomly assigned to receive or not to receive thiotepa. *J Urol* 1983, **130**, 677–690.
12. Crawford ED, *et al.* Adverse reactions to the intravesical administration of doxorubicin hydrochloride: a report of six cases. *J Urol* 1986, **136**, 668–669.
13. Witjes JA, vd Meijden APM, Debruyne FMJ. Use of intravesical Bacillus Calmette-Guerin in the treatment of superficial transitional cell carcinoma of the bladder: an overview. *Urol Int* 1990, **45**, 129–136.
14. Soloway MS. Introduction and overview of intravesical therapy for superficial bladder cancer. *Urology* 1988, **31**(Suppl.) 5–16.
14. Kurth KH, Schroeder FH, Tunn U, *et al.* Adjuvant chemotherapy of superficial transitional cell bladder carcinoma: preliminary results of a European Organization for Research on Treatment of Cancer randomized trial comparing doxorubicin hydrochloride, ethoglucid and transurethral resection alone. *J Urol* 1984, **132**, 258–262.
15. Debruyne FMJ, vd Meijden APM, Witjes JA, *et al.* Bacillus Calmette-Guerin versus mitomycin-C intravesical therapy in superficial bladder cancer. Results of a randomized trial after 21 months of follow up. *J Urol* (in press).
16. Huland H, Otto U, Droese M, Kloeppel G. Long-term mitomycin C instillation after resection of superficial bladder carcinoma: influence on recurrence, progression, and survival. *J Urol* 1984, **132**, 27–29.
17. Huland H, Kloeppel G, Feddersen I, *et al.* Comparison of different schedules of cytostatic intravesical instillations in patients with superficial bladder carcinoma: final evaluation of a prospective multicenter study with 419 patients. *J Urol* 1990, **144**, 68–72.
18. Chodak GW. Intravesical interferon treatment of superficial bladder cancer. *Urology* 1989, **34**, 84–96.
19. Hillyard RW, Jr Ladaga L, Schellhammer PF. Superficial transitional cell carcinoma of the bladder with mucosal involvement of the prostatic urethra: results of treatment with intravesical bacillus Calmette-Guerin. *J Urol* 1988, **139**, 290–293.
20. Morales A, Eidinger D, Bruce AW. Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumours. *J Urol* 1976, **116**, 180–183.
21. Lamm DL, *et al.* Complications of bacillus Calmette-Guerin immunotherapy: review of 2602 patients and comparison of chemotherapy complications. In: Debruyne FMJ, Denis L, vd Meijden APM eds. *EORTC Genito-Urinary Group Monograph 6: BCG in Superficial Bladder Cancer*. New York, Alan R. Liss, 1989, 335–355.
22. Lamm DL, Stogdill VD, Stogdill BJ, *et al.* Complications of bacillus Calmette-Guerin immunotherapy in 1278 patients with bladder cancer. *J Urol* 1986, **135**, 272–274.
23. Studer U, *et al.* Percutaneous bacillus Calmette-Guerin perfusion of the upper urinary tract for carcinoma *in situ*. *J Urol* 1989, **142**, 975–977.
24. Glashan RW. A randomized controlled study of intravesical a-2b-interferon in carcinoma *in situ* of the bladder. *J Urol* 1990, **144**, 658–661.
25. Bretton PR, *et al.* Intravesical bacillus Calmette-Guerin therapy for *in situ* transitional cell carcinoma involving the prostatic urethra. *J Urol* 1989, **141**, 853–856.

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Controversies in the Management of Localised and Metastatic Prostatic Cancer

L.J. Denis

INTRODUCTION

CLINICAL PROSTATIC cancer in its natural course is a single biological process with a usually slow but constant growth. This growth can be temporarily arrested by endocrine treatment offering palliation but never cure in the majority of patients with extraprostatic disease. The clinical stage and grade of the tumour as well as a number of prognostic factors define the outcome of the disease independent of a given treatment. This state of affairs is apt to create controversies in the management of the disease, leading to errors in treatment by commission or by omission. The lack of a clear consensus on grade and classification, the absence of a reliable indicator of metastatic potential and competing causes of death at the age of the peak incidence contribute to the chaos.

There is consensus that localised disease may be curable while metastatic disease is incurable. A renewed interest in radical prostatectomy has not solved the controversy on treatment but has brought new insight into the pathogenesis and biological aspects of the disease, while the development of a safe medical castration opened new avenues to improved quality of life as an end point in metastatic disease. The bottom line is that at this moment we cannot agree on a perfect treatment for any individual patient but we can improve management by improved detection and diagnosis. We review some basic concepts and the management of localised, metastatic and relapsed disease.

BASIC CONCEPTS

Any man in the industrialised nations of Western Europe has a one in ten chance to develop prostatic cancer. It is now the

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