REVIEW

Update on the management of non-muscle invasive bladder cancer

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Abstract

Non-muscle invasive bladder cancer (NMIBC) is a heterogeneous population of tumours accounting for 80% of bladder cancers. Over the years, the management of this disease has been changing with improvements in results and outcomes. In this review, we focus on the latest updates on the management of NMIBC.

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Résumé

Le cancer de la vessie sans envahissement musculaire est un groupe hétérogène de tumeurs représentant 80 % des cancers de la vessie. Au fil des années, la prise en charge de cette maladie a évolué, et les résultats et issues thérapeutiques se sont améliorés. Dans l'article qui suit, nous présentons les plus récents développements dans la prise en charge de ce type de cancer.

Introduction

Urothelial cancer (UC) of the bladder is the second most common genitourinary malignancy, with over 60 000 new cases annually in the United States and more than 13 000 deaths from the disease per year. Bladder cancer is the fourth most common male cancer accounting for 7% of all cancers and the eighth highest cancer-related mortality rate in American men.[1] Risk factors that have been associated with bladder cancer include smoking, chronic inflammatory changes in the bladder (due to persistent bladder stones, recurrent urinary tract infections, indwelling catheters, or schistosomiasis), and chemotherapeutic exposure, such as cyclophosphamide.[2-7] Other risk factors include pelvic irradiation, occupational exposure to chemicals from the aromatic amines family and chronic phenacetin use.[8-11]

Non-muscle invasive bladder cancer (NMIBC) accounts for about 80% of all bladder cancers;[12] Ta bladder cancer accounts for most of NMIBC (60%) where T1 and Tis (carcinoma in situ [CIS]) account for 30% and 10%, respectively. The actual prevalence of NMIBC is 10 times its incidence creating a major economic burden on health-care systems.[13] As measured on the basis of cumulative per patient cost from diagnosis until death, bladder cancer is the most expensive to treat. This review will focus on the contemporary management of NMIBC.

Factors influencing progression and recurrence

Stage and grade

The overall rate of recurrence for NMIBC is 60% to 70%, and the overall rate of progression is 20% to 30%.[14,15] Ta tumours (which are mostly low grade) rarely progress to a higher stage, but they tend to recur. High-grade Ta tumours account for only 2% to 9% of all cases of NMIBC.[16,17] Holmang and colleagues demonstrated that low-grade Ta tumours had a recurrence of 70%, with a progression of only 2%.[18] Heney and colleagues showed that the risk of progression to muscle invasion is strongly associated with tumour grade.[12] The risk of progression for Ta tumour was 2%, 11%, and 45% for grades 1, 2 and 3, respectively.[19] When stratified by stage, tumour grade continues to correlate with progression and mortality. Most subsequent studies suggested grade is a better prognostic indicator of progression and mortality than recurrence.[20-23] However, recurrence is still a significant challenge since 60% to 90% of NMIBC will recur if treated by transurethral resection (TUR) alone.[24]

T1 tumours represent a different entity. Some respond to conservative measures and behave in a non-lethal fashion, while others are more aggressive and tend to progress to muscle invasion and even metastasis. T1 tumours are mostly high grade with a higher potential for progression and death. When treated with TUR alone, T1 tumours have a high risk of progression to muscle invasion.[16,25,26] T1G3 tumours progress in more than 50% of cases; deaths from disease occur in 25% of patients in the first 5 years and in 10% of patients between 5 to 15 years.[27] Carcinoma in situ is mostly concomitant. Recurrence of NMIBC has been found to increase from 43% to 73% with concomitant CIS.[28] In addition, whether the cancer is primary or concomitant CIS, 50% progress to muscle invasion and 20% of patients

will ultimately die of metastatic disease if they are treated conservatively.[29-31]

Other factors

Tumour multiplicity has been shown to be an important factor in NMIBC recurrence and progression.[16,32,33] Herr suggested multifocality to be the most predictive factor of recurrence.[34] Size also influences tumour progression with rates of 9% for tumours less than 5 cm and 35% for tumours more than 5 cm.[16] However, size can also impact in tumour recurrence.[35] Other studies have used a 3-cm size cut-off for prognostication. Furthermore, the duration from TUR to first recurrence and frequency of previous recurrences dramatically influences the risk of tumour recurrence. Fitzpatrick and associates studied over 400 patients with Ta tumour.[36] Of the patients with no recurrence at first follow-up cystoscopy, 79% had no recurrence on subsequent follow-up. However, in patients with recurrence at 3 months, only 10% were without any recurrence during the 1-year follow-up. Lymphovascular invasion and the histological type of NMIBC also have a significant impact on outcome. With lymphovascular invasion, the death rate can be as high as 50%.[16,37,38] Divergent histology, such as micropapillary variant of TCC, has been shown to have poor response to conservative strategies with death rates reaching 50% at 5 years.[39]

Using 6 clinicopathologic parameters (grade, stage, tumour size, prior recurrence rate, presence of concomitant CIS and number of tumours), the probability of recurrence and progression of NMIBC can be calculated with risk tables provided by the European Organization for Research and Treatment of Cancer (EORTC). These tables were developed and based on individual patient data from 2596 patients diagnosed with Ta/1 tumours who were randomized in 7 EORTC trials (www.eortc.be/tools/bladdercalculator). In general, patients with NMIBC can be stratified into low risk disease (solitary, low grade Ta lesion, less than 3 cm), intermediate (greater than or equal to 3 cm, multiple, or multirecurrent low-intermediate grade tumours), and high-risk disease (high-grade Ta, T1 tumours or CIS).[40]

Management

The primary goal in managing patients with NMIBC is to completely remove the tumour and control the unpredicted risk of recurrence and progression to muscle invasion or distant metastasis.

TURBT

Transurethral resection of bladder tumour (TURBT) is the first and gold standard treatment option for NMIBC. Transurethral resection of bladder tumour eradicates all visible tumours and provides tissue for pathological analysis and determination of histological type, grade and depth of invasion. The quality of the initial TURBT specimen is extremely important.[41] Complete resection of the tumour, including areas of suspected CIS and abnormal areas in the prostatic urethra and bladder neck, should be performed. Detrusor muscle should be included in the specimen to rule out T2 disease and minimize the risk of under-staging. High-grade tumours lacking detrusor muscle in the initial resection specimen are subsequently associated with residual tumour or muscle invasive disease in up to 50% of cases.[42-44]

Second TURBT

Restaging TUR provides more tissue for pathologic examination and better staging as well as insight into the biology of the disease.[41,45] Herr reported 75% of patients who underwent repeat TURBT in 2 to 6 weeks after initial resection had residual tumour. Forty-four percent of them were found to have T1 or muscle invasive tumour. In patients with T1G3, re-TUR upstaged tumours to T2 disease in 49% of patients if muscularis propria was not present in the specimen compared to 14% upstage if the initial TUR showed benign muscularis propria.[43] Similarly, Zurkirchen and colleagues found that, in a study involving 214 patients with NMIBC undergoing repeat TURBT 4 to 6 weeks after the initial resection, persistent residual tumour was found in 27% of initial Ta and 37% of initial T1 tumours.[46] One recently reported series on re-staging TURBT for T1 bladder tumours demonstrated that residual T1 tumour was present in 15% to 53% of cases, and another 4% to 29% were upstaged to muscle invasion.[41] Re-staging TURBT improves the quality of resection and helps to locally control the disease. After 5 years follow-up of 124 patients, 63% of patients who underwent a second TURBT had tumour-free bladders compared with 40% after a single TURBT. Progression to muscle invasion was observed in only 2 (3%) patients after a re-staging TURBT.[47] Lastly, re-staging TURBT of high-risk NIMBC has also been shown to improve the initial response to BCG therapy.[48] Based on ample evidence, we recommend re-staging TURBT 4 to 6 weeks after the initial resection for all patients with T1 tumours, particularly when there is inadequate or no muscularis propria in the specimen. This will help to remove all residual tumours, improve accuracy of staging, improve response to BCG therapy, reduce the frequency of recurrence, and potentially delay tumour progression.[47]

Fluorescence cystoscopy

White light cystoscopy misses up to 20% of tumours.[49] Since 50% to 70% of superficial bladder cancers recur, efforts concentrated on better detection techniques. Fluorescence

cystoscopy has been shown to reduce recurrence rates after diagnosis.[50,51] This is performed by pre-instilling 5-aminolevulinic acid or hexylaminolaevulinate in the bladder 30 to 60 minutes prior to using ultraviolet/blue light cystoscopy. The substance accumulates in malignant cells, which can be easily identified with blue light cystoscopy. A study by Denzinger and colleagues showed that with fluorescence cystoscopy residual tumour rate was 4.5% compared to 25.2% with white light cystoscopy, and the recurrence free survivals for fluorescence cystoscopy and white light cystoscopy at 8 years were 71% and 45%, respectively.[52] False positive results were associated with previous TURBT, intravesical therapy, or nonspecific inflammation.[53] Recently a phase III multicentre study by Grossman and colleagues compared fluorescence and white light cystoscopy. Fluorescence cystoscopy detected at least 1 more Ta and T1 papillary tumour than the white light cystoscopy in approximately a third of the patients with such tumours.[54] However, whether blue light cystoscopy will affect long-term recurrence-free survival requires further investigation.

Follow-up

Although there are no prospective studies to identify an optimal surveillance protocol, a commonly used follow-up strategy includes cystoscopy and urine cytology every 3 months for 2 years, then every 6 months for the second 2 years, then yearly thereafter. Patients with a primary, solitary, low-grade Ta tumour may have less frequent cystoscopic examination (3 and 9 months, then annually thereafter). Annual upper tract imaging is recommended for patients with intermediate and high-risk NMIBC. Any recurrence resets the clock in the follow up schedule. Random and/or directed biopsies at the first 3 month follow-up visit may be performed for those high-risk patients. Any suspicious or positive cytology requires repeat biopsy. If negative, ureteral washings and radiological upper tract assessment with biopsy of the prostatic urethra should all be performed, as 20% of previously aggressive bladder cancer relapses outside the bladder.[55]

Intravesical therapy

Intravesical therapy can be either chemotherapy or immunotherapy and is either therapeutic (treatment of CIS or residual non-visible tumour), prophylactic (prevention of recurrence and progression of disease) or adjuvant in the immediate postoperative setting.

Chemotherapy

Single immediate postoperative instillation

Most patients with NMIBC will develop recurrences with a significant number recurring 3 months following TURBT. Incomplete TUR or tumour cell implantation post-TUR has been implicated to be responsible for the high recurrences at 3 months. As such, several studies have evaluated the role of a single postoperative intravesical instillation of chemotherapy. The commonly used intravesical chemotherapeutic agents are doxorubicin, epirubicin and mitomycin C (MMC). Sylvester and colleagues performed a meta-analysis of 7 randomized trials (n = 1476) on the outcome of TUR alone versus TUR plus 1 immediate postoperative instillation of intravesical chemotherapy.[56] Over a median follow-up of 3.4 years, patients who received 1 immediate instillation had recurrence rate of 37% compared with 48% of patients who had TUR alone. The benefit was more pronounced for patients with single low-grade papillary tumour compared with patients with multiple tumours. Another meta-analysis from the American Urological Association that focused only on MMC as a single instillation has demonstrated a reduction of the recurrence rate from 50% to 33% at 5 years. The efficacy of the immediate postoperative instillation is within 6 hours from the time of TUR and significantly decreases if given beyond 24 hours.[57] Immediate postoperative instillation of chemotherapeutic agent is recommended for all patients with NMIBC after TURBT. In patients who are planned to be treated with bacillus Calmette-Guerin (BCG), the use of an immediate postoperative instillation of chemotherapy is optional as its benefit in this situation is less clear. Overall, long-term recurrence reduction is similar (about 15%) between the different chemotherapeutic agents.

The evidence does not support differences in efficacy between the various chemotherapeutic agents when used in the postoperative setting; however the toxicity profiles among the agents are different. Mitomycin C is more commonly used in North America due to its decreased toxicity; since the molecule has a high molecular weight, absorption and myelosuppression due to MMC is uncommon. Patients with suspected bladder perforation should not receive an immediate instillation as severe complications have been reported in this setting.[58-60] The efficacy of MMC is dependent on the concentration at which the drug is administered. The dose commonly used is 40 mg in 40 mL of saline or water. Recently, Au and colleagues published a phase III, randomized trial that showed superiority and prolonged median time to recurrence (29.1 vs. 11.8 months, $p = 0.005$) with an "optimized" MMC administration which consisted of a period of dehydration (no fluids for 8 hours prior to treatment), urinary alkalinization, confirmation of complete bladder drainage prior to instillation and a higher MMC concentration (40 mg in 20 mL of water).[61]

Induction and maintenance intravesical chemotherapy

Patients with multiple or recurrent low-grade Ta disease will benefit from induction chemotherapy followed by maintenance therapy. There are no published trials that directly compared induction course of MMC to MMC induction with maintenance therapy; however a current meta-analysis suggested that long-term maintenance therapy enhances the effectiveness of MMC induction in preventing recurrences.[62] Two meta-analysis assessing the impact of intravesical chemotherapy in primary and recurrent NMIBC demonstrated a reduction in recurrences with the use of chemotherapy; the benefit appeared to be more significant when at least 1 to 2 years of maintenance therapy was used.[63,64] Optimal maintenance dose, schedule and duration remain unclear. Importantly, none of the studies incorporated the "optimized" administration of MMC which has been shown to significantly influence the drug's efficacy in a phase III trial. Furthermore, none of the trials directly compared MMC maintenance therapy to a single immediate postoperative instillation. Meta-analysis of 22 randomized, prospective studies evaluating the role of intravesical chemotherapy for NMIBC did not show any benefit in reduction of progression rates compared to TURBT alone.[65] Intravesical gemcitabine and docetaxel have been studied but there is insufficient evidence to support its superiority over the currently used intravesical chemotherapeutic agents.

Immunotherapy

Bacillus Calmette-Guerin is a live attenuated vaccine developed against tuberculosis and was noted to have an antineoplastic effect by Pearl in 1929.[66] Work by Zbar and colleagues,[67] published in 1972, suggested that the anticancer effect of BCG would be optimal under the following conditions: localized tumours, minimal tumour burden and the presence of direct contact between tumour cells and BCG. In the mid-1960s, Coe and Feldman[68] demonstrated that the bladder is able to mount a delayed-type hypersensitivity response to an antigenic challenge and therefore might be an ideal organ for immunotherapy. In 1976, Morales and colleagues[69] projected the conditions of Zbar and colleagues[67] to superficial bladder cancer and treated 9 patients with Ta/T1 tumours. The first controlled trial confirming the efficacy of BCG was reported by Lamm and colleagues in 1980.[70] It has since been shown to be the most effective agent for the treatment of NMIBC, especially CIS.[71] In 1990, BCG was approved by the Food and Drug Administration (FDA) for the treatment of CIS of the bladder. Since then, BCG immunotherapy has emerged as the standard against which all newer therapies are compared.

Efficacy

In patients with NMIBC, BCG reduces the risk of tumour recurrence and progression, increases disease-free interval and prolongs survival. Six controlled trials carried out from 1985 to 1996 showed that BCG decreases recurrence rates from 67% to 29%.[72-78] Six meta-analyses compared BCG with intravesical chemotherapy; all of them except 1 meta-analysis[79] showed superiority of BCG over chemotherapy in terms of decreasing recurrence.[79-84] The effect of BCG on tumour progression has been investigated by Herr and colleagues in 3 randomized trials, each of which demonstrated a significant reduction in disease progression to muscle invasion or metastasis.[74,75,85] In one study, Herr and colleagues evaluated 86 patients with high-risk NMIBC. In patients treated with BCG, the mortality rate decreased from 32% to 14%, and the rate of disease progression decreased from 35% to 28%.[85] Although this advantage diminishes after 15 years follow up,[86] BCG remains the only intravesical agent to have any effect on progression rates in patients with bladder cancer. Sylvester and colleagues carried out a meta-analysis of 24 trials on 4863 patients comparing TUR plus intravesical BCG with TUR alone or TUR plus treatment other than BCG.[80] With a median follow-up of 2.5 years, there was a statistically significant (27%) reduction in the odds of progression for patients who received BCG compared with the control group (9.8% vs. 13.8%, respectively). Lastly, although BCG can treat residual unresected cancer with some reports demonstrating response rates as high as 35% to 84%, BCG should not be a substitute for a complete surgical resection.[87]

Bacillus Calmette-Guerin is the treatment of choice for primary, secondary and concomitant CIS. The average complete response rate to BCG among several series that included more than 1000 patients with CIS was over 70%.[30] In contrast, the average complete response rate to chemotherapy is less than 50% (53% for MMC).[88] In 2005, Sylvester and colleagues reported their analysis of 12 different randomized trials that included patients with CIS. They compared BCG with different intravesical chemotherapy regimens.[89] There was a 68% versus a 48% complete response rate with BCG versus chemotherapy, respectively. The overall disease-free rates over a median follow up of 3.75 years were 51% versus 27% for BCG versus chemotherapy, respectively. Similarly, another meta-analyses of 9 randomized trials involving 700 patients with CIS evaluating BCG versus chemotherapy for the treatment of CIS, also by Sylvester and colleagues, showed complete response rates of 68.1% with BCG and 51.5% with chemotherapy.[84] In the largest study of these meta-analyses, the median duration of complete response with BCG was about 5 years, whereas less than 20% of patients treated with chemotherapy remain disease-free long term.[88] Takenaka and colleagues found

that with 8 weekly instillations of BCG in 185 patients with primary, concomitant or secondary CIS, there was an overall response of 86.6%, a 5-year progression-free survival rate of 78.5%, and a 5-year recurrence-free rate of 66%.[90] Most recurrences and progression occur within the first 5 years.[91] Non-responders of BCG therapy at 6 months have a higher risk of progression (greater than 90%), and these patients should be counselled for an early cystectomy.[92]

In agreement with the Canadian Urological Association guidelines, BCG is the standard of care following TURBT for high-risk NMIBC. Patients with intermediate risk NMIBC are recommended to receive either intravesical induction course with chemotherapy or BCG followed by maintenance. Patients with NMIBC who fail intravesical chemotherapy may benefit from BCG treatment. It is not recommended for muscle-invasive tumours, as up to 77% of such patients will develop systemic disease when treated with BCG.[93]

Treatment schedules

Bacillus Calmette-Guerin is given no earlier than 2 weeks from TURBT to avoid systemic side effects. Treatment schedules have not been established, but most experts agree that 6 weekly inductions is not enough.[94] A second induction has shown additional benefit of about 25% when used for prophylaxis and 30% when used for CIS,[94,95] but this is inferior to the additional 67% response rate seen in patients with CIS who are treated with maintenance therapy. Lamm and colleagues randomized patients with intermediate/high-risk NMIBC to receive 6 weekly inductions with BCG versus 6 weekly inductions followed by maintenance (3 weekly cycles at 3 months and 6 months then every 6 months up to 3 years). Patients receiving maintenance therapy compared to those who did not receive maintenance showed an improved median recurrence-free (77 vs. 35.7 months) and progression-free survival.[96] In a meta-analysis of 24 trials with 4863 patients, Sylvester and colleagues demonstrated the superiority of BCG over intravesical chemotherapy; however the significant impact of BCG on disease progression was significant only in the trials that used maintenance therapy ($p = 0.00004$, odds ratio [OR] 0.63).[80] Similarly, Bohle and colleagues had similar conclusions in their meta-analysis of 9 trials where 1328 patients with NMIBC treated with adjuvant MMC compared to 1421 patients treated with adjuvant BCG.[81,83] With a median follow-up of 26 months progression rates with adjuvant MMC compared with adjuvant BCG were 46.4% and 9.4% versus 38.6% and 7.7%, respectively ($p = 0.08$, OR 0.77). When only including trials using maintenance, the difference in progression rates became significant ($p = 0.02$, OR 0.66).

Collectively, BCG has shown to be better than intravesical chemotherapy in reducing recurrence, but undoubtedly superior in reducing progression. We recommend BCG induction and maintenance for intermediate- and high-risk patients according to the Southwest Oncology Group study (SWOG) 6+3 protocol for 3 years. However, BCG treatment is limited by its side effects. In the SWOG trial where patients were randomized to BCG maintenance therapy, 5% of patients stopped during induction, 20% stopped during maintenance and only 16% completed the 3-year maintenance schedule.[96] Lower-urinary-tract symptoms occur in up to 90% of patients and are more common after the third dose. These side effects may be treated symptomatically with anticholinergics, acetaminophen or phenazopyridine hydrochloride. In patients with increasing irritative symptoms, the BCG dose can be reduced. In a recent randomized prospective trial with a median follow-up of 61 months, patients treated with the reduced dose of BCG (27 mg) had a significant reduction in treatment toxicity without significant difference in efficacy (recurrence or progression) compared to those treated with the standard dose (81 mg).[97] Another study done by Ojea and colleagues compared the recurrence rate and toxicity profile of three groups of patients.[98] Patients were receiving either 30 mg MMC, one-third the standard BCG dose (27 mg), or one-sixth the standard BCG dose. The lowest recurrence rate was in the patient group receiving one-third the BCG dose, and toxicity was less in the one-third and one-sixth BCG dose groups compared to the standard BCG dose, but was still higher than the MMC group. Other studies reported similar findings and demonstrated significant reduction in side effects with reducing BCG dose without affecting overall efficacy.[76,99,100] The only exception to this may be when treating BCG-naïve patients who have no previous exposure to the mycobacterium or have not been vaccinated with BCG. Morales and colleagues have shown that dose reduction is associated with decreased efficacy in North American patients and they have hypothesized that a lower immune response may be induced in patients who do not have previous exposure or inoculation with tuberculosis.[101] A recent study by Colombel and colleagues showed that administration of ofloxacin with BCG-increased tolerance, decreased the incidence of moderate to severe side effects and improved compliance.[102]

BCG failure

BCG failure is defined as the presence of high-grade NMIBC at 6 months from time of TURBT (or at 3 months if the initial tumour is T1G3/T1 high grade) or any worsening of the disease (higher grade, stage, number of recurrences or appearance of CIS) while on BCG therapy despite initial response to BCG.[103] These patients should be strongly considered for radical cystectomy as disease-specific survival of patients with BCG failure who undergo early cystectomy before progression to muscle invasion is 80% to 90% at 5 years and

falls to 55% once the disease progresses to muscle invasion.[104-106] Herr and colleagues compared outcome of patients with NMIBC who received a radical cystectomy due to recurrence of disease within 2 years from initial BCG therapy with outcome of patients who received radical surgery after 2 years; early radical cystectomy was associated with significantly improved survival in patients with non-muscle invasive recurrence as well as muscle-invasive recurrence. Factors predicting treatment failure with increased risk of progression to muscle invasion include large multifocal high-grade Ta, T1 tumour with concomitant CIS, presence of lymphovascular invasion, prostatic urethral involvement or non-responders at 6 months from TURBT.[107,108] Although cystectomy is a major procedure with documented morbidity, with improved surgical technique and the existence of large oncology specialized centres these complications are significantly minimized. In addition, orthotopic reconstructive surgery has influenced urologists and patients towards an earlier cystectomy with reduced reluctance to such surgery.[109-111]

For patients who refuse surgery or who are poor surgical candidates other treatment options with reasonable results have been tested. When intravesical chemotherapy fails, switching to BCG has been shown to be successful. In contrast, chemotherapy is ineffective in achieving a disease-free state in BCG failures.[112] In patients with NMIBC treated with an induction course of BCG (without maintenance) and then later developed recurrence of disease, a second induction course may achieve up to 30% to 50% response rates.[95,113] Beyond 2 induction courses with BCG is not recommended, as there is a 7% actuarial risk of progression with each additional course.[114] Valrubicin is approved by the FDA for the treatment of BCG-refractory CIS in patients who either refuse or cannot undergo radical cystectomy.[115,116] Gemcitabine has initially been shown to have promising results in the context of BCG failure.[117-119] In patients with BCG-refractory disease, gemcitabine had a 75% recurrence-free rate in patients with intermediate risk NMIBC and 44% in those with high-risk disease. However, complete response is poor after longer follow-up; Dalbagni and colleagues showed that 2 out of 30 patients maintained complete response at 2 years.[120]

Interferon-alpha 2b has been shown to be inferior to BCG and chemotherapy when used alone as the primary therapy for NMIBC.[121,122] However, the combination of interferon and BCG yields better efficacy. In a recent large multicentre phase II trial, 467 BCG-failure patients received low-dose BCG and interferon alpha 2b and another 536 BCG-naïve patients received standard dose BCG with interferon alpha 2b.[123] After a median follow-up of 24 months, 45% and 59% of patients in the BCG-failure and BCG-naïve groups were disease-free. In addition, the combination therapy in the BCG-failure group was associated with reduced toxicity by 50%.[124]

Device-assisted therapy

Improving the delivery of the intravesical agent using device-assisted methods may improve efficacy. Thermotherapy works by inducing bladder wall hyperthermia via an energy-delivering unit in the tip of a special catheter; the bladder wall is warmed up to 42ºC to 43ºC. Thermotherapy was studied in combination with intravesical instillations of MMC (thermochemotherapy).[61,125] Van der Heijden and colleagues reported on the use of thermochemotherapy in 90 patients with intermediate- and high-risk NMIBC and showed recurrence rates of 14.3% and 24.6% after 1 and 2 years follow-up, respectively. In patients who failed BCG, thermochemotherapy was associated with reduced recurrence rates.[126] Witjes and colleagues studied 57 patients with CIS treated with 6 to 8 weekly and 4 to 6 monthly sessions of MMC thermochemotherapy and observed a 94% complete response.[127] Although the results are promising with thermochemotherapy, longer follow-up and better assessment of toxicity are needed before embarking on such therapy.

Di Stasi and colleagues have studied the impact of electromotive MMC. They compared patients treated with MMC only, MMC combined with electromotive delivery, and BCG in 108 high-risk patients.[128] Complete response rates were 31%, 58% and 64%, respectively after 6 months follow-up. Side effects with electromotive delivery were higher than passive MMC delivery but less than BCG. In another study, Di Stasi randomized 212 patients with stage T1 bladder cancer into 2 groups;[129] one group was receiving BCG alone and the other group receiving sequential BCG and electromotive MMC. Both groups received induction and maintenance therapy. At a mean follow-up of 88 months, patients treated with BCG plus electromotive MMC were associated with disease-free survival of 69 months versus 21 months in patients treated with BCG alone. Moreover, there was a lower recurrence rate (41.9% vs. 57.9%), lower progression rate (9.3% vs. 21.9%) and lower disease-specific mortality (5.6% vs. 16.2%) with the combination therapy. These studies are exciting and warrant further validation in other centres to evaluate such combination therapy in this select patient population.

Conclusion

Non-muscle invasive bladder cancer remains a significant urologic oncologic challenge and a significant economic burden on the health-care system. Repeat TURBT is gaining widespread importance in the evaluation of high-risk NMIBC. Bacillus Calmette-Guerin remains the standard therapy against which all new intravesical therapies are compared. Early cystectomy should be considered in patients who fail BCG. New investigational methods, such as fluorescence cystoscopy and novel intravesical drug combinations, are

under investigation to optimize the outcome and management of patients with NMIBC.

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References

1. Jemal A, Siegel R, Ward E, and colleagues. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43-66.
2. Kirkali Z, Chan T, Manoharan M, and colleagues. Bladder cancer: epidemiology, staging and grading, and diagnosis. *Urology* 2005;66:4-34.
3. Chow WH, Lindblad P, Gridley G, and colleagues. Risk of urinary tract cancers following kidney or ureter stones. *J Natl Cancer Inst* 1997;89:1453-7.
4. Kantor AF, Hartge P, Hoover RN, and colleagues. Urinary tract infection and risk of bladder cancer. *Am J Epidemiol* 1984;119:510-5.
5. Fioriti D, Pietropaolo V, Dal Forno S, and colleagues. Urothelial bladder carcinoma and viral infections: different association with human polyomaviruses and papillomaviruses. *Int J Immunopathol Pharmacol* 2003;16:283-8.
6. Mostafa MH, Sheweita SA, O'Connor PJ. Relationship between schistosomiasis and bladder cancer. *Clin Microbiol Rev* 1999;12:97-111.
7. Cannon J, Linke CA, Cos LR. Cyclophosphamide-associated carcinoma of urothelium: modalities for prevention. *Urology* 1991;38:413-6.
8. Kaldor JM, Day NE, Kittelmann B, and colleagues. Bladder tumours following chemotherapy and radiotherapy for ovarian cancer: a case-control study. *Int J Cancer* 1995;63:1-6.
9. Clayson DB. Specific aromatic amines as occupational bladder carcinogens. *Natl Cancer Inst Monogr* 1981:15-9.
10. Droller MJ. Alterations of the p53 gene in occupational bladder cancer in workers exposed to aromatic amines. *J Urol* 1998;160:618.
11. Piper JM, Tonascia J, Matanoski GM. Heavy phenacetin use and bladder cancer in women aged 20 to 49 years. *N Engl J Med* 1985;313:292-5.
12. Heney NM. Natural history of superficial bladder cancer. Prognostic features and long-term disease course. *Urol Clin North Am* 1992;19:429-433.
13. Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R. The health economics of bladder cancer: a comprehensive review of the published literature. *Pharmacoeconomics* 2003;21:1315-30.
14. Zlotta AR, van Vooren JP, Huygen K, and colleagues. What is the optimal regimen for BCG intravesical therapy? Are six weekly instillations necessary? *Eur Urol* 2000;37:470-7.
15. Soloway MS. Overview of treatment of superficial bladder cancer. *Urology* 1985;26:18-26.
16. Heney NM, Ahmed S, Flanagan MJ, and colleagues. Superficial bladder cancer: progression and recurrence. *J Urol* 1983;130:1083-6.
17. Jakse G, Loidl W, Seeber G, and colleagues. Stage T1, grade 3 transitional cell carcinoma of the bladder: an unfavorable tumour? *J Urol* 1987;137:39-43.
18. Holmang S, Hedelin H, Anderstrom C, and colleagues. Recurrence and progression in low grade papillary urothelial tumours. *J Urol* 1999;162:702-7.
19. Althausen AF, Prout GR Jr, Daly JJ. Non-invasive papillary carcinoma of the bladder associated with carcinoma in situ. *J Urol* 1976;116:575-80.
20. Holmang S, Hedelin H, Anderstrom C, and colleagues. The relationship among multiple recurrences, progression and prognosis of patients with stages Ta and T1 transitional cell cancer of the bladder followed for at least 20 years. *J Urol* 1995;153:1823-6; discussion 1826-7.
21. Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, and colleagues. Multivariate analysis of the prognostic factors of primary superficial bladder cancer. *J Urol* 2000;163:73-8.
22. Flamm J, Havelec L. Factors affecting survival in primary superficial bladder cancer. *Eur Urol* 1990;17:113-8.
23. Kiemeney LA, Witjes JA, Heijbroek RP, Verbeek AL, Debruyne FM. Predictability of recurrent and progressive disease in individual patients with primary superficial bladder cancer. *J Urol* 1993;150:60-4.
24. Lutzeyer W, Rubben H, Dahm H. Prognostic parameters in superficial bladder cancer: an analysis of 315 cases. *J Urol* 1982;127:250-2.
25. Pauwels RP, Schapers RF, Smeets AW, and colleagues. Grading in superficial bladder cancer. (1). Morphological criteria. *Br J Urol* 1988;61:129-34.
26. Abel PD, Hall RR, Williams G. Should pT1 transitional cell cancers of the bladder still be classified as superficial? *Br J Urol* 1988;62:235-9.
27. Herr HW. Tumour progression and survival in patients with T1G3 bladder tumours: 15-year outcome. *Br J Urol* 1997;80:762-5.
28. Kiemeney LA, Witjes JA, Heijbroek RP, and colleagues. Dysplasia in normal-looking urothelium increases the risk of tumour progression in primary superficial bladder cancer. *Eur J Cancer* 1994;30A:1621-5.
29. Riddle PR, Chisholm GD, Trott PA, and colleagues. Flat carcinoma in Situ of bladder. Br J Urol 1975;47:829-33.
30. Lamm DL. Carcinoma in situ. *Urol Clin North Am* 1992;19:499-508.
31. Jakse G, Hall R, Bono A, and colleagues. Intravesical BCG in patients with carcinoma in situ of the urinary bladder: long-term results of EORTC GU Group phase II protocol 30861. *Eur Urol* 2001;40:144-50.
32. Parmar MK, Freedman LS, Hargreave TB, and colleagues. Prognostic factors for recurrence and followup policies in the treatment of superficial bladder cancer: report from the British Medical Research Council Subgroup on Superficial Bladder Cancer (Urological Cancer Working Party). *J Urol* 1989;142:284-8.
33. Ali-El-Dein B, Sarhan O, Hinev A, and colleagues. Superficial bladder tumours: analysis of prognostic factors and construction of a predictive index. *BJU Int* 2003;92:393-9.
34. Herr HW. Intravesical BCG: current results, natural history and implications for urothelial cancer prevention. *J Cell Biochem Suppl* 1992;16I:112-9.
35. Bostwick DG. Natural history of early bladder cancer. *J Cell Biochem Suppl* 1992;16I:31-8.
36. Fitzpatrick JM, West AB, Butler MR, and colleagues. Superficial bladder tumours (stage pTa, grades 1 and 2): the importance of recurrence pattern following initial resection. *J Urol* 1986;135:920-2.
37. Reuter VE. Pathology of bladder cancer: assessment of prognostic variables and response to therapy. *Semin Oncol* 1990;17:524-32.
38. Lapham RL, Grignon D, Ro JY. Pathologic prognostic parameters in bladder urothelial biopsy, transurethral resection, and cystectomy specimens. *Semin Diagn Pathol* 1997;14:109-22.
39. Kamat AM, Gee JR, Dinney CP, and colleagues. The case for early cystectomy in the treatment of non-muscle invasive micropapillary bladder carcinoma. *J Urol* 2006;175:881-5.
40. Sylvester RJ, van der Meijden AP, Oosterlinck W, and colleagues. 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;49:466-75; discussion 475-7.
41. Herr HW. Surgical factors in the treatment of superficial and invasive bladder cancer. *Urol Clin North Am* 2005;32:157-64.
42. Freeman JA, Esrig D, Stein JP, and colleagues. Radical cystectomy for high risk patients with superficial bladder cancer in the era of orthotopic urinary reconstruction. *Cancer* 1995;76:833-9.
43. Herr HW. The value of a second transurethral resection in evaluating patients with bladder tumours. *J Urol* 1999;162:74-6.
44. Schips L, Augustin H, Zigeuner RE, and colleagues. Is repeated transurethral resection justified in patients with newly diagnosed superficial bladder cancer? *Urology* 2002;59:220-3.
45. Herr HW, Donat SM. A re-staging transurethral resection predicts early progression of superficial bladder cancer. *BJU Int* 2006;97:1194-8.
46. Zurkirchen MA, Sulser T, Gaspert A, and colleagues. Second transurethral resection of superficial transitional cell carcinoma of the bladder: a must even for experienced urologists. *Urol Int* 2004;72:99-102.
47. Grimm MO, Steinhoff C, Simon X, and colleagues. Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. *J Urol* 2003;170:433-7.
48. Herr HW. Restaging transurethral resection of high risk superficial bladder cancer improves the initial response to bacillus Calmette-Guerin therapy. J Urol 2005;174:2134-7.
49. Jocham D, Witjes F, Wagner S, and colleagues. Improved detection and treatment of bladder cancer using hexaminolevulinate imaging: a prospective, phase III multicenter study. *J Urol* 2005;174:862-6; discussion 866.
50. Riedl CR, Daniltchenko D, Koenig F, and colleagues. Fluorescence endoscopy with 5-aminolevulinic acid reduces early recurrence rate in superficial bladder cancer. *J Urol* 2001;165:1121-3.
51. Babjuk M, Soukup V, Petrik R, Jirsa M, Dvoracek J. 5-aminolaevulinic acid-induced fluorescence cystoscopy during transurethral resection reduces the risk of recurrence in stage Ta/T1 bladder cancer. *BJU Int* 2005;96:798-802.
52. Denzinger S, Burger M, Walter B, and colleagues. Clinically relevant reduction in risk of recurrence of superficial bladder cancer using 5-aminolevulinic acid-induced fluorescence diagnosis: 8-year results of prospective randomized study. *Urology* 2007;69:675-9.
53. Filbeck T, Roessler W, Knuechel R, and colleagues. 5-aminolevulinic acid-induced fluorescence endoscopy applied at secondary transurethral resection after conventional resection of primary superficial bladder tumours. *Urology* 1999;53:77-81.

54. Grossman HB, Gomella L, Fradet Y, and colleagues. A phase III, multicenter comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of superficial papillary lesions in patients with bladder cancer. *J Urol* 2007;178:62-7.
55. Schwalb MD, Herr HW, Sogani PC, and colleagues. Positive urinary cytology following a complete response to intravesical bacillus Calmette-Guerin therapy: pattern of recurrence. *J Urol* 1994;152:382-7.
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, quiz 2435.
57. Kaasinen E, Rintala E, Hellstrom P, and colleagues. Factors explaining recurrence in patients undergoing chemoimmunotherapy regimens for frequently recurring superficial bladder carcinoma. *Eur Urol* 2002;42:167-74.
58. Nieuwenhuijzen JA, Bex A, Horenblas S. Unusual complication after immediate postoperative intravesical mitomycin C instillation. *Eur Urol* 2003;43:711-2.
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;46:336-8.
60. Racioppi M, Porreca A, Foschi N, and colleagues. Bladder perforation: a potential risk of early endovesical chemotherapy with mitomycin C. *Urol Int* 2005;75:373-5.
61. Au JL, Badalament RA, Wientjes MG, and colleagues. Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase III trial. *J Natl Cancer Inst* 2001;93:597-604.
62. Hall MC, Chang SS, Dalbagni G, and colleagues. Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. *J Urol* 2007;178:2314-30.
63. Huncharek M, Geschwind JF, Witherspoon B, and colleagues. Intravesical chemotherapy prophylaxis in primary superficial bladder cancer: a meta-analysis of 3703 patients from 11 randomized trials. *J Clin Epidemiol* 2000;53:676-80.
64. Huncharek M, McGarry R, Kupelnick B. Impact of intravesical chemotherapy on recurrence rate of recurrent superficial transitional cell carcinoma of the bladder: results of a meta-analysis. *Anticancer Res* 2001;21:765-9.
65. Lamm DL, Riggs DR, Traynelis CL, and colleagues. Apparent failure of current intravesical chemotherapy prophylaxis to influence the long-term course of superficial transitional cell carcinoma of the bladder. *J Urol* 1995;153:1444-50.
66. Pearl R. Cancer and tuberculosis. *Am J Hyg* 1929;9:97.
67. Zbar B, Tanaka T. Immunotherapy of cancer: regression of tumours after intralesional injection of living Mycobacterium bovis. *Science* 1971;172:271-3.
68. Coe JE, Feldman JD. Extracutaneous delayed hypersensitivity, particularly in the guinea-pig bladder. *Immunology* 1966;10:127-36.
69. Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumours. *J Urol* 1976;116:180-3.
70. Lamm DL, Thor DE, Harris SC, and colleagues. Bacillus Calmette-Guerin immunotherapy of superficial bladder cancer. *J Urol* 1980;124:38-40.
71. Sylvester RJ. Natural history, recurrence, and progression in superficial bladder cancer. *ScientificWorldJournal* 2006;6:2617-25.
72. Lamm DL. Bacillus Calmette-Guerin immunotherapy for bladder cancer. *J Urol* 1985;134:40-7.
73. Nseyo UO, Lamm DL. Immunotherapy of bladder cancer. *Semin Surg Oncol* 1997;13:342-9.
74. Herr HW, Pinsky CM, Whitmore WF Jr, and colleagues. Experience with intravesical bacillus Calmette-Guerin therapy of superficial bladder tumours. *Urology* 1985;25:119-23.
75. Herr HW. Transurethral resection and intravesical therapy of superficial bladder tumours. *Urol Clin North Am* 1991;18:525-8.
76. Pagano F, Bassi P, Milani C, and colleagues. A low dose bacillus Calmette-Guerin regimen in superficial bladder cancer therapy: is it effective? *J Urol* 1991;146:32-5.
77. Melekos MD, Chionis H, Pantazakos A, and colleagues. Intravesical bacillus Calmette-Guerin immunoprophylaxis of superficial bladder cancer: results of a controlled prospective trial with modified treatment schedule. *J Urol* 1993;149:744-8.
78. Krege S, Giani G, Meyer R, and colleagues. A randomized multicenter trial of adjuvant therapy in superficial bladder cancer: transurethral resection only versus transurethral resection plus mitomycin C versus transurethral resection plus bacillus Calmette-Guerin. Participating Clinics. *J Urol* 1996;156:962-6.
79. Huncharek M, Kupelnick B. Impact of intravesical chemotherapy versus BCG immunotherapy on recurrence of superficial transitional cell carcinoma of the bladder: metaanalytic reevaluation. *Am J Clin Oncol* 2003;26:402-7.
80. Sylvester RJ, van der MA, 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.
81. Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. *J Urol* 2003;169:90-5.
82. Shelley MD, Wilt TJ, Court J, and colleagues. Intravesical bacillus Calmette-Guerin 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.
83. Bohle A, Bock PR. Intravesical bacille Calmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumour progression. *Urology* 2004;63:682-6; discussion 686-7.
84. Sylvester RJ, van der Meijden AP, Witjes JA, and colleagues. Bacillus Calmette-Guerin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials. *J Urol* 2005;174:86-91; discussion 91-2.
85. Herr HW, Laudone VP, Badalament RA, and colleagues. Bacillus Calmette-Guerin therapy alters the progression of superficial bladder cancer. *J Clin Oncol* 1988;6:1450-5.
86. Cookson MS, Herr HW, Zhang ZF, and colleagues. The treated natural history of high risk superficial bladder cancer: 15-year outcome. *J Urol* 1997;158:62-7.
87. Coplen DE, Marcus MD, Myers JA, and colleagues. Long-term followup of patients treated with 1 or 2, 6-week courses of intravesical bacillus Calmette-Guerin: analysis of possible predictors of response free of tumour. *J Urol* 1990;144:652-7.
88. Lamm DL. Long-term results of intravesical therapy for superficial bladder cancer. *Urol Clin North Am* 1992;19:573-80.
89. Sylvester RJ, van der Meijden A, Witjes JA, and colleagues. High-grade Ta urothelial carcinoma and carcinoma in situ of the bladder. *Urology* 2005;66:90-107.
90. Takenaka A, Yamada Y, Miyake H, and colleagues. Clinical outcomes of bacillus Calmette-Guerin instillation therapy for carcinoma in situ of urinary bladder. *Int J Urol* 2008;15:309-13.
91. Herr HW, Wartinger DD, Fair WR, and colleagues. Bacillus Calmette-Guerin therapy for superficial bladder cancer: a 10-year followup. *J Urol* 1992;147:1020-3.
92. Herr HW, Badalament RA, Amato DA, and colleagues. Superficial bladder cancer treated with bacillus Calmette-Guerin: a multivariate analysis of factors affecting tumour progression. *J Urol* 1989;141:22-9.
93. Rosenbaum RS, Park MC, Fleischmann J. Intravesical bacille Calmette-Guerin therapy for muscle invasive bladder cancer. *Urology* 1996;47:208-11.
94. Kavoussi LR, Torrence RJ, Gillen DP, and colleagues. Results of 6 weekly intravesical bacillus Calmette-Guerin instillations on the treatment of superficial bladder tumours. *J Urol* 1988;139:935-40.
95. Bretton PR, Herr HW, Kimmel M, and colleagues. The response of patients with superficial bladder cancer to a second course of intravesical bacillus Calmette-Guerin. *J Urol* 1990;143:710-2; discussion 712-3.
96. Lamm DL, Blumenstein BA, Crissman JD, and colleagues. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J Urol* 2000;163:1124-9.
97. Martinez-Pineiro JA, Martinez-Pineiro L, Solsona E, and colleagues. Has a 3-fold decreased dose of bacillus Calmette-Guerin the same efficacy against recurrences and progression of T1G3 and Tis bladder tumours than the standard dose? Results of a prospective randomized trial. *J Urol* 2005;174:1242-7.
98. Ojea A, Nogueira JL, Solsona E, and colleagues. 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.
99. Losa A, Hurle R, Lembo A. Low dose bacillus Calmette-Guerin for carcinoma in situ of the bladder: long-term results. *J Urol* 2000;163:68-71; discussion 71-2.
100. Mack D, Frick J. Five-year results of a phase II study with low-dose bacille Calmette-Guerin therapy in high-risk superficial bladder cancer. *Urology* 1995;45:958-61.
101. Morales A, Nickel JC, Wilson JW. Dose-response of bacillus Calmette-Guerin in the treatment of superficial bladder cancer. *J Urol* 1992;147:1256-8.
102. Colombel M, Saint F, Chopin D, and colleagues. The effect of ofloxacin on bacillus calmette-guerin induced toxicity in patients with superficial bladder cancer: results of a randomized, prospective, double-blind, placebo controlled, multicenter study. *J Urol* 2006;176:935-9.
103. Herr HW, Dalbagni G. Defining bacillus Calmette-Guerin refractory superficial bladder tumours. *J Urol* 2003;169:1706-8.
104. Witjes JA. Management of BCG failures in superficial bladder cancer: a review. *Eur Urol* 2006;49:790-7.
105. Stein JP, Lieskovsky G, Cote R, and colleagues. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001;19:666-75.
106. Kiemeney LA, Witjes JA, Verbeek AL, and colleagues. The clinical epidemiology of superficial bladder cancer. Dutch South-East Cooperative Urological Group. *Br J Cancer* 1993;67:806-12.
107. Huguet J, Crego M, Sabate S, and colleagues. Cystectomy in patients with high risk superficial bladder tumours who fail intravesical BCG therapy: pre-cystectomy prostate involvement as a prognostic factor. *Eur Urol* 2005;48:53-9; discussion 59.
108. Kurth KH, Denis L, Bouffioux C, and colleagues. Factors affecting recurrence and progression in superficial bladder tumours. *Eur J Cancer* 1995;31A:1840-6.

109. Parekh DJ, Gilbert WB, Koch MO, and colleagues. Continent urinary reconstruction versus ileal conduit: a contemporary single-institution comparison of perioperative morbidity and mortality. *Urology* 2000;55:852-5.
110. Parekh DJ, Clark T, O'Connor J, and colleagues. Orthotopic neobladder following radical cystectomy in patients with high perioperative risk and co-morbid medical conditions. *J Urol* 2002;168:2454-6.
111. Hautmann RE, Paiss T. Does the option of the ileal neobladder stimulate patient and physician decision toward earlier cystectomy? *J Urol* 1998;159:1845-50.
112. Malmstrom PU, Wijkstrom H, Lundholm C, and colleagues. 5-year followup of a randomized prospective study comparing mitomycin C and bacillus Calmette-Guerin in patients with superficial bladder carcinoma. Swedish-Norwegian Bladder Cancer Study Group. *J Urol* 1999;161:1124-7.
113. Bui TT, Schellhammer PF. Additional bacillus Calmette-Guerin therapy for recurrent transitional cell carcinoma after an initial complete response. *Urology* 1997;49:687-90; discussion 690-1.
114. Catalona WJ, Hudson MA, Gillen DP, and colleagues. Risks and benefits of repeated courses of intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. *J Urol* 1987;137:220-4.
115. Steinberg G, Bahnson R, Brosman S, and colleagues. Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. The Valrubicin Study Group. *J Urol* 2000;163:761-7.
116. Newling DW, Hetherington J, Sundaram SK, and colleagues. The use of valrubicin for the chemoresection of superficial bladder cancer — a marker lesion study. *Eur Urol* 2001;39:643-7.
117. Dalbagni G, Russo P, Sheinfeld J, and colleagues. Phase I trial of intravesical gemcitabine in bacillus Calmette-Guerin-refractory transitional-cell carcinoma of the bladder. *J Clin Oncol* 2002;20:3193-8.
118. Laufer M, Ramalingam S, Schoenberg MP, and colleagues. Intravesical gemcitabine therapy for superficial transitional cell carcinoma of the bladder: a phase I and pharmacokinetic study. *J Clin Oncol* 2003;21:697-703.
119. Witjes JA, van der Heijden AG, Vriesema JL, and colleagues. Intravesical gemcitabine: a phase 1 and pharmacokinetic study. *Eur Urol* 2004;45:182-6.
120. Dalbagni G, Russo P, Bochner B, and colleagues. Phase II trial of intravesical gemcitabine in bacille Calmette-Guerin-refractory transitional cell carcinoma of the bladder. *J Clin Oncol* 2006;24:2729-34.
121. Trkova M, Babjuk M, Duskova J, and colleagues. Analysis of genetic events in 17p13 and 9p21 regions supports predominant monoclonal origin of multifocal and recurrent bladder cancer. *Cancer Lett* 2006;242:68-76.
122. Belldegrun AS, Franklin JR, O'Donnell MA, and colleagues. Superficial bladder cancer: the role of interferon-alpha. *J Urol* 1998;159:1793-801.
123. Joudi FN, Smith BJ, O'Donnell MA. Final results from a national multicenter phase II trial of combination bacillus Calmette-Guerin plus interferon alpha-2B for reducing recurrence of superficial bladder cancer. *Urol Oncol* 2006;24:344-8.
124. O'Donnell MA, Lilli K, Leopold C. Interim results from a national multicenter phase II trial of combination bacillus Calmette-Guerin plus interferon alfa-2b for superficial bladder cancer. *J Urol* 2004;172:888-93.
125. Colombo R, Da Pozzo LF, Lev A, and colleagues. Neoadjuvant combined microwave induced local hyperthermia and topical chemotherapy versus chemotherapy alone for superficial bladder cancer. *J Urol* 1996;155:1227-32.
126. van der Heijden AG, Kiemeney LA, Gofrit ON, and colleagues. 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; discussion 71-2.
127. Witjes JA, Hendricksen K. Intravesical pharmacotherapy for non-muscle-invasive bladder cancer: a critical analysis of currently available drugs, treatment schedules, and long-term results. *Eur Urol* 2008;53:45-52.
128. Di Stasi SM, Giannantoni A, Stephen RL, and colleagues. Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer: a prospective randomized study. *J Urol* 2003;170:777-82.
129. Di Stasi SM, Giannantoni A, Giurioli A, and colleagues. Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. *Lancet Oncol* 2006;7:43-51.

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