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Superficial Bladder Cancer: Diagnosis, Surveillance and Treatment

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Abstract Approximately 70% of all bladder cancers are superficial at the time of presentation. Superficial bladder cancer includes tumors confined to the urothelium (clinical stage Ta) or lamina propria (stage T1) and flat carcinoma *in situ* (stage Tis). Because the biological behavior of bladder neoplasms is variable, several important prognostic factors must be addressed. Multivariate analyses have shown that factors predictive of tumor recurrence and tumor progression include multifocal tumors, high grade tumors, T1 tumors and positive urinary cytology after transurethral resection (TUR). The patient with superficial bladder cancer should be monitored via endoscopy supplemented by urinary cytology, using either voided or bladder irrigation specimens and urinalysis. Frequent intravenous urography is not required, even in high grade tumors, as long as the clinical and pathologic studies remain negative and the patient is asymptomatic.

The "gold standard" of treatment for superficial bladder carcinoma is TUR of the entire tumor. Despite TUR, new tumors will occur in approximately 50% of all patients; those at highest risk for tumor recurrence and progression require adjuvant intravesical therapy after TUR. A variety of drugs are used as intravesical therapy, including thiotepa, mitomycin C, doxorubicin hydrochloride, Bacillus Calmette-Guerin (BCG), epirubicin, and interferon. Although associated with the most toxicity, BCG appears to be the most efficacious agent in increasing the time to recurrence and progression and in reducing the recurrence rate.

Key words: intravesical therapy, superficial bladder cancer, transitional cell carcinoma

Tumor confined to the urothelium (stage Ta) or lamina propria (stage T1) and flat carcinoma *in situ* (stage Tis) are described as superficial bladder cancer. Approximately 70% of all bladder cancers are superficial at the time of presentation. Although "recurrence" can occur following initial therapy, muscle invasive tumors do not subsequently develop in 80% of these patients. Because the biological behavior of superficial bladder cancer is variable, it is important to identify tumors that are likely to relapse and to predict which will become invasive or metastatic.

PROGNOSTIC FACTORS

Multivariate analyses have shown that factors predictive of recurrence include history of superficial tumors, high tumor grade, T1 tumors, and positive urinary cytology after transurethral resection (TUR). The European Organization for Research and Treatment of Cancer (EORTC), Genitourinary Group, performed a large randomized prospective study that compared the efficacy of prophylactic intravesical chemotherapy with a control group [1]. Tumor grade was a prognostic factor in 371 evaluable patients. The recurrence rate per year was 0.3 for grade I lesions as compared to 0.66 for grade III tumors. The recurrence rate of those with grade II tumors or grade III lesions was 0.60. Only 2.2% of 199 patients with a stage Ta lesion and 13% with an initial T1 lesion progressed to stage T2 or greater. Similarly, the National Bladder Cancer Group's [2] data show that, in an average follow-up of a little over three years, only 4% of those with stage Ta tumors progressed, compared to 30% of those with T1 lesions. Muller *et al.* [3] have shown that patients with positive urinary cytology following tumor resection are at high risk for recurrence and progression. Most lesions recur at the same stage and grade within six to twelve months, but between 5% and 30% of all

cases will progress. Prognostic factors are essential to determine the surveillance and treatment of patients with superficial bladder cancer.

INITIAL EVALUATION OF PATIENTS WITH SUPERFICIAL BLADDER CANCER

Superficial bladder neoplasia must be considered in any patient with hematuria (gross or microscopic) or persistent irritative voiding symptoms. This is particularly true of groups likely to exhibit a higher incidence of transitional cell carcinoma (TCC), *i.e.*, males of age >50 or cigarette smokers. In such cases, a random voided urine specimen for cytology should be obtained prior to endoscopy. Cytology minimizes the risk of missing a high grade tumor. Urinary specimens are commonly obtained in three ways. Random voided urine and "cystoscopic" urine (obtained when the instrument is first introduced into the bladder) yield cells of similar preservation. Bladder washing specimens usually contain more and better-preserved urothelial cells than voided urine. In a recent prospective study, Matzkin *et al.* [4] compared the diagnostic outcome of paired voided urine cytology and bladder washings and found bladder washings superior. Bladder washing should be performed whenever instrumentation is otherwise required in patients suspected of harboring a bladder neoplasm.

A baseline intravenous urogram should be obtained in any patient undergoing a workup for TCC. Patients whose initial presentation of TCC is in the bladder have a 3% risk of developing an upper tract tumor. This risk is much higher in patients undergoing cystectomy for invasive disease or multifocal Tis.

A thorough physical and endoscopic examination requires anesthesia. The first procedure is a bimanual examination, which can detect any large, deeply invasive cancer as well as provide the patient with a thorough pelvic examination. After introduction of the cystoscope, the clinician collects the urine and combines it with a saline bladder washing. The endoscopic examination of the bladder begins with a 70 degree lens. The 0, 5, or 12 degree lens is used to review the trigone and to examine the entire urethra, with particular attention directed to the prostatic urethra. As part of the initial endoscopic session all visible tumor should be removed, including some muscle if there is any possibility that the neoplasm has extended beyond the basement membrane of the mucosa. Any areas suspected of premalignant lesions or Tis should also be biopsied and their location indicated on the pathology requisition. Mucosal biopsies are also indicated if cytology reveals the presence of a high grade tumor, but endoscopy suggests only papillary tumors of apparent low grade. Random mucosal bladder biopsies are necessary when considering a partial cystectomy.

When there is an apparent high grade tumor within the bladder, including Tis, the prostatic urothelium should be sampled by TUR biopsy. Indications for prostatic urethral biopsy at subsequent endoscopic examinations include (1) presence of high grade tumor cells in a cytological specimen but only low grade tumor in the histological material obtained during endoscopy; and (2) patients who are candidates for a continent diversion to the urethra.

SURVEILLANCE

The patient who has had a superficial bladder neoplasm should be monitored with endoscopy supplemented by urinary cytology using either voided or bladder irrigation specimens. Routine urinalysis for microscopic hematuria is a valuable adjunct procedure in follow-up. Use of a flexible endoscope over a rigid one has the advantage of allowing visualization of the entire bladder (including an excellent retrograde view of the bladder neck) and prostatic urothelium without changing lenses. Also, the flexible endoscope makes intravenous sedation unnecessary and improves comfort for male patients. Outpatient flexible cystoscopy and fulguration of superficial tumors have been utilized by Herr and associates [5] to treat recurrent tumors. Of 162 patients with variable stages of tumors who underwent outpatient fulguration of recurrent tumors, 32% (22) required TUR after failure of fulguration.

A surveillance schedule is determined by the prognostic factors listed above. In a Workshop on Response Criteria for Superficial Bladder Cancer, the participants recommended urinary cytology within the first month following resec-

tion of a high grade tumor [6]. Assuming complete endoscopic resection, the first endoscopic follow-up is at three months, and if no tumor is identified and the cytology is negative, the patient returns again in six months. If the second endoscopy and cytology remain negative at nine months, the follow-up intervals may be extended. Fitzpatrick and associates [7] emphasized that the initial three month evaluative cystoscopy was the most important. Patients who were tumor-free at this time (79%) remained free of tumor. On the other hand, 90% who had a tumor at three months had further recurrences. We believe that a patient who remains disease-free for five years needs only annual cystoscopy; however, urinary cytology should be continued more frequently. Morgan *et al.* [8] followed patients from one to fifteen years after intravesical chemotherapy. The annual initial recurrence risk fell after the first year but did not decline again until eight years. Patients who develop a positive cytology for high grade tumor cells or a urothelial carcinoma that is grade II or III are placed in the high risk group and monitored more frequently.

Urinary cytology should identify 95% of grade III lesions and 75% of patients with a grade II neoplasm [9]. Thus, negative cytology results should allow the clinician to be reasonably confident that there is no unsuspected high grade tumor. Since it has been demonstrated that grade I, stage Ta tumors are relatively benign, with less than a 5% to 10% chance of progression, there is little harm in using cytology more frequently and delaying routine endoscopy for six to twelve months as in the above recommended schedule. Monitoring these patients primarily by cytology should detect any high grade recurrence. There is no evidence to indicate that resection of grade I, stage Ta lesions before they reach a certain size will alter their natural history.

Those patients with an initial neoplasm that places them at high risk for recurrence or progression should undergo endoscopy and cytology at three and six months following the resection. For those who remain disease-free, the follow-up schedule is endoscopy every six months with urine cytologies more frequently (at three month intervals).

Intravenous urography may be widely spaced, even with high grade tumors, as long as the clinical and pathologic studies remain negative and the patient is asymptomatic.

CONTROVERSIAL CLINICAL STAGES

T1 Disease

Patients with T1 disease can undergo apparently successful TUR of the tumor, yet follow-up cytology often reveals residual high grade tumor cells. In such cases there are three alternatives: intravesical therapy, cystectomy, and repeat endoscopic resection to determine the presence and depth of remaining neoplasm. Advocates of a repeat resection believe that it minimizes understaging and has a better chance of rendering the patient disease-free. In a study from Hungary, 462 optically complete resections were performed [10]. Thirty-five percent of all patients had residual tumor on re-biopsy, with the highest risk of residual in pT1 tumors. One cannot underestimate the variable of endoscopic equipment and surgical technique in dealing with T1 TCC.

Tis Disease

The majority of pathologists define Tis as a flat, high grade urothelial tumor confined within the epithelium. The Mayo Clinic has completed one of the larger series of patients with Tis (G. Farrow and M. Leiber; personal communication). In this group with primarily diffuse, symptomatic Tis, the risk of understaging and subsequent progression was high. Yet Tis is not necessarily an ominous prognosis. A number of factors can determine the probable natural history of each patient's tumor diathesis: extent of endoscopic abnormality, symptoms, associated stage Ta or T1 tumor, prostatic urethra or ductal involvement, and response to intravesical therapy. This last factor is the most significant clinical parameter.

Prostatic Involvement

Mahadevia and associates [11] found that up to 40% of radical cystoprostatectomy specimens had TCC of the prostatic urothelium, ducts, or stroma. Most of these had Tis of the prostatic urothelium. Kirk and associates [12] and Schellhammer and colleagues [13] noted pros-

tatic involvement in 26% and 9%, respectively. When high grade TCC appears in a TUR biopsy of the prostatic urethra in a patient with superficial bladder cancer, the standard treatment is cystoprostatectomy and urethrectomy. TUR followed by intravesical therapy is an alternative when the tumor is confined to the mucosa, with no extension into the prostatic ducts or stroma. It is likely that intravesical agents do not routinely bathe the prostatic urothelium and certainly do not enter the prostatic ducts sufficiently to eradicate tumor in these sites; therefore, the risk of recurrence and progression is high. Admittedly, there is a lack of sufficient data on the efficacy of TUR and Bacillus Calmette-Guerin (BCG) for treatment of Tis within the prostatic urethra and ducts.

INTRAVESICAL THERAPY

Low risk patients derive little benefit from intravesical therapy. Most are well treated with TUR alone. However, TUR does not prevent new tumors. Two categories of intravesical therapy have been devised. Therapeutic intravesical therapy treats individuals with extensive but superficial lesions which are not amenable to complete TUR; those with positive cytology but no obvious neoplasm in the bladder, upper tracts or prostatic urethra; and those whose mucosal biopsies reveal Tis. Prophylactic intravesical therapy is designed to prevent recurrence and progression. Prophylactic therapy weighs the benefits of avoiding or delaying a subsequent endoscopic resection against the toxicity, cost, and additional catheterizations required for placement of the intravesical agent.

Dose, administration schedule, and timing of the onset of intravesical therapy after endoscopic resection of bladder tumors can vary widely. A cooperative, randomized study performed in England, using an agent of known efficacy (thiotepa), found no significant difference in recurrence rates in three groups of patients: those receiving only one instillation; those receiving an immediate dose plus instillations at each 3 month cystoscopy; and those receiving no intravesical therapy [14]. Based on this study, it appears that intravesical instillations must be given more frequently than five times within one year to make a significant difference in the recurrence rate.

Patients undergoing intravesical therapy are evaluated three months after the initial diagnostic resection by endoscopy and bladder washing cytology. Patients receiving intravesical therapy for prophylaxis are monitored according to their disease-free intervals; time to recurrence, time to progression and the recurrence rate are appropriate endpoints. Patients receiving intravesical therapy for treatment are monitored in terms of response. A complete response to any agent is expected by three months. A complete response is defined as (1) no tumor at endoscopy; (2) no tumor cells on cytology; and (3) no neoplasia in biopsies. A partial response should not be considered a success. Cant and colleagues [15] found that prognosis for "partial responders" more closely approximated that of patients who failed therapy than that of patients who responded completely.

Patients are followed according to the same schedule used for high risk patients if they are disease-free at the time of their follow-up cystoscopy. When there is a concern that tumor is still present in the bladder after a series of intravesical treatments, the patient is brought to the operating room for endoscopy and resection. If the tumor is clearly low grade and exophytic, it is unnecessary to proceed with a radical treatment. In such patients, tumor destruction with the roller electrode, resectoscope loop, or laser is probably all that is necessary. However, it is unlikely that further intravesical treatment using the same drug will be efficacious. A positive biopsy or positive urinary cytology demands an alternative therapeutic strategy, especially if the tumor persists beyond one year in nonresponding patients. Grade and stage of the persistent tumor determine which therapeutic alternative the clinician will choose.

There are few controlled studies that evaluate protracted (maintenance) therapeutic or prophylactic intravesical therapy. To determine the necessity of maintenance therapy, Hudson *et al.* [16] randomized patients to receive BCG in either a six-week course alone or a six-week course plus maintenance therapy every three months for one year. Overall, there was no significant difference in the recurrence rates. These findings have been supported in a similar study performed by Badalament and associates [17]. At the University of Iowa, a continuous intravesical drug system is currently being

tested on rats using a nephrostomy tube connected to a mini osmotic pump [18]; because maintenance therapy appears to offer no advantages in the treatment of superficial tumors, this system will probably not prove beneficial. Tumor recurrence also appears unaffected by when the first dose is administered. Huland *et al.* [19] compared three different first dose schedules and found the only significant difference to be in patient tolerance. Delayed intravesical therapy improved patient tolerance without affecting recurrence.

INTRAVESICAL AGENTS

When evaluating intravesical agents for efficacy one must measure time to recurrence, time to progression, and recurrence or response rate, depending upon how the drug is used. Other important endpoints include rate of cystectomy and overall survival. Stratification of tumor grade, stage and other potential prognostic factors must be sufficient to achieve statistical validity. Different results in studies evaluating the efficacy of the same agent are probably due, at least in part, to the use of different endpoints and improper stratification of risk groups. In many of these studies, cytology data were not obtained or were not negative prior to initiating treatment.

Thiotepa

Thiotepa, an alkylating agent, was the first intravesical agent used in the United States. Thiotepa has a molecular weight of only 189, allowing enough of the drug to be absorbed to produce myelosuppression. This is the only intravesical agent in which myelosuppression is likely to occur. There have been reports of aplastic anemia after intravesical therapy with thiotepa [20].

The National Bladder Cancer Collaborative Group conducted one of the largest clinical trials of thiotepa [21]. Patients were randomized to receive either thiotepa or no intravesical therapy following endoscopic resection. Overall, 53% of patients who received thiotepa were tumor-free after two years compared to only 27% of patients in the control group. Tumor grade was a factor in treatment outcome. Thiotepa did not significantly influence the recurrence rate for patients with grade II or III tumors; after two years, 56% of the thiotepa-treated group compared with 43% of the control group were disease-free. Patients with grade I lesions had better results; after two years, 57% of the thiotepa-treated group were disease-free, compared to 14% of the control group.

Mitomycin C

Mitomycin C is an antitumor antibiotic. The molecular weight is 329 and absorption is extremely low; thus, myelosuppression is rare. However, reduced bladder capacity after mitomycin C administration is an uncommon but serious complication of treatment. Eijsten *et al.* [22] treated 75 patients prophylactically with 20 or 30 mg of mitomycin C. Six patients developed decreased bladder capacity (<200 cc) and two required cystectomy. Bladder fibrosis and contracture resulting in renal failure has also been reported after mitomycin C. The effects of instillations of thiotepa, mitomycin C and doxorubicin on normal rat urothelium have been reported [23]. Only the mitomycin C group demonstrated significant fibroblastic atypia and submucosal fibrous plaques within the urothelium.

Huland and associates [24] performed a randomized prospective study comparing patients receiving mitomycin C with those who received no intravesical therapy following complete endoscopic resection. Only 10% of the mitomycin C group had subsequent tumor, compared to 51% of those who received no intravesical chemotherapy. The likelihood of cancer progression or death from bladder cancer for those receiving mitomycin C prophylaxis was significantly diminished.

Doxorubicin Hydrochloride

Like mitomycin C, doxorubicin has a relatively high molecular weight (580); thus, myelosuppression is rare. Most of the side effects related to intravesical doxorubicin are due to chemical cystitis which has been reported in up to 25% of patients [25].

Rubben *et al.* [26] reported a prospective randomized trial of intravesical doxorubicin. Patients with Ta or T1 TCC were randomized to receive either short-term or protracted doxorubicin, or no further treatment. Although

there was a slight difference in the mean interval to first recurrence between the treated and untreated groups (22 and 19 months, respectively), the recurrence rate was not significantly different in the three groups. Conversely, Garnick *et al.* [27] reported that time to recurrence and tumor progression data were similar to that obtained from other studies using mitomycin C.

Bacillus Calmette-Guerin

Although it is not clear how BCG produces an antitumor response, reports over the years attest to its efficacy. When instilled into the bladder, BCG produces a dramatic inflammatory response in most individuals; this response could trigger all or part of the antitumor effect. Montreal, Tice, Pasteur and Connaught strains of BCG have been used.

BCG not uncommonly causes such side effects as urinary frequency, dysuria, hematuria, fever, lethargy and malaise. Although attenuated, BCG organisms can cause systemic infection; renal tuberculosis and abscess formation, orchitis, sepsis and death have all been reported. If clinical infection occurs, antituberculous therapy must be instituted promptly. Herr and associates [28] conducted one of the largest prospective randomized studies comparing BCG to no intravesical therapy for prophylaxis following tumor resection. In the BCG group there was a reduction from the pre-treatment tumor frequency not seen in the control group: 3.6 tumors per patient reduced to 0.7 tumors. Fifteen patients who did not receive BCG prophylaxis had a cystectomy, compared to only three who had BCG. Haaff and coworkers [29] reported their results with intravesical Pasteur strain BCG in patients with Tis. The overall complete response rate for Tis was 68%. Herr [5] has also shown the efficacy of intravesical BCG for Tis, making it an appropriate alternative to radical surgery as first-line treatment for Tis or T1 TCC.

Comparative Studies

It appears that all chemotherapeutic agents are comparable when used as prophylaxis. For example, Flanigan *et al.* [30] performed a randomized prospective study comparing thiotepa to mitomycin C. Each agent was given weekly for eight weeks, followed by monthly treatments for two years. There was no significant difference in the recurrence rate. Immunotherapy with BCG, however, appears to be the most efficacious agent in increasing the time to recurrence and progression and reducing the recurrence rate in patients with superficial bladder tumor. A recent Southwest Oncology Group study compared intravesical doxorubicin with intravesical BCG for both treatment and prophylaxis of superficial bladder cancer [31]. In both comparisons, BCG was significantly superior. In a multicenter study of BCG versus doxorubicin, Khanna *et al.* [32] had 131 evaluable patients. Initial complete remissions with BCG and doxorubicin were 68% and 57%, respectively. The rate of complete remission for BCG rose to 85% when 7 patients (failures) taking doxorubicin were switched to BCG and the disease cleared. The rate of progression was 8% for BCG and 5% for doxorubicin. Martinez-Pinero *et al.* [33] followed 176 patients for three years after treatment with thiotepa, doxorubicin or BCG. BCG was superior in limiting recurrences and progression in high risk (pT1) tumors, although toxicity was highest in the BCG group. In a recent study, deKernion *et al.* [34] treated 13 patients with Tis who failed initial induction courses of intravesical mitomycin C, thiotepa, doxorubicin or BCG. Using up to four induction courses of BCG, they proved that the majority of patients will respond to conservative treatment.

NEWER AGENTS

Epirubicin

Epirubicin is one of a series of derivatives of doxorubicin designed to increase the antitumor activity and lower the toxicity of its parent compound. Epirubicin has been reported by Bonfante *et al.* [35] to produce the same therapeutic response as doxorubicin with less toxicity in patients with superficial bladder cancer. A controlled prospective study from Greece compared maintenance therapy using epirubicin to TUR alone in the treatment of Ta and T1 disease in 65 patients who were evaluated for recurrence and progression. Patients receiving epirubicin had 37% recurrence and 54% progression, compared to 9.3% and 22%, respective-

ly, for those receiving TUR alone [36]. Kurth *et al.* [37] proved that the agent is also useful in Tis. A phase I/II study of 22 evaluable patients showed that 59% of all patients had an initial complete response; after 8 instillations, 75% responded after further therapy. At 35 months, 36% remained in complete remission. Overall, 12% of the initial responders and 33% of the nonresponders had progression (18% total).

Interferon

In 1988, the Northern California Oncology Group first reported on the efficacy of recombinant interferon in TCC [38]. Although no significant dose-dependent toxicity is associated with the agent, the therapeutic dose is not clear. Chodak [39] reviewed a randomized, controlled trial in which equal numbers of patients with Tis were treated with low (10×10^6 IU) or high doses (100×10^6 IU). The follow-up period was two years. Initial complete responses were 6% and 45% for low and high dose groups, respectively. Progression was noted in 40% and 14%, respectively. Comparative studies with BCG are still needed for this agent.

CONCLUSION

Superficial bladder cancer comprises a heterogeneous group of tumors. Grade, stage, and positive cytology after resection appear to be the most useful of many prognostic factors to determine how aggressive therapy should be in each individual patient. The initial evaluation of these patients is critical; surveillance and treatment strategies should be based on their risk category. Low risk patients derive little benefit from intravesical therapy. In high risk patients, BCG appears to be the most efficacious agent in increasing the time to recurrence and progression and reducing the recurrence rate. The toxicity associated with BCG is higher than with other agents; the clinician must balance the benefits versus these side effects.

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