REVIEW PROF-535

SUPERFICIAL BLADDER CANCER ;

UPDATE TREATMENT

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SUMMARY

The management of superficial bladder cancer should be based on a careful assessment of cancer histopathology (grade, stage, size and number), previous history of bladder cancer (number & timing of recurrences) and patient/physician preference. Patients with favorable tumor profiles at the initial diagnosis do not require intravesical therapy. Alternatively, a single intravesical administration of chemotherapy may be performed following TUR. Patients with favorable tumor characteristics that recur with similar features may be best treated with intravesical chemotherapy. The induction regimen should consist of 6+3 instillation scheme. Patients failing a single 6-week course of BCG may respond to a second 6 week course. Those patients with significant risk of disease progression (high grade, T1 with/without CIS) should be managed with caution. Although such patients are candidates for early cystectomy, they are also candidates for intravesical BCG. Patients treated with BCG intravesical chemotherapy for high-grade superficial bladder cancer are at significant long-term risk for disease recurrence, progression and even death from disease. Careful and vigilant follow-up is necessary for life in these patients. The urologist must be extremely active and diligent when treating with superficial bladder cancer. An understanding of tumor biology and current intravesical therapies is important to appropriately treat these patients. Furthermore, and perhaps most important, the timely decision to abandon conservative therapy and proceed with radical cystectomy and urinary diversion should be kept in mind to prevent the potentially lethal sequelae of intravesical cancer.

INTRODUCTION

Transitional cell carcinoma (TCC) of the bladder is the second most common malignancy of the genitourinary tract and the second most common cause of death among genitourinary tumors. In USA, in 1999, 54200 new patients were diagnosed with bladder cancer and 12,100 died from the disease[1]. Practically bladder cancers are divided into:

i. Superficial bladder Cancer (Ta, T_1 & Tis)

ii. Deep (muscle invasive) bladder cancers (T_2, T_3, T_4)

Nearly 80% of all patients who initially present with bladder cancer have tumors confined to mucosa or lamina propria; so called superficial bladder cancers. Superficial bladder tumors represent a heterogeneous group of cancers that include: those that are papillary in nature and limited to the mucosa (Ta), those that are high grade, flat and confined to the epithelium (Tis) and those that invade the lamina propria (T1)[2]. These lesions range from totally benign exophytic urothelial papillomas to malignant, high-grade, invasive urothelial carcinomas, therefore, recently the term "superficial bladder cancer" has been challenged[3].

NATURAL HISTORY

The natural history of superficial bladder cancer is difficult to predict due to the tumor heterogeneity. The two features that characterize superficial disease are tumor recurrence & progression. The risks for both recurrence & tumor progression are related to multiple histo-pathological features including histological grade, depth of invasion, multiplicity, tumor size, presence or absence of vascular/lymphatic invasion& presence or absence of carcinoma in situ (CIS)[4,5].

Although 80% of bladder cancers are superficial at diagnosis & most of then (70%) are histologically stage Ta[6]. In general, Ta tumors are low-grade (G^1) cancers. Stage T1 tumors represent 30% of superficial tumors and (30%) of them are high-grade(G3)[7]. CIS by definition; is a high-grade tumor & comprises about 10% of all cases. Half, occurring as an isolated lesion (primary CIS) & rest along-with papillary or invasive lesion (secondary CIS)[8].

PROGNOSTIC CRITERIA

Many factors have been identified which predict tumor recurrence & progression: tumor stage (Ta vs. T1), tumor grade (low vs. high), tumor number (<4 vs. >4), tumor size (<3 vs. >3), prior tumor recurrence, time to first recurrence, tumor morphology (papillary or solid), lymph-vascular invasion & the presence of CIS [9,10,11,12].

MANAGEMENT GOALS

The overall treatment goals for superficial bladder cancer are three fold[13].

1. To reduce tumor recurrence & the subsequent need for additional therapies.
2. To prevent tumor progression.
3. To reduce the risk of cancer related death.

TREATMENT MODALITIES

For treatment purposes, superficial bladder cancers can be divided into three categories[14-16].

Low Risk Group:
Solitary, primary or recurrent pTa G_{1-2} tumors are considered to belong to low risk category.

Intermediate Risk Group:
Multiple primary or recurrent pTa G_{1-2} or solitary pT1 G2 belong to intermediate group.

High Risk Group:
pT1 G_3, pTa G_3 solitary or multiple or recurrent and primary or concomitant carcinoma in situ are considered to be high-risk tumors.

About 50% of all patients with superficial tumors belong to the low risk group. 30% have an intermediate risk & 15-20% have a high risk for recurrence & for progression. The different treatment modalities applied are [17,18].

i. Surgical Intervention

ii. Intravesical Instillation
iii. Combined

SURGICAL INTERVENTION

The therapeutic objectives in the initial management of superficial tumors are to remove completely the tumor, to assess the need for further therapy and to plan the follow-up. The standard initial method of management is trans-urethral resection (TUR) of the tumor. Virtually, all superficial papillary bladder carcinomas can be treated by TUR, even in cases where tumors are seen on multiple sites of the bladder[19]. Many patients are repeatedly treated by TUR during their life span because of tumor recurrence. Globally one may expect recurrence every 3 years. However, patients who remain free of recurrence during the first follow up year have good chance to remain tumor free for several years, whereas those patients who developed a recurrent tumor during the first year are at high risk for developing multiple recurrences in the future[20].

TUR of the bladder tumors should always be preceded by a thorough cystoscopy. The results of a prior cytology might indicate whether and to what extent mucosal biopsies should be performed. Mucosal biopsies are mainly indicated in patients with positive cytology in the absence of identifiable tumor. The location, appearance (papillary or nodular), size and number of all tumors are mapped on a diagram. Resection of the bladder muscle is necessary to allow the pathologist to determine whether the tumor has invaded the muscle layer. It is mandatory that the pathological report indicates tumor grade and depth of invasion and whether lamina propria and muscle are present in the specimen[21]. When all evident tumors could not be resected, residual tumors should be documented in the bladder diagram.

Mersdorf et al[22] performed a second TUR in 102 patients to avoid short-time recurrences at 3 months and to achieve complete resection. Patients had either a high-grade or multilocular superficial bladder cancer. Residual tumor was found in 15/49 patients (31%) with a pTa tumor and in 26/45 patients (58%) with pT1 tumor. Similarly vogeli et al[23] performed a second TUR 4-6 weeks after the first and detected residual tumor in 38%. In 75% of pTa and 85% of pT1 tumors, residual tumor was found at the same location and in 25% and 15% at another location, respectively. Thus one of the reasons of early recurrences at 3 months may be due to incomplete resection. Fluorescence cystoscopy may help to identify tumorous lesions not recognized by white light sources. Areas of dysplasia, CIS and papillary tumors fluoresce and become visible. The sensitivity of this technique was reported to be as high as 96%[24], however, specificity was low (34%) in the study reported by Filbect et al[25].

INTRAVESICAL INSTILLATION

Intravesical instillation is a mean by which a concentrated substance can be delivered directly to tumor bearing bladder mucosa. It can be therapeutic (treatment of residual or un resected disease or CIS) or prophylactic (prevention of the development of recurrent tumors). At the moment intravesical instillation can be of two types; chemotherapy or immunotherapy.

For low risk patients, intravesical chemotherapy (a single instillation) is the optimal therapy & BCG has to be avoided. For intermediate risk patients, intravesical immunotherapy with BCG is superior to chemotherapy with regard to time to first recurrence. For the high-risk patients, there is consensus that when intravesical therapy is considered, BCG is superior to any chemotherapeutic agent.

INTRAVESICAL CHEMOTHERAPY

Since the introduction of chemotherapy by Jones & Sweeney26 in 1961, many different chemotherapeutic agents have been used & studied including; thiotepa, adriamycin & mitomycin C. Thiotepa can cause myelosuppression & the other two can cause chemical cystitis (10% of cases with mitomycin & 25% with adriamycin). Thiotepa has small & the other two have large molecular weights. Intravesical chemotherapy reduces the recurrence rate (30% as compared to 50% in untreated patients) but not the progression rate (8.3% progression rate in 1039 treated patients compared to 8.6% in 573 untreated patients)[27].

For management of superficial bladder cancer, mitomycin administration gives a better complete response rate than other intravesical drugs (39% vs 27%, p=0.02)[28]. Overall, when comparing the various forms of intravesical chemotherapy employed for superficial bladder cancer prophylaxis, there appears to be little to no difference between thiotepa, adriamycin & mitomycin C[29]. Mitomycin C is the most commonly drug employed due to less side effects & better response rate. The most common administration dosage of mitomycin is 40 mg mixed with 40 ml of water[17].

INTRAVESICAL IMMUNOTHERAPY

The mechanism of action, the principles of treatment and the potential benefits of treatment with biological response modifiers are distinctly different from intravesical chemotherapy. Immunotherapy stimulates immune defences. Immunotherapy has the potential to induce specific immunity to tumors, making possible the prevention of tumors that have not yet developed. The best investigated form of immunotherapy is treatment with BCG. In case of BCG resistant cases, alternate form of therapy is employed[30].

BACILLUS CALMETTE-GUERIN (BCG):

In 1976, Morales first reported the results of BCG in the treatment of superficial bladder cnacer[31]. Since then many studies have been performed to evaluate the efficacy of BCG. The exact mechanism of action of BCG is still being elucidated. Ratliff demonstrated that the direct contact of the bacillus organism with the transitional epithelium allows cell surface binding through fibronectin binding sites and activation of the immune response[32]. An intact T cell system is required for appropriate CD3, CD4, and CD8 immunological response[33]. It has also been reported that the degree of T cell infiltration into the bladder wall is proportional to the clinical response of patients, with responders demonstrating more bladder infiltrate than monresponders[34]. BCG immunotherapy has been confirmed by investigators around the world to be highly effective in the reduction of tumor recurrence, the treatment of residual papillary transitional cell carcinoma and, more importantly, the treatment of CIS [35,36]. The response rate in the treatment of the papillary disease averages 55%[37]. In the treatment of CIS, which cannot be treated by electro resection because it is visible only microscopically, the average complete response is 73%[38]. In the prevention of tumor recurrence the relative benefit of BCG is 45%[39]. A direct prospective randomized comparison of BCG with intravesical chemotherapy has found it to be significantly superior to thiotepa, doxorubicin and to mitomycin [39,40]. In three other large studies where BCG was compared with mitomycin C, no difference in the prevention of tumor recurrence was found [41,42,43]. The studies differed in the type of patients recruited: whereas only patients with intermediate and high risk for recurrence were treated in studies showing superiority of treatment with BCG, also patients with low recurrence were recruited in the studies showing no advantage for BCG.

Unlike intravesical chemotherapy, there is some evidence to suggest that BCG may be effective in reducing tumor progression[44,45,46]. There are 3 published prospective randomized trials demonstrating that BCG delays tumor progression when compared to no treatment after TUR. Herr and associates performed a randomized trial between 1978 and 1981 and after 5 years demonstrated that intravesical BCG therapy delayed disease progression, prolonged the period of time for bladder preservation and improved servival[44]. With increased follow-up of 10 years, this trial demonstrated that BCG therapy maintained a progression, prolonged the period of time for bladder preservation and improved survival[45]. Not all studies show a superiority of BCG in delaying/preventing progression[47,48]. Lamm reported the rates of progression to muscle invasion were lower in the BCG group (8% vs. 3%) compared to control group but it did not reach statistical significance. A randomized study by Melekos and associates also failed to demonstrate any significant difference in stage progression among the BCG treated group compared to those treated with TUR alone[48].

The question of maintenance therapy with BCG is debatable. Intravesical BCG instillation induced a transient peripheral immune activation for less than 6 months against several purified BCG antigens[49]. An excellent prospective randomized trial was performed by the Southwest Oncology Group in which patients were assigned to receive no further treatment after a 6-week induction course, versus 3 weekly BCG instillation at 3 months, 6 months and every 6 months for 3 years[50]. This study reported an advantage of maintenance therapy (87% complete response versus 73%), reduced recurrence (83% versus 50%) and importantly prolonged survival (92% versus 86%). However, a significant increase in toxicity occurred with maintenance therapy. Grade-III toxicity developed in 9% of patients upon induction therapy and increased to 26% of those in maintenance therapy; with at least 10% refused to complete the prescribed course due to the severe toxicity[51]. There is clearly a toxicity price to pay with maintenance therapy and one must ask if this benefit outweighs the risk of toxicity.

The optimal course of BCG should prevent tumor recurrence and progression. It is clear that a single 6-week course of BCG therapy may be inadequate in a number of patients who may than respond to an additional 6-week course of BCG. Several groups have reported that higher success rates were achieved when a second and even third course of BCG was delivered following failure of an initial 6-week course[52,53]. An additional 7 to 32% of patient may benefit from a second course of BCG therapy. Again, treatment toxicity and tumor progression must be kept in mind in treating patients with additional therapy. Patients with persistent CIS or high-grade T1 tumors following two 6-week courses of BCG should be considered for alternative forms of therapy. Most agree that the preferred induction regimen consists of six weekly BCG treatments followed by a six-week hiatus and then followed by 3 weekly treatments (6+3 regimen).

Chemo-immunotherapy:

An anti-tumor effect may be potentiated when two separately effective treatment modalities are combined. This concept was tested by van der Meijden et al[37] in patients with a marker tumor measured between 0.5 and 1 cm. Instillation therapy with mitomycin 40mg in 50 ml saline was administered weekly for 4 consecutive weeks followed by BCG for 6 consecutive weeks. Complete response of the marker was observed in 19/35 patients (54%). Witjes et al[54] showed no superiority of chemo-immunotherapy over BCG alone. On the other hand Rintala et al[55] has demonstrated the superiority of chemo-immunotherapy over BCG in the management of carcinoma in situ. Though combining the two

biological response modifiers was the proposal of a North American consensus meeting conference[56], no concrete evidence demonstrated its superiority.

Alternative Forms of Therapy:

Although BCG is effective for superficial bladder disease; approximately 30% of patients manifest BCG refractory superficial disease. Several alternative agents and methods have been employed to treat or salvage these so-called "BCG-refractory" patients including; interferon, bropirimine, photo dynamic therapy and mega-dose vitamin therapy.

i. Interferon:

Interferons are naturally occurring glycoproteins with antiviral and anti-proliferative properties. The most active interferon for bladder cancer is interferon alpha, which primarily stimulates natural killer (NK) cell maturation. Initial studies with interferon alpha 2b as a single intravesical agent demonstrated activity in bladder cancer at doses of 50-100 MU with minimal toxicity[57,58]. As primary therapy for superficial bladder cancer, interferon is thought to be inferior to both BCG and intravesical chemotherapy. Interestingly, responses with interferon alpha 2b have been documented in patients who have failed BCG or intravesical chemotherapy. Response rates as high as 60% have reported which may make it potentially attractive option for second line therapy[58].

ii Bropirimine:

Bropirimine is an orally active immune modulator that induces a wide range of anti-tumor, antiviral and immuno-modulatory effects. Sarisdy[59] demonstrated in a phase I trial that bropirimine was effective for CIS. In phase II trial Sarosdy treated CIS patients with positive cytology following biopsy for 12 weeks (3 consecutive days per week). Over half (20 of 30) of the evaluable patients demonstrated a complete response including 6 of 12 (50%) patients who had not received any prior BCG[60]. Although there is evidence to suggest that bropirimine is an effective therapy for superficial bladder cancer, it failed FDA approval in 1996. It may be particularly attractive based on the fact that it can be administered orally and can potentially effect the upper tract urothelium[61].

iii Photodynamic Therapy

Photodynamic therapy was first introduced in 1976 as a potential alternative treatment for bladder preservation[62]. It requires the intravenous administration of a photosensitizing agent with subsequent in-site intravesical activation by whole bladder laser therapy with visible light. The tumor localizing photosensitizer is stimulated to generate an active form of molecular oxygen causing vascular damage and tumor cell death. This method has been effectively used to treat superficial TCC as well as BCG refractory CIS[63,64].

iv Vitamins:

There is increasing evidence to suggest that vitamins may play an important role in the prevention & management of various cancers. Recent studies have demonstrated that the efficacy of BCG may be enhanced by supplementation with mega-dose of vitamins & minerals[65]. Further research will be required to confirm these findings & more precisely identify which supplements provide this protective effect.

Novel Approaches:

In an attempt to reduce the local toxicity and side effects of intravesical therapies while maintaining efficacy, investigators are studying the usefulness and safety of low-dose BCG therapy, combination therapy of BCG with interferon and alternating BCG therapy with intravesical chemotherapy[66,67].

The initial therapy of any superficial tumor is the TUR, which is meant to eradicate all visible tumors completely. Although the incidence of T_1 G_3 transitional cell carcinoma of the urinary bladder is only about 15% of all superficial bladder cancers,

the special nature of this tumor makes a more detailed consideration[68,69]. In some series in which newly diagnosed T1 G3 were treated by TUR alone. The data shows that tumor recurrence will develop in 70% and tumor progression occurs in 30-50% within 5 years[70,71]. This data clearly indicates that T_1 G_3 tumors can rarely be treated by means of TUR alone. TUR plus additional therapy-intravesical chemotherapy, immunotherapy, systemic chemotherapy or radiotherapy or cystectomy and urinary diversion are the options that are available. There is evidence that radical cystectomy at the time of diagnosis will give an excellent cure rate as compare to TUR alone (90% vs. 62% respectively)[72]. There are two reasons for cystectomy that are mentioned most of the time in discussions on the proper management of T1 G3 tumors. These are under-staging of the tumor by TUR and the higher rate of regional and distant metastasis that increases by the number of previous TURs. If a second TUR is performed, it will detect residual tumors in about 50% and in some 5% muscle-infiltrating tumors will be present[73,74]. It has been clearly proven that TUR plus adjuvant chemotherapy or immunotherapy can preserve the bladder in a high percentage of patients without an extensive risk of death due to progressive tumor. Moreover, it indirectly indicates that metastatic disease is a rare event unless a muscle-invasive tumor develops during follow-up[75,76,77].

The question of the appropriate management of T1 G3 bladder cancer cannot be solved at present, mainly owing to the facts that first, the cystectomy series are usually a mixture of previous treated and untreated patients with different tumors grades and second, the TUR plus BCG series have a short follow-up and lack of consistent BCG protocols. At most of the centers bladder-sparing strategy for T_1 G_3 is practiced (TUR+ intravesical chemotherapy). Cystectomy is only performed in case of the first recurrent T_1 G_3 tumor or multiple Tis[78].

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