Urooncology / Üroonkoloji *Review / Derleme*

Management of bladder transitional cell carcinoma in stage T1G3

T1G3 evresindeki değişici epitel hücreli mesane kanserinin tedavisi

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Abstract

Urothelial cancer staged as T1G3 presents urologist with challenges, because it has poor outcome if treated as superficial bladder tumor. Transurethral resection is the standard treatment for the non-muscle-invasive bladder tumor. However, high-grade T1 bladder tumor has potentially bad prognosis and transurethral resection is not adequate treatment option. The recurrence rate after transurethral resection is 50-80% and progression rate to muscle-invasive disease is 27-63%. The treatment of choice for patients with high grade T1 bladder tumor is a matter of controversy. Herein, we reviewed the literature and guidelines regarding the management of patients diagnosed with high-grade T1 urothelial cancer.

Key words: Bladder; bladder tumor; T1G3.

Özet

T1G3 evresindeki ürotelyal kanserler yüzeyel mesane tümörü protokolleri ile tedavi edildiklerinde kötü prognoz göstermeleri nedeniyle ürologları zor durumda bırakabilmektedir. Kas invazyonu göstermeyen mesane tümörlerinde standart tedavi transuretral rezeksiyondur. Bununla birlikte yüksek grade'li T1 mesane tümörlerinde potansiyel olarak kötü prognoz bulunması nedeniyle transuretral rezeksiyon yeterli bir tedavi seçeneği değildir. Transuretral rezeksiyon sonrası rekürrens oranı %50-80, kasa invaze hastalığa progresyon oranı ise %27-63'dür. Yüksek grade'li T1 mesane tümörlü hastalarda tedavi seçeneği tartışmalı bir konudur. Bu yazıda, yüksek grade'li T1 ürotelyal kanser tanısı alan hastaların tedavisi ile ilişkili literatür ve tedavi kılavuzları gözden geçirilmiştir.

Anahtar sözcükler: Mesane; mesane tümörü; T1G3.

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High-grade bladder transitional cell carcinoma (TCC) infiltrating the lamina propria (T1G3) is an aggressive disease with a high-risk of recurrence and progression to muscle invasion. The best treatment for T1G3 TCC of the bladder is still a matter of controversy.

Cystourethroscopy and bladder tumor resection (TURBT)

The back bone in the diagnosis and treatment of non-muscle-invasive bladder cancer (NMIBC) is transurethral resection (TURBT). However, at cystectomy more than third of patients with clinical stage T1 TCC are found to have muscle infiltrating disease on TURBT.[1,2]

Re-TURBT

The significant risk of residual tumor after the initial TURBT of Ta T1 lesions has been documented.[3,4] In a prospective study conducted by Divrik et al.[5] residual tumors were detected in 27 (33.8%) of 80 patients with newly diagnosed G1-3 pT1 bladder cancers at the second TURBT. Klän et al.[6] reported a residual tumor rate of 50% in patients with G2-3 pT1 tumors. Mersdorf et al.[7] detected residual tumors in 58% (26 of 45 patients) of patients with G2-3 pT1 tumors. The highest percentage was reported by Herr,[8] where out of 96 cases with NMIBC (Ta, Tis, T1), 72 (75%) had residual non-invasive tumor. Furthermore, a muscle-invasive disease may be missed in the first TURBT and detected in re-TURBT. Herr[8] reported that 28 of 96 cases with NMIBC (29%) had muscle invasion in re-TURBT. Table 1. shows the results of 2nd TURBT regarding the rate of residual tumor and detection of muscle invasion.

Second TURBT should be considered if the initial resection was judged as incomplete, e.g. when multiple or large tumors are present or when the

pathologist reported no muscle tissue in the specimen. In addition, it should be carried out when a high-grade non-muscle-invasive tumor or a T1 tumor was detected at the initial TURBT. It has been stated that re-TURBT can enhance recurrence-free and progression-free survival.[5] Most authors recommend the second resection to be done 2-6 weeks after the initial TURBT. The procedure should include a resection of the primary tumor site.

Treatment

TURBT alone

TURBT is the first procedure for bladder carcinoma. When T1G3 tumors are treated with TURBT alone, recurrence and progression rates are high. The rate of recurrence is 50-90% and that of progression to muscle-invasive disease is 24-48% (Table 2). Finally, one third of patients with T1G3 bladder cancer treated only with TURBT would die from their disease.[12] Therefore, TURBT alone is not an accepted treatment for T1G3 bladder TCC.

Intravesical BCG therapy

BCG immunotherapy is the gold standard intravesical therapy for high risk Ta, T1, Tis bladder TCC, with subsequent decrease in recurrence and progression rates.[20,21] BCG is considered by many researchers and clinicians to be the first-line treatment for primary T1G3 bladder cancer.[22-27]

Table 1. Results of the second TUR considering residual tumor and upstaging to T2

Reference	Interval	pT2	Residual tumor	Number of patients
Brauers et al.[9]	4-6 weeks	4.7%	62%	42
Klan et al.[6]	1-2 weeks	2.0%	43%	46
Schwaibold et al.[10]	4-6 weeks	10.0%	55%	60
Schips et al.[11]	4-6 weeks	8.0%	33%	76

Table 2. Results of TURBT alone in patients with T1G3 bladder cancer

Reference	Follow-up (months)	Progression	Recurrence	Free
Heney et al.[14]	36	48%	79%	33%
Jakse et al.[15]	60/106	33%	80%	31%
Mulders et al.[16]	48	27%	75%	48%
Zungri et al.[17]	40	24%	50%	34%
Paez Borda et al.[18]	79	46%	85%	32%
Patard et al.[19]	62	47%	90%	30%

Quoted with modification from Emiliozzi et al.[13]

Immunotherapy with BCG after TURBT has been found to be more effective than TURBT alone for treating T1G3 bladder TCC. In a study of 80 patients treated with TURB plus BCG or TURB alone, with a follow-up of 61 to 65 months, cancer-specific survival was better in the BCG-treated than in the TURBT only group (90% vs. 70%, p=0.03)[25] Furthermore, recurrence rate was lower with BCG than TURBT only group (50% vs. 90%, p<0.01) and similarly, progression rate was lower in the BCG group (22% vs. 47%, p<0.001).

In a prospective randomized trial, 86 patients with high-risk NMIBC received TURB plus BCG or TURB alone. The 10-year progression rate was 38% and 63% for patients treated with BCG and the control group, respectively. The cancer-specific survival was 75% and 55% for these groups, respectively.[28]

The optimal BCG dose

To reduce toxicity, one-third and one-quarter dose of BCG was proposed. No overall difference was found in efficacy between one-third dose and full-dose. However, it was suggested that a full dose of BCG may be more effective in multifocal disease.[29] Fewer patients reported toxicity with the reduced dose, the incidence of severe systemic toxicity was similar. Further reduction to one-sixth dose was followed by a decrease of efficacy with equal toxicity.[30]

The optimal BCG schedule

For optimal efficacy, the BCG must be given in a maintenance schedule.[31,32] In the EORTC meta-analysis,[21] only patients receiving maintenance BCG benefited. In the four trials where no maintenance was given, no reduction in progression was observed. In the 20 trials in which some form of BCG maintenance was given, a reduction of 37% in the odds of progression was observed (p=0.00004). The meta-analysis was unable to determine which BCG maintenance schedule was the most effective.[21] In a meta-analysis, it was concluded that at least 1 year of maintenance BCG was required to show the superiority of BCG over mitomycin C (MMC) in preventing recurrence or progression.[33,34] Induction BCG instillations are classically given according to the empirical 6 weeks induction schedule, and many different maintenance schedules have been used with up to 30 instillations given over three years.[33] The optimal number of induction instillations and the optimal frequency and duration of maintenance instillations remain

unknown. Based on the extent of intravesical immune response, it is suggested that three consecutive weekly instillations give the maximum response.[34]

BCG toxicity

Deaths due to BCG sepsis and the high frequency of BCG-induced cystitis have compromised the use of BCG. However, with increased experience in applying BCG, the side-effects now appear to be less prominent. Serious side-effects are encountered in fewer than 5% of patients.[35] Major complications can appear after systemic absorption of the drug. BCG thus should not be administered during the first 2 weeks after TURBT, in patients with hematuria and after traumatic catheterization.

Adjuvant intravesical chemotherapy

Intravesical immunotherapy with BCG for T1 bladder cancer is superior to intravesical chemotherapy in decreasing recurrence rates. In 334 patients (303 T1) treated with intravesical BCG, epirubicin or adriamycin, the risk of recurrence was significantly higher with intravesical chemotherapy than with BCG. Combined therapy with BCG and epirubicin was associated with a lower recurrence rate.[36] In a randomized prospective study, Ali-Eldein et al.[37] also reported that sequential BCG and epirubicin are comparable to BCG alone in efficacy and superior in terms of toxicity. In a recent report, 191 patients with high-risk non-muscle-invasive bladder cancer were treated with BCG, mitomycin or adriamycin. Multivariate analysis showed that BCG treatment was associated with a reduced risk of disease progression at 73 months of follow-up.[38]

One immediate post-operative intravesical instillation

In a meta-analysis of seven randomized trials, one immediate instillation of chemotherapy after TUR decreased the recurrence rate by 12% and the odds of recurrence by 39%. The benefit was confirmed in single and multiple tumors.[39] The timing of the instillation is crucial. In all studies, the instillation was administered within 24 hours. One study reported that if the first instillation was not given at the same day of TUR, there was a twofold increase in the relative risk of recurrence.[40] MMC, epirubicin, and doxorubicin have all shown a comparable beneficial effect.[39] However, in a study on 168 patients, with mainly G2-3T1 bladder cancer, one dose of post-operative intravesical epirubicin did not reduce the recurrence rate for high-grade tumors.[41]

Treatment of failures of intravesical therapy

Patients with non-muscle-invasive recurrences after intravesical chemotherapy can benefit from BCG instillations.[42] Treatment with BCG is considered to have failed in following situations:

- If muscle-invasive tumor is detected.
- If high-grade non-muscle-invasive tumor is present at both 3 and 6 months.[43] In patients with tumor presence at 3 months, an additional BCG course provokes complete response in more than 50% of cases.[43,44]
- Any worsening of the disease under BCG treatment, such as a higher number of recurrences, higher T or grade, appearance of carcinoma in situ (CIS), in spite of initial response.

Changing from BCG to intravesical chemotherapy or device-assisted chemotherapy instillations can yield responses in selected cases with BCG failure. A second course of BCG might be an option for highly motivated selected patients with recurrent T1G3, although strict surveillance and adequate informed consent are mandatory.[45,46] Interferon has been added to BCG in salvage protocols.[47]

Intravesical gemcitabine might be an alternative to BCG refractory T1G3 bladder cancer.[48] Experience, however, is limited and these strategies are considered experimental. Because of the high risk of development of muscle-invasive tumor in these patients, immediate cystectomy is strongly advocated.[38,43]

Role of cystectomy in T1G3

In the last two decades, the role of radical cystectomy as a curative treatment for high-grade stage T1 transitional cell carcinoma has been discussed with controversial opinions on the timing of the operation. Malkowicz et al.[49] reported a survival rate of 80% and 78% for stage T1 and T1 plus carcinoma in situ tumors after radical cystectomy and strongly recommended early radical cystectomy in patients with high-risk stage T1 grade 3 with or without carcinoma in situ. Amling et al.,[50] however, recommended radical cystectomy only when conservative measures fail to treat this tumor category. The survival rates in these two studies were comparable for early radical cystectomy or radical cystectomy after failed bladder sparing treatment. Denzinger et al.[51] offered early cystectomy to 105 patients with pT1G3 disease with

two or three additional risk factors (size >3 cm, multifocality, and CIS). Fifty-four (51%) patients opted for early cystectomy, while 51 (49%) had deferred cystectomy. Early cystectomy was associated with a significantly better 10-year cancer specific survival rate compared to deferred cystectomy-78% versus 51%.[51] Cystectomy is advocated in patients with BCG failure. Delaying cystectomy in these patients may lead to decreased disease specific survival.[52] In 2001, Herr and Sogani[53] reported that early cystectomy for high-risk superficial bladder tumors that fail to respond to BCG therapy results in better long-term survival than continued bladder sparing strategies. In another study, they concluded that in patients with clinical and pathological non-muscle-invasive disease, radical cystectomy provides an excellent disease-free survival.[54] Many experts propose immediate cystectomy to patients at high-risk of progression. According to the risk tables of the EORTC, these patients have any of the following:

- Multiple recurrent high-grade tumors,
- High-grade T1 tumors,
- High-grade tumors with concomitant CIS.

Conclusion

High-grade T1G3 bladder cancer is a potentially lethal disease. TURB alone is not an adequate treatment option. Repeated TURBT is recommended in high-grade T1 tumors or if initial resection is incomplete and/or when there is no muscle in the specimen. In patients at high-risk of tumor progression, after an immediate instillation of chemotherapy, intravesical BCG for at least 1 year is indicated. Intravesical therapy with full- or reduced-dose BCG plus maintenance is the best bladder-sparing therapy for primary T1G3 bladder cancer. In BCG-refractory tumors, second-line treatments (second BCG course, intravesical chemotherapy, low-dose BCG plus interferon- α 2b, gemcitabine, radiotherapy) might be considered in highly selected patients, under strict control, or in patients refusing or unfit for open surgery. Immediate cystectomy may be offered to patients at highest risk of tumor progression. In patients with BCG failure, cystectomy is recommended.

Conflict of interest

No conflict of interest was declared by the authors.

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