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ROLE OF TRANSURETHRAL RESECTION OF SUPERFICIAL BLADDER TUMORS

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SUMMARY - Thirty percent all primary superficial bladder cancers do not recur at all, and hence do not need adjuvant treatment. Therefore, the most important isuse is proper selection of patients who need adjuvant measures. Cystoscopy findings three months after transurethral resection (TUR) are of paramount importance. If there is no recurrence, patients are in a good prognosis group and need no further prophylactic measures. Recurrence assessed at that point requires maintance therapy. Because of the low toxicity and defendable scientific background after any TUR of a tumor that appears superficial to the clinician, a single administration of a chemotherapeutic agent can be used within three days of operation in order to prevent tumor cell seeding in the wound bed or elsewhere in the bladder. After resection of any pT1 (grade III) or Tis tumor, BCG maintenance therapy is appropriate. The remainder of pTa/pT1(grade I and II) patients should be treated with intravesical chemotherapy in case of recurrence at three months. For patients who fail to respond to BCG treatment of pT1(grade III) or Tis and who are candidates for radical cystectomy, a new oral agent bromopirin with interferon inducing properties appears to offer some new hope. Patients with persistent positive high grade malignant citology are candidates for this new treatment.

Key words: *Bladder neoplasms; Bladder neoplasms - surgery; Bladder neoplasms - prevention*

Introduction

A majority of bladder neoplasms are either papillary tumors that involve only the mucosa (Ta) or submucosa (T1), or flat carcinomas in situ (Tis). The treatment of superficial bladder tumors has three objectives: to eradicate the existing disease, to inhibit tumor recurrence, and to prevent progression to muscle invasion or metastasis. Transurethral resection (TUR) is the primary modality for the removal of Ta/T1 lesions and focal Tis. TUR does not prevent the development of new tumors, which provides a rationale for adjuvant therapy. Intravesical therapy after TUR may be cytotoxic to residual overt or occult carcinomas and premalignant mucosal lesions.

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Natural History

The natural history of superficial bkadder cancer is largely unpredictable owing to tumor heterogeneity. In some patients, it is evidenced by rapid progression to deeply invasive disease but in a majority it is characterized by slow growth of multiple metachronous tumors that remain confined to the urothelium.

The rates of recurrence after initial TUR vary from 30% with a solitary papillary tumor to more than 90% in some cases of multiple tumors. Most lesions recur within 6 to 12 months at the same stage and grade, but between 5% and 30% of all cases exhibit progresion of the disease[5].

Multivariate analyses have shown that factors of recurrence include a history of superficial tumors, multiple tumors at diagnosis, high tumor grade (grade 3 versus grade 1 and 2), and tumor stage (T1 versus Ta).[2,9] Furthermore, response to therapy is highly significant. Patients whose disease fails to respond to TUR and intravesical therapy at 3 to 6 months, generally exhibit a pattern of frequent tu-

mor recurrences[10]. Thus, the extent and duration of the disease as well as the early response to therapy help define the majority of patients who will suffer tumor recurrences later.

Intravesical therapy for patients at a high risk of tumor recurrence is a valuable adjunct to TUR. Prevention of superficial tumors is an important goal, as it may spare patients further urinary symptoms and repeated endoscopic resections. However, because most tumors recur at the same low stage and grade, they pose little risk to the patients. Moreover, the number of tumor recurrences does not correlate with the development of invasive disease. A more appropriate assessment of the efficacy of intravesical therapy is prevention of disease progression. Stage T1 tumors, especially those of high grade (grade 3), respond less favorably to TUR and intravesical therapy than Ta or Tis lesions, and are more likely to progress. Furthermore, patients having persistent or recurrent Tis, Ta or T1 cancers despite therapy are at risk of muscle invasion.

Rationale for Intravesical Therapy

Intravesical therapy is divided into two major categories: 1) therapeutic, designed to treat established disease; and 2) prophylactic or adjuvant, designed to prevent recurrence and progression. Definitive therapy aims to treat a disease that cannot be resected surgically. This includes tumors that are too numerous or too large, inaccessible tumors, some invasive T1 cancers and Tis persisting after a TUR. Prophylactic therapy is given after a presumed complete TUR as an adjunct to prevent true recurrences due to incomplete resection or new tumor development resulting from multiple tumor origins.

Intravesical therapy brings high concentrations of drug in contact with tumor- bearing mucosa. Tumor implantation after resection may be inhibited by reducing the number or viability of free-floating malignant cells. Residual carcinoma or precursor mucosal lesions may be destroyed, thus preventing tumor recurrence. Progression of disease requiring more intense local therapy (cystectomy or systemic chemotherapy) may be delayed. The limited systemic absorption of intravesical agents minimizes serious toxicty. Most frequently used intravesical agents are thiotepa, doxorubicin (Adriamycin), mitomycin C, and bacille Calmette-Guerin (BCG). Individual drug doses and schedules vary widely. An inductive schedule of 4 to 8 weekly doses is given. In case of response, this may be followed by monthly doses for up to 1 year and, in some cases, for 2 years. Average chemotherapy doses are 30 to 60 mg thiotepa, 40 to 80 doxorubicin, and 20 to 40 mg mitomycin. The BCG product is a biological response modifier, and doses vary with strain: 120 mg (Pasteur), 2-8x108 viable organisms (Tice) and 60 mg (Connaught). Exceptions to the above doses and schedules are common.

Prophylactic Intravesical Therapy

In patients treated with TUR alone, the recurrence incidence over 1 year was 43% in patients presenting with their first Ta/T1 tumor and 70% in pateints with a prior history of bladder cancer. Overall, intravesical chemotherapy produced a small but mesurable effect on the observed recurrence rate, but it was less than that achieved with BCG. The net reduction in tumor recurrence among the treated patients relative to patients receiving TUR alone was 8% for thiotepa, 10% for doxorubicin, 12% for mitomycin, and 43 % for BCG.

Definite Intravesical Therapy

The data assembled for multiple studies provide a minimum of 6 months of follow-up and are given as the response rates of persistent papillary tumors and carcinoma in situ combined.[5] A complete response (CR) means no cystoscopic, biopsy or cytologic evidence of disease after therapy. A partial response (PR) is variously defined as a reduction in the number of tumors or involved bladder surface area, a 50% reduction in the size of overt lesions, and in case of Tis, a negative biopsy but positive urine cytology study. Failures (NR) are defined as no reduction in tumor number or size, or exhibited progression of disease. Such data must be interpreted cautiously, because assigning a patient to a definitive response category other than CR is subjective. In fact, most partial responses are short lived, and are similar to those in nonresponders.

The rate of complete response to BCG is significantly greater than that achieved with any of the chemotherapeutic agents, although there appears to be the same advantage of mitomycin C over doxorubicin or thiotepa. The responses of papillary tumors versus carcinoma in situ have not been stratified for the three drugs, whereas BCG seems to have a greater effect against Tis (73%) than papillary tumors (59%)[3,8].

Recommendations for Therapy

Many patients with primary low-grade (grade 1) papillary tumors derive little benefit from intravesical therapy. Most are well treated with TUR alone. Patients at highest risk for tumor recurrence and progression require adjuvant intravesical therapy after TUR. They include patients with T1 tumors (especially if multiple), multifocal papillary Ta cancers (grade 2 or 3), or Tis and persistently positive urinary cytology emanating from bladder after a TUR, in the event that all papillary or in situ tumors cannot be resected.

What Agent Should Be Initially Used?

The weight of evidence favors BCG over chemotherapy, as response rates to BCG appear to be somewhat greater and generally more durable, especially against carcinoma in situ[4]. Approaches other than single-agent instillations that use combinations of drugs, cycling of agents, and alternative drugs, are worthy of investigations.

When Should the Disease Be Considered to Have Failed to Respond to TUR and Intravesical Therapy?

This decision requires endoscopic experience and sound clinical judgment. A three- month period after the start of 6 to 8 weeks of therapy probably is not long enough to assess the results, but after 6 months one should expect a complete response to continued use of an active agent (two courses of treatment). It is unlikely that further intravesical treatment using the same drug will convert a failure into complete remission, and opens the risk of cancer progression. An occasional recurrent cytologically benign papillary tumor that is easily fulgurated does not require a radical change of treatment. However, a positive biopsy for persistent bladder cancer or positive urine citology study strongly argues for an alternative therapeutic strategy. Furthermore, there are no controlled studies and only a few circumstantial data to support protracted (maintenance) intravesical therapy given either therapeutically or prophylactically[1]. This is especially true among nonresponders. Inconvenience, expense, cumulative toxicity, and above all the risk of disease progession outweigh any individual long-term benefit.

For persistent superficial disease (especially Tis), alternative intravesical therapy is reasonable but should not be continued beyond 1 year in nonresponding patients. Persistent T1 disease portends an ominous prognosis, especially among patients who fail with carcinoma involving prostatic epithelium. Prostatic involvement, while not strictly a failure of intravesical therapy, generally demands aggressive measures. Cystectomy is currently the safest approach.

References

1. BADALEMENT RA, HERR HW, WONG GY et al. A prospective randomized trial of maintenance vs. nonmaintenance intravesical BCG therapy of superficial bladder cancer. J Clin Oncol 1987;5:441.
2. DALESIO O, SCHULMAN CC, SYLVESTER R et al. Prognostic factors in superficial bladder cancer? J Urol 1983;129:730.
3. GREEN OF, ROBINSON MGR, GLASHAN R. Does intravesical chemotherapy prevent invasive bladder cancer? J Urol 1983;131:33.
4. HERR HW, PINSKY CM, WHITMORE WF. Long-term effect of intravesical BCG on flat carcinoma in situ of the bladder. J Urol 1986;135:265.
5. HERR HW, LAUDONE VP, WHITHMORE WF. An overview of intravesical therapy. J Urol 1987;138:1363.
6. HERR HW, BADALEMENT RA, AMATO DA et al. Superficial bladder cancer treatment with BCG: a multivariate analysis of factor affecting tumor progression. J Urol 1989;141:22.
7. HERR HW, LAUDONE VP, BADALEMENT RA et al. BCG therapy alters the progression of superficial bladder cancer. J Clin Oncol 1989;6:9.
8. HULAND H, OTTO U. Mitomycin instillation to prevent recurrence of superficial bladder carcinoma. Eur Urol 1983;9:84.
9. Medical Research Council. Prognostic factors for recurrence on followup policies in the treatment of superficial bladder cancer. J Urol 1989;142:248.

Sažetak

ULOGA TRANSURETRALNE RESEKCIJE POVRŠINSKIH TUMORA MOKRAĆNOG MJEHURA

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Trideset posto svih primarnih površinskih tumora mokraćnog mjehura uopće ne recidiviraju, stoga ne zahtijevaju dodatno liječenje. Iz tih razloga je vrlo važan odabir onih bolesnika koji zaista trebaju dodatne mjere liječenja. Od velikog značenja je prvi kontrolni cistoskopski nalaz, tri mjeseca nakon transuretralne resekcije mokraćnog mjehura zbog tumora. Ne nađu li se znakovi recidiva osnovne bolesti, prognoza bolesti takvih bolesnika je povoljna te oni ne zahtijevaju dodatno liječenje. Ako se nađe recidiv bolesti, treba razmotriti daljnje modalitete liječenja.

Ključne riječi: *Neoplazme mokraćnog mjehura; Neoplazma mokraćnog mjehura - kirurgija; Neoplazme mokraćnog mjehura - trendovi*