

## How does the time interval between transurethral resection and cystectomy affect the oncological outcome after cystectomy in bladder cancer patients?

Mesane kanserinde transüretal rezeksiyon ile sistektomi arasında geçen süre, sistektomiden sonra onkolojik sonucu nasıl etkiliyor?

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### Abstract

**Objective:** The time interval between transurethral resection (TUR) and cystectomy can vary substantially in patients with bladder cancer. We evaluated the time intervals between the first and last TURs and between the last TUR and cystectomy in an attempt to define a relationship between the time interval and the oncological outcome after cystectomy.

**Materials and methods:** The study included 176 patients (128 males, 48 females; mean age 68 years; range 34-91 years) who underwent cystectomy for bladder cancer. Of these, 63 patients (35.8%) underwent multiple TURs prior to cystectomy. We evaluated the time intervals between the first and last TURs and between the last TUR and radical cystectomy and correlations were sought with tumor staging and grading.

**Results:** The average time intervals between the first and last TURs and between the last TUR and cystectomy were 924 days and 49 days, respectively. A significant correlation was found between the time interval from the first to the last TUR and alterations in both tumor stage and tumor grade ( $p=0.001$ ). With respect to tumor staging, understaging was found in 28 patients (44.4%) and overstaging was found in 10 patients (15.9%), while the stage of the tumor remained unchanged in 25 patients (39.7%). Undergrading was found in 19 patients (30.2%), overgrading in 11 patients (17.5%), and the grading did not change in 33 patients (52.4%). However, both tumor staging and grading did not show any significant correlation with the time interval between the last TUR and cystectomy ( $p=0.62$  and  $p=0.27$ , respectively).

**Conclusion:** The patients undergoing multiple TURs prior to cystectomy showed significant increases in both tumor stage and grade due to the prolonged waiting period compared to patients undergoing cystectomy directly after TUR. The time interval of 49 days was not associated with increases in tumor staging or grading by the time of cystectomy.

**Key words:** Cystectomy; neoplasm staging; time factors; urinary bladder neoplasms/surgery.

### Özet

**Amaç:** Mesane kanserli hastalarda transüretal rezeksiyon (TUR) ile sistektomi arasında geçen süre büyük ölçüde değişkenlik göstermektedir. Bu çalışmada, bu süre ile sistektomi sonrası onkolojik sonuçlar arasındaki ilişkiyi tanımlamak için, ilk ve son TUR uygulamaları arasındaki ve son TUR ile sistektomi arasındaki süreler değerlendirildi.

**Gereç ve yöntem:** Çalışmaya, mesane kanseri nedeniyle radikal sistektomi uygulanan 176 hasta alındı (128 erkek, 48 kadın; ort. yaş 68; dağılım 34-91). Bu hastaların 63'üne (%35.8) sistektomiden önce birden fazla TUR yapılmıştı. İlk ve son TUR uygulamaları arasındaki ve son TUR ile sistektomi arasındaki sürelerin tümör evrelemesi ve derecelendirmesi ile ilişkisi araştırıldı.

**Bulgular:** İlk ve son TUR arasındaki ortalama süre 924 gün, son TUR ile sistektomi arasındaki ortalama süre 49 gün idi. İlk ve son TUR arasındaki ortalama süre, hem tümör evresindeki hem de derecesindeki değişimlerle anlamlı ilişki gösterdi ( $p=0.001$ ). Bu açıdan, sistektomi sırasında 28 hastada (%44.4) tümör evresi artış gösterirken, 10 hastada (%15.9) daha düşük bulundu, 25 hastada (%39.7) ise değişmemişti. Sistektomi sırasındaki tümör dereceleri ise 19 hastada (%30.2) daha yüksek, 11 hastada (%17.5) daha düşük bulunurken, 33 hastada (%52.4) değişmemişti. Oysa, son TUR ile sistektomi arasındaki süre ile sistektomi sonrası tümör evrelemesi ve derecelendirmesindeki değişimler arasında anlamlı ilişki yoktu (sırasıyla,  $p=0.62$  ve  $p=0.27$ ).

**Sonuç:** Sistektomiden önce birden fazla TUR uygulanan hastalarda, TUR'dan sonra sistektomi uygulanmış hastalara göre, uzamış süreye bağlı olarak tümör evre ve derecesinde anlamlı artışlar meydana gelmektedir. Bulgularımız, TUR ile sistektomi arasındaki ortalama 49 günlük sürede tümör evre ve derecesinde anlamlı değişiklikler olmadığını göstermektedir.

**Anahtar sözcükler:** Sistektomi; neoplazi evrelemesi; zaman faktörü; mesane neoplazileri/cerrahi.

Invasive bladder cancer can be treated by means of transurethral resection (TUR) alone, early radical cystectomy, salvage cystectomy, local instillation therapy, systemic chemotherapy, or radiotherapy. All methods of treatment have their own indications, depending on tumor stage, tumor grade, localization, number of tumors in the bladder, presence of associated carcinoma *in situ*, and initial response to therapy.<sup>[1,2]</sup> These methods of treatment can be classified in two basic groups: bladder-sparing procedures and radical cystectomy. Patients scheduled for bladder-sparing procedures have a greater risk for recurrence and progression. Especially high-risk patients have a progressively increasing risk for developing extravesical recurrences even in case of successful primary treatment. A 10-year follow-up-study demonstrated that 34% of 99 patients with muscle-invasive bladder cancer treated by TUR as monotherapy developed relapses in the bladder with new muscle-invasive tumors.<sup>[3]</sup> Even low-risk tumors have a high recurrence rate of at least 20% in the first year after diagnosis.<sup>[4]</sup> High-risk patients and patients with tumor recurrence after bladder-sparing procedures should be informed on the risk for developing extravesical metastases and be advised to consider choosing early radical cystectomy. Even low-risk tumor patients must be informed about the pathogenesis of this panurothelial disease and about the way the tumor progresses. The final decision in favor of cystectomy, however, should be made in consideration of each individual case, based on the long-term survival chances and the expected quality of life of the patient.

The time interval between TUR of a bladder tumor and cystectomy can vary substantially. Despite the oncological guidelines concerning the actual tumor stage and tumor grading, this problem is essentially linked with the experience of the treating urologist and the pathologist responsible for preoperative tumor staging and tumor grading, which postoperatively often results in understaging. There are a number of methods to minimize the percentage of understaging, such as differential tumor resection, 5-ALA fluorescence, or employment of multivariate nomograms.<sup>[5-7]</sup>

However, the extent of understaging directly depends on the time between TUR and cystectomy.<sup>[5,8]</sup> In this study, the exact time intervals between the first and last TUR and between the last TUR and cystectomy were evaluated. The aim of this study was to correlate the time interval with both preop-

erative and postoperative tumor staging and grading. More specifically, the questions to be answered were: 1. How many days can pass between the first TUR-B and the last TUR-B and between the last TUR-B and cystectomy, before the specimens undergo histological differentiation? 2. If indicated, when is the ideal time for surgical intervention?

## Materials and methods

Between 2001 and 2004, 176 patients (128 males, 48 females, mean age 68 years; range 34-91 years) underwent cystectomy for bladder cancer in our department. Of these, 63 patients (35.8%) underwent multiple TURs prior to cystectomy. The time intervals between the first and last TURs and between the last TUR and radical cystectomy were evaluated retrospectively and correlated to tumor staging and grading for the first and last TUR as well as cystectomy. Statistical analysis was performed with the Pearson's two-sided chi-square-test.

## Results

The average time interval between the first and last TUR-B was 924 days. The average interval between the last TUR-B and cystectomy was 49 days.

A significant correlation was found between the time interval from the first to the last TUR-B and the progression in both tumor staging and tumor grading in 63 patients who had received multiple TUR-Bs prior to cystectomy ( $p=0.001$ ). With respect to tumor staging, understaging was found in 28 patients (44.4%) and overstaging was found in 10 patients (15.9%), while the stage of the tumor remained unchanged in 25 patients (39.7%).

Undergrading was found in 19 patients (30.2%), overgrading in 11 patients (17.5%), and the grading did not change in 33 patients (52.4%).

Both tumor staging and grading did not show any significant correlation with the time interval between the last TUR and cystectomy which was evaluated in 176 patients ( $p=0.62$  and  $p=0.27$ , respectively).

## Discussion

The causes for inaccurate or faulty diagnosis in staging and grading of bladder cancer can be either methodical or due to the subjective specimen evaluation of the treating urologist and pathologist. Methodical error sources are connected to the way that specimens are obtained through TUR of the bladder. This can be improved by means of differen-

**Table 1. Literature data on the alteration of tumor staging between TUR-B and cystectomy**

	No. of patients	Minimal tumor stage/grade after TUR-B	Time between TUR and cystectomy	Understaging (%)
Steiner et al. <sup>[12]</sup>	38	pT <sub>1</sub> G <sub>3</sub>	–	39
Denzinger et al. <sup>[13]</sup>	105	pT <sub>1</sub> G <sub>3</sub>	–	30
Karakiewicz et al. <sup>[5]</sup>	726	pT <sub>1</sub> G <sub>3</sub>	–	31
Hara et al. <sup>[8]</sup>	167	pT <sub>1</sub> G <sub>3</sub>	Group A-up to 3 months Group B. more than 3 months	Incidence of vascular involvement was higher in group B
This study	63	pT <sub>1</sub> G <sub>3</sub>	49 days Over 49 days	No 44.4

tial tumor resection, 5-ALA fluorescence, or employment of multivariate nomograms.<sup>[5,6]</sup>

The second error source, i.e. subjective specimen evaluation by pathologists and urologists, is of even greater significance as it is harder to eliminate. Pathologists play a pivotal role in the diagnosis and reporting the pathological features on which the prognosis is based. There are a few studies that have analyzed relevant reasons for diagnostic mistakes. The main problem is insufficient information from urologists and unsatisfactory communication between urologists and pathologists.<sup>[9]</sup> Another problem is limited communication among the urological and pathological communities, despite the presence of an increasing number of histological variants of urogenital carcinoma, which have been recognized but not mutually discussed between both communities.<sup>[10]</sup>

Substantial improvement in tumor staging and grading can be achieved if the following aspects are pursued: adequate information about the patient history, proper handling of the specimens, identification of reliable histopathological techniques necessary to achieve more detailed diagnostic information and to adequately evaluate the prognostic variables, as well as a standardized pathological report. The 2004 WHO grading system must become acceptable to clinicians, perhaps with a minimal modification of the present terminology. Simple transurethral resection biopsy should be expressed in terms of clinical rather than pathological staging.<sup>[11]</sup>

Correct diagnosis in bladder cancer patients is of enormous importance for the prognosis. Misinterpretation of the histological specimens has resulted in a number of problems. These are, in particular, understaging and overstaging. Understaging is a treacherous factor in tumor staging with subsequent inadequate therapy indication, which will even-

tually negatively influence the long-term prognosis of these patients. Several studies reported high rates of understaging following TUR-B (Table 1). In one study, 38 consecutive patients with T1G3 transitional cell carcinoma (TCC) were treated by radical cystectomy after staging TUR-B at six different centers. The bladder biopsies and cystectomy species were examined and compared for three different antibodies against p53. Fifteen of the patients (39%) were found to have a higher tumor stage in the cystectomy specimens.<sup>[12]</sup> Another study evaluated the pre-cystectomy prediction of pT and pN stages after cystectomy in 726 patients who were treated with radical cystectomy and bilateral pelvic lymphadenectomy.<sup>[5]</sup> The staging before and after the operation was compared. At TUR, 11% of the patients were staged as pT3-4 versus 42% at cystectomy, demonstrating that understaging was 31%. Lymph node metastasis was found in 24% of the patients at cystectomy (pN1-3).<sup>[5]</sup> In our study, 28 of 63 patients (44.4%) who underwent multiple TURs prior to cystectomy in the time interval of 924 days turned out to have been understaged.

Three aspects need to be discussed in the following:

I. What is the strategic outcome in the treatment of pT1G3 - early indication for cystectomy? What kind of treatment is better for the pT1G3 patient?

II. What is “the perfect time” for cystectomy? Can the same staging/grading in TUR and cystectomy specimens identify “this perfect time”?

III. What kind of morphological changes take place in the bladder wall during the follow-up between TUR and cystectomy?

I. A number of studies described treatment options for tumor stage pT1G3. There is an intense controversy over local instillation therapy, early cystectomy, and radiation therapy. Some recent studies

have investigated the option of early cystectomy. Denzinger et al.<sup>[13]</sup> analyzed data of 105 patients with pT1G3, where 51% of the patients underwent early cystectomy while 49% underwent deferred cystectomy for recurring bladder cancer. The 10-year cancer-specific survival rates were 78% and 51%, respectively ( $p < 0.01$ ). Understaging (i.e. upstaging in cystectomy specimens) was found in 30%. Early as opposed to deferred cystectomy seems to increase the cancer-specific survival rate in high risk pT1G3 bladder cancer.<sup>[13]</sup>

There have been attempts to determine whether p53 is helpful in making the decision to perform cystectomy in T1G3 TCC, by prospectively comparing the p53 status of bladder biopsies.<sup>[12]</sup> The results showed that the p53 status of the TUR-B specimens did not provide relevant information with regard to local tumor staging and thus, was not helpful in making the decision for or against cystectomy. However, the decision in favor or against early cystectomy can only be made on the basis of retrospective studies or in consideration of the experience of a particular urologist. This is due to the deficiency of prospective randomized studies.<sup>[14]</sup>

Moreover, radiation therapy for treatment of bladder cancer has become a potent and attractive alternative for some radiologists. There are a number of studies by radiologists that demonstrate an acceptable result of radiation therapy for bladder cancer. The largest randomized trial included 210 patients with pT1G3 disease, who were recruited from 37 centers over a period of 11 years.<sup>[15]</sup> The patients were randomized to observation or radiotherapy of the bladder in group 1 and to intravesical therapy or radiotherapy in group 2. No evidence for an advantage of radiotherapy was found in terms of a progression-free interval (hazard ratio 1.07; 95% CI 0.65, 1.74;  $p = 0.785$ ), progression-free survival (hazard ratio 1.35; 95% CI 0.92, 1.98;  $p = 0.133$ ), or overall survival (hazard ratio 1.32; 95% CI 0.86, 2.04;  $p = 0.193$ ). The results of this study showed no evidence that radiotherapy was better than more conservative treatment. The prognosis in this group of patients appears to be poor irrespective of the treatment. However, future studies should investigate a possible neoadjuvant radiation therapy prior to cystectomy from stage T<sub>2</sub> onwards, involving new technical options.<sup>[1]</sup>

It is also important to mention the possibility of BCG (bacille Calmette-Guérin) treatment of pT1G3. Endoscopic resection plus BCG treatment of pT1G3 tumors has been shown to provide 80% disease-free five-year survival with bladder preservation, provid-

ed that tumor staging and tumor grading are correctly made.<sup>[16]</sup> In our study, understaging ranged between 31% and 47%. The patients should be informed on the risk of understaging and make the final decision on the treatment strategy. Nevertheless, the method of choice for tumor stages higher than pT1G3 remains radical cystectomy.

II. The time interval between TUR-B and cystectomy must be considered critically, as a transurethral bladder resection alone does not mean that the tumor progression can be stopped. If the time between the first resection and cystectomy is too long, the specimens from both are highly likely to be different due to normal tumor progression. The same staging in TUR-B and cystectomy specimens must be a criterion for the time interval that can be identified as optimal. There is one study, in which the investigators examined two groups of bladder cancer patients.<sup>[8]</sup> The patients in both groups underwent radical cystectomy and the survival time of the patients was analyzed. The first group of patients underwent cystectomy within three months after the primary diagnosis and group 2 patients underwent cystectomy within three months after multiple TUR-Bs. No significant difference was observed in the patients' clinical and pathological characteristics between the two groups except for age. The median follow-up periods for the two groups were 53 months and 48 months, respectively.<sup>[8]</sup> The recurrence-free, cause-specific, and overall survival rates in the first group were significantly higher than those in the latter ( $p < 0.05$ ,  $p < 0.05$ , and  $p < 0.05$ , respectively). Final pathological analysis revealed that the two groups were similar with respect to pathological stage, tumor grade, and lymph node metastasis; however, the incidence of vascular involvement was significantly higher in the latter group ( $p < 0.05$ ), despite the lack of a significant difference in the incidence of vascular involvement in TUR specimens of the two groups. These findings suggest that radical cystectomy in the early disease process, especially before the occurrence of vascular involvement, may result in an improvement in survival of patients with invasive TCC of the bladder.

Two outcomes are important for our study. The first is the clinical aspect, i.e. the recurrence-free, cause-specific, and overall survival rates obtained in those patients with a three-month time interval between TUR-B and cystectomy. The second is the presence of vascular tumor involvement in specimens extracted beyond three months. Vascular involvement leads to a metastatic progress of the tumor. Thus, a time interval below three months after the primary

diagnosis must be aimed for in order to achieve a better surgical-oncological result.

III. In our study we identified the maximum time interval between TUR-B and cystectomy, during which there was no statistically significant histological tumor progression in 63 patients. On the basis of these results, we recommend a maximal period of 49 days as the optimal time from TUR-B to cystectomy. If this duration exceeds 49 days, the number of understaged cases will increase.

## Conclusion

Patients undergoing multiple TURs prior to cystectomy show a significant increase in tumor stage and grade due to the prolonged waiting time compared to patients undergoing cystectomy directly after TUR. We found that a mean time interval of 49 days between TUR and subsequent cystectomy did not have a statistically significant impact on tumor staging or grading at the time of cystectomy. Therefore, the indication for cystectomy in patients with transitional cell cancer of the bladder should not be delayed by multiple TUR-Bs.

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