OBJECTIVES
To report our experience with a select group of patients with low-risk tumors included in an observation and monitoring program after the diagnosis of recurrence.

METHODS
We performed a prospective cohort study in patients diagnosed with recurrent, nonmuscle-invasive bladder cancer maintained under an active surveillance protocol. The inclusion criteria were papillary tumors with negative cytology findings, previous nonmuscle-invasive tumor (Stage pTa, pT1a), grade 1-2, size <1 cm, and number of tumors <5. No symptomatic patients or those with carcinoma in situ or grade 3 tumors were included. A retrospective analysis of a control group of patients with clinical characteristics similar to those of the patients on active surveillance, but who underwent transurethral resection immediately after the recurrence was diagnosed was also performed.

RESULTS
The data from 64 patients (70 observation events) were analyzed. The mean patient age was 66.7 years. The median follow-up was 38.6 months. The median time patients remained in observation was 10.3 months. The tumor histologic features before observation were Stage pTa in 77.1%, Stage pT1a in 22.9%, grade 1 in 67.1%, and grade 2 in 23%. After 10.3 months, 93.5% of the patients had not progressed in stage and 83.8% had not progressed in grade. None of the patients experienced progression to muscle-invasive disease. A comparison between the rates of progression in the study and control groups showed no statistically significant difference.

CONCLUSIONS
Patients with recurrent, small (<1 cm), nonmuscle-invasive bladder tumors can be safely offered monitoring under an active surveillance protocol, with a minimal risk of progression in either grade or stage, thus reducing the amount of surgical intervention they might undergo throughout their life. UROLOGY 73: 1306 –1312, 2009. © 2009 Elsevier Inc.

N onmuscle-invasive bladder tumors are a very heterogeneous group, ranging from papillary tumors only affecting the mucosa and presenting as low grade (Stage Ta, G1) to high-grade tumors (Stage T1, G3) with associated carcinoma in situ (CIS). These tumors are associated with a high degree of recurrence throughout follow-up, and they are usually treated by resection or fulguration of the lesions, in addition to some form of chemotherapy or immunophylaxis.

Software tools are available that can help to predict the behavior of these tumors in terms of their risk of progression and recurrence. However, very little scientific evidence is available regarding the actual progression rates if surgical treatment is delayed in select patients with tumors considered low risk owing to their clinical characteristics.

An active surveillance program has been available for several years at our institution for patients with low-risk bladder cancer. This surveillance option was specifically intended for patients with recurrent nonmuscle-invasive bladder tumors, for whom, because of the clinical history or tumor characteristics, we did not believe that immediate resection was necessary after the diagnosis. This protocol was also designed to reduce the number of surgeries throughout the patients’ lifetime. This approach has been previously described by Soloway et al. in 2003 who concluded that, in selected cases, active surveillance is a safe and valid therapeutic alternative. The goal of the present study was to evaluate the long-term oncologic safety and to determine the risk of tumor progression among patients enrolled in an active surveillance program for low-risk bladder cancer.
MATERIAL AND METHODS

A prospective cohort study of patients who had undergone surgery at our hospital from 1999 to 2006 was initiated. Patients deemed to be candidates were offered entry into the study after the pathologic report showed nonmuscle-invasive tumor and if they presented with tumor recurrence during the follow-up period. We included these patients in an active surveillance program after the patients provided fully informed consent. They were allowed to undergo surgery if they chose at any point during the observation period.

The inclusion criteria for the observation program were recurrent papillary tumors with a previous finding of nonmuscle invasive urothelial carcinoma, Stage pTa and pT1a (extending into the lamina propria but above the level of the muscularis mucosa), low or intermediate grade (G1-G2), <1 cm in size, and with <5 tumor sites. No patients with a history of a high-grade tumor (G3), CIS, or positive cytologic findings were included in the observation and monitoring program.

All patients included in the observation group underwent close monitoring with cytology and flexible cystoscopy every 3-4 months. All pathologic studies were performed by a single experienced uropathologist and fully dedicated cytologists.

The patients discontinued the observation period and underwent transurethral resection when they presented with an increase in the number and/or size of the lesions, symptoms (mainly hematuria), or if the surveillance urine cytology findings were positive for malignancy.

During the study period, active surveillance was not used for all the patients diagnosed with tumors of these characteristics. Therefore, we decided to retrospectively review the data from patients in whom immediate transurethral resection was performed after the diagnosis of tumor with clinical characteristics identical to those of our observation group.

The variables included in our statistical analyses were the interval from the initial diagnosis to entry into the observation period, tumor size, number of tumors, interval that the patient remained in observation, reason for discontinuing observation, progression stage and/or grade of the tumor. The qualitative variables are presented by frequency distribution and the quantitative variables by the mean ± SD and median with the interquartile range. The comparison of qualitative variables was done using the χ² test. The probability of recurrence was studied using a survival analysis by the Kaplan-Meier method. The significance level in all the hypothesis tests was P = .05. The software used for the analysis was Statistical Package for Social Sciences, version 12 (SPSS, Chicago, IL).

RESULTS

A total of 273 patients with nonmuscle invasive tumors had undergone surgery at our hospital from 1999 to 2006. A series of 64 patients with a total of 70 observation events (some patients entered the observation program several times throughout their follow-up period) was studied. The mean age was 66.7 ± 13.1 years, and 82.9% of the patients were male. The median interval from the initial diagnosis to entering the observation period was 17.3 months (interquartile range 3.16). The median follow-up for all patients in the study was 38.6 months (interquartile range 36.7). The median interval during which the patients remained in observation was 10.3 months (range 1.13-47.5). The histologic features before observation were Stage Ta in 77.1% of the patients, Stage T1a in 22.9%, G1 in 67.1%, and G2 in 23%.

The most common reason for discontinuing the observation period (58.6%) was an increase in the number and/or size of the tumors. The other reasons were symptoms (4.3%), positive cytology onset (2.9%), increase in the size of the lesion and positive cytology (4.3%), noncancer-related death (4.3%) and patient request (1.4%). The rest of the patients (24.2%) were still under observation at the data analysis. No patient left the observation program because of poor compliance with the established follow-up protocol.

The pathologic findings at entry to the observation period and after completing this period are shown in Table 1. After remaining in observation for a median time of 10.3 months, 93.5% of the patients had not progressed in stage and 83.8% had not progressed in grade (Fig. 1). None of the patients experienced progression to muscle-invasive tumor. Only 3 patients in the whole series presented with progression to a high-grade tumor (G3) or presented with associated CIS. No adjustment for gender was made because the low number of women included in the study (n = 5) did not allow us to draw any conclusions.

Table 2 lists the data from the group control of patients in whom immediate transurethral resection was performed after the diagnosis of tumors with clinical characteristics identical to those of our observation group. In the control group, 11.2% of the patients presented with progression in stage (compared with 6.5% of the observation group), and 7.82% presented with progression in grade (compared with 16.2% in the

<table>
<thead>
<tr>
<th>Before Observation</th>
<th>After Observation</th>
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<tr>
<td>TaG1-G2</td>
<td>T1G1-G2</td>
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<tr>
<td>TaG1-G2</td>
<td>24</td>
</tr>
<tr>
<td>T1G1-G2</td>
<td>6</td>
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</table>

CIS = carcinoma in situ; NA = pathologic data not available because patient was in observation period or because of noncancer-related death.
observation group). Only 4 patients (4.40% vs 4.28% in the observation group) developed progression to G3 or presented with associated CIS. No significant differences were found when we compared the progression rates in grade and stage in the 2 groups. In the control group, progression to infiltrating tumor was found in 2 patients.

**COMMENT**

Nonmuscle-invasive bladder tumors are associated with a high degree of recurrence throughout the follow-up period.\(^1,^6\) Transurethral resection is the therapeutic option of choice, not only because it eradicates existing visible bladder lesions, but also because it provides sufficient material for a correct diagnosis and tumor graded determination. The method of surgical resection also provides histologic information that makes it possible to establish prognostic information. Some form of chemoprophylaxis (immediate single-dose mitomycin C) for low- to intermediate-risk patients or immunoprophylaxis with bacille Calmette-Guérin for intermediate- to high-risk patients is commonly used. Repeat transurethral resection is only performed in our practice for patients with an initial pT1G3 tumor or whenever muscularis propria is absent in the surgical specimen.

Patients with bladder cancer will often undergo several transurethral resections to treat recurrent lesions, which can be associated with complications and side effects. The low likelihood of progression and the indolent nature of certain types of bladder tumors will have a negligible effect on survival in select patients.\(^7\)

It has been shown that in patients with negative cytologic findings, the correlation between the cystoscopic findings and the histologic features of the tumor is high, with an accuracy of \(\leq 98\%\).\(^8\) The cystoscopic findings of bladder cancer can also predict for muscle invasion.\(^9\) It has been described as accepted practice to perform office fulguration of small recurrent papillary tumors. Fulguration achieves sufficient control of this type of tumor.\(^10\) At our center, fulguration of these recurrent tumors is not the regular practice, because we believe that no sort of active treatment is needed for this tumor type according to its biologic behavior. In addition, we believe that active surveillance can be conducted in selected patients with recurrent tumors that we consider to be low risk to avoid repeated surgery.

The observation of these tumors, without active treatment, is a common clinical practice; however, although routinely performed by some urologists, it has not been included in any clinical guidelines. Therefore, to begin an active surveillance program, no inclusion or exclusion criteria have been determined beyond those reasonably assumed by the urologist who

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**Table 2.** Group of patients with similar characteristics who underwent surgery immediately after diagnosis of recurrent tumor

<table>
<thead>
<tr>
<th>Initial Tumor Stage and Grade</th>
<th>At Recurrence</th>
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<tr>
<td></td>
<td>TaG1-G2</td>
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<tr>
<td>TaG1-G2</td>
<td>47</td>
</tr>
<tr>
<td>T1G1-G2</td>
<td>6</td>
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</tbody>
</table>

CIS = carcinoma in situ.
evaluates the specific comorbidity of each patient and the risk of progression and/or recurrence of each tumor.

The decision to include patients in this program was not determined by patient age or associated comorbidities, but rather by the clinical characteristics of the tumor (cystoscopic appearance of a low-grade tumor) and the absence of symptoms, mainly hematuria, and negative cytology findings. In all cases, the individual clinical features were taken into account, and they were considered a very important criterion to reach an agreement with the patients about the course of action, after explaining the risks and benefits and ensuring that they understood that an observation program was not included in the recommendations of the clinical guidelines approved by the different urologic associations.

The tumor grade was the most important of the inclusion criteria. It is well established that the risk of progression of low-grade, Stage Ta lesions to muscle-invasive cancer is small, generally around 5%-10%. These tumors do not share the biologic potential of tumors that invade the lamina propria (Stage T1), because the latter have a greater probability of muscular invasion and they tend to be of a higher cytologic grade. Including patients with tumors that invade the lamina propria in this observation program would be questionable. Nevertheless, a different prognosis can be made according to the depth of lamina propria invasion, beyond the muscularis mucosa (T1b), with a probability of progression of ≤53% compared with those with more superficial invasion of the lamina propria (T1a), whose probability of progression is similar to that of those with Stage Ta, about 5%.11 We therefore decided to include these selected patients with Stage T1a in our group because they were not at a greater risk than other patients with Stage Ta tumors.

Our group of patients remained in observation for a median of 10.3 months. The most common cause to proceed to surgery was an increase in the tumor number or size. The chronology of the tumor occurrence is an aspect that must be taken into account when deciding on the therapeutic options. Disease recurrence is closely linked to the duration of the period free of disease after the first transurethral resection; however, almost 50% of patients will undergo another transurethral resection during their lifetime and almost three quarters will undergo ≥3 additional operations. It is therefore a sensible approach to regard stability in the size and number of tumors at cystoscopy during the follow-up period as a follow-up criterion.

To our knowledge, this is the largest series published on patients with nonmuscle-invasive tumors under observation.4,5,12-14 The results in the series by Soloway et al.4 (which included Stage T1 and high-grade tumors) were similar to ours (6.7% with progression to high grade vs 4.28% in our series). In another study by Gofrit et al.,5 no progression in any of the high-grade tumors was detected; however, we must consider that this was a more homogeneous series, because all initial tumors were Stage TaG1-G2 (Table 3).

The choice of 5 papillary tumors as a maximal inclusion criterion was arbitrary. Low-grade bladder tumors are normally multifocal, and they can appear throughout the urothelium, simultaneously or over time, with the rest of the mucosa endoscopically and histologically normal. This fact speaks in favor of the biologic indolence of the disease and must be differentiated from the concept of a diffuse lesion in the urothelium with adjacent involvement of premalignant (dysplasia) or malignant (CIS) lesions. The progression rate in these low-grade multiple tumors was comparable to that described in other series in which resection was performed immediately after the diagnosis.

The follow-up of the patients in the present series consisted of cystoscopy and cytology every 3-4 months for the first year. We consider that flexible cystoscopy is a well-tolerated examination with a much lower rate of complications than surgery and with a high acceptance of ≥99.5.15 Once the treatment alternatives were explained, a high percentage of patients preferred to undergo close monitoring by cystoscopy and to delay the surgery for as long as possible. At the end of the recruitment period for the present study, we modified the schedule of endoscopic examinations. In patients who had completed their first year follow-up, the studies were done on an alternating basis between ultrasonography and cystoscopy plus cytology, and in these cases, the follow-up intervals were increased to every 6 months. Bladder ultrasonography is an accepted diagnostic modality as recognized in the current clinical guidelines16 and allows for the detection of growth or permanence as low-burden disease while remaining undetectable on ultrasound.

We consider urinary cytology a pivotal examination for patients participating in an observation and monitoring program. The cytologic identification of high-grade

Table 3. Comparison between progression rates in grade and stage for each group

<table>
<thead>
<tr>
<th>Investigator</th>
<th>n</th>
<th>Median Time in Observation (mo)</th>
<th>Pathologic Findings Before Observation</th>
<th>Progression To High Grade (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soloway et al.,4 2003</td>
<td>44</td>
<td>10.09</td>
<td>TaT1/G1-G3</td>
<td>6.7</td>
</tr>
<tr>
<td>Martinez Caceres et al.,12 2005</td>
<td>15</td>
<td>5.76</td>
<td>TaT1/G1-G3</td>
<td>6.67</td>
</tr>
<tr>
<td>Gofrit et al.,5 2006</td>
<td>38</td>
<td>13.5</td>
<td>Ta/G1-G2</td>
<td>0</td>
</tr>
<tr>
<td>Pruthi et al.,13 2008</td>
<td>22</td>
<td>NA</td>
<td>TaT1/G1-G3</td>
<td>9</td>
</tr>
<tr>
<td>Present study</td>
<td>70</td>
<td>10.3</td>
<td>Ta-T1a/G1-G2</td>
<td>4.28</td>
</tr>
</tbody>
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NA = not available.
lesions is diagnostically important and offers great value as a prognostic risk factor. Its performance is excellent, with a sensitivity of 90% in these high-grade cases and a specificity of 98%-100%. In our program, it was therefore a critical point to discontinue the observation, regardless of the number and/or size of the lesions being controlled. Our experiences with other markers such as BTA TRAK or NMP22 assays have not changed our attitude, given their high rate of false-positive results in the context of infection, lithiasis, or instrumentation. In the end, we have always resorted to selective urine cytology to support our approach to a given case.17

Finally, the criteria for discontinuing the observation included the symptoms caused by the tumor. In the case of hematuria, even if it was self-limited, our approach was to remove the patient from active surveillance and propose surgery. This active surveillance program was not used for all patients diagnosed with a recurrence during follow-up at our center. The patients were included in this study on the basis of the attending urologist’s preference. This has enabled us to retrospectively review and select patients with identical clinical characteristics who had undergone immediate resection after diagnosis, with the finding that the incidence of progression in grade and stage in these patients was no different from that of the patients in our observation group. A limitation of this study was the lack of randomization between the groups, which would have allowed for more robust conclusions to be drawn. To minimize the selection bias due to nonrandomization, the histopathologic characteristics of both groups, as listed in Table 2, were equivalent in terms of grade and stage.

The benefits achieved with this practice were mainly a reduction in the number of resections that patients would undergo in their lifetime, with the attendant potential complications. Postoperative bleeding and bladder perforation are the most common immediate complications and vesicoureteral reflux, bladder retraction, and urethral stenosis the most common later complications.6 This potential benefit was difficult to quantify with the present study design, and only a randomized study would be able to answer that point. The goal was to avoid excessive treatments as much as possible without putting patients into danger of an adverse clinical course. Although it was not an objective of our study, this practice also involves an added economic benefit by sparing the patients the expense of a surgical intervention.

CONCLUSIONS

Patients with small recurrent nonmuscle-invasive bladder tumors of a low-grade cystoscopic appearance can be placed into an observation protocol without an increased risk of progression either in grade or stage, thus reducing the amount of surgery that patients undergo throughout their lifetime, as well as reducing potential complications associated with such procedures.

References


EDITORIAL COMMENT

The authors propose that patients with low-grade papillary bladder tumors could be monitored safely, deferring therapy unless the recurrent tumors increased in size or number. Few patients (6.5%) had stage progression, and more (16%) developed recurrence with higher grade tumors; however, none progressed to muscle-invasive disease. Although this report confirms several recent reports that active surveillance of small papillary bladder tumors might be a reasonable strategy, reducing the burden of frequent transurethral resections, the study had 3 main weaknesses.

First, only 64 patients underwent observation for a median of 10 months. Thus, too few were followed up for too short a time.