Bladder Cancer

Bladder Preservation in Selected Patients with Muscle-Invasive Bladder Cancer by Complete Transurethral Resection of the Bladder Plus Systemic Chemotherapy: Long-Term Follow-up of a Phase 2 Nonrandomized Comparative Trial with Radical Cystectomy

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Abstract

Background: Many phase 2 bladder-sparing programmes using transurethral resection of the bladder (TURB) plus chemotherapy or radio-chemotherapy have been undertaken, but some controversies remain.

Objective: To determine the efficacy of complete TURB plus three cycles of cisplatin-based chemotherapy in selected patients with muscle-invasive bladder cancer (MIBC).

Design, setting, and participants: A phase 2 nonrandomized trial was designed that included patients with MIBC who underwent complete TURB with positive biopsies of the tumour bed. Patients with negative biopsies of the tumour bed, with macroscopically residual tumour, with hydronephrosis, or with distant metastasis were excluded from this trial. Patients included in this trial were offered three cycles of systemic chemotherapy or radical cystectomy (RC). Clinical response (cR) was denoted by either no tumour or the presence of Ta1–Tis bladder tumour at 3-mo evaluation; clinical non-response (cNR) was denoted by cases of muscle-invasive tumour or distant metastasis. Of 146 patients who entered this trial, 75 choose the bladder-sparing programme and 71 chose RC.

Measurements: At 5 yr and 10 yr, the cancer-specific survival (CSS) rate was 64.5% and 59.8%, respectively, with no significant difference compared to the RC arm (p = 0.544). The progression-free survival with bladder preserved was 52.6% and 34.5%, respectively. In multivariate analysis, cR was the only predictive factor for survival (p = 0.001) and bladder preservation (p = 0.000).

Results and limitations: This was not a randomized trial, and patients were included over 16 yr. However, no modifications were made to the therapy schedule except from chemotherapy schemes considered standard at the time.

Conclusions: Patients with microscopic residual cancer after complete TURB seem to be good candidates for the bladder-sparing programme using three cycles of systemic chemotherapy, with CSS comparable to RC.

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1. **Introduction**

Although radical cystectomy (RC) remains the standard of care for patients with muscle-invasive bladder cancer (MIBC), over the past decades, many phase 2 bladder-sparing programmes using transurethral resection of the bladder (TURB) plus chemotherapy or radio-chemotherapy have been undertaken. However, some controversies and questions remain.

In general, initial clinical response is significantly higher in TURB plus radio-chemotherapy than in TURB plus chemotherapy programmes [1,2]. However, with long-term follow-up, there is no clear advantage between the programmes in terms of survival and bladder preservation rates [3–6], giving rise to the controversy concerning which is the more reliable method for bladder sparing.

The contribution of each method to survival in multimodal strategies is difficult to interpret [5]. This is an important issue in order to optimize the most appropriate schedule for achieving the best balance among survival, bladder preservation, and toxicity.

No specific inclusion criteria for bladder-sparing programmes have been established. However, in multivariate analysis, complete TURB, low clinical stages, and the absence of hydronephrosis are the most important predictive factors for survival [7–11]. The balance between these prognostic factors can have an important impact on survival that precludes knowing the real efficacy of the therapy schedule. Therefore, inclusion criteria can be crucial in identifying the efficacy of a bladder-sparing programme and in defining the most suitable patients for such a programme.

To define the efficacy of systemic chemotherapy on MIBC, we designed a prospective, comparative, nonrandomized study of patients with very strict inclusion criteria (ie, patients with residual microscopic tumours after complete TURB), offering them three cycles of systemic cisplatin-based chemotherapy (75 patients) or RC (71 patients). The treatment protocol was approved by the Ethical Committee of our institution. Patients were informed about the advantages and disadvantages of both procedures, and they chose the approach.

2. **Methods**

2.1. **Patients and inclusion criteria**

This trial started in April 1989 and included 146 patients through June 2005. Patients with MIBC who underwent a complete fractionated TURB of bladder tumour [12] with no repeat transurethral resection (TUR) performed at 2–6 wk were eligible for this trial if biopsies of the tumour bed (>5) on macroscopic apparently healthy muscularis propria, which were routinely taken after the tumour was completely resected, were positive for tumour. If these biopsies were negative, patients were only observed. If TURB reached perivesical fat and this tissue was infiltrated by tumour cells, patients were excluded from this programme. Similarly, those patients with residual macroscopic tumour after TURB were excluded undergoing an RC (Fig. 1). Urinary cytology; random bladder mucosa biopsies, including prostatic urethra and bimanual examination under anaesthesia; blood analysis; chest x-ray; and abdominal-pelvic computed tomography (CT) scan or magnetic resonance imaging (MRI) were systematically performed. Patients with lymph node involvement, distant metastases, or hydronephrosis were also excluded for this trial. Patients who fulfilled the inclusion criteria were offered three cycles of cisplatin-based chemotherapy (75 patients) or RC (71 patients). The treatment protocol was approved by the Ethical Committee of our institution. Patients were informed about the advantages and disadvantages of both procedures, and they chose the approach.

2.2. **Clinical response assessment and follow-up**

Clinical response (cR) consisted of patients achieving a clinically complete response (cCR) or a partial response (cPR). Patients included in the bladder-sparing programme were assessed at the end of the third cycle of chemotherapy for cR. Clinical response criteria and the follow-up schedule are displayed in Table 1. Progression occurred when MIBC (cT ≥ 2 M0—local progression), lymph node involvement, or distant metastases were developed after bladder preservation; recurrence occurred in cases of non–muscle-invasive bladder tumour (cTa1–Tis) development.

The follow-up schedule for patients treated with radio-chemotherapy was similar to those included in the bladder-sparing series, excluding the endoscopic evaluation and including physical examination, urethral cytology, and/or
upper urinary examination in patients at risk of recurrence in these locations.

### 2.3. Treatment schedule

Chemotherapy combinations were different, because standard treatment had changed during that period: 14 patients received cisplatin, methotrexate, and vinblastine (CMV) (cisplatin 100 mg/m², methotrexate 30 mg/m² days 1 and 8, vinblastine 4 mg/m² days 1 and 8, every 21 d); 39 patients received methotrexate, vinblastine, adriamycin, and cisplatin (M-VAC) (cisplatin 70 mg/m² day 2; adriamycin 30 mg/m² day 2; methotrexate 30 mg/m² days 1, 15, and 22; vinblastine 3 mg/m² days 1, 15, and 22; every 28 d); and 22 patients received cisplatin combined with gemcitabine (cisplatin 70 mg/m² day 1 and gemcitabine 1000 mg/m² days 1, 8, and 15; every 28 d). In patients with impaired renal function or important co-morbidities, cisplatin was replaced by carboplatin at a dose of 350 mg/m² or area under the curve (AUC) of 5 (3 patients).

Patients with cPR and those who developed recurrence were slated to receive intravesical bacillus Calmette-Guérin (BCG) for high-risk non–muscle-invasive bladder cancer (NMIBC) and mitomycin C (MMC) for intermediate-risk NMIBC; patients with cNR as well as those who developed local progression were prepared for RC.

### 2.4. Statistical analysis

The cancer-specific survival (CSS) rate was the primary end point, and the progression-free survival with bladder preserved rate was the secondary end point for patients included in the bladder-preservation programme. Both end points were calculated from the time of the initial TUR to the time of the last follow-up or death by tumour using the Kaplan-Meier method. Differences were established using the log-rank test. The chi-square (2-tailed) test was used to determine statistical significance between proportions, and the student t test was used for continuous variables. The level of significance was 0.05 (two-sided) in all of the statistical testing. Multivariate analyses were performed using logistic regression analysis for clinical response and the Cox proportional hazard model for progression, CSS, and progression-free survival with bladder preserved. The following factors were tested for predictive and prognostic impact on clinical response, progression, and survival: age, sex, presence of bladder Tis, antecedents, size, clinical response, and chemotherapy modality. Morphology, grading, and multifocality were excluded, because the small number of one co-variable (≥4) does not provide significant information. The statistical analysis was performed using SPSS v.13 (SPSS, Chicago, IL, USA) for Microsoft Windows.

### 3. Results

#### 3.1. Characteristics of patients

Both the bladder-sparing and RC series have no significant differences between clinical and pathological characteristics (Table 2).

#### 3.2. Clinical response and follow-up

In the bladder-sparing series, 40 (53.3%) patients achieved cCR, 12 (14.6%) patients achieved cPR, and 23 (32%) were cNR. Patients from this trial were followed until July 2007; all patients alive had a
minimum follow-up of 24 mo. Among 51 patients in whom the bladder was initially preserved, 16 (31.3%) developed recurrence with an interval of 9–103 mo, and 15 (29.4%) developed progression—10 as local progression (7–135 mo), and 5 as distant metastasis without local progression (13–19 mo). The pathological pattern of both progression and recurrence according to clinical response is displayed in Table 3. As a whole, 38 (76%) patients of those with initial cR achieved a durable local complete response, with a mean and median follow-up of 87.2 and 84 mo (24–211 mo), respectively. However, five of these patients developed local failure.

### Table 2 – Characteristics of patients included in both series: bladder-sparing programme and RC

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TURB + chemotherapy</th>
<th>Cystectomy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. %</td>
<td>No. %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>75 71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at baseline, yr Mean age (range)</td>
<td>60.8 (36–82)</td>
<td>62.8 (35–71)</td>
<td>0.1782</td>
</tr>
<tr>
<td>Median age</td>
<td>62 64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male 90.6 9.3 Female</td>
<td>Male 87.3 12.6</td>
<td>0.6010</td>
</tr>
<tr>
<td>Antecedent history</td>
<td>Primary tumour 69.3 30.6</td>
<td>Recurrent tumour 80.2 19.7</td>
<td>0.1823</td>
</tr>
<tr>
<td>Papillary tumour</td>
<td>72 96</td>
<td>64 90.1</td>
<td>0.2001</td>
</tr>
<tr>
<td>Size of tumours, cm</td>
<td>38 50.6</td>
<td>34 47.8</td>
<td>0.7438</td>
</tr>
<tr>
<td>Number of tumours</td>
<td>38 49.3</td>
<td>37 52.1</td>
<td></td>
</tr>
<tr>
<td>Solitary</td>
<td>72 96</td>
<td>63 88.7</td>
<td>0.1223</td>
</tr>
<tr>
<td>Grade of tumour</td>
<td>2 75</td>
<td>9 12.6</td>
<td>0.1508</td>
</tr>
<tr>
<td>3</td>
<td>71 25</td>
<td>62 87.3</td>
<td></td>
</tr>
<tr>
<td>Bladder Tis</td>
<td>Yes 65.3</td>
<td>40 56.3</td>
<td>0.3099</td>
</tr>
<tr>
<td>No</td>
<td>26 34.6</td>
<td>31 43.6</td>
<td></td>
</tr>
<tr>
<td>Follow-up, mo</td>
<td>Mean follow-up (range)</td>
<td>65.1 (9–211)</td>
<td>67.5 (1–215)</td>
</tr>
<tr>
<td>Median</td>
<td>45</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

TURB, transurethral resection of the bladder.

### Table 3 – Clinical response, progression, and recurrence: pathological pattern

<table>
<thead>
<tr>
<th>Response</th>
<th>No. (%)</th>
<th>Progression</th>
<th>Pathological pattern</th>
<th>Recurrence</th>
<th>Pathological pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (%)</td>
<td>T ≥ 2M0</td>
<td>T ≥ 2M1</td>
<td>T0M1</td>
<td>Total (%)</td>
</tr>
<tr>
<td>cCR</td>
<td>40 53.3</td>
<td>9 (22.5)</td>
<td>5</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>cPR</td>
<td>12 16</td>
<td>6 (50)</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>cNR</td>
<td>23 30.6</td>
<td>22</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>75 15 (29.4)</td>
<td>32</td>
<td>1</td>
<td>5</td>
<td>16 (31.3)</td>
</tr>
</tbody>
</table>

cCR, clinically complete response; cPR, clinical partial response; cNR, clinical non-response; RC, radical cystectomy; TUR, transurethral resection.

* Percentage over 51 patients at risk of progression and recurrence of 52 with cCR and cPR (2 patients underwent RC, 1 with cCR by personal election and 1 with cPR by Tis in prostatic ducts), and 1 with cNR who refused RC was treated with TUR plus chemotherapy again by personal election, preserving the bladder.
patients developed distant metastasis with no bladder tumour, and 33 (66%) patients remained free of progression and with bladder preserved. Among the whole series, 54 (72%) patients needed rescue therapies (Table 4).

### 3.3. Survival and bladder preservation

Of the patients included in the bladder-sparing series, CSS and progression-free survival with bladder preserved at 5 yr and at 10 yr were 64.5% and 59.8%, respectively, and 52.6% and 34.5%, respectively. Comparing the CSS of both the RC and bladder-sparing series, there was no significant difference between them (Fig. 2).

### 3.4. Pathology of patients treated with radical RC

No patient included in the RC arm received neoadjuvant chemotherapy or radiotherapy (RT). Patients undergoing initial RC showed a pathological exam of 1 (1.4%) P0N0; 7 (9.9%) P1-PisN0; 46 (64.7%) P2-4N0; and 17 (24%) P0-4N1-3 lymph node involvement. The pathology of 34 patients treated with rescue RC was 2 (5.9%) P0N0, 2 (5.9%) PisN0, 19 (55.8%) P2-4N0, and 11 (32.3) P2-4N1-3.

### 3.5. Toxicity

The incidence of toxicity resulting from chemotherapy was high, but no patient died from toxicity. The

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**Table 4 – Additional and rescue therapies after TURB plus systemic chemotherapy**

<table>
<thead>
<tr>
<th>Rescue therapy</th>
<th>Patients</th>
<th>Reasons for rescue therapy</th>
<th>Death of bladder tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravesical therapy (*)</td>
<td>10</td>
<td>Ta–1 recurrence after cCR and cPR</td>
<td>0</td>
</tr>
<tr>
<td>RC</td>
<td>34</td>
<td>T ≥ 2M0: progression or cNR (27) Tis in prostatic ducts in cPR (1) G3–Tis recurrence refractory to BCG (4) Personal election after cCR (1)</td>
<td>17</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>1</td>
<td>T ≥ 2M0 progression unfit for RC</td>
<td>1</td>
</tr>
<tr>
<td>TURB + chemotherapy</td>
<td>2</td>
<td>T ≥ 2M0 late recurrence (135 ms)</td>
<td>0</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>7</td>
<td>T ≥ 2M0 (personal election after cNR)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T ≥ 2M1 (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>T0M1 (5)</td>
<td></td>
</tr>
</tbody>
</table>

(*) as unique therapy.

**cCR, clinically complete response; cPR, clinical partial response; RC, radical cystectomy; cNR, clinical non-response; BCG, bacillus Calmette-Guérin; TURB, transurethral resection of the bladder.**

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**Fig. 2 – Phase 2 nonrandomized trial comparing cancer-specific survival between TURB plus three cycles of chemotherapy and radio-chemotherapy.**

Abbreviations: RCT, radio-chemotherapy; chemo, chemotherapy; TURB, transurethral resection; TURB, transurethral resection of the bladder.
maximum toxicity per patient is evaluated in Table 5.

3.6. Predictive factors

In univariate analysis, bladder Tis was the only significant variable for predicting cPR ($p = 0.001$). Clinical response was also the only significant variable for predicting CSS and progression-free survival plus bladder preservation ($p = 0.000$, $p = 0.014$), but no variable was able to predict progression. Both variables are entered in the multivariate analysis model, shown in Table 6.

4. Discussion

In our series, CSS and progression-free survival with bladder preserved rates were 64.5% and 58.9% at 5 yr and 53.9% and 38.4% at 10 yr, respectively. These figures were comparable to 63–56% and 59–42% at 5 yr and 46–42% and 45–27% at 10 yr, respectively, in radio-chemotherapy series [3,4]. These data show that in selected patients with MIBC, bladder preservation by TURB and three courses of cisplatin-based chemotherapy are feasible and safe.

In patients with MIBC, one problem related to the multimodal approach is that the contribution of each method to survival is difficult to establish. Our trial was designed to determine the efficacy of three courses of cisplatin-based chemotherapy in a select group of patients with microscopic residual MIBC after complete TURB. Although this is not a randomized trial and some bias can be observed, according to pathological findings of the RC arm, we can speculate that around 98% of patients included in our bladder-sparing programme had residual bladder tumour, 89% of them as residual MIBC. With three courses of chemotherapy, 50.5% of durable cCR was achieved. In consequence, cisplatin-based chemotherapy seems to be effective in approximately 45% of patients in eradicating microscopic residual invasive cancer of the bladder.

Although a re-TUR was not performed in our series, the quality of our TURB technique was proven. If biopsies of the tumour bed were negative, TURB was considered radical, as the understaging rate was 6.7% [13], with similar survival at 10 yr compared to that of Herr’s series, which included a systematic re-TUR (T0-1) as inclusion criteria [14]. In contrast, when biopsies were positive, TURB was considered microscopically incomplete because in the control arm of this trial, invasive residual tumour was found in 89% of cases. Moreover, although some patients with positive biopsies can be cured by radical TURB and with re-TUR, this procedure seems insufficient. In a previous study, patients with negative biopsies after radical TURB had significantly better survival than those with positive biopsies receiving immediate radical RC ($p < 0.001$) or three courses of chemotherapy ($<0.001$) [13]. Our interpretation of these data is that positive biopsies after TURB identified a group of patient of worse prognosis, probably because of the presence of a diffuse character of residual invasive tumour not totally controlled with radical RC or

### Table 5 – Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Grade 1 (No. (%))</th>
<th>Grade 2 (No. (%))</th>
<th>Grade 3 (No. (%))</th>
<th>Grade 4 (No. (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucopenia</td>
<td>20 (25.9)</td>
<td>23 (29.8)</td>
<td>21 (27.2)</td>
<td>4 (5.1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (7.8)</td>
<td>6 (7.8)</td>
<td>28 (36.3)</td>
<td>23 (29.8)</td>
</tr>
<tr>
<td>Aenemia</td>
<td>21 (27.2)</td>
<td>18 (23.3)</td>
<td>8 (10.3)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>6 (7.8)</td>
<td>8 (10.3)</td>
<td>13 (16.8)</td>
<td>6 (7.8)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>21 (27.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (14.2)</td>
<td>18 (23.3)</td>
<td>8 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>6 (7.8)</td>
<td>4 (5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
<td>8 (10.3)</td>
</tr>
<tr>
<td>Febril neutropenia</td>
<td>2 (2.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjuntivitis</td>
<td>4 (5.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin.
* Only MVAC; 9 patients reduced doses because of haematologic toxicity.

### Table 6 – Prognostic factors in multivariate analysis for patients included in the TURB plus chemotherapy series

<table>
<thead>
<tr>
<th>Outcome tested</th>
<th>Variables</th>
<th>HR (95% CI)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>cPR</td>
<td>Bladder Tis (No vs Yes)</td>
<td>13.219 (2.580–67.725)</td>
<td>0.002</td>
</tr>
<tr>
<td>CSS</td>
<td>Clinical response (cCR vs cPR vs cNR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-cPR</td>
<td>4.013 (1.224–13.152)</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>-cNR</td>
<td>7.273 (2.602–20326)</td>
<td>0.000</td>
</tr>
<tr>
<td>Progression-free survival plus bladder preservation</td>
<td>Clinical response (cCR vs cPR)</td>
<td>2.240 (1.577–3183)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

CI, confidence interval; cPR, clinical partial response; CSS, cancer-specific survival; cCR, clinically complete response; cNR, clinical non-response; RC, radical cystectomy.
* Patients with cNR were excluded, as they were to undergo RC.
systemic chemotherapy and obviously even less by radical TURB alone.

With respect to the best patients for bladder-sparing programmes, whether our restrictive inclusion criteria improved the final outcome is difficult to determine. Nevertheless, in the large Erlander series, in which patients received trimo- dal therapy, Duns [7] reported that patients with R0 tumour (no evidence of microscopic residual tumour after complete TURB) had a 5-yr survival rate of 81%, similar to 79% of the two prospective series of patients with muscle-invasive bladder tumour treated with radical TURB alone [12,14]. In patients with R1 tumour (macroscopically complete TURB with evidence of microscopic residual tumour), which, to some extent, corresponded with the inclusion criteria of the present series, the 5-yr CSS rate was quite similar to our series: 53% and 64.5%, respectively. In patients with R2 tumour (macroscopically incomplete TURB), the 5-yr survival was 31%—lower than the 51.6% of our series of RC with no neoadjuvant chemotherapy and including 298 patients with only macroscopic residual tumours. As a result of these data, patients with microscopic residual tumour seem to be the ideal patients for a bladder preservation programme, achieving the best balance between survival and over- or undertreatment. In patients with complete TURB and no microscopic residual tumour, chemotherapy or radio-chemotherapy would represent an overtreatment for most patients. In those with macroscopic residual tumours, radio-chemotherapy would be an insufficient treatment compared to RC.

Otherwise, in the absence of a random trial in the literature comparing RC and bladder-sparing strategies, our trial could establish a suitable comparison between two series with similar clinical-pathologic characteristics in which patients fulfilled the same inclusion criteria. Although some bias should be assumed in this comparison, there was no significant survival difference between the RC and bladder-sparing series (Fig. 1), meaning that the survival of patients with invasive bladder tumour and residual microscopic tumour does not seem threatening after receiving three courses of cisplatin-based chemotherapy. The current trend is to administer more than three courses of chemotherapy to consolidate the clinical response. However, at that time, patients received only three cycles in concordance with other trials [2,15,16], guided by the results of trials using the same number of cycles in neoadjuvant settings, including patients with macroscopic bladder cancer with a rate of P0 in cystectomy specimen (32.5–38%) [17,18].

In multivariate analysis, the presence of bladder Tis was the only predictive factor for cPR. This fact can be explained by the well-established bladder Tis chemoresistance [19]. However, the presence of bladder Tis was not related to progression and CSS as well as bladder-preserved rates, although in this item, the trend is to decrease the number of bladder-preserved series compared to the whole series—38.4% versus 46.9%, respectively. According to these data, the presence of bladder Tis should not be an exclusion criterion for bladder-preservation programmes, but patients should be aware that they are at high risk of rescue RC. Although bladder Tis is chemoresistant, patients with bladder Tis at the beginning were not initially treated with BCG, because the potential local and systemic toxicity of BCG could delay the administration of chemotherapy cycles. All patients with persistent bladder Tis after three courses of chemotherapy at 3-mo evaluation received BCG.

With the inclusion criteria used in the present trial, cR was the only predictive factor for survival and bladder preservation in multivariate analysis. Clinical non-response was expected to be related with survival, as in other series [11,15,16,19]; however cPR was also related to survival, raising the question of whether RT has a role in these patients. Of 12 patients with cPR, five (41.6%) developed local progression in a very short interval (7–13 mo). Therefore, in some of these patients, adjuvant radio-chemotherapy could shift cPR in cCR, but whether his effect would be temporary or definite cannot be answered in this trial. Nevertheless, its impact on survival and bladder preservation of the global series would be minimal. Whether patients with cPR should be treated with intravesical BCG, RC, or consolidation radio-chemotherapy remains to be answered.

Our results encourage the use of this bladder-sparing programme, applying our inclusion criteria, but patients should be aware that 56% of patients who achieved a cR developed progression or recurrence, as a result of which, 72% required additional therapies, and 45% required RC. Although the toxicity rate is high, no patient died as a result of it; neutropenia was nearly universal, and one-third grade IV and nephrotoxicity were not a serious problem in these patients who had, in general, good performance status.

To our knowledge to date, this is the first prospective, comparative, nonrandomized trial including patients who fulfilled the same inclusion criteria and in which both have similar clinical-pathologic characteristics. But this study has some limitations. First, this is not a randomized trial, and some bias can be observed. Therefore, conclusions
should be taken cautiously. Second, although 76 patients were included over a period of 16 yr, no modifications were made to the therapy schedule except from chemotherapy schemes administered according to the standard schedule considered at the time. Nevertheless, there are no significant differences between the three chemotherapy schemes used in this trial in terms of progression and survival.

5. Conclusions

Our results justify bladder preservation in select patients with MIBC. Three cycles of cisplatin-based chemotherapy are effective in controlling microscopic residual invasive bladder tumour in about 45% of patients. Patients with microscopic, residual invasive cancer after complete TURB seem to be good candidates for a bladder-sparing programme. Whether these results could be improved by adding radio-chemotherapy remains to be answered.

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Study concept and design: Solsona, Climent.
Acquisition of data: Solsona, Iborra.
Analysis and interpretation of data: Solsona, Climent.
Drafting of the manuscript: Solsona, Collado.
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**Editorial Comment on: Bladder Preservation in Selected Patients with Muscle-Invasive Bladder Cancer by Complete Transurethral Resection of the Bladder Plus Systemic Chemotherapy: Long-Term Follow-up of a Phase 2 Nonrandomized Comparative Trial with Radical Cystectomy**

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The European Association of Urology (EAU) guidelines on muscle-invasive bladder cancer do not recommend transurethral resection (TUR), radiotherapy, or chemotherapy alone as potential bladder-sparing approaches [1]. Interestingly, Herr recently reported a 64% survival rate with >5yr of follow-up and 54% with intact bladders in a selected group of patients who refused cystectomy after neoadjuvant chemotherapy [2]. The EAU guidelines, however, do consider the combination of deep resection, radiotherapy, and chemotherapy as an alternative to radical surgery. In selected patients, 5-yr survival is 50–60%, which is comparable to cystectomy series.

In the bladder-sparing approach used by Solsona et al, patients are offered three cycles of cisplatin-based chemotherapy or direct cystectomy after TUR [3]. The selection criteria are very strict (eg, microscopically residual tumour should be present, but not macroscopically). Obvious study limitations are limited sample size, long “recruitment” time, patient selection, different chemotherapy schedules, and absence of randomisation. Comparison with the large Erlander series, in which patients received trimodality therapy, is useful (reference 7 in the paper). First, the Erlander series certainly raises questions about the role of radiotherapy.

Second, it clearly demonstrates that residual disease after TUR is very important, as in all bladder-sparing approaches. Third, it confirms the cancer-specific survival data of Solsona et al [3] and the EAU guidelines, which should be interpreted with care when considering patient selection. Solsona et al indicate that 54 of 75 patients needed rescue therapy; only 33 (44%) remained progression-free with preserved bladders, and toxicity of chemotherapy is described as high. Apparently, the advantages of bladder sparing come with considerable chemotherapy toxicity, recurrences, and progression.

The authors conclude that their results encourage the use of bladder-sparing programs [3]. Personally, I prefer the EAU guidelines, concluding that with a limited level of evidence, multimodality therapy might be an option in very select and motivated patients.

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Optimal local control and survival of muscle-invasive bladder cancer is provided by neoadjuvant cisplatin-based chemotherapy followed by a quality radical cystectomy and a thorough pelvic lymph node dissection [1]. An alternative approach in selected patients is a bladder-sparing strategy. The most common is trimodality (maximum transurethral resection [TUR] and chemoradiation) therapy, which achieves 5-yr survival rates of 50–60%, with about half the patients preserving their bladders [2]. The key to successful bladder preservation is, of course, strict patient selection. Ideal patients have a solitary tumor <5 cm in size; a visibly complete TUR; and no palpable mass, hydronephrosis, or evidence of lymph node metastases.

In this issue of European Urology, Solsona and colleagues from the highly regarded urology department in Valencia, Spain, report their results in 75 patients who chose to keep their bladders after undergoing an aggressive TUR and three cycles of chemotherapy [3]. None of the patients received radiation therapy. The 5- and 10-yr cancer-specific survival rates were 65% and 60%, respectively—similar to 71 nonrandomized control patients who selected cystectomy after chemotherapy. The bladder was preserved in half the patients. The authors are quick to point out that one-third of the patients progressed with persistent or new invasive tumors in the bladder, and about half the patients preserving their bladders [2].

Patients ask me, “What is the chance that I will die of bladder cancer if I do not have cystectomy now?” Sparing the bladder does not spare the patient from developing new tumors in the retained bladder, and some of these may prove to be lethal, despite salvage therapies. What patients are really asking is whether, by opting to save their bladders, they are increasing their risk of dying of bladder cancer. To put it more succinctly, what are the chances of a preventable death? Good question! Certainly, some patients die of bladder cancer that could have been prevented by a timely cystectomy, but what is the magnitude of the risk? Answers are buried in the bladder-sparing literature.

Solsona et al report that of 51 patients who responded to TUR and chemotherapy, 10 had another invasive tumor in the bladder without metastasis, and 5 (10%) died [3]. Shipley reported that of 121 cases responding completely to trimodality therapy, 19 developed new invasive cancers, and 10 (8%) eventually died [7]. Rodel found that among 288 complete responders to combined-modality treatment, 42 relapsed in the bladder >2 yr later and half (7%) died despite salvage cystectomy [2]. We had 16% of patients who suffered a late cancer death from a new invasive bladder cancer, despite successful treatment of the initial invasive bladder tumor by TUR alone [5]. We also showed that of 63 patients who responded completely to intense chemotherapy after a radical TUR and subsequently refused their planned cystectomy, 19 (30%) relapsed later in the bladder and died, including 9% who had favorable tumor features predicting successful bladder preservation [8]. If we assume that all of these deaths from locally invasive recurrences might have been prevented by earlier cystectomy, then the mortality risk the patient assumes by electing to preserve his or her bladder is between 7% and 16%. It is not always possible to ascertain whether lethal metastases emanate from a new or the original invasive tumor, and salvage cystectomy does not save all relapsed patients, but any local therapy does not prevent new tumors from developing in the preserved bladder.

There are many ways to spare the bladder, all achieving more or less similar results, but they control microscopic residual disease in the bladder in only half the cases. That may be acceptable to patients if they could be assured they would be saved by salvage treatment in the event the tumor recurs. Clearly, some will not. For some, a preventable 10% risk of later dying of bladder cancer may also be acceptable to preserve the bladder; for others, it may be too high!

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