Elective bladder-sparing treatment for muscle invasive bladder cancer

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KEYWORDS
Bladder-sparing; Bladder cancer; Radiotherapy; Chemotherapy; Transurethral resection

Abstract
Objectives: Radical cystectomy is the standard treatment for localized muscle invasive bladder cancer (MIBC). We offer a bladder-sparing treatment with TURB ± Chemotherapy + Radiotherapy to selected patients as an alternative.

Material and methods: We analyze, retrospectively, 30 patients diagnosed with MIBC from March 1991 to October 2010. The mean age was 62.7 years (51–74). All patients were candidates for a curative treatment, and underwent strict selection criteria: T2 stage, primary tumor, solitary lesion smaller than 5 cm with a macroscopic disease-free status after TURB, negative random biopsy without hydronephrosis. Staging CT evaluation was normal. Restaging TURB or tumor bed biopsy showed a disease-free status or microscopic muscle invasion. 14 patients underwent TURB alone, 13 TURB + Chemotherapy and 3 TURB + Chemotherapy + Radiotherapy.

Results: The mean follow up was 88.7 months (19–220). 14 patients remained disease free (46.6%), 10 had recurrent non-muscle invasive bladder cancer (33%). 81.3% complete clinical response. 71% bladder preserved at 5-years. Overall, 5-years survival rate was 79% and 85% cancer-specific survival rate.

Conclusions: Although radical cystectomy is the standard treatment for localized MIBC, in strictly selected cases, bladder-sparing treatment offers an alternative with good long term results.

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PALABRAS CLAVE
Conservación vesical; Cáncer vesical; Radioterapia; Quimioterapia; Resección transuretral

Preservación vesical electiva en tumor vesical músculo invasivo

Resumen
Objetivos: La cistoprostatectomía radical es el tratamiento de elección en el carcinoma vesical músculo invasivo localizado. Planteamos la posibilidad de ofrecer a pacientes estrictamente seleccionados la preservación vesical con RTU ± quimioterapia (QMT) y radioterapia (RDT) como tratamiento alternativo.

Material y métodos: Analizamos retrospectivamente 30 pacientes diagnosticados de carcinoma vesical músculo invasivo entre marzo de 1991 y octubre de 2010. La media de edad es de 62,7 años (51–74). Todos ellos eran candidatos a tratamiento curativo y han seguido estrictos criterios de selección: estadio T2, primario, único y menor de 5 cm, con impresión macroscópica de RTU completa en profundidad, sin repercusión en tracto urinario superior y BMN negativa. La TAC de extensión fue siempre negativa y la re-RTU o biopsia de lecho negativa para tumor o con infiltración muscular microscópica. Catorce de estos pacientes fueron tratados con RTU monoterapia, 13 con RTU + QMT y 3 RTU + QMT + RDT.

Resultados: El seguimiento medio ha sido de 88,7 meses (19–220). Catorce han permanecido libres de recidiva (46,6%) y 10 han presentado recidiva superficial (33,3%). Conseguimos un 81,3% de respuestas completas y un 71% de conservación vesical a los 5 años. La supervivencia global a los 5 años fue de 79%, siendo la cáncer específica del 85%.

Conclusiones: Aunque la cistoprostatectomía radical continúa siendo el tratamiento de elección ante el tumor vesical infiltrante localizado, en casos estrictamente seleccionados, la conservación vesical ofrece una alternativa válida con buenos resultados a largo plazo.

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Introduction

Radical cystoprostatectomy is currently the treatment of choice for localized muscle-invasive bladder cancer, providing the highest long-term survival rates. In the event of organ-confined disease (≤T3a) the 5-year overall survival rate is around 65–71%, whereas the cancer-specific survival rate is between 76 and 81%. Techniques for neurovascular bundle preservation and low-pressure intestinal neobladders have improved the quality of life of these patients. Nevertheless, it is still mutilating surgery with non-negligible early and late complication rates.

We raised the possibility of offering bladder preservation with TURP ± CT and RT to carefully selected patients as an alternative and effective therapy for the control of the disease. We presented our experience with 30 patients. This study does not aim to defend a specific form of bladder preservation or to make comparisons with radical cystoprostatectomy, but to analyze the outcomes in our series with acceptable long-term follow-up in order to determine the effectiveness and safety of bladder preservation as an alternative therapeutic option in our field.

Materials and methods

Those patients with muscle-invasive bladder tumors and complete macroscopic resection were electively included in our bladder preservation protocol. With prior detailed information and under strict selection criteria, they opted for a bladder-preserving approach as an alternative to radical cystoprostatectomy. The selection criteria were the following: clinical stage T2, a single primary tumor smaller than 5 cm, with macroscopic impression of a complete TURP in depth, with no impact on the upper urinary tract, a negative multiple bladder biopsy with no urethral involvement, and normal bladder capacity. All the cases had to show a negative extension study with a negative abdominal-pelvic CT scan. It was compulsory to have a TURP-biopsy sample of macroscopically healthy tissue obtained either after initial TURP, or by a time-delayed re-TURP after 4–6 weeks. Its outcome will determine the preservation approach depending on whether it is tumor-negative (R0) or there is microscopic muscle infiltration (R1) (Fig. 1).

In the case of single tumors smaller than 3 cm, monotherapy with TURP as a bladder-preservation approach was considered sufficient. We performed re-TURP + standard multiple biopsy in these patients after 3 months, with 3 possibilities: follow-up, in the case of a negative re-TURP (R0), trimodality bladder preservation therapy (CT + RT) in the case of a positive re-TURP on healthy-looking tissue (microscopic infiltration R1), and finally cystectomy if re-TURP showed an infiltrating tumor on macroscopically infiltrated tissue (R2).

In tumors between 3 and 5 cm with complete macroscopic resection and in all those cases with a positive biopsy of healthy-looking tissue (microscopic infiltration R1), we considered trimodality bladder preservation therapy with CT + RT. Tumors larger than 5 cm were never included in the bladder preservation protocol due to the high risk of residual tumor. The framework for preservation with trimodal therapy at our hospital is based on the administration of RT (64 Gy) with weekly concomitant cisplatin at 50 mg/m². In our service, and despite the fact that no benefits on survival were proven in the EORTC phase II trial (it lacked enough power to prove survival benefits), we treated our patients with 2 cycles of CT prior to RT to avoid periods of no treatment. No re-evaluation of the patient in the middle
of therapy was done. All the patients in the trimodality bladder preservation protocol subsequently underwent another TURP procedure after treatment with CT/RT to confirm complete response (CR), radical surgery being indicated in those patients with persistent tumor-infiltrating cells.

Follow-up consisted of strict controls with cytology and cystoscopy every 3 months for 2 years, biannually until year 5, and annually thereafter indefinitely. We also asked for thorax-abdominal CT scan every 6 months the first 2 years and annually until year 5. No metastatic involvement was documented after this time, with no evidence for progression in the bladder. Besides, control of the upper urinary tract was performed by IVU or TAC in the event of hematuria or positive cytology with normal cystoscopy. The recurrence of a new non-muscle-invasive bladder tumor (Ta-1-Tis) will be treated with bladder instillations according to protocol. Local progression will be managed with salvage cystectomy provided that the patient’s general condition permits it and that the extension study is negative. No bladder biopsies were performed on a routine basis during follow-up, as recommended by the NCCN and performed by other groups such as Solsona et al., since we considered the sensitivity of the combination of cytology and cystoscopy sufficient for the detection of bladder recurrence.

Results

We analyzed 30 patients, 27 men and 3 women, who were diagnosed with muscle-invasive bladder carcinoma between March 1991 and October 2010. The mean age at the time of diagnosis was 62.7 years (51–74). 14 patients were treated with TURP monotherapy. No infiltrating tumors were evidenced on the resection bed or in the subsequent TURP (R0) in none of the patients, and in no case did they exceed 3 cm size. Other 13 patients followed a protocol of TURP + CT. Finally, 3 cases were treated with TURP + CT + RT (trimodal scheme) after having detected microscopic infiltration on the resection bed, either on the initial resection or on the subsequent re-TURP (R1). No subgroup analyses were performed on treatment modalities due to the limited number of patients.

The mean follow-up period was 88.7 months (19–220). Of the 30 patients, 14 were recurrence-free (46.6%), 10 had superficial recurrence (33.3%), 4 of them twice, using complementary treatment of the bladder with BCG and/or mitomycin C. Two of these patients required cystectomy during follow-up, one of them due to persistent carcinoma in situ (cis) and another due to progression to muscle-infiltrating tumor. 6 cystectomies were performed in total (Table 1): 2 due to infiltrating recurrence (6.6%), pT0 in both cases, although there was involvement of the perivesical nodes in one of them; another was due to persistent cis and the remaining 3 cystectomies due to residual tumors after treatment, these being the most unfavorable conditions (pT2a, pT3b and pT4a). Among the cystectomies performed, there were 2 cancer-specific deaths, both of them with incomplete response. Two cases showed progression of distant metastasis, one of them with simultaneous muscle-invasive bladder recurrence and another with no evidence of tumor in the bladder. We obtained 81.3% of complete responses and a 71% rate of bladder preservation at year 5. The overall 5-year survival was 79%, with cancer-specific survival rates being 85% (Fig. 2); we used the Kaplan–Meier method to analyze both variables. Four patients died of tumor progression, 2 of them after salvage cystectomy.

Discussion

There are different options of conservative treatment. TURP monotherapy can be sufficient for small tumors after complete resection and in the absence of residual tumor in a
Table 1  Description of the patients who received cystectomy.

<table>
<thead>
<tr>
<th>No.</th>
<th>Cause</th>
<th>Modality</th>
<th>Stage</th>
<th>Survival (months)</th>
<th>Exitus (SC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Relapsing Cis</td>
<td>TUR-CT</td>
<td>Multifocal Cis</td>
<td>168</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>IR</td>
<td>TUR-CT</td>
<td>pT3a N+</td>
<td>40</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>IR</td>
<td>TUR-CT</td>
<td>pT2b</td>
<td>61</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Infiltrating recurrence</td>
<td>TUR mono</td>
<td>pT0</td>
<td>49</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Infiltrating recurrence</td>
<td>TUR mono</td>
<td>pT0 N+</td>
<td>80</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>IR</td>
<td>Trimodal</td>
<td>pT4a</td>
<td>19</td>
<td>Yes</td>
</tr>
</tbody>
</table>

SC: specific cancer; Cis: carcinoma in situ; CT: chemotherapy; IR: incomplete response; TUR: transurethral resection.

Figure 2  Kaplan–Meier curves. (A) Kaplan–Meier overall survival. (B) Kaplan–Meier cancer specific survival. (C) Kaplan–Meier bladder preservation.

bed biopsy or re-TURP. The groups Solsona et al. and Herr presented series with a higher number of patients and follow-up with TURP monotherapy. Both are based on a strict selection of patients confirming the absence of residual cells in the tumor bed after complete macroscopic resection (bed biopsy in the series of Solsona et al. and early re-TURP in that of Herr). Solsona et al. published cancer-specific survival rates of 81.9, 79.5 and 76.7% at years 5, 10 and 15, and bladder preservation rates of 75.5, 64.9 and 58% equally at years 5, 10 and 15. Herr obtained an overall survival rate of 76% and a bladder preservation rate of 57% at year 10.

Trimodality bladder preservation therapy with TURP+CT–RT is currently the best evaluated approach in prospective studies with more than 1000 patients, with described CR rates of 70–80%, long-term bladder preservation rates of 50–60% and survival rates similar to those of radical cystectomy, although no prospective or randomized comparative trials of both therapeutic options have been performed. Clinical guidelines recommend the modality of trimodal treatment for those patients who are not candidates for radical cystectomy due to clinical reasons (age, basic disease) or who reject it for personal reasons. This modality is based on local control with TURP and RT and systemic control of the disease (micrometastasis) with CT, which shows a radiosensitivity effect. The major prognostic factor is negative re-TURP after CT and RT (complete response). This must be performed 8 weeks after the treatment, and in this group of patients the survival rates are similar to those of initial cystectomy. There are several prognostic factors for CR such as stage (cT2), complete resection, absence of hydronephrosis and RT doses of more than 60 Gy. A key point in the strategy for bladder preservation is early cystectomy in those patients who do not achieve CR (positive re-TURP), since this implies a poor prognostic factor and cystectomy shows worse survival rates and more complications (overall survival rate of 25–30% at year 10). There were 3 incomplete responses in our protocol. We performed early cystectomy in these cases, with unfavorable anatomies and cancer-specific success in 2 of them. If we take the 16 patients in our series who received complementary treatment to TURP, we obtain a CR rate of 81.3%. The Massachusetts (MGH) and Erlangen groups have greater experience with this treatment strategy. Both of them used complementary treatment with CT and RT after a complete TURP. The main difference is that MGH carried out a re-evaluation of the patients in the middle of therapy, in order to early identify non-responders, with a minimum delay of cystectomy and
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thus maximizing their curative potential. On the other hand, the Erlangen group carried out the re-evaluation of the patient after completing the treatment, as we do in our center. This increases the chances of bladder preservation since the percentage of CR is increased. In the MGH group, with a series of 348 patients (cT2–T4), they reached overall survival rates of 52 and 35% at years 5 and 10 (61 and 43% in the T2 subgroup), a complete response rate of 72% (78% in the T2 subgroup) with a bladder preservation rate of over 70%. The Erlangen group had equivalent results, so the optimal regimen of CT/RT is not established.

There are groups advocating for bimodal preservation with TURP + CT with satisfactory results. According to them, an aggressive TURP can assume the role of CT. Solsona et al. presented in 2009 the results of a comparative study of cystectomy versus TURP + CT in patients with microscopic residual tumors after a complete TURP. The cancer-specific survival rates were of 64.5 and 59.8% at years 5 and 10, with no significant differences with the cystectomy group and being comparable to the CT–RT series. The percentages of bladder preservation at years 5 and 10 were 52.6 and 34.5%. Sternberg et al. published 5-year results of overall survival of 67%, with a bladder preservation rate of 44%. In this study, the sample was not so carefully selected as in the case of Solsona et al. or in our series (only 36% of the patients included were at the T2 stage before CT and hydropnephrosis was not an exclusion criterion), though their results are superimposable. Bimodal therapy with TURP + CT may have the same curative options as trimodal therapy in selected patients with a minimum residual tumor burden, although no controlled, comparative trials of both modalities are available. When comparing different series, a higher complete response rate is observed with trimodal therapy, though the survival rate is similar.

Our study is limited by the fact that this series is small and historical, with variations in the action protocol throughout time. We initially followed stricter inclusion criteria, especially in terms of tumor size, and all patients followed a bimodal preservation modality (TURP + CT). Once we overcame this overcautious attitude with experience, and given the possibility of overtreating completely resected small tumors, we included TURP monotherapy as a preservation approach for these tumors, reserving TURP + CT for larger tumors. Nowadays we follow the protocol previously described in agreement with the Oncology Department at our hospital. Thus, we have moved away from bimodal preservation with TURP + CT, which is only used in the event of small tumors with vascular/lymphatic infiltration in the TURP sample. Beyond a bladder preservation approach, either in monotherapy or multimodal, we propose a bladder preservation program with strict criteria for inclusion. Once the patient has been included in it, the endoscopic impression and the anatopathological results of the tumor and the tumor bed, along with its size, will reveal the proper treatment schedule (Fig. 1).

There are several limiting factors, though not excluding, of bladder preservation such as the occurrence of cis, which is a factor predicting progression. We considered bladder preservation with BCG in selected cases of local cis. Lymphovascular invasion increases the risk of micrometastasis, so we added adjuvant CT to treatment. Hydropnefrsis is another poor prognostic factor, although in the case of a disobstructive and complete TURP, we can consider bladder preservation. Patients with multiple relapses or high-grade recurrence after BCG treatment are “high-risk bladders”, so they are poor candidates for preservation. Finally, size increases the risk of residual tumor, so we did not include patients with tumors larger than 5 cm in our group.

The importance of an initial macroscopically complete resection as a basic criterion for inclusion must be emphasized, as well as the requirement of posttreatment re-TURP in any bladder preservation protocol, since obtaining a complete response (negative re-TURP with no residual disease) is the main prognostic factor with survival rates similar to those of cystectomy in these cases. Other key point in any preserving strategy is strict follow-up and early salvage cystectomy in those cases of failed bladder preservation, in order to minimize the impact on survival in non-responders or muscle-invasive recurrences after initial response.

The progression rate in our series was 23.33% (7 cases), 3 of which were incomplete responses to initial treatment (3 patients out of 16 who received complementary treatment thus representing 18.7%) and requiring early cystectomy. Undoubtedly, this is the main prognostic factor for survival, since they are potentially more dangerous and advanced tumors. Late infiltrating recurrence behaves like a primary tumor with regard to survival, without being a poor prognostic factor per se. In any bladder preservation protocol, the patient must assume the risk caused by the delay when indicating cystectomy (incomplete responses or muscle-invasive progression). Herr estimated it around 8–16%, which for some will be acceptable for the sake of preserving their native bladder, whereas this percentage will seem rather high to others. In our series, we presumably might have saved 3 patients with early cystectomy (2 cancer-specific deaths after incomplete response and a patient with local and distant recurrence), which implies an avoidable risk of 10%. 33.33% of patients showed superficial relapse (10 patients) and 4 of them twice. Superficial recurrences are managed according to the usual protocol with endovesical treatment, and they do not have an impact on these patients’ survival, although they seem to increase the risk of tumor progression, thus decreasing the bladder preservation rate (it is not a risk factor according to Solsona et al. in their 15-year follow-up). In our series, radical cystectomy was performed in 2 of these 10 patients with superficial relapse, one of them due to tumor progression after 53 months and the other one due to diffuse recurrent cis after 78 months with a good evolution in both cases.

With regard to the conservative management of muscle-invasive bladder tumors, there are some questions to consider: the first of them would be the possibility of including complementary BCG treatment in the TURP monotherapy protocols, since once the infiltrating tumor has been totally resected and the absence of residual disease is confirmed by re-TURP, the attitude toward the preserved bladder should not be different to that toward a GIII T1 tumor. The Ulm group published their series with good results pointing in that direction, although they assessed patients who were not candidates for radical cystectomy and there was a limited number of patients to draw any definite conclusions (overall survival rate of 69.1% and cancer-specific survival rate of 94%). We did not initially consider this option in our protocol, unless we found high-grade superficial tumor or cis in
re-TURP. In the 5 cases where we adopted this approach, neither success nor complications were registered, presenting a case of tumor progression with subsequent cystectomy and a good evolution. Well-designed studies and with a greater number of patients would be needed to draw any conclusion in this respect, though the proposal included in this reflection does not seem illogical to us.

The next point on which we would like to reflect is the role of lymphadenectomy (LDN) in bladder preservation protocols. After a review on literature, we only found it included in the scheme proposed by the Tokyo group.\textsuperscript{26} Nobody doubts that LDN is an essential part of the comprehensive surgical management of bladder cancer, its therapeutic value having been proven. Therefore, in a strictly conservative surgical sense, the ideal alternative to cystectomy should combine radical TURP and laparoscopic LDN. On the other hand, taking into consideration the fact that around 25\% of cystectomy specimens show positive nodes, and that around 8–13\% of patients included in trimodal bladder preservation protocols will show pelvic node recurrence, we could conclude that CT–RT have limited effect on eradicating node micrometastases. For all those reasons, it will be possible to include laparoscopic LDN in the surgical strategy of bladder preservation protocols in the near future.\textsuperscript{21,26}

Conclusions

Although radical cystoprostatectomy remains the treatment of choice for localized invasive bladder cancer, in strictly selected cases, bladder preservation offers a valid alternative, with good long-term results published that match our experience.

Conflict of interest

The authors declare that they have no conflict of interest.

References

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