

Initial Results of Retrospective Study: Preoperative Transurethral Excision Plus Chemotherapy and Radiation Therapy and Trial of Bladder Preservation

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ABSTRACT

Background: For patients with invasive bladder cancer the usual recommended treatment is radical cystectomy, although transurethral resection of the tumor, systemic chemotherapy, and radiotherapy are each effective in some patients. This retrospective study evaluated the experience of the Clinical Oncology Department, Tanta University Hospital with combined modality treatment and selective bladder preservation in patients with muscle-involving bladder cancer with assessment of its safety, tolerance, and efficacy to determine whether these treatments in combination might be as effective as radical cystectomy and thus might allow the bladder to be preserved and the cancer cured and to identify factors that may predict treatment response, risk of relapse and survival.

Patients and Methods: Between January 2000 and January 2006, 55 consecutive patients with muscle-involving bladder cancer (stages T2 through T4, NX M0) were treated with as complete transurethral surgery as possible, followed by induction combination chemotherapy, and irradiation with 4500 cGy with concurrent cisplatin administration. Urologic evaluation by cystoscopy, cytology, and rebiopsy 2-3 weeks later of the tumor response directed further therapy: either radical cystectomy in the patients who had incomplete responses, or additional chemotherapy with the same drugs and doses and radiotherapy up to 6480 cGy in the patients who had complete responses. The median follow-up was 48 months.

Results: In 37 patients (67.3%) the bladder was free of invasive tumor and functioning well, even though in 13 (23.6%) a superficial tumor recurred and required further transurethral surgery and intravesical drug therapy. Of the 18 (32.7%) patients who still had detectable tumor after initial treatment, all of them underwent radical cystectomy. None of the patients had required a cystectomy for radiation toxicity. Of the 37 (67.3%) patients who had complete responses with no tumor detectable on urine cytology or rebiopsy after initial treatment, 89.2% had functioning tumor-free bladders. The overall survival (OAS) at 5 years

is 43.12%. The three year bladder intact survival rate is 60%. A total of 10 patients (18.2%) developed grade 3 hematologic toxicity in conjunction with this treatment. Complete response (CR) was achieved in 67.3% of patients. Local control after CR without muscle-invasive relapse was maintained in 60% of patients at 3 years. Distant metastases were diagnosed in 24 patients (43.6%) with an actuarial rate of distant metastasis-free survival of 43.68% at 5 years. Early tumor stage, absence of hydronephrosis and a complete response were the most important factors predicting bladder preservation rate and survival (all $p \leq 0.001$).

Conclusions: Conservative combination treatment may be an acceptable alternative to immediate cystectomy in selected patients with bladder cancer. Both the 67.3% complete response rate to induction therapy and the 60% three-year survival with an intact bladder are encouraging, although a randomized clinical trial that included a group for simultaneous comparison would be required to produce definitive results. Longer follow-up will be necessary to assess efficacy.

Key Words: Bladder cancer – Muscle invasive tumor – Neoadjuvant chemotherapy – Radiotherapy.

INTRODUCTION

The treatment of patients with invasive bladder cancer is undergoing dramatic changes [1,2], incorporating many potentially effective and complementary therapies from several disciplines, including transurethral surgical resection, systemic chemotherapy, improved techniques of radiotherapy and advanced methods of surgical construction of a substitute bladder [3-16]. All have the potential to improve the quality of life [17-19] and cure the disease as reported by several institutions and cooperative groups over the last 15 years [20-29]. Based on the results of these studies, together with those of other studies, Gospodarowicz [30] commented that 'these

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results certainly offer hope and indeed opportunity for bladder preservation in a significant proportion of patients who currently undergo cystectomy.

Radical cystectomy has been the conventional treatment of muscle-invasive bladder cancer in the United States for the past two decades. This procedure is associated with excellent local control of the primary tumor, but it has a high probability, approaching 50 percent, of subsequent distant metastases, generally occurring within two years of diagnosis [31]. Thus, the question has been raised whether chemotherapy can reduce the rate of distant metastases [32,33] and improve survival. Combination chemotherapy has been used to treat both advanced local tumors in the bladder and metastatic disease, with encouraging results reported for several series of patients [34-36]. Although systemic chemotherapy used as an adjuvant to radical cystectomy delays the appearance of recurrent disease, it has no effect on survival [37]. Improved multidrug regimens, however, incorporating both cisplatin and methotrexate [38] are superior to the regimens used in a reported randomized trial comparing cystectomy alone with cystectomy and adjuvant chemotherapy [37]. In the 1980s, several studies indicated that selected patients with invasive bladder cancer could be successfully treated by transurethral resection alone or in combination with radiotherapy with or without cisplatin [39-43]. Two large randomized trials showed no significant advantage to immediate cystectomy as compared with cystectomy deferred until a recurrence after external-beam irradiation [44,45].

Thus, during the mid-1980s a regimen was developed that would spare the bladder in selected patients, on the basis of the following observations: (1) radical cystectomy is not curative in more than 50 percent of patients, mainly because of the appearance of distant metastases [32,37,44,45], (2) a thorough transurethral resection of the primary bladder tumor is important in any approach for sparing the bladder [39,40,42], (3) maintaining bladder function after combined treatment with cisplatin and radiation is feasible [41,43,46], (4) radiation combined with cisplatin is more effective against the primary tumor than radiation alone [47] and (5) multiagent chemotherapy combining cisplatin, methotrexate and vinblastine with doxorubicin is significantly more effective than single-agent chemotherapy in terms of both the response rate and survival of patients with advanced bladder cancer [48]. Thus close coordination among all disciplines is required to achieve optimal results [49]. Recent investigations focus on (1) optimizing radiation techniques [50-57] and incorporating more effective systemic chemotherapy [58-63] and (2) the proper selection of patients based on molecular markers [64-70].

After a median follow-up of 48 months, we now report our results with the use of transurethral resection; systemic multidrug chemotherapy with methotrexate, cisplatin, vinblastine (MCV); and pelvic irradiation. Our criteria for selecting patients whose bladders might be preserved included safeguards so that those selected for full chemotherapy and radiotherapy had the highest likelihood of local cure of invasive bladder cancer. Patients had to have a complete response of their primary tumor to the initial combination treatment with chemotherapy and radiotherapy to continue receiving full doses of chemotherapeutic drugs and radiation. All patients who were medically fit for cystectomy and did not have a complete response to the initial therapy were advised to undergo radical cystectomy. This was an attempt to ensure that conservative treatment with bladder preservation would not compromise survival in patients who did not have an immediate complete response and to minimize the possible need for salvage cystectomy after full doses of radiation had been given. The protocol was designed to test the safety, tolerance and efficacy of this selective bladder preservation approach and report on clinicopathologic and treatment-related factors that may predict treatment response, risk of relapse and long-term survival.

PATIENTS AND METHODS

Selection of patients:

We studied 55 consecutive patients, 36 to 73 years old (mean age, 58.8), with biopsy-confirmed bladder cancer invading muscle (clinical stages T2 through T4, NXM0) who were treated at our Clinical Oncology Department, Tanta University Hospital between January 2000 and January 2006. The pretreatment evaluation included history taking, physical examination, chest radiograph, excretion urography, a complete blood count, measurement of blood urea

nitrogen, serum creatinine and creatinine clearance, liver-function studies and as thorough as possible transurethral resection of the bladder tumor (TURBT). Bone scanning and abdominal computed tomography (CT) were performed to detect any metastatic disease. Patients were ineligible for this study if they had metastases to distant sites or to lymph nodes above the bifurcation of the common iliac vessels, had a white-cell count <4,000 per μl and an absolute neutrophil count (ANC) <1,800 per μl , a platelet count <100,000 per μl , a serum creatinine >1.5 mg/dl, a creatinine clearance of <50 ml/min (0.84 ml per second); were incapable of self-care; or had severe hearing loss. Pretreatment patient characteristics are listed in Table (1).

Table (1): Pretreatment characteristics (n=55).

Patients and tumors' characteristics	No.	%
<i>Pathological tumor type:</i>		
Transitional cell carcinoma	49	89.1
Squamous cell carcinoma	5	9.1
Adenocarcinoma	1	1.8
<i>Tumor grading:</i>		
Grade II	8	14.6
Grade III	38	69.1
Grade VI	7	12.7
Unknown	2	3.6
<i>Visibly complete TURBT performed:</i>		
No	12	21.8
Yes	42	76.4
Unknown	1	1.8
<i>Palpable mass or induration persistent after the TURBT:</i>		
No	46	83.6
Yes	9	16.4
<i>Tumor stage:</i>		
T2	43	78.2
T3a	7	12.7
T3b	4	7.3
T4a	1	1.8
<i>Age in years:</i>		
≤ 60	22	40
> 60	33	60
<i>Gender:</i>		
Male	44	80
Female	11	20

The clinical stage of the primary tumor was T2 in 43 (78.2%) patients, T3a in 7 (12.7%) patients, T3b in 4 (7.3%) patients and T4a in 1 (1.8%) patient. Pathological review, performed in all 55 patients, confirmed that all had tumors invading the muscularis propria. Forty-nine (89.1%) patients had transitional-cell carcinoma of the bladder, 5 (9.1%) had squamous-cell carcinoma and 1 (1.8%) had adenocarcinoma.

The study protocol combined a transurethral resection of the bladder tumor (as thoroughly as was judged safely possible); systemic multi-drug chemotherapy with the combination methotrexate, vinblastine and cisplatin and pelvic external-beam radiation combined with two additional courses of cisplatin. Radical cystectomy was recommended for all patients who had less than a complete response to the initial two cycles of combination chemotherapy plus radiotherapy (4500 cGy) with two additional courses of intravenous cisplatin. Patients who responded completely were given consolidation treatment with additional radiation (1980 cGy) and also received one additional course of intravenous cisplatin.

Systemic chemotherapy:

Complete blood counts and blood chemical values, including measurements of creatinine, calcium, magnesium, bilirubin, aspartate aminotransferase and alkaline phosphatase, were obtained before each dose of cisplatin was given. Complete blood counts were determined weekly during chemotherapy, as were the levels of blood urea nitrogen, creatinine, aspartate aminotransferase and alkaline phosphatase.

For both induction and consolidation therapy, Methotrexate (30 mg per square meter of body-surface area) was given on days 0, 14 and 21 of a 28-day cycle, cisplatin (70 mg per square meter) on day 1, and vinblastine (3 mg per square meter) on days 1, 14 and 21. The doses of methotrexate and vinblastine were reduced if severe leukopenia or thrombocytopenia occurred or the serum bilirubin concentration rose above 2.0 mg per deciliter. The doses of methotrexate and cisplatin were reduced if the serum creatinine concentration rose above 1.5 mg per deciliter. The doses of cisplatin and vinblastine were reduced if neuropathy (including a lack of deep tendon reflexes), weakness, or severe paresthesias occurred. The doses of methotrexate were reduced for stomatitis. If hematologic

toxicity developed (platelets <50,000 per μl or ANC <1,800 per μl), then both the chemotherapy and radiation therapy were discontinued for one week and resumed when the ANC returned to 1,800 per μl and the platelet count returned to 100,000 per μl .

Radiation therapy:

Patients were treated once daily. During the induction phase, external beam radiation therapy was delivered at 1.8 Gy once daily to the whole bladder, bladder tumor volume and the pelvic lymph nodes. Thus, at the end of the induction phase these structures received 45 Gy in 25 fractions over 5 weeks. Complete responders underwent external beam radiation consolidation therapy which began 7 to 10 days after the re-evaluation cystoscopy using ^{60}Co photons and a 4-field box technique with individually shaped portals and daily fractions of 1.8 Gy on 5 consecutive days per week to receive the final booster dose of 1980 cGy to the whole bladder and bladder tumor volume. Thus, at the end of the consolidation phase the whole bladder and bladder tumor volume had received 6480 cGy in 36 fractions and the pelvic lymph nodes had received 45 Gy in 25 fractions.

Chemotherapy combined with radiotherapy:

The bladder and pelvic lymphatic systems were treated according to a four-field box technique with carefully contoured fields; a total of 4500 cGy was given over a period of five weeks, in fractions of 180 cGy during each of five treatment sessions per week. Cisplatin (70 mg per square meter) was given the day before radiation therapy started, 21 days later and again during the consolidation phase if consolidation treatment was administered. Patients selected for consolidation radiotherapy received radiation to whole pelvic fields, for a total dose of 4500 cGy followed by an interval of two to three weeks to allow tumor regression. Patients were considered complete responders only if there was no visible mass, no tumor in a tumor site on repeat biopsy, and a negative urine cytology. Complete responders underwent consolidation chemotherapy/radiation, beginning 7 to 10 days after the re-evaluation cystoscopy. Therapy in all patients undergoing consolidation treatment was then simulated by introducing radiopaque material into the bladder and rectum to outline the fields to receive the final booster dose of 1980 cGy to the bladder only, for a total dose

of 6480 cGy. All radiation was delivered by megavoltage beams from ^{60}Co machine. Incomplete responders were advised to undergo a prompt radical cystectomy.

Criteria for Response and Follow-up Procedures:

Urologic evaluation categorized the response of the primary tumor. Response quality was evaluated by cystoscopy and deep TUR of the former tumor bed. A complete response (CR) required the absence of any endoscopically visible tumor, the absence of any microscopic tumor in the biopsy specimen, as well as negative urine cytology. Patients underwent cystoscopy, biopsy of the tumor site, manual examination under anesthesia and urinary cytologic examination every three months for two years and every six months thereafter. Follow-up pelvic and abdominal CT scans were obtained after the initial 4500-cGy dose of radiation, three months after the completion of treatment, and then every six months thereafter. At each follow-up, evaluation consisted of pertinent medical history, physical examination, assessment of hematologic indexes, measurement of serum creatinine, liver-function studies, urine cytology and cystoscopy with biopsies of all suspected areas. In case of persistent or recurrent tumor, additional treatment, such as transurethral resection, followed by intravesical therapy for superficial tumors or salvage cystectomy for muscle-invasive tumors, was recommended and initiated at the earliest opportunity. Evaluation of treatment-related toxicity was performed according to the Standard WHO toxicity criteria [71]. Median follow-up for the entire group was 48 months (range 12-85 months).

Statistical analysis:

SPSS [Statistical package (version 12.0)] was used for data analysis. Mean and standard deviation were estimates of quantitative data. Chi-square/ Fischer exact were tests of proportion independence. Kaplan-Meier method [72] was used for estimating survival and Breslow test to compare curves. Cox-regression analysis was used to estimate odds of recurrence and 95% CI. *p* value was significant at 0.05 level [73].

RESULTS

Fifty-five patients completed the induction chemotherapy and radiation therapy. The acute

reactions of different grades according to the Standard WHO toxicity criteria [71] attributable to the chemotherapy included leukopenia (<3000 white cells per microliter) in 34% of the patients, oral ulcers in 24%, alopecia in 100%, diarrhea in 10%, nausea and vomiting in 73%. There were no deaths attributable to drug toxicity. The acute reactions attributable to chemotherapy combined with radiotherapy of different grades included bladder irritation in 32% of the patients, diarrhea in 26%, fatigue in 21% and leukopenia in 8%. Among the 37 patients receiving chemotherapy and the complete dose of radiation (6480 cGy), 4 had transient hematuria and symptomatic urinary frequency; none of these 37 patients had incontinence. When questioned at the follow-up examinations after the completion of treatment, all patients reported that their bladder function had remained satisfactory.

The percentages of patients sustaining a grade III or greater leukopenia, thrombocytopenia, neutropenic fever, infection, nausea/vomiting, or bladder irritation during the protocol are shown in Table (2). During the chemoradiation, the most common grade 3 non-hematological toxicities were reported in the gastrointestinal tract in 9 patients and in the bladder in 4 patients. No grade 4 toxicities were recorded.

Table (2): Grade3 treatment-related toxicity among the 37 patients receiving chemotherapy and the complete dose of radiation.

Toxicity	Number	%
Hematological	10	27
Gastrointestinal	9	24.3
Bladder	4	10.8
Other	3	8.1

The percentage of patients sustaining late morbidity reported during the follow-up phase of this study is shown in Table (3). Grade 3 toxicities were reported in three patients for bladder reactions, four patients for gastrointestinal tract reactions and in eight patients for hematologic toxicity. There were two late grade 4 events due to hematologic and gastrointestinal tract toxicity. All but one of the late toxicities have resolved with subsequent treatment and follow-up. In one patient, a grade 3 bladder reaction persisted.

Table (3): Late toxicity following treatment among the 37 patients receiving chemotherapy and the complete dose of radiation.

	Number	%
<i>Grade III toxicity:</i>		
Hematological	8	21.6
Bladder	3	8.1
Gastrointestinal tract	4	10.8
Other	2	5.4
<i>Grade IV toxicity:</i>		
Hematological	2	5.4
Gastrointestinal tract	2	5.4

Table (4) shows the complete response rates of the primary tumor following induction therapy. Thirty-seven of 55 evaluable patients were complete responders (67.3%) after induction chemoradiation therapy. In the 18 patients who had persistent tumor and who were evaluated for response, none exhibited tumor progression. In the 18 patients who underwent cystectomy for an incomplete response, cancer was found in the cystectomy specimens of all patients. Ileal conduit urinary diversions were performed on all of the patients undergoing radical cystectomy.

Table (4): Clinical response rates after induction chemoradiation among the 55 evaluable patients.

Clinical response	Number	%
Complete	37	67.3
Partial	15	27.2
Stable disease	3	5.5
Progressive disease	0	0

The median follow-up was 48 months. Seventeen of the 37 patients who were clinical complete responders following induction chemoradiation therapy and completed consolidation chemoradiation therapy have developed a bladder recurrence. Four of these 17 patients have had an invasive recurrence and have undergone a cystectomy; the remainder were superficial tumors and have been treated, so far, successfully with conservative methods.

Of the 55 patients studied, 33 (60%) survived with bladders apparently free of tumor at 3 years. In 13 patients (23.6% of all studied)

among the 37 surviving with disease-free bladders, superficial tumors recurred but were successfully eradicated by TURB and intravesical drug therapy. The 3-year overall survival is 79.23% and 60% are alive without a cystectomy at three years (Fig. 1). The actuarial five-year overall survival was 43.12% among all 55 patients completing the study (Fig. 2).

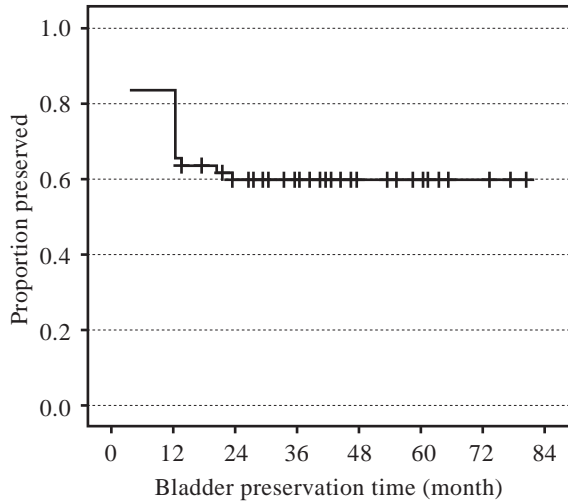


Fig. (1): Bladder preservation rate.

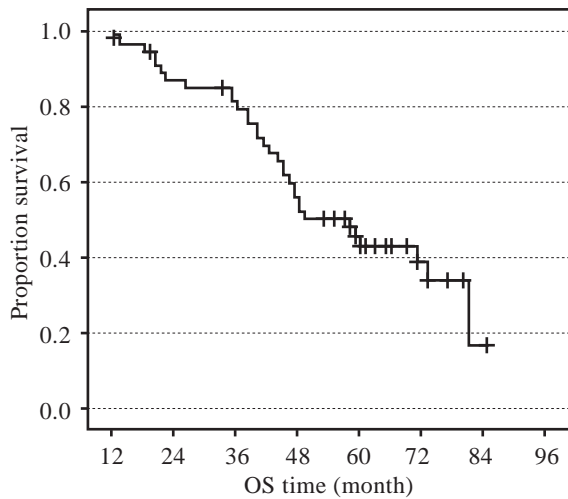


Fig. (2): Overall survival (OS).

The median overall survival of the 43 patients with stage T2 disease was 73 months - significantly better than that of patients in stages T3 and T4 which was 21 months ($p = <0.001$). Five-year overall survival rate was 55.82% for patients with T2 disease but dropped for patients in stages T3 and T4 with no patient alive at 5 years (Fig. 3).

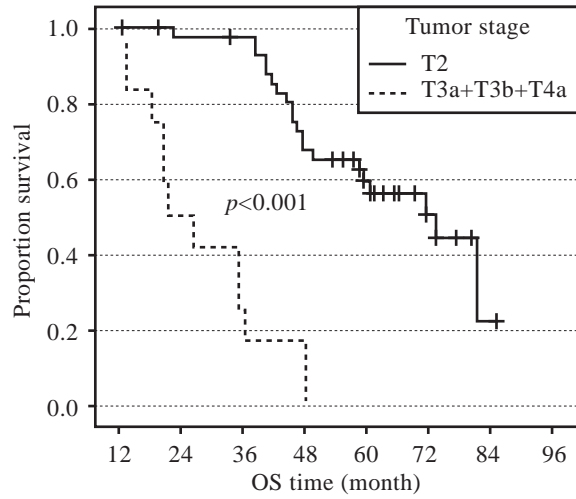


Fig. (3): Overall survival according to clinical stage.

Among the 37 patients with complete responses, the overall actuarial survival was significantly better than among the 18 with incomplete responses to the initial chemotherapy combined with radiotherapy. Five-year overall survival rate was 59.15% for patients with complete responses but dropped to 6.32% for patients with incomplete responses to the initial chemotherapy combined with radiotherapy ($p = <0.001$) (Fig. 4).

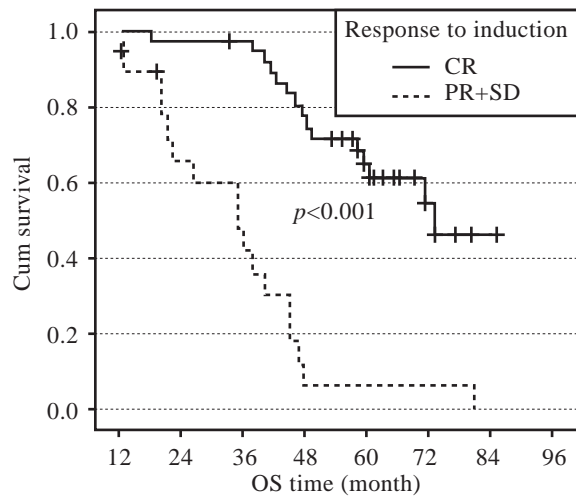


Fig. (4): Overall survival according to response to induction therapy.

Among the 40 patients who did not have hydronephrosis at presentation, overall survival was significantly better. Five-year overall survival rate was 52.88% for patients without hydronephrosis at presentation but dropped to 15.66% for patients with hydronephrosis at presentation ($p = <0.001$) (Fig. 5).

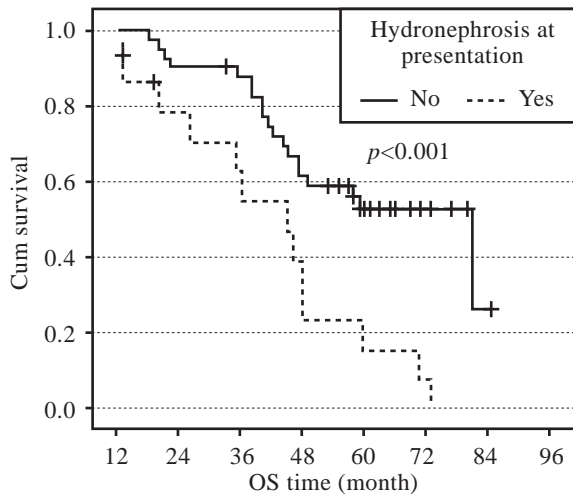


Fig. (5): Overall survival according to absence or presence of hydronephrosis at presentation.

Among the 37 patients who underwent bladder preservation, the overall actuarial survival was significantly better than among the 18 who underwent radical cystectomy. Five-year overall survival rate was 66.49% for patients with bladder preservation but dropped to 5.05% for patients who underwent radical cystectomy ($p < 0.001$) (Fig. 6).

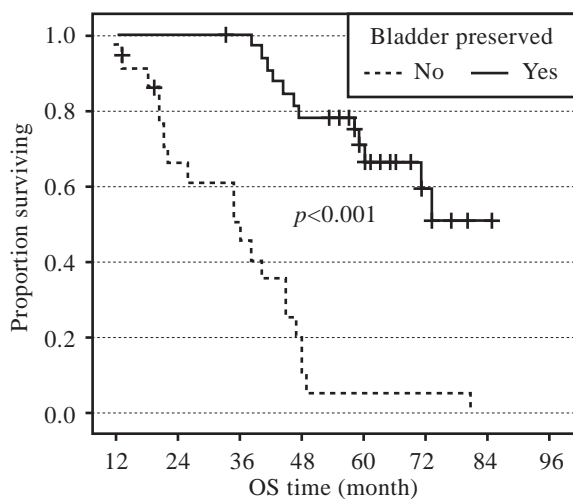


Fig. (6): Overall survival according to type of surgery (Bladder preservation vs. radical cystectomy).

Distant metastases:

Distant metastases were diagnosed in 24 of 55 (43.6%) patients with an actuarial rate of distant metastases free survival of 58.72% and 43.68% at 3 and 5 years, respectively. Five-year distant metastases-free survival rate was 53.55% for patients without hydronephrosis at presentation but dropped to 16.05% for patients with hydronephrosis at presentation (Fig. 7).

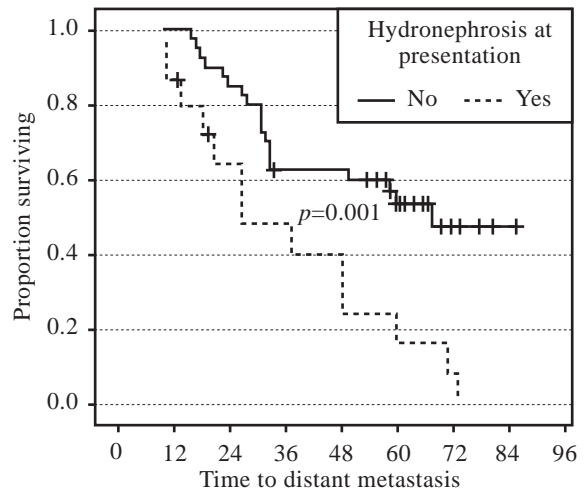


Fig. (7): Survival without metastatic disease according to absence or presence of hydronephrosis at presentation.

Local control:

Among 37 patients who had no evidence of disease at restaging-TUR, 20 (54.05% of the 37 patients) have been continuously free of tumor in their bladder, 13 patients (35.13% of the 37 patients) experienced a noninvasive local relapse, 4 patients (10.81% of the 37 patients) had a muscle-invasive relapse. For the whole group of patients, local control without any relapse at 3 and 5 years were 57.89% and 25.95%, respectively. Interestingly, three-year local recurrence-free survival rate was 61.29% for patients without hydronephrosis at presentation but dropped to 15.79% for patients with hydronephrosis at presentation (Fig. 8). Hazard ratio of local recurrence in hydronephrotics is 2.985 (95% CI is 1.5-5.98).

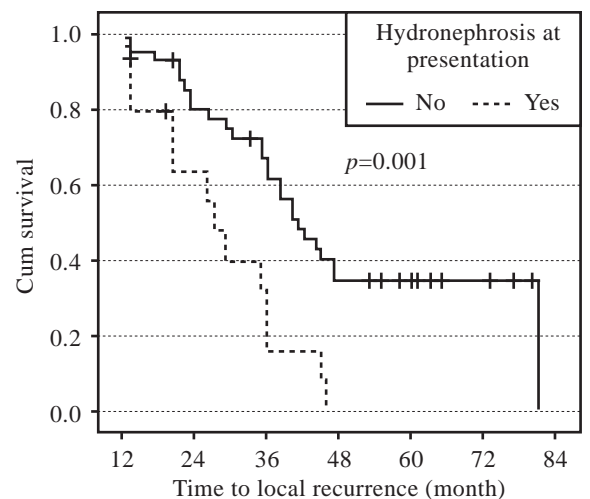


Fig. (8): Survival without local recurrence according to absence or presence of hydronephrosis at presentation.

Among the 43 patients with stage T2 disease, the rate of bladder preservation was significantly higher than that of patients in stages T3 and T4. The rate of bladder preservation was 76.5% at 5 years for patients with stage T2 disease with no patient alive with preserved bladder at 2 years of the group of patients in stages T3 and T4 ($p = <0.001$) (Fig. 9).

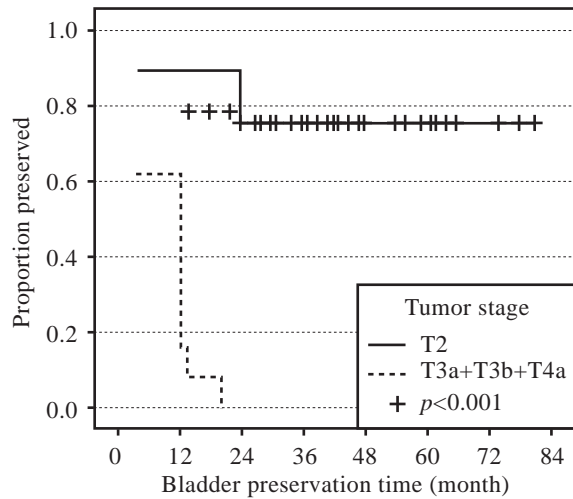


Fig. (9): Bladder preservation rate according to stage of the disease.

Among the 40 patients without hydronephrosis at presentation the rate of bladder preservation was significantly higher than among the 15 who had hydronephrosis at presentation. The rate of bladder preservation was 72.22% at 3 years for the 40 patients without hydronephrosis at presentation compared with 26.67% for patients who had hydronephrosis at presentation ($p = 0.001$) (Fig. 10).

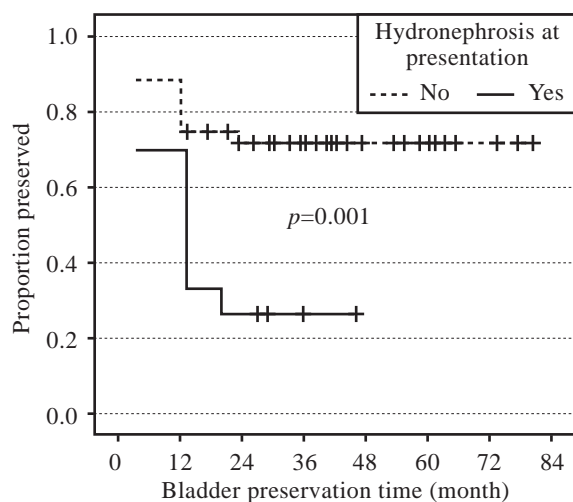


Fig. (10): Bladder preservation rate according to absence or presence of hydronephrosis at presentation.

The morbidity of this protocol was documented. Ten patients (18.2%) required modification of the induction or consolidation chemotherapy doses due to acute toxicity. One (1.8%) of the 55 patients experienced urinary frequency during induction therapy but it was not sufficient to interrupt therapy or to discontinue the protocol. There have been four reported cases of hematuria. No patient required a cystectomy for a bladder complication.

Proportional-hazards analysis:

Multivariate and univariate analyses were used to provide quantitative estimates of the association of the following eight clinical and pathological tumor factors with overall survival in the 55 studied patients: clinical stage (T2 vs. T3 and T4) ($p = <0.001$), the presence or absence of tumor-associated hydronephrosis ($p = <0.001$), bladder preservation ($p = <0.001$), age of the patients ($p = 0.59$), response to induction therapy (complete response vs. incomplete response) ($p = <0.001$), sex ($p = 0.54$), pathological subtype ($p = 0.29$) and the tumor grade ($p = 0.23$). Thus this analysis of overall survival showed that the presence or absence of hydronephrosis, response to induction therapy as well as the clinical stage all approached statistical significance (all $p = <0.001$). Univariate and, multivariate analysis of the rate of bladder preservation without recurrence of invasive tumor in relation to all studied tumor factors revealed a significant difference in only two comparisons, that of patients who had hydronephrosis with those who did not ($p = 0.0014$) and clinical stage (T2 vs. T3 and T4) ($p = <0.001$).

DISCUSSION

Transurethral resection of invasive bladder cancer as thorough as possible, followed by multidrug chemotherapy and external-beam irradiation with concurrent administration of cisplatin, was fairly well tolerated by the patients we studied (mean age, 58.8 years). Fatigue, gastrointestinal complications, bladder irritation that is usually reversible and hematologic toxicity have been the main adverse systemic effects which are comparable with other studies [20,46]. The patients' pelvic tissues tolerated the combination therapy well. No patient who received complete treatment with chemotherapy and radiotherapy had a permanent major complication involving the bladder or the rectum, although three had intermittent hematuria and

symptomatic urinary frequency which were controlled by conservative measures. Our results and those of the Radiation Therapy Oncology Group [21] suggest that combining cisplatin with radiation may not have any important synergistic toxic effects on the bladder or bowel. Furthermore, Coppin et al. [74] reported an improved local control rate when cisplatin was given in conjunction with radiation.

The rate of complete responses to our initial program of combined therapy was 67.3% among the 55 patients enrolled which is comparable to that achieved by Claus et al. [75] and it was 77.5% among our 40 patients who did not have tumor-associated hydronephrosis at presentation. During a median follow-up of four years, 4 of 37 patients (10.8%) with complete responses to the full courses of chemotherapy and radiotherapy had local recurrence of an invasive tumor. Thirteen patients (35.14% of the complete responders) had recurrence of a superficial bladder cancer, successfully managed by further transurethral surgery and intravesical drug therapy. Future recurrences are of concern but are less of a worry now, since we have followed the patients for a median of four years. No invasive bladder tumor has recurred in 33 patients, or 60% of those studied - a rate higher than that achieved with transurethral surgery alone [40,42], radiation therapy alone [31,39,44], or systemic chemotherapy alone [76]. Although it is not possible to attribute these results to one of these treatments rather than to another, the combination of all three is fairly well tolerated. Results of the use of a similar therapeutic strategy by a multi-institutional national group in 91 patients also indicate a high initial response rate and low morbidity [74]. In conclusion, we have learned that any component of the trimodality therapy contributes considerably to the overall success [77,78]. Of concern is that within 48 months of median follow-up, this incidence of local recurrence among our complete responding patients who completed the protocol is higher than had been reported by Housset and colleagues [79] who reported a bladder recurrence rate of only 17% (12 of 71 complete responding patients). Clearly these comparisons are subject to unknown biases and the follow-up on these series is too short for any substantive conclusions, in addition they used different radiation fractionation and different chemotherapy schedules.

According to multivariate and univariate analyses of tumor factors possibly influencing overall survival after our combination treatment, only the presence or absence of hydronephrosis, response to induction therapy and the tumor stage independently approached statistical significance (all $p < 0.001$). This was comparable with Scrimger et al. [80] in their published article. Using a multivariate analysis, the authors found that hydronephrosis, tumor stage and response to radiation did predict for overall survival. The actuarial overall survival rate of 43.12% at five years in our series is not significantly inferior to that reported in other trials, randomized [37,44,45] or not [35,41-43], most of which included radical cystectomy for all patients. Multivariate analysis also showed that the only independent prognostic factor indicating that the bladder would remain free from invasive tumor was the absence of hydronephrosis at the time of diagnosis ($p = 0.001$). Patients with hydronephrosis at the time of presentation should not be treated with the combination treatment used in our study, because hazard ratio of local recurrence in hydronephrotics is 2.985 (95% CI is 1.5-5.98). Such patients should be considered for cystectomy. The success rate of bladder preservation was 89.2% among the patients with complete responses to initial treatment and this finding supports the strategy of combination therapy and bladder preservation in selected patients. The addition of chemotherapy did not show any impact on the development of distant metastases, which is also reflected in the contradictory results of adjuvant and neoadjuvant chemotherapy in cystectomy-based series [81-83].

This study evaluated only a relatively small number of patients. It did not include those with advanced T4 tumors and so it is difficult to compare these results with other published bladder-sparing results. The overall three-year survival rate of 79.23% compares favorably with the prior RTOG protocol 89-03 (59% for the 99 patients without hydronephrosis) [23] and is comparable to that reported by other studies but with different radiation fractionation and different chemotherapy schedules (83%) [84,85]. Five-year overall survival rates of 43.12% which have been reported in our study are comparable to those stated by Claus et al. [49]. The likelihood of being alive at three years with a functioning treated bladder (60%) is encouraging relative

to the 46% for the 99 patients without hydronephrosis entered on RTOG 89-03 at three years [23] and inferior to that reported from an institutional pilot at the Massachusetts General Hospital using a different chemoradiotherapy schedule (78%) [84] and that reported by Claus et al. (75%) [49].

In looking to reduce the toxicity of neo-adjuvant CMV and to improve survival further in patients with apparently localized disease, novel treatment approaches are required. Newer chemotherapeutic agents, particularly gemcitabine [86-90], trastuzumab [64] and the taxanes [91-93] are now being tested in combination with RT and may further improve organ preservation in bladder cancer.

Our results are equivalent to those reported for radical cystectomy [20-23,94-97], but our conclusions are weakened by the absence of a simultaneous, randomized control group. Without a randomized comparison of conventional cystectomy with chemotherapy, radiotherapy, and bladder-preserving treatment combined, our findings about overall survival may have been influenced by an unknown sample bias. Scrimger et al. [80] found no significant differences in survival between patients treated with primary surgery vs. organ-preservation approaches. A survival advantage associated with the incorporation of chemotherapy into the management schema was detected on multivariate, but not univariate, analysis. Thus stratification of patients based on tumor characteristics is imperative in clinical trials for invasive bladder cancer.

Notwithstanding the limitations of nonrandomized comparison, this analysis indicates that selective bladder preservation by trimodality treatment may result in long-term cure and survival rates comparable to the best cystectomy series. Prospective, randomized trials will have to be conducted to evaluate whether selective bladder preservation relying on chemotherapy and radiotherapy is an effective alternative to radical cystectomy. Unfortunately, it may be difficult, however, to recruit patients for a trial comparing cystectomy and bladder-preserving treatment because of patients' strong preference for bladder preservation. Needless to say, the quality of life of the patient with the bladder preserved is definitely better since urinary diversion is avoided [98].

As more experience is acquired with organ-sparing treatment, it is clear that future directions of clinical and basic research will focus on two main topics: (1) the optimization of the treatment modalities, including incorporation of new cytotoxic agents and (2) the proper selection of patients who will most probably benefit from the respective treatment alternatives. As demonstrated in our study, clinical criteria helpful in determining patients for bladder preservation include such variables as early tumor stage, a complete response to induction treatment and the absence of hydronephrosis at the time of diagnosis. Furthermore, future clinical trials incorporating targeted therapies with novel clinical end points may accelerate development of therapeutic strategies for locally advanced muscle invasive bladder cancer. Evaluation of molecular markers may further help to stratify patients to a risk-adapted approach. Therefore, the use of neo-adjuvant therapy in muscle-invasive bladder cancer may help us to refine further the answers to the two most valuable questions: Who to treat? and What to treat with?.

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