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Bladder perservation by combined modality treatment in invasive bladder cancer

Tanja Čufer,[1] Jožica Červek,[1] Branko Zakotnik,[1] Borut Kragelj,[1] Simona Borštnar,[1] Mirjana Žumer-Pregelj[2]

[1]Institute of Oncology, Ljubljana, Slovenia, [2]Department of Urology, University Medical Center, Ljubljana, Slovenia

105 patients with biopsy-proven invasive bladder cancer were entered into the study of combined modality treatment with bladder sparing approach. After a maximal transurethral resection of the tumor, the patients were treated with 2 - 4 cycles of MCV (methotrexate, cisplatinum, vinblastine) polychemotherapy. Re-evaluation including cystoscopy with tumor-site biopsy and urine cytology was performed thereafter. In patients with a complete response (CR), the treatment was continued by radiotherapy, whereas in all other patients cystectomy was performed whenever feasible. The CR after TUR and chemotherapy was achieved in 52% of patients. After a median follow-up of 42 months, 52 out of 75 (69%) patients selected for bladder preservation were without evidence of disease in the bladder. The 3.5-year actuarial survival in the entire group of 105 patients was 62%, whereas the survival with the bladder intact was 49%. The survival was significantly better in patients who responded to chemotherapy than in nonresponders. The actuarial survival of complete responders was 82%, whereas their survival with the bladder intact was 78%. In non-responders there was no significant difference in survival between patients who underwent cystectomy and those who completed treatment with radiotherapy. We found that the bladder sparing approach is safe and does not compromise the survivall in patients with invasive bladder cancer.

Key words: bladder neoplasms; combined modality therapy; treatment outcome; survival rate

Introduction

Radical cystectomy still represents the standard treatment for muscle invasive bladder carcinoma. This procedure provides good local control but is associated with a high probability, approaching 50 %, of subsequent distant metastases.[1] The other drawback of this treatment approach lies in the fact that neovesica can never substitute the patients original bladder.

In view of the above problems, in the 80's several clinical studies were initiated using bladder sparing approach to the treatment of this disease.[2-10] In the last decade, the most promising advance has been achieved using transurethral surgery (TUR) and combined chemo-radiotherapy regimens.[2-6,8] This treatment approach takes the advantages of favorable effects of cis-platinum based chemotherapy as well as the synergistic effects of chemotherapy and radiotherapy.[11] The results of these combined chemo-radiotherapy programs showed the overall survival rates of 47-62% at 4-5 years and these results are similar to that obtained by radical cystectomy.[1] Moreever, bladder preservation was possible in 58-79% of patients entered into these studies.[2,4,6,8]

Our study, which was started in 1989, represents one of the first attempts to introduce such an organ sparing program. The preliminary results were published in 1993.[8] The high response rate and the number of preserved bladders, as well as the overall survival rates justified the continuation of our study.

Correspondence to: Tanja Čufer, MD, PhD, Institute of Oncology, Zaloška 2, 1105 Ljubljana, Slovenia.

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Our therapeutic approach remained basically unchanged. However, the greater number of patients and the longer duration of follow-up in the present study render the obtained results more reliable.

Materials and methods

Between December 1988 and June 1995, 105 patients with biopsy-proven invasive bladder cancer were entered into the study. There were 83 males and 22 females with the age range of 34 to 77 years (median, 62). The distribution of patients by clinical stage was as follows: cT1 in 7, cT2-3 in 78 and cT4 in 20 patients. All patients with T1 stage had grade 3 tumor, nonresectable by transurethral surgery. Of the 105 patients, 84 had pure transitional cell carcinoma, of these 25 were grade 2, and 59 grade 3. The remaining 21 patients had either transitional cell carcinoma with metaplasia, or anaplastic carcinoma. Transurethral resection of the tumor was judged to be complete by the urological surgeon in 27 patients.

After maximal transurethral resection of the tumor, the patients were treated with 2 - 4 cycles of polychemotherapy according to MCV schedule (methotrexate (M) 30 mg/m^2 i.v. on days 1, 14; cisplatinum (C) 100 mg/m^2 i.v. on day 2 and vinblastine (V) 3 mg/m^2 i.v. on days 1, 14). The cycles were repeated after 21 days. Cystoscopic evaluation was performed after 3 - 4 cycles of MCV. Restaging included examination under anesthesia, cystoscopy with tumor-site biopsy, and urine cytology. Patients were considered to have complete response if there was no evidence of tumor on all of the above investigations. In patients with a complete response, the treatment was continued by radiotherapy, whereas in all other patients cystectomy was performed whenever feasible.

Radiotherapy was started within 2-3 weeks after completed chemotherapy. Patients were treated in a supine position, using 8 or 10 MV linear accelerator, and the following technique: a four-field arrangement to the pelvis and a three-field arrangement coned down on the urinary bladder. Total dose to the urinary bladder was 50 Gy and to the regional lymph nodes 40 Gy, given in five 2 Gy fractions per week.

Three months after completed chemotherapy and radiotherapy, cystoscopic re-evaluation, chest X-ray and CT-scan were done. Thereafter, follow-up examinations (clinical and laboratory diagnostic studies, cystoscopy, urine cytology, chest X-ray, CT-scan) were performed every 3 months for 2 years and every 6 months thereafter.

Actuarial survival was calculated according to the method of Kaplan and Meier.[12] For comparison of survival curves, the log- rank test was used. Survival was measured from the date of diagnosis. The comparison of survival of complete responders vs. non-complete responders was calculated using the land mark method as proposed by Anderson.[13,14]

Results

The present report includes 105 patients with a median follow-up of 42 months (range, 4 - 96). The complete response after TUR and chemotherapy was achieved in 52% of patients and it was higher in those with lower T stage (Table 1). All patients with complete response after TUR and chemotherapy were irradiated. Four patients, who were not completely evaluated for response after chemotherapy, were treated with radiotherapy and complete response was obtained in three of them; 46 patients with the residual disease at restaging were assigned to cystectomy and 30 of them underwent recommended cystectomy while 16 did not owing to medical or other reasons.

Table 1. Patients with complete response (CR)

Tumor stage	Number of patients CR/total	%
All patients	55/105	52
Stage cT1	5/7	71
Stages cT2T3	43/78	55
Stage cT4	7/20	35

TUR = transurethral resection; ChT = chemotherapy; RT = radiotherapy

After a median follow-up of 42 months, 52 out of 75 (69%) patients selected for bladder preservation were without evidence of disease in the bladder. Freedom from local failure in complete responders to chemotherapy was 80% (95% CI, 69% to 91%) at 3.5 years (Figure 1). Eleven out of 55 complete responders to TUR and chemotheray developed bladder recurrences which were found to be invasive in 7 patients and non invasive in 4 patients. Additional three patients, complete responders to chemotherapy and radiotherapy, developed bladder recurrences, which were found to be invasive in two and non invasive in one patient. Non invasive recurrences were managed by

transurethral resection, which had to be repeated in two patients, in one patient invasive cancer occurred subsequently. Salvage cystectomy was performed in 7 patients with invasive recurrences.

The 3.5-year actuarial survival in the entire group of 105 patients was 62% (95% CI, 51% - 72%), whereas the survival with the bladder intact was 49% (95% CI, 38%-60%) (Figure 2). As shown in Figure 3, the 3.5-year actuarial survival was significantly better in patients who responded to chemotherapy (82%) than in nonresponders (35%, $p < 0.0001$). The 3.5-year actuarial survival of complete responders was 82%, whereas their survival with the bladder intact was 78% (Figure 4). In nonresponders there was no significant difference in survival between patients who underwent cystectomy and those who completed treatment with radiotherapy (approx. 30% at 3-year) (Figure 5).

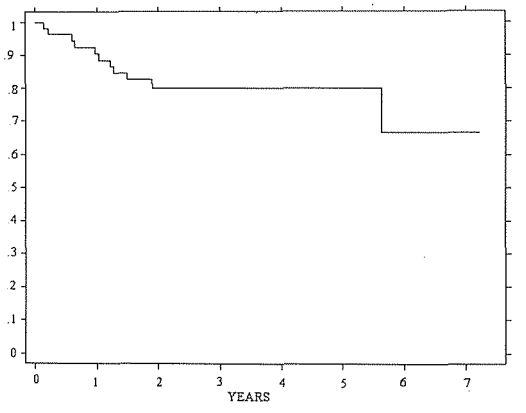

Figure 1. Freedom from local failure in 55 patients with complete response.

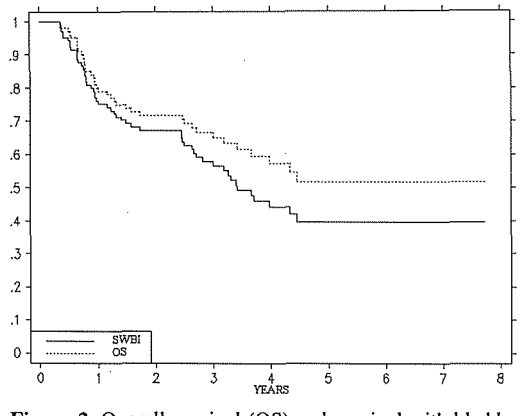

Figure 2. Overall survival (OS) and survival with bladder intact (SWBI) (all patients).

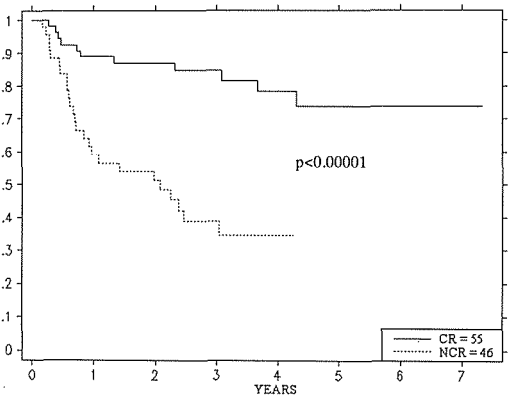

Figure 3. Overall survival according to response to transurethral resection and chemotherapy (CR = complete responders, NCR = non-responders).

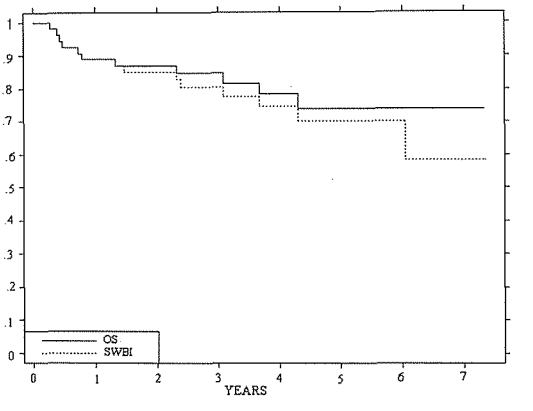

Figure 4. Overall survival (OS) and survival with bladder intact (SWBI) (55 patients with complete response).

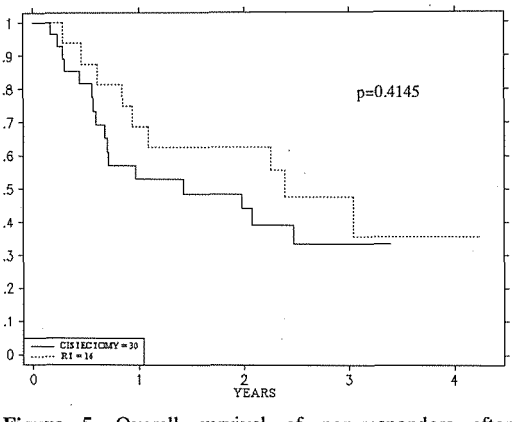

Figure 5. Overall survival of non-responders after transurethral resection and chemotherapy according to local therapy (RT = radiotherapy).

Discussion

Our results obtained by combined modality treatment in invasive bladder cancer patients are encouraging. Out of 105 patients entered into the study, 75 (71%) had their bladder preserved; after a median follow-up of 3.5 years, 69% (52/75) of them have an intact functioning bladder. The 3.5-year survival of the entire group is 62% whereas the survival with the bladder intact is 49%. The 3.5-year survival of complete responders is 82% and the survival with the intact functioning bladder in these patients is almost the same.

Survival and bladder preservation rates in our patients are similar to the results obtained in other studies with combined chemo-radiotherapy, either concomitant[2,4-6] or sequential.[3] They report the bladder preservation in 58-79% of patients, in our case 71%, with an overall survival rates of 47-62% at 4-5 years, in our case 62% at 3.5 years. The same authors report a freedom from local failure from 73-89% at 4-5 years,whereas in our study it was 80% at 3.5 years. In contrast, we had a higher proportion of invasive bladder recurrences compared to non-invasive ones, which was not the case in other studies.[6,15] The reason for this could be in that not always biopsies were performed on follow-up cystoscopies.

Consistently with other authors,[4,5] we found that the patients with complete response to chemotherapy have a better prognosis than the patients who do not respond to chemotherapy. Their survival with intact functioning bladder was found to be 78% at 3.5-year. Moreever, we have found that non-responders have a dismal prognosis, regardlass what treatment they receive afterwards. Complete response after TUR and chemotherapy seems to be a very important prognostic factor for the further course of disease.

In conclusion, we found that invasive bladder cancer is a heterogeneous disease. Among the patients affected, there are more than a half in whom the bladder sparing approach is safe and does not compromise the survival outcome. However, there are some patients with biologically more aggressive tumors that are not manageable either by cystectomy or other combined modality treatment Apparently, the development of biologic markers which could predict chemoradiotherapy responsiveness might be extremely useful in the selection of patients for bladder preservation by combined modality treatment.

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