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Muscle-invasive bladder cancer treated with TURB followed by concomitant boost with small reduction of radiotherapy field with or without of chemotherapy

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ABSTRACT

Aim: To evaluate the clinical outcome and toxicity of the treatment of muscle-invasive bladder cancer (MIBC) that combined transurethral resection of bladder tumor (TURB) with "concomitant boost" radiotherapy delivered over a shortened overall treatment time of 5 weeks, with or without concurrent chemotherapy.

Background: Local control of MIBC by bladder-sparing approach is unsatisfactory. In order to improve the effectiveness of radiotherapy, we have designed a protocol that combines TURB with a non-conventionally fractionated radiotherapy "concomitant boost".

Materials and methods: Between 2004 and 2010, 73 patients with MIBC cT2-4aN0M0, were treated with "concomitant boost" radiotherapy. The whole bladder with a 2–3 cm margin was irradiated with fractions of 1.8 Gy to a dose of 45 Gy, with a "concomitant boost" to the bladder with 1–1.5 cm margin, during the last two weeks of treatment, as a second fraction of 1.5 Gy, to a total dose of 60 Gy. Radiochemotherapy using mostly cisplatin was delivered in 42/73(58%) patients, 31/73(42%) patients received radiotherapy alone.

Results: Acute genitourinary toxicity of G3 was scored in 3/73(4%) patients. Late gastrointestinal toxicity higher than G2 and genitourinary higher than G3 were not reported. Complete remission was achieved in 48/73(66%), partial remission in 17/73(23%), and stabilization disease in 8/73(11%) patients. Three- and five-year overall, disease specific and invasive locoregional disease-free survival rates were 65% and 52%, 70% and 59%, 52% and 43%, respectively.

Conclusions: An organ-sparing approach using TURB followed by radio(chemo)therapy with "concomitant boost" in patients with MIBC allows to obtain long-term survival with acceptable toxicity.

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1. Introduction

Bladder cancer is the second most common malignancy of the genitourinary tract.[1] The average age at the time of diagnosis is about 70, which requires consideration of co-morbidities and performance status in the choice of management strategy.[2]

Radical cystectomy is the standard treatment for patients with MIBC.[3] Radical bladder-sparing therapy, with cystectomy reserved for persistent or recurrent disease, is used only in patients who are not surgical candidates or those who refuse surgery. Trimodality bladder-sparing approaches consisting of TURB, followed by radiotherapy and systemic chemotherapy yielded the 5-year overall survival rates of 50–63%, and approximately above 70% of surviving patients maintained their bladder.[4–7] In patients who underwent local conservative treatment, that is TURB followed by radiotherapy, the 5-year overall and disease-specific survival rates were 20–40% and 31–56.8%, respectively.[8–11] As the cure rates offered by local conservative treatment are significantly inferior to those offered by trimodality bladder-preserving therapies, this approach is used exclusively for patients with MIBC who have to be excluded from chemotherapy for medical reasons. However, the demand for local treatment, involving TURB and radiotherapy, is increasing worldwide especially for the group of elderly patients, with significant co-morbidities.

Local control of MIBC by a bladder-sparing approach, both local or multimodality is unsatisfactory. Many studies have been performed with an attempt to obtain better efficacy of radiotherapy by escalation of total dose, use of non-conventional fractionation schemes, reduction of overall treatment time, combining external radiotherapy with interstitial brachytherapy, and the use of new radiotherapy treatment techniques, radiosensitizers or hyperthermia.[12–21]

Thus, in order to improve the effectiveness of treatment of MIBC, we have designed a treatment protocol that combines TURB with a non-conventionally fractionated radiotherapy "concomitant boost" delivered over a shortened overall treatment time of 5 weeks, with or without concurrent chemotherapy. This paper focuses on analyzing the clinical outcomes of this approach and evaluation of toxicity.

2. Material and methods

Between March 2004 and March 2010, 73 patients with histologically confirmed MIBC including stages cT2-4aN0M0, who were not candidates for radical surgery or refused it, were conservatively treated with "concomitant boost" radiotherapy. All patients underwent maximal TURB prior to initiation of chemoradiation, which was delivered in 42/73 (58%) patients. Those who were considered poor candidates for chemotherapy due to general medical condition or/and significant co-morbidities received radiotherapy alone – 31/73 (42%). Patient and tumor characteristics are shown in Table 1. Systemic therapy consisted of induction chemotherapy and concurrent radiochemotherapy. In the period from 4 to 8 weeks after TURB, two cycles of neoadjuvant chemotherapy using gemcitabine and cisplatin were administered, as gemcitabine

Table 1 – Patient and tumor characteristics.

Characteristics	Patients *n* (%)
Age	
Median (range)	67 (47–85)
Sex	
Female	10 (14%)
Male	63 (86%)
Karnofsky status	
<80%	48 (65%)
≥80%	25 (35%)
T stage	
T2	27 (37%)
T3	34 (47%)
T4a	12 (16%)
Histological grade	
G2	18 (25%)
G3	55 (75%)
Multifocality	
No	36 (50%)
Yes	37 (50%)
TURB macroscopically complete	
Yes	24 (33%)
No	49 (67%)
Hydronephrosis	
Yes	16 (22%)
No	57 (78%)

intravenous infusion at dose of 1000 mg/m^2 on days 1, 8 and 15 plus cisplatin 70 mg/m^2 on day 2, of the 28-day cycle. In patients with abnormal renal function and/or severe heart disease, gemcitabine and carboplatin scheme was applied, using gemcitabine at dose of 1000 mg/m^2 on days 1, 8, 15 and carboplatin at dose of area under the curve 5 (AUC5) on day 2 of each 28-day cycle. Concurrent chemotherapy was delivered on days 1, 2, 15, 16, 29, 30 of the radiation therapy and consisted of cisplatin 20 mg/m^2 as a 30 min infusion, 3–4 h before radiation. Since 2008, cisplatin was administered on days 1, 8, 15, 22, 29 of radiotherapy.

External beam radiotherapy with computed tomography-based images was applied with 6MV or 18MV photon beams from the linear accelerator. Three-dimensional conformal radiotherapy (3D-CRT) technique was used with individually shaped portals by multi-leaf collimators (MLC). Patients were treated with an empty bladder. Radiotherapy started about 4–6 weeks after neoadjuvant chemotherapy or, in the case of local treatment, 4–8 weeks after TURB. The whole bladder with a 2–3 cm margin was irradiated to a dose of 45 Gy in 25 daily fractions of 1.8 Gy. Additionally, patients received a "concomitant boost" to the whole bladder with a smaller margin of 1–1.5 cm, during the last two weeks of treatment, as a second fraction of 1.5 Gy, with a minimum of a 6-h gap between fractions, to a total dose of 60 Gy, with overall treatment time equal to 5 weeks.

Acute toxicities were assessed weekly throughout treatment according to the Common Toxicity Criteria for Adverse Events v.3.0 (CTCAE). The Radiation Therapy Oncology Group/The European Organization for Research and Treatment of Cancer (RTOG/EORTC) Late Radiation Morbidity Scoring Scheme was used to score late toxicity. The worst late toxicity grade occurring a year or more after the start of

therapy was reported in patients alive without locoregional disease and with an intact bladder.

Treatment response was evaluated six to eight weeks after completion of the conservative therapy by control cystoscopy with biopsy of the tumor bed and normal bladder, or re-TURB if macroscopic disease was present. Computed tomography of the abdomen and the pelvis was also performed.

Statistical analysis was performed using Statistica 10.0 software. Survival rates were estimated according to the Kaplan–Meier method, and differences were compared by a log-rank test. All survivals were calculated from the start of therapy. Overall survival was defined as time to the date of death of any cause, disease specific survival to the date of death due to bladder cancer, bladder-intact survival to the date of salvage cystectomy or death of any cause, invasive locoregional disease-free survival to the date of invasive locoregional bladder failure.

3. Results

3.1. *Toxicity of treatment*

All patients treated with combined radiochemotherapy completed their course of radiation therapy, while in the group that received radiotherapy alone, in two patients irradiation had to be terminated at an earlier date due to a worsening performance status and acute toxicity.

Acute toxicity in this group of patients and in the subgroups with reference to the type of delivered treatment are shown in Table 2. Assessment of late toxicity was available for 45 patients. Evaluation of late toxicity was not reported in 3 of eligible patients. Grade 1–3 genitourinary late toxicity occurred in 9/45 (20%), 4/45 (9%) and 2/45 (4%) patients, respectively. Late gastrointestinal toxicity grade 1 and 2 were observed in 3/45 (7%) and 2/45 (4%) patients, respectively.

In the combined radiochemotherapy group, thirty two patients 32/42 (76%) received two cycles of neoadjuvant chemotherapy, and ten of them 10/42 (24%) only one, due to treatment related toxicity. Sixteen patients 16/42 (38%) continued chemotherapy combined with radiotherapy.

3.2. *Response to therapy and failure pattern*

Complete remission (CR) was achieved in 48/73 (66%), partial remission (PR) in 17/73 (23%), and stabilization disease (SD) in 8/73 (11%) patients. Three out of 25 patients with incomplete response were treated with salvage cystectomy. The remaining patients were found unfit to surgery due to their stage of disease and/or performance status. They were treated by TURB and/or systemic chemotherapy. It should be pointed that 76% (19/25) of the group with persistent disease consisted of patients with advanced clinical stages cT3–T4.

Local recurrence was observed in 16/73 (22%) patients, in 11/73 (15%) noninvasive, in 5/73 (7%) invasive. Median time to local failure was 25 months (range 12–78 months).

Regional lymph node metastasis developed in 6/73 patients, without coexisting local failure only in one case. Three patients with invasive recurrence underwent salvage cystectomy, two were treated by TURB. Patients with superficial relapse were treated by TURB followed or not by endovesical chemotherapy.

Distant metastases were found in 18% of patients (13/73), 11% of patients (8/73) experienced both local and distant failure. These patients received palliative care including systemic chemotherapy and/or TURB or symptomatic treatment.

3.3. *Survival*

At the time of analysis the median follow-up for surviving patients was 67 months. There were 33/73 (45%) deaths, 28 from bladder cancer, 5 from other causes.

Three- and five-year overall, disease specific, bladder-intact and invasive locoregional disease-free survival rates were 65% and 52%, 70% and 59%, 62% and 47%, 52% and 43%, respectively. Five-year rates of overall survival were 59% in the radiochemotherapy group and 41% in the radiotherapy group $p = 0.0520$ (Fig. 1).

4. Discussion

The main treatment failure of radical conservative protocol in MIBC is an incomplete response or recurrence observed in 40–60% patients, within one to two years, which indicates a rapid proliferation of clonogenic cells.[8,9] In a retrospective study performed by Maciejewski and Majewski, the potential doubling time for tumor repopulation in transitional cell cancer of bladder cancer is estimated at 5–8 days, the accelerated repopulation of clonogenic tumor cells becomes visible in the 5th–6th week of conventionally fractionated radiotherapy.[22] Measurement of cell kinetics in transitional cell cancer of the bladder cancer in vivo using bromodeoxyuridine incorporation also indicates short potential doubling time of 3–8 days.[23]

Table 2 – Incidence of acute toxicity according to CTCE v.3.0.

Acute toxicity	Combined treatment: TURB + radiochemotherapy 42 patients	Local treatment: TURB + radiotherapy 31 patients	All patients 73
Gastrointestinal			
G1	17 (40%)	11 (35%)	28 (38%)
G2	3 (7%)	4 (12%)	7 (10%)
Genitourinary			
G1	22 (52%)	17 (54%)	39 (53%)
G2	11 (26%)	8 (25%)	19 (26%)
G3	1 (2%)	2 (6%)	3 (4%)

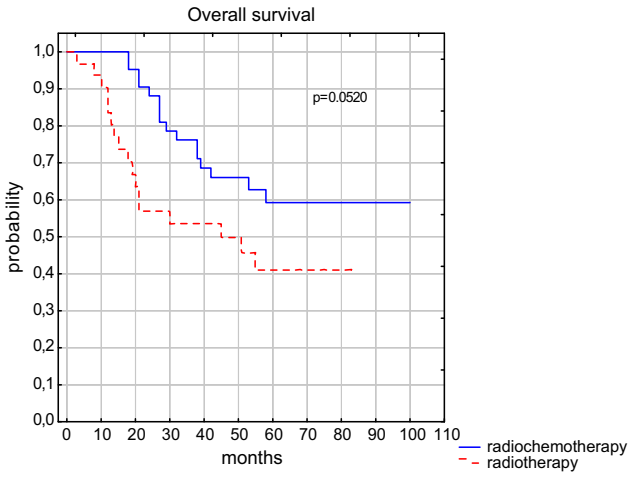

Fig. 1 – Kaplan–Meier curve for overall survival depending on the type of treatment.

Various attempts are made to overcome this negative effect by reducing the overall treatment time via application of an unconventional dose fractionation. One of the altered fractionation schedules, used in the treatment of muscle-invasive bladder cancer is the "concomitant boost" approach. The treatment regimen presented in this paper allows to shorten the radiotherapy treatment time to 5 weeks. This potentially eliminates accelerated repopulation of clonogenic tumor cells and improves the quality of life by reducing the overall treatment time, which is important with respect to the median age of patients suffering from bladder cancer. Radiotherapy with a concomitant boost technique allows to obtain 3-year locoregional and overall survival rates of 56–64% and 36–46%, respectively.[12–14] The results observed in our study are equivalent, as the 3-year locoregional and overall survival rates amount to 52% and 65%, respectively. The obtained outcomes are more favorable as compared to conventionally fractionated radiotherapy used in the treatment of invasive bladder cancer.[8–11]

Radical radiotherapy for invasive bladder cancer using hypofractioned regimens of total dose of 52.5–57.5 Gy in 20 daily fractions of 2.6–2.9 Gy is a widespread approach in the United Kingdom. Presented hypofractionated and conventionally fractionated (60–64 Gy in 30–32 daily fractions) radiation schedules are equivalent in terms of toxicity, both acute and late, and treatment results.[6,24]

However, the role of overall treatment time in therapy of invasive bladder cancer still remains an unsolved problem.[15,16,25,26] Some authors report disadvantage of prolonged treatment time, others conclude that the impact of the total duration of treatment on the patient outcomes is of limited importance, as no statistically significant relationships are observed.

The use of concomitant boost radiotherapy schedule in patients with MIBC results in CR rate of 74–84%.[12–14] In our study, we observed a substantial percentage of response failure, as only 66% of patients achieved CR. It should be pointed, however, that our study group consisted of a significant percentage of patients with known unfavorable prognostic factors (Table 1).[4,7,27,28]

Local recurrence was observed in a relatively small percentage of patients (22%), and most of these were noninvasive (15%). However, considering patients with incomplete response and recurrence, the results of local control are unsatisfactory. On the other hand, the obtained treatment outcomes and the possibility of further oncologic therapy, either salvage and/or palliative, result in 5-year overall and disease specific survival rates of 52% and 59%, respectively.

Failure involving regional lymph nodes was observed in 6/73 (8%) patients, only one patient developed isolated regional lymph node metastases without local failure. The presented technique of radiotherapy, with "bladder only in the target volume" offers a possibility of reducing irradiation treatment volume wile maintaining locoregional control. The value of pelvic lymph nodes elective irradiation in patients with bladder cancer is still ambiguous. Data from retrospective analyses which assessed irradiation of regional lymph nodes in patients with bladder cancer are inconsistent.[8,29–31] A prospective randomized clinical trial conducted on the group of 230 patients with invasive bladder cancer (T2–T4, N0) who received radiochemotherapy combined with cisplatin showed similar rates of bladder preservation, disease-free and overall survival rates in both treatment arms: radiotherapy of bladder alone vs. radiotherapy of bladder together with pelvic nodes.[31] Another prospective randomized trial comparing radiotherapy with radiochemotherapy, (irradiated volume encompassed bladder only) revealed low isolated pelvic node relapse rate of 6.7% and 4.9%, respectively.[6]

The toxicity of radiotherapy is closely correlated with the extent of irradiated volume. The high rate of complications is also the result of administration of a high dose to the minor pelvic area. Application of the "concomitant boost" radiotherapy in the treatment of muscle-invasive bladder cancer was generally well tolerated. Acute gastrointestinal toxicity higher than G2 and genitourinary toxicity higher than G3 were not observed. Integrating of chemotherapy with radiation did not significantly increase acute gastrointestinal and genitourinary toxicity (Table 2). Observed acute gastrointestinal toxicity was lower compared with the reported toxicity of "concomitant boost" regimen when the bladder was irradiated together with the pelvic lymph nodes.[12–14] A randomized study that compared two arms: bladder with regional lymph nodes vs. bladder only radiochemotherapy, showed significantly lower rates of acute toxicity when irradiation concerned a limited area. Symptoms of G3–G4 acute toxicity: overall and gastrointestinal were reported in 17.6% and 13.3%; and 3.9% and 2%, ($p = 0.05$), respectively.[32] Irradiation limited only to the bladder with a margin in patients with lymph node-negative MIBC seems to be an effective approach with less severe toxicity profile and low risk of isolated locoregional lymph node relapse.

Low rate of concomitant cisplatin-based chemotherapy during radiotherapy (38%) after neoadjuvant chemotherapy consisting of gemcitabine with cisplatin or gemcitabine with carboplatin indicates that this regimen appears to be poorly tolerated by most patients. James et al. in a multicenter phase 3 trial revealed significantly improved locoregional control in bladder cancer patients treated with

synchronous chemotherapy combined with radiotherapy as compared with radiotherapy alone.[6] The effect of combined radiochemotherapy did not vary significantly with neoadjuvant chemotherapy subgroup. Randomized phase 3 trial failed to show any significant benefit of neoadjuvant chemotherapy in MIBC patients treated with selective bladder-preservation by combining radiation therapy and synchronous chemotherapy.[33] Radiochemotherapy without neoadjuvant chemotherapy seems to be a more appropriate approach allowing to reduce overall treatment time and decrease toxicity.

Rates of late toxicity of presented multimodal conservative approach are relatively low. Late gastrointestinal toxicity higher than G2 and genitourinary higher than G3 were not reported. Our observations are consistent with other studies.[34–36] Phase II trials from the Trans Tasman Radiation Oncology Group presented late G≥3 urinary and bowel toxicity in 4% and 2% of 113 patients with bladder cancer treated with irradiation limited only to the bladder with concurrent cisplatin, respectively.[34] However, in all of these cases, observed symptoms were subsequently found to be secondary to persistent or recurrent disease rather than treatment. Henningsohn et al. reported about three-fourths of patients after radical bladder only radiotherapy for bladder cancer with good long-term urinary bladder function measured as a little or no distress from urinary tract.[35] The frequency rate of patients with moderate or much distress from symptoms from gastrointestinal tract was 32%. Seven percent of patients with MIBC undergoing combine-modality conservative treatment (TURB, irradiation to bladder and regional lymph nodes, chemotherapy: RTOG 89-03, 95-06, 97-06, 99-06) experienced late G≥3 pelvic toxicity: 5.7% genitourinary and 1.9% gastrointestinal.[36] James at al. observed no significant increase in adverse late events of synchronous chemotherapy with fluorouracil and mitomycin C combined with radiotherapy as compared with radiotherapy alone in MIBC.[6]

Our study has some limitations, such as the relatively low number of patients with assessed late toxicity and the single center design. Toxicity was assessed by a physician using a standardized late toxicity scoring schema RTOG, evaluation of the quality of life (QoL) reported by patients was not done. Combined QoL assessment by patients with physician-reported late radiation morbidity schema should reduce the risk of underestimated toxicity.

Presented patients who received radiotherapy alone and those treated with radiochemotherapy are incomparable due to different selection criteria. Multimodality combined treatment, that involves TURB, radiotherapy and chemotherapy, is the most successful conservative approach in selected patients with MIBC. The results of trimodality management which are equivalent to surgery are achieved in patients with favorable prognostic factors: clinical stage T2N0, macroscopically or/and microscopically complete TURB, absence of CIS (carcinoma in situ), no hydronephrosis, lack of serious co-morbidities and at least good performance status.[4,7,27,28] Entry criteria of many randomized prospective trials for combined conservative treatment of MIBC include the above mentioned requirements. However, in the group of operable patients with muscle-invasive bladder cancer, but at the same time suffering from severe co-morbidities that may make radical surgery too risky, as well as those who refused surgery, only 6–19% fulfill the optimal entry criteria to multimodality conservative approach.[37] Our study includes patients with both favorable and unfavorable prognostic factors who were treated with bladder preserving method (Table 1). In this whole unselected group of patients with MIBC who were treated conservatively with TURB followed by "concomitant boost" radiotherapy, a trend toward an increased overall survival rate in the radiochemotherapy group could be observed (Fig. 1). These differences may result from the use of combined multimodality approach to treatment, different selection criteria, or both.

It should be emphasized that also in patients with unfavorable prognostic factors the use of conservative local treatment: TURB and "concomitant boost" radiotherapy, can provide long-term survival.

5. Conclusion

Radical conservative approach: TURB followed by "concomitant boost" radio(chemo)therapy in patients with MIBC, who are not surgical candidates or refuse surgery, can yield good long-term survival with acceptable toxicity.

Conflict of interest

None declared.

Financial disclosure

None declared.

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