Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

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

Jadwiga Nowak-Sadzikowska, Tomasz Skóra, Bogumiła Szyszka-Charewicz, Jerzy Jakubowicz*

Oncology Clinic, Gastrointestinal and Urological Cancer Unit, Centre of Oncology, Maria Skłodowska-Curie Memorial Institute, Cracow Branch, Kraków, Poland

ARTICLE INFO

Article history:
Received 27 February 2015
Received in revised form
15 June 2015
Accepted 2 September 2015
Available online 29 September 2015

Keywords:
Muscle-invasive bladder cancer
Radical conservative treatment
Radiotherapy
Concomitant boost

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.

* *Corresponding author at*: Gastrointestinal and Urological Cancer Unit, Centre of Oncology, Maria Skłodowska-Curie Memorial Institute, Cracow Branch, 11 Garncarska Street, 31-115 Kraków, Poland. Tel.: +48 126348305; fax: +48 126348305.
E-mail address: Z5sadzik@cyfronet.krakow.pl (J. Nowak-Sadzikowska).

http://dx.doi.org/10.1016/j.rpor.2015.09.001

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