JBUON 2013; 18(4): 942-948
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Evaluation of efficacy and toxicity in two different hypofractionated 3D-conformal external beam radiotherapy schedules in localised muscle invasive bladder cancer

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Summary

Purpose: *To evaluate the efficacy as well as acute and late toxicity of two different accelerated hypofractionated 3D-conformal radiotherapy (Hypo-3DCRT) schedules in patients with bladder cancer.*

Methods: *Between February 2006 and June 2011, 50 elderly patients with cT1-2N0 bladder carcinoma were treated with Hypo-3DCRT. Mean age was 75 years. All patients were medically inoperable, with poor performance status, who couldn't tolerate either cystectomy or radical external beam irradiation on a daily basis. A dose of 36 Gy in 6 weekly fractions (arm A, N=39) or 39.96 Gy of 3.33 Gy twice daily, once a week, for 6 weeks (arm B, N=11) were prescribed. The primary study endpoints were the evaluation of acute/late gastrointestinal (GI) toxicity according to the EORTC/RTOG scale together with the visual analogue bladder-related pain score (VAS).*

Results: *The GI acute toxicities were: grade 1: arm A 24/39 (61.5%), arm B 9/11 (81.8%); grade 2: arm A 14/39 (35.9%), arm B 1/11 (9.1%); grade 3: arm A 1/39 (9.1%) (x^2, p=0.29). Only grade 1 late GI toxicity was seen and was significantly higher in arm A: arm A 17/39 (43.6%) and arm B 1/11 (9.1%) (x^2, p=0.037). The reduction of VAS score was similar in both arms (p=0.065). The median relapse free survival (RFS) was 15 and 16 months for arm A and B, respectively (log rank, p=0.71).*

Conclusions: *Beyond the non-randomized design of the trial, the Hypo-3DCRT schedules used appear to be an acceptable alternative to the traditional longer radiotherapy (RT) schedules for elderly patients unfit for daily irradiation.*

Key words: *bladder cancer, hypofractionated radiotherapy, radiobiology, relapse free survival, toxicity*

Introduction

Bladder cancer represents the fourth most common cancer and is three times more common in men than in women in the United States. It is a common disease with increased prevalence in the elderly. It is rarely diagnosed in individuals younger than 40 years. Because of the fact that the median age at diagnosis is 65 years, medical comorbidities are a frequent consideration in patient management [1].

Bladder cancer is estimated to have an annual incidence in the United States of 68,810 cases, accounting for 5% of all newly diagnosed cancers. Approximately 14,100 people per year will die of this disease, accounting for 2.5% of all cancer-related mortality and 3% of all cancer deaths in men [2]. The highest incidence rates are found in Western countries [3].

The standard of care treatment for muscle invasive transitional cell carcinoma of the bladder is radical cystectomy. Employed as a single modality, however, the results were disappointing, with high local failure rates and poor survival [4-6]. Despite cystoscopy and debulking, up to 80% of patients with bladder cancer have persistent

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Received: 30/11/2012; Accepted: 22/12/2012

urinary symptoms [7].

A group of patients encompasses the invasive lesions, and the first question to be answered is to determine whether the bladder should be removed or preserved without compromising survival. Second, to determine whether the primary lesion can be managed independently or patients are at high risk for distant spread requiring approaches to improve the likelihood of cure [8].

RT can be an effective alternative in medically inoperable patients, in poor performance status, who cannot tolerate cystectomy or chemotherapy [9,10].

High dose RT with associated morbidity may be required to control the disease [11].

Surprisingly, there is little consensus of opinion on dose, fractionation and technique for palliation following a Royal College of Radiologists survey [12].

Proper patient selection and the use of chemotherapy in combination with modern RT have improved the clinical outcome considerably [13].

Despite the fact that there are no reported modern prospective randomized studies directly comparing definitive chemoradiation with surgery, in a recent analysis of 458 patients with invasive bladder cancer treated with either radical RT or cystectomy, there was no significant difference in the 10-year overall survival between the two treatment groups (22 and 24%, respectively), although for patient survival more than 2 years, the final outcome was marginally better in those treated with cystectomy [13,14].

A succession of trials by the RTOG has investigated selective bladder conservation treatment strategies. Following reports from several institutions the complete response (CR) rates were improved by accelerated RT schedules [15-17].

The aim of the present study was to investigate the efficacy and toxicity of two hypofractionated RT schedules with weekly sessions of irradiation.

Methods

We investigated two different weekly regimens, of equivalent biological effective dose to many commonly used schedules, to assess efficacy, toxicity, convenience and correlation with RFS.

The treatment schedule was designed for patients who were unsuitable for conventional fractionation, due to two important reasons: first, because of medical problems that could have made daily attendance for treatment on an outpatient basis impractical; second, because most of them were elderly people, coming from Greek countryside and from the islands, unable for social reasons to follow daily schemes of classic radiotherapy delivery.

We completed a prospective study of localized bladder cancer patients (cT1-2N0). All patients received dose-escalated radiation using two hypofractionated RT schedules with either 36 Gy in 6 weekly fractions or 39.96 Gy in 6 weekly fractions, with 3.33/fraction, twice daily [19]. The primary endpoint of this study was to assess acute/late GI toxicity as well as bladder-related pain/dysouria or tumor-related haematouria from patients treated only with 3D conformal RT technique without previous cystectomy. The second endpoint was the estimation of RFS of each regimen.

Patients offered definitive irradiation have typically been non-surgical candidates with various comorbidities and more advanced disease, contributing to poorer prognoses than those selected for surgery. In addition, surgical series have the benefit of accurate pathologic staging, whereas radiation series rely on clinical staging with its intrinsic inaccuracies related to understaging.

Patient characteristics – methodology

Between February 2006 and June 2011, 50 patients (39 males, 11 females) with a mean age of 75 years (range 68-89), with muscle invasive bladder carcinoma, received two different schedules of hypofractionated RT (Table 1). Selection for these schedules was based on the clinical judgment that the patients would find it difficult to attend a program of daily hospital visits for a period of 6.5 weeks, in order to complete the conventional radical RT regimen of 66 Gy in 33 fractions. The patients were referred either to Attiko University Hospital or Metaxa Cancer Hospital of Piraeus, after a transurethral diagnosis and resection and after histological confirmation of malignancy. All patients had transitional cell bladder carcinoma.

The pretreatment evaluation included pathology review, cystoscopy with bladder mapping and bimanual examination under anaesthesia before and after transurethral resection from urologists. Laboratory studies included complete blood count, liver function tests, BUN, serum creatinine, alkaline phosphatise, uric acid, urine cytology and staging exams (computed tomography/CT and/or magnetic resonance imaging/MRI of the abdomen and pelvis). TNM staging system was used [19]. Eligible patients had histologically confirmed clinical localized bladder cancer stage (cT1-2 N0) (American Joint Committee on Cancer staging manual, 6th edition, 2002 and 7th edition, 2010) and adequately functioning bladder after urologic evaluation. It was also mandatory that a visibly complete or maximum transurethral resection of the bladder tumor had been performed prior to radiation.

Patients were excluded if they had history of previous pelvic RT, lymph node metastatic involvement, hydronephrosis, distant metastases, or had a hip pros-

thesis. All patients were required to sign informed consent concerning the side effects of irradiation.

For treatment planning purposes, each patient underwent a CT scan in supine position, using "knee sponge" to consistently align thighs [20].

Patients were instructed to have an empty bladder and rectum during simulation and for the whole course of treatment. Planning CT scan of the pelvis was performed with 3mm spacing between slices. The CT datasets were transferred either to the Prosoma® Virtual simulation or to Masterplan® treatment planning system, through a DICOM network and contouring of target volumes and normal structures (organs at risk-OARs) was performed. The following structures were delineated: clinical target volume (CTV), planning target volume (PTV) according to the International Commission on Radiation Units and Measurements (ICRU) criteria. Rectum was manually contoured from the distal ischiatic branch to the sigmoid flexure. In addition, small bowel and femoral heads were contoured.

The CTV was the bladder; the PTV was obtained by expanding CTV with a margin of 1 cm in each direction, and 0.7 cm posteriorly. The entire bladder was treated using a four-field technique. No patient received pelvic node irradiation.

Weighted beams and wedges were used as necessary to improve dose homogeneity. The fields were placed isocentrically. Dose calculation was performed and normalized to isocenter. For the treatment technique, histograms were generated; a number of parameters, including mean, median and maximum dose, were evaluated. Patient setup was monitored weekly using portal films.

The dose that was administered weekly and that was prescribed to 95% at the ICRU reference points, at the intersection of the central axis of the treated beam in the midplane of the target volume, was either 6 Gy once daily or 3.33 Gy twice daily, with a break of 3 hours. Total doses of 36 Gy and 39.96 Gy respectively were prescribed in 6 daily sessions. Patients were treated either on a VARIAN CLINAC 2100C Linac with 15 MV photons, or ELECTA 6MV Linac.

Dose calculations were performed using either the treatment planning system of Eclipse (Varian Associates, Palo Alto, CA) or Masterplan, to deliver the prescribed dose to the ICRU reference point [21,22].

Patients were monitored weekly during treatment and reviewed every month later on, after the completion of RT, in order to assess acute/ late rectal toxicities. To evaluate the dose constraints for normal tissues we used the QUANTEC trial corrected for hypofractionation [23].

We used linear-quadratic (LQ) modelling in order to equate the hypofractionation schedules to the Normalised Total Dose (NTD) if delivered in 2 Gy fractions [18]. Thus, NTD represents the dose given in 2 Gy fractions that would give the equivalent biologic effect to the new hypofractionated dose:

$$NTD = D_{new} \frac{d_{new} + \alpha/\beta}{2 + \alpha/\beta}$$

Where, Dnew and dnew are respectively the total dose and dose per fraction for a suggested hypofractionation scheme. NTD was calculated and tabulated for both bladder (α/β=10 Gy) and late reacting tissues (α/β=3 Gy) [24].

When the h_m [25] as the incomplete repair factor is entered in the radiobiological LQ model for the two daily fractions (group B), then the above equation is transformed into:

$$NTD = D_{new} \frac{(1 + h_m)d_{new} + \alpha/\beta}{2 + \alpha/\beta}$$

Assuming that the t1/2 is respectively 1 hour and 1.5 hours for acute and late reacting tissues, respectively, then h_m is also 0.125 and 0.25 for acute and late reacting tissues, respectively [26]. Considering that α+β=10, NTD was 48 Gy and 45.7 Gy for group A and B, respectively. Considering that α/β=3, NTD was 64.8 Gy and 57.24 Gy for group A and B, respectively.

Data at diagnosis (baseline), end of RT and all monthly follow up visits 6 months after finishing RT were analyzed in this report. Symptoms occurring in the interval between the start of RT and 90 days after this time point were classified as "acute". Symptoms occurring 6 months after the end of treatment were defined as "late". Maximum acute or late toxicity scores monitoring during irradiation or thereafter were confirmed as the final toxicity score. Evaluation of acute and late radiation-induced toxicity was performed with the EORTC/RTOG toxicity criteria scale [27]. Bladder-related pain and dysouria were evaluated with the VAS score [28]. The mean value of the two related parameters was taken as the final VAS score. Tumor-related macroscopic haematouria was evaluated as yes or no.

Statistics

In order to assess the difference between the reduction of VAS score between arm A and B, we used the Mann-Whitney non-parametric test. Chi square test was used for the evaluation of the difference in the incidence of toxicity between arm A and B. The significance level was set at 0.05. The Kaplan – Meier method and the log-rank test were used for the assessment of the difference in RFS between the two arms. The statistical analysis was performed with the SPSS v 10 (Chicago, IL, USA).

Results

All patients had good performance status (0-1) according to the Eastern Cooperative Oncology Group performance score. All patients completed

Table 1. Patient characteristics (N=50)

Characteristics	*Patients N (%)*
Sex	
Male / female	7/43
Tumor size	
T1	31 (62)
T2	19 (38)
Grade	
G2	28 (56.7)
G3	22 (44)
Dose (Gy)	
36 (6 Gy once a week), arm A	39 (78)
39.94 (3.33 Gy twice daily, once a week), arm B	11 (22)

Table 2. Acute and late GI toxicity for arm A and B, according to EORTC/RTOG criteria

Toxicity	*Arm A N (%)*	*Arm B N (%)*	x^2, *p*
Acute toxicity			
Grade 1	24/39 (61.6)	9/11 (81.8)	
Grade 2	14/39 (35.9)	1/11 (9)	
Grade 3	-	1/11 (9)	0.29
Late toxicity			
Grade 1	17/39 (43.6)	1/11 (9.1)	0.037

the planned 3D-CRT. Median follow-up duration was 15 months (range 9-36).

Assessment of tolerability and acute treatment-related toxicity

Arm A and B of patients receiving 36 Gy and 39.94 Gy in two different weekly fractionations were analyzed separately to assess whether a dose response could be identified. Treatment compliance was excellent.

The incidence of moderate and severe toxicity increased during treatment, with a peak at the third and fourth weeks of irradiation, and then progressively decreased up to 3 months after the end of RT. The GI acute toxicities were: grade 1: arm A 24/39 (61.5%), arm B 9/11 (81.8%); grade 2: arm A 14/39 (35.9%), arm B 1/11 (9.1%); grade 3: arm A 1/39 (2.6%) (x^2, p=0.29). Only grade 1 late GI toxicity was seen and was significantly higher in arm A: arm A 17/39 (43.6%) and arm B 1/11 (9.1%) (x^2, p=0.037). The results are shown in Table 2.

The treatment administered for the RT-induced toxicity was non steroidal anti-inflammatory drugs (NSAIDs) for dysuria, urgency, frequency, nocturia; diet and anti-diarrheals were prescribed for diarrhea; and rectal NSAIDs and steroids for rectal irritation, pain, and bleeding.

The incidence of tumor-related haematouria

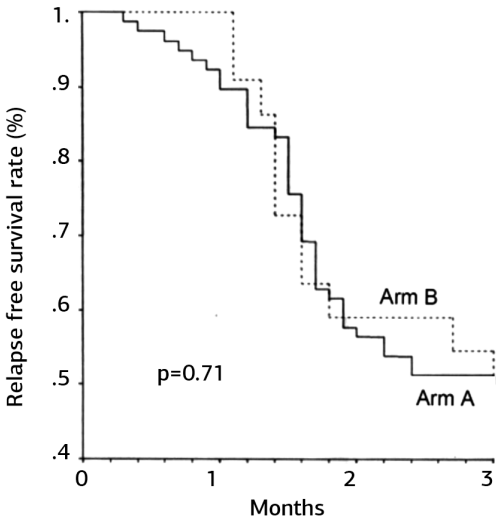

Figure 1. Kaplan-Meier survival curve for relapse free survival in arm A and B.

at baseline was 30/39 (76.9%) and 10/11 (90.9%), for arms A and B, respectively. After the completion of RT, no patient in arm A or B developed macroscopic haematouria, while microscopic haematouria was noted in 5/39 (12.8%) and in 2/11 (18.2%) patients for arms A and B, respectively. No significant difference was noted between arms A and B concerning the reduction of VAS score (p=0.065). The median RFS was 15 and 16 months for arms A and B, respectively (log rank, p=0.71). The Kaplan-Meier distribution of RFS is shown in Figure 1. The 2-year RFS was 51% and 58% for arm A and B, respectively (p=0.71).

Both arms, that of the once-a-week fractionation and that of the twice daily – once a week fractionation, showed similar results regarding RFS and VAS.

Discussion

Bladder cancer occurs commonly in elderly people. These patients may suffer from concurrent illnesses, such as heart failure or chronic obstructive pulmonary disease and difficulty in attending a daily treatment of 6.5 weeks duration. Moreover they might be unable to tolerate the acute morbidity of a conventional radical RT schedule. With hypofractionated schemes, the early rather than the late effects of RT maybe dose-limiting. At the same time the large fraction size may lead to an increased risk of late normal tissue damage, unless the total dose is adjusted. A guide to the appropriate adjustment is based on the formula for the biologically effective dose delivered from linear-quadratic cell survival model [18,25,29].

Table 3. Local control rates after external beam radiotherapy for different hypofractionation schedules in published clinical trials

Trials		*Total dose Gy*	*Schedule Gy*	*Local control rate (%)*
Cowan et al. [36]	T1 = 0 T2 = 17 T3 = 42 T4 = 1	52.5	20 x 2.63	58 (5-year)
Cowan et al. [36]	T1 = 1 T2 = 16 T3 = 28 T4 = 0	55	16 x 3.44	34 (5-year)
Pos et al. [35]	T2 = 28 T3 = 16 T4 = 6	*55*	20 x 2.75	55
Cowan et al. [36]	T1 = 1 T2 = 10 T3 = 33 T4 = 0	57.5	20 x 2.88	59 (5-year)
Joce et al. [31]	T2-T4 = 65	36	6 x 6	25
Scholten et al. [33]	T2-T3 = 124	36	6 x 6	31

Assuming an α/β ratio for late bladder or bowel toxicity of 3 Gy, a dose of 64 Gy in 32 fractions would be estimated to be equivalent to a dose of 36 Gy in 6 fractions given the same overall treatment time [30].

Invasive bladder cancer presents with two distinct problems from the outset. On the one hand, radical resection of the tumor is highly successful but carries a considerable impact on quality of life. On the other hand, bladder-conserving trimodality therapy has been developed to offer the patient the opportunity to preserve the bladder while not sacrificing the high level of local control offered by cystectomy [31].

In an attempt to improve external beam RT in bladder cancer, the current study investigated the impact of larger than conventional doses of irradiation. Shortening the sessions of RT with hypofractionation could increase treatment efficacy but could also increase toxicity. However, severe acute toxicity was observed only in 9% of the patients in arm B, while no severe late toxicity was observed. A large study applying 36 Gy in 6 fractions in 18 days reported an acceptable severe late toxicity but only a 31% 5-year local control rate [31]. Results from the RTOG 95-06 [32] and from the RTOG 97-06 trial [4] argue that more aggressive RT may benefit from techniques that spare the bowel. Bowel sparing would not only reduce treatment toxicity, but would also enhance the surgeon's ability to create continent diversions after pelvic RT, especially when induction involves higher doses or aggressive fractionation.

Pos et al. Treated 50 patients with a T2-T4 N0M0 transitional cell carcinoma of the bladder. A dose of 40 Gy in 2-Gy fractions was administered to the small pelvis with a concomitant boost limited to the bladder tumor area plus margin of 15 Gy in fractions of 0.75 Gy. The total tumor dose was 55 Gy in 20 fractions in 4 weeks. Severe acute urinary toxicity (G3) was observed in 7 patients (14%). Severe late urinary toxicity (G3) was observed in 6 patients (13%). Thirty-seven patients (74%) showed complete and 5 (10%) partial remission after treatment [33]. In Table 3, several hypofractionated trials and schedules for bladder carcinoma are shown in terms of response rates to treatment [31,32,34]. In all trials the range of 5-year RFS was 31-59%. In our study the 2-year RFS rate was 51 and 59% for arm A and B, respectively.

When radical RT is used in the treatment of bladder cancer, the majority of patients experience acute side effects. A hypofractionated schedule is specifically designed to decrease this incidence based on radiobiological principles.

It is reasonable to irradiate only the bladder with a margin, as in advocated by Sengelov et al. [35]. This modelling study documented that the choice of margins was as important as the choice of fractionation in terms of intestine and rectum dose volume histogram (DVH) data and normal tissue control probability (NTCP) predictions [36].

Arm B, with the twice daily and once a week RT regimen seemed to produce better results regarding late GI toxicity. In terms of late effect, the radiobiological equivalent dose in arm B was 57.24 Gy vs 64.8 Gy in arm A. This is due to the 3-hour time interval between the two fractions, which helped nor-

mal tissue repair. Fractionation in RT was initiated in order to spare normal tissue (by repair of sublethal damage and repopulation from surviving cells) and also to increase the damage to the tumor (by reoxygenation of hypoxic cells and redistribution of cells along the cell style). Together with radiosensitivity these radiobiological processes represent the foundation on fractionation in RT and are called "the 5R'S" of radiobiology. Repair and repopulation confer resistance to the tissue between two radiation doses, while redistribution and reoxygenation are expected to make the tissue more sensitive to a subsequent dose [16,37].

Last but not least, the LQ radiobiological model managed to predict acute and late GI toxicity. The higher incidence of late GI toxicity presented in arm A vs arm B patients is in accordance with the current literature, since the NTD was finally higher in arm A. The twice-daily of the weekly schedule refers to higher incidence of acute and lower incidence of late toxicity. However, no significant difference was noted concerning acute toxicity, possibly due to the small number of patients. Hyperfractionated schedules with twice daily sessions have the advantage of reducing late toxicity [18,37]. With the clinical data currently available, a reliable estimation of the α/β for bladder cancer is not feasible [38]. It seems reasonable to use a conventional α/β ratio of 10 Gy for the tumor and this was the case for our calculations in the present study. Although there is still no evidence to support large fraction sizes in RT for bladder cancer, our study showed that response and toxicity of the hypofractionated schedules used were equivalent with the conventional schemes [31-34].

Conclusions

The present study showed that 3D-CRT is a feasible and safe modality allowing for hypofractionation up to either 36 Gy or 39.6 Gy. This study demonstrates that in patients unsuitable for standard daily radical RT, it is possible to deliver hypofractionated 3DCRT to the bladder with an acceptable acute and late toxicity rate. However, due to the non-randomized design of the trial, no definite conclusion can be drawn. More patients in a randomized prospective way stand in need for the confirmation of the results presented herein.

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