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ORIGINAL ARTICLE

A weekly hypofractionated radiotherapeutic schedule for bladder carcinoma in elderly patients: local response, acute and late toxicity, dosimetric parameters and pain relief

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Summary

Purpose: *To investigate the early and late toxicity of a hypofractionated radiotherapy (RT) schedule to treat muscle-invasive bladder cancer in relation to radiation parameters according to the organs at risk.*

Methods: *Forty-three patients with T2-T3 bladder carcinoma were irradiated with a weekly hypofractionated schedule with a total dose of 36 Gy in 6 fractions. Included in this study were elderly patients with poor performance status or unfit for surgery, while they complained of daily pain on urination. Pain evaluation was assessed with the use of the visual analogue scale (VAS) of pain, acute and late toxicities were assessed using the combined RTOG/EORTC criteria by using a dose of 50 Gy (D50), and the relapse free survival (RFS) was estimated from the date of recurrence.*

Results: *No acute side effects were observed in the majority of the patients. Grade I rectal toxicity was registered in 67.4% of the patients, while grade II and III were noted in 30.25% and 2.3% of the patients, respectively. The worst late rectal toxicity was grade I in 30.2% of the patients. The VAS score of pain showed a significant improvement after the hypofractionated schedule. There was a significant correlation between acute and late toxicity on the one hand and the D50 dosimetric parameter on the other. The Kaplan-Meier plot showed a median RFS of 15 months, while age did not have any impact on RFS in patients above or under 75 years of age.*

Conclusion: *The performed hypofractionated schedule permitted delivery of an increased radiation dose without increased toxicity, and with a high probability of local control for elderly patients with low survival perspective.*

Key words: *bladder cancer, elderly patients, hypofractionation, radiotherapy*

Introduction

An estimated number of 104,400 incident cases of bladder cancer were diagnosed in Europe in 2006, 82,800 (79.31%) of which were found in men and 21,600 (20.69%) in women. These figures represent 6.6% of the total number of cancers in men and 2.1% in women. The frequency of bladder cancer is analogous to age and peaks at the 6th and 7th decade of life and it is 2.5-fold more common in men than in women. A significant number of these patients will have poor performance status [1].

Bladder cancer can be treated by surgery, RT, chemotherapy or combinations of these 3 modalities. The standard surgical approach for the treatment of muscle-invasive bladder cancer is radical cystoprostatectomy in the male patient and anterior exenteration in the female patient, coupled with pelvic lymphadenectomy and some form of urinary reconstruction or diversion [2].

The procedure is associated with significant mortality (2%) and up to 30% of patients experience at least one complication up to 3 months

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postoperatively. Therefore, short courses of hypofractionated RT have been advocated for the elderly patients and those with poor performance as an effective alternative to surgery [3].

The first end point of this study was to register the early and late toxicities of a hypofractionated RT schedule in relation to the radiation parameters according to the organs at risk (rectum) in elderly people. The second end point was to estimate the RFS.

Methods

Patient characteristics

From January 2005 to January 2009, 43 patients with advanced bladder carcinoma were retrospectively analysed. They all received a hypofractionated accelerated RT scheme. All of them had muscle- invading tumors (T2-T3 stage). Included and registered were elderly patients with poor performance status unsuitable for chemotherapy or patients unfit for surgery; all of them complained of daily pain on urination. Their median age was 75 years (range 68-90) (Table 1). All patients signed informed consent for study inclusion.

Radiotherapy

All patients underwent a treatment planning computed tomography (CT) scan of 5mm slice thickness in supine position, with a triangle sponge placed under their knees. All CT scans were contrast-enhanced while no patient had node-positive disease, so no attempt was made to electively irradiate the draining pelvic lymph nodes. The bladder was empty during the CT scan. All CT films were transferred to the treatment planning system. The clinical target volume (CTV) included the whole bladder and the planning target volume (PTV) consisted of the CTV plus a uniform margin of 2 cm in all directions, including the rectum margin. The rectum was outlined from the anal verge to the rectosigmoid junction. The small intestine was contoured from the promontorium downward [4].

All patients were irradiated with a weekly hypofractionated schedule with a total dose of 36 Gy in 6 fractions. The biologically effective dose (BED) was calculated using the following formula:

$$BED = D_{total}\left(1+\frac{d}{(\alpha/\beta)}\right)-K\cdot\left(T-T_{delay}\right)$$

where D is the total dose, d is the dose per fraction, a and β are the coefficients for the linear and quadratic terms in the LQ model, K is the daily BED equivalent for repopulation in units of Gy per day, T is the overall time and Td is the delay time before the onset of repopulation.

We considered that α/β=10, K=0.36 Gy/d and T delay = 20 days, BED = 57.6 Gy without including repopulation and 51.1 Gy including repopulation [5].

The minimum and maximum dose within the PTV was >95% and <107% of the isocentric dose, respectively. The maximum radiobiological equivalent dose to the posterior rectal wall and to the femoral heads was <55 Gy and <45 Gy, respectively.

Patient monitoring and follow up

The follow up was 3-monthly for the first 12 months, 6-monthly for the next 2 years and then annually.

Acute toxicity was assessed on a weekly basis during treatment and 4 weeks post completion of treatment. Late toxicity was assessed 9 months post treatment. The maximum score for either acute or late toxicity was chosen as the final toxicity score.

The follow up evaluation included cystoscopy under general anesthesia; 3 months post treatment and cystoscopy with urine cytology where necessary (pathologic cystoscopic findings). CT scan of the pelvis was done every 3 months for the first 12 months, every 6 months for the next 2 years and then annually. Patients were regarded as having local failure if they had cystoscopic proof of persistent or recurrent invasive disease and/or imaging evidence of local tumor extension beyond the bladder wall. Patients who failed to have cystoscopic assessment because of early development of metastatic disease or death from intercurrent illness, were deemed not to have achieved local control. Distant failure was diagnosed on the basis of radiological or pathological findings.

The combined RTOG/EORTC criteria were employed to assess acute and late toxicity [6]. VAS was used for pain assessment at the beginning and the completion of RT, with 0 indicating no pain and 10 indicating intractable pain [7].

Statistics

The time to acute and late toxicity was calculated from the beginning of the treatment. RFS was defined as the time period until the first local and distant failure or death due to cancer. The statistical difference before and after the treatment, in terms of VAS score, was calculated with the Wilcoxon non parametric test. The Spearman's rho non-parametric test was used to assess any correlation between toxicity (acute or late) and either age or percentage of the rectum receiving a dose of 50 Gy (D50). D50 was assessed from a regular dose volume histogram (DVH) which was radiobiologically converted to an equivalent dose of compatible scheme (2 Gy per fraction; α/β=10 for acute toxicity, α/β=3 for late toxicity). Survival analysis was performed with the Kaplan-Meier method, while the comparison of acute and late toxicity was done using the log-rank test. Patients were also divided in 2 age groups (less or more than 75 years) to see for any impact on survival.

Table 1. Patient characteristics (N=43)

Characteristics	*N*	*%*
Sex		
Male	31	72
Female	12	28
Age (years)		
Median	75	
Range	68-90	
T stage		
T2	18	42
T3	25	58
N stage		
N0	43	100
NI	0	0
Histological grade		
II	2	5
III	41	95

Table 2. Spearman's rho non parametric correlation between acute and late toxicity as well as D50

		Acute	*Late*	*Age*
D50	Spearman rho	0.39	0.46	
	p-value	0.01	0.002	NS
Acute	Spearman rho	-	0.63	
	p-value	-	<0.001	NS

NS: non significant

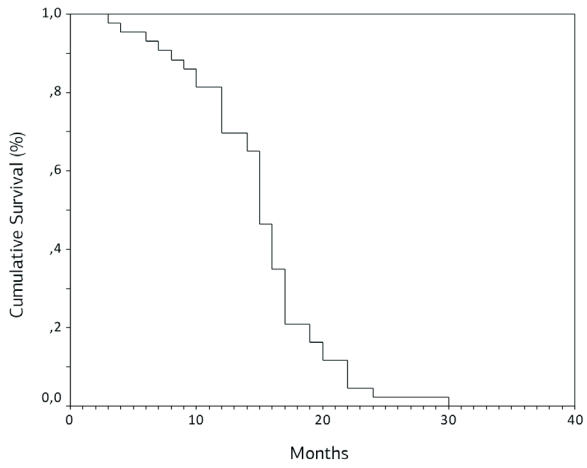

Figure 1. Kaplan-Meier curve of relapse free survival (median = 15 months).

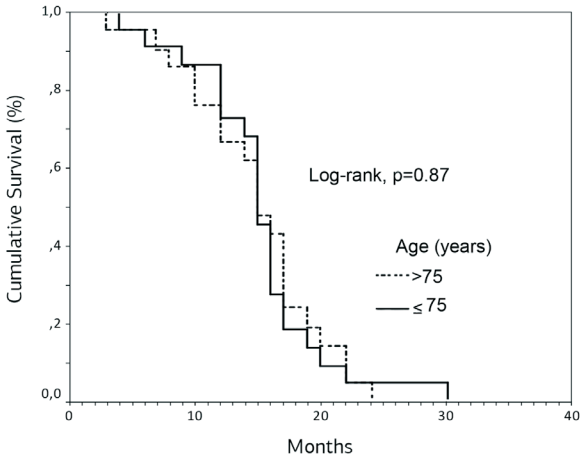

Figure 2. Kaplan-Meier curve of relapse free survival for ages over and under 75 years.

Results

Basic patient and disease characteristics are shown in Table 1. The majority of patients tolerated the treatment well without major acute side effects. Grade 1 rectal toxicity was seen in 67.4% of the patients, grade 2 in 30.2% and grade 3 in 2.3%.

The worst late rectal toxicity seen during follow up was grade 1 in 30.2% of the patients, while 69.8% of the patients had grade 0 toxicity.

Spearman's rho test showed a significant correlation between acute and late rectal toxicity (rho=0.63, p<0.001). Moreover, there was a significant correlation between either acute or late toxicity with the D50 dosimetric parameter, as shown in Table 2.

VAS before and after treatment was 3.93 (SE/standard error 1.12) vs 1.86 (SE 0.60), respectively (Wilcoxon test, p<0.001).

Kaplan-Meier method showed a median RFS of 15 months (Figure 1), while no impact of age (above or under 75 years) on RFS was noted (log-rank, p=0.87) (Figure 2).

Discussion

The literature contains 8 studies for bladder cancer that have dealt with hypofractionated schedules with daily doses greater than 2.5 Gy [8-15].

Five of them were published more than 20 years ago, while 3 are the most recent ones [12-14]. In the RTOG 7104 trial [8] the conventional fractionation of 2 Gy/day to a total of 60 Gy was compared to 55 Gy in 20 fractions (split 10+10 with 2 weeks gap). No difference in tumor control rates or in side effects was registered.

Quilty et al. showed that 55 Gy was the optimal dose when using 20 fractions over 4 weeks; this study was carried out before the application of conformal techniques [9]. Subsequently, the recommended dose was reduced to 52.5 Gy [10].

In the most recent trial Cowan et al. used modern conformal techniques and 3D planning [12]. They studied the whole bladder irradiation with a total dose of 52.5 Gy in 20 fractions, and

partial bladder irradiation using a 20-fraction and a 16-fraction regimen. The prescribed doses for the partial bladder irradiation schedules varied according to the size of the PTV (52.5-57.5 Gy for the 20 fractions; 50-55 Gy for the 16 fractions). Statistically, there was no significant difference between the 3 arms in 5-year local control. Inadequate results were observed with the 16-fraction schedule which was abandoned for the treatment of bladder. Gastrointestinal and genitourinary toxicity rates were similar in all 3 arms (grade I).

In conclusion for radical RT only to the bladder, hypofractionated schedules are neither better nor worse than regimens of 60-66 Gy in 30-33 daily fractions when using modern planning (IMRT, IGRT) and conformal techniques.

In our departments we use hypofractionated schedules in elderly people for the treatment of bladder, prostate and breast cancer because of the long waiting lists and the lower treatment costs [16-19]. Radiobiological modeling can provide guidelines for the design of new treatment schemes. When treating tumors in which the α/β ratio is lower than that of the surrounding late-reacting normal tissues (as proposed for prostate cancer) the use of hypofractionation could enhance the therapeutic ratio. For bladder tumors there is no reliable estimation of the value of the α/β ratio. According to few clinical reports, it seems reasonable to use a conventional α/β ratio of 10-15 Gy [16].

A retrospective analysis by Maciejewski and Majewksi suggested that tumor clonogenic repopulation in transitional cell carcinoma of the bladder accelerates after a lag period of 5-6 weeks after the start of treatment and that a dose increment of 0.36 Gy/d is required to compensate for this repopulation [17].

Late responding bowel, rectum and bladder tissues have been reported with α/β ratio between 3 and 6 Gy. Rectal BED is calculated 97.7 Gy (α/β=3.5Gy)

The conventional fractionation of 2 Gy/day up to a total dose of 66 Gy results in bladder BED 79.2 Gy (without repopulation) and 70.2 Gy (with repopulation) whereas rectal BED is 103.7 Gy.

Comparing the conventional fractionation treatment scheme with other hypofractionation schedules, since the bladder a/b ratio is 10 Gy, it comes that short overall treatment times and large fraction sizes have no potential of increasing the therapeutic ratio and therefore cannot be a treatment of choice [8-15].

However, there are pragmatic benefits in reducing the number of treatment sessions and travelling requirements for elderly patients and enabling better use of limited resources. Given the often limited department resources and the long waiting lists, a reduction in the overall treatment time is often realized by hypofractionation. Moreover, one must remember that almost all studies that have investigated changes in the fractionation schedule were published before the widespread introduction of conformal RT. It is quite possible that any improvement in the therapeutic ratio resulting from optimizing the radiobiological parameters with altered fractionation may be nullified by poor dose distributions, exceeding the normal tissue tolerance doses.

The D50 has already been used as a favorable dosimetric factor for radiation-induced rectal toxicity [18,19]. In our study, there was a significant correlation between late and acute toxicity on the one hand and the D50 dosimetric parameter on the other, which is in accordance with previous publications [18,19]. Age did not exert any impact on toxicity or RFS, whereas VAS score showed a significant improvement with the hypofractionated schedule in our study.

According to various studies, it is known that bladder volume changes during RT [20]. Furthermore, changes in rectal filling may lead to positional changes [16,20]. In addition, Henry et al. applied cone beam computed tomography imaging (CBCT) during a course of RT [21] and showed that there are systematic and random variations in bladder volume. Various studies showed greater movements towards the anterior and superior direction (up to 30 mm) than towards laterally, inferiorly and posteriorly (requiring margins of about 10 mm) [22,23].

In any case, set-up errors seem to be relative to the uncertainty of the urinary content of the bladder during a course of radiotherapy [22-24].

The problem could possibly be solved by applying fiducial markers into the mucosa or perivescical fat around the tumor bed and into the lateral wall. Fiducial markers can be displayed by using electronic portal imaging for IGRT [20,25] or by assisting the delineation of gross tumor volume (GTV), when the bladder is partially radiated. Mangar et al. implanted 5-6 gold seeds into the bladder wall, one week before planning computed tomography in 8 patients [26]. Similar techniques have also been used for the delineation of GTV in various studies [20,27]. The placement of the fiducial markers enables reducing the treatment volume. Anyway, advances in imaging and techniques of RT planning, verification and delivery

offer the potential to keep both acute and late toxicity acceptable. The introduction of conformal RT improved the dose distribution to the target volume and normal tissues, with a possibility for dose escalation or for sparing normal tissues. However, a possibility to conform the radiation dose closely around the target volume could result in reduced dosage to some parts of the target volume (geographic miss) because of organ movement, setup errors, and several differences in PTV delineation [23,24]. This could lead to a substantial decrease in the treatment outcome. A routine practice is to add safety margins around the target volume to overcome the risk of a geographic miss; in any case, this can result in unnecessary overtreatment of the surrounding critical tissues.

The application of new techniques, such as IMRT and IGRT, has led to the use of hypofractionated accelerated schemes with concomitant boost of the tumor bed [28]. Furthermore, these applications allowed the delivery of an increased radiation dose with acceptable acute and late toxicity. The study of Muren et al. showed the clinical and technical feasibility of an IMRT delivered intergraded tumor boost for bladder. This dose escalation leads to improvement of local control and overall survival [28].

Conclusions

In conclusion, our study showed that for elderly patients with poor performance status and for those with expected low survival hypofractionation remains a valuable technique. Hypofractionated schedule permitted delivery of an increased radiation dose without increased toxicity and with high probability of local control. However, speaking of radical treatment, hypofractionated RT deserves further investigation with the application of modern techniques.

References

1. Stenzl A, Cowan N, De Santis M et al. The update EAU guidelines on muscle invasive and metastatic bladder cancer. Eur Urol 2002; 55: 815-825.
2. Kotwal S, Choudhury A, Johnston C, Paul A, Whelan P, Kiltie A. Similar treatment outcomes for radical cystectomy and radical radiotherapy in invasive bladder cancer treated at a United Kingdom specialist treatment center. Int J Radiat Oncol Biol Phys 2008; 70: 456–463.
3. Hautmann E, Gschwend E, De Petriconi C, Kron M, Volkmer G. Cystectomy for transitional cell carcinoma of the bladder: Results of a surgery only series in the neobladder era. J Urol 2006; 176:486–492.
4. International Commission on Radiation Units and Measurements.Report 50: Prescribing, recording and reporting photon beam therapy. Bethesda: ICRU, 1993.
5. Jones B, Dale R, Deehan C, Hopkins K, Morgan D. The role of biologically effective dose (BED) in clinical oncology. Clin Oncol 2001; 13:71-81.
6. Cox D, Stetz J, Pajak F. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995; 31:1341–1346.
7. Lasagna L. The clinical measurement of pain. Ann N Y Acad Sci 1960; 86: 28-37.
8. Marcial A, Amato A, Brady W et al. Split course radiotherapy of carcinoma of the urinary bladder stages C and D1. A Radiation Therapy Oncology Group Study. Am J Clin Oncol 1985; 8:185-199.
9. Quilty M, Duncan W, Kerr R. Results of a randomized study to evaluate influence of dose on morbidity in radiotherapy for bladder. Clin Radiol 1985; 36:615-618.
10. Whillis D, Howard C, Kerr R, Fowler J, Hargreave B, Chisholm D. Radical radiotherapy with salvage surgery for invasive bladder cancer: results following a reduction in radiation dose. J R Coll Surg Edinb 1992; 37:42-45.
11. Kob D, Kloetzer H, Kriester A et al. Results of radiotherapeutic optimization within the scope of combined operative radiologic therapy of urinary bladder cancer. Z Urol Nephrol 1985; 78:545-550.
12. Cowan R, McBain C, Ryder W et al. Radiotherapy for muscle-invasive carcinoma of the bladder: results of a randomized trial comparing conventional whole bladder with dose escalated partial bladder radiotherapy. Int J Radiat Oncol Biol Phys 2004; 59: 197–207.
13. Scholten A, Leer J, Collins D, Wondergem J, Hermans J, Timothy A. Hypofractionated radiotherapy for invasive bladder cancer. Radiother Oncol 1997; 43:163–169.
14. Rostom Y, Tahir S, Gershuny A, Kandil A, Folkes A,White W. Once weekly irradiation for carcinoma of the bladder. Int J Radiat Oncol Biol Phys 1996; 35:289-292.
15. Gospodarowicz M, Rider W, Keen C et al. Bladder cancer: long term follow up results of patients treated with radical radiation. Clin Oncol R Coll Radiol 1991; 3: 155–161.
16. Pos F, Hulshof M, Lebesque J et al. Adaptive radiotherapy for invasive bladder cancer: a feasibility study. Int J Radiat Oncol Biol Phys 2006; 64: 862–868.
17. Maciejewski B, Majewski S. Dose fractionation and tumour repopulation in radiotherapy for bladder cancer. Radiother Oncol 1991; 21:163–170.

18. Sale A, Yeoh E, Scutter S, Bezak E. 2D versus 3D radiation therapy for prostate carcinoma: a direct comparison of dose volume parameters. Acta Oncol 2005; 44:348-354.
19. Matzinger O, Duclos F, Van den Bergh A et al; EORTC Radiation Oncology Group.Acute toxicity of curative radiotherapy for intermediate- and high-risk localised prostate cancer in the EORTC trial 22991. Eur J Cancer 2009 ; 45:2825-2834.
20. Button M, Staffurth J. Clinical application of image guided radiotherapy in bladder and prostate cancer. Clin Oncol 2010; 22:698-706.
21. Henry A, Stratford J, McCarthy C et al. X-ray volume imaging in bladder radiotherapy verification. Int J Radiat Oncol Biol Phys 2006; 64: 1174–1178.
22. Meijer G, Rasch C, Remeijer P, Lebesque J. Three-dimensional analysis of delineation errors, setup errors, and organ motion during radiotherapy of bladder cancer. Int J Radiat Oncol Biol Phys 2003; 55: 1277–1287.
23. Muren L, Smaaland R, Dahl O. Organ motion, set-up variation and treatment margins in radical radiotherapy of urinary bladder cancer. Radiother Oncol 2003; 69: 291–304.
24. Foroudi F, Haworth A, Pangehel A et al. Inter-observer variability of clinical target volume delineation for bladder cancer using CT and cone beam CT. J Med Imaging Radiat Oncol 2009; 53: 100–106.
25. Lalondrelle S, Thompson A , Khoo V. Fiducial markers in external beam radiotherapy for bladder cancer. Radiother Oncol 2007; 85: 324.
26. Mangar S, Thompson A, Miles E, Huddart R, Horwich A, Khoo V. A feasibility study of using gold seeds as fiducial markers for bladder localization during radical radiotherapy. Br J Radiol 2007; 20: 279–283.
27. Pos F, Bex A, Dees-Ribbers H, Betgen A, Van Herk M, Remeijer P. Lipiodol injection for target volume delineation and image guidance during radiotherapy for bladder cancer. Radiother Oncol 2009; 93: 364–367.
28. Muren L, Redpath A, McLaren D et al. A concomitant tumour boost in bladder irradiation: patient suitability and the potential of intensity modulated radiotherapy. Radiother Oncol 2006; 80:98–105.