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Original Article

Radiotherapy in muscle-invasive bladder cancer: the latest research progress and clinical application

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Abstract: The role of radiotherapy (RT) in the management of urinary bladder cancer has undergone several alterations along the last decades. Recently, many protocols have been developed supporting the use of multi-modality therapy, and the concept of organ preservation began to be reconsidered. Advances in radiotherapy planning, verification, and delivery provide a method to optimize radiotherapy for bladder cancer and overcome difficulties which have previously limited the success of this treatment. They offer the opportunity to enhance the therapeutic ratio by reducing the volume of normal tissue irradiated and by increasing radiation dose or using more intensive fractionation and synchronous chemotherapy regimes. These techniques have a large potential to improve the therapeutic outcome of bladder cancer. In the near future, it should be possible to offer selected patients with muscle-invasive bladder cancer an organ-sparing, yet effective combined-modality treatment. In this review, we aim to present the role of radiotherapy in the management of muscle invasive bladder cancer. Alternative methods of improving treatment accuracy such as helical tomotherapy, adaptive radiotherapy and radiochemotherapy are also discussed.

Keywords: Urinary bladder cancer, radiotherapy, HT, VMAT, ART

Introduction

Carcinoma of the bladder of all histologic types remains a major global health issue, with more than 385,000 new cases worldwide in 2008 [1]. In the USA, approximately 14,100 people per year will die of this disease, accounting for 2.5% of all cancer-related mortality [2]. Transitional cell carcinoma (TCC) represents over 90% of bladder cancers and less common types include squamous cell carcinoma, adenocarcinoma and small cell carcinoma [3].

Bladder cancer can be clinically classified by stage as either muscle invasive or non-muscle-invasive based on involvement of the detrusor muscle. Around 70-85% of patients present with superficial disease and are now commonly named non-muscle invasive bladder cancer (NMIBC) [4]. Muscle invasive bladder cancer (MIBC) (T2-T4), on the other hand, represents a potentially grave danger, with long-term survival of approximately 50% [5, 6].

Radical cystectomy with urinary diversion has long been considered the standard of treatment for MIBC [7]. Contemporary series described 5-year overall survival rates of 45-67% with radical cystectomy alone with recurrence-free survival ranging from 62-71% [8-10]. Despite aggressive and often early intervention, many patients with MIBC treated by surgery alone still remain at considerable risk for recurrence and death from bladder cancer. The majority of recurrences occur within 3 years of surgery and 75% of these patients fail with distant metastases [11].

Radiotherapy (RT) is an alternative treatment with comparatively good results for those who are too frail to undergo cystectomy or for those who refuse operation [12, 13] (**Table 1**). Hayter et al. [14] reported 20,906 new cases of bladder cancer diagnosed in Canada. Among patients with MIBC, no difference in survival was seen between those treated with RT and those who underwent cystectomy. The 5-year cause specific survival for radiation-treated patients was 41%. About one-quarter of patients receiving RT could survive 5 years while retaining the bladder. Radical RT with cystectomy for salvage is comparable with initial

Table 1. Radiotherapy alone for invasive bladder cancer

Study	Patients (n)	Stage	Treament (Gy)	3-to 5-year OS (%)	3-to 5-year LCR (%)
Moonen et al. (1998)	379	T1G3-T3a	RT alone 50-75 Gy		40.3
Piet et al. (2008)	92	T2-T4	RT alone 55 Gy	36	56
Jenkins et al. (1988)	182	T2-T3	RT alone	40	
Moonen et al. (1994)	40	T1G3-T3a	TUR + RT 30 Gy	86	84
Yavuz et al. (2004)	87	T1-T4	RT alone 67.5 Gy	46	64
Horwich et al. (2005)	229	T2-T3	AF (60.8 Gy) n = 129	54 VS. 47	
			CF (64 Gy) n = 100	37 VS. 40	

OS = overall survival, DSS = disease-specific survival, RT = radiotherapy, TUR = transurethral resection, AF = accelerated fractionation, CF = conventional fractionation.

cystectomy and has the advantage of preserving normal bladder function [15, 16].

Multiple institutions and cooperative groups have played a role in developing and refining the modern approach to radiotherapy-based bladder preservation [6, 17]. Bladder preservation with aggressive transurethral surgery (TUR), systemic chemotherapy, and RT has resulted in 5-year survival rates approximately equivalent to those after cystectomy (60%), with 40% of patients surviving with an intact bladder [15]. Comparing approaches by TUR plus chemotherapy alone with TURBT plus concurrent chemotherapy and radiotherapy, the 5-year survival rates with a preserved bladder for all patients entered ranges from 20-33% when radiotherapy was not used and from 41-45% when radiotherapy was used [18]. Thus, the use of radiotherapy concurrent with chemotherapy after TUR increases the probability of surviving without invasive tumor recurrence. This review will focus on the current application of the radiotherapy in MIBC, and the evidence to support this management.

Conventional radiotherapy

Usually, RT is fractionated in 1.8 to 2 Gy per day, 5 days a week. A total dose of 45 to 50 Gy is delivered to the pelvis and 55 to 70 Gy to the bladder tumor bed, achieving advantageous rates of local control [19].

A Canadian study reported long follow-up results of patients with MIBC treated with radical RT [20]. 247 patients received RT alone. 36 patients received RT and concurrent cisplatin chemotherapy, and 57 patients received neoadjuvant chemotherapy followed by RT. Complete response (CR) rate was 63.5% for the whole group. 10-year overall, cause-specific survival and local control rate were 19%, 35%, and 32%. In 131 patients with disease limited to the bladder wall (T2N0M0), 10-year cause-specific survival and local relapse-free rates cause-specific survival were 68% and 60%.

Between 1996 and 2000, Kotwal et al. [21] compared outcomes between patients receiving either radical surgery or RT as therapeutic treatment for bladder cancer. There was no difference in overall, cause-specific, and distant recurrence-free survival at 5 years between the two groups, despite the RT group being older (median age, 75.3 years vs. 68.2 years). In a more recent cohort, the median age of RT patients was higher than in the above-mentioned cohort and the patients undergoing radical cystectomy were significantly younger than the RT patients (median age, 67.9 years vs. 78.4 years), nevertheless, treatment modality did not influence survival. Radical RT is a feasible treatment option for these patients, with the advantage of organ preservation.

Conventional RT concurrent with chemotherapy, or alone, provides benefits for locally advanced bladder cancer patients. However, patients developed grade 3 or 4 hematologic toxicity or pelvic toxicities in the studies where radiation was delivered by conventional RT techniques. In the RTOG 95-06 study, 21% of patients with MIBC who underwent TUR plus concomitant chemotherapy and RT had grade 3 or 4 hematologic toxicity and 15% had 3 bowel toxicity [22]. The conventional RT, in which the dose cannot be reduced to critical organs, and thus, causes unavoidable side effects.

Three-dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT)

Great advance in techniques for both medical imaging and conformal dose delivery has taken place during the last decades. Advances in RT delivery such as 3D-CRT and IMRT have been devised to concentrate the radiation on the target organ, deliver high enough doses to the tumor to stop its growth without inducing unacceptably high rates of normal tissue adverse effects.

3D-CRT

Shen et al. [23] studied the efficacy, late complications and prognostic factors of 3D-CRT for bladder cancer. Between 1995 and 2007, 109 patients with primary bladder cancer were retrospectively analyzed. The median age was 68 years. 3D-CRT was given with a median total dose of 49.2 Gy (39.3-62.2 Gy) after TUR. The 1, 3 and 5-year local control rate were 63%, 47% and 42%, respectively. The 1, 3 and 5-year overall survival rate were 80%, 48% and 37%, respectively. Among the 109 patients, 33 died of tumor progression or metastasis. 42 showed local recurrence and 22 had lymph node metastasis. Grade 1, 2, 3 and 4 radiation related early urological side effects were 22%, 59%, 12% and l%, respectively. The corresponding late urological side effects were 29%, 28%, 2% and l%, respectively.

IMRT

Turgeon et al. [24] reported their experience with bladder preserving treatment using IMRT for elderly patients with MIBC. 24 patients with a median age of 79 years were eligible. A CR was confirmed in 83% of the patients. The overall and cancer-specific survival rates at 3 years were 61% and 71%, respectively. Of the surviving patients, 75% have a disease-free and functioning bladder. Only 4% of the patients occurred acute grade 3 gastrointestinal or genitourinary toxicities, and acute grade 3 or 4 hematologic toxicities, liver toxicities, or both were experienced by 17% of the cohort. No patient experienced grade 4 gastrointestinal or genitourinary toxicity.

Hsieh et al. [25] found that IMRT provided good locoregional progression free survival particularly in the elderly bladder cancer group. The median patient age was 80 years old. The median survival was 21 months (5 to 26 months). Of the 19 eligible patients, 17 (89.5%) had no local recurrence. The 2-year overall survival rates for T3-T4 was 35.4%.

Compared to standard CRT, IMRT techniques give even better shaping of the dose distribution around the tumor, with potentially larger reductions in normal tissue late effects and/or larger increases in tumor control. Meijer et al [26] reported 20 patients with T2-T4N0M0 invasive bladder carcinoma. The IMRT treatment was very well tolerated; all treated patients completed their prescribed regimen without interruption. No grade 3 toxicities were observed. van Rooijen et al. [27] also mentioned the similar report with IMRT for bladder cancer that a statistically significant dose decrease to the small intestines can be achieved while covering both tumor.

However, the potential negative of IMRT include the increased time required for RT delivery and the associated risk of bladder filling and changes in bladder shape and size. The magnitude of bladder filling during treatment delivery has recently been demonstrated to be approximately 1 cm^3 per minute, but with wide inter patient variation [28]. Another disadvantage of IMRT is the increased number of monitor units (MU) needed, which results in a greater integral body dose, with a potential increased risk of second malignancies [29]. Nevertheless, Ruben et al. [30] found that the effect on secondary cancer induction by spreading out the low to intermediate dose with IMRT is small. While IMRT increases the MU demand compared to 3D-CRT, the smaller field size and reduced average filed intensity have been reported to reduce the scatter more than sufficiently to compensate for any increase in head leakage.

Helical tomotherapy (HT)

Helical tomotherapy (HT), an image-guided IMRT that was developed at the University of Wisconsin, USA, delivers highly conformal dose distributions to the targets, concurrent with critical organ sparing [25]. Several studies have been published comparing HT with other IMRT manners [31, 32]. It introduces the ring gantry concept into RT using a combination of a mega-

voltage (MV) CT scanner and a therapeutic linear accelerator [33]. Radiation is emitted as a fan beam by a linear accelerator mounted on the rotating gantry and is modulated by a fast pneumatically driven binary slit collimator. During treatment, the patient is moved through the gantry bore while the gantry is rotating continuously resulting in a helical dose application. HT can achieve highly conformal dose distributions at various locations for many different tumor entities [33-35]. Besides these abilities in terms of achievable dose distributions, HT offers a unique system of image guidance. The realization of a ring gantry enabled the integration of MV-CT imaging. Owing to the shape and location, the extent of bladder tumors make them well suited for HT.

Hsieh et al. [25] reported their clinical experience with bladder cancer patients treated with IMRT or HT for organ preservation, focusing on feasibility of HT, clinical outcome, and early toxicities. They enrolled 19 bladder cancer patients, 9 in the IMRT and 10 in the HT group. The patients received 64.8 Gy to the bladder with or without concurrent chemotherapy. The median survival was 21 months. The actuarial 2-year overall survival for the IMRT and HT group were 26.3% vs. 37.5%, respectively; the 2-year disease-free survival were 58.3% vs. 83.3%, respectively. Three of 19 patients (16%) experienced grade 3/4 anemia, two in the IMRT group and one in the HT group. HT had statistically significantly better organ sparing results.

The HT system with its integrated MV-CT allows the treatment of standard cases in an excellent way, treat multiple targets faster than conventional techniques when several target points were necessary. It was possible to achieve highly conformal dose distributions for targets of all sizes and multiple targets within one procedure. This was feasible even if the desired immobilization was not possible due to obesity, claustrophobia, pain, or neurologic impairment. Long-term follow-up is needed to confirm these preliminary findings.

Volumetric-modulated arc therapy (VMAT)

VMAT is a new modality of IMRT, allows for change in the dose rate, speed of gantry rotation, and multi-leaf positions (MLC) during rotation of the gantry in a full 360 degree arc. It was recently introduced in clinical practice for comparing with conventional RT modalities in various malignancies, including brain, head and neck, prostate, anal canal, and cervix tumors [36-38]. In VMAT, gantry speed, MLC position and dose rate are dynamically varied during rotation of the gantry yielding a fast and highly conformal treatment delivery [39]. RapidArc (Varian Medical Systems, Palo Alto, CA) utilises the optimisation algorithm first described by Otto, K [40] to plan VMAT. This technology has recently been implemented clinically and is becoming more widely practicable in radiotherapy centres. The advantage of VMAT is a large reduction in the number of MUs, with an associated reduction in treatment time.

Foroudi et al. [37] compared the tumor control and normal tissue complication probabilities of 3D-CRT with IMRT and VMAT plans for 15 patients with T2-4N0M0 bladder cancer. Mean planning time for 3D-CRT, IMRT and VMAT was 30.0, 49.3, and 141.0 minutes respectively. The mean PTV conformity index (CI) for 3D-CRT, IMRT and VMAT was 1.32, 1.05, and 1.05. The PTV homogeneity index (HI) was 0.080 for 3D-CRT, 0.073 for IMRT and 0.086 for VMAT. Tumor control and normal tissue complication probabilities were similar for them. Average treatment delivery time were 2:25 min (range 2:01-3:09) for 3D-CRT; 4:39 min (range 3:41-6:40) for IMRT; and 1:14 min (range 1:13-1:14) for VMAT. VMAT is associated with faster delivery times than 3D-CRT and IMRT. Cozzi et al. [38] found that RapidArc improved dose homogeneity and sparing of the rectum, bladder and small bowel in the medium to high dose region. The improved sparing of the bladder, rectum and pelvis bone at medium to high doses using VMAT as compared with IMRT is expected to further reduce the acute and late toxicities, especially for patients requiring a local boost and concurrent/sequential chemotherapy.

A number of studies in other tumor sites have shown that VMAT results in similar plan quality with substantially reduced treatment times compared to IMRT [40, 41]. Given the benefits in terms of reduced MU as well as treatment time, VMAT appears to be the ideal technology to be used with daily image guided or adaptive radiotherapy for MIBC. This reduction in treatment delivery time is clinically relevant in relation to patient comfort and infra-fraction

motion. Faster delivery could improve patient adherence to treatment and reduce intra-fractional motion. In addition, the higher delivery efficiency also allowed for more time to carry out image-guided radiotherapy, further reducing the treatment margin and toxicity. At present, there is very little in the literature, regarding the optimal planning of bladder using VMAT. The clinical significance of these differences with regard to dosimetry and radiation delivery efficiency needs to be further investigated.

Adaptive radiotherapy (ART)

Adaptive radiotherapy is one of the new approaches that make extensive use of new technology. It is generally defined as the use of high quality images acquired of the patient during or just prior to treatment delivery for modification of treatment plans and thereby deal with treatment variations caused by organ motion. Methods of both offline ART, where a single adaptive treatment plan is generated using various repeated CT or cone-beam computed tomography (CBCT) scans; and online ART, where the daily treatment plan is chosen from a library of pre-planned treatment plans based on CBCT imaging, have been studied [42, 43]. The former is a common strategy for head and neck cancer where complex decisions and a complete replan may be necessary [44]. In the latter case the images are directly utilised not only to move the patient in the correct position but also to affect the treatment plan executed on the day. Adaptive treatment strategies of bladder cancer have been investigated among several research groups [42-45].

Foroudi et al. [42] concluded that an offline adaptive treatment strategy yields a higher conformity index and improves clinical target volume (CTV) dose coverage compared to conventional planning. The NKI group reported 21 patients with solitary T1-T4N0M0 bladder cancer treated with offline adaptive radiotherapy using repeat CT [45]. The offline adaptive procedure proved to be effective and treatment volumes were reduced by 40%.

Radiotherapy for bladder cancer has been demonstrated by several groups to benefit significantly from online adaptive radiotherapy [45-48]. Due to the daily variation in bladder volume it is possible to prepare plans for different bladder sizes and select the most appropriate plan for the patient as he/she presents on the day. The plans can either be prepared with predetermined margins or based on results of daily volumetric imaging during the first week of treatment [48, 49]. Prior to delivery of every fraction, the best plan is selected by treatment staff based on insitu volumetric imaging such as CBCT.

A comparisons were made between adaptive and conventional treatment on the basis of CTV coverage and normal tissue sparing [48]. 27 patients with T2-4 transitional cell carcinoma of the bladder were treated with daily online adaptive image-guided RT using CBCT. Mean volume of normal tissue receiving a dose > 45 Gy was 29%, less with adaptive RT compared with conventional RT. The mean volume of normal tissue receiving > 5 Gy was 15%, less with adaptive RT compared with conventional RT. Online adaptive radiotherapy is feasible in an academic radiotherapy center. The volume of normal tissue irradiated can be significantly smaller without reducing CTV coverage.

Vestergaard et al. [46] compared the normal tissue sparing potential of two ART strategies: daily plan selection (PlanSelect) and daily plan re-optimisation (ReOpt). Seven patients with bladder cancer were included in the study. For the PlanSelect strategy, a patient-specific library of three plans was generated, and the most suitable plan based on the pre-treatment CBCT was selected. For the daily ReOpt strategy, plans were re-optimised based on the CBCT from each daily fraction. Accumulated dose distributions for the ART strategies as well as the non-adaptive RT were calculated. Compared to non-adaptive RT, the volume receiving more than 57 Gy (corresponding to 95% of the prescribed dose) was reduced to 66% (range 48-100%) for PlanSelect and to 41% (range 33-50%) for ReOpt. This study demonstrated a considerable normal tissue sparing potential of ART for bladder irradiation, with clearly superior results by daily adaptive re-optimisation.

McDonald et al. [50] assessed the target coverage and normal tissue sparing of ART strategies. Conformal plans were developed for 25 patients. The mean coverage of the clinical target volume by the 95% isodose was 99%. The mean reduction in the volume of normal tissue treated to 95% of the prescription dose was 219 cm^3 compared with the previous institu-

tional standard approach. Good concordance in plan selection is shown with clinical implementation of the adaptive strategy. Adequate target coverage was achieved with reduction in the volume of normal tissue irradiated to a high dose compared with the previous standard approach.

In the attempt to minimize radiation-induced side effect to normal tissues, ART has emerged as an alternative method to conventional RT. The effect of ART on spared volume of the bowel at the selected dose level is determined and compared with the traditional non-adaptive RT with constant margins based on a single set of treatment planning images. In addition the CTV coverage is compared between both adaptive and non-adaptive techniques to get a confidence of not missing the target when introducing more complicated adaptive procedures into daily RT practice. The strategy provides adequate target coverage with an associated reduction in normal tissue irradiation. Using the published dose-volume dependency of small bowel toxicity [51], it can be estimated that the probability of grade ≥ 2 acute gastrointestinal toxicity (diarrhoea) requiring frequent medications was reduced from a normal tissue complication probability of 35% to as low as 7% on average. In order to show the clinical significance of ART in the treatment of bladder cancer and reducing the acute bowel toxicity, a long-term close follow-up and larger number of patients would be required.

Brachytherapy

Brachytherapy, as an alternative to external-beam (EBRT) treatment, allows a high dose of radiation to be delivered focally to a small area of the bladder with relative sparing the rest of the bladder wall and organs in the close neighborhood, such as the small intestine.

Several radiation oncologists have reported good results with the combination of limited surgery after external beam radiotherapy (EBRT) followed by brachytherapy in MIBC [52-56]. Koning et al. [52] collected data from 12 of 13 departments in a multicenter database, resulting about 1040 patients: 811 males and 229 females with a median age of 66 years (range 28-92 years). Results were analyzed according to tumor stage and diameter, histology grade, age and brachytherapy technique, continuous low-dose rate (CLDR) and pulsed dose rate (PDR). At 1, 3 and 5 years, the local recurrence-free survival was 91%, 80% and 75%, metastasis-free survival was 91%, 80% and 74%, disease-free survival was 85%, 68% and 61% and overall survival survival was 91%, 74% and 62%, respectively.

De Neve et al. [54] have reported the results from 32 patients selected for implantation in a retrospective study. Treatment schedule included external radiotherapy with 12 Gy in two to three fractions followed by implantation of 4 to 6 cesium-filled needles in the tumor under general or spinal anesthesia. The dose of brachytherapy was median 53 Gy. This group of patients was retrospectively compared to patients with stage T1 and T2 receiving radical radiotherapy or preoperative radiotherapy and cystectomy. Bladder cancer-specific survival was improved to 76% in the brachytherapy group compared to 50% and 49% in the two other groups.

In conclusion, EBRT followed by brachytherapy, combined with limited surgery, offers excellent results in terms of bladder sparing for selected groups of patients suffering from bladder cancer.

Dose and fractionation

The regimes most commonly employed in conventional treatment of the whole bladder are 60-66 Gy in 30-33 fractions [57, 58]. A Dutch review [59] emphasized the importance of the treatment dose in which 10 Gy increments in the final dose of RT yielded an increase of about 50% in local control rate in three years. Expansion of the radiation dose using conventional fractionation results in increased normal tissue toxicity, particularly gastrointestinal, and may lengthen treatment time. Attempts to increase the effective radiation dose delivered have therefore focused more on dose intensification using accelerated hyperfractionation.

Accelerated hyperfractionated fractionation: Accelerated RT implies in the administration of the same number of fractions in a shorter period of time, in other words, an equivalent higher total dose [60].

A Poland research institute evaluated the toxicity, clinical efficiency and survival rate of TUR,

Table 2. Hypofractionated Radiotherapy for bladder cancer

Study	Patients (n)	Stage	Treament (Gy)	Outcome
McLaren et al. (1997)	65	T2-T4	30 Gy/5F (n = 53) 36 Gy/6F (n = 12)	OS 9 months
Turgeon et al. (2008)	24	T2-T3	50 Gy/20F	3-year OS 61% 3-year DSS 71%
Kouloulias et al. (2013)	58	T1-T2	36 Gy/6F	PFS 14 months
Fosså et al. (1991)	39	T4	30 Gy/10F	OS 7.5 months
Salminen et al. (1992)	94	T1-T4	30 Gy/6F	DSS 13.3 months 5-year OS 13%

OS = overall survival, DSS = disease-specific survival, PFS = progression-free survival.

neoadjuvant chemotherapy and accelerated hyperfractionated radiotherapy in patients with MIBC [61]. Between 2004 and 2009, 35 patients with histologically proven invasive carcinoma of the bladder (T2-T4aN0-1M0), were selected for the bladder-sparing protocol. The overall actuarial survival rates at 3 and 5 years were 75% and 66%, respectively. Disease-specific actuarial survival rates at 3 and 5 years were 81% and 71%, respectively.

Yavuz et al. [62] evaluated the toxicity and clinical effectiveness of accelerated superfractionated radiotherapy in locally invasive carcinoma of the bladder. 87 patients (unsuitable or refusing cystectomy) with invasive bladder cancer were selected. Initially, the whole pelvis was treated by 1.8 Gy conventional daily fractions up to a total dose of 45 Gy. A small field boost covering gross disease was added as a second daily fraction (1.5 Gy) during the last 3 weeks of the 5-week schedule up to a total dose of 67.5 Gy. The interfraction interval was a minimum of 6 h. The 3-year actuarial local control, distant disease control, cause-specific survival, and overall survival rate was 64%, 78%, 58%, and 46%, respectively. For Stage T2 and T3, the 3-year local control rate was 77% and 48%, respectively.

Hypofractionated: Hypofractionated RT which consists of the administration of larger daily fractions (2.5 Gy to 6 Gy, in general) was also studied. One study evaluated acute toxicity and symptoms palliation of a weekly hypofractionated 3D-CRT schedule as radical treatment in elderly patients with organ confined bladder cancer [63] (**Table 2**). 58 patients who diagnosed with bladder cancer were treated with external 3D-CRT between 2005 and 2011. All candidates were medically inoperable, with poor performance status, and with age ranged from 75 to 88 years. A dose of 36 Gy in 6 weekly fractions was prescribed. The gastrointestinal acute toxicities were 13/58 (22.4%) and 5/58 (5.6%), for grade I and II respectively. The genitourinary acute toxicities were 19/58 (32.7%) and 10/58 (17.2%), for grade I and II respectively. In terms of clinical outcome, 55/58 patients (94.8%) reported palliation of haematuria, while 19 out of 58 reported no change in frequency and dysuria. All patients reported significant improvement ($P < 0.01$) for pain, concerning the visual analogue score before and after radiotherapy. The median progression free survival was 14 months.

McLaren et al. [64] reported a study of 55 elderly patients (median age 78 years), to minimise acute radiation affects and maximise patient tolerance and convenience in this frail group, who underwent weekly scheme with 6 Gy per session, while the total dose ranged from 30-36 Gy. Totally 13% of the patient noticed an improvement at a 1 month review. 92% of patients with haematuria were completely palliated compared to only 24% of those with dysuria and frequency. Median overall survival was as low as 9 months (range 2-41 months). Grade 3 acute urinary and bowel treatment related toxicity recorded in 18% and 9% of patients.

Turgeon et al. [24] reported 24 patients with a median age of 79 years were eligible. The overall and cancer-specific survival rates at 3 years were 61% and 71%, respectively. Of the surviving patients, 75% have a disease-free and functioning bladder. It is possible to deliver hypofractionated RT to the bladder with an acceptable acute toxicity rate in a poor prognostic patient group.

Radiotherapy and chemotherapy

Effective chemotherapeutic agents, working locally as radio-sensitizers (and systemically by

preventing metastatic growth), are fundamental for an organ-sparing approach. Cisplatin alone or in combination has been the most frequently used radiosensitizer [65], while paclitaxel and gemcitabine more recently have been added to the choices of chemotherapeutic agents. Chemotherapy attempts to eliminate local and systemic disease and increase RT effect on locoregional control (**Table 3**).

Concomitant chemotherapy may sensitize bladder tumors and increase response. Improved local control will reduce the need for cystectomy and add opportunity to bladder preservation, and a survival benefit of combination chemotherapy with methotrexate, vinblastine, adriamycin and cisplatin (MVAC) has been documented in randomized phase III trial [66]. MVAC was for many years the preferred regime; however, patients experienced high toxicity levels. Newer chemotherapy regimes have attempted to offer analogous or better efficacy in terms of overall survival, response rates, and time to disease progression while decreasing toxicity.

In a British multicenter phase III trial, 360 patients with MIBC underwent RT with or without synchronous chemotherapy [1]. The regimen consisted of fluorouracil during fractions 1 to 5 and 16 to 20 of radiotherapy and mitomycin C on day 1. At 2 years, rates of locoregional disease-free survival were 67% in the chemoradiotherapy group and 54% in the radiotherapy group. Five-year rates of overall survival were 48% in the chemoradiotherapy group and 35% in the radiotherapy group. Grade 3 or 4 adverse events were slightly more common in the chemoradiotherapy group than in the radiotherapy group during treatment (36.0% vs. 27.5%, P = 0.07) but not during follow-up (8.3% vs. 15.7%, P = 0.07).

RTOG 0233 trial assessed effectiveness, safety, and tolerability of paclitaxel or fluorouracil when added to radiation plus cisplatin followed by adjuvant chemotherapy for patients [67]. Ninety three patients with T2-4a transitional cell carcinoma were randomly allocated to receive paclitaxel plus cisplatin (paclitaxel group) or fluorouracil plus cisplatin (fluorouracil group). All patients had TUR and twice-daily radiotherapy to 40.3 Gy, along with allocated chemotherapy, followed by cystoscopic and biopsy assessment of response. Patients who had a tumour response with downstaging received consolidation chemoradiotherapy to 64.3 Gy, with the same chemotherapy regimen. When the tumor was stage T1 or worse after induction chemoradiotherapy, cystectomy was recommended. Of 46 patients in the paclitaxel group, 31 completed the entire protocol with adjuvant chemotherapy. Of 47 patients in the fluorouracil group, 25 completed the entire protocol. 5-year overall survival was 71% in the paclitaxel group and 75% in the fluorouracil group. 5-year bladder-intact survival was 67% in the paclitaxel group and 71% in the fluorouracil group. Overall, this randomised study showed that cisplatin with either paclitaxel or fluorouracil in combination with radiotherapy achieves good results in terms of cancer control and bladder preservation.

A phase II trial estimated the response of MIBC to concurrent chemoradiotherapy of weekly gemcitabine with 4 weeks of radiotherapy [68]. Fifty patients with transitional cell carcinoma, stage T2-3N0M0 after TUR and magnetic resonance imaging, were recruited. All patients completed RT, 46 patients tolerated all four cycles of gemcitabine. 47 patients had a post-treatment cystoscopy, 44 (88%) achieved a complete endoscopic response. At a median follow-up of 36 months, 36 patients were alive, and 32 of these had a functional and intact bladder. By using Kaplan-Meier analyses, 3-year cancer-specific survival was 82%, and overall survival was 75%. Similarly, Atasoy et al. [69] reported twenty-six patients were recruited to determine the efficacy and the toxicity of low dose weekly gemcitabine with radiation therapy. Median follow-up was 51 months (range 14-118 months). CR rate was 62.5%. The 5-year local progression-free survival, disease-specific survival and overall survival rates were 40.6%, 59.5% and 58.5%, respectively.

An alternative approach to radiosensitization would be to address tumor hypoxia, as reported in another phase III trial in the United Kingdom [70]. In that trial, 333 patients were randomly assigned to undergo either RT alone or RT with synchronous nicotinamide and carbogen. Analysis of the primary outcome of 3-year locoregional relapse-free survival did not meet statistical significance (54% for combined therapy vs. 43% for RT alone; hazard ratio, 0.88; 95% CI, 0.76 to 1.01; P = 0.06), although significant improvements in 3-year overall survival

Table 3. Radical radiotherapy or radiochemotherapy for invasive bladder cancer

Study	Patients (n)	Stage	Experimental arm	Control arm	3-to 5-year OS (%)	3-to 5-year DSS (%)
Rödel et al. (2002)	415	T1-T4	TUR + RCT (DDP/CBP/PF) n = 289	TUR + RT n = 126	51	56
Atasoy et al. (2014)	26	T2-T4a	RCT (GEM)		58.5	59.5
James et al. (2012)	360	T2-T4a	RCT (MMC + 5Fu) n = 182	RT alone n = 178	48 VS. 35	
Choudhury et al. (2011)	50	T2-T3	RCT (GEM)		75	82
Mitin et al. (2013)	93	T2-T4a	TUR + RCT (DDP + TAX) + GTP n = 46	TUR + RCT (DDP + 5Fu) + GTP n = 47	71 VS. 75	
Hoskin et al. (2010)	333	T1G3-T4a	RCT (CON) n = 168	RT alone n = 165	59 VS. 46	
Kaufman et al. (2000)	34	T2-T4a	TUR + RCT (PF)		83	
Nowak-Sadzikowska et al. (2013)	35	T2-T4a	TUR + NEO (GP/GC) + RT + DDP		75 VS. 66	81 VS. 71

OS = overall survival, DSS = disease-specific survival, TUR = transurethral resection, RCT = radiochemotherapy, RT = radiotherapy, GEM = gemcitabine, MMC = mitomycin C, CON = carbogen and nicotinamide, NEO = neoadjuvant, MCV = methotrexate, cisplatin, vinblastine, DDP = cisplatin, CBP = carboplatin, PF = cisplatin and fluorouracil, GP = gemcitabine, cisplatin, GC = gemcitabine, carboplatin, GTP = gemcitabine + paclitaxel + cisplatin-.

were reported (59% for combined therapy vs. 46% for RT alone; hazard ratio, 0.86; 95% CI, 0.74 to 0.99; P = 0.04). No increase in the rate of acute toxic effects was noted with combined therapy.

Quality of life (QoL)

A radical cystectomy has been considered the gold standard treatment for invasive bladder cancer. Although complications and mortality rates have decreased due to advances in surgical techniques and perioperative patient care, the operation have the potential for lowering the quality of life (QoL) [71, 72]. The loss of one's own bladder function can be considered a major kind of mutilation [73, 74]. Therefore, a lot of patients experience great anxiety regarding the removal of their bladder. The bladder preservation therapy offers a curative option to patients medically unfit for radical surgery and an alternative conservative treatment for selected patients who are potential candidates for cystectomy. Lagrange et al. [75] evaluated bladder preservation and functional quality after concurrent chemoradiotherapy for MIBC in 53 patients. Pelvic irradiation delivered 45 Gy, followed by an 18 Gy boost. Patients initially suitable for surgery were evaluated with macroscopically complete TUR after 45 Gy, followed by radical cystectomy in case of incomplete response. The questionnaire, specific items on bladder function and the late effects in normal tissues, were used to evaluate QoL before treatment and 6, 12, 24, and 36 months after treatment. Median follow-up was 8 years. Bladder was preserved in 67% of patients. Satisfactory bladder function was reported for 100% of patients with preserved bladder and locally controlled disease 6-36 months after the beginning of treatment. Satisfactory bladder function was reported for 35% of patients before treatment and for 43%, 57%, and 29%, respectively, at 6, 18, and 36 months.

A study with long-term follow-up (median 6.3 years) evaluated QoL and bladder function assessed by urodynamics [76]. They surveyed 71 surviving patients who received bladder preservation therapy, 75% of the patients retained normal bladder function. Urinary flow problems were reported in 6% of patients, urgency in 15% and urinary leakage in 19%.

This prospective evaluation supports the published retrospective data suggesting good QoL for those invasive bladder cancer patients managed by bladder preservation after TUR and concurrent chemoradiotherapy.

Palliative radiotherapy

Short courses of hypofractionated regimens have been used for palliation of local symptoms, as many fractions are burdensome for the patients. Improving Outcomes in Urological Cancers published by the National Institute of Clinical Excellence stated that palliative care is an integral part of the management of patients with urological cancers and should be available if needed to provide symptom control as well as social, spiritual, and psychological support [77].

A research assessed short and mid-term clinical efficacy of RT to achieve hemostasis in patients with bladder-cancer related gross hematuria who were unfit for surgery [78]. Thirty-two patients were included for hemostatic RT. The standard treatment was 30 Gy in 10 fractions over 2 weeks. More severe patients underwent a hypofractionated regimen, with 20 Gy in 5 fractions over a one week period. At 2 weeks, 69% of patients were hematuria-free. Subgroup analysis showed that 79% of patients undergoing hypofractionated regimen were hematuria-free. A total of 54% were hematuria-free with the standard regimen. Based on tumor stage, hematuria was controlled at 2 weeks for 57% of non-muscle invasive tumors and 72% of muscle-invasive tumors. After 6 months, 69% of patients had relapsed, regardless of tumor stage or therapy schedules.

McLaren et al. [79] reported the effect of 36 Gy in 6 fractions to 65 patients unsuited for surgery. Palliation was achieved in 52% of patients. Similar results were confirmed in a study by Salminen including 94 symptomatic patients treated with 30 Gy in 6 fractions with 2 fractions/week. Pain was reduced in 68% and urgency in 55% of the patients [80]. However, less encouraging results have been achieved in a prospective study by Fosså et al. [81] including mostly patients with T4 tumors and concurrent distant metastases using 30 Gy in 10 fractions. We considered that the difference was because in the latter the majority of patients had occured advanced cancer and distant metastases. Palliative treatment must strike the right balance between efficacy, convenience, toxicity and duration.

Conclusions

In all organ-sparing management, RT remains the principal part of the local treatment. With further development of both RT and the other modalities in these programmes, it may in the near future be possible to offer selected patients a multimodality conservative treatment and resulted in good long-term bladder function and low rates of salvage cystectomy, all of which are important to the elderly, relatively frail group of patients.

Recent advances in the techniques of radiotherapy treatment planning, verification, and delivery offer the possible to overcome obstacles that have previously restricted the achievement of bladder RT. The current techniques using HT, VMAT and ART allow a greater dose-escalation to the treatment targets, with lower doses to the normal surrounding tissues and, consequently, less treatment related toxicity. The advantage of reducing the volume of normal tissue irradiated will enable clinicians to enhance the effectiveness of RT by increasing radiation dose, exploring intensive fractionation and combination regimens with systemic therapies.

Improve QoL with organ preservation is a significant consideration for patients with bladder cancer. The newest modern technologies have been applied to improve QoL while achieving comparable long term survival. Optimization of radiotherapy delivery in combination with newer systemic therapies may allow for future improvements and adoption of an organ preservation strategy for a larger number of patients with bladder cancer. These strategies need full cooperation of urologists, radiation and medical oncologists.

Disclosure of conflict of interest

The authors declare that they have no competing interests.

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References

[1] James ND, Hussain SA, Hall E, Jenkins P, Tremlett J, Rawlings C, Crundwell M, Sizer B, Sreenivasan T, Hendron C, Lewis R, Waters R, Huddart RA; BC2001 Investigators. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med 2012; 366: 1477-1488.

[2] Siegel R and Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012; 62: 10-29.

[3] Moyer VA. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. Ann Intern Med 2012; 157: 120-134.

[4] Griffiths TRL. Current perspectives in bladder cancer management. Int J Clin Pract 2013; 67: 435-448.

[5] Shelley MD, Barber J, Wilt T and Mason MD. Surgery versus radiotherapy for muscle invasive bladder cancer. Cochrane Database Syst Rev 2002; CD002079.

[6] Kozak KR, Hamidi M, Manning M and Moody JS. Bladder preservation for localized muscle-invasive bladder cancer: the survival impact of local utilization rates of definitive radiotherapy. Int J Radiat Oncol Biol 2012; 83: e197-e204.

[7] Stein JP and Skinner DG. Surgical atlas. Radical cystectomy. BJU Int 2004; 94: 197-221.

[8] Madersbacher S, Hochreiter W, Burkhard F, Thalmann GN, Danuser H, Markwalder R and Studer UE. Radical cystectomy for bladder cancer today-a homogeneous series without neoadjuvant therapy. J Clin Oncol 2003; 21: 690-696.

[9] Lin T, Fan X, Zhang C, Xu K, Liu H, Zhang J, Jiang C, Huang H, Han J, Yao Y, Xie W, Dong W, Bi L and Huang J. A prospective randomised controlled trial of laparoscopic vs open radical cystectomy for bladder cancer: perioperative and oncologic outcomes with 5-year follow-up T Lin et al. Br J Cancer 2014; 110: 842-849.

[10] Kitamura H, Tsukamoto T, Shibata T, Masumori N, Fujimoto H, Hirao Y, Fujimoto K, Kitamura Y, Tomita Y, Tobisu K, Niwakawa M, Naito S, Eto M, Kakehi Y; Urologic Oncology Study Group of the Japan Clinical Oncology Group. Randomised phase III study of neoadjuvant chemotherapy with methotrexate, doxorubicin, vinblastine and cisplatin followed by radical cystectomy compared with radical cystectomy alone for muscle-invasive bladder cancer: Japan Clinical Oncology Group Study JCOG0209. Ann Oncol 2014; 25: 1192-1198.

[11] Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, Skinner E, Bochner B, Thangathurai D, Mikhail M, Raghavan D and Skinner DG. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001; 19: 666-675.

[12] Piet AH, Hulshof MC, Pieters BR, Pos FJ, de Reijke TM and Koning CC. Clinical results of a

concomitant boost radiotherapy technique for muscle-invasive bladder cancer. Strahlenther Onkol 2008; 184: 313-318.

[13] Koning CC, Blank LE, Koedooder C, van Os RM, van de Kar M, Jansen E, Battermann JJ, Beijert M, Gernaat C, van Herpen KA, Hoekstra C, Horenblas S, Jobsen JJ, Krol AD, Lybeert ML, van Onna IE, Pelger RC, Poortmans P, Pos FJ, van der Steen-Banasik E, Slot A, Visser A and Pieters BR. Brachytherapy after external beam radiotherapy and limited surgery preserves bladders for patients with solitary pT1-pT3 bladder tumors. Ann Oncol 2012; 23: 2948-2953.

[14] Hayter CR, Paszat LF, Groome PA, Schulze K, Math M and Mackillop WJ. A population-based study of the use and outcome of radical radiotherapy for invasive bladder cancer. Int J Radiat Oncol Biol 1999; 45: 1239-1245.

[15] Rödel C, Grabenbauer GG, Kühn R, Papadopoulos T, Dunst J, Meyer M, Schrott KM and Sauer R. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. J Clin Oncol 2002; 20: 3061-3071.

[16] Hautmann RE, Gschwend JE, de Petriconi RC, Kron M and Volkmer BG. Cystectomy for transitional cell carcinoma of the bladder: results of a surgery only series in the neobladder era. J Urol 2006; 176: 486-492.

[17] Kaufman DS, Shipley WU and Feldman AS. Bladder cancer. Lancet 2009; 374: 239-249.

[18] Shipley WU, Kaufman DS, Zehr E, Heney NM, Lane SC, Thakral HK, Althausen AF and Zietman AL. Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. Urology 2002; 60: 62-67.

[19] Moonen L, vd Voet H, de Nijs R, Horenblas S, Hart AA and Bartelink H. Muscle-invasive bladder cancer treated with external beam radiation: influence of total dose, overall treatment time, and treatment interruption on local control. Int J Radiat Oncol Biol 1998; 42: 525-530.

[20] Chung PW, Bristow RG, Milosevic MF, Yi QL, Jewett MA, Warde PR, Catton CN, McLean M, Moore M, Tannock IF and Gospodarowicz MK. Long-term outcome of radiation-based conservation therapy for invasive bladder cancer. Urol Oncol 2007; 25: 303-309.

[21] Kotwal S, Choudhury A, Johnston C, Paul AB, Whelan P and Kiltie AE. 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 2008; 70: 456-463.

[22] Kaufman DS, Winter KA, Shipley WU, Heney NM, Chetner MP, Souhami L, Zlotecki RA, Sause WT and True LD. The initial results in muscle-invading bladder cancer of RTOG 95-06: phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on the initial response. Oncologist 2000; 5: 471-476.

[23] Shen J, Liu X, Zhang FQ, Hu K, Hou XR and Lian X. Outcome of three-dimensional conformal radiotherapy for 109 patients with bladder cancer. Chin J Radiat Oncol 2009; 18: 115-119.

[24] Turgeon GA, Souhami L, Cury FL, Faria SL, Duclos M, Sturgeon J and Kassouf W. Hypofractionated Intensity Modulated Radiation Therapy in Combined Modality Treatment for Bladder Preservation in Elderly Patients With Invasive Bladder Cancer. Int J Radiat Oncol Biol 2014; 88: 326-331.

[25] Hsieh CH, Chung SD, Chan PH, Lai SK, Chang HC, Hsiao CH, Wu LJ, Chong NS, Chen YJ, Wang LY, Hsieh YP and Shueng PW. Intensity modulated radiotherapy for elderly bladder cancer patients. Radiat Oncol 2011; 6: 75.

[26] Meijer GJ, van der Toorn PP, Bal M, Schuring D, Weterings J and de Wildt M. High precision bladder cancer irradiation by integrating a library planning procedure of 6 prospectively generated SIB IMRT plans with image guidance using lipiodol markers. Radiother Oncol 2012; 105: 174-179.

[27] van Rooijen DC, van de Kamer JB, Hulshof MC, Koning CC and Bel A. Improving bladder cancer treatment with radiotherapy using separate intensity modulated radiotherapy plans for boost and elective fields. J Med Imaging Radiat Oncol 2010; 54: 256-263.

[28] McBain CA, Khoo VS, Buckley DL, Sykes JS, Green MM, Cowan RA, Hutchinson CE, Moore CJ and Price PM. Assessment of bladder motion for clinical radiotherapy practice using cine-magnetic resonance imaging. Int J Radiat Oncol Biol 2009; 75: 664-671.

[29] Hall EJ and Wuu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. Int J Radiat Oncol Biol 2003; 56: 83-88.

[30] Ruben JD, Davis S, Evans C, Jones P, Gagliardi F, Haynes M and Hunter A. The effect of intensity-modulated radiotherapy on radiation-induced second malignancies. Int J Radiat Oncol Biol 2008; 70: 1530-1536.

[31] Chen YJ, Liu A, Han C, Tsai PT, Schultheiss TE, Pezner RD, Vora N, Lim D, Shibata S, Kernstine KH and Wong JY. Helical tomotherapy for radiotherapy in esophageal cancer: a preferred plan with better conformal target coverage and more homogeneous dose distribution. Med Dosim 2007; 32: 166-171.

[32] Iori M, Cattaneo GM, Cagni E, Fiorino C, Borasi G, Riccardo C, Iotti C, Fazio F and Nahum AE.

Dose-volume and biological-model based comparison between helical tomotherapy and (inverse-planned) IMAT for prostate tumours. Radiother Oncol 2008; 88: 34-45.
[33] Welsh JS, Patel RR, Ritter MA, Harari PM, Mackie TR and Mehta MP. Helical tomotherapy: an innovative technology and approach to radiation therapy. Technol Cancer Res Treat 2002; 1: 311-316.
[34] Soisson ET, Tomé WA, Richards GM and Mehta MP. Comparison of linac based fractionated stereotactic radiotherapy and tomotherapy treatment plans for skull-base tumors. Radiother Oncol 2006; 78: 313-21.
[35] Bauman G, Yartsev S, Rodrigues G, Lewis C, Venkatesan VM, Yu E, Hammond A, Perera F, Ash R, Dar AR, Lock M, Baily L, Coad T, Trenka K, Warr B, Kron T, Battista J and Van Dyk J. A prospective evaluation of helical tomotherapy. Int J Radiat Oncol Biol 2007; 68: 632-41.
[36] Fogliata A, Clivio A, Nicolini G, Vanetti E and Cozzi L. Intensity modulation with photons for benign intracranial tumours: a planning comparison of volumetric single arc, helical arc and fixed gantry techniques. Radiother Oncol 2008; 89: 254-62.
[37] Foroudi F, Wilson L, Bressel M, Haworth A, Hornby C, Pham D, Cramb J, Gill S, Tai KH and Kron T. A dosimetric comparison of 3D conformal vs intensity modulated vs volumetric arc radiation therapy for muscle invasive bladder cancer. Radiat Oncol 2012; 7: 111.
[38] Cozzi L, Dinshaw KA, Shrivastava SK, Mahantshetty U, Engineer R, Deshpande DD, Jamema SV, Vanetti E, Clivio A, Nicolini G and Fogliata A. A treatment planning study comparing volumetric arc modulation with RapidArc and fixed field IMRT for cervix uteri radiotherapy. Radiother Oncol 2008; 89: 180-191.
[39] Guckenberger M, Richter A, Krieger T, Wilbert J, Baier K and Flentje M. Is a single arc sufficient in volumetric-modulated arc therapy (VMAT) for complex-shaped target volumes? Radiother Oncol 2009; 93: 259-65.
[40] Otto K. Volumetric modulated arc therapy: IMRT in a single gantry arc. Medical Physics 2007; 35: 310-317.
[41] Dobler B, Weidner K and Koelbl O. Application of volumetric modulated arc therapy (VMAT) in a dual-vendor environment. Radiat Oncol 2010; 5: 95.
[42] Foroudi F, Wong J, Haworth A, Baille A, McAlpine J, Rolfo A, Kron T, Roxby P, Paneghel A, Williams S, Duchesne G and Tai KH. Offline adaptive radiotherapy for bladder cancer using cone beam computed tomography. J Med Imaging Radiat Oncol 2009; 53: 226-233.
[43] Pos F and Remeijer P. Adaptive management of bladder cancer radiotherapy. Semin Radiat Oncol 2010; 20: 116-120.
[44] van Kranen S, van Beek S, Mencarelli A, Rasch C, van Herk M and Sonke JJ. Correction strategies to manage deformations in head-and-neck radiotherapy. Radiother Oncol 2010; 94: 199-205.
[45] Pos FJ, Hulshof M, Lebesque J, Lotz H, van Tienhoven G, Moonen L and Remeijer P. Adaptive radiotherapy for invasive bladder cancer: a feasibility study. Int J Radiat Oncol Biol 2006; 64: 862-868.
[46] Vestergaard A, Muren LP, Søndergaard J, Elstrøm UV, Høyer M and Petersen JB. Adaptive plan selection vs. re-optimisation in radiotherapy for bladder cancer: a dose accumulation comparison. Radiother Oncol 2013; 109: 457-462.
[47] Tuomikoski L, Collan J, Keyriläinen J, Visapää H, Saarilahti K and Tenhunen M. Adaptive radiotherapy in muscle invasive urinary bladder cancer--an effective method to reduce the irradiated bowel volume. Radiother Oncol 2011; 99: 61-66.
[48] Foroudi F, Wong J, Kron T, Rolfo A, Haworth A, Roxby P, Thomas J, Herschtal A, Pham D, Williams S, Tai KH and Duchesne G. Online adaptive radiotherapy for muscle-invasive bladder cancer: results of a pilot study. Int J Radiat Oncol Biol 2011; 81: 765-771.
[49] Murthy V, Master Z, Adurkar P, Mallick I, Mahantshetty U, Bakshi G, Tongaonkar H and Shrivastava S.'Plan of the day'adaptive radiotherapy for bladder cancer using helical tomotherapy. Radiother Oncol 2011; 99: 55-60.
[50] McDonald F, Lalondrelle S, Taylor H, Warren-Oseni K, Khoo V, McNair HA, Harris V, Hafeez S, Hansen VN, Thomas K, Jones K, Dearnaley D, Horwich A and Huddart R. Clinical implementation of adaptive hypofractionated bladder radiotherapy for improvement in normal tissue irradiation. Clin Oncol (R Coll Radiol) 2013; 25: 549-556.
[51] Roeske JC, Bonta D, Mell LK, Lujan AE and Mundt AJ. A dosimetric analysis of acute gastrointestinal toxicity in women receiving intensity-modulated whole-pelvic radiation therapy. Radiother Oncol 2003; 69: 201-207.
[52] Koning CC, Blank LE, Koedooder C, van Os RM, van de Kar M, Jansen E, Battermann JJ, Beijert M, Gernaat C, van Herpen KA, Hoekstra C, Horenblas S, Jobsen JJ, Krol AD, Lybeert ML, van Onna IE, Pelger RC, Poortmans P, Pos FJ, van der Steen-Banasik E, Slot A, Visser A and Pieters BR. Brachytherapy after external beam radiotherapy and limited surgery preserves bladders for patients with solitary pT1-pT3 bladder tumors. Ann Oncol 2012; 23: 2948-2953.
[53] Pos F and Moonen L. Brachytherapy in the treatment of invasive bladder cancer. Semin Radiat Oncol 2005; 15: 49-54.

[54] Van Poppel H, Lievens Y, Van Limbergen E and Baert L. Brachytherapy with Iridium-192 for Bladder Cancer. Eur Urol 2000; 37: 605-608.

[55] De Neve W, Lybeert ML, Goor C, Crommelin MA and Ribot JG. T1 and T2 carcinoma of the urinary bladder: Long term result with external, preoperative, or interstitial radiotherapy. Int J Radiat Oncol Biol 1992; 23: 299-304.

[56] Wijnmaalen A, Helle PA, Koper PC, Jansen PP, Hanssens PE, Boeken Kruger CG and van Putten WL. Muscle invasive bladder cancer treated by transurethral resection, followed by external beam radiation and interstitial iridium-192. Int J Radiat Oncol Biol 1997; 39: 1043-1052.

[57] Cowan RA, McBain CA, Ryder WD, Wylie JP, Logue JP, Turner SL, Van der Voet J, Collins CD, Khoo VS and Read GR. 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 2004; 59: 197-207.

[58] McBain CA and Logue JP. Radiation therapy for muscle-invasive bladder cancer: treatment planning and delivery in the 21st century. Semin Radiat Oncol 2005; 15: 42-48.

[59] Pos FJ, Hart G, Schneider C and Sminia P. Radical radiotherapy for invasive bladder cancer: What dose and fractionation schedule to choose? Int J Radiat Oncol Biol 2006; 64: 1168-1173.

[60] Marta GN, Hanna SA, Gadia R, Correa SF, Silva JL and Carvalho Hde A. The role of radiotherapy in urinary bladder cancer: current status. Int Braz J Urol 2012; 38: 144-156.

[61] Nowak-Sadzikowska J, Jakubowicz J, Skóra T and Pudełek K. Transurethral resection, neoadjuvant chemotherapy and accelerated hyperfractionated radiotherapy (concomitant boost), with or without concurrent cisplatin, for patients with invasive bladder cancer - clinical outcome. Contemp Oncol (Pozn) 2013; 17: 302-306.

[62] Yavuz AA, Yavuz MN, Ozgur GK, Colak F, Ozyavuz R, Cimsitoglu E and Ilis E. Accelerated superfractionated radiotherapy with concomitant boost for invasive bladder cancer. Int J Radiat Oncol Biol 2003; 56: 734-745.

[63] Kouloulias V, Tolia M, Kolliarakis N, Siatelis A and Kelekis N. Evaluation of Acute Toxicity and Symptoms Palliation in a Hypofractionated Weekly Schedule of External Radiotherapy for Elderly Patients with Muscular Invasive Bladder Cancer. International Braz J Urol 2013; 39: 77-82.

[64] McLaren DB, Morrey D and Mason MD. Hypofractionated radiotherapy for muscle invasive bladder cancer in the elderly. Radiother Oncol 1997; 43: 171-174.

[65] Coppin CM, Gospodarowicz MK, James K, Tannock IF, Zee B, Carson J, Pater J and Sullivan LD. Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1996; 14: 2901-2907.

[66] Loehrer PJ, Einhorn LH, Elson PJ, Crawford ED, Kuebler P, Tannock I, Raghavan D, Stuart-Harris R, Sarosdy MF and Lowe BA. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol 1992; 10: 1066-1073.

[67] Mitin T, Hunt D, Shipley WU, Kaufman DS, Uzzo R, Wu CL, Buyyounouski MK, Sandler H and Zietman AL. Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): a randomised multicentre phase 2 trial. Lancet Oncol 2013; 14: 863-872.

[68] Choudhury A, Swindell R, Logue JP, Elliott PA, Livsey JE, Wise M, Symonds P, Wylie JP, Ramani V, Sangar V, Lyons J, Bottomley I, McCaul D, Clarke NW, Kiltie AE, and Cowan RA. Phase II study of conformal hypofractionated radiotherapy with concurrent gemcitabine in muscle-invasive bladder cancer. J Clin Oncol 2011; 29: 733-738.

[69] Atasoy BM, Dane F, Cetin IA, Ozgen Z, Ucuncu Kefeli A, Ibrahimov R, Turhal NS, Abacioglu U, Turkeri L. Concurrent chemoradiotherapy with low dose weekly gemcitabine in medically inoperable muscle-invasive bladder cancer patients. Clin Transl Oncol 2014; 16: 91-95.

[70] Hoskin PJ, Rojas AM, Bentzen SM and Saunders MI. Radiotherapy with concurrent carbogen and nicotinamide in bladder carcinoma. J Clin Oncol 2010; 28: 4912-4918.

[71] Froehner M, Brausi MA, Herr HW, Muto G and Studer UE. Complications following radical cystectomy for bladder cancer in the elderly. Eur Urol 2009; 56: 443-454.

[72] Liedberg F, Holmberg E, Holmäng S, Ljungberg B, Malmström PU, Månsson W, Nunez L, Wessman C, Wijkström H and Jahnson S. Long-term follow-up after radical cystectomy with emphasis on complications and reoperations: a Swedish population-based survey. Scand J Urol Nephrol 2012; 46: 14-18.

[73] Osman Y, Abol-Enein H, Nabeeh A, Gaballah M and Bazeed M. Long-term results of a prospective randomized study comparing two different antireflux techniques in orthotopic bladder substitution. Eur Urol 2004; 45: 82-86.

[74] Froehner M, Brausi MA, Herr HW, Muto G and Studer UE. Complications following radical cystectomy for bladder cancer in the elderly. Eur Urol 2009; 56: 443-54.
[75] Lagrange JL, Bascoul-Mollevi C, Geoffrois L, Beckendorf V, Ferrero JM, Joly F, Allouache N, Bachaud JM, Chevreau C, Kramar A, Chauvet B; Study Group on Genito-Urinary Tumors. Quality of life assessment after concurrent chemoradiation for invasive bladder cancer: results of a multicenter prospective study (GETUG 97-015). Int J Radiat Oncol Biol Phys 2011; 79: 172-178.
[76] Zietman AL, Sacco D, Skowronski U, Gomery P, Kaufman DS and Clark JA. Organ conservation in invasive bladder cancer by transurethral resection, chemotherapy and radiation: results of a urodynamic and quality of life study on long-term survivors. J Urol 2003; 170: 1772-1776.
[77] Fletcher A, Choudhury A and Alam N. Metastatic bladder cancer: a review of current management. ISRN Urology 2011; 2011: 545241.
[78] Lacarrière E, Smaali C, Benyoucef A, Pfister C and Grise P. The efficacy of hemostatic radiotherapy for bladder cancer-related hematuria in patients unfit for surgery. International Braz J Urol 2013; 39: 808-16.
[79] McLaren DB, Morrey D and Mason MD. Hypofractionated radiotherapy for muscle invasive bladder cancer in the elderly. Radiother Oncol 1997; 43: 171-4.
[80] Salminen E. Unconventional Fractionation for Palliative Radiotherapy of Urinary Bladder Cancer; A retrospective review of 94 patients. Acta Oncologica 1992; 31: 449-54.
[81] Fosså SD and Hosbach G. Short-term moderate-dose pelvic radiotherapy of advanced bladder carcinoma. A questionnaire-based evaluation of its symptomatic effect. Acta Oncologica 1991; 30: 735-738.