Radiotherapy and Oncology 109 (2013) 222–228

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Prostate cancer

Postoperative high-dose pelvic radiotherapy for N+ prostate cancer: Toxicity and matched case comparison with postoperative prostate bed-only radiotherapy

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ARTICLE INFO

Article history:
Received 6 May 2013
Received in revised form 12 August 2013
Accepted 12 August 2013
Available online 7 September 2013

Keywords:
Prostate cancer
Lymph node involvement
Intensity-modulated arc therapy
Pelvic irradiation

ABSTRACT

Purpose: To report on toxicity of postoperative high-dose whole-pelvis radiotherapy (WPRT) with androgen deprivation therapy for lymph node metastasized (N1) prostate cancer (PC). To perform a matched-case analysis to compare this toxicity profile to postoperative prostate bed-only radiotherapy (PBRT).

Materials and methods: Forty-eight N1-PC patients were referred for WPRT and 239 node-negative patients for PBRT. Patients were matched 1:1 according to pre-treatment demographics, symptoms, treatment and tumor characteristics. Mean dose to the prostate bed was 75 Gy (WPRT–PBRT) and 54 Gy to the elective nodes (WPRT) in 36 or 37 fractions. End points are genito-urinary (GU) and gastro-intestinal (GI) toxicity.

Results: After WPRT, 35% developed grade 2 (G2) and 4% G3 acute GU toxicity. Acute GI toxicity developed in 42% (G2). Late GU toxicity developed in 36% (G2) and 7% (G3). One patient had G4 incontinence. Recuperation occurred in 59%. Late GI toxicity developed in 25% (G2) with 100% recuperation. Incidence of acute and late GI toxicity was higher following WPRT compared to PBRT ($p \leqslant 0.041$). GU toxicity was similar. With WPRT mean dose to bladder and rectosigmoid were higher.

Conclusions: Postoperative high-dose WPRT comes at the cost of a temporary increase in G2. GI toxicity compared to PBRT because larger volumes of rectosigmoid are irradiated.

The optimal management of lymph node metastasized (N1) prostate cancer (PC) remains controversial [1]. Nowadays these patients are no longer deemed incurable, resulting in a shift toward more aggressive treatment regimes, including radical prostatectomy (RP) with pelvic lymph node dissection (PLND) and immediate adjuvant androgen deprivation therapy (ADT) [2–4]. Nevertheless, patients with ⩾2 positive pelvic lymph nodes (PLNs) are at increased risk of local relapse, systemic progression and PC-death compared to patients with a single positive PLN after RP and ADT [5]. These data indicate that, certainly for patients with several positive PLNs, additional locoregional therapy might improve disease outcome [6]. Some studies suggest that conventional-dose postoperative whole-pelvis radiotherapy (WPRT) can provide an additional benefit on biochemical recurrence-free and overall survival [7–9]. Further improvement in outcome can be expected from dose escalation as there is evidence that the dose–response relationship in primary and postoperative radiotherapy (RT) for PC is similar [10]. However, concerns about severe toxicity have been an argument against irradiation and dose escalation to the prostate bed and PLNs. With intensity-modulated RT a better sparing of the organs at risk (OARs) is obtained [11–15]. Consequently, this fear of excessive toxicity might be inappropriate. We prospectively followed our patients treated with RP-PLND and high-dose postoperative WPRT with 2–3 years ADT (i.e. trimodality therapy) and report on acute and late toxicity. These patients were matched with pN0-PC patients receiving postoperative prostate bed-only RT (PBRT) to quantify the added toxicity of including the PLNs in the target volume. Toxicity and clinical outcome of PBRT were reported on earlier [16,17]. While previous studies have retrospectively compared toxicity of WPRT and PBRT [14], to the best of our knowledge this is the first matched case analysis performed with this intention.

Materials and methods

Patients

Patients with M0-PC were referred to our center for postoperative WPRT ($n = 48$, 2007–2012) or PBRT ($n = 239$, 1998–2012) following RP-PLND. All patients receiving PBRT had pN0-PC. RT was administered in the adjuvant or salvage setting, the latter in case

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http://dx.doi.org/10.1016/j.radonc.2013.08.021

of prostate-specific antigen (PSA) failure (postoperative rising PSA >0.2 ng/ml). Indications for adjuvant PBRT were positive surgical margins or seminal vesicle invasion. Adjuvant or salvage WPRT was performed in case of positive PLNs on PLND ($n = 38$) or presence of pathologically enlarged PLNs on planning CT (i.e. for round lymph nodes: a diameter of $\geqslant 1$ cm; for oval lymph nodes: a shortest axis of $\geqslant 8$ mm; $n = 7$, Fig. 1). Three patients were treated electivally to the PLNs because they only had <5 lymph nodes removed on PLND with a risk of positive nodes >15% as calculated by Roach's formula (% risk = 2/3 PSA + 10 × [Gleason score − 6]).

WPRT patients were matched 1:1 with 48 PBRT patients. Matching was performed blinded toward patient outcome according to patient characteristics (age at RT, pre-RT symptoms [nocturia, dysuria, incontinence, abdominal cramps, diarrhea, gastrointestinal urgency and frequency], diabetes, smoking), treatment characteristics (RT setting [adjuvant/salvage], time between surgery and RT, follow-up time) and tumor characteristics (pT stage, primary and secondary Gleason grade, pre-operative PSA [<10, 10–20 or >20 ng/ml], positive surgical margins).

Radiotherapy planning and dose prescription

For PBRT, details about pre-treatment imaging, target volume definitions and plan optimization have been described previously [18–21]. For WPRT, pre-treatment imaging consisted of a T2-weighted MRI and CT scan (Siemens Somatom 4+, Siemens, Erlangen, Germany) in supine position using 5 mm thick contiguous slices (diaphragm until 10 cm caudal to the testes). The clinical target volume (CTV) included the prostate bed and seminal vesicle remnants [22]. The planning target volume (PTV) consisted of a 7-mm 3-dimensional isotropic expansion of the CTV. The PLNs along the common, internal and external iliac vessels, obturator fossa and presacral nodes were merged to create a PLN target volume (LNN), regardless of the extent of previous PLND. CTV_LNN and PTV_LNN consisted of an isotropic expansion of the LNN of 2 and 7 mm, respectively [23]. Both for WPRT and PBRT, in the adjuvant setting a median dose of 74 Gy in 36 fractions was prescribed to the PTV with a 72 Gy constraint on the maximal rectal and sigmoid dose. In the salvage setting, this was 76 Gy in 37 fractions with a 74 Gy rectal/sigmoid constraint [16,17]. For WPRT, the minimal dose prescribed to PTV_LNN was 45 Gy in 36–37 fractions. The dose was increased up to 72 Gy in 2 Gy fractions on remaining macroscopic disease after PLND. Concerning the OARs, additional rectal and sigmoid dose-volume constraints were implemented as published previously [18]. Briefly, the following planning objectives were used: the volume of the rectum/sigmoid receiving 40 Gy, 50 Gy, 60 Gy and 65 Gy was kept lower than 84%, 68%, 59% and 48%, respectively. The maximal tolerated dose to the bladder, small intestine and cauda equina was 80 Gy, 70 Gy and 50 Gy, respectively. If a plan did not meet all planning objectives, each case was looked at individually. If acceptable, planning criteria were loosened in that particular case. For instance, an under dosage on the target was tolerated if compensation for this under dosage would lead to an unacceptable over dosage on the OAR.

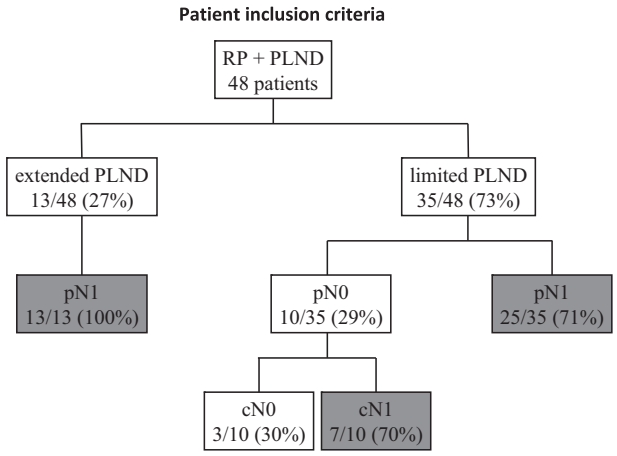

Fig. 1. Patient inclusion criteria for whole-pelvis radiotherapy. All patients underwent previous radical prostatectomy (RP) and pelvic lymph node dissection (PLND). PLND was anatomically defined as extended when the lymph nodes from the obturator fossa and along internal and external iliac vessels were removed. All patients were treated with whole-pelvis intensity modulated arc therapy and androgen deprivation therapy was prescribed for 2–3 years. Indication was pN1 or cN1 prostate cancer (indicated in gray), except for 3 patients (6%) who were treated electivally because they only had <5 lymph nodes removed on PLND with a risk of positive nodes >15% as calculated by Roach's formula (% risk = 2/3 PSA + 10 × [Gleason score − 6]).

Radiotherapy delivery

WPRT was delivered on an Elekta 18-MV linear accelerator (LINAC, Crawley, UK) or a Clinac ix (Varian Medical Systems, Palo Alto, California, USA). The intensity-modulated arc therapy (IMAT) technique used on the Elekta LINAC has been described previously [23]. Rotational intensity-modulated radiotherapy performed with a Varian LINAC (RapidArc) was planned with Eclipse (Varian planning system). For the latter, 2 arcs (1 full arc clockwise – 1 full arc counter clockwise) were used. All patients were treated in supine position with a knee and ankle fix (Sinmed, Cablon Medical, Leusden, The Netherlands). Both for PBRT and WPRT, patients were instructed to use a daily rectal suppository and to have a comfortably filled bladder. Patient positioning was controlled daily by portal imaging or cone beam CT. For PBRT treatment delivery has been detailed previously [19,21]. An example of a WPRT and PBRT sagittal dose distribution is presented in Supplementary Fig. 1.

Androgen deprivation therapy

For WPRT all patients received 2–3 years of ADT, except for two: one refused ADT and in another it was discontinued after 8 months by the referring urologist due to intolerance. For adjuvant PBRT ADT administration was at the treating physician's discretion. For salvage PBRT ADT was administered in case of seminal vesicle invasion, pre-prostatectomy PSA >20 ng/ml, Gleason score >7 or preference of the radiation oncologist.

Evaluation of toxicity

At the patient's first admission, a standard questionnaire was used to register medical and surgical history and any pre-RT upper and lower gastro-intestinal (GI) and genito-urinary (GU) symptoms. To score acute toxicity, patients were seen weekly during RT and 1 and 3 months thereafter. Late toxicity (>3 months after RT) was scored 3-monthly in the first year, 6-monthly 2–5 years post-RT and yearly thereafter. For lower GI toxicity an in-house developed toxicity scale (supplementary Table 1) was used consisting of five symptoms from Radiation Therapy Oncology Group (RTOG) toxicity scale plus rectal urgency, anal pain and incontinence [17,24]. For GU toxicity the scale was based on RTOG, Common Toxicity Criteria for Adverse Events (CTCAE) and SOMA/LENT toxicity scales [18]. Upper GI toxicity was recorded using the RTOG toxicity scale exclusively following WPRT (not for PBRT) [24]. If a toxic event occurred just once, it was registered as RT-induced toxicity. GU and GI symptoms present before RT and not worsening after treatment were not considered RT-induced toxicity. Patients recovered when toxicity moved to a lower grade or disappeared.