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Prostate cancer

# Hypofractionated intensity-modulated arc therapy for lymph node metastasized prostate cancer: Early late toxicity and 3-year clinical outcome

Valérie Fonteyne [a,*], Nicolaas Lumen [c], Piet Ost [a], Charles Van Praet [c], Katrien Vandecasteele [a], Werner De Gersem Ir [a], Geert Villeirs [b], Wilfried De Neve [a], Karel Decaestecker [c], Gert De Meerleer [a]

[a] Department of Radiation-Oncology; [b] Department of Radiology; [c] Department of Urology, Ghent University Hospital, Belgium

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ABSTRACT

*Background and purpose:* For patients with N1 prostate cancer (PCa) aggressive local therapies can be advocated. We evaluated clinical outcome, gastro-intestinal (GI) and genito-urinary (GU) toxicity after intensity modulated arc radiotherapy (IMAT) + androgen deprivation (AD) for N1 PCa.

*Material and methods:* Eighty patients with T1-4N1M0 PCa were treated with IMAT and 2–3 years of AD. A median dose of 69.3 Gy (normalized isoeffective dose at 2 Gy per fraction: 80 Gy [$\alpha/\beta = 3$]) was prescribed in 25 fractions to the prostate. The pelvic lymph nodes received a minimal dose of 45 Gy. A simultaneous integrated boost to 72 Gy and 65 Gy was delivered to the intraprostatic lesion and/or pathologically enlarged lymph nodes, respectively.

GI and GU toxicity was scored using the RTOG/RILIT and RTOG-SOMA/LENT-CTC toxicity scoring system respectively. Three-year actuarial risk of grade 2 and 3/4 GI–GU toxicity and biochemical and clinical relapse free survival (bRFS and cRFS) were calculated with Kaplan–Meier statistics.

*Results:* Median follow-up was 36 months. Three-year actuarial risk for late grade 3 and 2 GI toxicity is 8% and 20%, respectively. Three-year actuarial risk for late grade 3–4 and 2 GU toxicity was 6% and 34%, respectively. Actuarial 3-year bRFS and cRFS was 81% and 89%, respectively. Actuarial 3-year bRFS and cRFS was, respectively 26% and 32% lower for patients with cN1 disease when compared to patients with cN0 disease.

*Conclusion:* IMAT for N1 PCa offers good clinical outcome with moderate toxicity. Patients with cN1 disease have poorer outcome.



High dose external beam radiotherapy (EBRT) is an excellent treatment option for patients with prostate cancer (PCa). For localized PCa, higher radiotherapy (RT) doses result in reduction of biochemical [1] and clinical failure [2]. Intraprostatic failure mainly originates at the initial tumor location [3]. Targeting this location with even higher doses could further increase local control. The concept of optimizing local control to reduce distant metastases and PCa-death is gaining interest resulting in a shift toward more aggressive local therapies, certainly for high risk patients [4]. Although longer follow up is mandatory, hypofractionated radiotherapy schedules seem promising and show equivalent biochemical control without increasing late toxicity [5–6].

In contrast with the excellent results obtained with radical prostatectomy, high dose EBRT or brachytherapy for localized and locally advanced PCa [7–9], the optimal treatment strategy for N1 PCa is less defined. For N1 PCa single modality treatment options have been proposed resulting in disappointing to mediocre clinical results (5-year bRFS <65%) [10]. The addition of androgen deprivation (AD) to surgery or EBRT in N1 PCa patients improves disease free survival with approximately 40% when compared to surgery or EBRT alone indicating that long term clinical outcome can be obtained with combined therapies [10].

In an attempt to improve the outcome of N1 PCa patients and based on above-mentioned evidence from localized and locally advanced PCa, patients with N1 PCa are treated with high-dose hypofractionated, pelvic intensity modulated arc radiotherapy [11] and a simultaneous integrated boost (SIB) to the intraprostatic lesion (IPL) and/or pathological enlarged lymph nodes combined with 2–3 years of androgen deprivation (AD) at Ghent University Hospital. In this manuscript we report on late toxicity and preliminary clinical outcome of this approach.

* Corresponding author. Address: Department of Radiotherapy, Ghent University Hospital, De Pintelaan 185, 9000 Gent, Belgium.
*E-mail address:* valerie.fonteyne@uzgent.be (V. Fonteyne).

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## Materials and methods

### *Patients*

Between January 2005 and May 2012, 80 patients with clinically (c)N1 M0 or pathologically (p)N1 M0 PCa were referred to our center for primary radiotherapy. None of the patients had a radical prostatectomy. After informed consent the patients entered a study using IMAT to irradiate the prostate and regional lymph node (lnn) chains. The study was approved by our local committee of Ethics (Project EC UZG 2006/018).

T-stage was determined by digital rectal examination and magnetic resonance imaging (MRI). An MRI was performed in all but 3 patients (because of a pacemaker (2 patients) and prior TURp (1 patient)). Abdominopelvic CT scan was used to check for pathologically enlarged lnn (i.e. for round lymph nodes: a diameter of $\geqslant$1 cm; for oval lymph nodes: a shortest axis of $\geqslant$8 mm). Pathological N-stage was determined on pelvic lymph node dissection, which was advised in all patients for whom the risk of lnn metastases was $\geqslant$15% according to the Roach formula (2/3 PSA + (Gleason score $-$ 6) $\times$ 10) or who had enlarged lnn on abdominopelvic CT-scan. Ten patients with cN1 disease were included in the IMAT protocol despite the absence of pN1 disease (Fig. 1). Four of them had pathologically enlarged lnn on staging CT and underwent a lymph node dissection with negative histopathological result (pN0). However, the initially enlarged lnn on the diagnostic CT-scan were still present on planning CT-scan so that the lymph node regions at risk were included in the treatment field and a SIB on the pathologically enlarged lnn was performed. Two and 4 patients did not have pelvic lymph node dissection because of inoperability or initiation of AD by the referring urologist respectively (pNx). Five patients had a positive lymph node dissection with remaining pathologically enlarged lnn on planning CT. These lnn were also included for SIB.

A bone scan was performed to rule out the presence of bone metastases. Patients were advised to receive 2–3 years of concomitant and adjuvant AD consisting of a luteinizing hormone-releasing hormone (LHRH)-analog or antiandrogen (bicalutamide 150 mg), which was started no longer then 3 months prior to radiotherapy.

### *Targets and organ at risk (OAR)*

The delineation of the targets and organs at risk has been published previously [11].

In brief, the clinical target volume (CTV) included the prostate and whole seminal vesicles. The planning target volume consisted of a 3-dimensional isotropic expansion of the CTV of 7 mm. The lymph node regions at risk were the lnn along the common, internal and external iliac blood vessels, the lnn in the obturator fossa and the presacral nodes. These regions were merged to a summed lnn-structure. The CTV_lnn and PTV_lnn were created by performing an isotropic expansion of 5 and 7 mm around this summed lnn-structure, respectively. The CTV + CTV_lnn and PTV + PTV_lnn were summed to CTV_All and PTV_All, respectively.

The information of MRI +/− spectroscopy (MRS) was used to delineate the IPL.

Pathologically enlarged lnn on imaging for IMAT planning were delineated as GTV_lnn. An isotropic expansion of 7 mm was applied to create a PTV_GTV_lnn.

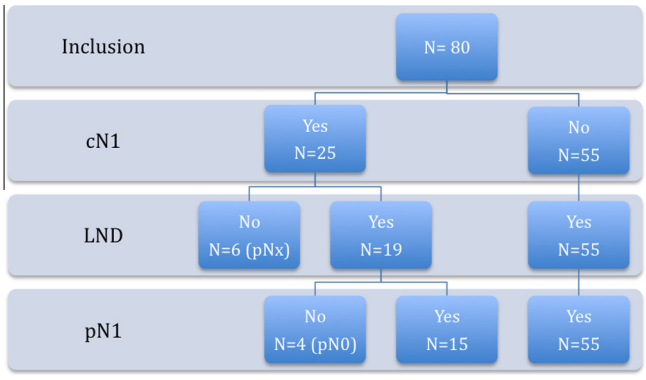


**Fig. 1.** Lymph node status of the included patients. *Abbreviations:* cN1: clinically enlarged lymph nodes on CT, pN1: pathologically enlarged lymph nodes; LND: lymph node dissection.

### *Dose prescription*

We prescribed a median dose of 69.3 Gy, delivered in 25 fractions, to the prostate (corresponding with a normalized isoeffective dose at 2 Gy ($NID_2$) of 80 Gy for $\alpha/\beta$ of 3) [12]. A minimal dose of 48 Gy and 45 Gy was prescribed to the elective lymph node regions: CTV_lnn and PTV_lnn, respectively as well as CTV_All and PTV_All. If an IPL or GTV_lnn was present on planning CT this was delineated separately and implemented in the treatment planning to perform a SIB to a median dose of 72 Gy ($NID_2$ of 84 Gy for $\alpha/\beta$ of 3) and 65 Gy ($NID_2$ of 72.8 Gy for $\alpha/\beta$ of 3), respectively. Sixty-nine patients (84%) had a morphological/spectroscopic IPL. Eighty-seven percent of them (=60 patients) received a SIB on the IPL. In 9 patients the IPL encompassed approximately the whole peripheral zone of the prostate. These large lesions were not implemented in the treatment planning for separate SIB in order to avoid an overdosage on the rectal wall. Fifteen patients (19%) had remaining pathologically enlarged lnn, which were implemented for SIB.

The maximal tolerated dose to the rectum and sigmoid was 66.9 Gy ($NID_2$ of 76 Gy for $\alpha/\beta$ of 3). The maximal tolerated dose received by 30%, 40% and 50% of the volume of the rectum and sigmoid was 63.3 Gy ($NID_2$ of 70 Gy for $\alpha/\beta$ of 3), 60.1 Gy ($NID_2$ of 65 Gy for $\alpha/\beta$ of 3) and 56.9 Gy ($NID_2$ of 60 Gy for $\alpha/\beta$ of 3), respectively. Since April 2007, the planning criteria for the rectum were adapted confer our publication on late rectal toxicity after recalculation for this hypofractionation scheme with a $\alpha/\beta$ of 3 ($N$ = 69) [13]. The following constraints were then used: the volume of the rectum and sigmoid receiving a dose of 36, 45, 54, 57 and 66 Gy should be kept below 84%, 69%, 59%, 48% and 30%, respectively. The maximal tolerated dose to the bladder and small intestine was 69.3 Gy and 63.3 Gy, respectively. If a plan did not meet all planning objectives, each case was looked at individually and planning criteria were loosened in favor of the organs at risk. An under dosage on the target for example was tolerated if compensation for this under dosage would lead to an unacceptable over dosage on the OAR.

### *IMAT planning procedure and delivery*

Treatment was delivered on an Elekta 18-MV linear accelerator (LINAC, Crawley, UK) ($N$ = 78) or a Clinac ix (Varian Medical Systems, Palo Alto, California, USA) ($N$ = 2). The IMAT technique used on the Elekta LINAC has been described previously [11]. 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). Patients' positioning was controlled by daily portal imaging ($N$ = 78) or cone beam CT ($N$ = 2).