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SHORT COMMUNICATION

Intensity-modulated salvage radiotherapy with simultaneous integrated boost for local recurrence of prostate carcinoma: a pilot study on the place of PET-choline for guiding target volume delineation

^{1,2}AURÉLIEN WAHART, MD, ¹JEAN-BAPTISTE GUY, MD, ¹ALEXIS VALLARD, MD, ³BENJAMIN GEISLER, MD, ¹MAJED BEN MRAD, MD, ⁴ALEXANDER T FALK, MD, ²NATHALIE PREVOT, MD, ¹GUY DE LAROCHE, MD, ¹CHLOÉ RANCOULE, MD, ⁵CYRUS CHARGARI, MD, PhD and ¹NICOLAS MAGNÉ, MD, PhD

¹Department of Radiotherapy, Institut de cancérologie de la Loire—Lucien Neuwirth, Saint-Priest en Jarez, France

²Department of Nuclear Medicine, Hôpital Nord, CHU de Saint Etienne, France

³Centre d'Imagerie Nucléaire, Hôpital Privé de la Loire, Saint Etienne, France

⁴Department of Radiotherapy, Centre Antoine Lacassagne, Nice, France

⁵Radiation Oncology, Hôpital d'Instruction des Armées du Val-de-Grâce, Paris, France

Address correspondence to: Professor Nicolas Magné

E-mail: nicolas.magne@icloire.fr

Objective: The aim of this study was to report the first cases of salvage radiotherapy (RT) using the intensity-modulated radiotherapy (IMRT) with simultaneous integrated boost (SIB) targeted on choline positron emission tomography (PET) uptake in a local recurrent prostate cancer, after a radical prostatectomy.

Methods: Four patients received salvage irradiation for biochemical relapse that occurred after the initial radical prostatectomy. The relapse occurred from 10 months to 6 years with PSA levels ranging from 2.35 to 4.86 ng ml⁻¹. For each patient, an ¹⁸F-choline PET-CT showed a focal choline uptake in prostatic fossa, with standardized uptake value calculated on the basis of predicted lean body mass (SUL) max of 3.3–6.8. No involved lymph node or distant metastases were diagnosed. IMRT doses were of 62.7 Gy (1.9 Gy/fraction, 33 fractions), with a SIB of 69.3 Gy (2.1 Gy/fraction, 33 fractions) to a PET-guided target volume.

Results: Acute toxicities were limited. We observed no gastrointestinal toxicity $\geq$ grade 2 and only one grade 2 genitourinary toxicity. At 1-month follow-up evaluation, no complication and a decrease in PSA level (6.8–43.8% of the pre-therapeutic level) were reported. After 4 months, a decrease in PSA level was obtained for all the patients, ranging from 30% to 70%. At a median follow-up of 15 months, PSA level was controlled for all the patients, but one of them experienced a distant lymph node recurrence.

Conclusion: Salvage irradiation to the prostate bed with SIB guided by PET-CT is feasible, with biological efficacy and no major acute toxicity.

Advances in knowledge: IMRT with PET-oriented SIB for salvage treatment of prostate cancer is possible, without major acute toxicity.

INTRODUCTION

Curative salvage radiotherapy (RT) is the cornerstone of local prostate adenocarcinoma recurrence treatment, after radical prostatectomy (RP).¹ A clinical examination cannot usually determine the site (local, regional and systemic) of the recurrence in case of biochemical relapse (prostate-specific antigen (PSA) > 0.2 ng ml⁻¹). As a consequence, various image modalities were developed. Positron emission tomography (PET) labelled with ¹¹C-choline or with ¹⁸F-choline was shown to be more sensitive than the conventional imaging techniques for detection of prostate cancer recurrence,² with a sensitivity and a specificity (depending on PSA value and PSA kinetics) up to 75.4%

and 82%, respectively.³ As suggested in a recent meta-analysis, choline PET-CT can be proposed as the first image examination for patients with biochemical relapse and PSA levels between 1 and 50 ng ml⁻¹.⁴ Because salvage RT was shown to be more effective when the treatment is delivered at the earliest sign of the recurrence, an early relapse imaging is of primary importance for therapeutic decision.

Intensity-modulated radiation therapy (IMRT) with simultaneous integrated boost (SIB) allows the simultaneous delivery of different doses, to different target volumes, within a single RT fraction. The possibility to determine

the target volume delineation for a recurrent prostate cancer by choline PET-CT has been demonstrated and choline PET-CT was proven to impact the planning target volume (PTV) of patients experiencing salvage RT.^{5,6}

The aim of this pilot study was to report the first cases of salvage RT using IMRT with SIB targeted on choline PET-CT uptake in prostate cancers' local recurrence.

METHODS AND MATERIALS

The institutional review board approved the study, which was conducted in compliance with the Helsinki declaration. All patients signed informed consent.

Patient population

Patients with a local recurrence within the prostatic fossa confirmed by a choline PET-CT, were included in 2013 after multidisciplinary team decision. Inclusion criteria were a biochemical relapse after previous RP, an intense focal choline uptake near vesicourethral anastomosis in the prostatic fossa and the absence of metastases (confirmed by a CT scan and a bone scintigraphy). All choline PET-CT were performed in the same nuclear medicine department. The patients' characteristics (age, pre-operative D'Amico risk classification, time to biochemical relapse and hormonal treatment) and the prior treatment history (pelvic lymphadenectomy and surgical margins of resection) were reported.

Choline PET-CT characteristics

Choline PET-CT were performed on the same PET-computed tomography (Discovery™, GE Healthcare, Milwaukee, WI). Patients received 2 MBq kg⁻¹ of ¹⁸F-choline (IASOCholine®; AAA, IASON Graz, France). PET was acquired by a time-of-flight technique in 3D mode with a Discovery 690 system. CT images were used for attenuation correction and topographic localization. The emission data were corrected for scatter and attenuation, then reconstructed by a fully OSEM 3D iterative algorithm. Pelvic static acquisition was performed 5- to 10-min post-choline injection. A whole-body scan was acquired 60 min after choline injection. Images were reviewed by a nuclear medicine and molecular imaging physician. Evaluation was based on visual and semiquantitative analysis of SUL_{max} (maximum standard uptake value normalized to lean body mass) to reduce body fat percentage related variability. The uptake in prostatic fossa was considered pathological when it was higher than baseline and associated with a rising SUL_{max} between the two PET-CT acquisitions.

Treatment definition

Simulation CT scan

Maximum delay between the choline PET-CT and the simulation CT scan was 1 week. Patients underwent simulation CT scan on a Discovery CT Simulator (GE Healthcare) in supine position with 2.5-mm slice thickness, without contrast agent infusion.

Volume definition

All plans were delineated and calculated using the Eclipse™ treatment planning system (Varian® Medical Systems, Palo Alto, CA). The clinical target volume (CTV) delineation was based on

the Radiation Therapy Oncology Group Guidelines and included the prostatic fossa and the periprostatic tissue. The planning target volume number 1 (PTV1) was generated using a 5-mm margin to the CTV. The delineation of the choline PET-CT uptake in prostatic bed was performed after PET-CT images fusion based on rigid transformations (Registration; Varian Medical Systems). This biological target volume (BTV) was approved by one nuclear medicine and molecular imaging physician and one radiation oncologist. The BTV was transferred to the contouring and simulation system (Eclipse, SomaVision; Varian Medical Systems). Planning target volume number 2 (PTV2) was generated using an 8-mm margin to the BTV. Segmented organs at risk (OAR) were the femoral heads, the bowel, the bladder and the rectum.

Dosimetry

The calculation was performed with the Eclipse treatment planning system (Varian Medical Systems) based on the AAA algorithm and a grid of 2 mm. The optimization process was based on the iterative algorithm Helios-DVO-10028 (Varian Medical Systems). International commission guidelines on radiation units and measurements (ICRU 83 report) were applied. Dose constraints to OAR were optimized using the QUANTEC dose constraints.⁷

Dose prescription and delivery

Prescribed doses were 62.7 Gy (1.9 Gy/fraction, 33 fractions) to PTV1, and 69.3 Gy (2.1 Gy/fraction, 33 fractions, *i.e.* a biologically equivalent dose of 70 Gy at 2 Gy/fraction) to PTV2. Patients were treated using Varian linear accelerators (Clinac® iX and 2100C upgraded with multi-leaf collimators and an on board imaging system; Varian, Salt Lake City, UT) in IMRT.

Toxicity evaluation and follow-up

The follow-up was calculated from the end of RT. Patients were assessed for toxicity every week during RT, 1 month after RT completion and every 3 months after this. RT-related toxicities were graded using the Common Terminology Criteria for Adverse Events v. 4.0 (CTCAEv4.0). Acute toxicities were defined by toxicity occurrences within 3 months from the beginning of the RT. Late toxicities occurred after these 3 months. Simultaneously, the PSA was assessed 1 month after RT completion and every 3 months after this.

RESULTS

Patient characteristics

Four consecutive patients were treated using IMRT with SIB for a local prostate cancer recurrence, after RP. At the time of the RT, mean age was 66.8 years. At diagnosis, based on D'Amico classification, two patients were staged "intermediate risk", one "low risk" and one "high risk". One patient was diagnosed with positive resection margins. One patient received a 6-month hormonal treatment after surgery, because of a detectable PSA. Patients and prior-to-treatment characteristics are reported in Table 1.

Treatment characteristics

The dose constraints to PTVs and OAR were respected. The mean PTV1 and PTV2 were 188 cm³ (range: 133–255 cm³) and

Table 1. Patient and prior to radiation therapy characteristics

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	52	72	72	71
d'Amico risk stratification ^a	High	Intermediate	Intermediate	Low
Gleason ^a	8 (4 + 4)	7 (3 + 4)	7 (3 + 4)	7 (3 + 4)
PSA ^a	36	15.3	12.5	9.9
Radical prostatectomy	+	+	+	+
Pelvic lymphadenectomy	+	+	+	–
pTNM	pT3a pN0 M0	pT2c pN0 M0	pT2c pN0 M0	pT2a Nx M0
Resection margins	R1	R0	R0	R0
Post-operative detectable PSA	–	–	–	+
Short hormonal treatment ^b	–	–	–	+
Adjuvant radiotherapy	–	–	–	–
Long hormonal treatment ^c	–	–	–	–
Time to biochemical relapse (months)	10	85	29	88

PSA, prostate-specific antigen.

^aIn clinical pre-operative setting.^bIn 6-month duration.^cIn 36-month duration.

21 cm³ (range: 12–40 cm³), respectively. The mean dose received by 95% (D95) of the PTV1 and PTV2 were 61.4 and 68.4 Gy, respectively. The mean maximal dose received by the PTV1 and PTV2 were 64.0 and 70.8 Gy, respectively. The mean

percentage of bladder and rectal wall volume receiving at least 60 Gy (V₆₀) were 34% (21–41%) and 24% (20–31%), respectively. PTV and OAR dose–volume histograms are resumed in Figure 1.

Figure 1. Delineation of PTV1 (clear blue) and PTV2 (red), and HDV of PTV1 (clear blue), PTV2 (red), the bladder (blue), the rectum (brown) and the femoral heads (grey). PTV, planning target volume. For colour image see online.

Toxicities

The median follow-up was 15 months (range: 15–23 months). No grade 3, 4 or 5 toxicities were reported. One acute grade 2 genitourinary toxicity was reported (pollakiuria). One patient experienced acute grade 1 gastrointestinal toxicity (diarrhoea). The other two patients experienced grade 1 genitourinary (pollakiuria) and gastrointestinal (diarrhoea) toxicities. Two months after RT completion, all acute toxicities were resolved. Three patients experienced late toxicities at last follow-up. One grade 2 digestive toxicity was reported, with bleeding haemorrhoids. One grade 1 digestive toxicity (haemorrhoids) and one grade 1 urinary toxicity (pollakiuria) were also diagnosed.

Efficacy

At last follow-up, all patients were alive. One month after RT, the mean PSA level decreased for all patients [from 3.22 ng ml⁻¹ (range: 2.77–4.86 ng ml⁻¹) to 2.37 ng ml⁻¹ (range: 2.19–2.70 ng ml⁻¹)] corresponding to a decrease of 7–44%. Three months later, the PSA decreased with values ranging from 0.86 to 1.55 ng ml⁻¹, corresponding to a decrease of 29–64% compared with the first PSA measurement and a decrease of 34–70% compared with the PSA value before the salvage RT. At last follow-up, PSA level was stable, in constant decline or undetectable for all but one patient. One patient presented a biochemical recurrence 11 months after the salvage radiation therapy. The choline PET-CT confirmed an abnormal uptake on one left iliac lymph node. This patient could be included in the GETUG P07 protocol and SIB-IMRT could be performed again, concurrently with a hormonal treatment. 54 Gy/1.8 Gy on pelvic lymph nodes, with a 66 Gy/2.2 Gy boost on the abnormal PET-CT uptake were delivered in 30 fractions. 23 months after the initial radiation therapy, the PSA level was undetectable. Data on efficacy are summarized in Table 2.

DISCUSSION

In case of a biochemical relapse, all conventional imaging modalities have shown a limited sensitivity for the relapsing site detection. The choline PET-CT has the advantage to localize all sites of the disease with a good sensitivity and specificity.³ Of course, PET-CT sensitivity depends on the PSA value, and the present study could not have been conducted if the PET-CT had been performed at time of biochemical recurrence (PSA > 0.2 ng ml⁻¹), because of the low sensitivity of the choline PET at these PSA values. It is well recognized that the salvage

radiation therapy probably has better results when it is performed on patients with a PSA < 0.5 ng ml⁻¹. The present study highlights particular cases where the salvage RT cannot be performed at low values of PSA, either because of an extremely fast rising of the PSA level (Patient 1: +2 ng l⁻¹ in 9 months) or because of an elderly age and reluctance to treat patients with rising PSA (Patients 2, 3 and 4). In these specific situations, the choline PET-CT might improve the salvage RT's efficacy, with a higher dose delivered on the detected local recurrence area. This strategy is not validated and should not be an option for patients with low PSA values, since it is not ethical to wait until the PSA is rising to high levels to be able to find a corresponding localization on the PET-CT. However, salvage RT indications in patients with a PSA level > 1 ng ml⁻¹ is becoming a daily routine situation, especially among a geriatric population that wants to defer the treatment as much as possible. In these particular cases, the PET-CT-guided integrated dose escalation could be a good treatment option. In the present study, the delineation of the choline uptake volume was performed manually, based on a visual analysis. The manual delineation of target volumes is the most used technique, despite its highly operator-dependent nature. Automated delineation might not only reduce the operator's error and subjectivity, improve the reproducibility, but also increase the volumes.⁸ Several studies described different techniques for the delineation of volumes, using the choline uptake for salvage RT after an initial irradiation. Even so, the choice of the optimal BTV delineation technique remains an unanswered question. Pinkawa *et al*⁹ defined the BTV using a tumour-to-background uptake ratio >2 in choline PET-CT. Wang *et al*¹⁰ suggested that the semiautomated techniques might replace the manual delineation for partial prostate reirradiation especially with the threshold-based approaches with a median value ≈44%. The post-operative volumes delineation is also a controversial matter. Malone *et al*¹¹ compared four of the guidelines and reported that the recommended CTV was significantly different between all these guidelines. A recent study¹² described an optimal target volume for the salvage RT, including 97% of the suspected tumour recurrences.

To our knowledge, the present study is the first report on IMRT with an integrated boost and a dose escalation in the prostatic fossa. Only one study described a salvage RT after a RP with integrated boost targeted on local relapses in the prostatic bed visualized on endorectal MRI but no data on efficacy was

Table 2. Data on efficacy

Characteristics	Patient 1 ^a	Patient 2	Patient 3	Patient 4
Initial PSA, before radical prostatectomy ^b	36.00	15.30	12.51	9.94
PSA at biochemical recurrence (baseline) ^b	2.77	2.89	2.35	4.86
M1 post-salvage radiotherapy PSA ^b	2.39	2.19	2.19	2.70
M4 post-salvage radiotherapy PSA ^b	0.86	0.95	1.55	1.45
PSA at last follow-up ^b	<0.03	0.23	1.59	0.5
Month post-salvage radiotherapy	M23	M15	M17	M15

M, month; PSA, prostate-specific antigen.

^aPatient who was diagnosed with a biochemical recurrence 11 months post-salvage radiation therapy.

^bAll PSA values are given in nanograms per millilitre.

provided.¹³ Regarding the acute toxicities, no major toxicities were reported, in accordance with other authors.^{14,15} Regarding the efficacy, although the very small number of patient is a limitation, the image-guided radiation therapy with choline PET might be an attractive solution, in the particular cases of biochemical relapses with PSA values >1.0. The development of more specific PET radiotracers (e.g. prostate-specific membrane antigen) or hybrid PET-MRI, which could improve target volume delineation, is also truly challenging. The PET-CT using prostate-specific membrane antigen (PSMA) (68Ga-labelled-PSMA PET/CT) might be a very interesting option in a close future. Preliminary studies suggested a better sensitivity and specificity compared to the choline PET, especially when it is associated with low PSA levels (<0.5 ng ml⁻¹).¹⁶ Early imaging of targets in case of a biochemical relapse might allow image-guided dose escalation with a PSA level <0.5 ng ml⁻¹.

CONCLUSION

The present pilot study suggests that a salvage RT of a local recurrent prostate cancer confirmed by choline PET-CT can be performed with IMRT-SIB. Dose escalation on the choline uptake could be performed without any excessive acute toxicity and with acceptable efficacy. These results are very preliminary and should be confirmed by a future phase I/II trial evaluating the true clinical benefit of this strategy. Salvage radiation therapy should be performed when PSA <0.5 ng ml⁻¹ for a maximal efficacy, indeed. PET-CT-guided integrated dose escalation could be a treatment option only for patients who decide not to be treated by salvage RT as soon as the biochemical relapse is diagnosed.

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