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Salvage involved-field and extended-field radiotherapy in PET-positive nodal recurrent prostate cancer: outcomes and patterns of failure

Adeline Pêtre[1] MD, Magali Quivrin[2] MD, Nathalie Briot[3] BS, Jihane Boustani[2] MD, Etienne Martin[2] MD, Igor Bessieres[4] MS, Alexandre Cochet[5] PhD, Gilles Créhange[6] PhD

[1] Department of Radiation Oncology, Centre Léon Bérard, Lyon, France
[2] Department of Radiation Oncology, Centre Georges François Leclerc, Dijon, France
[3] Department of Biostatistics Unit, Centre Georges François Leclerc, Dijon, France
[4] Department of Medical Physics and Radiation Oncology, Centre Georges François Leclerc, Dijon, France
[5] Department of Nuclear Medicine, Centre Georges François Leclerc, Dijon, France
[6] Department of Radiation Oncology, Institut Curie, Saint-Cloud, France

Short running title: Nodal salvage radiotherapy in prostate cancer

Corresponding author: Adeline Pêtre, Department of Radiation Oncology, Centre Léon Bérard, Lyon, France, mail address: adelinepetre@hotmail.fr

Statistical analysis author's: Nathalie Briot, Department of Biostatistics, Centre Georges François Leclerc, 1 rue Professeur Marion, Dijon, mail address: nbriot@cgfl.fr

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Abstract

Introduction: The optimal salvage pelvic treatment for nodal recurrences in prostate cancer is not yet clearly defined. We aimed to compare outcomes of salvage involved-field radiotherapy (s-IFRT) and salvage extended-field radiotherapy (s-EFRT) for positron emission tomography/computed tomography (PET/CT)-positive nodal-recurrent prostate cancer and to analyze patterns of progressions after salvage nodal radiotherapy.

Materials and methods: Patients with ^{18}F-fluorocholine or ^{68}Ga prostate specific membrane antigen ligand PET/CT-positive nodal-recurrent prostate cancer and treated with s-IFRT or s-EFRT were retrospectively

selected. Time to biochemical failure (TTF), time to palliative androgen deprivation therapy (ADT) and distant metastasis-free survival (DMFS) were analyzed.

Results: Between 2009 and 2019, 86 patients were treated with salvage nodal radiotherapy, 38 with s-IFRT and 48 with s-EFRT. After a median follow-up of 41.9 months (5.4–122.1 months), 47 patients presented a further relapse, 31 after s-IFRT and 16 after s-EFRT with only one in-field relapse. The median time to palliative ADT was 24.8 months (95% CI: 13.3-93.5 months) in the s-IFRT group and not yet reached (95% CI: 40.3 months to not yet reached) in the s-EFRT group (p = 0.010). The 3-year biochemical failure-free rate was 70.2% (95% CI: 51.5-82.9%) with s-IFRT and 73.9% (95% CI: 55.4-85.7%) with s-EFRT (p=0.657). The 3-year DMFS was 74.1% (95% CI: 56.0-85.7%) with s-IFRT and 82.0% (95% CI: 63.0-91.8%) with s-EFRT (p=0.338).

Conclusion: s-EFRT and s-IFRT for PET-positive nodal-recurrent prostate cancer provide excellent local control. Time to palliative ADT was longer following s-EFRT than following s-IFRT.

Abbreviations: ADT: androgen deprivation therapy, BF: biochemical failure, DMFS: distant metastasis-free survival, FCH PET/CT: ^{18}F-fluorocholine positron emission tomography/computed tomography, LA: lumboaortic, LN: lymph node, MDT: metastasis-directed therapies, PSMA PET/CT: ^{68}Ga prostate specific membrane antigen ligand positron emission tomography/computed tomography, RT: radiotherapy, s-IFRT: salvage involved-field radiotherapy, s-EFRT: salvage extended-field radiotherapy, TTF: Time to biochemical failure

Key words: prostatic neoplasms, recurrence, lymph nodes, positron emission tomography computed tomography, salvage therapy, radiotherapy

Introduction

Despite the improvement of therapeutic strategies in the management of localized prostate cancer in recent years, 20 to 50% of patients present biochemical failure (BF) [1–6]. Conventional imaging (such as computed tomography (CT) scan or bone scintigraphy) performed in cases of BF usually locates recurrences at an already advanced stage, with diffuse nodal or distant progression. The only treatments proposed for these patients are palliative systemic therapies, including ADT [7], which have substantial side effects that impair quality of life [8]. New functional imaging has recently been developed in prostate cancer, opening up new therapeutic perspectives. ^{18}F-fluorocholine Positron Emission Tomography/CT (FCH PET/CT) and more recently ^{68}Ga prostate specific membrane antigen ligand PET/CT (PSMA PET/CT) are increasingly being performed to stage patients with BF after curative treatment for localized prostate cancer. They have better sensitivity and specificity than conventional imaging and make it possible to identify recurrence sites with accuracy at an earlier stage [9–12]. The earlier detection of nodal and metastatic relapses, potentially making patients eligible for local salvage treatment, has led to a growing interest to treat these patients with curative intent. Several studies have shown promising results, suggesting that salvage local treatments can delay the initiation of palliative androgen deprivation therapy (ADT) and improve progression-free survival (PFS) with acceptable toxicities [13–15]. However, the modalities for salvage treatment in LN recurrences of prostate cancer are not clearly established [16,17] as no published randomized studies to date have assessed different local salvage treatments.

Moreover, as some patients will inevitably progress after individualized salvage treatment, we need better knowledge of the course of the disease in this population in order to properly select patients and to propose the most appropriate therapeutic strategy.

The objective of this study was two-fold. First, we assessed and compared the feasibility and the efficacy of salvage nodal involved-field radiotherapy (s-IFRT) and salvage nodal extended-field radiotherapy (s-EFRT) in patients with FCH or PSMA PET-positive nodal recurrence from prostate cancer. Second, we analyzed the patterns of failure after salvage nodal radiotherapy in this same population.

Materials and Methods

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Study population

After institutional review board approval, we retrospectively identified patients with nodal recurrence after local curative therapy for prostate cancer, detected with FCH or PSMA PET/CT and treated with salvage radiotherapy with curative intent in our institution.

FCH and PSMA PET/CT were performed as described previously [18,19].

Radiotherapy

An abdominopelvic planning CT scan with 2.5 mm slice thickness was performed starting 5 cm above the diaphragm and ending 2 cm below the ischial tuberosities. Contrast agent was injected in the absence of contraindications. Patients were immobilized in the supine position in a custom blue bag device (VacLok® system; CIVCO Medical Solutions, Orange City, IA).

Organs at risk (OAR) were the rectum in toto, the bladder in toto and the bowel loops (defined as the entire abdominal cavity minus the clinical target volume (CTV); 2cm above and below the CTV) and the kidneys.

For s-EFRT, a prophylactic CTV including the whole pelvis was delineated as defined by the RTOG consensus atlas. In patients with PET-positive LN in the common iliac region or lower para-aortic region, this CTV was extended up to the L2/L3 space (9). When LA PET-positive LN were involved, the prophylactic CTV was extended up to the renal arteries and a 7-mm margin around the LA vessels anteriorly and laterally (minus the bowel loops, the bones and the muscles). For the boost to PET-positive LN, GTV was defined as any PET-positive LN delineated after fusion between the planning CT and the CT images from PET/CT. Each CTV was equal to the GTV. A 5-mm margin around the GTV was applied to obtain each PTV. For the bowels, the dose received by 2% of the bowel volume had to be <60 Gy, the mean dose had to be 30 Gy and the volume of bowels receiving 30 Gy had to be <30%. The prescription to the PTV was expressed in terms of minimum and maximum acceptable dose: 100% of the PTV was covered by the 95% isodose and no point dose within the PTV could exceed 110%.

For s-IFRT, Gross tumour volume (GTV) was defined as any PET-positive LN delineated after fusion between the planning CT and the CT images from PET/CT. Each CTV was equal to the GTV. A 5-mm margin around the GTV was applied to obtain each planning target volume (PTV). Three-dimensional radiotherapy (3D-RT) or intensity modulated radiotherapy (IMRT) were used with the same dose constraints as described for s-EFRT. For stereotactic body radiation therapy (SBRT), the absorbed dose to 0.5 cm3 of any part of the gastrointestinal (GI) tract had to be 30 Gy with a maximum of 36 Gy. For lumboaortic (LA) LN treated with SBRT, the maximum absorbed doses to the kidneys and spinal cord had to be <12 Gy and <18 Gy, respectively. Treatment was prescribed to the periphery of the PTV (80% of the dose covering 100% of the PTV) and dose distributions were normalized to the isocentre.

The choice of irradiation was determined according to the previous treatments, the characteristics of the patient and the practices of the physician.

Irradiation was performed on either a TrueBeam, Trilogy or Novalis linear accelerator equipped with a 120-leaf collimator (Varian Medical Systems, Palo Alto, California) depending on the technique used. A cone beam CT (CBCT) scan was performed before each fraction for all patients over the entire course of the radiotherapy to set-up patients and verify targets; all shifts were corrected with no minimal action level. In each treatment group, all techniques of radiotherapy were included and the dose prescription was decided at the discretion of the physician.

Treatment characteristics are summarized in table 2.

Follow-up after salvage nodal radiotherapy

Follow-up was performed as described previously [18]. For patients with a second clinical relapse after salvage radiotherapy without diffuse metastases, imaging was fused with the planning CT of the salvage radiotherapy. The second relapses were delineated and classified as out of field (if <20% was within the 95% isodose line with normofractionated treatment or within the 80% isodose line with SBRT), marginal (if 20-95%

was within the 95% isodose in normofractionated treatment or within the 80% isodose in SBRT) or in field (if 95% was within the 95% isodose in normofractionated treatment or within the 80% isodose in SBRT) [20,21]. Oligometastases were defined as five or fewer metastases.

Statistical analysis

Median follow-up times were calculated using the reverse Kaplan-Meier method.

In this analysis, a BF was defined using the Phoenix definition [22].

Time to biochemical failure (TTF) was defined as the time between the PET/CT diagnosing the nodal relapse before salvage nodal RT and the BF. Time to palliative ADT was defined as the time between the PET/CT diagnosing the nodal relapse before salvage nodal RT and the initiation of palliative life-long ADT. Distant metastasis-free survival (DMFS) was defined as the time between the PET/CT diagnosing the nodal relapse before salvage nodal RT and distant metastatic progression (including supra-diaphragmatic LN, bone and visceral metastases) or death.

The outcomes were determined by the Kaplan-Meier method. Hazard ratios (HR) and 95% confidence intervals (CI) for univariate and multivariate analyses were estimated using a Cox's proportional hazards regression model with a backward procedure.

The s-IFRT and s-EFRT groups were compared using Fisher's test or the chi-squared test for categorical variables, and Student's t test or the Mann-Whitney test for quantitative variables (depending on the normality of the distribution).

Statistical analyses were performed using SAS 9.4 software.

Results

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Characteristics of primary disease and at the time of first PET-positive nodal relapses

Between January 2009 and April 2019, 86 patients with BF after primary local therapy for prostate cancer had FCH PET/CT or PSMA PET/CT, on which only nodal relapses were diagnosed (82 using FCH PET/CT and 4 using PSMA PET/CT).

Patients' characteristics at diagnosis and at the time of first PET-positive nodal relapses are summarized in tables 1 and 2, respectively.

At the time of primary disease, 89% were initially treated with exclusive or postoperative radiotherapy in the s-IFRT group and 66% in the s-EFRT group. 21% and 12.5% had pelvic irradiation in the s-IFRT group and in the s-EFRT group, respectively.

48 patients were treated with s-EFRT and 38 with s-IFRT. There was a significantly higher number of PET-positive LN in the s-EFRT group than in the s-IFRT group (p=0.019). In the s-IFRT population, almost 87% of patients had only one or two positive LN compared to less than 60% in the s-EFRT group. The topography of involved LN was comparable in the two populations, more than a quarter of patients had an extra-pelvic nodal recurrence. 84% of patients in the s-IFRT group were treated with SBRT, the median dose per fraction to the PET-positive LN was 7.5Gy. Almost 96% of patients in the s-EFRT group were treated with IMRT/volumetric modulated arc therapy (VMAT) techniques including 31% with a simultaneous integrated boost. The median prophylactic total dose to the pelvis was 45Gy and the median total dose to the PET-positive LN was 60Gy in the s-EFRT group. 29 patients in the s-EFRT group and 3 in the s-IFRT group received concomitant/adjuvant ADT.

Acute and late toxicities of salvage nodal radiotherapy

There was no significant difference between the two groups for acute GI and GU toxicities. More than 89% of patients did not experience acute GI and GU toxicities. No grade 3 or more acute GI and GU toxicity was observed.

There was no significant difference between the two groups for late GI and GU toxicities. More than 73% of patients did not experience late GI and GU toxicities. One patient had grade 4 late GI and GU in the s-EFRT group.

Acute and late toxicities are reported in details in Table 3.

Time to biochemical failure

For the whole population, the median follow-up was 41.9 months (5.4-122.1 months). In the s-IFRT and s-EFRT populations, the median follow-up was 63.2 months (6.2-122.1 months) and 33.8 months (5.4-93.2 months), respectively.

Overall, 35 patients had a BF after nodal salvage radiotherapy, 20 in the s-IFRT group (52.6%) and 15 in the s-EFRT group (31.3%). For the whole population, the median TTF was 60 months (95% CI: 40.1-82.4 months) and the 3-year BF-free rate was 72.3% (95% CI: 59.8-81.5%). In the s-IFRT and in the s-EFRT populations, the median TTF was 63.2 months (95% CI: 37-82.4 months) and 58.5 months (95% CI: 38.3 months to not yet reached), respectively, and the 3-year BF-free rate was 70.2% (95% CI: 51.5-82.9%) and 73.9% (95% CI: 55.4-85.7%), respectively (p= 0.657). TTF in both groups is presented in figure 1A.

Univariate and multivariate analyses are reported in Table 4 A. Predictive factors for BF were PSA level at the time of failure>3ng/mL (HR = 3.23, 95%CI: 1.45-7.18, p = 0.004) and >2 PET-positive LN at the time of failure (HR = 3.65, 95%CI: 1.65-8.05, p = 0.001) in multivariate analysis.

Time to palliative ADT

Palliative ADT was introduced after nodal salvage radiotherapy in 35 patients. The median time to palliative ADT for the whole population was 41.9 months (95% CI: 29.1 to not yet reached), the 3-year palliative ADT-free rate was 60.7% (95% CI: 47.9-71.2%). In the s-IFRT and s-EFRT groups, the median time to palliative ADT

was 24.8 months (95% CI: 13.3-93.5 months) and not yet reached (95% CI: 40.3 months to not yet reached), respectively, and the 3-year palliative ADT-free rate was 46.3% (95% CI: 29.3-61.6%) and 73.8 (95% CI: 54.5-85.9%), respectively (p=0.010). Time to palliative ADT following both treatments is presented in Figure 1 B.

The only predictive factor for the initiation of palliative ADT was PSA >3ng/mL at the time of nodal failure (HR = 3.46, 95%CI: 1.58-7.58, p = 0.002, in multivariate analysis). Patients treated with s-EFRT were less likely to start palliative ADT (HR = 0.43, 95%CI 0.20-0.91, p = 0.028 in multivariate analysis). Univariate and multivariate analyses are detailed in Table 4 B.

Distant metastasis-free survival

At last follow-up, 26 patients had distant progression, 17 in the s-IFRT group and 9 in the s-EFRT group. For the whole population, the median DMFS was 82.4 months (95% CI: 52.67 to not yet reached) and the 3-year DMFS was 78.3% (95% CI: 66.3-86.4%). In the s-IFRT and s-EFRT populations, the median DMFS was 82.4 months (95% CI: 39.0 months to not yet reached) and not yet reached (95% CI: 50.1 months to not yet reached), respectively, and the 3-year DMFS was 74.1% (95% CI: 56.0-85.7%) and 82.0% (95% CI: 63.0-91.8%), respectively (p=0.338). DMFS of both treatment groups is shown in figure 1 C.

Predictive factors for distant metastasis were >2 PET positive-LN (HR = 4.33, 95% CI: 1.80-10.42, p = 0.001) and PSA > 3ng/mL at the time of nodal failure (HR = 3.02, 95% CI: 1.25-7.34, p = 0.015) in multivariate analysis. Univariate and multivariate analyses are detailed in table 4 C.

Deaths

6 patients died, all of whom were in the s-IFRT group. 2 patients died because of the disease; the cause of death for the other four patients was unknown.

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Patterns of clinical progression after salvage nodal radiotherapy

Overall, 47 patients out of 86 relapsed after salvage radiotherapy, 31 in the s-IFRT group and 16 in the s-EFRT group.

Regarding the second relapse, 33 patients developed clinical relapses. There was 1 local recurrence in the s-IFRT group that was out of field of the nodal salvage radiotherapy. There were 14 pelvic and/or LA nodal recurrence, 12 in the s-IFRT group and 2 in the s-EFRT group. Of the 9 relapses evaluated, all were out of field of the nodal salvage radiotherapy. There was 1 local and LA nodal recurrence in the s-EFRT group. Only the nodal relapse was in the field of nodal salvage radiotherapy. There were 10 distant metastatic recurrences: 3 in the s-IFRT group and 7 in the s-EFRT group (3 patients with supra diaphragmatic LN, 6 bone metastases and 1 pulmonary metastasis). 7 were oligometastatic and all were out of field of nodal salvage radiotherapy. There were 5 pelvic and/or LA nodal and distant metastatic recurrences: 4 in the s-IFRT group and one in the s-EFRT group. Location according to the previous irradiation field was not evaluated because all patients had a diffuse supra diaphragmatic and bone metastatic progression. And there were 2 local, pelvic and/or LA nodal and distant metastatic recurrence: 1 in the s-IFRT group and 1 in the s-EFRT group. All patients also presented diffuse supra diaphragmatic and bone metastatic progression.

The distribution of clinical second relapses are presented in figure 2.

At the second relapse, 9 patients were treated with new salvage radiotherapy (with or without concomitant ADT). One of these patients received a third salvage radiotherapy after new nodal failure.

Discussion

The emergence of FCH and thereafter PSMA PET/CT has made it possible to detect relapse sites in prostate cancer earlier and led to an evolution in therapeutic strategies in recent years. Different local salvage

treatments, also named metastasis-directed therapies (MDT), were assessed to provide local control and to delay palliative ADT.

A randomized phase II trial compared the time to the start of palliative ADT following surveillance or MDT (with surgery or SBRT) for PET-positive nodal and/or distant oligorecurrent prostate cancers. The study showed longer ADT-free survival with MDT than with surveillance (median ADT-free survival was 21 months (80% CI: 14-29 months) and 13 months (80% CI: 12-17 months), respectively, HR = 0.60 (80% CI: 0.40-0.90), p = 0.11). Tolerance was good in the MDT group with no grade   2 toxicity observed and quality of life was similar in both groups [14].

Ost et al also showed a good tolerance of salvage SBRT for FCH PET-positive nodal oligorecurrences with similar PFS [23,24]. But more than half of patients had a further relapse after SBRT. Most relapses were in LN. Equivalent results were found with surgical treatments [25]. In our population, almost 82% of patients treated with s-IFRT relapsed. The most frequent location of relapses following s-IFRT were also in LN. However, none of the nodal relapses were in the irradiation field. These data corroborate others showing that FCH PET/CT misses microscopic disease. Thus, focal salvage treatments, including s-IFRT and nodal dissection, based exclusively on PET-positive LN, seem to be insufficient. The addition of extended-field radiotherapy could potentially delay or even prevent this relapse. Few trials have compared outcomes of s-EFRT (including whole pelvic radiotherapy and a boost of nodal recurrences) with those of s-IFRT in nodal oligorecurrent prostate cancer. In a preliminary analysis, our group showed better TTF with s-EFRT than with s-IFRT (median TTF not yet reached and 39.7 months (95% CI: 10.9 months to not yet reached), respectively, p = 0.009) [18]. With a longer follow-up, our study still showed good outcomes with s-EFRT. Although not significant, patients treated with s-EFRT tended, over time, to have better biochemical TTF and DMFS than did those treated with s-IFRT but time to palliative ADT was significantly longer with s-EFRT. A larger retrospective multicentric study confirmed fewer nodal recurrences and longer metastasis-free survival after s-EFRT than after SBRT (HR = 0.50, (95% CI: 0.30-0.85), p = 0.009) [13]. The addition of adjuvant pelvic radiotherapy after lymph node dissection also showed improved PFS [25].

For BF in prostate cancer, the addition of 6 to 24 months of ADT to postoperative radiotherapy compared with radiotherapy alone for microscopic residual disease led to benefits in PFS and overall survival [26,27]. A favorable effect could also be expected in nodal recurrences. The phase II OLIGOPELVIS study assessed the feasibility of s-EFRT (54Gy to the pelvis and 66G to the LN, both 30 fractions) with short-course ADT (6 months) in nodal oligorecurrent prostate cancers [28]. They showed a relatively good tolerance of the treatment combination [15]. In our study, concomitant/adjuvant ADT was associated with radiotherapy in 61% of patients in the s-EFRT group versus less than 8% in the s-IFRT group. We also found similar, low toxicity in the two groups, thereby confirming the feasibility of s-IFRT and s-EFRT radiotherapy associated or not with concomitant /adjuvant ADT.

In terms of patterns of failure after salvage nodal radiotherapy, we found an excellent local control and a trend towards a shift in locations. Almost 64% of pelvic LN relapses treated with salvage radiotherapy, the disease progressed to extra-pelvic LN or became metastatic, and almost 64% of extra-pelvic LN relapsed with bone metastases.

PSMA PET/CT performed following BF of prostate cancer showed better detection of relapses with low PSA values. Currently, very few data concerning MDT guided specifically with PSMA PET/CT are available. No interpretation could be given in our study; there were only four nodal relapses diagnosed with PSMA PET/CT and one of these presented diffuse progression. In a retrospective study that assessed patients exclusively treated with PSMA PET/CT-guided radiotherapy for recurrent oligometastatic prostate cancer, 59% of oligorecurrences were LN and were treated with an extended irradiation field. The authors showed that salvage radiotherapy for PSMA PET/CT-positive oligometastases resulted in effective local control with prolonged biochemical PFS (median of 22 months (95% CI: 20.2-24.0 months)). They also reported a shift in new progressions towards distant LN and skeletal metastases [29].

So far, most published studies on MDT, including those discussed here, have been small, retrospective studies with heterogeneous populations, and have included distant and nodal recurrences. As a result, they cannot be used to establish the optimal management for nodal only oligorecurrent prostate cancers [13].

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Further specific prospective studies are needed. Currently there are two ongoing randomized trials. The European PEACE V study is a randomized phase II trial assessing the impact of adding whole pelvic radiotherapy to MDT (salvage lymph node dissection or SBRT) associated with 6 months of ADT in oligorecurrent nodal prostate cancers. The primary endpoint is metastasis-free survival [30]. OLIGOPELVIS 2 is a french randomized phase III trial, based on the hypothesis that salvage pelvic radiotherapy may prolong the interval between the first and second intermittent ADT in nodal oligorecurrent prostate cancer. The authors are comparing intermittent ADT (6 months) alone with intermittent ADT associated with s-EFRT. In these two trials, nodal recurrences will be detected with FCH or PSMA PET/CT.

Conclusion

Our study showed the feasibility of s-IFRT and s-EFRT for PET-positive nodal-recurrent prostate cancer with excellent local control. Time to the initiation of palliative ADT was longer following S-EFRT than following s-IFRT.

References

[1]   Kupelian PA, Potters L, Khuntia D, Ciezki JP, Reddy CA, Reuther AM, et al. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or =72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. Int J Radiat Oncol Biol Phys 2004;58:25–33. https://doi.org/10.1016/s0360-3016(03)00784-3.

[2]   Bolla M, Maingon P, Carrie C, Villa S, Kitsios P, Poortmans PMP, et al. Short Androgen Suppression and Radiation Dose Escalation for Intermediate- and High-Risk Localized Prostate Cancer: Results of EORTC Trial 22991. J Clin Oncol 2016;34:1748–56. https://doi.org/10.1200/JCO.2015.64.8055.

[3]   Bolla M, Collette L, Blank L, Warde P, Dubois JB, Mirimanoff R-O, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Lancet 2002;360:103–6. https://doi.org/10.1016/s0140-6736(02)09408-4.

[4]   Morris WJ, Tyldesley S, Rodda S, Halperin R, Pai H, McKenzie M, et al. Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer. Int J Radiat Oncol Biol Phys 2017;98:275–85. https://doi.org/10.1016/j.ijrobp.2016.11.026.

[5]   McCormick BZ, Mahmoud AM, Williams SB, Davis JW. Biochemical recurrence after radical prostatectomy: Current status of its use as a treatment endpoint and early management strategies. Indian J Urol 2019;35:6–17. https://doi.org/10.4103/iju.IJU_355_18.

[6]   Lépinoy A, Cochet A, Cueff A, Cormier L, Martin E, Maingon P, et al. Pattern of occult nodal relapse diagnosed with (18)F-fluoro-choline PET/CT in prostate cancer patients with biochemical failure after prostate-only radiotherapy. Radiother Oncol 2014;111:120–5. https://doi.org/10.1016/j.radonc.2014.03.008.

[7]   Rozet F, Hennequin C, Beauval J-B, Beuzeboc P, Cormier L, Fromont-Hankard G, et al. [French ccAFU guidelines - Update 2018-2020: Prostate cancer]. Prog Urol 2018;28 Suppl 1:R81–132. https://doi.org/10.1016/j.purol.2019.01.007.

[8]   Ahmadi H, Daneshmand S. Androgen deprivation therapy: evidence-based management of side effects. BJU Int 2013;111:543–8. https://doi.org/10.1111/j.1464-410X.2012.11774.x.

[9]   Evangelista L, Zattoni F, Guttilla A, Saladini G, Zattoni F, Colletti PM, et al. Choline PET or PET/CT and biochemical relapse of prostate cancer: a systematic review and meta-analysis. Clin Nucl Med 2013;38:305–14. https://doi.org/10.1097/RLU.0b013e3182867f3c.

[10]   Evangelista L, Briganti A, Fanti S, Joniau S, Reske S, Schiavina R, et al. New Clinical Indications for (18)F/(11)C-choline, New Tracers for Positron Emission Tomography and a Promising Hybrid Device for Prostate Cancer Staging: A Systematic Review of the Literature. Eur Urol 2016;70:161–75. https://doi.org/10.1016/j.eururo.2016.01.029.

[11]   Eiber M, Maurer T, Souvatzoglou M, Beer AJ, Ruffani A, Haller B, et al. Evaluation of Hybrid ^{68}Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. J Nucl Med 2015;56:668–74. https://doi.org/10.2967/jnumed.115.154153.

[12]   Beheshti M, Manafi-Farid R, Geinitz H, Vali R, Loidl W, Mottaghy FM, et al. Multi-phasic 68Ga-PSMA PET/CT in detection of early recurrence in prostate cancer patients with PSA < 1 ng/ml: a prospective study of 135 cases. J Nucl Med 2020. https://doi.org/10.2967/jnumed.119.238071.

[13]   Ost P, Bossi A, Decaestecker K, De Meerleer G, Giannarini G, Karnes RJ, et al. Metastasis-directed therapy of regional and distant recurrences after curative treatment of prostate cancer: a systematic review of the literature. Eur Urol 2015;67:852–63. https://doi.org/10.1016/j.eururo.2014.09.004.

[14]   Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial - PubMed n.d. https://pubmed-ncbi-nlm-nih-gov.docelec.univ-lyon1.fr/29240541/ (accessed January 30, 2021).

[15]   Vaugier L, Palpacuer C, Rio E, Goineau A, Pasquier D, Buthaud X, et al. Early Toxicity of a Phase 2 Trial of Combined Salvage Radiation Therapy and Hormone Therapy in Oligometastatic Pelvic Node Relapses of Prostate Cancer (OLIGOPELVIS GETUG P07). Int J Radiat Oncol Biol Phys 2019;103:1061–7. https://doi.org/10.1016/j.ijrobp.2018.12.020.

[16]   Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol 2017;71:630–42. https://doi.org/10.1016/j.eururo.2016.08.002.

[17]   Professionals S-O. EAU Guidelines: Prostate Cancer. Uroweb n.d. https://uroweb.org/guideline/prostate-cancer/#6 (accessed August 25, 2020).

[18]   xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.

[19]   xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.

[20]   Rouard N, Peiffert D, Rio E, Mahé M-A, Delpon G, Marchesi V, et al. Intensity-modulated radiation therapy of anal squamous cell carcinoma: Relationship between delineation quality and regional recurrence. Radiother Oncol 2019;131:93–100. https://doi.org/10.1016/j.radonc.2018.10.021.

[21]   Yang X, Ren H, Yu W, Zhang X, Sun Y, Shao Y, et al. Analysis of Clinical Target Volume Delineation in Local-regional Failure of Nasopharyngeal Carcinoma after Intensity-modulated Radiotherapy. J Cancer 2020;11:1968–75. https://doi.org/10.7150/jca.39588.

[22]   Roach M, Hanks G, Thames H, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006;65:965–74. https://doi.org/10.1016/j.ijrobp.2006.04.029.

[23] Decaestecker K, De Meerleer G, Lambert B, Delrue L, Fonteyne V, Claeys T, et al. Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence. Radiat Oncol 2014;9:135. https://doi.org/10.1186/1748-717X-9-135.

[24] Ost P, Jereczek-Fossa BA, Van As N, Zilli T, Tree A, Henderson D, et al. Pattern of Progression after Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Nodal Recurrences. Clin Oncol (R Coll Radiol) 2016;28:e115-120. https://doi.org/10.1016/j.clon.2016.04.040.

[25] Rischke HC, Schultze-Seemann W, Wieser G, Krönig M, Drendel V, Stegmaier P, et al. Adjuvant radiotherapy after salvage lymph node dissection because of nodal relapse of prostate cancer versus salvage lymph node dissection only. Strahlenther Onkol 2015;191:310–20. https://doi.org/10.1007/s00066-014-0763-5.

[26] Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial - PubMed n.d. https://pubmed-ncbi-nlm-nih-gov.docelec.univ-lyon1.fr/31629656/ (accessed February 7, 2021).

[27] Shipley WU, Seiferheld W, Lukka HR, Major PP, Heney NM, Grignon DJ, et al. Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer. N Engl J Med 2017;376:417–28. https://doi.org/10.1056/NEJMoa1607529.

[28] Supiot S, Rio E, Pacteau V, Mauboussin M-H, Campion L, Pein F. OLIGOPELVIS – GETUG P07: a multicentre phase II trial of combined salvage radiotherapy and hormone therapy in oligometastatic pelvic node relapses of prostate cancer. BMC Cancer 2015;15. https://doi.org/10.1186/s12885-015-1579-0.

[29] Soldatov A, von Klot CAJ, Walacides D, Derlin T, Bengel FM, Ross TL, et al. Patterns of Progression After 68Ga-PSMA-Ligand PET/CT-Guided Radiation Therapy for Recurrent Prostate Cancer. Int J Radiat Oncol Biol Phys 2019;103:95–104. https://doi.org/10.1016/j.ijrobp.2018.08.066.

[30] De Bruycker A, Spiessens A, Dirix P, Koutsouvelis N, Semac I, Liefhooghe N, et al. PEACE V – Salvage Treatment of OligoRecurrent nodal prostate cancer Metastases (STORM): a study protocol for a randomized controlled phase II trial. BMC Cancer 2020;20. https://doi.org/10.1186/s12885-020-06911-4.

Figure captions

Figure 1: Kaplan Meier analysis of probability in both treatment groups for PET-positive nodal recurrences of biochemical failure (A), introduction of palliative androgen deprivation therapy (B) and distant metastasis (C). *S-IFRT = salvage involved-field radiotherapy, s-EFRT = salvage extended-field radiotherapy, ADT = androgen deprivation therapy.*

Figure 2: Migration plot showing the relationship between the location of the first nodal relapse treated with salvage extended-field or involved-field radiotherapy (left side) with the location of the second clinical relapse (right side). *LN = lymph node. If a patient presented different relapse locations, he was classified in the most advanced location (defined in ascending order: local, pelvic lymph node, extra-pelvic lymph node including lumboaortic LN and supra diaphragmatic LN), bone/visceral metastases).*

Table 1: Initial patient characteristics.

		Total (n=86)	s-IFRT (n=38, 44.2%)	s-EFRT (n=48, 55.8%)	p value
T stage (UICC 2002), *n* (%)	1	15 (17.4%)	5 (13.2%)	10 (20.8%)	0.005
	2	40 (46.6%)	17 (44.7%)	23 (47.9%)	
	3	13 (15.1%)	11 (28.9%)	2 (4.2%)	
	Missing	18 (20.9%)	5 (13.2%)	13 (27.1%)	
N stage (UICC 2002), *n* (%)	0	45 (52.3%)	17 (44.7%)	28 (58.3%)	0.005
	1	5 (5.8%)	0 (0%)	5 (10.4%)	
	X	36 (41.9%)	21 (55.3%)	15 (31.3%)	
Gleason score, *n* (%)	6	28 (32.6%)	17 (44.7%)	11 (22.9%)	0.047
	7	34 (39.6%)	14 (36.8%)	19 (39.6%)	
	8	12 (13.9%)	2 (5.3%)	10 (20.8%)	
	Missing	12 (13.9%)	5 (13.2%)	8 (16.7%)	
Baseline PSA value (ng/mL)	Mean (SD)	15.0 (19.6)	18.7 (24.4)	12.1 (14.3)	0.309
	Median [range]	9.3 [3.3 - 129.0]	9.3 [4.0 - 129.0]	8.8 [3.3 - 99.7]	
Primary treatments, *n* (%)					
Radical prostatectomy		60 (69.8%)	29 (76.3%)	31 (64.6%)	0.239
Pelvic lymph node dissection		48 (55.8%)	23 (60.5%)	25 (52%)	0.906
Radical prostatectomy followed by postoperative RT		40 (46.5%)	25 (65.8%)	15 (31.3%)	0.017
Prostate RT		24 (27.9%)	8 (21%)	16 (33.3%)	0.032
Whole pelvic RT		14 (16.3%)	8 (21%)	6 (12.5%)	0.590
Brachytherapy*		3 (3.5%)	1 (2.6%)	2 (4.2%)	1
Concomitant/adjuvant ADT		27 (31.4%)	12 (31.6%)	15 (31.3%)	0.974

S-IFRT = salvage involved-field radiotherapy, s-EFRT = salvage extended-field radiotherapy, RT = radiotherapy, ADT = Androgen deprivation therapy.

*Boost or exclusive brachytherapy

Table 2: Patient characteristics at the time of PET-positive nodal failure.

		Total (n=86)	s-IFRT (n=38, 44.2%)	s-EFRT (n=48, 55.8%)	p value
Age (years)	Mean (SD)	69.6 (7.5)	70.0 (8.1)	69.3 (7.0)	0.676
	Median [range]	70.4 [53.0 - 85.7]	70.3 [54.6 - 84.8]	70.4 [53.0 - 85.7]	
Time from diagnosis of prostate cancer (years)	Mean (SD)	6.4 (4.0)	6.9 (3.9)	6.0 (4.2)	0.347
	Median [range]	5.6 [0.3 - 16.0]	6.5 [1.7 - 14.7]	5.3 [0.3 - 16.0]	
PSA value (ng/mL)	Mean (SD)	4.4 (4.4)	5.1 (5.1)	3.8 (3.7)	0.061
	Median [range]	3.1 [0.2 - 29.2]	3.9 [0.4 - 29.2]	2.5 [0.2 - 19.0]	
Number of PET-positive LN per patient, *n* (%)	Mean (SD)	2.1 (1.8)	1.6 (1.1)	2.5 (2.1)	0.012
	Median [range]	1.0 [1.0 - 12.0]	1.0 [1.0 - 7.0]	2.0 [1.0 - 12.0]	
	1 LN	45 (52.3%)	24 (63.2%)	21 (43.7%)	0.019
	2 LN	16 (18.6%)	9 (23.7%)	7 (14.6%)	
	3 LN	11 (12.8%)	3 (7.9%)	8 (16.7%)	
	4 LN	12 (14%)	1 (2.6%)	11 (22.9%)	
	Missing	2 (2.3%)	1 (2.6%)	1 (2.1%)	
Topography of involved LN per patient, *n* (%)	Common iliac	23 (26.7%)	10 (26.3%)	13 (27%)	0.672
	Internal iliac	20 (23.2%)	7 (18.4%)	13 (27%)	0.202
	External iliac	30 (34.9%)	8 (21%)	22 (45.8%)	0.391
	Obturator	10 (11.6%)	7 (18.4%)	3 (6.25%)	0.663
	Inguinal	2 (2.3%)	1 (2.6%)	1 (2.1%)	NA
	Lumboaortic	24 (27.9%)	9 (23.7%)	15 (31.25%)	0.216
	Mediastinum	1 (1.2%)	1 (2.6%)	0 (0%)	NA
Postoperative salvage RT to prostate bed	Number of patients (%)	12 (14.0%)	0 (0.0%)	12 (25%)	<0.001
	Total dose (Gy), median [range]	68.0 [60.0 - 70.2]	-	68.0 [60.0 - 70.2]	
	Dose per fraction (Gy), median [range]	2.0 [1.8 - 2.2]	-	2.0 [1.8 - 2.2]	
Whole-pelvis irradiation	Number of patients (%)	43 (50.0%)	-	43 (89.6%)	<0.001
	Total dose (Gy), median [range]	46.0 [45.0 - 54.0]	-	46.0 [45.0 - 54.0]	
	Dose per fraction (Gy), median [range]	1.8 [1.8 - 2.2]	-	1.8 [1.8 - 2.2]	
Lumboaortic irradiation	Number of patients (%)	19 (22.1%)	-	19 (39.6%)	<0.001
	Total dose (Gy), median [range]	46.0 [45.0 - 59.4]	-	46.0 [45.0 - 59.4]	
	Dose per fraction (Gy), median [range]	1.8 [1.8 - 2.0]	-	1.8 [1.8 - 2.0]	
Salvage RT dose to	Total dose (Gy),	-	36.0 [30.0 - 66.0]	60.0 [18.0 - 66.6]	<0.001

positive LN	median [range]				
	Dose per fraction (Gy), median [range]	-	7.5 [2.0 - 15.0]	2.2 [1.8 - 10.0]	
Radiotherapy techniques, n (%)	3D-RT	1 (1.2%)	1 (2.6%)	0 (0.0%)	
	IMRT/VMAT	36 (41.9%)	5 (13.2%)	31 (64.6%)	
	SIB	15 (17.4%)	-	15 (31.3%)	
	SBRT	34 (39.5%)	32 (84.2%)	2* (4.2%)	
Concomitant/adjuvant ADT	Number of patients (%)	32 (37.2%)	3 (7.9%)	29 (60.7%)	<0.001
Time of ADT (months)	Mean (SD)	11.7 ± 14.4	3.8 (2.7)	12.6 (14.9)	0.149
	Median [range]	5.9 [0.9 - 58.0]	4.4 [0.9 - 6.0]	5.9 [2.5 - 58.0]	

*both patients were treated with a combination of ENI with IMRT and a nodal SBRT boost.

S-IFRT = salvage involved-field radiotherapy, s-EFRT = salvage extended-field radiotherapy, RT = radiotherapy, LN = lymph node, 3D-RT = Three dimensional radiotherapy, IMRT = intensity modulated radiotherapy, VMAT = volumetric modulated arc therapy, SIB = simultaneous integrated boost, SBRT = stereotactic body radiotherapy, ADT = Androgen-deprivation therapy.

Table 3: acute and late toxicities of patients treated with salvage involved field radiotherapy and salvage extended field radiotherapy for PET-positive nodal recurrences.

	Total	s-IFRT	s-EFRT	p value
Acute GI, n (%)				1
0	80 (93.0%)	36 (94.7%)	44 (91.7%)	
1	3 (3.5%)	1 (2.6%)	2 (4.2%)	
2	3 (3.5%)	1 (2.6%)	2 (4.2%)	
3	0 (0%)	-	-	
4	0 (0%)	-	-	
Acute GU, n (%)				0.314
0	77 (89.5%)	34 (89.5%)	43 (89.6%)	
1	5 (5.8%)	1 (2.6%)	4 (8.3%)	
2	4 (4.7%)	3 (7.9%)	1 (2.1%)	
3	0 (0%)	-	-	
4	0 (0%)	-	-	
Late GI, n (%)				0.275
0	76 (88.4%)	32 (84.2%)	44 (91.7%)	
1	8 (9.3%)	5 (13.2%)	3 (6.3%)	
2	1 (1.2%)	1 (2.6%)	-	
3	0 (0%)	-	-	
4	1 (1.2%)	-	1 (2.1%)	
Late GU, n (%)				0.455
0	63 (73.3%)	25 (65.8%)	38 (79.2%)	
1	8 (9.3%)	5 (13.2%)	3 (6.3%)	
2	12 (14.0%)	7 (18.4%)	5 (10.4%)	
3	2 (2.3%)	1 (2.6%)	1 (2.1%)	
4	1 (1.2%)	-	1 (2.1%)	

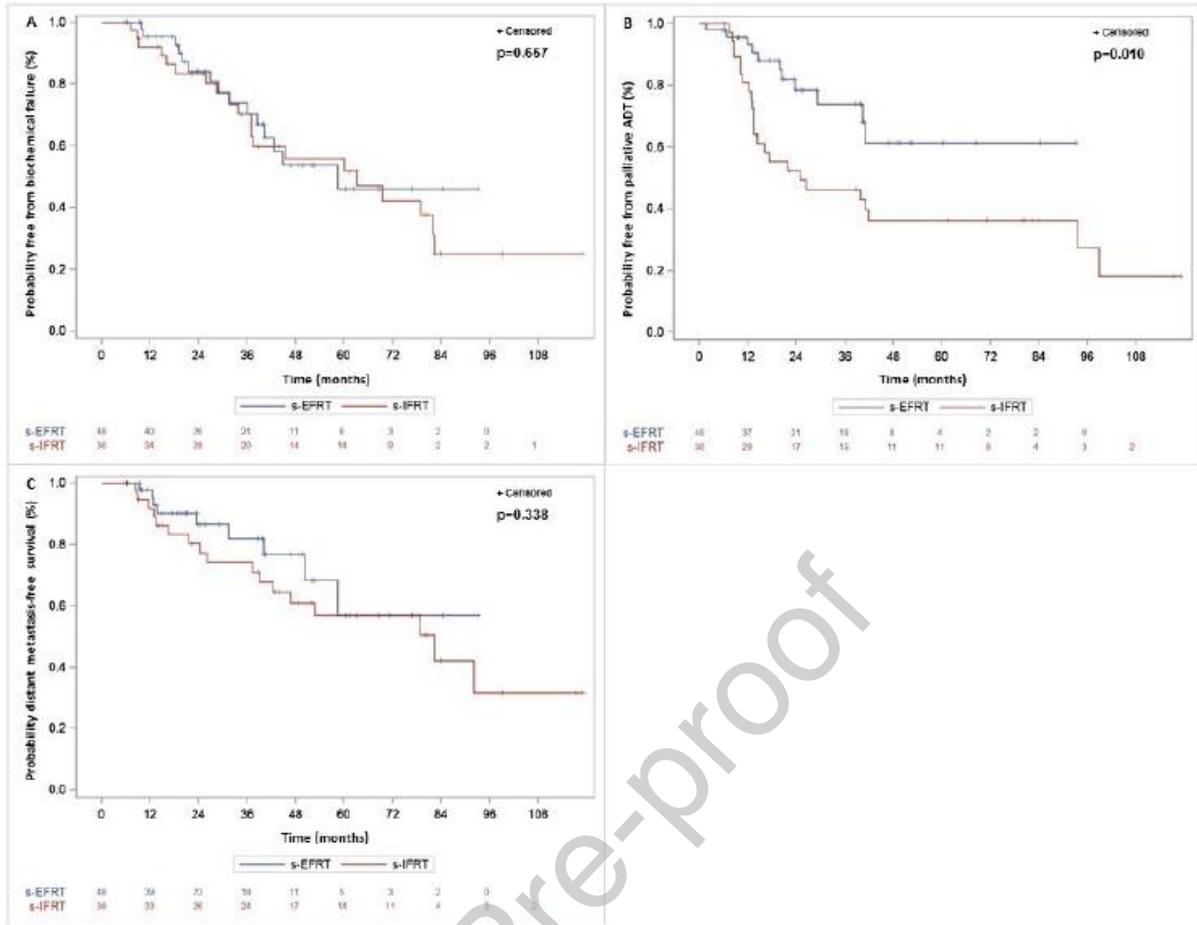GI = gastrointestinal, GU = genitourinary.

Table 4: Univariate and multivariate analyses of biochemical failure-free (A), palliative androgen deprivation therapy-free (B) and distant metastasis-free survival (C).

A						
Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Number of PET positive LN						
>1 vs. 1	1.64	0.83 - 3.25	0.152			
>2 vs. 2	2.11	1.00 - 4.45	0.049	3.23 3.25*	1.45 - 7.18 1.45 - 7.27	0.004 0.004
PSA level at time of PET/CT						
>3 vs. 3ng/mL	2.90	1.39 - 6.02	0.004	3.65 3.69*	1.65 - 8.05 1.66 - 8.20	0.001 0.001
Radiotherapy modality						
s-EFRT vs. s-IFRT	0.86	0.43 - 1.70	0.658			
Time between primary diagnosis and PET positive LN						
>5 vs. 5 years	0.81	0.41 - 1.60	0.552			
Concomitant/adjuvant ADT						
Yes vs. no	0.90	0.41-1.97	0.798			
B						
Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Number of PET-positive LN						
>1 vs. 1	1.67	0.84 - 3.33	0.145			
>2 vs. 2	1.48	0.68 - 3.22	0.323			
PSA level at time of PET/CT						
>3 vs. 3ng/mL	2.77	1.33 - 5.77	0.006	3.46	1.58 - 7.58	0.002
Radiotherapy modality						
s-EFRT vs. s-IFRT	0.40	0.19 - 0.83	0.013	0.43	0.20 - 0.91	0.028

Time between primary diagnosis and PET-positive LN						
>5 vs. 5 years	0.54	0.28 - 1.06	0.073			
C						
Variable	Univariate analysis		Multivariate analysis			
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Number of PET-positive LN						
>1 vs. 1	2.56	1.16 - 5.64	0.020			
>2 vs. 2	3.31	1.45 - 7.56	0.005	4.33 4.32*	1.80 - 10.42 1.80 - 10.30	0.001 0.001
PSA level at time of PET/CT						
>3 vs. 3ng/mL	2.53	1.08 - 5.95	0.033	3.02 2.82*	1.25 - 7.34 1.16 - 6.84	0.015 0.022
Radiotherapy modality						
s-EFRT vs. s-IFRT	0.67	0.29- 1.53	0.341			
Time between primary diagnosis and PET-positive LN						
>5 vs. 5 years	1.12	0.51 - 2.45	0.77			
Concomitant/adjuvant ADT						
Yes vs. no	0.47	0.16 - 1.39	0.173			

*Cox proportional hazards regression after adjusting for androgen deprivation therapy (ADT).

LN = lymph node, S-IFRT = salvage involved-field radiotherapy, s-EFRT = salvage extended-field radiotherapy