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ORIGINAL ARTICLE

Salvage extended field or involved field nodal irradiation in ^{18}F-fluorocholine PET/CT oligorecurrent nodal failures from prostate cancer

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Abstract

Purpose The concept of metastasis-directed therapy for nodal oligorecurrences with stereotactic body radiotherapy is increasingly accepted. Hence, the comparison between salvage extended field radiotherapy (s-EFRT) and salvage involved field radiotherapy (s-IFRT) in patients with ^{18}F-fluorocholine (FCH) PET/CT+ nodal oligorecurrences from prostate cancer is worthy of investigation.

Methods Patients with oligorecurrent nodes on FCH PET/CT treated with salvage radiotherapy between 2009 and 2017 in a single tertiary cancer centre were selected for this study. Patients treated with s-IFRT were compared with those treated with s-EFRT. Toxicities and times to failure (TTF) were compared between the two groups.

Results The study included 62 patients with positive lymph nodes only who underwent FCH PET/CT for a rising PSA level after radical prostatectomy or radiotherapy. Of these patients, 35 had s-IFRT and 27 had s-EFRT. After a median follow-up of 41.8 months (range 5.9–108.1 months), no differences were observed in acute or late gastrointestinal and genitourinary toxicities of grade 2 or more between the two groups. The 3-year failure rates were 55.3% (95% CI 37.0–70.3%) in the s-IFRT group and 88.3% (95% CI 66.9–96.1%) in the s-EFRT group ($p = 0.0094$). In multivariate analysis of TTF, an interval of >5 years was significantly correlated with better outcomes (HR = 0.33, 95% CI 0.13–0.86, $p = 0.023$). There was a strong trend toward better outcomes with s-EFRT even after adjusting for concomitant androgen-deprivation therapy (HR = 0.38, 95% CI 0.12–1.27, $p = 0.116$).

Conclusion FCH PET-positive node-targeted s-EFRT is feasible with low rates of toxicity and longer TTF, suggesting that oligorecurrent nodal disease diagnosed on FCH PET is unlikely.

Keywords Prostate cancer · Nodal failure · ^{18}F-Fluorocholine · PET/CT · Salvage radiotherapy

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Introduction

Biochemical failure can occur in 20–50% of patients after radical prostatectomy (RP) or after external beam radiotherapy (EBRT) [1]. With the advent of functional imaging such as ^{18}F-choline or ^{11}C-choline (choline-based) PET/CT, isolated occult low-volume nodal metastases at the time of biochemical failure after primary treatment of the prostate with curative intent are emerging as a new clinical entity. Whether such nodal failure is a regional disease or a gateway for metastatic disease is unresolved. With the advent of stereotactic body radiotherapy (SBRT), a growing number of studies of the management of oligometastatic disease with salvage focal radiotherapy have shown 3-year in-field local control rates above 80% with rare significant toxicities

[2–9]. Most of these studies included mixed populations of patients with nodal and bone failures, which propagate and disseminate via different pathways. Whether patients with a few recurrent lymph nodes (LN) or even a single LN on choline PET may be defined as harbouring oligometastatic disease is a matter of debate.

The purpose of this study was twofold:

1. To establish the feasibility of salvage nodal radiotherapy in patients with ^{18}F-fluorocholine (FCH) PET-positive nodal recurrence only from prostate cancer
2. To compare nodal salvage involved field radiotherapy (s-IFRT) and nodal salvage extended field radiotherapy (s-EFRT) combined with a protracted FCH PET-positive LN.

Materials and methods

Selection of patients

Between January 2009 and April 2017, all patients with pathologically proven prostate adenocarcinoma and biochemical failure after curative local therapy (e.g. exclusive radiotherapy or RP followed by radiotherapy of the prostatic fossa only) underwent FCH PET/CT at Unicancer-Georges François Leclerc Cancer Center. ^{18}F-FCH PET/CT was performed when the rising PSA value reached 2 ng/ml or above during follow-up. For patients who had a PSA value less than 2 ng/ml, a PSA doubling time of <6 months was required. Thus, 62 patients underwent salvage EBRT as either s-IFRT targeted to a single or a few LN or s-EFRT with curative intent in those with FCH PET-positive LN.

^{18}F-Choline PET/CT procedure

All FCH PET/CT studies were performed using an integrated PET/CT system (Gemini, Philips, The Netherlands) on an outpatient basis. As a routine protocol, imaging was started immediately after intravenous injection of 3–4 MBq/kg body mass of FCH (IASOcholine, IASON; Advanced Accelerator Applications, Saint-Genis-Pouilly,France) with acquisition of dynamic PET images of the pelvic region for 8 min (to overcome the effect of urinary activity in the bladder), followed by a whole-body acquisition. Each PET acquisition was followed by a low-dose unenhanced CT scan (80 mA, 0.5 s per rotation, 140 kV, 4.25 mm reconstructed section thickness). CT images were used for attenuation correction and fusion with PET images.

To our knowledge, there is no reported SUVmax cut-off value to differentiate malignant from benign lesions on FCH PET/CT. In our study, as in previous studies from other teams, the diagnosis of malignant LN was based on visual assessment of focally increased FCH uptake, higher than background, corresponding to LN on CT. LN with increased FCH uptake were considered positive even if they were smaller than 10 mm. LN without abnormal tracer uptake were considered negative even if larger than 10 mm [10]. Dynamic FCH PET images were also taken into account to differentiate FCH positivity from urinary accumulation in the ureters, given the fact that FCH uptake in LN appears sooner than urinary elimination of FCH. Finally, faint FCH uptake in inguinal LN was interpreted as reactive and was excluded [11].

Radiotherapy: immobilization, preparation, CT planning and volumes

Specific recommendations were suggested regarding daily preparation. Patients were asked to drink 250–300 ml of water just after voiding for the planning CT, and this was repeated 30 min before each daily fraction. For the planning CT only, a rectal enema was performed. No preventive dietary advice was given unless diarrhoea of grade 1 or higher occurred during treatment. Patients were immobilized in the supine position in a custom blue bag device (VacLok® system; CIVCO Medical Solutions, Orange City, IA). 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 to improve visualization of the abdominopelvic vessels. 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 CTV; 2cm above and below the CTV) and the kidneys. Treatment was performed on either a TrueBeam or a Trilogy linear accelerator equipped with a 120-leaf collimator (Varian Medical Systems, Palo Alto, California).

Salvage involved field nodal radiotherapy (s-IFRT)

Gross tumour volume (GTV) was defined as any FCH PET-positive LN delineated after automatic coregistration between the planning CT images and the CT images from FCH 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). In most of the patients treated with s-IFRT a stereotactic approach was used (82.9%, see Table 2). In the six other patients, three-dimensional radiotherapy or intensity-modulated radiotherapy was used with the same dose constraints as described for s-EFRT (see paragraph below).

For SBRT, the absorbed dose to 0.5 cm^3 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. The treatment was delivered with two arcs using a 6-MV photon beam (one clockwise arc from 179° to 181°, collimator 45°, and one counterclockwise arc from 181° to 179°, collimator 315°). 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. Figure 1a shows an example patient treated with linear accelerator-based SBRT to two FCH PET-positive pelvic LN.

Salvage extended field nodal radiotherapy (s-EFRT)

A prophylactic CTV including the whole pelvis as defined by the RTOG consensus atlas was delineated for all patients in the group treated with elective nodal irradiation (ENI). In patients with FCH PET-positive LN in the common iliac station or lower paraaortic station, this CTV was extended up to the L2/L3 space in accordance with a previous report from our group [1]. When LA FCH PET-positive LN were involved, this 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 FCH PET-positive LN, GTV was defined as any FCH PET-positive LN delineated after automatic coregistration of the planning CT images and the CT images from FCH 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 less than 60 Gy, the mean dose had to be 30 Gy and the volume of bowels receiving 30 Gy had to be less than 30%.

The treatment was delivered with two arcs using a 6-MV photon beam (one clockwise arc from 179° to 181°, collimator 45°, and one counterclockwise arc from 181° to 179°, collimator 315°). 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%. Doses and techniques are shown in detail in Table 2. Figure 1b, c shows an example patient treated with LA and pelvic ENI for a single iliac LN using volumetric modulated arc therapy.

Repositioning

A kilovoltage cone beam CT (CBCT) scan was performed before each fraction over the entire course of the radiotherapy in both groups to set-up patients and verify targets; all shifts were corrected with no minimal action level. Automatic matching was done using soft tissue window settings for LN and/or vessels in the case of ENI.

Follow-up

Acute genitourinary (GU) and GI toxicities were scored every week during radiotherapy using the Common Terminology Criteria for Adverse Events (CTC-AE) v4.0 and were defined as toxicities occurring up to 3 months after completion of radiation. Late GU/GI toxicities were evaluated prospectively using CTC-AE v4.0. Disease response was assessed every 3 months for 2 years and then every 6 months thereafter. A PSA sample was required for each visit. A new work-up including ^{18}F FCH PET/CT was performed at the time of failure.

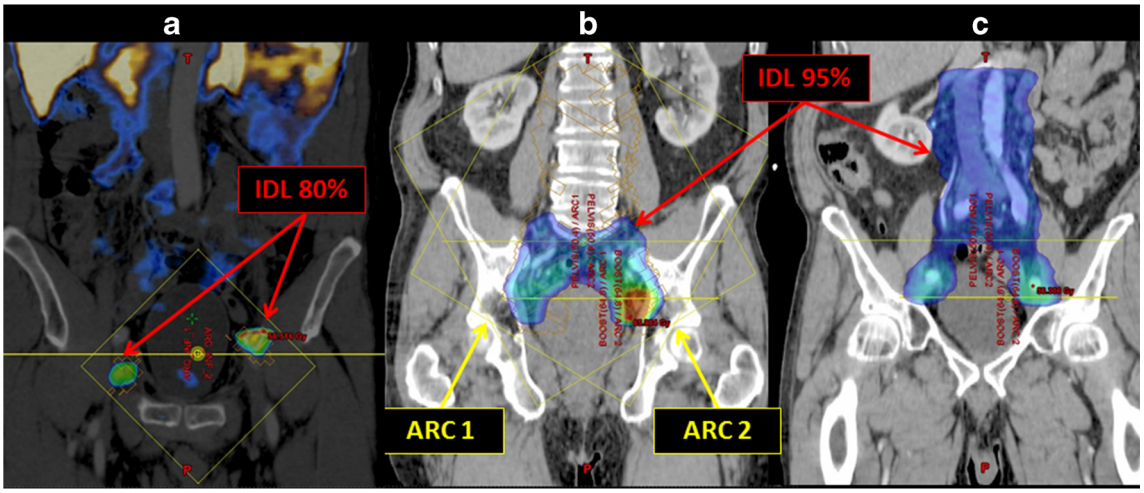

Fig. 1 Techniques of salvage involved field nodal radiotherapy (s-IFRT) and salvage extended field nodal radiotherapy (s-EFRT) in an example patient with two FCH PET-positive pelvic LN. **a** s-IFRT with linear accelerator-based stereotactic body radiation therapy. Coronal superimposed FCH PET/CT image shows two FCH PET-positive pelvic LN: a left external iliac LN and another smaller right external iliac LN. The edge of the colour-wash area is the 80% (45 Gy) isodose line (*IDL 80%*). **b**, **c** s-EFRT with a boost to the FCH PET-positive LN. Coronal superimposed VMAT dosimetry images: **b** pelvic image with two arcs (collimator at 45° and 315°, respectively); **c** lumboaortic image. The edge of the colour-wash areas are the 95% (47.5 Gy) isodose lines (*IDL 95%*)

Statistical analysis

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). Median follow-up times were calculated using the reverse Kaplan-Meier method. Failure was defined as a rising PSA value higher than the maximal pretherapy PSA value followed by two consecutive rises or nodal or distant metastatic failure or the initiation of any salvage therapy (i.e. new salvage radiotherapy and/or surgery and/or androgen-deprivation therapy). Time to failure (TTF) was defined as the time between the FCH PET/CT scan and failure. TTF was determined by the Kaplan-Meier method. Hazard ratios (HR) and 95% confidence intervals (CI) for univariate and multivariate analyses of TTF were estimated using a Cox's proportional hazards regression model with a backward procedure. Statistical analyses were performed using SAS 9.4 software.

Results

Characteristics of primary disease and FCH PET-positive nodal failures

The characteristics of the two groups were well balanced with no significant differences except for T stage and PSA value at the time of FCH PET/CT. The characteristics of primary prostate cancer disease at baseline and PET-based oligorecurrent nodal disease are shown in Table 1.

Table 1 Characteristics of the patients at baseline and at the time of FCH PET diagnosis of relapse in each group

		Total	s-IFRT	s-EFRT	*p* value
Primary disease					
T stage (UICC 2002), *n* (%)	1	9 (14.5)	4 (11.4)	5 (18.5)	0.016
	2	30 (48.4)	16 (45.7)	14 (51.9)	
	3	10 (16.2)	10 (28.6)	0 (0)	
	Missing	13 (20.9)	5 (14.3)	8 (29.6)	
N stage (UICC 2002), *n* (%)	0	24 (38.7)	14 (40.0)	10 (37.0)	0.065
	1	3 (4.8)	0 (0)	3 (11.1)	
	X	35 (56.5)	21 (60.0)	14 (51.9)	
Gleason score, *n* (%)	≤6	23 (37.1)	15 (42.9)	8 (28.6)	0.325
	7	22 (35.5)	13 (37.1)	9 (33.4)	
	≥8	7 (11.3)	2 (5.7)	5 (18.5)	
	Missing	10 (16.1)	5 (14.3)	5 (18.5)	
Pretherapy maximal PSA value (ng/ml)	Mean ± SD	15.6 ± 19.8	19.5 ± 25.2	10.5 ± 6.1	0.363
	Median (range)	9.4 (4.0–129)	9.4 (4.0–129)	9.3 (5.0–33)	
Relapse diagnosed on FCH PET					
Age (years)	Mean ± SD	69.2 ± 8.0	69.3 ± 7.8	68.9 ± 8.2	0.845
	Median (range)	70.0 (53.0–85.7)	70.0 (53.0–85.7)	69.4 (53.0–85.7)	
Time from diagnosis of prostate cancer (years)	Mean ± SD	5.8 ± 3.5	6.3 ± 3.4	5.8 ± 3.5	0.210
	Median (range)	4.9 (0.1–14.7)	5.4 (1.7–14.7)	4.9 (0.1–13.4)	
PSA value (ng/ml)	Mean ± SD	4.0 ± 4.3	5.0 ± 5.2	2.7 ± 2.5	0.0059
	Median (range)	3.0 (0.3–29.2)	3.9 (0.4–29.2)	2.3 (0.3–11.2)	
Total number of FCH PET-positive LN		88	51	37	0.360
Number of FCH PET-positive LN per patient, *n* (%)	1	33 (53.2)	19 (54.3)	14 (51.9)	0.244
	2	13 (21.0)	9 (25.7)	4 (14.8)	
	3	9 (14.5)	5 (14.3)	4 (14.8)	
	4+	7 (11.3)	2 (5.7)	5 (18.5)	
Topography of involved LN, *n* (%)	Common iliac	10 (14.7)	8 (19.5)	2 (7.4)	0.690
	Internal iliac	12 (17.6)	7 (17.1)	5 (18.5)	0.080
	External iliac	20 (29.4)	8 (19.5)	12 (44.5)	0.317
	Obturator	7 (10.3)	6 (14.7)	1 (3.7)	0.683
	Inguinal	1 (1.5)	1 (2.4)	0 (0)	NA
	Lumboaortic	17 (25.0)	10 (24.4)	7 (25.9)	0.369
	Mediastinum	1 (1.5)	1 (2.4)	0 (0)	NA
Mean SUV of involved LN	Mean ± SD	4.7 ± 1.6	5.0 ± 1.5	4.4 ± 1.7	0.176
	Median (range)	4.7 (2.1–8.4)	4.8 (2.2–8.4)	3.7 (2.1–8.3)	
Maximum SUV of involved LN	Mean ± SD	5.37 ± 1.97	5.75 ± 2.09	4.87 ± 1.71	0.081
	Median (range)	5.0 (2.2–11.1)	5.2 (2.2–11.1)	4.2 (2.7–8.3)	
Metabolic tumour volume (ml)	Mean ± SD	7.0 ± 6.7	7.2 ± 7.2	6.8 ± 6.1	0.777
	Median (range)	4.5 (0.7–29.4)	4.1 (0.7–29.4)	4.7 (1.0–25.1)	

s-IFRT salvage involved field nodal radiotherapy, *s-EFRT* salvage extended field nodal radiotherapy, *UICC* Union Internationale Contre le Cancer, *NA* not available

The mean PSA value of FCH PET-positive LN, was significantly lower in the s-EFRT group (2.7 ± 2.5 ng/ml vs. 5.0 ± 5.2 ng/ml; $p = 0.006$). Among the 62 patients, 88 LN were diagnosed on FCH PET/CT. The time between diagnosis and nodal failure on FCH PET was not significantly different between the groups (6.3 ± 3.4 months in the s-IFRT and 5.8 ± 3.5 months in the s-EFRT group, $p = 0.21$). The median number of FCH PET-positive LN per patient was 1 (range 1–7) in the s-IFRT group and 1 (range 1–5) in the s-EFRT group ($p = 0.36$).

s-IFRT to the involved LN was used exclusively in 35 patients, and s-EFRT in 27 patients. The characteristics of salvage nodal radiotherapy are summarized in Table 2. Androgen-deprivation therapy was administered to 2 patients (5.7%) and 13 patients (48.1%) in the s-IFRT and the s-EFRT groups, respectively ($p = 0.0002$).

Acute toxicity

Most patients had no acute toxicity (90.3% no GI toxicity, 85.5% no GU toxicity). The rate of any acute GI toxicity was significantly higher in the s-EFRT group, but there was no significant difference in the rates of GU toxicity ($p = 0.005$ and $p = 0.373$, respectively). No GI toxicity of grade 3 or higher was observed in either group. Very few patients overall had acute grade 2 GU toxicity (6.5%, two patients in each group) or grade 3 GU toxicity (6.5%, one patient in the s-

Table 2 Treatments at baseline and at the time of relapse diagnosed on FCH PET in each group

		Total	s-IFRT	s-EFRT	*p* value
Primary disease, *n* (%)					
Radical prostatectomy		48 (77.4)	27 (77.1)	21 (77.8)	0.953
Pelvic lymph node dissection		36 (61.0)	23 (67.7)	13 (50.0)	0.344
Radical prostatectomy followed by postoperative RT[a]		34 (72.3)	23 (74.2)	11 (68.8)	0.473
Prostate only RT[a]		13 (27.7)	8 (25.8)	5 (31.3)	0.473
Whole pelvic RT[a]		9 (19.6)	6 (20.0)	3 (18.8)	0.622
Androgen-deprivation therapy		19 (30.7)	12 (34.3)	7 (25.9)	0.335
Relapse diagnosed on FCH PET					
Postoperative salvage RT to prostate bed	Number (%) of patients	8 (12.9)	–	8 (29.6)	0.001
	Total dose (Gy), median(range)	–	–	66.0 (60.0–70.2)	
	Dose per fraction (Gy), median (range)	–	–	2.0 (1.8–2.2)	
Salvage whole-pelvis elective nodal irradiation	Number (%) of patients	24 (38.7)	–	24 (88.9)	<0.0001
	Total dose (Gy), median(range)	–	–	50.0 (45.0–54.0)	
	Dose per fraction (Gy), median (range)	–	–	1.8 (1.8–2.2)	
Salvage lumboaortic elective nodal irradiation	Number (%) of patients	8 (13.1)	–	8 (29.6)	0.001
	Total dose (Gy), median(range)	–	–	46.0 (45.0–59.4)	
	Dose per fraction (Gy), median (range)	–	–	1.9 (1.8–2.0)	
Salvage RT dose to FCH PET-positive LN	Total dose (Gy), median(range)	–	36.0 (30.0–66.0)	66.0 (18.0–66.0)	<0.0001
	Dose per fraction (Gy), median (range)	–	7.5 (2.0–15.0)	2.2 (1.8–10.0)	
Radiotherapy techniques	3D-RT	1 (1.6)	1 (2.9)	–	
	IMRT	20 (32.3)	5 (14.3)	15 (55.6)	
	VMAT	8 (12.9)	–	8 (29.6)	
	SIB	2 (3.2)	–	2 (7.4)	
	SBRT	31 (50.0)	29 (82.9)	2 (7.4)	
Androgen-deprivation therapy	Number (%) of patients	15 (24.2)	2 (5.7)	13 (48.1)	0.0002
Androgen-deprivation therapy duration (months)	Mean ± SD	13.7 ± 18.1	2.6 ± 2.5	15.4 ± 18.9	0.051
	Median (range)	6.0 (0.9–58.0)	2.6 (0.9–4.4)	6.0 (2.5–58.0)	

[a] For RT: 48 patients

s-IFRT salvage involved field radiotherapy, *s-EFRT* salvage extended field radiotherapy, *RT* radiotherapy, *3D-RT* three-dimensional radiotherapy, *IMRT* intensity-modulated radiotherapy, *VMAT* volumetric modulated arc therapy, *SIB* simultaneous integrated boost, *SBRT* stereotactic body radiotherapy

IFRT group and three patients in the s-EFRT group). Acute toxicities are shown in Table 3.

Late toxicity

Most patients had no late GI or GU toxicity (80.7% no toxicity). There was no significant difference in late GI or GU toxicities between the two groups ($p = 0.576$ for both group). Only one patient had one grade 4 GI/GU toxicity (rectovesical fistula) in the s-EFRT group, which occurred 66 months after completion of salvage radiotherapy.

Late toxicities are reported in Table 3.

Time to failure

After a median follow-up of 41.8 months (5.9–108.1 months), 27 patients had biochemical failure, 23 in the s-IFRT group and 4 in the s-EFRT group. For the whole series, the median TTF was 37.0 months (95% CI 10.9 months to not yet reached) and the 3-year overall failure rate was 69.5% (95% CI 56.0–79.6%). The median TTF was 39.7 months (95% CI 10.9 months to not yet reached) in the s-IFRT group and not yet reached in the s-EFRT group, while the 3-year failure rate was 55.3% (95% CI 37.0–70.3%) in the s-IFRT group and 88.3% (95% CI 66.9–96.1%) in the s-EFRT group ($p = 0.0094$). Figure 2 shows TTF in relation to treatment group. Among the 47 patients without androgen-deprivation therapy, the 3-year TTF rate was 55.7% (95% CI 36.7–71.0%) in the s-IFRT group and 76.9% (95% CI 44.2–91.9%) in the s-EFRT group ($p = 0.14$).

Table 3 Acute and late toxicities in the 62 patients with oligorecurrent FCH PET-positive LN in the s-IFRT and s-EFRT group

	Total	s-IFRT	s-EFRT	*p* value
Acute GI				
0	56 (90.3)	35 (100.0)	21 (77.8)	0.005
1	4 (6.5)	–	4 (14.8)	
2	2 (3.2)	–	2 (7.4)	
3	–	–	–	
4	–	–	–	
Acute GU				
0	53 (85.5)	32 (91.4)	21 (77.8)	0.373
1	1 (1.6)	–	1 (3.7)	
2	4 (6.5)	2 (5.7)	2 (7.4)	
3	4 (6.5)	1 (2.9)	3 (11.1)	
4	–	–	–	
Late GI				
0	50 (80.7)	27 (77.1)	23 (85.2)	0.576
1	2 (3.2)	1 (2.9)	1 (3.7)	
2	8 (12.9)	6 (17.1)	2 (7.4)	
3	1 (1.6)	1 (2.9)	–	
4	1 (1.6)	–	1 (3.7)	
Late GU				
0	50 (80.7)	27 (77.1)	23 (85.2)	0.576
1	2 (3.2)	1 (2.9)	1 (3.7)	
2	8 (12.9)	6 (17.1)	2 (7.4)	
3	1 (1.6)	1 (2.9)	–	
4	1 (1.6)	–	1 (3.7)	

The data presented are numbers (%) of patients

Predictors of time to failure (Cox model)

In the univariate analysis, patients with a PSA level at the time of failure of >3 ng/ml, patients treated with s-IFRT at the time of nodal failure on FCH PET and patients with ≤5 years between diagnosis and nodal failure on FCH PET were more likely to fail after salvage nodal radiotherapy (Table 4). In the multivariate analysis, >5 years between diagnosis and nodal failure on FCH PET was significantly correlated with better outcomes (HR = 0.33, 95% CI 0.13–0.86, $p = 0.023$). There was a strong trend toward better outcomes with s-EFRT (HR = 0.34, 95% CI 0.11–1.04, $p = 0.058$), even after adjusting for concomitant androgen-deprivation therapy (HR = 0.38, 95% CI 0.12–1.27, $p = 0.116$).

Distant failures

Among the 15 patients (24.2%) who developed distant metastases, 10 were in the s-IFRT group and 5 were in the s-EFRT group ($p = 0.27$).

Discussion

A critical issue in prostate cancer treatment is determining the best time to start systemic treatment for biochemical failure after RP and/or EBRT. Because of the protracted natural history of prostate cancer, delaying clinical disease progression may enable patients to avoid subsequent systemic treatments, which can cause life-long therapy-related symptoms. ^{11}C-Choline and ^{18}F-choline PET/CT are helpful for the assessment of recurrent regional LN involvement after RP or EBRT [11–13]. Nevertheless, the value of choline-based PET/CT in guiding lesion-targeted salvage therapies in patients with recurrent prostate cancer is still a matter of debate. Even though its sensitivity and specificity in detecting recurrent occult clinical disease are promising, its power to map positive targets accurately still seems to be lower than expected [14]. Indeed, Passoni et al. evaluated the ability of ^{11}C-choline PET/CT to identify patients with a single positive LN in relation to the results of extensive pelvic LN dissection in 46 patients with a single recurrent ^{11}C-choline PET-positive LN [15]. Only 30 patients (65%) had pathologically involved LN, and of these only 16 had pathologically involved LN in the same area (35%). The authors concluded that the positive predictive

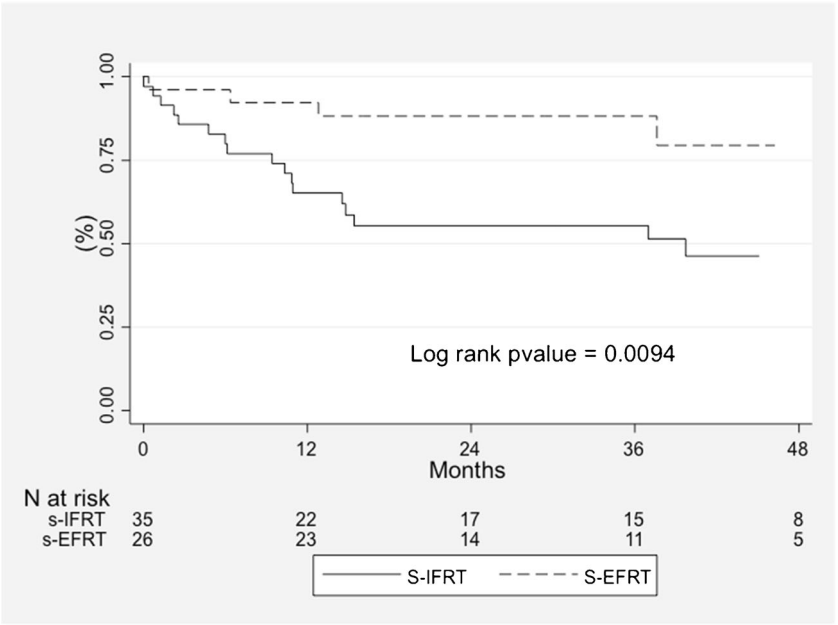

Fig. 2 Kaplan Meier analysis of the probability of failure in the two treatment groups with or without elective nodal irradiation

value of ^{11}C-choline PET/CT in correctly identifying patients with a single involved LN was poor (24%).

In another study of salvage extended pelvic LN dissection in 59 patients with a single nodal failure (41 patients) or two nodal failures (18 patients) detected on ^{11}C-choline PET/CT, Suardi et al. found a mean of 8.9 involved LN after removing a mean of 29.5 LN [16]. ^{68}Ga PET/CT had higher rates of detection (per LN) in patients with rising PSA levels after RP and/or radiotherapy (sensitivity 84–94%, specificity 82–99%) [17, 18] than ^{11}C-choline PET/CT (sensitivity about 65%, specificity 90–95%) [19, 20]. More LN and smaller LN are found on ^{68}Ga PET/CT than on ^{18}F-choline or ^{11}C-choline PET/CT, suggesting that s-IFRT or oligometastasis-directed therapy will inevitably be unsuccessful [21]. Although there is no level I evidence, in a number of single-arm studies including nearly 500 patients with recurrent prostate cancer who underwent oligometastasis-directed salvage therapy (surgery or radiotherapy) with curative intent, nearly 50% of the patients remained free of any disease progression after 3 years of follow-up [4].

Stereotactic radiotherapy of small-volume nodal and/or bone oligometastases has shown promising short-term local control (in-field) rates ranging between 70% and 90% at 2 years with very low rates of toxicity [2, 4, 6–9, 22, 23]. The randomized phase II trial STOMP found no significant improvement in ADT-free survival with metastasis-directed therapy (mostly s-IFRT with SBRT) compared to surveillance

Table 4 Predictive factors for failure

Variable	Number of patients	Univariate analysis			Multivariate analysis		
		Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Number of FCH PET-positive LN	58						
>1 vs. ≤1		1.08	0.44–2.65	0.863			
>2 vs. ≤2		0.77	0.225–2.63	0.676			
PSA level at time of FCH PET/CT	58						
>3 vs. ≤3 ng/ml		2.66	1.02–6.95	0.046	2.65	0.98 – 7.19	0.055
					2.59[a]	0.96–7.02[a]	0.061[a]
Radiotherapy technique	61						
s-EFRT vs. s-IFRT		0.26	0.09–0.78	0.016	0.34	0.11 – 1.04	0.058
					0.38[a]	0.12–1.27[a]	0.116[a]
Concomitant ADT	61						
Yes vs. no		0.29	0.07–1.23	0.093	0.67	0.14–3.38	0.627
Time between primary diagnosis and oligorecurrent LN on FCH PET/CT	57						
>5 vs. ≤5 years		0.37	0.15–0.92	0.033	0.33	0.13 – 0.86	0.023
					0.33[a]	0.12–0.85[a]	0.021[a]

s-IFRT salvage involved field radiotherapy, *s-EFRT* salvage extended field radiotherapy,*ADT* androgen-deprivation therapy

[a] Cox proportional hazards regression after adjusting for androgen-deprivation therapy

only in patients with oligorecurrent nodal failure on FCH PET, although a trend was observed [24]. One may hypothesize that this trend may become significant if metastasis-directed therapy of oligorecurrent LN was based on the oligorecurrent LN found on ^{68}Ga PET/CT. It is more likely that patients with only a few LN found on ^{68}Ga PET/CT may have true oligometastatic disease.

In a large multicentre retrospective study, Ost et al. found that 14% of patients treated with s-IFRT had grade 1 toxicity, 3% had grade 2 toxicity and none had grade 3 or higher toxicity [4]. These results are very close to ours. Although we found a significantly higher rate of acute GI toxicity with s-EFRT, acute toxicities were low and manageable in both groups. Nevertheless, we found a 3-year failure rate of 55.3% with s-IFRT. The 2-year and 3-year progression-free survival rates after s-IFRT were 35% and 59%, respectively, in the two largest studies on this topic [2, 6].

To our knowledge, no study has been published so far on the feasibility of s-EFRT (large volumes) with a boost to FCH PET-positive nodes. Our study is the first to compare the outcomes of the two techniques, s-IFRT and s-EFRT. We must acknowledge that our study suffered from some limitations due to its retrospective nature among which are the small sample size, imbalances between the two groups with respect to the primary disease (T stage), PSA level at relapse, and interobserver variations regarding PET/CT analyses. We found that both s-IFRT and s-EFRT provide similar low rates of toxicity in the short term, which is in keeping with the low toxicity rates observed when pelvic LN are irradiated in the primary management of prostate cancer patients with stage N0 and a high risk of nodal failure or stage N1 [25, 26]. Even though our results are preliminary and need to be confirmed prospectively in a larger study, we found a difference in TTF favouring s-EFRT with a significant absolute improvement of +33% compared with s-IFRT.

Conclusion

FCH PET-positive LN-targeted salvage radiotherapy is feasible with very low rates of toxicity. Freedom from failure was improved with s-EFRT, suggesting that nodal disease diagnosed on FCH PET may not be oligometastatic disease.

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent All the patients included in this study provided signed informed consent for their data to be used for research purposes.

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