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# ***<sup>18</sup>F-choline PET/CT for early detection of metastases in biochemical recurrence following radical prostatectomy***

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## ***Abstract***

**Purpose:** Salvage radiotherapy (SRT) for biochemical recurrence (BCR) following radical prostatectomy (RP) should if possible be added at a prostate-specific antigen (PSA) level of less than 1-2 ng/mL. The value of positron emission tomography combined with computed tomography (PET/CT) at such low PSA values is not defined. The purpose was to determine what proportion of a well-defined cohort of hormone-naïve patients who were candidates for early salvage radiotherapy had <sup>18</sup>F-choline PET/CT findings suggesting metastases.

**Materials and methods:** Patients with untreated BCR following RP, PSA < 2 ng/mL, and Gleason score ≥ 7 or PSA doubling time ≤ 6 months underwent <sup>18</sup>F-choline PET/CT. Focal choline uptake in lymph nodes or skeletal sites were recorded.

**Results:** PET/CT indicated metastases in 16 (28%) of 58 patients. In five (9%) patients the scans suggested bone metastases and in 11 (19%) the scans suggested regional lymph node metastases only. For patients with PSA levels < 1.0 ng/mL, the PET/CT scans indicated metastatic recurrence in 25%.

**Conclusions:** <sup>18</sup>F-choline PET/CT may be valuable for selecting patients with BCR following RP for SRT or experimental treatment of oligometastases, even at low PSA values.

## ***Introduction***

Radical prostatectomy (RP) is one of the cornerstones in curative treatment of prostate cancer [1], significantly reducing cancer-specific mortality compared to watchful waiting [2]. Still, a large proportion of patients, up to 60% depending on tumour characteristics [3,4], will develop biochemical recurrence (BCR) and may need additional treatment. BCR is usually treated with either radiotherapy (RT) or hormonal therapy (HT), depending on the likelihood that the recurrence is local only [5]. Salvage RT, which is the curative option, is associated with significant risk of morbidity [6] and should therefore only be given when there is a reasonable chance for cure. A high prostate-specific antigen (PSA) value, short time to relapse, short PSA doubling time, Gleason score 8-10 and lymph node metastases at lymphadenectomy are associated with increased risk of metastatic recurrence, and reduced chance of complete remission after salvage therapy [7,8]. Especially PSA > 2.0 ng/mL has been associated with a low probability of complete remission [8–10]. However, even in the group of patients with PSA < 2.0 ng/mL, some have metastatic disease and require systemic therapy, rather than local RT.

<sup>18</sup>F-choline positron emission tomography combined with computed tomography (PET/CT) has been studied as a modality for detecting regional and distant metastases in patients with newly detected prostate cancer, but the role of PET/CT in restaging after post-surgical recurrence is still uncertain [11,12]. Few previous studies have reported specifically on patients with low PSA values, i.e. when the choice of secondary treatment usually has to be made [13–18]. Most of the studies included a large proportion of patients on HT, for whom the association between PSA values and tumour burden is different than for hormone-naïve patients, and for whom treatment with additional RT is not evidence based. The primary aim of this study was to determine how large a proportion of hormone-naïve patients with BCR after RP would have positive <sup>18</sup>F-choline PET/CT findings at PSA values < 2 ng/mL.

## ***Materials and methods***

### ***Patients***

Between June 2008 and November 2012, urologists in the Southern health-care region of Sweden were invited to refer patients with BCR after RP for a whole-torso  $^{18}\text{F}$ -choline PET/CT scan according to a specific protocol. The inclusion criteria were: a rising PSA  $\geq 0.2$  ng/mL below 2 ng/mL, eligibility for salvage RT, and either Gleason Score  $\geq 7$  at prostatectomy or a PSA doubling time  $\leq 6$  months. Patients with ongoing or previous androgen deprivation therapy or anti-androgens were excluded. Enrollment was prospective according to the protocol, but the acquisition of the outcome data was performed retrospectively at the end of the study. The study aimed at including 50 patients. It was approved by the Research Ethical Review Board at the University of Lund (EPN Dnr 552/2007).

### ***Imaging***

$^{18}\text{F}$ -choline was synthesized according to the method described by Kryza et al [19] using the TracerLab MXFDG module (GE Healthcare, Stockholm, Sweden). PET/CT images were obtained using an integrated PET/CT system (Philips Gemini TF, Philips Medical Systems, Ohio, USA) at the Center for Medical Imaging and Physiology, Skåne University Hospital in Malmö and Lund. All patients were fasting for four hours before tracer injection. Whole-torso PET was performed 1-1½ after intravenous injection of 4 MBq/kg of  $^{18}\text{F}$ -choline, using 2 minutes per bed position. A CT scan was performed immediately prior to the PET scan with a multi-detector CT scanner using 5 mm reconstructed slice thickness. 1000 ml oral contrast (Omnipaque, GE Healthcare, Stockholm, Sweden) was given 1 hour before the scan. The CT scan was performed in three phases; the liver was scanned without contrast, the thorax was scanned with intravenous contrast in arterial phase during breath-holding, and then a femur to skull base scan was obtained in portal contrast phase during normal breathing [20].

All PET/CT scans were interpreted by a nuclear medicine physician as well as by a radiologist. Focal tracer uptakes in regional or retroperitoneal lymph nodes, or in skeletal sites without evidence

of degenerative causes or fractures, were considered positive findings. Focal uptake in the prostatic bed was noted, but was not included in further analyses.

## ***Statistics***

Statistical analysis was performed using SPSS Statistics 22 (IBM, Chicago, Ill, USA). PSA levels at the time of PET/CT, PSA doubling time, PSA nadir after RP and time to BCR were categorized according to Table 1. PSA doubling time was calculated by the log/slope method [21], using all available PSA levels after prostatectomy.

## ***Results***

A total of 58 patients were included. The clinical characteristics of all the patients are presented in Table 1. The PET/CT scans indicated metastases in 16 patients (28%): regional lymph node metastases in 11 (19%) and distant metastases in 5 (9%). At PSA cutoff levels of 1.5, 1.0 and 0.5 ng/mL, metastatic recurrence was indicated in 26%, 25% and 24%, respectively. Local PET tracer uptake in the prostatic bed was noted in four patients (7%), none of which had evidence of metastases.

## ***Discussion***

We investigated the utility of <sup>18</sup>F-fluorocholine PET/CT in men with BCR after RP and PSA values in the low range (< 2 ng/mL), when the decision whether to add salvage RT usually has to be made. The PET/CT scans suggested metastatic recurrence in 28% of the patients, who were selected by having either Gleason score  $\geq 7$  cancers or a PSA doubling time shorter than 6 months. In the patients with PSA < 1.5 ng/mL 26% of the scans suggested metastases, and for patients with PSA < 1.0 ng/mL the corresponding figure was 25%.

There are only few other reports on PET/CT in patients with untreated BCR after RP and PSA < 2.0 ng/mL. Castelluci et al reported <sup>11</sup>C-choline PET/CT scans indicating metastases in 23% of 605 patients with PSA < 2 ng/mL, and in 18% of 291 patients with PSA < 1.0 ng/mL [15]. This is slightly less than in our study, but almost 25% of the patients in their study received HT at the time of the PET/CT investigation, which is known to affect the sensitivity of choline PET/CT [22]. Also, their study population included more patients with Gleason Score 5-6, with a lower likelihood of metastatic recurrence [7]. From a similar study, Giovacchini and associates reported 29% positive PET/CT scans in 358 patients with PSA < 2 ng/mL, but 43% of the patients received androgen deprivation therapy and it is unclear how many of the positive findings were metastases and how many were local recurrences [14]. These results are in contrast to those from a study including patients with very low PSA levels only ( $\leq 0.76$  ng/mL); PET/CT scans indicated metastases in only 1 of 22 patients [13]. However, taken together, these studies suggest that a significant proportion of patients with BCR after RP and PSA levels < 2.0 ng/mL have metastatic recurrence, rather than local recurrence only. However, a limitation in our study, as well as in the others, is the lack of histopathological verification of the suspected metastases. Tilki et al reported a positive predictive value of only 50% for choline PET/CT compared to a secondary lymphadenectomy following BCR after RP and PSA < 2.0 ng/mL [23]. However, their study included only 12 patients. In contrast, Jilg and associates found a positive predictive value of 89% in a similar study, but with much more heterogeneous clinical characteristics [24]. Further validation is therefore required before choline PET/CT should be recommended outside clinical trials in the setting of BCR.

PET tracer uptake suggesting local recurrence was noted in only four patients. However, since all patients were planned to receive salvage RT if the scan did not reveal convincing evidence of metastases, we do not consider the absence or presence of uptake in the prostatic fossa as clinically relevant.



The most common purpose of using PET/CT for patients with BCR is to exclude those with metastases from local salvage RT. However, it is possible that aggressive treatment of oligo-metastatic disease, as determined by PET/CT, could lead to improved survival. Suardi recently reported 59% complete biochemical response and 17% recurrence-free 5-year survival following salvage lymphadenectomy in patients with nodal metastases only on choline PET/CT [25]. Schick et al reported similar results of RT targeted against oligometastases for BCR after RP or RT [26]. Further prospective, randomized trials in this setting could possibly lead to an improved management of patients with BCR.

## ***Conclusions***

In this study of hormone-naïve patients with BCR after RP,  $^{18}\text{F}$ -choline PET/CT scans indicated metastatic recurrence in 28% of patients with PSA < 2 ng/mL, and in 25% of patients with PSA < 1 ng/mL. These results suggest that  $^{18}\text{F}$ -choline PET/CT may be valuable in selecting patients for local salvage RT or experimental treatment of regional oligometastases.

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## ***Conflict of interest***

The authors declare that they have no conflict of interest.

## ***Authors' contribution***

H Kjölhede: Data collection, data analysis, manuscript writing.

G Ahlgren: Protocol, manuscript editing

H Almquist: Protocol, data collection, manuscript editing

F Liedberg: Data analysis, manuscript editing

K Lyttkens: Protocol, data collection, manuscript editing

T Ohlsson: Data collection, manuscript editing

O Bratt: Protocol, data analysis, manuscript writing

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