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[11C]Choline PET/CT for Targeted Salvage Lymph Node Dissection in Patients with Biochemical Recurrence after Primary Curative Therapy for Prostate Cancer

Preliminary Results of a Prospective Study

Ludwig Rinnab[a] Felix M. Mottaghy[b, d] Joerg Simon[a] Bjoern G. Volkmer[a] Robert de Petriconi[a] Richard E. Hautmann[a] Markus Wittbrodt[e] Guenther Egghart[e] Peter Moeller[c] Norbert Blumstein[b] Sven Reske[b] Rainer Kuefer[a]

Departments of [a]Urology, [b]Nuclear Medicine and [c]Pathology, University of Ulm, Ulm, Germany; [d]Department of Nuclear Medicine, University of Leuven, Leuven, Belgium; [e]Department of Urology, District Hospital Sigmaringen, Sigmaringen, Germany

Key Words
[11C]choline PET/CT · Prostate cancer · Salvage lymph node dissection · Rising prostate-specific antigen

Abstract
Introduction: In this prospective study we set out to investigate the diagnostic value of [11C]choline-PET/CT in patients with suspected lymph node metastases before salvage lymph node dissection. ***Patients and Methods:*** 15 consecutive patients with rising PSA underwent [11C]choline-PET/CT and consecutive open salvage pelvic/retroperitoneal extended lymph node dissection due to uptake of [11C]choline in at least 1 lymph node. Mean age was 62.1 (range 53–73). ***Results:*** [11C]choline-PET/CT results were compared with the histopathology reports and clinical follow-up (mean 13.7 months, range 6–24). Mean time to progression was 23.6 months (range 4–81). [11C]choline uptake was observed in nodes along the external and internal and common iliac arteries and in the paraaortic region. A positive histology was reported in 8/15 patients. Only one patient had a PSA nadir of <0.1 ng/ml after salvage surgery. Another patient had stable disease with a PSA of 0.5 ng/ml. Three patients developed bone metastases during follow-up. ***Conclusions:*** This interim analysis indicates that [11C]choline-PET/CT may be a useful technique in detection of lymph node metastases when rising PSA occurs after definite prostate cancer therapy. The presented cohort is limited in size, but there is still strong evidence that the patients benefit from [11C]choline-PET/CT and consecutive salvage lymph node dissection is rather small.

Introduction

The precise visualization of a recurrence after primary treatment of prostate cancer (PCA) is a diagnostic challenge. Relapse occurs in up to 50% of patients within ten years after radical prostatectomy [1]. Failure after curative therapy is detected in most cases by an increase in the serum value of prostate-specific antigen (PSA). PSA alone cannot distinguish between a local recurrence, lymph node metastases or far distant failure. PSA doubling time

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Ludwig Rinnab, MD
Department of Urology, University of Ulm
Prittwitzstrasse 43, D–89075 Ulm (Germany)
Tel. +49 731 500 58030, Fax +49 731 500 33166
E-Mail ludwig.rinnab@uniklinik-ulm.de

and PSA velocity may provide additional information [2]. Obviously, the visualization of a locus of recurrence is not possible based on serum markers.

Several innovative imaging techniques are available but until now they all failed to produce reliable results especially if the PSA level is still very low but steadily increasing. Transrectal ultrasonography (TRUS) has a limited sensitivity of 25–50% when PSA is $\leq$ 1.0 ng/ml [3]. Endorectal magnetic resonance imaging (MRI) or MRI spectroscopy may be promising tools in the future for the detection of a local recurrence [4]. Bone scans rarely demonstrate skeletal metastases below a PSA of approximately 30 ng/ml [5]. This demonstrates that the precise localization of a recurrence is challenging but also crucial as the decision process for up-to-date therapeutic options depends on these findings.

A small recurrence, being responsible for biochemical failure, does not cause dramatic anatomic changes. These locations are not detectable by conventional CT scan or MRI due to limited resolution. Hope for improvement is given by the invention of imaging modalities based on increased metabolic turnover in neoplastic cells. ^{11}C- or ^{18}F-labeled choline derivatives and positron emission tomography (PET) have been successfully used for the detection of primary prostate cancer [6, 7]. This technique is based on increased content of phosphorylcholine [8, 9], upregulated key enzymes of choline metabolism [10, 11], increased phosphatidylcholine turnover and metabolic flux of radiolabeled choline through phospholipid biosynthesis and degradation in neoplastic cells [12].

Based on our own experience with [^{11}C]choline PET/CT in prostate cancer disease [13], we investigated in the present study the value of [^{11}C]choline PET/CT for the detection of recurrent lymph node metastases after primary treatment of PCA with radical prostatectomy. The [^{11}C]choline PET/CT images were compared with histopathology reports after salvage lymph node dissection and an anticipated clinical benefit for the patients was evaluated in the follow-up.

Patients and Methods

Study Protocol

This is a bicenter prospective trial that was initiated in January 2004. All patients received a regular oncological follow-up, including PSA measurements every 3 months. The first inclusion criterion into the study was a documented rising PSA in three consecutive drawings or a PSA doubling time >0.75 ng/ml yearly. These patients were elected for [^{11}C]choline PET/CT imaging if conventional diagnostic imaging (ultrasound and/or CT and/or MRI and/or bone scintigraphy) showed no evidence for local recurrence or distant metastases. The further inclusion criteria were based on the results of the [^{11}C]choline PET/CT. Patients had to have at least one PET positive lymph node and no evidence for a local recurrence or bone metastases.

Exclusion criteria were suspected distant metastases and systemic treatment, i.e. hormonal deprivation, before salvage lymph node dissection. Patients with a nadir >0.2 ng/ml after radical prostatectomy were also excluded. Patients who had undergone local radiation therapy during follow-up after prostatectomy due to histology proven local recurrence were not excluded.

Finally, if all the indications were met and all contraindications were excluded, the patients were informed about the possible risks and benefits to undergo a salvage lymph node dissection as part of an individualized therapeutic regimen. If the patient agreed to the surgical approach the surgery was first theoretically planned in a consensus conference with at least two urological surgeons and one nuclear medicine specialist. During surgery the surgeons had access to the imaging material and were able to adjust their approaches based on the image information. The histological material was routinely evaluated; in detail described below. A repeat [^{11}C]choline PET/CT scan some weeks after surgery was not routinely performed, however repeated PSA measurements served as reference.

Patient Cohort

In total, 15 patients were in the follow-up at the Department of Urology between January 2004 and December 2006. All patients presented with a rising PSA, and further diagnostic approaches were performed. This included the performance of a [^{11}C]choline PET/CT scan. This cohort had a mean age of 62.1 years (median age of 60 years, range 53–73). In all cases, the salvage lymph node dissection was performed by at least one of the four most experienced surgeons of the Department of Urology in Ulm or by the urological surgeon of the Department of Urology in Sigmaringen. All patients got a PSA measurement on the day of [^{11}C]choline PET/CT examination.

[^{11}C]Choline PET/CT

[^{11}C]choline was synthesized according to the loop methylation method described by Wilson et al. [14]. [^{11}C]choline PET/CT was performed after 5–8 h fasting with an integrated PET/CT scanner (GE Discovery LS) following intravenous injection of 1,112 $\pm$ 131 MBq [^{11}C]choline. Due to the half-life of [^{11}C]choline, PET images were acquired 5–10 min after injection starting from the distal margin of the pelvic floor with a 3-min acquisition time per bed position. Contrast-enhanced CT (140 kV, 160 mAs, pitch 1.5) was acquired with 120 ml nonionic contrast given intravenously as bolus (Ultravist, Schering) immediately before the PET acquisition. PET images were reconstructed with the iterative reconstruction ordered-subset expectation maximum likelihood algorithm of the manufacturer after attenuation correction based on the CT data set. Consecutive transverse PET/CT slices of 4.25 mm thickness were generated.

Image Analysis

The PET/CT scans were independently assessed by two experienced nuclear physicians and two radiologists blinded to clinical data and results of previous imaging studies. Criteria for diagnosing lymph node recurrence at visual analysis were mono- or multifocal [^{11}C]choline uptake in the node defined by CT signifi-

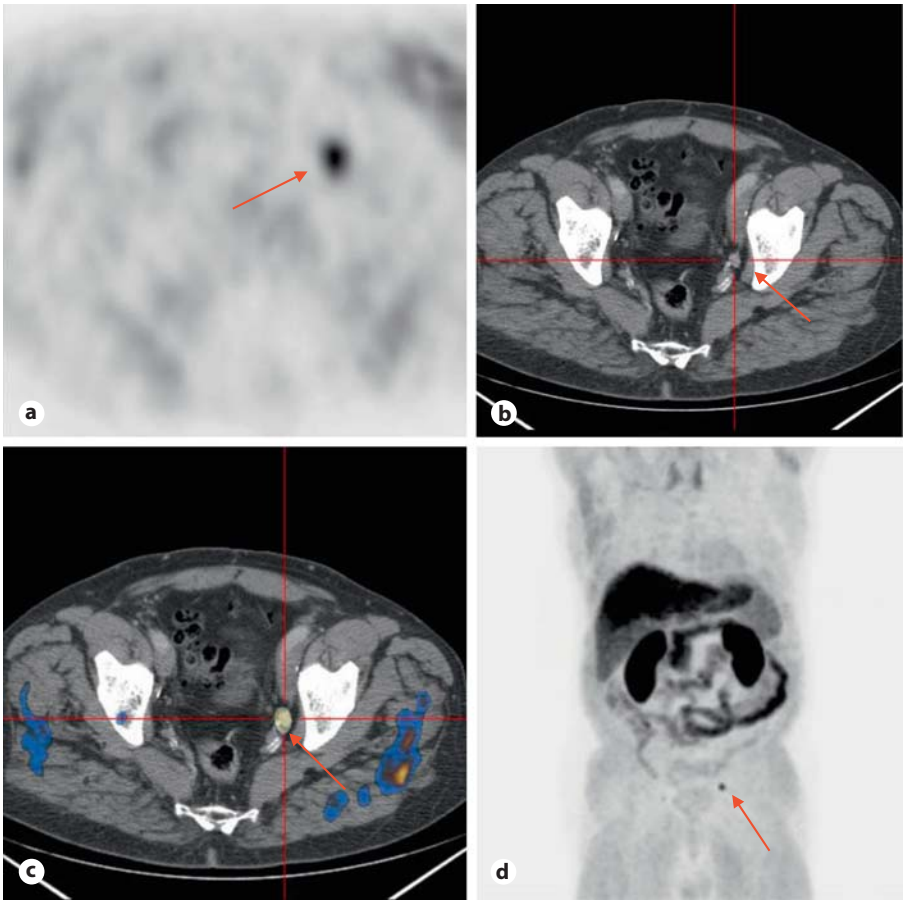

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Fig. 1. [^{11}C]choline PET/CT (transaxial slices) of patient 6 after radical prostatectomy (pT3b pN0 cM0 GII Gl. 7 R1). **a** [^{11}C]choline PET image (transaxial slice). **b** Corresponding contrast-enhanced 4-row helical CT scan (transaxial slice). **c** Fused PET/CT image. **d** PET image (coronary slice, MIP maximal intension procedure) with one suspicious lymph node in the small pelvis (arrow). The PSA level at the time of imaging was 1.3 ng/ml. [^{11}C]choline PET/CT shows intensive focal uptake in the lymph node ventral A. iliaca externa. Pathohistology after salvage lymphadenectomy confirmed the presence 3 of 12 lymph node metastases. The subsequent treatment was watchful waiting. After a follow-up of 6 months the PSA is stable with 0.1 ng/ml.

cantly higher than [^{11}C]choline uptake in surrounding soft tissue [15]. For quantitative assessment, maximal [^{11}C]choline standardized uptake value (SUV_{max}) in the lymph nodes was determined using a circular region of interest. Standardized uptake value is defined as the measured activity concentration divided by the injected radioactivity normalized to body weight [16].

Surgery and Histopathology

Standardized radical retropubic or perineal prostate-vesiculectomy in conjunction with or without lymphadenectomy of the fossa obturatoria had been performed in the past. All patients in this study underwent extended field lymph node dissection at least including the internal, external and common iliac arteries of both sides. The field for resection was extended if choline uptake was documented at other sites. These were discussed in the consensus conference with the urologists and the nuclear medicine physicians on the day prior to the surgery. This approach was offered the patients as an individualized treatment strategy and written consent was mandatory as mentioned earlier. The resected tissue was labeled according to the location, sectioned at 3-mm intervals, formalin fixed and submitted for paraffin embedding. Microslices were placed on glass slides and stained with hematoxylin and eosin. Immunhistochemistry was performed if needed. The [^{11}C]choline PET/CT findings were correlated with the histological information from the step-sectioned lymphatic tissue.

Statistical Analysis

To asses the potential value of [^{11}C]choline-PET, the positive predicted values (ppV) were calculated. In this study context, the ppV is the proportion of patients for which [^{11}C]choline-PET diagnosed a specific tumor stage and which was pathological confirmed as metastases.

Results

Detailed data of the urological past medical history of the study cohort is given in table 1. At time of [^{11}C]choline PET/CT the mean PSA was 2.34 ng/ml (median PSA 1.98 ng/ml, range 1–8). At surgery an average of 13.9 lymph nodes was removed (min 3 nodes, max 45 nodes). There were 7 false-positive cases and 8 right-positive cases. Mean PSA in false-positive [^{11}C]choline PET/CT cases was 1.70 ng/ml (median PSA 1.73 ng/ml, range 1–2). Mean PSA in true positive imaging was 2.89 ng/ml (median PSA 2.04 ng/ml, range 1–8). This difference was statistically not different (Man Whitney U-test p = 0.2; fig. 1). The SUV_{mean} of the entire cohort was 2.33 (range

Table 1. Patient details and results after radical prostatectomy

Patient No.	Age, years	PSA 1 ng/ml	TMN stage (2002 ed.)	PSA nadir	Primary therapy	PSA 2 at PET/CT	PET/CT	Localization of positive uptake	Histo result	PSA 3 with follow-up months	Subsequent treatment
1	67	6.89	pT2c pN0 cM0 GIII Gl.7 R0	<0.1	RP (NS)	0.8	positive	uptake 1 LN A. iliaca ext. left	negative	<0.1 (23)	RT, antiandrogen up to date: Avodart®, Diet
2	60	4.8	pT2b pN0 cM0 Gl.7 R0	<0.1	RP (NS)	1.73	positive	uptake LN V. iliaca com. right	negative	0.07 (18)	RT
3	59	14	pT3b pN1(13/28) cM0 L1 GIII Gl.9 R0	<0.1	RP HT, RT	8.0	positive	uptake LN under and upper aortic bifurcation	positive	>100 (19)	MAB Zometa®
4	73	13	pT3b pN1(2/19) cM0 GIII Gl.9 R0	0.2	RP HT, RT	1.74	positive	uptake 2 LN parailiacal com. right	positive	12.16 (8)	Zometa®, LH-RH analogs, Docetaxel®
5	57	3.8	pT2b cNx cM0 GII Gl.7 R0	0.1	pRP	2.2	positive	uptake 1 LN glutea inf. left	negative	0.19 (15)	LH-RH analogs
6	67	11.2	pT3b pN0 cM0 GII Gl.7 R1	0.1	RP	1.3	positive	uptake 2 parailiacal lymph nodes both sides –> A. obtur. right (0.5 cm) and left (1.5 cm), no uptake local, no distant metastasis	positive	0.1 (6)	ww
7	60	10.6	pT3a pNx cM0 GII Gl.5 R1	0.1	pRP	2.44	positive	uptake LN A. obturatoria int. right, LN between M. psoas right and A. iliaca ext.	positive	2.7 (6)	antiandrogen
8	56	26.2	pT3b pN0 (0/17) cM0 GIII Gl.8 R0	0.18	RP RT	2.40	positive	uptake LN relapse iliacal right	negative	0.07 (7)	LH-RH analogs
9	68	10.1	pT3a pN1 cM0 GII Gl.7 R1	0.1	RP	1.4	positive	uptake LN paraaortal left (LWK III)	positive	1.49 (16)	ww
10	63	9.1	pT3a pN1 cM0 GII Gl.7 R1	0.05	RP RT	1.98	positive	uptake LN A. iliaca right	positive	1.03 (24)	MAB
11	66	36	pT4 pN1 cM0 GII Gl.7 R1	0.03	RP HT	1.85	positive	uptake multiple LN parailiacal and paraaortal (under HT at PET/CT)	positive	35.8 (21)	Docetaxel®, Thalidomid® LH-RH analogs
12	67	125	pT3b pN1 cM0 GII Gl.5 R0	0.02	RP HT	3.8	positive	uptake LN presacral	negative	13,4 (16)	MAB Zometa®
13	53	7.8	pT2a pN0 cM0 GII Gl.7 R0	<0.1	RP	2.1	positive	uptake in 1 LN left iliacal	positive	0.46 (13)	LH-RH analogs
14	60	13.1	pT3b pN1 (1/26) pL1 cM0 GIII Gl. 8 R1	0.2	RP (NS)	1.15	positive	uptake in 1 LN A. iliaca ext. right	negative	0.47 (6)	antiandrogen
15	55	54.7	pT3b pN0 cM0 GII Gl.7 R0	0.1	RP HT	1.2	positive	uptake in 1 LN A. iliaca int. left	negative	? (7)	RT including pelvic region

PSA 1 = PSA at diagnosis; p = perineal; NS = nerve-sparing; HT = hormone therapy; RP = radical prostatectomy; PSA 2 = PSA at PET/CT; RT = radiotherapy; ww = watchful waiting.

0–4), the $SUV_{max.}$ was 2.65 (range 0–4). The positive predictive value (ppV) of [^{11}C]choline PET/CT as goes for the correct detection of lymph node metastases was 53%.

Salvage lymph node dissection was generally well tolerated. In one case with lymph node dissection including the paraaortic region a postoperative paralytic ileus was observed. In another case, a temporary hydrone-

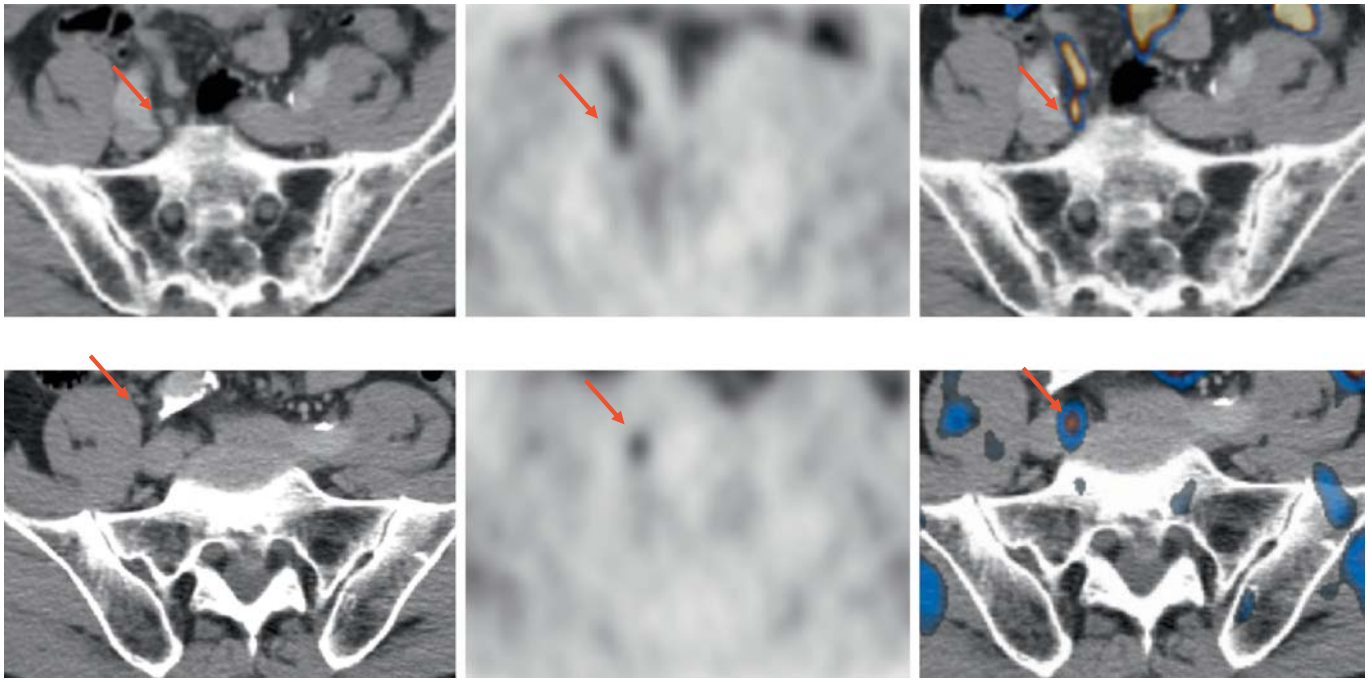

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Fig. 2. [^{11}C]choline PET/CT (transaxial slices) of patient 4 after radical prostatectomy (pT3b pN1 cM0 GIII Gl. 9 R0). Two lymph nodes (arrows) medial of the right common iliac artery are depicted and show an intensive focal uptake. Transaxial slices (from left to right) of the CT, the PET and the fused PET/CT images are shown for both lymph nodes. The histology after right salvage lymphadenectomy confirmed the presence of lymph node metastases. Still, after 3 months PSA started to rise again and in the further course the patient developed bone metastases.

phrosis occurred following ureteral mobilization during extensive lymph node dissection. Treatment was a temporary ureteral stenting. One lymphocele requiring drainage.

Discussion

Although PSA is a very sensitive serum marker for detecting biochemical failure, it can not precisely distinguish between a local or metastatic (i.e. lymph node or far distant) clinical progression. Although PSA screening caused a stage shift in prostate cancer it is estimated that about 30–50% of patients after curative primary surgical treatment will still get into progression at some stage [17]. The percentage of recurrences after external beam radiation or brachytherapy is less clear. Physical examination and conventional imaging techniques are not sensitive enough for the detection of recurrent disease. CT scans identify lymph node metastases covering a wide range of sensitivity. The main problem when applying conventional CT scans is that in lymph node metastases an accumulation of contrast medium is not present and size alone is not reliable [18]. Several studies showed [15, 19, 20] that [^{11}C]choline-PET/CT effectively visualized both prostatic tumors and metastases, and that the major clinical role of this modality is the restaging of patients with serum increase of PSA after radical treatment. Although the extent of required diagnostic means to finally improve survival is controversially discussed a precise localization of the source of clinical recurrence seems to be crucial as tailored subsequent therapeutic strategies depend on this information.

A limitation of this study which is worth mentioning is that the surgeon had knowledge of the PET/CT results before the salvage lymphadenectomy was performed. On the other hand during surgery, the presence or absence of tumor tissue was assessed by systematic evaluation of the specific anatomical sites, independent of positive or negative [^{11}C]choline PET/CT imaging results. Furthermore, the study was limited by the small sample size and the inhomogeneous distribution of the study cohort. Considering the false-positive nodes, we cannot exclude the possibility that the surgeon was unable to remove neoplastic

tissue with positive imaging despite excessive surgical dissection.

Recent data suggest that [^{11}C]choline PET and PET/CT are promising tools to detect clinical relapse after primary therapy of prostate cancer [20–22]. Scattoni et al. [23] investigated in a study with 25 patients the detection of lymph-node metastases with integrated [^{11}C]choline PET/CT in patients after radical retropubic prostatectomy and confirmed the results by open pelvic or retroperitoneal lymphadenectomy. A lesion-based analysis showed that [^{11}C]choline PET/CT sensitivity, specificity, positive, negative predictive value, and accuracy were 64, 90, 86, 72 and 77%, respectively. Choline, as a modern tracer, is a component of phosphatidylcholine, an essential element of phospholipids in the cell membrane [24]. It is well known that cancer is associated with increased cell proliferation as well as up-regulation of the specific enzyme choline-kinase. The upregulation provides the rationale for the use of [^{11}C]choline PET in malignant diseases. An advantage of [^{11}C]choline is that this tracer is in at least 30% of patients slowly excreted in the urine providing clear images of the small pelvis including the prostatic fossa and the lymphatic drainage of that region [25, 26]. PET imaging based on [^{18}F]fluorodesoxyglucose also has proved increasing usefulness in clinical oncology for disease staging, prognostic stratification and early detection of recurrent disease. However, its use in prostate cancer has been reported to be limited due to low sensitivity because of the high urinary excretion and the variable uptake into the primary tumor and metastases [27, 28].

In the presented study, an integrated contrast-enhanced PET/CT scanner was used. PET applied on its own visualizes localized relapse or metastasis as an active focus, but the risk of false positive results is given. However, areas with increased metabolism can be assigned to anatomical structures by fused PET/CT. Fusion images help to distinguish the often more symmetric physiological uptake [29] for example in the intestines from pathological uptake in metastases by providing more accurate information on the anatomical relationship. The combination of versatile PET based metabolic imaging together with high resolution CT may provide the basis for targeted surgical procedures or modern conventional radiation approaches.

This study provides information of a salvage strategy offered to patients with suspected lymphatic metastases as an individualized therapeutic concept with the potential intention to cure. To provide a most uniform cohort, data of two neighboring centers were combined. Imaging studies were all performed at the same institution. The analysis of the reported data was carried out to provide valuable information in order to set up a randomized prospective study. Due to the current setup some limitations are obvious. A second [^{11}C]choline PET/CT study was not carried out as a standard procedure in all individuals after salvage lymph node dissection. This means that it cannot be ruled out that some true-positive lymph nodes were not removed by surgery and thus the imaging was depicted as false-positive. In a prospective randomized clinical study the application of such a second [^{11}C]choline PET/CT should be considered. A substantial issue in any study design is to find out the real false negative rate as it is not possible to perform lymph node dissections in patients with a negative imaging study. We also do not know if the presented results are reproducible in the case of previous hormonal therapy. In patients, having been treated with hormonal therapy, the level of PSA is suppressed and may not correlate with tumor size or metabolism. Up to now it is not known whether the influence on choline metabolism and on PSA is in the same direction [30, 31].

To our knowledge this is one of the first reports [32] investigating the association between [^{11}C]choline PET/CT imaging and histology results after salvage lymph node dissection in patients with suspected clinical relapse from prostate cancer. The aim of the study was also to evaluate a potential benefit on the course of the disease by means of a schematic patient follow-up. The presented results demonstrate that almost all patients experienced further progress after salvage surgery in a relatively short period of time. This gives rise to the hypothesis that salvage lymph node dissection removes only the tip of an iceberg as more micrometastases are likely to be present at this stage. The surgical approach might be more effective if imaging tracers are used, that can be identified intraoperatively. For other tumor entities this has been demonstrated [33].

Conclusions

[^{11}C]choline-PET/CT imaging may be useful tool for restaging relapsing prostate cancer patients after initial curative treatment. The presented data show that this technique is able to suggest lymph node recurrences responsible for rising PSA. Yet, the clinical value of [^{11}C]choline-PET/CT targeted salvage lymph node dissection is questionable as in our study all patients got further progression within a limited period of time having

undergone the risk of potential morbidity due to a second operation. Systemic therapy is not avoidable by means of salvage surgery. The clinical course of the disease observed in this study cohort is a hurdle to set up prospective studies with greater sample size and longer follow up to conclusively determine a survival benefit of patients undergoing salvage surgery based on [^{11}C]choline-PET/CT imaging.

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