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Angaben zur Veröffentlichung / Publication details:

Bluemel, Christina, Markus Krebs, Bülent Polat, Fränze Linke, Matthias Eiber, Samuel Samnick, Constantin Lapa, et al. 2016. "68Ga-PSMA-PET/CT in patients with biochemical prostate cancer recurrence and negative 18F-choline-PET/CT." *Clinical Nuclear Medicine* 41 (7): 515–21. <https://doi.org/10.1097/rnu.0000000000001197>.

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^{68}Ga -PSMA-PET/CT in Patients With Biochemical Prostate Cancer Recurrence and Negative ^{18}F -Choline-PET/CT

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Conflicts of interest and sources of funding: S.K. and H.J.W. are CEOs and shareholders of Scintomics, the company distributing PSMA-directed peptide ligands. Both coauthors have not influenced data acquisition or analysis but contributed to conception/design, drafting of manuscript, administrative, technical or material support, and supervision.

Author contributions: Conception and design: C.B., K.H., A.K.B., H.J.W., and J.C. Acquisition of data: C.B., C.L., M.L., and K.H. Analysis and interpretation of data: C.B., B.P., M.K., F.L., C.L., T.B., and K.H. Drafting of manuscript: C.B., J.C., C.L., A.K.B., H.J.W., and K.H. Critical revision of manuscript: M.E., D.R., J.C., and K.H. Administrative, technical, or material support: M.W., S.K., S.S., and H.J.W. Supervision: S.S., M.L., H.R., D.R., A.K.B., and H.J.W.

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Approximately one third of prostate cancer patients experience biochemical recurrence within 5 years of primary curative treatment.¹ A variety of treatment options including salvage radiation therapy and/or systemic treatment are available for these patients.² Salvage radiotherapy after biochemical recurrence after radical prostatectomy improved biochemical recurrence-free survival in patients with serum PSA levels greater than 0.5 ng/mL.³ Moreover, prostate cancer specific survival improved after salvage radiotherapy if the PSA doubling time is less than 6 months.⁴ Therefore, localization of recurrent disease is important as it may enable early and/or personalized rational therapeutic interventions that may lead to improved outcomes.

Several imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI) and transrectal ultrasound (TRUS) are used to identify sites of recurrence.⁵ PET imaging using probes of lipid and amino acid metabolism has also been used successfully to detect recurrent disease and has shown impact on patient management.^{5,6} However, when serum PSA levels are less than 3 ng/mL, recurrence sites are only detected in 40% to 60% of patients.^{7–10}

Expression of the transmembrane folate hydrolase prostate-specific membrane antigen (PSMA) has been described in normal and hyperplastic prostate tissue, prostatic intraepithelial neoplasia, and invasive carcinomas.^{11–13} Moreover, elevated PSMA expression in prostate cancer carries a poor prognosis.¹⁴ Different groups have reported the successful radiolabeling of peptide ligands that specifically bind to PSMA.^{15,16} ^{68}Ga -PSMA-PET/CT detects sites of recurrence with high accuracies ranging from 74% to 89%.^{17–19} However, ^{68}Ga -labelled compounds are produced in generators that provide limited activity per synthesis. Thus, depending on the age of the generator, only 1 to 4 patient doses per elution can be produced. In contrast, more than 10 times the activity of ^{18}F -choline can be provided by one cyclotron production.

To optimize resource utilization, we developed a sequential clinical imaging approach as follows: patients with biochemical relapse after primary curative treatment underwent an ^{18}F -choline-PET/CT scan first. If this scan was negative, patients were offered an additional ^{68}Ga -PSMA-PET/CT using EuK-Sub-kff- ^{68}Ga -DOTAGA.²⁰ The aim of this sequential molecular imaging approach was to determine whether the addition of

TABLE 1. Site of Recurrence (n = 125 Patients)*

Choline-Positive Lesions (n = 93 Patients)	n (%)
LR	19 (20%)
LN	42 (45%)
Bone	13 (14%)
LR and LN	4 (4%)
LR and bone	2 (2%)
LN and bone	7 (8%)
LR, LN, and bone	2 (2%)
Distant metastases	4 (4%)
PSMA-positive lesions (n = 14/32 patients)	
LR	8 (57%)
LN	6 (43%)

*Patients, who refused additional ⁶⁸Ga-PSMA-PET/CT (n = 9) and patients with equivocal findings (n = 5) were excluded. LR indicates local recurrence; LN, lymph node metastases; bone, bone metastases.

a ⁶⁸Ga-PSMA-PET/CT scan in patients with biochemical recurrence and a negative ¹⁸F-choline scan provided incremental diagnostic value.

MATERIALS AND METHODS

Sequential Molecular Imaging Approach

The sequential imaging approach is used routinely in our clinic commences with an ¹⁸F-choline-PET/CT. In case of a positive choline-result, no further imaging is performed. Patients with a negative ¹⁸F-choline study are offered an additional ⁶⁸Ga-PSMA-PET/CT study. Informed consent for the clinical scans was obtained from all individuals. Because of the retrospective design, a need for formal review was waived by the ethics committee of the Universitätsklinikum Würzburg, Germany.

Patients

From January 2014 to May 2015, 139 consecutive patients with biochemical relapse defined as serum PSA values of 0.2 ng/mL or greater after radical prostatectomy or 2 ng/mL or greater in

patients treated with radiation therapy were offered the sequential imaging approach. The mean patient age was 69.4 ± 6.8 years (range, 46.8–83.0 years). Initial treatment included radical prostatectomy (RPT; 58 patients; 42%), radiotherapy (24 patients; 17%), or a combination of both (56 patients; 40%). One patient (1%) underwent focused high intensity ultrasound ablation (HIFU). The mean serum PSA level at recurrence was 5.4 ± 12.73 ng/mL (range, 0.20–126.56 ng/mL; median, 1.96 ng/mL). The PSA doubling time was 9.9 ± 10.6 months, and the PSA velocity was 7 ± 25 ng/mL per year.

Choline-PET/CT

¹⁸F-choline was synthesized as previously described.²¹ Images were acquired using a Biograph mCT 64 (Siemens Medical Solutions, Germany). Patients fasted for at least 4 hours before the PET/CT scans. 311 ± 27 MBq ¹⁸F-choline (range, 229–385 MBq) were injected intravenously, and patients received 10 mg of furosemide at the same time. Sixty minutes later, the emission data were acquired from the base of skull, or the vertex, to the proximal thighs (2–3 minutes per bed position). Subsequently, contrast-enhanced CT (CECT) images were acquired. After decay and scatter correction, PET data were reconstructed iteratively with attenuation correction using dedicated software (HD-PET; Siemens e-soft, Germany).

PSMA-PET/CT

⁶⁸Ga-PSMA I&T was synthesized as described previously.¹⁶ A mean of 133 ± 20 MBq (range, 79–161 MBq) of ⁶⁸Ga-PSMA was injected. This was followed 60 minutes later by a low-dose CT acquisition for attenuation correction and lesion localization. PET emission data were then acquired for 2 to 3 minutes per bed position. PET data were also corrected for dead-time, random events, and scatter.

Image Analysis

PET/CT images were visually analyzed by 3 experienced nuclear physicians (C.B., C.L., and K.H.) for the presence and localization of suspicious lesions; in doubtful cases, diagnosis was reached by consensus. In PET, any focal uptake higher than the surrounding background and not associated with physiological uptake

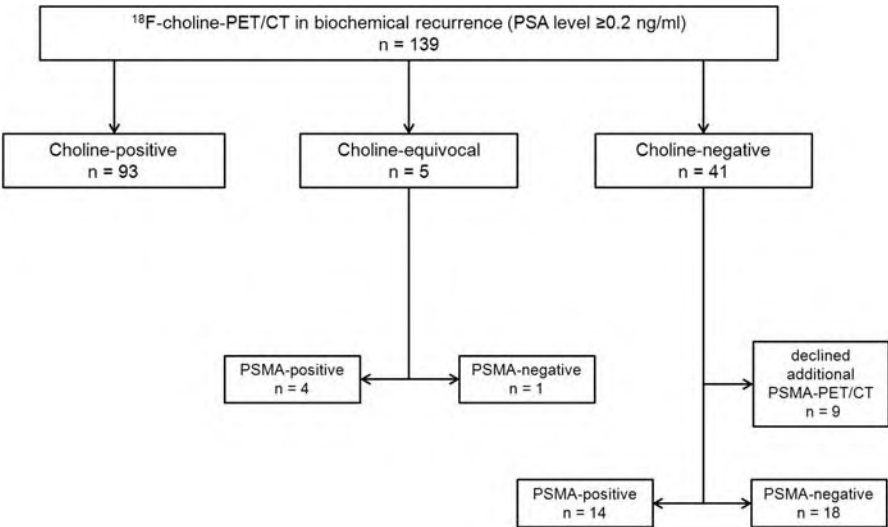


FIGURE 1. Flow diagram: sequential imaging approach (n = 139 patients).

was considered suspicious. Lesions were classified as malignant, equivocal, or benign. Visual findings were rated as equivocal if the uptake was not typical for metastasis or local recurrence but nevertheless unclear. Lesions were further classified by localization as listed in Table 1.

Statistical Analysis

Descriptive analysis was performed by calculating the median, mean, standard deviation, and range. PSA kinetics were calculated according to Pound et al.²² The detection rate on a per patient basis (patients with at least 1 positive finding) was plotted against the absolute PSA value and PSA kinetics according to previously published studies.^{7,19} Two-sample *t* test was used to evaluate differences in the Gleason score between subgroups. The Mann-Whitney *U* test was used to evaluate differences in PSA kinetics among subgroups with and without pathological uptakes. All tests were performed 2-sided, and a level of significance of $\alpha = 5\%$ was used. Statistical analyses were conducted with SPSS statistics software (version 22.0; SPSS, Inc., Chicago, IL).

RESULTS

Sequential imaging findings: Data of 139 consecutive patients were analyzed. The clinical report was positive in 93 (66.9%), negative in 41 (29.5%), and equivocal in 5 (3.6%) patients. Approximately 32 (78.0%) of 41 patients with a negative ¹⁸F-choline-PET/CT agreed to undergo an additional ⁶⁸Ga-PSMA-scan, whereas 9 (22.0%) of 41 declined participation (Fig. 1). The time interval between ¹⁸F-choline- and ⁶⁸Ga-PSMA-PET/CT was 19 ± 16 days (range, 5–51 days; median, 11 days).

Patients with an equivocal ¹⁸F-choline study (*n* = 5) were excluded from the overall analysis. However, because all 5 patients with equivocal ¹⁸F-choline-PET/CT scans underwent an additional ⁶⁸Ga-PSMA scan, their findings are mentioned separately (see below in “Results” section). Those patients who declined the ⁶⁸Ga-PSMA PET/CT study (*n* = 9) were excluded from further analysis. Thus, data from 125 patients were analyzed.

Detection rates and lesion localization: The overall detection rate of the sequential molecular imaging approach was 85.6% (107/125). ¹⁸F-choline-PET/CT detected disease recurrence in 74.4% (93/125), whereas additional ⁶⁸Ga-PSMA-PET/CT identified recurrence in 14 of 32 patients with negative choline scans (43.8%). Thus, the overall detection rate increased by 11.2% (14/125). For details, see Figure 2 and Table 2. Choline-negative but ⁶⁸Ga-PSMA-positive lesions occurred in the prostatic bed in 8 (25.0%) and in lymph nodes in 6 (18.8%) of the 32 patients (Table 1).

Serum PSA level: The sequential imaging approach and ¹⁸F-choline-PET/CT alone detected recurrence best when PSA levels were 2 ng/mL or greater. Corresponding detection rates were 97.0% (64/66) for the sequential imaging approach and 89.4% (59/66) for ¹⁸F-choline alone.

Detection rates decreased with lower PSA values. For the sequential imaging approach, they were 81.8% (27/33) for PSA values of 1 to 2 ng/mL and 61.5% (16/26) for PSA values of 0.2 ng/mL or greater to less than 1 ng/mL. Detection rates for ¹⁸F-choline-PET/CT were lower at 66.7% for PSA of 1 to 2 ng/mL and 46.1% for PSA levels of 0.2 ng/mL or greater to less than 1 ng/mL. More detailed results are displayed in Figure 2 and Table 2.

The highest rate of positive ⁶⁸Ga-PSMA findings occurred when PSA was greater than 2 ng/mL (Figs. 3 and 4). Approximately 71.4% (5/7) of these patients had positive ⁶⁸Ga-PSMA scans. When PSA levels were 1 to 2 ng/mL and 0.2 ng/mL or greater to less than 1 ng/mL, ⁶⁸Ga-PSMA detection rates were 45.5% (5/11) and 28.6% (4/14), respectively.

PSA doubling time and PSA velocity: Detection rates of sequential imaging were unrelated to PSA doubling time. The highest detection rate was found in patients with PSA doubling time of greater than 4 to 6 months (95.7%; 22/23).

In patients with PSA velocity of 5 ng/mL per year or greater, ¹⁸F-choline-PET/CT successfully detected sites of recurrence in all patients (*n* = 27). The added value of ⁶⁸Ga-PSMA-PET/CT was highest in patients with a PSA velocity of 2 to less than 5 ng/mL

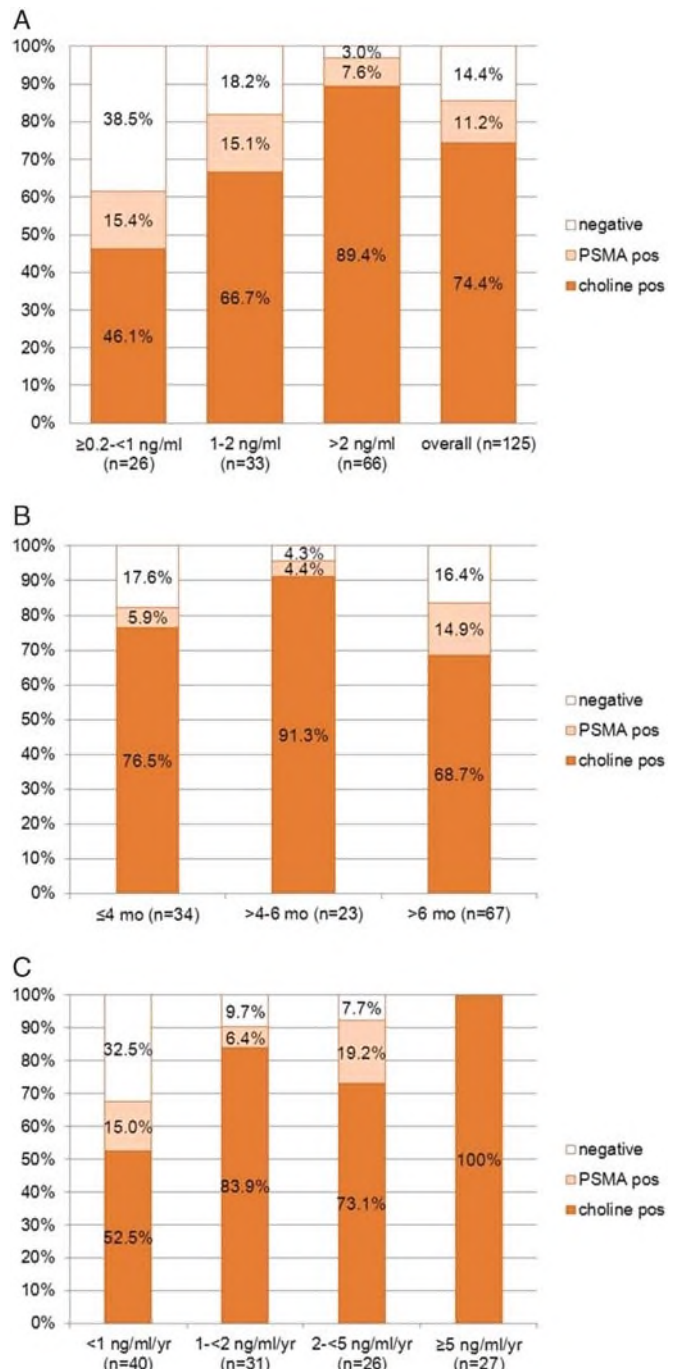


FIGURE 2. Detection rates in relation to PSA levels (A), PSA doubling time (B), and PSA velocity (C) at the time point of PET/CT (*n* = 125; PSA kinetics in 1 patient unavailable).

TABLE 2. Biochemical Findings and Lesion Detectability

	n	Sequential Imaging Approach Positive, n (%)	¹⁸ F-Choline Positive, n (%)	⁶⁸ Ga-PSMA Positive, n in Choline-Negative Patients (%)
Overall	125	107/125 (85.6%)	93/125 (74.4%)	14/32 (43.8%)
PSA level (ng/mL)				
≥0.2– < 1	26	16/26 (61.5%)	12/26 (46.1%)	4/14 (28.6%)
1–2	33	27/33 (81.8%)	22/33 (66.7%)	5/11 (45.5%)
>2	66	64/66 (97.0%)	59/66 (89.4%)	5/7 (71.4%)
PSA doubling time (mo)*				
≤4	34	28/34 (82.4%)	26/34 (76.5%)	2/8 (25.0%)
>4–6	23	22/23 (95.7%)	21/23 (91.3%)	1/2 (50.0%)
>6	67	56/67 (83.6%)	46/67 (68.7%)	10/21 (47.6%)
PSA velocity (ng/mL per year)*				
<1	40	27/40 (67.5%)	21/40 (52.5%)	6/19 (31.5%)
1– < 2	31	28/31 (90.3%)	26/31 (83.9%)	2/5 (40.0%)
2– < 5	26	24/26 (92.3%)	19/26 (73.1%)	5/7 (71.4%)
≥5	27	27/27 (100%)	27/27 (100%)	—

PSA indicates prostate-specific antigen; PSMA, prostate-specific membrane antigen; *PSA kinetics not available in 1 patient;

per year (71.4%; 5/7). Further details (detection rates of ¹⁸F-choline-PET/CT, ⁶⁸Ga-PSMA-PET/CT, and the sequential imaging approach) are depicted in Figure 2 and Table 2. The comparison of PSA levels and kinetics in the choline-positive versus choline-negative and PSMA-positive versus PSMA-negative subgroup is presented in Table 3.

Equivocal Findings

All 5 patients with equivocal findings in the ¹⁸F-choline-PET/CT underwent an additional ⁶⁸Ga-PSMA-PET/CT. In 1 patient, ⁶⁸Ga-PSMA-PET/CT excluded liver and lymph node metastases confirmed using lymphadenectomy. The PSA value

was stable (1.6 ng/mL postsurgery vs 1.7 ng/mL presurgery). In 2 patients with equivocal ¹⁸F-choline-findings, intense focal ⁶⁸Ga-PSMA uptake confirmed suspicion for local recurrence and bone metastasis. The patient with bone metastases was started on antihormonal treatment. The patient with suspected local recurrence was advised to undergo salvage radiotherapy but opted for antihormonal treatment. In both patients, no follow-up serum PSA values are available.

In the remaining 2 patients, no increased ⁶⁸Ga-PSMA uptake was found throughout the scan, especially not in lieu of equivocal ¹⁸F-choline uptake. One patient with equivocal ¹⁸F-choline uptake in the prostatic fossa showed stable PSA of 0.25 ng/mL 2 months later. The other patient with equivocal uptake in a vertebral body

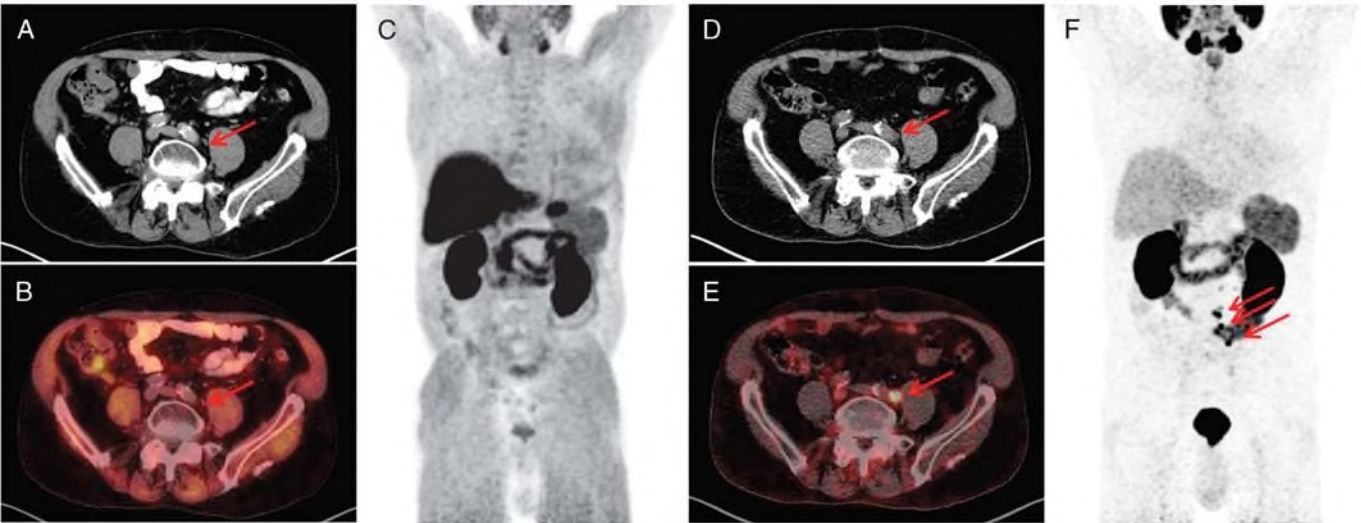


FIGURE 3. A 64-year-old patient with PSA relapse (T3aNO; Gleason score, 8; PSA level, 4.0 ng/mL; PSA doubling time, 5.9 months) radical prostatectomy, lymphadenectomy, and radiotherapy. ¹⁸F-choline-PET/CT showed no suspicious lesion (A–C); ⁶⁸Ga-PSMA-PET/CT (D–F) showed multiple iliac and retroperitoneal lymph node metastases (arrows) without ¹⁸F-choline-uptake (arrows in panel A, B).

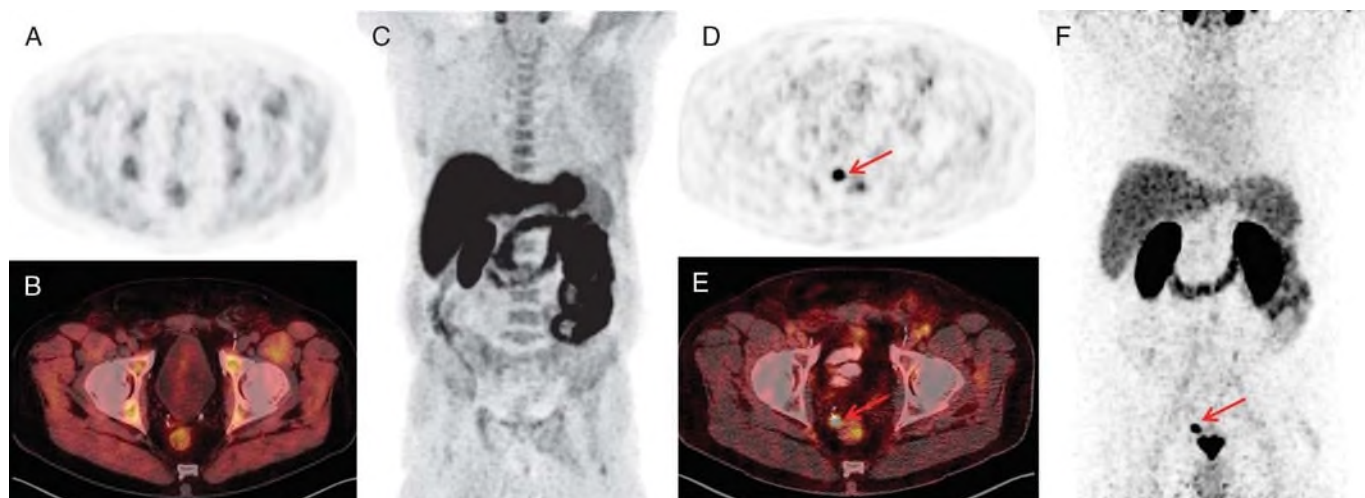


FIGURE 4. A 72-year-old patient with PSA relapse (T2cN0; Gleason score, 7; PSA level, 1.43 ng/mL; PSA doubling, 17.6 months) after radical prostatectomy and lymphadenectomy. ^{18}F -choline-PET/CT showed no suspicious lesion (A–C), but ^{68}Ga -PSMA-PET/CT demonstrated local recurrence (D–F, arrow).

(no sclerosis in CT) showed a rising PSA level (from 0.44 to 1.1 ng/mL) 4 months later; also, the follow-up ^{68}Ga -PSMA-PET/CT was read negative.

DISCUSSION

We demonstrate that ^{68}Ga -PSMA-PET/CT detects disease in 43.8% of patients with PSA recurrence but negative ^{18}F -choline scans. Adding ^{68}Ga -PSMA PET/CT in patients with negative choline scans improved the overall recurrence detection rate from 74.4% to 85.6%. The detection rate of the proposed sequential imaging approach is thus comparable to that of ^{68}Ga -PSMA-PET/CT range from 74.2% to 89.5%).^{17–19,23,24} In the present cohort, additional lesions detected with ^{68}Ga -PSMA-PET/CT were located in lymph nodes and prostate bed.

The current results are consistent with ^{68}Ga -PSMA-PET/CT detection rates of 89.5% in 248 patients¹⁹ and 82.8% in 319 patients.¹⁸ In contrast, Ceci et al recently reported a lower detection rate of 74.2% for ^{68}Ga -PSMA-PET/CT in 70 patients with biochemical recurrence.¹⁷ However, the inclusion criteria were different to our cohort, and in these studies, all patients underwent ^{68}Ga -PSMA-PET/CT and no sequential imaging.

The sequential imaging approach we developed and proposed detected recurrence at a higher rate than the majority of studies using C-11- (pooled detection rate of 62%, ranging from 28% to 88%)^{25–28} or ^{18}F -choline (ranging from 43% to 84%).^{29,30} The detection rate of ^{18}F -choline-PET/CT in the present study was consistent with these previous reports.^{29,30}

The detection of recurrence is most challenging in patients with low serum PSA values. In patients with PSA values less than 1 ng/mL, the detection rate of the sequential imaging approach (61.5%) was in the range of recently published values for ^{68}Ga -PSMA-PET/CT (53% and 67%).^{18,19} It was superior to the reported choline-PET/CT detection rates (19%–36% in PSA levels ≤ 1.5 ng/mL).^{7,8,31–33}

In a preliminary study comparing ^{68}Ga -PSMA and ^{18}F -choline PET/CT in 32 patients, Afshar-Orohmiéh et al demonstrated that ^{68}Ga -PSMA-PET/CT detected more lesions than ^{18}F -choline-PET/CT (78 vs 56).²³ Recently, Morigi et al confirmed these results.³⁴ A comparison of lesion detectability between the 2 approaches was, by design, not possible in the current study as only choline-negative patients underwent ^{68}Ga -PSMA-PET/CT. However, the clinical relevance of detecting additional lesions in patients with known metastatic disease and multiple lesions (>5) on choline-PET is debatable. In contrast, PSMA-positive findings in choline-negative patients are highly likely to impact patient management.

Recent introduction of $^{68}\text{Ge}/^{68}\text{Ga}$ -generators, automation of the radiopharmaceutical production, advances in peptide chemistry, and identification of relevant imaging targets have led to the successful clinical translation of ^{68}Ga -PSMA imaging.³⁵ However, generators provide limited activity of ^{68}Ga -labeled compounds per synthesis (1–4 patient doses depending on the generator age). The limited activity needs to be allocated to several other receptor-based imaging approaches including somatostatin and CXCR4 receptor imaging.³⁶ In light of the high clinical demand for

TABLE 3. Relationship Between GLEASON Score, Biochemical, and Scan Finding (n = 125 Patients; Mean (Range) and Median)

PET/CT	Choline-Positive (n = 93)	Choline-Negative (n = 32)	P	PSMA-Positive (n = 14)	PSMA-Negative (n = 18)	P
Gleason score	7 (5–10) 7	7 (6–9) 7	>0.05	7 (6–9) 7	7 (6–9) 7	>0.05
PSA level (ng/mL)	7.42 (0.22–126.59) 2.84	1.34 (0.23–4.39) 1.05	<0.001	2.01 (0.53–4.39) 1.47	1.09 (0.30–2.55) 0.74	0.054
PSA doubling time (mo)#	8.2 (0.7–51.1) 5.2	12.1 (2.1–59.6) 9.0	0.005	10.7 (2.1–19.3) 9.4	12.2 (2.4–59.6) 7.6	0.540
PSA velocity (ng/mL per year)#	10.1 (0.1–267.8) 1.4	1.0 (0.1–3.5) 0.7	<0.001	1.3 (0.2–3.5) 1.0	0.9 (0.1–2.9) 0.6	0.226

#PSA kinetics not available in one patient.

PSA indicates prostate-specific antigen; PSMA, prostate-specific membrane antigen.

peptide receptor imaging in prostate cancer patients (20–40 patients per week in many centers), the adequate supply of ^{68}Ga -activity to various imaging tests presents a clinical challenge.

In contrast, ^{18}F -labeled probes such as choline are available in near unlimited quantities. To exploit this advantage and to overcome the limited ^{68}Ga -supply, we have introduced the sequential imaging approach. An ^{18}F -choline-PET/CT study is performed first and is followed by a ^{68}Ga -PSMA-PET/CT only if the choline scan is negative. ^{18}F -choline detected sites of recurrence in 67% of all patients. Thus, the current results suggest that the need for ^{68}Ga -PSMA-PET/CT could be reduced by two thirds. This, in turn, allows for more efficient workflows and resource allocation.

The current approach is translatable and can be adopted at any imaging center. In addition, centers without access to ^{68}Ga -PSMA could perform a choline-scan first and, in case of a negative study, refer the patient to one specialized imaging centers. A disadvantage of the current approach is the additional radiation exposure. The introduction of ^{18}F -labeled PSMA tracers^{37,38} and their successful translation into the clinical routine would solve the logistical problems.³⁹ However, until ^{18}F -labeled PET probes are widely available, a sequential imaging approach combining choline and ^{68}Ga -PSMA tracers might be an attractive interim solution.

The current study has several limitations: First, the study group was heterogeneous and included patients after radical prostatectomy but also after other treatments with curative intent. However, the population appropriately reflects the usual clinical referral pattern. Second, this was a retrospective analysis of consecutive patients referred for PET/CT imaging. Thus, referral bias cannot be excluded. Third, subgroup analyses may be of limited value because of the small sample size. Fourth, no lesion-based analysis could be performed because, by design, ^{68}Ga -PSMA scans were only performed in choline-negative patients. Thus, it is unknown whether some ^{18}F -choline-positive lesions may have been ^{68}Ga -PSMA negative. Alternatively, ^{68}Ga -PSMA PET/CT might have revealed additional lesions. Lastly, all patients had biochemical recurrence and we calculated detection rates. However, verification of all imaging findings especially in patients with multiple lesions is practically impossible, and we accordingly refrained from calculating sensitivity or specificity.

CONCLUSIONS

The sequential imaging approach designed to limit ^{68}Ga -PSMA imaging to patients with negative choline scans resulted in comparable detection rates as reported for ^{68}Ga -PSMA PET/CT alone. Moreover, ^{68}Ga -PSMA PET/CT identified sites of recurrent disease in 43.8% of the patients with negative ^{18}F -choline PET/CT scans.

ACKNOWLEDGMENT

The authors thank Simone Seifert, Simone Groß, Michael Schulze-Glück (members of the nuclear medicine PET team), and Inge Grelle for the support and assistance.

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