¹¹C- or ¹⁸F-Choline PET/CT for Imaging Evaluation of Biochemical Recurrence of Prostate Cancer

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Recurrence of prostate cancer is suspected when an increase in the prostate-specific antigen level is detected after radical treatment; the recurrence could be local relapse, distant relapse, or both. Differentiation between the two patterns of relapse is critical for choosing the proper treatment strategy. Choline PET/CT could be of help in discriminating patients with local, lymph node, and bone recurrences, thus having an impact on patient management.

Key Words: prostate cancer; biochemical recurrence; ¹¹C-choline; ¹⁸F-choline; PET/CT

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fter radical treatment for prostate cancer (PCa), prostatespecific antigen (PSA) is a sensitive biomarker indicating the presence of recurrent disease. However, it does not provide information regarding the sites of recurrent disease, which is mandatory for correct treatment planning (1). PET/CT with a choline tracer radiolabeled with either ¹¹C (¹¹C-choline) or ¹⁸F (¹⁸F-choline) has been successfully used to identify and localize recurrences of PCa. The rate of detection by choline PET/CT may vary according to the PSA level, with a higher accuracy for PSA levels of greater than 1 ng/mL. However, recent data also showed the potential of this imaging modality in patients experiencing low PSA levels (<1 ng/mL) (2,3). Recently, European Association of Urology guidelines (4) suggested the use of choline PET/CT in patients with biochemical relapse (BR) and PSA levels of 1-2 ng/mL. The main advantage of choline PET/CT in recurrent PCa is represented by the possibility of detecting distant metastases (Fig. 1), thus influencing patient management, especially for patients with a single site of disease or oligometastatic disease.

This review provides an overview of the diagnostic performance of ¹¹C-choline and ¹⁸F-choline PET/CT in detecting local, lymph node, and bone recurrences, with a specific focus on the influences of PSA levels and PSA kinetics.

METHODS

A comprehensive PubMed literature search up to February 2016 was performed, and articles related to ¹¹C-choline and ¹⁸F-choline PET/CT in BR of PCa were identified. Search terms used to identify such articles were "PET" or "PET/CT," "¹¹C-choline," "¹⁸F-choline," "prostate cancer," "biochemical recurrence," and "recurrent." Original publications, meta-analyses, and reviews were selected for inclusion in this review. Table 1 and Table 2 show studies reporting the sensitivity and specificity of ¹¹C- choline and ¹⁸F-choline, respectively, in recurrent PCa, for a total of 36 studies and 3,493 patients.

¹¹C-CHOLINE PET/CT IN RECURRENT PCA

Local Recurrence

The available data regarding the diagnostic performance of ¹¹Ccholine PET/CT in detecting local recurrence in patients with BR are limited and controversial. Reske et al. evaluated the role of ¹¹C-choline PET/CT in 36 patients with biopsy-proven low-volume local recurrence after radical prostatectomy (RP), reporting a sensitivity and a specificity of 73% and 88%, respectively (5). Souvatzoglou et al. found ¹¹C-choline uptake in the prostatic bed in 7 of 37 patients (19%) who had PSA failure after RP and were candidates for salvage radiotherapy (RT) of the prostatic fossa (6). These data were substantially confirmed by Kitajima et al., who found a sensitivity of 54% and a specificity of 92% for ¹¹C-choline PET/CT in the detection of local relapse in 87 patients after RP (7).

Lymph Node Recurrence

Few prospective studies investigating the accuracy of ¹¹C-choline PET/CT in detecting lymph node metastases in patients with BR and having histopathology as a reference standard are currently available. One of the first studies was performed by Scattoni et al. (8). Using a per-lesion analysis, they found sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of 64%, 90%, 86%, 72%, and 77%, respectively, for ¹¹C-choline PET/CT (8). Similar results were reported by Schilling et al. (9) and Rinnab et al. (10), supporting the use of ¹¹C-choline PET/CT in patients with BR and suspected lymph node metastases. Kitajima et al. compared ¹¹C-choline PET/CT results with multiparametric MRI results in 115 patients with BR after RP (7). They reported patientbased sensitivity, specificity, and accuracy of 90%, 100%, and 93%, respectively, for ¹¹C-choline PET/CT in the detection of lymph node recurrence; with MRI, sensitivity, specificity, and accuracy for pelvic nodal involvement were 64%, 85%, and 70%, respectively (7).

Bone Metastases

¹¹C-choline PET/CT is an imaging modality that can be useful in detecting bone metastases. Fuccio et al. compared ¹¹C-choline

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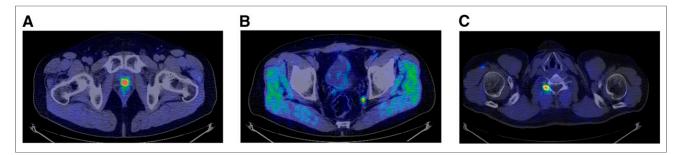


FIGURE 1. ¹¹C-choline PET/CT fusion images in 57-y-old patient with pathologic uptake. (A) Local recurrence. (B) Involvement of left internal iliac lymph node. (C) Bone metastases to seventh cervical vertebra.

PET/CT and bone scanning in 25 patients who had BR and only 1 bone lesion on bone scanning (11). ¹¹C-choline PET/CT detected multiple sites of relapse in 44% of the patients, with a sensitivity and a specificity of 86% and 100%, respectively (11). A direct comparison of ¹¹C-choline PET/CT and bone scanning was performed by Picchio et al. in 78 patients with PSA progression after primary treatment (12). They found a lower sensitivity for ¹¹C-choline PET/CT than for bone scanning (89% vs. 100%) but a higher specificity (98% vs. 75%) (12). Ceci et al. used ¹¹C-choline PET/CT to study 304 bone lesions (184 osteoblastic, 99 osteolytic, and 21 bone marrow lesions) in 140 patients during BR (13). They found a significant difference in the SUV_{max} between osteoblastic lesions (lower values) and osteolytic lesions (higher values) (13).

INFLUENCE OF PSA ON RATE OF DETECTION BY ¹¹C-CHOLINE PET/CT

Various studies have investigated the diagnostic accuracy of ¹¹C-choline PET/CT for detecting PCa recurrence and have reported different values for sensitivity and specificity (*5*,*7*–*9*,*11*,*12*,*14*). These variations could be attributed to the heterogeneity of patient populations in terms of inclusion criteria (i.e., PSA level, staging, and presence or absence of androgen deprivation therapy [ADT]). In addition to the largely documented influence of serum PSA measurement on the rate of detection of PCa recurrence by ¹¹C-choline PET/CT (*10*,*14*,*15*), several studies have reported that PSA kinetics, including PSA doubling time (PSAdt) and PSA velocity (PSAvel), are strong predictors for positive PET scan results.

Castellucci et al. investigated 190 patients with BR, subdividing the population into different groups according to trigger PSA levels, and identified an optimal PSA level of 2.43 ng/mL for detecting recurrent disease with a sensitivity and a specificity of 73% and 69%, respectively (*16*). The same group found that ¹¹C-choline PET/CT results were positive in 28% of 102 patients who experienced only slight increases in PSA levels (<1.5 ng/mL), with 7 patients having local recurrence, 13 having bone metastases, and 9 having lymph node relapse (*17*).

Using a larger cohort of patients, Giovacchini et al. found a patientbased sensitivity of 85%, specificity of 93%, and accuracy of 89% for ¹¹C-choline PET/CT in the detection of recurrent disease in 358 patients previously treated for PCa (*18*). As expected, the rate of positive scan results increased with increasing PSA levels (19% for PSA levels of 0.23–1 ng/mL, 46% for PSA levels of 1–3 ng/mL, and 82% for PSA levels of >3 ng/mL); the optimal PSA level was identified as 1.4 ng/mL (sensitivity, 73%; specificity, 72%) (*18*). Using a cohort of 170 patients with BR of PCa, the same group demonstrated that—like PSA—PSAdt is an independent predictor for ¹¹C-choline PET/CT (*19*).

Rybalov et al. evaluated 185 patients with BR to assess the impact of PSA levels and PSA kinetics on rates of detection by ¹¹C-choline PET/CT (20). A significant difference in the area under curve was observed between total PSA (0.721; P < 0.001) and PSAvel (0.730; P < 0.001) (20). Moreover, detection rates were less than 50% for PSA levels of less than 2 ng/mL or PSAvel of less than 1 ng/mL/y (20). Bertagna et al. suggested that the highest accuracy for patients with BR and treated only with RT is reached when ¹¹Ccholine PET/CT is performed above a cutoff value for PSA of 2.0 ng/mL (21). Mamede et al. evaluated the role of ¹¹C-choline in 71 patients who had BR after RP and a PSA level of less than 0.5 ng/mL and found true-positive findings in 21.1% of the patients (22). The mean ± SD PSA level, PSAdt, and PSAvel for patients with ¹¹Ccholine PET/CT-positive results were 0.37 ± 0.1 ng/mL, 3.4 ± 2.1 mo, and 0.05 ± 0.1 ng/mL/y, respectively (22). Interestingly, only PSAdt and the ongoing hormonal treatment were statistically significant in the prediction of positive PET/CT scan results in a multivariate analysis (22). Mitchell et al. evaluated the performance of ¹¹C-choline PET/CT in 176 patients with BR after treatment and found sensitivity, specificity, PPV, and NPV of 93%, 76%, 91%, and 81%, respectively (23). Moreover, the optimal PSA level for lesion detection was shown to be 2.0 ng/mL, and a multivariate analysis demonstrated that PSA (hazard ratio, 1.37; P = 0.04) and clinical stage at initial diagnosis (hazard ratio, 5.19; P =0.0035) were significant predictors of positive ¹¹C-choline PET/CT scan results (23). In a recent metaanalysis, Fanti et al. reported a ¹¹Ccholine PET/CT rate of detection of PCa at any site of relapse of 62% (95% confidence interval, 53%-71%), a pooled sensitivity of 89% (95% confidence interval, 83%-93%), and a pooled specificity of 87% (95% confidence interval, 71%-95%); these results were similar to previously reported results (24).

¹⁸F-CHOLINE PET/CT IN RECURRENT PCA

Local Recurrence

As for ¹¹C-choline PET/CT, limited diagnostic accuracy of ¹⁸F-choline PET/CT in detecting local recurrence has been reported. Using ¹⁸F-choline and ¹¹C-acetate PET/CT in a small cohort of 22 patients referred for salvage or adjuvant RT, Vees et al. observed a rate of detection of 55% for PSA levels of less than 1 ng/mL (25). In that study, MRI results were positive in 83% of the patients; this finding suggested that MRI may be more useful than PET/CT in patients with a low likelihood of distant metastases because the sensitivity and specificity of PET/CT were too low to justify its use as a standard diagnostic imaging modality for identifying early relapse (25). Panebianco et al. compared MRI performance and ¹⁸F-choline

 TABLE 1

 Summary of Studies with ¹¹C-Choline

		No. of	Type of data	PSA (ng/mL)				Assessed
Study	Year	patients	collection	Median	Range	Sensitivity (%)	Specificity (%)	parameters
de Jong et al. (43)	2003	36	Prospective	NA		55	100	LR, N, B
Scattoni et al. (8)	2007	25	Prospective	1.98	0.23–23.12	100	66	Ν
Rinnab et al. (10)	2007	50	Retrospective	2.42*	0.5–13.1	95	40	LR, N, B
				0.95†	0.41-1.40			
Schilling et al. (9)	2008	10	Retrospective	1.0 ^{‡,§}	0.7–1.4	NA	NA	Ν
				15.1 ^{‡,}	2.2–24.8			
Krause et al. (44)	2008	63	Retrospective	2.15	0.2–39	36/43/62/73¶	NA	LR, N, B, M
Reske et al. (5)	2008	36	Retrospective	2.0#	0.3–12.1#	73	88	LR
Rinnab et al. (14)	2009	41	Retrospective	2.1	0.41–11.6	93	36	LR, N, B
Castellucci et al. (16)	2009	190	Retrospective	2.1	0.2–25.4	73**	69**	LR, N, B, M
Giovacchini et al. (18)	2010	358	Retrospective	1.27	0.23–45	85	93	LR, N, B
Giovacchini et al. (19)	2010	170	Retrospective	1.25	0.23-48.6	87	89	LR, N, B
Fuccio et al. (11)	2010	25	Retrospective	6.3	0.2–37.7	86	100	В
Breeuwsma et al. (15)	2010	70	Prospective	10.7	0.6–54.7	81	100	LR, N, B
Bertagna et al. (21)	2011	210	Retrospective	5.9 [‡]	19.6 [‡] , ^{††}	77	93	LR
Castellucci et al. (17)	2011	102	Retrospective	0.93	0.67–1.10	93‡‡	74 ^{‡‡}	LR
Picchio et al. (12)	2012	78	Retrospective	2.4	0.2–500	89	98	В
Mitchell et al. (23)	2013	176	Retrospective	7.2	2.2–1,028	93	76	LR, N, B, M
Rybalov et al. (20)	2013	185	Retrospective	18.45 [‡]		80 ^{§§}	65 ^{§§}	LR, N, B, M
Mamede et al. (22)	2013	71	Retrospective	0.34 [‡]	0.1–0.5	88	98	LR, N, B, M
Kitajima et al. (7)	2014	115	Retrospective	2.5	0.58–68.3	54	92	LR
						90	100	N
						81	99	В

*Positive scan results.

[†]Negative scan results.

[‡]Mean.

[§]Negative histologic results.

Positive histologic results.

¹Expressed as rate of detection. The different sensitivity values are for different PSA levels: 36 for PSA less than 1, 43 for PSA between 1 and 2, 62 for PSA between 2 and 3, and 73 for PSA 3 or higher.

[#]PSA level in control patients was 0.1 (0.0–0.2).

**Cutoff value for trigger PSA was 2.43 ng/mL.

††SD.

^{‡‡}Cutoff value for PSAdt was 7.25 mo.

§§Data are for LR only.

NA = not available; LR = local recurrence; N = lymph node involvement; B = bone metastases; M = distant metastases.

PET/CT performance in patients with PCa recurrence (26). The population was subdivided into 2 groups: group A, including 28 patients with lesion sizes of 5–7.2 mm and a reduction in PSA levels after RT, and group B, including 56 patients with lesion sizes of 7.6–19.4 mm. In group A, the sensitivity, specificity, PPV, and accuracy of PET/CT in identifying local recurrence were 62%, 50%, 88%, and 60%, respectively (26). The diagnostic performance of MRI was better, given that the sensitivity, specificity, PPV, and accuracy were 92%, 75%, 96%, and 89%, respectively (26). Also, in group B, the performance of PET/CT was poorer than that of MRI, given that the sensitivity, specificity, PPV, and accuracy of PET/CT were 92%, 33%, 98%, and 91%,

respectively, whereas those of MRI were 94%, 100%, 100%, and 94%, respectively (26).

Lymph Node Recurrence

Few of the studies currently available have assessed the role of ¹⁸F-choline PET/CT in detecting recurrence in the lymph nodes. Husarik et al. studied 111 patients who had PCa and underwent ¹⁸F-choline PET/CT; 68 of these patients underwent this scan for the purpose of restaging (27). Local recurrence was correctly identified in 36 of 68 patients (27). Twenty-three patients had ¹⁸F-choline lymph node uptake, and in 20 of these 23 patients, lymph nodes were surgically removed (27). Histopathology confirmed metastases in all lymph

TABLE 2								
Summary of Studies	with	¹⁸ F-Choline						

		No. of	Type of data	PS	SA (ng/mL)			Assessed
Study	Year	patients	collection	Median	Range	Sensitivity (%)	Specificity (%)	parameters
Cimitan et al. (33)	2006	100	Prospective	1.98*,†	0.12–14.3	NA	NA	LR, N, B
				48.28*,‡	0.22-511.79			
Vees et al. (25)	2007	11	Retrospective	0.35	0.11–0.73	45 (PSA < 1)		LR, N, B
Pelosi et al. (34)	2008	56	Prospective	4.59*	0.1–39	43	NA	LR, N, B, M
Beheshti et al. (30)	2008	38	Prospective	56*		74	99	В
Husarik et al. (27)	2008	111	Prospective	10.81*		86	NA	LR, N, B
Beheshti et al. (29)	2010	70	Prospective	39.65*	0.1–239	79	97	В
Langsteger et al. (31)	2011	42	Prospective	NA		89	96	В
McCarthy et al. (32)	2011	26	Prospective	10.5	1.6–250	96	96	В, М
Henninger et al. (37)	2012	35	Retrospective	1.33 [§]	0.11–3.06	80 [§]	NA	LR, N, B
				1.17	0.13–2.94	50		
Panebianco et al. (26)	2012	84	Prospective	1.1* ^{,¶}	0.8–1.4	62¶	50¶	LR
				1.9*,#	1.3–2.5	92#	33#	
Schillaci et al. (39)	2012	49	Prospective	4.13*	0.09–15.51	67	NA	LR, N, B
Graute et al. (38)	2012	82	Retrospective	2.4	0.03–36	82**	74**	LR, N, B
Chondrogiannis et al. (<i>35</i>)	2013	46	Retrospective	6.5*	1.1–49.4	80 ^{††}	NA	LR, N, B
Marzola et al. (40)	2013	233	Retrospective	1.9 *,†	0.01–20.8	54 ⁺⁺	NA	LR, N, B
				14.7* ^{,‡}	0.01–300			
Beheshti et al. (36)	2013	250	Prospective	46.9*	314.7 ^{‡‡}	78/81/85/93 ^{§§}	NA	LR, N, B
Detti et al. (41)	2013	170	Retrospective	16.31	0.5–66	100	57	LR, N, B
Chiaravalloti et al. (42)	2016	79	Retrospective	1.37*	0.21–2	64	60	LR, N, B

*Mean.

[†]Negative scan results.

[‡]Positive scan results.

[§]Patients receiving ADT.

Patients not receiving ADT.

[¶]Lesion size of 5–7.2 mm.

[#]Lesion size of 7.6–19.4 mm.

**PSA threshold was 1.74 ng/mL.

^{††}Expressed as rate of detection.

^{‡‡}SD.

^{\$\$}The different sensitivity values are for different PSA levels: 78 for PSA more than 0.5, 81 for PSA more than 1, 85 for PSA more than 2, and 93 for PSA more than 4.

^{||||}PSAdt cutoff value was 6 mo.

NA = not available; LR = local recurrence; N = lymph node involvement; B = bone metastases; M = distant metastases.

nodes but also revealed 2 additional metastases that were not detected by ¹⁸F-choline PET/CT (*27*). Tilki et al. used ¹⁸F-choline PET/CT to study 56 PCa patients who had BR after RP and who subsequently underwent bilateral pelvic or retroperitoneal lymphadenectomy on the basis of positive ¹⁸F-choline PET/CT findings (*28*). Of 1,149 lymph nodes that were removed and histologically evaluated, 282 (24.5%) harbored metastases (*28*). A lesion-based analysis yielded ¹⁸F-choline PET/CT sensitivity, specificity, PPV, and NPV of 39.7%, 95.8%, 75.7%, and 83.0%, respectively (*28*).

Bone Metastases

Regarding the diagnostic performance of ¹⁸F-choline PET/CT in detecting bone metastases, Beheshti et al. compared the uptake

of ¹⁸F-fluorocholine in bone metastases in 70 patients before and after treatment for PCa with morphologic changes identified on CT (29). Overall sensitivity, specificity, and accuracy were 79%, 97%, and 84%, respectively, with lytic lesions showing higher metabolism than sclerotic lesions (29). The same group compared the potential value of ¹⁸F-choline with that of ¹⁸F-fluoride in detecting bone metastases in a cohort of 38 patients that included 21 patients with BR and suspected bone metastases (*30*). They reported sensitivity, specificity, and accuracy of 74%, 99%, and 85%, respectively, for ¹⁸F-choline and 81%, 93%, and 86%, respectively, for ¹⁸F-fluoride (*30*). Langsteger et al. compared the diagnostic performance of ¹⁸F-choline with that of ¹⁸F-fluoride (sodium fluoride) and found a significantly higher specificity for ¹⁸F-choline than for

¹⁸F-fluoride (96% vs. 91%; P = 0.033), although the sensitivities were the same (89%) (*31*). McCarthy et al. investigated 26 patients who had castration-resistant PCa and underwent ¹⁸F-choline PET/CT, bone scanning, and CT within 2 mo for suspected bone metastases (*32*). The result of this study showed good initial concordance (81%) of ¹⁸F-choline PET/CT with bone scanning and CT; the sensitivity, specificity, accuracy, PPV, and NPV of ¹⁸F-choline for lesion detection were 96%, 96%, 96%, 99%, and 81%, respectively (*32*).

INFLUENCE OF PSA ON RATE OF DETECTION BY ¹⁸F-CHOLINE PET/CT

As for ¹¹C-choline, the role of ¹⁸F-choline has been largely investigated in the setting of BR of PCa, and it appears that the sensitivity of this imaging modality is influenced by PSA levels and PSA kinetics. Cimitan et al. included 100 patients with BR after primary treatment for PCa in a study assessing the role of this imaging modality in detecting recurrent PCa (*33*). Interestingly, 89% of negative PET/CT scans were obtained in patients with serum PSA levels of less than 4 ng/mL and 87% of such scans were obtained in patients with a Gleason score of less than 8 (*33*). Pelosi et al. reported a sensitivity of 42.9% in detecting PCa lesions in 56 patients with BR after RP; detection rates increased with increasing PSA levels (20% at PSA levels of <1 ng/mL, 44% at PSA levels of 1–5 ng/mL, and 82% at PSA levels of >5 ng/mL) (*34*).

More recent studies reported a better rate of detection by ¹⁸Fcholine PET/CT in PCa restaging. Chondrogiannis et al. reported a positive detection rate of 80.4% in 46 patients with a suspected relapse after RT (35). Similarly to Pelosi et al. (34), this group also found increasing detection rates with increasing trigger PSA levels and reported that the detection rate was not influenced by ADT (35). Similar results were reported by Beheshti et al. in a population of 250 patients with BR; ¹⁸F-choline PET/CT detected malignant lesions in 185 of the 250 patients (74%) (36). The sensitivities of ¹⁸F-choline PET/CT increased with increasing trigger PSA levels (77.5%, 80.7%, 85.2%, and 92.8% at trigger PSA levels of >0.5, 1.0, 2.0, and 4.0 ng/mL, respectively) and were higher in patients who were receiving ongoing ADT (85%) than in patients who were not (59.5%) (P = 0.001) (36). Other investigators have suggested that ADT may be withheld before examination to reduce the risk of false-negative scans and thereby to increase the rate of detection by ¹⁸F-choline PET/CT (5.10.27.37).

Using a cohort of 82 patients with BR after RP, Graute et al. reported a detection rate of 62% and observed that the median PSA level was significantly higher in patients with PET-positive results than in those with PET-negative results (4.3 vs. 1.0 ng/mL; P < 0.01) (38). An optimal PSA threshold of 1.74 ng/mL for detecting recurrent disease was demonstrated by receiver operating characteristic curve analysis (area under the curve, 0.818; 82% sensitivity; 74% specificity) (38). Moreover, significant differences between patients with PET-positive results and those with PET-negative results were found for median PSAvel (6.4 vs. 1.1 ng/mL/y; P < 0.01) and PSA progression (5.0 vs. 0.3 ng/mL/y; P < 0.01), with corresponding optimal thresholds of 1.27 and 1.28 ng/mL/y, respectively (38).

Similar results were reported by Schillaci et al., who found that the rate of detection by ¹⁸F-choline imaging was closely related to PSA levels and PSA kinetics (*39*). In particular, this group recommended ¹⁸F-choline PET/CT in patients with PSA levels of greater than 2 ng/mL, PSAdt of less than or equal to 6 mo, and PSAvel of greater than 2 ng/mL/y (*39*). Marzola et al. investigated 233 patients with BR after RP and a high risk for relapse and reported an overall rate of detection by ¹⁸F-choline PET/CT of 54%; this rate increased significantly with increasing PSA levels (P < 0.001) (40). Interestingly, patients with positive PET/CT scan results had faster PSA kinetics (mean PSAdt, 6 mo; mean PSAvel, 9.3 ng/mL/y) than patients with negative PET scan results (mean PSAdt, 15.4 mo; mean PSAvel, 0.9 ng/mL/y) (40).

Detti et al. evaluated the potential of ¹⁸F-choline in 129 patients who underwent PET/CT for the purpose of restaging (41). They observed sensitivity and specificity of 100% and 56.9%, respectively, and found that PSA levels of greater than or equal to 1 ng/mL at the time of restaging were statistically significant predictive factors for PET-positive results, through either univariate analysis (P < 0.0001) or multivariate analysis (P < 0.0001) (41).

Recently, Chiaravalloti et al. investigated the performance of ¹⁸F-choline in detecting recurrent PCa and its relationship with PSAdt and PSAvel in 79 patients who were treated with RP and had low PSA levels (<2 ng/mL) (42). They found significant differences in PSAvel and PSAdt between patients with positive ¹⁸F-PET/CT scan results and those with negative ¹⁸F-PET/CT scan results (42). Using thresholds of 6 mo for PSAdt and 1 ng/mL/y for PSAvel, they found detection rates of 65% for PSAdt of less than or equal to 6 mo and 67% for PSAvel of greater than 1 ng/mL/y (42). These results suggested that ¹⁸F-choline PET/CT could be considered for the evaluation of patients with BR of PCa and with low PSA levels and that fast PSA kinetics could be useful in the selection of patients (42).

CONCLUSION

In patients with BR of PCa, either ¹¹C-choline PET/CT or ¹⁸Fcholine PET/CT has good accuracy in detecting lymph node and distant metastases, with the main advantage of being a single wholebody examination. However, limited accuracy regarding its role in detecting local recurrence is still being reported. The influence of PSA levels and PSA kinetics on the rate of detection by choline PET/CT should always be considered when this examination is performed in order to obtain a better patient selection.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

REFERENCES

- von Eyben FE, Kairemo K. Meta-analysis of ¹¹C-choline and ¹⁸F-choline PET/CT for management of patients with prostate cancer. *Nucl Med Commun.* 2014;35: 221–230.
- Mapelli P, Panebianco V, Picchio M. Prostate cancer recurrence: can PSA guide imaging? Eur J Nucl Med Mol Imaging. 2015;42:1781–1783.
- Castellucci P, Picchio M. ¹¹C-choline PET/CT and PSA kinetics. *Eur J Nucl Med Mol Imaging*. 2013;40(suppl 1):S36–S40.
- Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer, part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol.* 2014;65:467–479.
- Reske SN, Blumstein NM, Glatting G. [¹¹C]choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy. *Eur J Nucl Med Mol Imaging*, 2008;35:9–17.
- Souvatzoglou M, Krause BJ, Purschel A, et al. Influence of ¹¹C-choline PET/CT on the treatment planning for salvage radiation therapy in patients with biochemical recurrence of prostate cancer. *Radiother Oncol.* 2011;99:193–200.
- Kitajima K, Murphy RC, Nathan MA, et al. Detection of recurrent prostate cancer after radical prostatectomy: comparison of ¹¹C-choline PET/CT with pelvic multiparametric MR imaging with endorectal coil. J Nucl Med. 2014;55:223–232.

- Scattoni V, Picchio M, Suardi N, et al. Detection of lymph-node metastases with integrated [¹¹C]choline PET/CT in patients with PSA failure after radical retropubic prostatectomy: results confirmed by open pelvic-retroperitoneal lymphadenectomy. *Eur Urol.* 2007;52:423–429.
- Schilling D, Schlemmer HP, Wagner PH, et al. Histological verification of ¹¹Ccholine-positron emission/computed tomography-positive lymph nodes in patients with biochemical failure after treatment for localized prostate cancer. *BJU Int.* 2008;102:446–451.
- Rinnab L, Mottaghy FM, Blumstein NM, et al. Evaluation of [¹¹C]-choline positronemission/computed tomography in patients with increasing prostate-specific antigen levels after primary treatment for prostate cancer. *BJU Int.* 2007;100: 786–793.
- Fuccio C, Castellucci P, Schiavina R, et al. Role of ¹¹C-choline PET/CT in the restaging of prostate cancer patients showing a single lesion on bone scintigraphy. Ann Nucl Med. 2010;24:485–492.
- Picchio M, Spinapolice EG, Fallanca F, et al. [¹¹C]choline PET/CT detection of bone metastases in patients with PSA progression after primary treatment for prostate cancer: comparison with bone scintigraphy. *Eur J Nucl Med Mol Imaging*. 2012;39:13–26.
- Ceci F, Castellucci P, Graziani T, et al. ¹¹C-choline PET/CT identifies osteoblastic and osteolytic lesions in patients with metastatic prostate cancer. *Clin Nucl Med.* 2015;40:e265–e270.
- Rinnab L, Simon J, Hautmann RE, et al. [¹¹C]choline PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy. World J Urol. 2009;27:619–625.
- Breeuwsma AJ, Pruim J, van den Bergh AC, et al. Detection of local, regional, and distant recurrence in patients with PSA relapse after external-beam radiotherapy using ¹¹C-choline positron emission tomography. *Int J Radiat Oncol Biol Phys.* 2010;77:160–164.
- Castellucci P, Fuccio C, Nanni C, et al. Influence of trigger PSA and PSA kinetics on ¹¹C-choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy. *J Nucl Med.* 2009;50:1394–1400.
- Castellucci P, Fuccio C, Rubello D, et al. Is there a role for ¹¹C-choline PET/CT in the early detection of metastatic disease in surgically treated prostate cancer patients with a mild PSA increase <1.5 ng/ml? *Eur J Nucl Med Mol Imaging*. 2011;38:55–63.
- Giovacchini G, Picchio M, Coradeschi E, et al. Predictive factors of [¹¹C]choline PET/CT in patients with biochemical failure after radical prostatectomy. *Eur J Nucl Med Mol Imaging*. 2010;37:301–309.
- Giovacchini G, Picchio M, Scattoni V, et al. PSA doubling time for prediction of [¹¹C]choline PET/CT findings in prostate cancer patients with biochemical failure after radical prostatectomy. *Eur J Nucl Med Mol Imaging*. 2010;37:1106–1116.
- Rybalov M, Breeuwsma AJ, Leliveld AM, Pruim J, Dierckx RA, de Jong IJ. Impact of total PSA, PSA doubling time and PSA velocity on detection rates of ¹¹C-choline positron emission tomography in recurrent prostate cancer. World J Urol. 2013;31:319–323.
- Bertagna F, Abuhilal M, Bosio G, et al. Role of ¹¹C-choline positron emission tomography/computed tomography in evaluating patients affected by prostate cancer with suspected relapse due to prostate-specific antigen elevation. *Jpn J Radiol.* 2011;29:394–404.
- Marnede M, Ceci F, Castellucci P, et al. The role of ¹¹C-choline PET imaging in the early detection of recurrence in surgically treated prostate cancer patients with very low PSA level <0.5 ng/mL. *Clin Nucl Med.* 2013;38:e342–e345.
- Mitchell CR, Lowe VJ, Rangel LJ, Hung JC, Kwon ED, Karnes RJ. Operational characteristics of ¹¹C-choline positron emission tomography/computerized tomography for prostate cancer with biochemical recurrence after initial treatment. *J Urol.* 2013;189:1308–1313.
- Fanti S, Minozzi S, Castellucci P, et al. PET/CT with ¹¹C-choline for evaluation of prostate cancer patients with biochemical recurrence: meta-analysis and critical review of available data. *Eur J Nucl Med Mol Imaging*. 2016;43:55–69.
- Vees H, Buchegger F, Albrecht S, et al. ¹⁸F-choline and/or ¹¹C-acetate positron emission tomography: detection of residual or progressive subclinical disease at very low prostate-specific antigen values (<1 ng/mL) after radical prostatectomy. *BJU Int.* 2007;99:1415–1420.

- 26. Panebianco V, Sciarra A, Lisi D, et al. Prostate cancer: 1HMRS-DCEMR at 3T versus [¹⁸F]choline PET/CT in the detection of local prostate cancer recurrence in men with biochemical progression after radical retropubic prostatectomy (RRP). *Eur J Radiol.* 2012;81:700–708.
- Husarik DB, Miralbell R, Dubs M, et al. Evaluation of [¹⁸F]-choline PET/CT for staging and restaging of prostate cancer. *Eur J Nucl Med Mol Imaging*. 2008;35:253–263.
- Tilki D, Reich O, Graser A, et al. ¹⁸F-fluoroethylcholine PET/CT identifies lymph node metastasis in patients with prostate-specific antigen failure after radical prostatectomy but underestimates its extent. *Eur Urol.* 2013;63:792–796.
- Beheshti M, Vali R, Waldenberger P, et al. The use of F-18 choline PET in the assessment of bone metastases in prostate cancer: correlation with morphological changes on CT. *Mol Imaging Biol.* 2010;12:98–107.
- Beheshti M, Vali R, Waldenberger P, et al. Detection of bone metastases in patients with prostate cancer by ¹⁸F fluorocholine and ¹⁸F fluoride PET-CT: a comparative study. *Eur J Nucl Med Mol Imaging*. 2008;35:1766–1774.
- 31. Langsteger W, Balogova S, Huchet V, et al. Fluorocholine (¹⁸F) and sodium fluoride (¹⁸F) PET/CT in the detection of prostate cancer: prospective comparison of diagnostic performance determined by masked reading. *Q J Nucl Med Mol Imaging*. 2011;55:448–457.
- McCarthy M, Siew T, Campbell A, et al. ¹⁸F-fluoromethylcholine (FCH) PET imaging in patients with castration-resistant prostate cancer: prospective comparison with standard imaging. *Eur J Nucl Med Mol Imaging*. 2011;38:14–22.
- Cimitan M, Bortolus R, Morassut S, et al. [¹⁸F]fluorocholine PET/CT imaging for the detection of recurrent prostate cancer at PSA relapse: experience in 100 consecutive patients. *Eur J Nucl Med Mol Imaging*. 2006;33:1387–1398.
- Pelosi E, Arena V, Skanjeti A, et al. Role of whole-body ¹⁸F-choline PET/CT in disease detection in patients with biochemical relapse after radical treatment for prostate cancer. *Radiol Med (Torino).* 2008;113:895–904.
- Chondrogiannis S, Marzola MC, Ferretti A, et al. Role of ¹⁸F-choline PET/CT in suspicion of relapse following definitive radiotherapy for prostate cancer. *Eur J Nucl Med Mol Imaging.* 2013;40:1356–1364.
- Beheshti M, Haim S, Zakavi R, et al. Impact of ¹⁸F-choline PET/CT in prostate cancer patients with biochemical recurrence: influence of androgen deprivation therapy and correlation with PSA kinetics. J Nucl Med. 2013;54:833–840.
- Henninger B, Vesco P, Putzer D, et al. [¹⁸F]choline positron emission tomography in prostate cancer patients with biochemical recurrence after radical prostatectomy: influence of antiandrogen therapy—a preliminary study. *Nucl Med Commun.* 2012;33:889–894.
- Graute V, Jansen N, Ubleis C, et al. Relationship between PSA kinetics and [¹⁸F]fluorocholine PET/CT detection rates of recurrence in patients with prostate cancer after total prostatectomy. *Eur J Nucl Med Mol Imaging*, 2012;39:271–282.
- Schillaci O, Calabria F, Tavolozza M, et al. Influence of PSA, PSA velocity and PSA doubling time on contrast-enhanced ¹⁸F-choline PET/CT detection rate in patients with rising PSA after radical prostatectomy. *Eur J Nucl Med Mol Imaging*. 2012;39:589–596.
- Marzola MC, Chondrogiannis S, Ferretti A, et al. Role of ¹⁸F-choline PET/CT in biochemically relapsed prostate cancer after radical prostatectomy: correlation with trigger PSA, PSA velocity, PSA doubling time, and metastatic distribution. *Clin Nucl Med.* 2013;38:e26–e32.
- Detti B, Scoccianti S, Franceschini D, et al. Predictive factors of [¹⁸F]-choline PET/CT in 170 patients with increasing PSA after primary radical treatment. *J Cancer Res Clin Oncol.* 2013;139:521–528.
- 42. Chiaravalloti A, Di Biagio D, Tavolozza M, Calabria F, Schillaci O. PET/CT with ¹⁸F-choline after radical prostatectomy in patients with PSA ≤2 ng/ml: can PSA velocity and PSA doubling time help in patient selection? *Eur J Nucl Med Mol Imaging*. 2016;43:1418–1424.
- de Jong IJ, Pruim J, Elsinga PH, Vaalburg W, Mensink HJ. ¹¹C-choline positron emission tomography for the evaluation after treatment of localized prostate cancer. *Eur Urol.* 2003;44:32–38.
- 44. Krause BJ, Souvatzoglou M, Tuncel M, et al. The detection rate of [¹¹C]choline-PET/CT depends on the serum PSA-value in patients with biochemical recurrence of prostate cancer. *Eur J Nucl Med Mol Imaging*. 2008;35:18–23.