Choline PET or PET/CT and Biochemical Relapse of Prostate Cancer

A Systematic Review and Meta-Analysis

Laura Evangelista, MD, PhD, Fabio Zattoni, MD,† Andrea Guttilla, MD,† Giorgio Saladini, MD,* Filiberto Zattoni, MD,† Patrick M. Colletti, MD,‡ and Domenico Rubello, MD§*

Aim: The increase of prostate-specific antigen (PSA) after radical retropubic prostatectomy (RP) or external beam radiotherapy (EBRT) is the most sensitive tool for detecting prostate cancer (PCa) recurrence, although this measure cannot distinguish between local, regional, or distant recurrence. The aim of this meta-analysis was to evaluate the diagnostic performance of ^{18}F-choline and ^{11}C-choline PET or PET/CT in detection of locoregional or distant metastases in PCa.

Materials and Methods: Medline, Web of Knowledge, and Google Scholar search was carried out in order to select English-language articles dealing with diagnostic performance of both ^{18}F-choline and ^{11}C-choline PET for the detection of PCa recurrence after RP or EBRT. Articles were included only if absolute numbers of true-positive, true-negative, false-positive, and false-negative test results were available or derivable from the text and regarded local, lymph node, and distant metastases. Reviews, clinical reports, and editorial articles were excluded. All complete studies were re-analyzed thus performing a quantitative analysis.

Results: From the years 2000 to 2012, we found 53 complete articles that critically evaluated the role of choline PET in restaging patients with PCa recurrence. The meta-analysis was carried out and dealt with 19 selected studies (12 studies for all sites of disease, 3 for lymph node metastases, and 4 for local recurrence), with a total of 1555 patients. The meta-analysis provided a pooled sensitivity of 85.6% (95% CI: 82.9%–88.1%) and pooled specificity of 92.6% (95% CI: 90.1%–94.6%) for all sites of disease (prostatic fossa, lymph nodes, and bone), a pooled sensitivity of 75.4% (95% CI: 66.9%–82.6%) and pooled specificity of 82% (95% CI: 68.6%–91.4%) for prostatic fossa recurrence, and a pooled sensitivity of 100% (95% CI: 90.5%–100%) and pooled specificity of 81.8% (95% CI: 48.2%–97.7%) for lymph node metastases. The heterogeneity ranged between 0.00% and 88.6%. The diagnostic odds ratios were 62.123 (95% CI: 24.783–155.72), 5.869 (95% CI: 1.818–18.946), and 138.57 (95% CI: 11.27–1703.8), respectively, for all sites of disease, local recurrence, and lymph node disease.

Conclusions: Choline PET and PET/CT represent high sensitivity and specificity techniques for the detection of locoregional and distant metastases in PCa patients with recurrence of disease. Moreover, a high diagnostic odds ratio was found for the identification of lymph node disease in patients with biochemical recurrence of PCa.

Key Words: prostate cancer, biochemical recurrence, choline PET, meta-analysis

(*Clin Nucl Med* 2013;38: 305–314)

Received for publication November 26, 2012; and revision accepted December 17, 212.

From the *Radiotherapy and Nuclear Medicine Unit, Istituto Oncologico Veneto IOV—IRCCS, Padua, Italy; †Department of Oncological and Surgical Sciences, Urology Clinic, University of Padua, Padua, Italy; ‡Department of Radiology, University of Southern California, Los Angeles, California; and §Department of Nuclear Medicine, Santa Maria della Misericordia Hospital, Rovigo, Italy.

Conflicts of interest and sources of funding: none declared.

Reprints: Domenico Rubello, MD, Department of Nuclear Medicine, Medial Physics, Radiology, Neuroradiology, Head Service of Nuclear Medicine & PET/CT Centre, Santa Maria della Misericordia Hospital, Via Tre Martiri 140, 45100 Rovigo, Italy. E-mail: domenico.rubello@libero.it.

ISSN: 0363-9762/13/3805–0305

During follow-up, the monitoring of prostate-specific antigen (PSA) serum levels (trigger PSA) and its kinetics, PSA doubling time (PSAdt) and PSA velocity (PSAvel), has proven to be a highly sensitive marker for early recognition of relapsing disease[1] after radical retropubic prostatectomy (RP) or external beam radiotherapy (EBRT), although these measures cannot definitely distinguish between local, regional, or distant recurrence. Following RP, 2 consecutive PSA values of 0.2 ng/mL and above are considered to represent recurrent cancer. After initial EBRT, 3 consecutive increasing PSA values above the previous PSA nadir measured at 3-month interval represent recurrent disease.[2] Local recurrence occur in 30%–50% of patients within 10 years after RP[3] and 16%–35% of these patients receive second-line treatment within 5 years after surgery.[4] Patients with T1-T2 disease after EBRT have a recurrence in up to 30%–40% within 10 years.[5,6] Transurectal ultrasonography (TRUS)-guided biopsy has a limited sensitivity of 25%–54%, particularly when the PSA level is <1.0 ng/mL.[6] Peri-anastomotic biopsies are questionable, as a positive result does not exclude metastatic disease and a negative result does not exclude local recurrence.[7] Contrast-enhanced CT is not sufficiently sensitive for detecting local recurrence until the PSAvel is >20 ng/mL/year.[8] Encouraging results were reported for endorectal magnetic resonance imaging (MRI) and MRI spectroscopy in small retrospective series.[9] Promising new sequences could further increase the accuracy of MRI to detect local recurrence after RP if PSA serum levels exceed 2 ng/mL. Similar data were obtained in a cohort of 64 patients with PSA progression following EBRT.[10]

CT is the primary imaging modality used in the evaluation of nodal metastases (sensitivity ranged between 27% and 75%, and specificity ranged between 66% and 100%[11,12]). The depiction of nodal disease relies on the fact that nodal size and the fraction of the CT-detected lymph node metastases are generally correlated with PSA values.[12–14] The performance of MRI for lymph node detection is similar to that of CT. Bone scintigraphy is generally used to exclude the presence of bone metastases, but it is unlikely to be positive in patients with a serum PSA <7 ng/mL. Positron emission tomography (PET) has been successfully applied in many human cancers for early identification of local or systemic recurrences. Choline, as a component of the phosphatidylcholines, is highly increased in PCa and can be simply radiolabeled with either ^{11}C (^{11}C-choline) or ^{18}F (^{18}F-choline). In PCa, there are published data on the clinical efficacy of choline PET in detecting local and distant recurrences after RP, especially when an increase in PSA value is detected.[15–22]

The aim of this meta-analysis was to provide an analysis about the diagnostic performance of ^{18}F/^{11}C-choline PET or PET/CT in detection of locoregional or distant metastases in PCa.

MATERIALS AND METHODS

Literature Review

A computer literature research about studies in human subjects was performed to identify articles about the diagnostic performance of choline PET or choline PET/CT for the detection of recurrent

PCa. The Medline and Web of Knowledge/Google Scholar databases, from 2000 to November 2012, were used with the following key words "prostatic neoplasm" OR "prostatic" AND "neoplasm" OR "prostate" AND "cancer" OR "prostate cancer" AND "choline" OR "choline" AND "PET" OR "PET/CT" AND "relapse". For the MEDLINE research, the following limits were used: species (human), article type (reviews, clinical trial and randomized clinical trial, original articles, comparative studies, and multicenter study) and language (English). The references of articles and reviews, found in the literature search, were also examined to find additional reports that met the inclusion criteria. The following items were searched for in each of these series: number of patients, mean or median age, design of the study, reference standard, sensitivity, specificity, and other diagnostic data of choline PET or PET/CT scan. Articles containing information on the results of PET or PET/CT for local, for lymph nodes, and for distant recurrence of PCa and published in English language were reviewed. The list of articles was supplemented with extensive cross-checking of the reference lists of all retrieved articles.

Selection of Studies

Two observers, LE and DR, who had 5 and 22 years of work experience in the field of nuclear medicine independently, evaluated retrieved articles. Disagreements were resolved in consensus. Articles were included if (1) the absolute numbers of true-positive (TP), false-negative (FN), false-positive (FP), and true-negative (TN) test results were available or derivable from the articles, which allowed us to construct 2 × 2 contingency tables; (2) the reference standard was pathology or other common imaging modalities; and (3) a sample size ≥10 patients. Abstracts were excluded from this analysis because of insufficient data to evaluate the methodological quality and to allow the calculation of diagnostic accuracy. Reviews, clinical reports, and editor comments were also excluded.

Data Extraction

Three observers (LE, FaZ, and AG) independently extracted relevant data about study characteristics and examination results by using a standardized form. Observers were not blinded with regard to unnecessary information as the journal name, the authors, the authors' affiliation, or year of publication because such blinding has been shown to be unnecessary.[23] The reviewers (FaZ and AG) examined relevant studies with Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS) criteria.[24] The evaluation was based on a 14-point scale. Each item were answered as "yes," "no," or "unclear". Inconsistent findings between the 2 readers were discussed and agreed upon by consensus (LE). For each included study, information were collected concerning basic study (author name, journal, year of publication, country of origin, and study design), patients' demographic and clinical characteristics (mean age and number of patients), technical parameters (radiopharmaceutical injected type), and PET or PET/CT choline evaluation (visual or semiquantitative analysis).

Statistical Analysis

The number of TP, TN, FP, and FN were extracted or computed from each selected study based on the choline PET as the index test. The analysis was computed according to the site of disease (eg, for lymph node metastases, prostatic fossa recurrence, and all sites of distant relapse); therefore, only reports with a clear definition of the region of recurrent disease were used for the meta-analysis. The pooled sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio (LR), accuracy, and diagnostic odds ratio (DOR) were calculated with 95% confidence intervals (CI) of each noninvasive technique. We also calculated summary receiver operating characteristics curves (SROC) and the area under the curve. A random-effects model was used. The between-study heterogeneity was assessed using the chi-square and I-square tests. The chi-square test provided an estimate of the between-study variance, and I-square test measured the proportion of inconsistency in individual studies that cannot be explained by chance. According to Higgins et al,[25] the value of 25%, 50%, and 75% for heterogeneity (I-square) were considered low, moderate, and high, respectively. The area under the curve was calculated to measure the accuracy of choline PET/CT in diagnosis of lymph node involvement in PCa. All statistical analyses were performed using Meta-Disc statistical software version 1.4 (Unit of Clinical Biostatistics, Ramòn y Cajal Hospital, Madrid, Spain).[26] The Duval and Tweedie "trim and fill" method was developed to estimate potential publication bias (available in CMA, version 2).

RESULTS

Identification of Studies

From 2000 to today, the Medline using Mesh terms generated 71 results (26 reviews and 45 original articles) and 66 results from Web of Knowledge/Google Scholar (16 reviews and 50 original articles). Fifty-two articles were the same and therefore considered one time. Eighty-five articles on the use of choline PET or PET/CT for PCa restaging were identified, 53 original articles and 32 reviews. Some of these articles (n = 36) were focused on the value of ^{11}C-choline or ^{18}F-choline PET or PET/CT in detection of PCa recurrence. The characteristics of selected studies are reported in Table 1. For the meta-analysis assessment, we evaluated the performance of ^{11}C-choline and ^{18}F-choline PET or PET/CT in 19 original articles (Fig. 1).

Qualitative Analysis

The pattern of choline PET/CT in PCa is consistent with the natural spread of disease. In particular, pelvic and retroperitoneal lymph nodes, prostate bed, and finally the skeleton are the most frequently affected site of significant uptake, relating to 66%, 34%, and 29% of patients, respectively.[27]

Local Recurrence Detection

Vees et al[17] demonstrated that both ^{18}F-choline and ^{11}C-acetate PET/CT studies was able to identify local residual or recurrent disease in about half of the enrolled patients with a PSA levels of <1 ng/mL after RP. A recent study performed by Panebianco et al[28] compares the accuracy to detect locoregional recurrence of PCa in patients with biochemical relapse of proton magnetic resonance spectroscopic imaging (HMRSI) and dynamic contrast-enhanced (DCE) MRI combined techniques at 3-T magnet versus ^{18}F-choline PET/CT. The study reported a higher accuracy of HMRSI-DCEMRI than of PET/CT (89% vs. 60%). Vees et al[17] and Panebianco et al[28] considered a subset of patients with very low PSA (range between 0.11 and 2.5 ng/mL) demonstrating different sensitivities of choline PET/CT in detecting prostatic fossa recurrence (43% and 83%, respectively). Reske et al[29] considered a group of patients with heterogeneous biochemical recurrence (median PSA value: 0.3 ng/mL; range: 0.0–8.0 ng/mL) who performed PET/CT choline for suspicion of local recurrence providing a sensitivity of 73% and a specificity of 88%, but nevertheless none of these studies[17,18,28] suggested the use of choline PET/CT scanning for the detection and the definition of radiation target volume in local recurrence, mainly because its sensitivity at the local level is limited. As suggested by Bertagna et al,[30] the main limitations of PET/CT in detecting local recurrence are firstly the presence of microscopic extension of the diseases is beyond the resolution power of the method, and secondly there may be inflammatory uptake at the prostatic site. Souvatzoglou et al[31] recently suggested that ^{11}C-choline PET/CT is useful in the extension of planning target volume in more than 10% of participants,

TABLE 1. Basic Study and Patients' Characteristics

No.	Author	Journal	Country	Year	No. of Patients	Age*	Type of Study	Radiopharmaceutical and Imaging Scan	Scan	Semiquantitative Measures
1	Kotzerke et al[15]	EJNMMI	Germany	2000	11	66.7 ± 6.5	Prospective	^{11}C-choline	PET	No
2	Picchio et al[58]	J Urol	Italy	2003	100	70.52 (45–81)	Prospective	^{11}C-choline	PET	No
3	de Jong et al[39]	Eur Urol	The Netherlands	2003	36	68 ± 9	Prospective	^{11}C-choline	PET	no
4	Heinisch et al[56]	Mol Imaging Biol	Austria	2006	45	69.9	Prospective	^{18}F-choline	PET/CT	No
5	Cimitan et al[46]	EJNMMI	Italy	2006	100	49–81	Prospective	^{18}F-choline	PET/CT	Yes
6	Scattoni et al[32]	Eur Urol	Italy	2007	25	65.5 ± 7.5	Prospective	^{11}C-choline	PET/CT	Yes
7	Vees et al[17]	BJU Int	Spain	2007	11	62 (54–67)	Prospective	^{18}F-choline	PET/CT	Yes
8	Rinnab et al[35]	BJU Int	Belgium	2007	50	65.9 (52–79)	Retrospective	^{11}C-choline	PET/CT	No
9	Reske et al[29]	EJNMMI	Germany	2008	49	51–78	Prospective	^{11}C-choline	PET/CT	Yes
10	Krause et al[44]	EJNMMI	Germany	2008	63	68.8 ± 6.9	Prospective	^{11}C-choline	PET/CT	No
11	Husarik et al[33]	EJNMMI	Switzerland, France	2008	68	66.4	Prospective	^{18}F-choline	PET/CT	Yes
12	Schilling et al[34]	BJU Int	Germany	2008	10	n.a.	Retrospective	^{11}C-choline	PET/CT	No
13	Pelosi et al[40]	Rad Med	Italy, France	2008	56	67.9 ± 7	Prospective	^{18}F-choline	PET/CT	No
14	Rinnab et al[18]	Urol Int	Germany	2008	15	62.1 (53–73)	Prospective	^{11}C-choline	PET/CT	Yes
15	Steiner et al[57]	Nuclearmedizin	Geneva, Switzerland, Spain	2009	36	47–87	Retrospective	^{18}F-choline	PET/CT	Yes
16	Rinnab et al[22]	World J Urol	Germany, Belgium	2009	41	66 (52–76)	Retrospective	^{11}C-choline	PET/CT	No
17	Richter et al[19]	Mol Imaging Biol	Spain	2009	73	65.62 (41–78)	Prospective	^{11}C-choline	PET/CT	No
18	Castellucci et al[45]	JNM	Italy	2009	190	68 (54–83)	Retrospective	^{11}C-choline	PET/CT	No
19	Giovacchini et al[27]	EJNMMI	Italy	2010	358	67 ± 6	Retrospective	^{11}C-choline	PET/CT	No
20	Breeuwsma et al[60]	Int J Radiat Oncol Biol Phys	The Netherland	2010	70	71	Prospective	^{11}C-choline	PET	No
21	Winter et al[14]	Urol Int	Germany	2010	6	61.7 (49–64)	Prospective	^{11}C-choline	PET/CT	No
22	Fuccio et al[36]	ANM	Italy	2010	25	70.2 (58–80)	Retrospective	^{11}C-choline	PET/CT	Yes
23	Hodolic et al[21]	Radiol Oncol	Slovenia	2010	50	67.7	Prospective	^{18}F-choline	PET/CT	No
24	Panebianco et al[28]	Eur J Radiol	Italy	2010	84	56–72	Prospective	^{18}F-choline	PET/CT	No
25	Giovacchini et al[49]	EJNMMI	Italy	2010	170	n.a.	Retrospective	^{11}C-choline	PET/CT	No
26	Giovacchini et al[42]	J Urol	Italy	2010	109	66.4 ± 6.2	Retrospective	^{11}C-choline	PET/CT	No
27	Bertagna et al[30]	Jpn J Radiol	Italy	2011	210	70 ± 7	Retrospective	^{11}C-choline	PET/CT	No
28	Castellucci et al[43]	EJNMMI	Italy	2011	102	68 (54–82)	Retrospective	^{11}C-choline	PET/CT	No
29	Rigatti et al[13]	Eur Urol	Italy	2011	72	66.9 (61–73.6)	Prospective	^{11}C-choline	PET/CT	No
30	Giovacchini et al[48]	Clin Nucl Med	Italy	2012	170	n.a.	Retrospective	^{11}C-choline	PET/CT	No
31	Kwee et al[20]	Ann Nucl Med	USA	2012	50	69 ± 8.9	Prospective	^{18}F-choline	PET/CT	No
32	Henninger et al[51]	Nucl Med Commun	Austria	2012	35	n.a.	Retrospective	^{18}F-choline	PET	No
33	Schillaci et al[41]	EJNMMI	Italy	2012	49	70.9 ± 7	Prospective	^{18}F-choline	PET/CT	No
34	Graute et al[50]	EJNMMI	Germany	2012	82	67.1 ± 7	Prospective	^{18}F-choline	PET/CT	No
35	Fuccio et al[38]	Eur Radiol	Italy	2012	102	67.6 (54–83)	Retrospective	^{11}C-choline	PET/CT	No
36	Marzola et al[59]	Clin Nucl Med	Italy	2012	233	69.4 ± 6.5	Retrospective	^{18}F-choline	PET/CT	No

*Expressed as median (range) or as mean ± standard deviation.

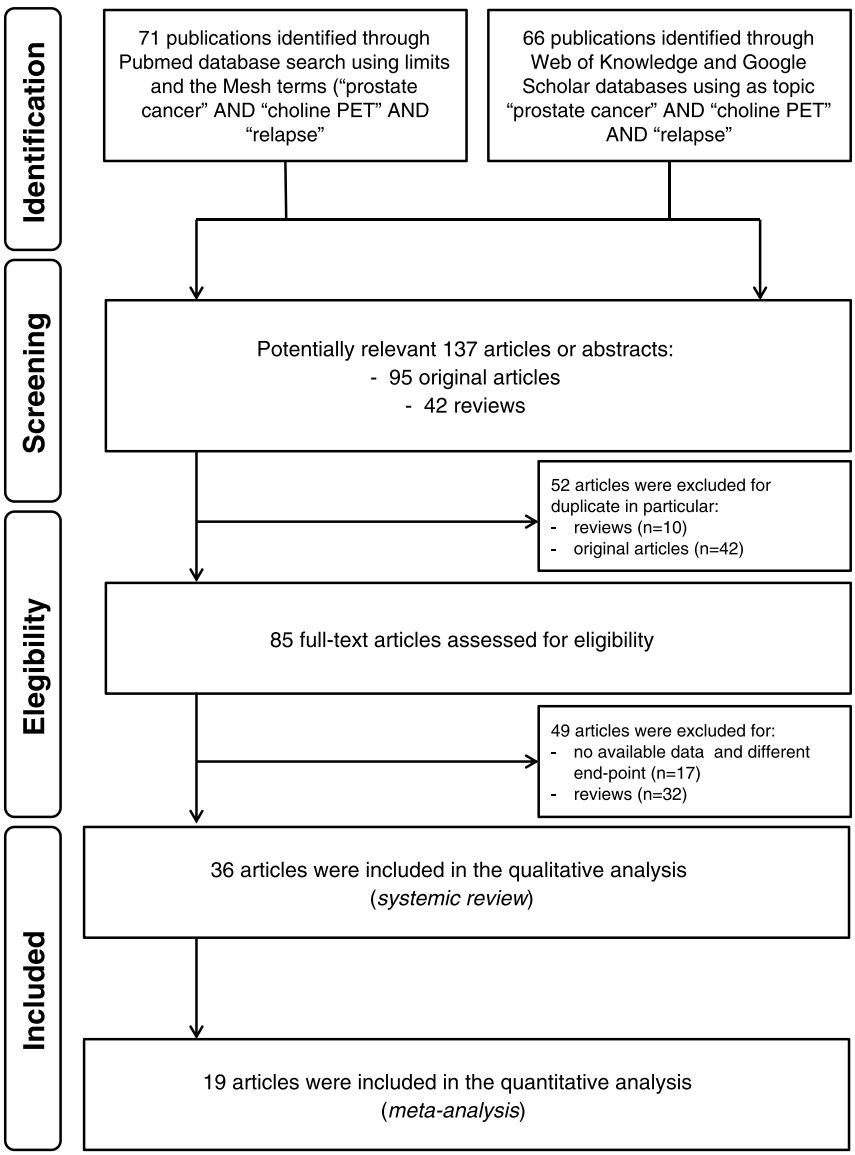

FIGURE 1. Flow diagram of selected studies for the accuracies of choline PET and PET/CT in lymph node metastasis according to PRISMA standard.

particularly when performed in a group of patients with biochemical recurrence after RP.

Lymph Node Metastases

Scattoni et al[32] demonstrated that 90% of patients with a positive choline PET/CT after RP presented histologically proven metastases at the lymph node level. The data were confirmed also by Husarik et al,[33] Schilling et al,[34] and Rinnab et al,[18,35] supporting the use of choline PET/CT in patients with suspected lymph node recurrence after RP and with biochemical relapse of disease.

Distant Metastases

Considering the detection of bone metastases by choline PET/CT, recently Fuccio et al[36] described the utility of ^{11}C-choline PET/CT in unknown bone lesions, underlying the advantage of this technique in the early detection of bone marrow involvement before and after therapy. Furthermore, PET/CT is useful in detection of oligometastatic disease, being useful for appropriate treatment planning.[36] Lastly, Picchio et al[37,38] demonstrated a clear advantage of PET/CT scan in comparison to bone scintigraphy in detecting bone metastases in PCa patients (diagnostic accuracy: 95% vs. 83%, respectively).

PSA Values and Other Predictive Variables

de Jong et al,[39] Pelosi et al,[40] and Richter et al[19] reported that in the case of PSA value >5 ng/mL, the PET/CT detection rate, independently from the site of disease recurrence, was between 71.5% and 100%. Recently, Schillaci et al[41] demonstrated a high detection rate (86.7%) when PSA value was >4 ng/mL, while Giovacchini et al[42] and Panebianco et al[28] concluded that a PSA value >3 ng/mL was associated with a high detection rate of 81.9% and 73%, respectively, for all sites of disease and local recurrence. Conversely, Husarik et al[33] and Castellucci et al[43] reported a moderate and low detection rate in

case of PSA value <2 ng/mL and <1.5 ng/mL (71.4% and 28%), respectively. Therefore, the role of ^{11}C-choline PET/CT in men with biochemical recurrence after RP have shown that metastases were more likely to be identified at higher PSA levels, with the detection rate of local metastases ranged between 20% and 36% for patients with PSA levels <1 ng/mL, and increasing to 63%–83% for men with PSA levels >3 ng/mL.[18,44,45] Using ^{18}F-choline PET/CT, Cimitan et al[46] suggested that choline PET/CT could be helpful in a selected patient population with higher PSA levels and/or poorly differentiated PCa (Gleason score >7) to exclude distant metastases when salvage local treatment is intended. Giovacchini et al[42] at multivariate analysis demonstrated that lymph node involvement and seminal vesicles invasion were independently correlated with an abnormal PET/CT, while Gleason score lost statistical significance. As recently reported by a review from Picchio et al,[47] the routine use of ^{11}C-choline PET/CT cannot be recommended for PSA values <1 ng/mL, but a cutoff for properly referring patients to choline PET/CT imaging must yet be defined. The accuracy of PET is correlated to PSA value, PSAdt, and other pathological features. For example, it has been shown that PSAvel is a predictor of a positive ^{11}C-choline PET/CT and it can be used to stratify the risk of positive ^{11}C-choline PET/CT in PCa patients with biochemical failure.[48] The authors concluded that a PSAvel >1 ng/mL/year should be selected to increase the positive detection rate of ^{11}C-choline PET/CT. Recently, Giovacchini et al[48,49] and Castellucci et al[43] reported that the choline detection rate tends to be higher in patients with PSAdt <2 or 3 months than the others with a PSAdt >6 months (60%–80% and 40%–60%, respectively). Therefore, according to these results and Graute et al,[50] a PSAdt <3 months can be considered a strong predictor of PET positivity.

Anti-androgenic Therapy

The effects of anti-androgenic therapy (ADT) on radiolabeled-choline uptake, especially in the skeleton, are of great importance and still under investigation. Patients who present with a progressive, rising PSA during androgen-deprivation therapy are those who are no longer sensitive to the regulatory control of anti-androgenic drugs. This is associated with an unfavorable prognosis with respect to those patients who are still sensitive. In several studies, a negative influence of anti-androgen therapy (ADT) on choline PET efficacy has been suggested.[27] As demonstrated by the authors, by univariate analysis, ADT was significantly associated with an increased risk for positive choline PET/CT results; at multivariate analysis, the effect of ADT therapy was no longer significant. The lack of association between choline PET/CT positivity and ADT effect can be easily explained by the greater aggressiveness of disease in hormone-resistant PCa patients. Other studies have reported higher percent values in hormone-resistant patients than in hormone-sensitive patients (detection rates ranged between 56% and 85% and between 36% and 85%, respectively, for resistant and sensitive subjects[19,33,42,44,49]). In the absence of strong evidence for an inhibitory effect of ADT in hormone-resistant PCa patients,[51] the prolonged withdrawal of ADT in oncological patients experiencing progression of disease may be ethically questionable.[52]

Quantitative Analysis (Meta-analysis)

Based on the QUADAS, the studies were considered to be of a good quality (n = 16; score 7–10) and high quality (n = 3; score 11–14). Among all the selected articles, a total of 1555 patients were recorded and included in the meta-analysis (n = 1316 for all sites, n = 73 for lymph node recurrence, and n = 189 for prostatic fossa relapse). The characteristics of each study are reported in Table 1. The age range of the entire population studied was between 41 and 87 years. The value of TP, TN, FP, FN, and the diagnostic accuracies for each selected studies are presented in Table 2.

The pooled diagnostic performance results of choline PET/CT in the 19 included studies are presented in Table 3. In all sites of disease, sensitivity and specificity of choline PET/CT in PCa patients ranged from 60.6% to 100% and from 36.4% to 100%, reaching a pooled sensitivity of 85.6% (82.9%–88.1%) and a pooled specificity of 92.6% (90.1%–94.6%). A comparison across different radioisotopes demonstrated that ^{18}F-choline provided a higher sensitivity than ^{11}C-choline (pooled sensitivity: 91.8% vs. 81.8%, respectively, for ^{18}F-choline and ^{11}C-choline) but a similar specificity (pooled specificity: 95.6% vs. 91.4%, respectively, for ^{18}F-choline and ^{11}C-choline) for all sites of disease (see Table 3).

In lymph node metastases, sensitivity and specificity of choline PET/CT in PCa patients showed a pooled sensitivity of 100% (90.5%–100%) and a pooled specificity of 81.8% (48.2%–97.7%). Finally, with recurrence in the prostatic fossa, sensitivity and specificity of choline PET/CT in PCa patients ranged from 42.9% to 82.9% and from 50.0% to 91.4%, reaching a pooled sensitivity of 75.4% (66.9%–82.6%) and a pooled specificity of 82.0% (68.6%–91.4%) (Table 4). The trim and fill procedure showed no publication bias for all sites of disease and recurrence in prostatic fossa. Publication bias procedures were not performed for lymph node metastases because at least 3 rows of data are required. There was heterogeneity for most noninvasive modalities, which was confirmed either by likelihood ratio chi-square test or I-square index, as shown in Table 5. There was no conclusive evidence of a cutoff effect for any modalities according to Spearman correlation coefficients ($P < 0.4$) for all sites of disease and for prostatic fossa, while abnormal values were reported for lymph nodes (Table 5). The SROC curves are shown in Figure 2. As illustrated, the areas under curve were 0.949 ($P < 0.05$) and 0.752 ($P = 0.09$) for all lesion sites and for prostatic fossa relapse, respectively. It was not computed for lymph node metastases due to the small number of studies (n = 2).

DISCUSSION

Although the velocity of PSA increase has been used to distinguish local recurrence from systemic disease,[53] PSA is not a specific indicator, and multiple diagnostic tests are necessary to stage disease recurrence. Research has shown that a median PSAdt of <4 months might be associated with distant relapse, whereas a median PSAdt of >12 months predicts local failure.[54] According to a recent study,[55] PSAvel of <0.75 ng/mL/year was observed in 94% of patients with local recurrence, whereas 56% of patients with distant metastases demonstrated a PSAvel of >0.75 ng/mL/year. Recently, the introduction of choline PET/CT as a hybrid molecular and anatomical imaging tool has changed the diagnostic approach to PCa, and many efforts have been made for lining up the biochemical features of disease and identifying the best time to perform PET/CT imaging. As previously described, Castellucci et al[45] and Giovacchini et al[48,49] defined the association of PET/CT positivity and the kinetics of PSA value. The low detection rate of choline PET/CT with low PSA values[17,43,56] is still a troublesome in clinical practice. According to the included studies, the detection rate of PET/CT for all disease sites ranged between 7.6% (19) and 100%,[19,34,35] being higher in patients with PSA value >2 ng/mL and reaching a plateau of 80%–85% for PSA value >10 ng/mL.

The relative low values of recurrence detected with PET (sensitivity ranges between 43% and 83% and specificity ranges between 50% and 91%) compared to other imaging techniques (ie, TRUS and MRI) underlines the limited diagnostic capabilities of PET with radiolabeled choline in the postsurgical prostatic bed. The main limitation is probably related to the limited size of recurrent lesions, the partial volume effect, and the presence of urine in case of ^{18}F-choline.

TABLE 2. Summary of Studies Included for the Meta-analysis (Patient-Based Analysis)

No.	Author	No. of Patients	Site of Disease	Standard of Reference	Sens. % (95% CI)	Spec. % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Acc. % (95% CI)	TP	TN	FP	FN
1	de Jong et al[39]	22*	All sites	Histological examination	100	83.3 (62–100)	83.3 (62-100)	100	90.9 (79–100)	10	10	2	0
2	Picchio et al[58]	100	All sites	Biopsy/histology and imaging/FUP	80 (69–91)	93.3 (86–100)	94 (87–100)	79 (67–91)	86 (79–93)	44	42	3	11
3	Scattoni et al[32]	25	Lymph nodes	Histological examination	100	66.6 (29–100)	90.4 (77–100)	100	92 (81–100)	19	4	2	0
4	Vees et al[17]	11	Local recurrence	Histological examination	43 (6–71)	50 (10–99)	60 (23–96)	33 (12–79)	45 (16–74)	3	2	2	4
5	Rinnab et al[35]	50	All sites	Histological examination	94.8 (88–100)	36.3 (8–65)	84 (73–96)	66.6 (39–95)	82 (71–93)	37	4	7	2
6	Reske et al[29]	49	Local recurrence	Histological examination	69.9 (54–85)	66.6 (13–100)	95.8 (89–100)	16.6 (2–59)	69.4 (54–84)	23	2	1	10
7A	Husarik et al[33]	68	All sites	Histological examination	90 (83–97.7)	100	100	45.5 (18–89)	91.1 (84–98)	57	6	0	5
7B	Husarik et al[33]	23	Lymph nodes	Histological examination	100	0	78.2 (59–97)	—	78 (61–95)	18	0	5	0
8	Schilling et al[34]	10	Lymph nodes	Histological examination	100	0	70 (36–100)	—	70 (41.5–98.4)	7	0	3	0
9	Pelosi et al[40]	56	All sites	Biopsy/imaging/FUP	82.7 (69–97)	96.2 (89–100)	96 (89–100)	83.8 (70–98)	89.2 (81–97)	24	26	1	5
10	Rinnab et al[18]	15	Lymph nodes	Histological examination	100	0	60 (27.9–92)	—	60 (35–84.7)	9	0	6	0
11	Richter et al[19]	73	All sites	Histological examination	61 (49–72)	100	100	7 (0–41)	62 (50–73)	43	2	0	28
12	Giovacchini et al[27]	358	All sites	Biopsy/imaging/FUP	85 (79-90)	93 (89–96)	91 (87–95)	87 (82–92)	89 (86–92)	145	173	14	26
13	Panebianco et al[28]	84	Local recurrence	TRUS biopsy and PSA values	83 (74–91)	63 (29–96)	95 (91–100)	28 (3–59)	81 (73–89)	63	5	3	13
14	Giovacchini et al[49]	170	All sites	Biopsy/histology and imaging/FUP	86.7 (79–94)	89.5 (83–96)	86.7 (79–94)	89.5 (83–96)	88.2 (83–93)	65	85	10	10
15	Bertagna et al[30]	45†	Local recurrence	Mapping	60 (30–90)	91 (82–100)	67 (37–96)	89 (78–99)	84 (74–95)	6	32	3	4
16	Castellucci et al[43]	102	All sites	Biopsy/histology and imaging/FUP	83 (70–95)	100	100	92 (85–98)	94 (90–99)	29	67	0	6
17	Henninger et al[51]	35	All sites	Biopsy/histology and imaging/FUP	64.3 (47–82)	57.1 (21–94)	85.7 (73–99)	28.6 (5–62)	62.9 (47–79)	18	4	3	10
18	Schillaci et al[41]	49	All sites	Biopsy/histology and imaging/FUP	91.7 (83–100)	100	100	81.3 (60–100)	93.9 (87–100)	33	13	0	3
19	Marzola et al[59]	233	All sites	Biopsy/histology and imaging/FUP	100	97 (94–100)	98 (95–100)	100	99 (97–100)	126	104	3	0

IC indicates interval confidence; PPV, positive predictive value; NPV, negative predictive value; FUP, follow-up

*Only patients with biochemical recurrence were considered.

†45/210 patients were available for the quantitative analysis.

TABLE 3. Pooled Diagnostic Accuracies for $^{11}C/^{18}F$-Choline PET and PET/CT in all Sites of Disease

	All	^{11}C-Choline	^{18}F-Choline
	Pooled value (95% CI)	Pooled value (95% CI)	Pooled value (95% CI)
Sensitivity	85.6% (82.9–88.1)	81.8% (77.9–85.2)	91.8% (88.0–94.7)
Specificity	92.6% (90.1–94.6)	91.4% (88.3–93.9)	95.6% (91.2–98.2)
Positive likelihood ratio	8.53 (3.62–20.09)	7.19 (2.59–19.99)	11.75 (1.86–74.39)
Negative likelihood ratio	0.17 (0.11–0.28)	0.20 (0.13–0.29)	0.11 (0.03–0.46)
Diagnostic odds ratio	62.123 (24.78–155.72)	53.77 (29.02–99.62)	132.55 (7.59–2315.5)

Steiner et al[57] concluded that 3-phase PET/CT can contribute to the increase in diagnostic assessment of local recurrence disease.

On the other hand, when a distant recurrence is suspected, choline PET/CT could be performed as the first procedure in restaging PCa because choline PET/CT findings may provide a basis for further treatment decisions such as a lymph node dissection or, in case of oligometastatic disease, can address potential use of target therapies. Furthermore, an effective single imaging modality for the entire body may be clinically efficacious and cost-efficient. Evidence supports the use of choline PET/CT for detection of nodal and bone lesion in the setting of rising PSA.[37,58,59] In the setting of nodal involvement, we found high sensitivity values (100% in 3 studies), while the specificity was between 0% and 66%. At quantitative analysis, the pooled sensitivity was 100% and the pooled specificity was 81.8%, underlying moderate rate of FP. Lack of specificity in small recurrent lymph nodes implies that it may be inappropriate to assume that there are metastases in all choline PET/CT apparently positive lymph nodes. There are at least 2 reasons for this: firstly, frequent inflammatory changes in or around the suspect lymph nodes may account for choline PET positivity; and secondly, artifacts or possibly small bowel activity can mime nodal positivity. In our meta-analysis, we considered only 2 studies that meet the inclusion criteria and therefore other prospective trials are warranted. Moreover, as recently reported by Graute et al,[50] the use of diagnostic quality CT in conjunction with contrast enhancement during PET may favor the allocation of focal uptake to diseased lymph nodes.

The heterogeneous study groups that have undergone different treatment modalities such as RP and EBRT account for varying results with regard to diagnostic accuracy. In a common clinical setting, patients are referred to choline PET scan when a progressive PSA serum level increase occurs, independently of the type of primary radical treatment previously performed. However, the clinical conditions differ greatly. PCa patients radically treated by EBRT are different from those successfully prostatectomized patients, as in the former, residual prostate tissue may remain viable.[60] The presence of post-EBRT residual viable prostate tissue may be responsible for an increased choline uptake at that site and therefore the local recurrence can be easily missed. Currently, the role of choline PET/CT to detect local or systemic recurrences in men with PSA relapse following EBRT is unclear and based on very few studies.[29,34] From our systemic literature research, it appeared that only 78 patients of retrieved articles were treated by EBRT (vs. 1346 subjects treated by RP); therefore, the PET/CT detection rate in the EBRT group was very difficult to define. de Jong et al[39] and Cimitan et al[46] reported the value of the positive detection rate in the different treatment categories, but neither formal statistical testing nor potential differences in the prevalence of other risk factors were performed.

The optimal tracer for PET imaging of patients with PCa has been a matter of debate. Kotzerke et al[15] reported a potential use of ^{11}C-acetate PET as a new tool for the diagnosis of PCa recurrence with an important impact also on treatment management. A recent review found that ^{11}C-labeled and ^{18}F-labeled choline afforded similar tumor detection in different clinical settings.[61] The rapid and extensive clearance of the several radiolabeled cholines from blood following intravenous injection allows early PET acquisition for the pelvis prior to extensive tracer accumulation in the urinary bladder. Whereas the urinary excretion of ^{18}F-choline seems to exceed that of ^{11}C-choline, the latter tracer also exhibits early accumulation in the bowel, which may also interfere with the interpretation of pelvic imaging.[19,40,47] However, the main practical difference between these tracers is the 5-fold longer physical half-life of ^{18}F, which makes ^{18}F-choline potentially available to institutions lacking a cyclotron/radiochemistry facility. In addition, the longer half-life allows more delayed acquisitions, which are likely to provide superior lesion-to-blood pool ratios than are provided by ^{11}C-choline, and the rapid washout of ^{18}F-choline leads, in the course of a more delayed recording, to more favorable tumor-to-background ratios. For the present meta-analysis, it emerged that both ^{18}F-choline PET and PET/CT had a higher sensitivity than ^{11}C-choline (sensitivity: 81.8% and 91.8%, respectively, for ^{11}C-choline and ^{18}F-choline) in detecting all sites of PCa recurrence, while the specificity is similar for both. This might reflect the recent progress in handling and interpreting choline PET/CT scan by the nuclear medicine specialists. In conclusion, choline PET and PET/CT represent high sensitivity and specificity techniques for the detection of locoregional and distant metastases in PCa patients with recurrence of disease. Moreover, a high diagnostic odds ratio was found for the identification of lymph node disease in patients with biochemical recurrence of PCa.

Implications for Research

In summary, the role and the diagnostic accuracy of choline PET/CT in men with rising PSA following RP is dependent on the absolute PSA, PSAdt, and PSAvel. The higher the PSA level and the faster the PSAdt, the better will be the predictive value of this imaging modality. However, even in patients with PSA values >2 ng/mL and negative imaging studies, choline PET/CT is positive in less than one fourth of patients. Therefore, a well-structured randomized prospective clinical trial should be planned. In particular, the values of PSA trigger, PSAdt, and PSAvel should be better

TABLE 4. Pooled Diagnostic Accuracies for $^{11}C/^{18}F$-Choline PET and PET/CT in Lymph Node Metastases and Prostatic Fossa

	Lymph Node Mets	Prostatic Fossa Relapse
	Pooled Value (95% CI)	Pooled Value (95% CI)
Sensitivity	100% (90.5–100)	75.4% (66.9–82.6)
Specificity	81.8% (48.2–97.7)	82.0% (68.6–91.4)
Positive likelihood ratio	3.72 (0.98–14.17)	2.35 (1.03–5.39)
Negative likelihood ratio	0.03 (0.05–0.23)	0.44 (0.26–0.74)
Diagnostic odds ratio	138.5 (11.27–1703.8)	5.86 (1.81–18.94)

Mets indicate metastases.

TABLE 5. Test for Heterogeneity and Threshold Effect in the Meta-analysis for all Sites, Lymph Node, and Prostatic Fossa Recurrence

	All Sites			Lymph Node Mets			Prostatic Fossa Relapse		
	Likelihood			Likelihood			Likelihood		
	χ^2	*P*	I^2 Index	χ^2	*P*	I^2 Index	χ^2	*P*	I^2 Index
Sensitivity	85.69	<0.001	87.2%	0.00	1.000	0.0%	7.55	0.056	7.55%
Specificity	50.14	<0.001	78.1%	2.79	0.095	64.2%	6.71	0.082	55.3%
Positive LR	96.10	<0.001	88.6%	1.32	0.251	24.1%	5.56	0.135	46.0%
Negative LR	43.81	<0.001	74.9%	0.02	0.879	0.0%	4.22	0.239	28.9%
DOR	34.00	<0.001	67.7%	0.45	0.503	0.0%	4.19	0.242	28.4%

LR indicates likelihood ratio; DOR, diagnostic odd ratio.

defined on the basis of PCa recurrence risk patients, the type of therapy (EBRT vs. RP and ADT alone), and the time of hormonal therapy starting. The definition of significant choline uptake represents another important issue to discuss. A multidisciplinary team could be drawn to the correct study design. Furthermore, new tracers could be used for the detection of local relapse and the optimization of PET instruments spatial resolution seems mandatory.

Implication for Practice

Choline PET/CT can be used for the identification of lymph node recurrence, but due to the loss in specificity it could determine unnecessary surgical treatments. The advantage of a single scan for the detection of all sites of disease in case of biochemical relapse should be considered, particularly when bone metastases are suspected. The strongest predictors of PET positivity for the

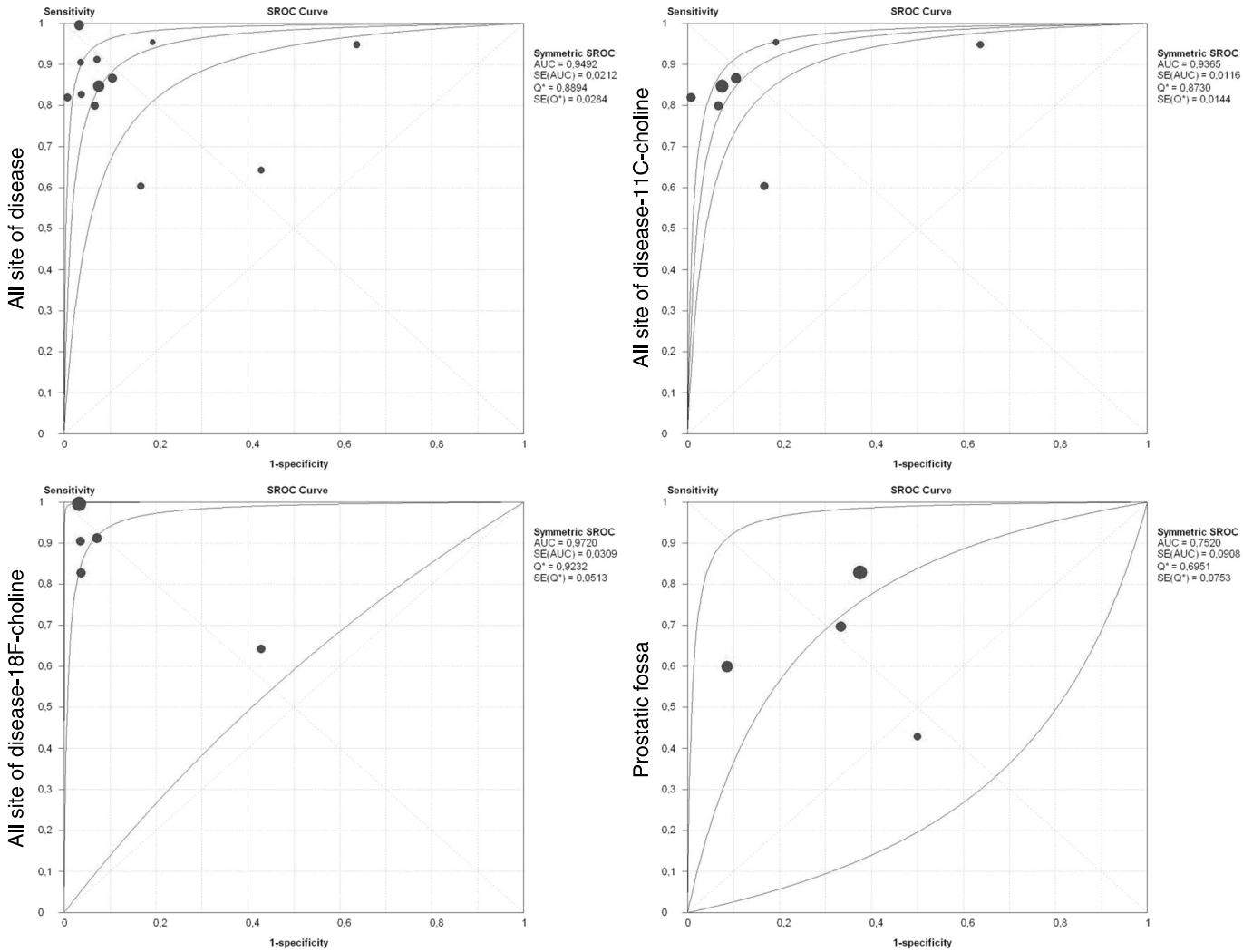

FIGURE 2. SROC curves showing the performance of PET and PET/CT in the diagnosis of distant and local recurrence and prostatic fossa.

identification of relapse in PCa patients are a PSA value >1 ng/mL, PSAvel >1 ng/mL/year, and a PSAdt <3 months. Ongoing hormonal therapy does not represent a limitation in diagnostic accuracy. Conversely, choline PET/CT does not seem indicated for the detection of local recurrence.

REFERENCES

1. Roberts SG, Blute ML, Bergstralh EJ, et al. PSA doubling time as a predictor of clinical progression after biochemical failure following radical prostatectomy for prostate cancer. *Mayo Clin Proc*. 2001;76:576–581.
2. Aus G, Abbou CC, Bolla M, et al. European Association of Urology. *Eur Urol*. 2005;48:546–551.
3. Morgan WR, Bergstralh EJ, Zincke H. Long-term evaluation of radical prostatectomy as treatment for clinical stage C (T3) prostate cancer. *Urology*. 1993; 41:113–120.
4. Bott SR. Management of recurrent disease after radical prostatectomy. *Prostate Cancer Prostatic Dis*. 2004;7:211–216.
5. Stamey TA, Ferrari MK, Schmid HP. The value of serial prostate specific antigen determinations 5 years after radiotherapy: steeply increasing values characterize 80% of patients. *J Urol*. 1993;150:1856–1859.
6. Boccon-Gibod L, Djavan DW, Hammerer P, et al. Management of prostate-specific antigen relapse in prostate cancer: a European Consensus . *Int J Clin Pract*. 2004;58:382–390.
7. Bott SR, Ahmed HU, Hindley RG, et al. The index lesion and focal therapy: an analysis of the pathological characteristics of prostate cancer. *BJU Int*. 2010;106:1607–1611.
8. Cher ML, Bianco FJ Jr, Lam JS, et al. Limited role of radionuclide bone scintigraphy in patients with prostate specific antigen elevations after radical prostatectomy. *J Urol*. 1998;160:1387–1391.
9. Sella T, Swarthz LH, Swindle PW, et al. Suspected local recurrence after radical prostatectomy: endorectal coil MR imaging. *Radiology*. 2004;231:379–385.
10. Thompson IM Jr, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA*. 2006;296:2329–2335.
11. Flanigan RC, McKay MT, Olson M, et al. Limited efficacy of preoperative computed tomographic scanning for the evaluation of lymph node metastasis in patients before radical prostatectomy. *Urology*. 1996;48:428–432.
12. Seltzer MA, Barbaric Z, Belldegrun A, et al. Comparison of helical computerized tomography, positron emission tomography and monoclonal antibody scans for evaluation of lymph node metastases in patients with prostate specific antigen relapse after treatment for localized prostate cancer. *J Urol*. 1999;162:1322–1328.
13. Rigatti P, Suardi N, Briganti A, et al. Pelvic/retroperitoneal salvage lymph node dissection for patients with radical prostatectomy with biochemical recurrence and nodal recurrence detected by (11C)choline positron emission tomography/computed tomography. *Eur Urol*. 2011;60:935–943.
14. Winter A, Uphoff J, Henke R, et al. First results of [11C]choline PET/CT-guided secondary lymph node surgery in patients with PSA failure and single lymph node recurrence after radical retropubic prostatectomy. *Urol Int*. 2010; 84:418–423.
15. Kotzerke J, Volkmer B, Neumaier B, et al. Carbon-11 acetate positron emission tomography can detect local recurrence of prostate cancer. *Eur J Nucl Med Mol Imaging*. 2002;29:1380–1384.
16. Martorana G, Schiavina R, Corti B, et al. 11C-choline positron emission tomography/computerized tomography for tumor localization of primary prostate cancer in comparison with 12-core biopsy. *J Urol*. 2006;176:954–960.
17. Vees HBS, Albrech S, Khan H, et al. 18F-choline and 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.
18. Rinnab L, Buchegger F, Simon J, et al. [11C]Choline PET/CT for targeted salvage lymph node dissection in patients with biochemical recurrence after primary curative therapy for prostate cancer. *Urol Int*. 2008;81:191–197.
19. Richter JA, Rodriguez M, Rioja J, et al. Dual tracer 11C-choline and FDG-PET in the diagnosis of biochemical prostate cancer ralpse after radical treatment. *Mol Imaging Biol*. 2010;12:210–217.
20. Kwee SA, Coel MN, Lim J. Detection of recurrent prostate cancer with 18-fluorocholine PET/CT in relation to PSA level at the time of imaging. *Ann Nucl Med*. 2012;26:501–507.
21. Hodolic M. Role of ^{18}F-choline PET/CT in evaluation of patients with prostate carcinoma. *Radiol Oncol*. 2011;45:17–21.
22. Rinnab L, Simon J, Hautmann RE, et al. [(11)C]choline PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy. *World J Urol*. 2009;27:619–625.
23. Berlin JA. Does blinding of readers affect the results of meta-analyses? University of Pennsylvania Meta-analysis Blinding Study Group. *Lancet*. 1997;350: 185–186.
24. Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol*. 2003;3:25.
25. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
26. Zamora J, Abraira V, Muriel A, et al. Mata-Disc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodolol*. 2006;6:31.
27. 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.
28. Panebianco V, Schiarra 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.
29. 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.
30. 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.
31. Souvatzoglou M, Krause B, Purschel A, et al. Influence of 11C-choline PET/CT on the treatment planning for salvage radiation therapy in patients with biocehmical recurrence of prostate cancer. *Radiother Oncol*. 2011;99: 193–200.
32. 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.
33. Husarik DB, Mirabell 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.
34. Schilling D, Schlemmer HP, Wagner PH, et al. Histological verification of 11C-choline-positron emission/computed tomography-positive lymph nodes in patients with biochemical failure after treatment for localized prostate cancer. *BJU Int*. 2008;102:446–451.
35. Rinnab L, Mottaghy FM, Blumstein NM, et al. Evaluation of (11C)-choline positron-emission/computed tomography in patients with increasing prostate-specific antigen levels after primary treatment for prostate cancer. *BJU Int*. 2007;100:786–793.
36. 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.
37. 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.
38. Fuccio C, Castellucci P, Schiavina R, et al. Role of 11C-choline PET/CT in the restaging of prostate cancer patients with biochemical relapse and negative results at bone scintigraphy. *Eur J Radiol*. 2012;81:e893–e896.
39. de Jong IJ, Prium J, Elsinga PH, et al. 11C-choline positron emission tomography for the evaluation after treatment of localized prostate cancer. *Eur Urol*. 2003;44:32–39.
40. 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*. 2008;113:895–904.
41. 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.
42. Giovacchini G, Picchio M, Briganti A, et al. (11C)choline positron emission tomography/computerized tomography to restage prostate cancer cases with biochemical failure after radical prostatectomy and no disease evidence of conventional imaging. *J Urol*. 2010;184:938–943.
43. 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.

44. Krause BJ, Souvatzoglou SM, 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.
45. 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.
46. Cimitan M, Bortolus R, Morassut S, et al. (18F)fluorocholine PET/CT imaging for the detection of recurrent cancer at PSA relapse: experience in 100 consecutive patients. *Eur J Nucl Med Mol Imaging*. 2006;33:1387–1398.
47. Picchio M, Briganti A, Fanti S, et al. The role of choline positron emission tomography/computed tomography in the management of patients with prostate-specific antigen progression after radical treatment of prostate cancer. *Eur J Urol*. 2011;59:51–60.
48. Giovacchini G, Picchio M, Parra RG, et al. Prostate-specific antigen velocity versus prostate specific antigen doubling time for prediction of 11C choline PET/CT in prostate cancer patients with biochemical failure after radical prostatectomy. *Clin Nucl Med*. 2012;37:325–331.
49. 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 prostatectomy. *Eur J Nucl Med Mol Imaging*. 2010;37: 1106–1116.
50. 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.
51. 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.
52. Giovacchini G, Breeuwsma AJ. Restaging prostate cancer patients with biochemical failure with PET/CT and radiolabeled choline. *Q J Nucl Med Mol Imaging*. 2012;56:354–366.
53. Partin AW, Pearon JD, Landis PK, et al. Evaluation of serum prostate-specific antigen velocity after radical prostatectomy to distinguish local recurrence from distant metastases. *Urology*. 1994;43:649–659.
54. Trapasso JG, deKernion JB, Smith RB, et al. The incidence and significance of detectable levels of serum prostate specific antigen after radical prostatectomy. *J Urol*. 1994;152:1821–1825.
55. Lange PH, Ercole CJ, Lightner DJ, et al. The value of serum prostate specific antigen determinations before and after radical prostatectomy. *J Urol*. 1989;141: 873–879.
56. Heinisch M, Dirisamer A, Loidl W, et al. Positron emission tomography/computed tomography with F-18-fluorocholine for restaging of prostate cancer patients: meaningful at PSA < 5 ng/ml? *Mol Imaging Biol*. 2006;8:43–48.
57. Steiner C, Vees H, Zaidi H, et al. Three-phase 18F-fluorocholine PET/CT in the evaluation of prostate cancer recurrence. *Nuklearmedizin*. 2009;48:1–9.
58. Picchio M, Messa C, Landoni C, et al. Value of (11C)choline positron emission tomography for re-staging prostate cancer: a comparison with (18F)fluorodeoxyglucose-positron emission tomography. *J Urol*. 2003;169: 1337–1340.
59. Marzola MC, Chondrogianis S, Ferretti A, et al. Role of 18F-choline PET/CT in biochemically relpased prostate cancer after radical prostatectomy. *Clin Nucl Med*. 2013;38:e26–e32.
60. Breeuwsma AJ, Pruim J, van den Bergh ACM, 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.
61. Jadvar H. Prostate cancer: PET with 18F-FDG, 18F- or 11C-acetate, and 18F- or 11C-choline. *J Nucl Med*. 2010;52:81–89.

