Review – Prostate Cancer


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Abstract

Context: Determination of tumour involvement of regional lymph nodes in patients with prostate cancer (PCa) is of key importance for the proper planning of treatment. Objectives: To provide a critical overview of published reports and to perform a meta-analysis about the diagnostic performance of 18F-choline and 11C-choline positron emission tomography (PET) or PET/computed tomography (CT) in the lymph node staging of PCa. Evidence acquisition: A Medline, Web of Knowledge, and Google Scholar search was carried out to select English-language articles published before January 2012 that discussed the diagnostic performance of choline PET to individualise lymph node disease at initial staging in PCa patients. 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 focused on lymph node metastases. Reviews, clinical reports, and editorial articles were excluded. All complete studies were reviewed; thus qualitative and quantitative analyses were performed. Evidence synthesis: From the year 2000 to January 2012, we found 18 complete articles that critically evaluated the role of choline PET and PCa at initial staging. The meta-analysis was carried out and consisted of 10 selected studies with a total of 441 patients. The meta-analysis provided the following results: pooled sensitivity 49.2% (95% confidence interval [CI], 39.9–58.4) and pooled specificity 95% (95% CI, 92–97.1). The area under the curve was 0.9446 (p < 0.05). The heterogeneity ranged between 22.7% and 78.4%. The diagnostic odds ratio was 18.999 (95% CI, 7.109–50.773). Conclusions: Choline PET and PET/CT provide low sensitivity in the detection of lymph node metastases prior to surgery in PCa patients. A high specificity has been reported from the overall studies. Studies carried out on a larger scale with a homogeneous patient population together with the evaluation of cost effectiveness are warranted.

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1. Introduction

Lymph node metastases are found in up to 25% of patients with prostate cancer (PCa) depending on the tumour stage and grade [1,2]. Lymph node involvement is correlated with progressive disease in most patients, and the 5-yr disease-free survival rate subsequently decreases from 85% (nonmetastatic) to approximately 50% for pN1 disease [1]. The prognosis of PCa is directly linked to tumour size and lymph node histologic status. A strong association between nodal status and distant metastases has been demonstrated [3]. Determination of tumour involvement of regional lymph nodes is of key importance for the proper planning of treatment [4]. Pelvic lymphadenectomy is the gold standard for lymph node staging in PCa. This approach is associated with several limitations, however. First, the area of surgical exploration is limited to patients presenting external iliac obturator nodes, but so-called skip metastases to the internal and common iliac nodes are not uncommon and therefore go undetected. Second, the rates of morbidity and complications, ranging from 4% to 5% with this invasive technique, are not negligible. Third, the dissection of pelvic lymph nodes is expensive and requires hospitalisation. Fourth, it is a typical onetime procedure performed at the beginning of cancer treatment [5].

The nomograms could be used for defining patients with a low risk of nodal metastasis, thus sparing N-staging procedures [6]. In the current literature, computed tomography (CT) and magnetic resonance imaging (MRI) have demonstrated low diagnostic accuracy in this setting, although CT seems to be slightly superior [7]. Finally, a fine-needle aspiration biopsy may be useful in the case of positive imaging findings, but a false-negative rate of 40% has been reported [8].

Recent developments of new positron emission tomography (PET) ligands such as 11C- and 18F-labelled choline analogues, 11C-acetate, and 18F-fluorodihydrotestosterone have shown promising results in the detection of extraprostatic malignant lesions in PCa [9–12]. The major advantages of 18F- versus 11C-labelled choline tracers is the substantially longer half-life of the fluorochrome compound that allows the distribution of this tracer to PET institutions without an on-site cyclotron, very much like the common distribution of fluorodeoxyglucose. Urinary excretion of 18F-choline is comparatively higher than that of 11C-choline, but the overall imaging methods are similar between the different choline agents. The rationale of using PET imaging with radio-labelled choline analogues is the main role of choline because it is the precursor for the biosynthesis of phosphatidylcholine and of other phospholipids, which are the major components of cell membranes [13]. Data from Schmidt et al. [14] suggest that choline PET/CT is of limited use for the evaluation of primary T staging because benign prostatic hyperplasia cannot be differentiated from PCa tissue. However, choline PET/CT could be useful in a specific patient population with higher prostate-specific antigen (PSA) levels or elevated extensions of disease for lymph node staging [15,16]. The present review and meta-analysis has been conceived to explore the accuracy of choline PET/CT in the detection of lymph node involvement before radical prostatectomy in patients with PCa.

2. Evidence acquisition

2.1. Study identification

Articles containing information dealing with the results of choline PET or choline PET/CT for patients with PCa before surgery and published in the English language before January 2012 were reviewed. Articles were identified by an electronic search of PubMed/Medline using Medical Subject Headings (MeSH) term (Choline/diagnostic use) with limits activated (Humans, Clinical trial, Meta-analysis, Review, Classical Articles) or specific keywords (ie, positron emission tomography, choline, prostate cancer, initial staging) and Web of Knowledge/Google Scholar databases using terms such as choline PET, choline PET and prostate cancer, choline PET/CT, choline PET/CT AND prostate cancer, choline PET OR PET/CT AND lymph node, and choline PET OR PET/CT AND initial staging AND prostate cancer. The references of the articles and reviews found in the literature search were also examined to find additional reports that met the inclusion criteria. Studies with potentially overlapping study populations were excluded. The following items were searched in each of these series: number of patients, mean age, design of the study, reference standard, sensitivity, specificity, and other diagnostic data of choline PET or PET/CT scan.

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 article, which allowed us to construct 2 × 2 contingency tables; (2) the reference standard was pathology or other common imaging modalities; and (3) the sample size was >10 patients.

2.2. Study eligibility and quality

Two independent reviewers (LE and FaZ) independently evaluated potential English-language studies for inclusion, and the eventual disagreement was resolved by a third reviewer (AG). Abstracts were excluded from this analysis due to insufficient data to evaluate the methodological quality and to allow the calculation of diagnostic accuracy. Reviews, clinical reports, and editor comments were also excluded. The reviewers (FaZ and AG) evaluated the methodology of the selected studies using the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS) [17]. The evaluation was based on a 14-point scale. Each item was answered as yes, no, or unclear. Inconsistent findings between the two readers were discussed and agreed on by consensus (LE).

2.3. Data abstraction

For each included study, information concerning the basic study (author name, journal, year of publication, country of origin), patients’ demographic and clinical characteristics
(mean age, number of patients, risk category), technical parameters (radiopharmaceutical injected type), and PET or PET/CT choline evaluation (visual or semiquantitative analysis) was collected.

2.4. Statistical analysis

The number of TPs, TNs, FPs, and FNs were extracted or computed from each selected study based on the choline PET as the index test. The pooled sensitivity, specificity, positive predictive value (PPV), negative predictive value, likelihood ratio (LR), accuracy, and diagnostic odds ratio were calculated. A random-effects model was used. The between-study heterogeneity was assessed using the chi-square and $I^2$ tests. The chi-square test provided an estimate of the between-study variance, and the $I^2$ test measured the proportion of inconsistency in individual studies that cannot be explained by chance. According to Higgins et al. [18], the values of 25%, 50%, and 75% for heterogeneity ($I^2$) were considered low, moderate, and high, respectively. The area under the curve was calculated to measure the accuracy of choline PET/CT in the diagnosis of lymph node involvement regarding PCa. All statistical analyses were carried out using MetaDiSc statistical software, v.1.4 (Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain) [19]. The Duval and Tweedie’s “trim-and-fill” method was developed to estimate potential publication bias (available in CMA, v.2).

3. Evidence synthesis

3.1. Identification of studies

From the year 2000 until today, the Medline that uses MeSH terms has generated 45 results (27 reviews and 18 original articles) and 59 results from the common Medline/Web of Knowledge/Google Scholar (42 reviews and 17 original articles). Forty-two articles were the same and therefore considered only once. Fifty-six articles on the use of choline PET or PET/CT for PCa staging/restaging were identified, together with 25 other original articles and 31 reviews. Some of these articles (n = 18) focused on the value of 11C-choline or 18F-choline PET or PET/CT in the detection of PCa at initial staging. For the meta-analysis assessment, we analysed the performance of 11C-choline and 18F-choline PET or PET/CT in 10 original articles (Fig. 1).

3.2. Qualitative analysis

Although there were variations in the populations examined, in the doses, and in the type of radioisotope for choline, the series of selected studies were comparable. The results were similar to Hacker et al. [20], Husarik et al. [21], and Budiharto et al. [22], concluding that PET/CT with choline is not suitable for the initial staging of PCa, whereas studies by de Jong et al. [16,23], Schiavina et al. [24], and Poulsen et al. [25] seemed promising for initial lymph node

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**Fig. 1** – Flow diagram of selected studies for the accuracies of choline positron emission tomography (PET) and PET/computed tomography in lymph node metastasis according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis standard. MeSH = Medical Subject Headings.
staging due to a high sensitivity and specificity of the nuclear medicine technique. The different results probably can be found in smaller study populations [20,23,25–27] in some reports and in the lower number of examined lymph nodes [21,22,25]. Many of the authors underlined the low sensitivity of PET: It means a high false-negative rate in relation to the small dimension of a lymph node and its correlation with the spatial resolution of the PET scanner [20,21,26,28,29]. In contrast, Beheshti et al. [15] reported a similar PPV for 18F-choline PET/CT in lymph nodes both <5 mm and >5 mm in diameter (PPVs = 82%). Hara et al. [30] also concluded that choline PET is able to identify small foci of metastases that could not be identified by other diagnostic means, even in the case of small lymph nodes. As suggested by these two groups [15,25], the FP rate can be reduced by acquiring delayed images rather than early images.

The analysis of the selected reports showed that different populations had been considered: low-intermediate [16,23], intermediate [20], intermediate-high [15], and high risk [14,26]. The inclusion criteria of selected populations could induce biases in the final results.

Many of the studies reported that the main advantage of PET/CT is its ability to visualise lymph node metastases outside the field of a standard pelvic lymph node dissection and in particular in the detection of presacral/common iliac metastatic nodes [23,24,28]. The Italian groups [24] demonstrated the advantages of using 11C-choline PET/CT in comparison with the clinical nomograms (the Briganti and the Kattan nomograms) [6,31].

Budiharto et al. [22] found that the sensitivities and specificities, on a patient-based analysis, for PET/CT and MRI were 18.8% versus 42.9% and 95% versus 81.8%, respectively; they underlined that the poor performance of the investigated functional imaging may be due to the 53.1% positive nodes containing only micrometastases (>0.2 mm and <2 mm) or isolated tumour cells (<0.2 mm). Finally, Contractor et al. [27] reported the advantages of the hybrid PET/CT machine versus PET alone for the detection of lymph nodes in PCa (sensitivity: 51.9% vs 40.7%; specificity: 98.4% vs 98.4%) and concluded that choline PET is highly specific and more sensitive than MRI (51.9% vs 18.5%). However, comparing the existing studies on choline PET/CT for lymph node staging, there is an apparent improvement in accuracy over the studies. This might reflect progress in handling and interpreting the choline PET/CT scan by nuclear medicine specialists. In most of the reports, the standard uptake values in lymph node metastases were collected. The values were described differently, such as median and mean; thus no standardisation can be made. The minimum value was 2.70 (range: 2–4.17), provided by Budiharto et al. [22]; the maximum value was reported by Beheshti et al. [15] (9.1; range: 2.1–33.8).

3.3. Quantitative analysis (meta-analysis)

Based on the QUADAS, the studies were considered to be of high quality (n = 10; score: 11–14). Among all the selected
Table 2 – Summary of studies for choline positron emission tomography (PET) and PET/computed tomography and prostate cancer (patient-based analysis)

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>PPV, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
<th>Accuracy, % (95% CI)</th>
<th>True positive</th>
<th>True negative</th>
<th>False positive</th>
<th>False negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kotzerke et al. [26]</td>
<td>12</td>
<td>50 (19–100)</td>
<td>90 (71–100)</td>
<td>50 (19–100)</td>
<td>90 (71–100)</td>
<td>83 (62–100)</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>de Jong et al. [23]</td>
<td>25</td>
<td>80 (45–100)</td>
<td>95 (85–100)</td>
<td>80 (45–100)</td>
<td>95 (86–100)</td>
<td>92 (81–100)</td>
<td>4</td>
<td>19</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>de Jong et al. [16]</td>
<td>67</td>
<td>80 (60–100)</td>
<td>96 (91–100)</td>
<td>86 (68–100)</td>
<td>94 (88–100)</td>
<td>93 (86–99)</td>
<td>12</td>
<td>50</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hacker et al. [20]</td>
<td>20</td>
<td>10 (8–29)</td>
<td>80 (55–100)</td>
<td>33 (4–63)</td>
<td>47 (16–78)</td>
<td>45 (23–67)</td>
<td>1</td>
<td>8</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Schavina et al. [24]</td>
<td>57</td>
<td>60 (35–85)</td>
<td>98 (93–100)</td>
<td>90 (75–100)</td>
<td>87 (77–97)</td>
<td>88 (79–96)</td>
<td>9</td>
<td>41</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Husarik et al. [21]</td>
<td>43</td>
<td>20 (15–55)</td>
<td>100</td>
<td>100</td>
<td>90 (81–100)</td>
<td>91 (82–99)</td>
<td>1</td>
<td>38</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Beheshti et al. [15]</td>
<td>130</td>
<td>45 (30–60)</td>
<td>96 (91–100)</td>
<td>82 (70–94)</td>
<td>79 (71–88)</td>
<td>80 (73–87)</td>
<td>18</td>
<td>86</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Poulsen et al. [25]</td>
<td>25</td>
<td>100</td>
<td>95 (87–100)</td>
<td>75 (26–100)</td>
<td>100</td>
<td>96 (88–100)</td>
<td>3</td>
<td>21</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Buddharto et al. [22]</td>
<td>36</td>
<td>19 (3–38)</td>
<td>95 (85–100)</td>
<td>75 (54–96)</td>
<td>59 (38–81)</td>
<td>61 (45–77)</td>
<td>3</td>
<td>19</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Contractor et al. [27]</td>
<td>26</td>
<td>78 (51–100)</td>
<td>82 (64–100)</td>
<td>70 (40–99)</td>
<td>88 (72–100)</td>
<td>81 (66–96)</td>
<td>7</td>
<td>14</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value. *The values refer to positron emission tomography/computed tomography findings.

Table 3 – Pooled diagnostic accuracies for choline positron emission tomography/computed tomography

<table>
<thead>
<tr>
<th>Likelihood</th>
<th>Pooled value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>49.2</td>
<td>39.9–58.4</td>
</tr>
<tr>
<td>Specificity</td>
<td>95</td>
<td>92–97.1</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>8.346</td>
<td>4.499–15.482</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.549</td>
<td>0.366–0.824</td>
</tr>
<tr>
<td>Diagnostic odds ratio</td>
<td>18.999</td>
<td>7.109–50.773</td>
</tr>
</tbody>
</table>

Table 4 – Test for heterogeneity and threshold effect in the meta-analysis

<table>
<thead>
<tr>
<th>Likelihood</th>
<th>I² index, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-square</td>
<td>p value</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>31.81</td>
</tr>
<tr>
<td>Specificity</td>
<td>11.65</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>12.21</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>41.72</td>
</tr>
<tr>
<td>Diagnostic odds ratio</td>
<td>15.91</td>
</tr>
</tbody>
</table>

3.4. Discussion

Although the percentage of patients with positive lymph nodes has declined, a significant number of patients have lymph node–positive cancer (about 39% in high-risk patients). Establishing lymph node status helps inform decisions on therapy, predict recurrence, and assess prognosis. Imaging has not been reliable in identifying lymph node disease; until recent times, lymph node size was the only widely used method of ascertaining nodal disease [32]. In patients with positive nodes, an increased risk of local relapse and metastatic disease has already been reported. The more lymph nodes involved, the worse the survival potential [32]. For example, for patients who had two or three involved lymph nodes, the 5-yr survival rate appeared to be more promising than for patients who had more than three involved lymph nodes [33,34]. Therefore, preoperative measures to identify lymph node metastases are highly desirable before radical prostatectomy or ablation radiotherapy.

Multiple prognostic factors have emerged to identify patients with nodal disease and thus prevent unnecessary...
Table 6 – Pooled diagnostic accuracies for 18F-choline and 11C-choline positron emission tomography (PET)-PET/computed tomography

<table>
<thead>
<tr>
<th></th>
<th>18F-choline</th>
<th>11C-choline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pooled value (95% CI)</td>
<td>Pooled value (95% CI)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.40 (0.27–0.53)</td>
<td>0.58 (0.45–0.70)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.96 (0.91–0.98)</td>
<td>0.94 (0.90–0.97)</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>6.44 (1.64–25.30)</td>
<td>8.99 (4.43–18.27)</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.74 (0.45–1.21)</td>
<td>0.39 (0.16–0.92)</td>
</tr>
<tr>
<td>Diagnostic odds ratio</td>
<td>10.64 (1.32–85.91)</td>
<td>29.19 (10.44–81.57)</td>
</tr>
</tbody>
</table>

CI = confidence interval.

Local therapy. A serum PSA level ≥20 ng/ml, a Gleason score ≥7, and clinically evident extraprostatic disease are risk factors for pelvic lymph node metastases. However, the loss of specificity for PSA value and the underestimation of staging before surgery cannot adequately stratify the risk. A recent widespread use of PSA screening has led to earlier detection and a dramatic downstaging of PCa at diagnosis but has also resulted in the overdiagnosis and overtreatment of indolent disease. Although serum PSA level correlates positively with clinical stage, tumour volume, histologic grade, and the presence of capsular perforation and seminal vesicle invasion, it is of limited value in stage prediction for individual patients [35]. Grading on biopsies may not correlate with the prostatectomy specimen because of sampling problems, and cases of morphologically identical PCa can behave differently [36].

Nomograms that have been developed and validated internationally identify individuals at high risk for progression after definitive local therapy [37], but to our knowledge a probability cut point that separates patients at high risk from those at low risk has not been determined. The nomograms may offer more precise predictions of a prognosis or therapeutic response than staging alone. However, these models provide general probabilities, not the specific risk for an individual patient. However, among all patients undergoing prostatectomy for organ-confined disease, more than a third will relapse, indicating that the tumour was not confined to the prostate [38].

Extended pelvic staging lymphadenectomy in patients with clinically localised PCa, based on anatomic lymphatic drainage, detected lymph node metastasis in 26.2% and resulted in a diagnostic benefit of 15% compared with standard lymphadenectomy, according to Heidenreich et al. [39]. This concept can address the advantage of a tailored surgery that could be designed using an imaging modality. Unfortunately, no data are available.

The prediction of the failure of local therapy and an optimal high-risk definition should balance sensitivity, that is, encompassing patients with locally advanced or occult metastatic disease with an acceptable level of specificity (ie, excluding those with localised tumours). As reported by Amling et al. [40], standard pelvic lymphadenectomy does not involve the primary and quaternary lymphatics of the prostate, thereby decreasing the opportunity for adequate regional staging. This hypothesis is further substantiated by a systemic recurrence rate of 6–16% in patients with stages pT1/2 and pT3a PCa, respectively, implying occult lymph node disease at radical retropubic prostatectomy. The additional value of the imaging procedure in the depiction of positive lymph nodes could mean a better definition in the surgical field.

Imaging using radiologic and nuclear medicine tools should satisfy these two end points. As reported by Davis et al. [41], choline PET is superior to transrectal ultrasound biopsy and MRI for altering the treatment plan of radical prostatectomy, reporting a sensitivity and accuracy of 0.83 and 0.75, respectively, but a low specificity (0.44). In contrast to our report, the study by Davis et al. did not differentiate primary tumour from lymph node and distant metastases.

Unfortunately, the major weakness of the imaging devices is that up to 45% of metastatic lymph nodes are <0.4 cm in diameter [42], a value below the spatial resolution of PET/CT and below the adopted criteria of anatomic imaging tools such as MRI and CT. PET technologies have evolved in the last few years, but the most important change has been the introduction of hybrid tools in clinical practice. In the present meta-analysis, we found a significant difference between PET alone and PET/CT in sensitivity values (74% vs 43%, respectively), but the loss of sensitivity could be explained by inexperienced physicians who read the images or by the difficulty in differentiating urinary tract and pelvic lymph nodes. As already stated by Park et al. [43], more sophisticated image fusion software for accurate registration of anatomic MRI, diffusion MRI, 11C-choline PET, and histologic sections of the prostate gland-fusion may be facilitated by the emergence of the hybrid PET/MRI system. As reported by Harisinghani et al. [44], lymphotropic nanoparticle-enhanced MRI is a promising technique for malignant nodal evaluation. This technique is highly accurate because it evaluates nodal macrophage function and does not rely on nodal size to detect metastatic disease [45]. The association of PET as a metabolic and functional tool and MRI as a functional and anatomic device could reduce the FP and FN rates for the detection of lymph nodes in PCa.

There are many reasons for enlargement in nonmetastatic lymph nodes that can mimic a neoplastic lesion: first, a draining reaction to reactive lymphadenopathy [46,47]; second, elderly patients [48]; and finally, the inflammation from prostate needle biopsy. This is the first meta-analysis focusing on the evaluation of the diagnostic abilities of choline PET and PET/CT when assessing the involvement of lymph nodes at initial staging. Limited evidence for PET/CT

indication regarding lymph node involvement detection was found, in particular for the low sensitivity (pooled value: 49.2%). The main reasons for these findings can be summed up as follows: (1) the analysed studies tended to be of a limited size, and (2) they were carried out on an inhomogeneous spectrum of patients. In fact, only a few studies have given a detailed description of enrolled patients, such as PSA before nuclear medicine testing, Gleason score, and others.

3.4.1. Implications for research
In our opinion, future studies should focus on the evaluation of lymph node involvement in a stricter selection of patient population, such as those with a very high risk of lymph node dissemination. The pathologic reference standard for the presence of cancer should be homogeneously defined, together with a previously planned type of surgery. To improve the detection of lymph node metastases, a standard protocol should be performed (ie, delayed PET/CT images). Finally, having both 18F-choline and 11C-choline contributes a very high specificity; the availability of one or the other radioisotope is thus fundamental.

3.4.2. Implication for practice
Based on the evidence of this present review, the broad application of the PET/CT methodology is premature. We speculate that further improvement of technology (ie, PET/MRI) will increase diagnostic accuracy. The large distribution of 18F-choline in all European countries could increase the knowledge curve of nuclear medicine specialists, thus reducing the FP and FN findings.

4. Conclusions
Data from literature are discordant about the role of choline PET and PET/CT in the detection of lymph node metastases prior to prostate surgery. A high specificity is reported from the numerous available studies, but a stronger and more specific experience with a homogeneous patient population, together with the evaluation of cost effectiveness, must be investigated.

Author contributions: Laura Evangelista had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Evangelista, Filiberto Zattoni.
Acquisition of data: Evangelista, Fabio Zattoni, Guttilla.
Analysis and interpretation of data: Evangelista, Filiberto Zattoni, Fabio Zattoni, Guttilla Muzzio.
Drafting of the manuscript: Evangelista, Fabio Zattoni, Guttilla.
Critical revision of the manuscript for important intellectual content: Filiberto Zattoni.
Statistical analysis: Evangelista, Fabio Zattoni, Guttilla.
Obtaining funding: None.
Administrative, technical, or material support: Evangelista.
Supervision: Filiberto Zattoni, Muzzio.
Other (specify): None.

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References