Relationship between prostate-specific antigen kinetics and detection rate of radiolabelled choline PET/CT in restaging prostate cancer patients: A meta-analysis

ARTICLE in CLINICAL CHEMISTRY AND LABORATORY MEDICINE · DECEMBER 2013
Impact Factor: 2.96 · DOI: 10.1515/cclm-2013-0675 · Source: PubMed

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Relationship between prostate-specific antigen kinetics and detection rate of radiolabelled choline PET/CT in restaging prostate cancer patients: a meta-analysis

Abstract

Background: The aim of the article was to systematically review published data about the relationship between prostate-specific antigen (PSA) kinetics, including PSA doubling time (PSAdt) and PSA velocity (PSAvel), and detection rate (DR) of positron emission tomography/computed tomography (PET/CT) using radiolabelled choline in restaging prostate cancer (PCa).

Methods: A comprehensive literature search of studies published through July 2013 regarding the relationship between PSA kinetics and DR of radiolabelled choline PET/CT was carried out. Furthermore, a meta-analysis was performed in order to establish the DR of radiolabelled choline PET/CT using different cut-off values of PSAdt (≤ or >6 months) and PSAvel (>1 or ≤1 ng/(mL year) and >2 or ≤2 ng/(mL year)). Moreover, a pooled analysis to establish whether PSAdt and PSAvel (using the abovementioned cut-off values) may predict positive PET/CT results was carried out.

Results: Fourteen articles were selected. The pooled DR of radiolabelled choline PET/CT in restaging PCa was 58% [95% confidence interval (CI) 55–60]. Most articles reported a relationship between PSA kinetics and DR of PET/CT. Pooled DR of radiolabelled choline PET/CT increased to 65% (95% CI 58–71) when PSAdt was ≤6 months and to 71% (95% CI 66–76) and 77% (95% CI 71–82) when PSAvel was >1 or >2 ng/(mL year), respectively. PSAdt ≤6 months and PSAvel >1 or >2 ng/(mL year) proved to be relevant factors in predicting the positive result of radiolabelled choline PET/CT.

Conclusions: Due to the strong relationship between PSA kinetics and DR of radiolabelled choline PET/CT, beyond PSA values, PSAdt and PSAvel should be taken into account in the selection of PCa patients who should undergo radiolabelled choline PET/CT for restaging.

Keywords: choline; positron emission tomography; prostate cancer; prostate-specific antigen (PSA); PSA kinetics

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Introduction

Prostate cancer (PCa) is the most frequently diagnosed malignancy in men, and its incidence has been increasing in the last decades [1]. The clinical outcome of PCa is highly variable. In some patients, the tumor can grow so slowly that it may never be life-threatening, while in other patients it can exhibit an aggressive pattern implying early spread to the skeleton and death [2, 3].

Following primary surgery or external radiotherapy, biochemical failure of PCa, characterized by measureable or rising prostate-specific antigen (PSA) levels, occurs in about 30–50% of patients within 10 years following treatment [4]. The PSA threshold used for the definition of biochemical failure depends on the primary treatment. Following radical prostatectomy, PSA levels >0.2 ng/mL on at least two consecutive samples at 3 months apart indicate biochemical failure [5]. In patients treated with radiotherapy, a PSA value >2 ng/mL above the nadir after therapy represents recurrent cancer [6]. A critical step in this process is to differentiate patients who have local recurrence of disease or loco-regionally confined disease from patients with distant disease. This distinction has therapeutic implications because patients with local recurrence or limited lymph node metastases are preferentially treated with salvage radiotherapy and,
in sporadic cases, with salvage lymphadenectomy. On the contrary, androgen deprivation therapy is generally offered to patients with distant metastases [3].

The increase in PSA serum levels after radical prostatectomy or external beam radiotherapy is the most sensitive marker for detecting PCa recurrence, although this measure cannot distinguish between local, regional, or distant recurrence. Conversely, PSA kinetics, including PSA doubling time (PSAdt) and PSA velocity (PSAvel), have been used with success to predict the site of the disease.

The temporal PSA trends in untreated patients conform to an exponential model, suggesting that prostate cancer has a typically slow log-linear growth rate. As a consequence, PSAdt is often calculated by assuming an exponential rise in serum PSA and first-order kinetics. PSAvel is frequently calculated using regression analysis of multiple PSA measurements during an interval of 18 to 24 months [7]. Short PSAdt or high PSAvel is predictive of distant disease, whereas long PSAdt or low PSAvel is predictive of local disease. Furthermore, PSA kinetics was found to be correlated with poor outcome and/or fast progression of PCa [7–10].

Different imaging methods can be used for imaging PCa recurrence. In recent years, positron emission tomography/computed tomography (PET/CT) using choline radiolabelled with carbon-11 (11C) or fluorine-18 (18F) has been shown to be useful for restaging PCa patients with biochemical failure after radical prostatectomy or radiotherapy [11]. Radiolabelled choline is biochemically indistinguishable from natural choline; thus, it can be considered as a true tracer of cancer cell metabolism [12, 13]. As tumor cells present a high metabolic rate, choline uptake increases in tumor tissue to keep up with the demands of the synthesis of phospholipids in cellular membranes [14]. The greatest advantage of radiolabelled choline PET/CT lies in its ability to assess disease recurrence at multiple anatomical sites at a single time while preserving an accuracy similar to or greater than that of other conventional imaging techniques [15, 16]. Several studies have shown that the positive detection rate (DR) of the technique increases with increasing PSA levels [17]. However, the threshold for referring patients with PCa to radiolabelled choline PET/CT is less defined. While there is generally good agreement that patients with a PSA >1.5 ng/mL should be referred for radiolabelled choline PET/CT, the use of this technique is less established for lower PSA values when the positive detection rate definitely decreases [16]. The efficacy of salvage therapy is greater for low PSA values when the disease is more likely to be locally confined. Thus, early diagnosis of PCa recurrence could be of primary importance for successful treatment [2, 3]. However, due to the low positive DR of radiolabelled choline PET/CT for low PSA values, the use of this imaging method for early restaging would be burdened by the high cost of many false-negative scans [16].

The aim of this article was to systematically review the literature about the relationship between PSA kinetics (including PSAdt and PSAvel) and DR of radiolabelled choline PET/CT findings. Furthermore, we would like to clarify, by using a meta-analytic quantitative approach, whether PSAdt and PSAvel using specific cut-off values are relevant factors in predicting the positive result of radiolabelled choline PET/CT and in guiding the appropriate use of this method in restaging PCa patients.

Materials and methods

Search strategy

A comprehensive computer literature search of the PubMed/MEDLINE and Scopus databases was conducted to find relevant published articles on the correlation of PSA kinetics (including PSAdt and PSAvel) and radiolabelled choline PET/CT findings. We used a search algorithm that was based on a combination of the terms (a) “PSA” or “prostate-specific antigen” AND (b) “kinetic” or “doubling time” or “velocity” AND (c) “PET” or “positron emission tomography” AND (d) “choline”. No beginning date limit and language restriction were used; the search was updated until July 31, 2013. To expand our search, the references of the retrieved articles were also screened for additional studies.

Study selection

Studies or subsets in studies investigating the correlation between PSA kinetics and DR of radiolabelled choline PET/CT were eligible for inclusion. The exclusion criteria were (a) articles not within the field of interest of this review, and (b) review articles, editorials or letters, comments and conference proceedings. Two researchers (GT and LG) independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. Articles were rejected if they were clearly ineligible. The same researchers then independently reviewed the full-text version of the remaining articles to determine their eligibility for inclusion.

Data extraction

For each included study, information was collected concerning basic study (authors, journals and year of publication, country of origin, study design), patient characteristics (number and mean age, type of population), type of treatment, radiotracer used, PSA mean value, PSA kinetic parameters assessed and their relationship with the DR of radiolabelled choline PET/CT findings.
Statistical analysis

A pooled analysis of the DR of radiolabelled choline PET/CT in PCa patients with biochemical recurrence was performed using data retrieved by the selected studies. In case of several studies of the same group (possible overlap in patient data), only the most complete article was used for the meta-analysis. Pooled DRs of radiolabelled choline PET/CT taking into account PSAdt (≤ or >6 months) and PSAvel (>1 or ≤1 ng/(mL year) and >2 or ≤2 ng/(mL year)] were also calculated, including in the analysis only articles with sufficient data to calculate these pooled DRs.

Whenever possible, the odds ratios (ORs) of a positive radiolabelled choline PET/CT in patients with PSAdt ≤6 months compared to PSAdt >6 months, PSAvel >1 ng/(mL year) compared to PSAvel ≤1 ng/(mL year) and PSAvel >2 ng/(mL year) compared to PSAvel ≤2 ng/(mL year) were obtained from individual studies, and a pooled OR was calculated for these parameters in order to establish whether PSAdt and PSAvel may predict the positive result of radiolabelled choline PET/CT.

A random-effects model was used for statistical pooling of the data, taking into account the heterogeneity between studies. The different weight of each study in the pooled analysis was related to the different sample size. Pooled data were presented with their respective 95% confidence interval (CI), and data were displayed using plots. An I² index was used to test for heterogeneity between studies. Publication bias was evaluated graphically by using a funnel plot.

Statistical analyses were performed using the StatsDirect statistical software (StatsDirect Ltd., Altrincham, UK).

Results

Qualitative analysis (systematic review)

The comprehensive computer literature search from PubMed/MEDLINE and Scopus databases revealed 50 articles published in the last 5 years. Reviewing titles and abstracts, we excluded 36 articles because they were not within the field of interest or they were review articles, editorials or letters. Finally, 14 articles were selected and included in the systematic review (Figure 1). The characteristics of the included studies [16–29] are shown in Table 1. Most of the included studies are retrospective. There is heterogeneity between the selected studies concerning the characteristics of the patients included, such as type of previous treatment before biochemical recurrence and PSA values.

Most of the included studies reported a statistically significant relationship between PSA kinetics and PET/CT findings (Table 2). In particular, a statistically significant difference in mean and/or median trigger PSA (PSA at the time of PET/CT scan) value [17, 18, 21, 22, 24–27, 29,
PSAdt [18, 20–24, 28–30] and PSAvel [18, 20, 21–28, 30] was often shown in comparing patients with positive and those with negative radiolabelled choline PET/CT. Therefore, patients with positive PET/CT usually have higher PSA values, shorter PSAdt and higher PSAvel than patients with negative PET/CT. Nevertheless, a significant overlap in PSA, PSAdt and PSAvel values between these two groups has been reported. Logistic regression analysis was used to determine whether there was a relationship between trigger PSA levels or PSA kinetics and DR of relapse of PCa using radiolabelled choline PET/CT, but different results were reported in the included studies. In some studies, trigger PSA [17, 18, 21, 22, 24, 29, 30], PSAdt [18–20, 22, 24, 28, 29] and PSAvel [18, 30] were found to be independent predictive factors for a positive PET/CT result at multivariate logistic regression analysis.

Quantitative analysis (meta-analysis)

Excluding some articles for possible data overlap (as they were performed by the same group), we found that 8 of 14 studies included in this systematic review were eligible for the pooled calculation of the DR of radiolabelled choline PET/CT in PCa patients with biochemical recurrence [17, 21, 22, 24–28]. This DR was 58% (95% CI 55–60). The heterogeneity between the included studies was high (I²=80%), and the presence of publication bias should be taken into account as demonstrated by the funnel plot (Figure 2).
Table 2  PSA kinetics and radiolabelled choline PET/CT findings.

<table>
<thead>
<tr>
<th>Authors</th>
<th>PSA mean/median value, ng/mL</th>
<th>PSAdt mean/median value, months</th>
<th>PSAvel mean/median value, ng/(mL year)</th>
<th>PSAdt cut-off value used, months</th>
<th>PSAvel cut-off value used, ng/(mL year)</th>
<th>Overall PET/CT detection rate</th>
<th>Statistical significant relationship between tPSA and PET/CT findings</th>
<th>Statistical significant relationship between PSAdt and PET/CT findings</th>
<th>Statistical significant relationship between PSAvel and PET/CT findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beheshti et al. [17]</td>
<td>46.9/5.6</td>
<td>NA</td>
<td>NA</td>
<td>10</td>
<td>NA</td>
<td>74%</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Ceci et al. [18]</td>
<td>8.3/4.4</td>
<td>5.3/3</td>
<td>22.1</td>
<td>n.a</td>
<td>n.a</td>
<td>66%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Giovacchini et al. [19]</td>
<td>0.71/0.61</td>
<td>11.5/10.1</td>
<td>NA</td>
<td>6</td>
<td>NA</td>
<td>21%</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>Mamede et al. [20]</td>
<td>0.34</td>
<td>7.1</td>
<td>0.19</td>
<td>6.23</td>
<td>NA</td>
<td>21%</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Marzola et al. [21]</td>
<td>7.4</td>
<td>10.1</td>
<td>5.7</td>
<td>NA</td>
<td>NA</td>
<td>54%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rybalov et al. [22]</td>
<td>4.8</td>
<td>NA</td>
<td>3, 6, 9, 12, 24</td>
<td>1, 2, 4, 6, 10</td>
<td>36%</td>
<td>65%</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Breeuwsma et al. [23]</td>
<td>4.6/1.4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>36%</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Giovacchini et al. [24]</td>
<td>3.24/1.25</td>
<td>NA</td>
<td>3.75/0.99</td>
<td>NA</td>
<td>1 and 2</td>
<td>44%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Graute et al. [25]</td>
<td>4.4/2.4</td>
<td>7.5/4.8</td>
<td>10.7/2.3</td>
<td>3.2</td>
<td>1</td>
<td>62%</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Schillaci et al. [26]</td>
<td>4.1</td>
<td>NA</td>
<td>10.3</td>
<td>6</td>
<td>2</td>
<td>67%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Casamassima et al. [27]</td>
<td>n.a.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>55%</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Castellucci et al. [28]</td>
<td>0.86/0.93</td>
<td>NA</td>
<td>NA</td>
<td>7.25</td>
<td>NA</td>
<td>28%</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Giovacchini et al. [29]</td>
<td>3.24/1.25</td>
<td>9.4/7</td>
<td>NA</td>
<td>3, 6, 9, 12, 15</td>
<td>NA</td>
<td>44%</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>Castellucci et al. [30]</td>
<td>4.2/2.1</td>
<td>NA</td>
<td>2, 4, 6</td>
<td>1, 2, 5</td>
<td>39%</td>
<td>39%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NA, not available; tPSA, trigger PSA; PSAdt, PSA doubling time; PSAvel, PSA velocity.

Figure 2  Plot of the pooled detection rate of radiolabelled choline PET/CT (including 95% confidence intervals) in the included studies (on the left). The size of the squares indicates the weight of each study. A funnel plot evaluating the publication bias is shown on the right.
Only some articles contained sufficient data to be eligible for the pooled calculation of the DR of radiolabelled choline PET/CT based on PSAdt ≤ 6 or > 6 months [22, 26, 29, 30], PSAvel ≤ 1 or > 1 ng/(mL year) [22, 24, 25, 30] and PSAvel ≤ 2 or > 2 ng/(mL year) [22, 24, 26, 30].

Pooled DR of radiolabelled choline PET/CT increased to 65% (95% CI 58–71) in patients with PSAdt ≤ 6 months, to 71% (95% CI 66–76) in patients with PSAvel > 1 ng/(mL year) and to 77% (95% CI 71–82) in patients with PSAvel > 2 ng/(mL year) and to 77% (95% CI 71–82) in patients with PSAdt > 6 months, to 26% (95% CI 20–32) in patients with PSAvel ≤ 1 ng/(mL year) and to 36% (95% CI 30–41) in patients with PSAvel ≤ 2 ng/(mL year), showing a statistically significant difference between these groups (Figure 3).

Figure 3  Plot of the pooled detection rate of radiolabelled choline PET/CT (including 95% confidence intervals) in the included studies, considering only patients with PSA doubling time > 6 months (A1), ≤ 6 months (A2), PSA velocity ≤ 1 ng/(mL year) (B1), > 1 ng/(mL year) (B2), ≤ 2 ng/(mL year) (C1) and > 2 ng/(mL year) (C2). The size of the squares indicates the weight of each study.
The pooled OR of PSAdt ($\leq$6 vs. $>$6 months) for the positivity of PET/CT scan was 3.20 (95% CI 2.14–4.79). The pooled ORs of PSAvel using two cut-off values [$\leq$1 vs. $\leq$1 ng/(mL year) and $>\geq$ vs. $>\leq$2 ng/(mL year)] for the positivity of PET/CT scan were 7.45 (95% CI 4.87–11.41) and 5.95 (95% CI 3.93–9.01), respectively (Figure 4). These pooled results show that PSAdt and PSAvel are relevant factors in predicting the positivity of radiolabelled choline PET/CT scan.

**Discussion**

To the best of our knowledge, this meta-analysis is the first to evaluate the relationship between PSA kinetics and DR of radiolabelled choline PET/CT in restaging PCa patients with biochemical recurrence [31]. Several studies have reported data about this relationship with discordant results (Table 1). In order to derive more robust estimates in this regard, we have pooled published studies. A systematic review process was adopted in ascertaining studies, thereby avoiding selection bias. Pooled results of our meta-analysis show that there is a significant correlation between PSA kinetics (including PSAdt and PSAvel) and DR of radiolabelled choline PET/CT in evaluating PCa patients with biochemical recurrence. Furthermore, as shown by the pooled OR provided by our analysis, PSAdt $\leq$6 months and PSAvel $>1$ and $>2$ ng/(mL year) are strong predictors of the positivity of radiolabelled choline PET/CT scan.

The relatively high DR of radiolabelled choline PET/CT in patients with fast PSA kinetics is not surprising: PSA kinetics is, in fact, an expression of prostatic tissue growth, and a functional modality, such as choline PET/CT, is thus an appropriate modality for detecting recurrences. None of the known risk factors, including Gleason score and TNM score, seems to influence the DR of radiolabelled choline PET/CT as much as PSA kinetics does [32].

Possible limitations of our analysis could be the arbitrary cut-off values chosen for PSA kinetics and the heterogeneity between the included studies. An arbitrary cut-off of 6 months for PSAdt and 1 or 2 ng/(mL year) for PSAvel were chosen because these values were adopted by most of the studies. This choice has limited the number of studies included in the related pooled analyses. Nevertheless, we could not retrieve sufficient data from the included articles to perform a receiver operating characteristic curve in order to establish the optimal cut-off value in this setting. The heterogeneity between the included studies likely derives from the baseline differences among the included patients, such as previous treatment and different PSA values (Tables 1 and 2). However, the heterogeneity between studies was accounted for in a random-effects model in our pooled analysis. The strict correlation between PSA kinetics and radiolabelled choline PET/CT findings shown by our pooled analysis could be the rationale for recommending this imaging method as a first-line diagnostic procedure in PCa patients with biochemical relapse showing fast PSA.

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![Figure 4](image-url)

**Figure 4** Plot of the pooled odds ratio of PSA doubling time [$\leq$6 vs. $\leq$6 months (A) and PSA velocity [$\geq$1 vs. $\leq$1 ng/(mL year) (B), $>\geq$2 vs. $\leq$2 ng/(mL year) (C)] for the positivity of radiolabelled choline PET/CT, including 95% confidence intervals. The size of the squares indicates the weight of each study.
kinetics, in particular those with PSAdt ≤ 6 months and/or PSAvel > 1 ng/(mL year), as recently suggested by a non-systematic review written by international experts [31]. At any rate, more prospective studies and cost-effectiveness analyses about the use of radiolabelled choline PET/CT in restaging PCa patients are needed to strengthen the usefulness of this method, particularly in patients with fast PSA kinetics. Similarly, it is conceivable that further developments in molecular imaging such as hybrid PET/magnetic resonance imaging will provide relevant information in this regard [33, 34].

Conclusions

Due to the strong relationship between PSA kinetics and DR of radiolabelled choline PET/CT, beyond PSA values, PSAdt and PSAvel should be taken into account in the selection of patients who should undergo radiolabelled choline PET/CT, in order to optimise the use of this imaging method in restaging PCa patients.

Conflict of interest statement

Authors’ conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Received August 21, 2013; accepted November 4, 2013

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