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TOPIC PAPER

# The utility of PET-based imaging for prostate cancer biochemical recurrence: a systematic review and meta-analysis

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## Abstract

**Introduction** Conventional imaging modalities have been poor in characterizing the true extent of disease in men with biochemical recurrence following primary treatment for prostate cancer. Functional imaging with positron emission tomography (PET) has shown promise of being a superior imaging modality. We conducted a systematic review and meta-analysis to define the diagnostic accuracy of PET/CT using 11C-choline, 18F-FACBC, or 68Ga-PSMA in detecting recurrent prostate cancer.

**Methods** We searched multiple databases in line with the preferred reporting items for systematic review and meta-analysis (PRISMA) statement to define the diagnostic accuracy of 11C-choline, 18F-FACBC, or 68Ga-PSMA PET/CT. Only studies secondarily staging participants with biochemical recurrence and those with an appropriate reference standard (pathology, further imaging, and/or clinical response) were eligible for analysis.

**Results** Twenty-one studies with 3202 participants met the inclusion criteria. Of these, 11C-choline, 18F-FACBC, and 68Ga-PSMA were the tracer investigated in 16, 5, and 1 studies, respectively. The summary sensitivity for each tracer was 80.9% (95% CI 70.4–88.3%), 79.7% (95% CI 51.9–93.4%), and 76.4% (95% CI 68.3–82.9%), respectively. The corresponding summary specificity was 84.1% (95% CI 70.2–92.2%), 61.9% (95% CI 41.1–79.0%), and 99.8% (95% CI 97.5–100%), respectively. Detection rates ranged between 58.6 and 82.8%. All included studies were judged to be at high risk of bias primarily due to study limitations pertaining to the reference standard.

**Conclusion** There is a lack of high-quality data to verify the accuracy of PET-based imaging using 11C-choline, 18F-FACBC, or 68Ga-PSMA. The early results are encouraging that these techniques are superior to conventional imaging modalities, which would allow salvage therapies to be optimized.

**Keywords** Cancer staging · Positron emission tomography · Prostate cancer · Systematic review

## Introduction

Local treatment with either surgery or radiation therapy remains the gold standard for intermediate- and high risks, localized prostate cancer. While these are both effective forms of management, approximately 30–40% of cancers still recur following treatment [1, 2], manifesting as a rising prostate-specific antigen (PSA)—this is termed biochemical recurrence (BCR). At this stage of the disease, it is important to determine the location and extent of metastases to determine the next course of management: metastasis-targeted and/or systemic treatment [3]. Historically, conventional imaging modalities such as computer tomography (CT), bone scintigraphy (BS), and magnetic resonance imaging (MRI) have been the mainstay in the secondary staging landscape [4, 5]. However, the sensitivities of these modalities are particularly poor in detecting low-volume metastatic/locally recurrent disease especially at low levels of PSA when salvage therapy would be most effective [6]. It has been show that only 14–30% of CT scans are positive in detecting recurrent tumors [7, 8]. The yield of BS is even lower with fewer than 5% of scans being positive when the PSA is less than 7 ng/mL [9].

Over the last decade, there has been substantial development in using positron emission tomography (PET) to detect metastases in the early BCR stage [10]. PET is an established, non-invasive, molecular imaging modality that uses

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different radiolabeled tracers, a combination of a radionuclide and a biologically active molecule, targeted to specific receptors to localize disease. Initial results suggest that the combination of functional and morphological imaging has a superior diagnostic ability than the latter form alone [10]. Of the range of radiolabeled tracers that have been evaluated, 11C-choline and 18F-FACBC (fluciclovine) are two that are currently FDA approved in the United States for use in this setting [11]. In other parts of the world, 68Ga-PSMA has been more routinely employed in clinical practice. Investigations into the use of these tracers, especially 18F-FACBC and 68Ga-PSMA, are still in its infancy, and therefore, it is important to consider all the available evidences when assessing their utility.

The objective of this study was to perform a systematic review and meta-analysis to assess the diagnostic ability of 11C-choline, 18F-FACBC, and 68Ga-PSMA PET/CT in detecting local recurrent and metastatic disease in men with BCR.

## Methods

The preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [12] and Cochrane Handbook for diagnostic test accuracy [13] framework were used for this review. The protocol for this review was published in the international prospective register of systematic reviews (PROSPERO) (CRD42018094741).

### Searches

A search was conducted in the scientific literature databases (MEDLINE, EMBASE, ScienceDirect, The Cochrane Library, the HTA database, Google Scholar, and Web of Science) up to April 2018. The keywords for the search included "prostate cancer" or "prostate" or "prostatic neoplasm" or "prostate malignancy"; "positron emission tomography" or "PET"; "18F-FACBC" or "fluciclovine" or "axumin"; "68-Ga-PSMA" or "prostate-specific membrane antigen"; "11C-choline" or "choline".

Proceedings of international urology meetings held over the last 3 years were also searched for relevant abstracts which may not have been published at the time of the initial literature search.

In addition, the reference lists of all relevant studies were checked, the 'related articles' and 'find similar' features in PubMed and Ovid were also used to identify further studies, and citation alerts were placed on relevant studies to identify any recent publications that should also be included.

Case reports, letters to the editor, editorial comments, and conference proceedings were excluded, but no restrictions were placed on study location or on the language of publication.

### Selection of studies

The results of the search were screened initially by title and abstract for relevance before full-text review by two independent authors (N.S. and M.B.) with a senior author (B.K.) consulted to resolve any disagreements. Both retrospective and prospective trials in which patients who have evidence of biochemical recurrence undergoing PET-based imaging were included. BCR was defined as a PSA > 0.2 ng/mL after radical prostatectomy or a rise by at least 2 ng/mL above the PSA nadir after radiotherapy [14, 15]. Only studies using one of the following PET tracers were included: 68Ga-PSMA, 18F-FACBC (fluciclovine), and 11C-choline. Other PET tracers were not included in this review, because they are not routinely used in clinical practice and remain experimental.

It is not feasible—nor ethical when imaging is negative—to obtain histological data to confirm the results of staging results. Therefore, studies which validated the results of imaging using a combination of histology, further imaging and/or clinical follow-up with PSA results or response to treatment initiated based on the results of PET imaging were included. We recognize that this may not reflect the true disease state and is not the gold-standard reference, but suggests that it is the best possible reference in real-world clinical practice.

We excluded studies in which only cases with positive PET/CT scans were included and followed-up. In addition, studies in which only the outcomes of a single type or site of metastasis was included (e.g., bone, local recurrence, or nodal) were excluded. Patients who were undergoing PET-based imaging for primary staging or have already been diagnosed with castration-resistant disease were excluded.

### Data extraction

The above authors independently extracted data from included studies using a data collection form developed a priori. Information recorded from each study included publication details, patient demographics, imaging protocols, imaging results, and results of verification. Where a participant underwent multiple PET/CT scans, only the results of the first scan were used for analysis.

### Assessment of methodological quality

Studies were assessed for quality using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [16] by two independent authors (N.S. and M.B.), with

consultation with a senior author (B.K.) to resolve any disagreements.

### Statistical analysis

Extracted data were collated in Excel (Microsoft Corporation, Redmond, CA, USA) and analysis performed in R Statistical Software (Foundation for Statistical Computing, Vienna, Austria) using the 'meta' and 'mada' packages [17, 18]. Using a $2 \times 2$ table that was constructed for each study during the data extraction process, pooled estimates for sensitivity and specificity were calculated for each biomarker using a bivariate random-effects regression model [19]. The diagnostic performance of the different radiotracers was calculated on a per-patient and per-lesion basis. In addition, detection rate was meta-analysed with a random-effects model using DerSimonian and Laird method. Proportions were transformed with the Freeman–Tukey double inverse sine transformation, and confidence intervals were calculated using the Score method. Heterogeneity within and between groups were assessed using the $I^2$ statistic [20]. We were unable to perform the intended subgroup analyses on PSA level and the receipt of salvage therapy because of insufficient data.

## Results

The literature flow diagram provides an overview of the search and study selection process (Fig. 1). The search identified 2978 articles of which 87 were duplicates. After two authors independently screened the abstracts and titles, 191 articles were selected for full-text review. Of these, 21 studies with 3202 patients met the eligibility criteria and their characteristics are outlined in Table 1. 11C-choline, 18F-FACBC and 68Ga-PSMA were the tracer investigated in 16 [21–36], 5 [34, 37–40], and 1 [41] studies, respectively. The included studies were primarily retrospective in nature ($n = 20$) and were conducted in the United States or Europe, expect for one which was conducted in Japan [23]. The population of men included in each study varied widely between the studies with the proportion of those initially treated with radical prostatectomy or radiation therapy ranging from 0 to 100%, respectively. Seven studies included patients who had already undergone salvage treatment [27, 28, 32, 34, 39–41]. Four studies included patients who had the previous negative conventional imaging prior to PET/CT [25, 28, 38, 41]; however, most did not explicitly report this in their demographic section. In

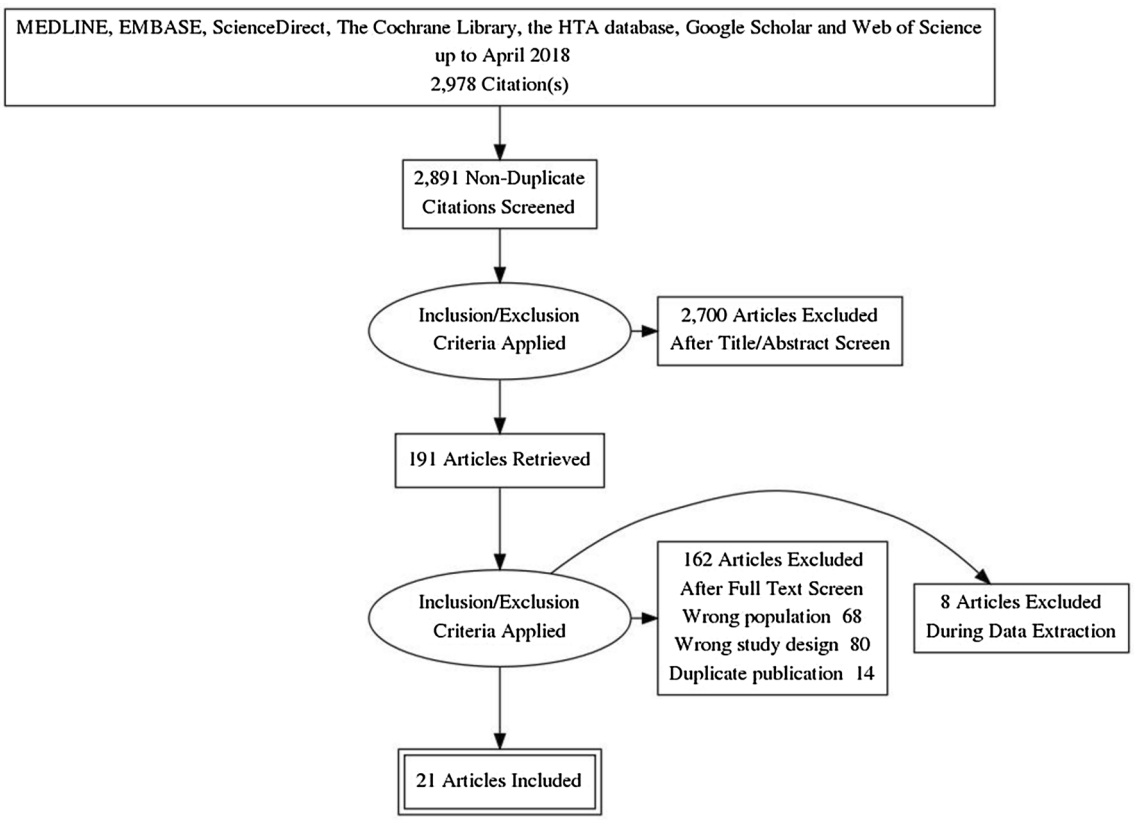


**Fig. 1** PRISMA flow diagram

**Table 1** Study characteristics

| Author | Year | Location | Study type | Tracer | Uptake time (min) | CT technique | Cohort *N* | Previous RP (%) | Previous RT (%) | Previous salvage (%) | Previous conventional imaging | median age | Median PSA | Total positive scans (per-patient) | PSA < 1 total | PSA < 1 positive | PSA < 1 sensitivity | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Afshar-Oromieh | 2015 | Germany | Retrospective | PSMA | 60 | NCE | 319 | 70.8 | 55.5 | Yes | Yes | 68 (range 46–86) | 4.59 (range 0.01–41395) | 264 | 51 | 27 | NR | Pathological tissue |
| Bach-Gansmo | 2017 | Multi-institutional (Europe) | Retrospective | Fluciclovine | NR | NR | 595 | 4.9 | 2.8 | Yes | NR | 68 (range 47–90) | 3.6 (range 0.11–44.76) | 403 | NR | NR | NR | Histopathology |
| Breeuwsma | 2010 | Netherlands | Prospective | Choline | 5 | NR | 70 | 0.0 | 100.0 | No | No | NR | 10.7 (range 0.6–54.7) | 57 | NR | NR | NR | Biopsy, imaging and/or clinical course |
| Castellucci | 2014 | Italy | Retrospective | Choline | 3–5 | NR | 605 | 100.0 | 0.0 | No | No | 70 (range 47–84) | 1.1 (0.2–2) | 172 | NR | NR | NR | Biopsy, imaging and/or clinical course |
| Ceci | 2014 | Austria & Italy | Retrospective | Choline | 3–5 | NR | 150 | 60.7 | 20.0 | Yes | No | 71 (range 53–86) | 2.3 (range 0.2–39.4) | 109 | NR | NR | NR | Biopsy, imaging and/or clinical course |
| De Jong | 2003 | Netherlands | Retrospective | Choline | 5 | NR | 20 | 59.4 | 40.6 | No | NR | 71 (range 43–79) | 4.95 (range 0.5–120) | 11 | 2 | 0 | 0.0% | Biopsy, imaging and/or clinical course |
| Giovacchini | 2010 | Italy | Retrospective | Choline | 5 | Low dose | 358 | 100.0 | 0.0 | 12.0 | NR | 67 (range 51–83) | 1.27 (range 0.23–45.2) | 161 | 141 | 27 | NR | Biopsy, imaging and/or clinical course |
| Gómez-de la Fuente | 2017 | Spain | Retrospective | Choline | 20 | NCE | 41 | 88.0 | 0.0 | No | NR | 65.9 (mean) (range 52–80) | 0.40 (mean) (range 0.008–0.94) | 12 | NR | NR | NR | Biopsy, imaging and/or clinical course |
| Kairemo | 2014 | Finland | Retrospective | Fluciclovine | 4–16 | Low dose | 13 | 0.0 | 30.8 | Yes | NR | 68.1 (range 56 to 77) | 7.9 (range 0.11–69) | 6 | NR | NR | NR | Further imaging, biopsy and/or clinical course |
| Mamede | 2013 | Multi-institutional | Retrospective | Choline | 3–5 | NR | 71 | NR | 0.0 | NR | No | 66.2 (mean) (range 54–81) | 0.34 (mean) (0.1–0.5) | 16 | NR | NR | NR | Biopsy, imaging and/or clinical course |
| Mitchell | 2012 | USA | Retrospective | Choline | NR | NR | 176 | NR | NR | 100.0 | 19.3 | 61 (range 42–78) | NR | 132 | NR | NR | NR | Histological, radiographic and clinical |
| Nanni | 2016 | Italy | Prospective | Fluciclovine | 3–5 | Low dose without contrast | 89 | 100.0 | 0.0 | Yes | NR | 69 (range 55–83) | 3.35 (range 0.2–20.72) | 33 | NA | 21% | 21.0% | Re-evaluation of the clinical and imaging history after the 18F-FACBC PET/CT scan |

**Table 1** (continued)

| Author | Year | Location | Study type | Tracer | Uptake time (min) | CT technique | Cohort *N* | Previous RP (%) | Previous RT (%) | Previous salvage (%) | Previous conventional imaging | median age | Median PSA | Total positive scans (per-patient) | PSA < 1 total | PSA < 1 positive | PSA < 1 sensitivity | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nanni | 2016 | Italy | Prospective | Choline | 3–5 | Low dose without contrast | 89 | 100.0 | 13.0 | Yes | NR | 69 (range 55–83) | 3.35 (range 0.2–20.72) | 30 | NA | 14% | 14.0% | Re-evaluation of the clinical and imaging history after the 18F-FACBC PET/CT scan |
| Parker | 2017 | USA | Retrospective | Choline | NR | NR | 184 | 0.0 | 56.5 | No | NR | 65 (IQR 60–70) | 5.7 (IQR 3.4–8.9) | 161 | 2 | 2 | NR | Biopsy, imaging and/or clinical course |
| Picchio | 2003 | Italy | Retrospective | Choline | 5 | NR | 100 | 77.0 | 23.0 | NR | No | 70.5 (range 45–81) | 6.57 (mean) (range 0.14–171) | 49 | NR | NR | NR | Clinical follow-up with PSA and/or conventional imaging |
| Richter | 2009 | Spain | Retrospective | Choline | 5 | NR | 73 | 67.1 | 32.9 | No | Yes | 65.6 (mean) | NR | 43 | 15 | 1 | 7.7% | Biopsy and/or PSA response |
| Rinnab | 2007 | Germany | Retrospective | Choline | 5–10 | CE | 50 | 62.0 | 6.0 | NR | NR | 67 (range 52–79) | 2.4 (range 0.41–13.1) | 44 | 5 | 2 | 40.0% | Histopathology |
| Rinnab | 2009 | Germany | Retrospective | Choline | 5 | CE | 41 | 78.0 | 0.0 | No | NR | 66 (range 52–76) | 2.1 (range 0.41–11.6) | 36 | NR | NR | NR | Histopathology |
| Rybalov | 2013 | Netherlands | Retrospective | Choline | 5 | Low dose | 185 | 33.0 | 67.0 | NR | NR | 69 (mean) | 18.45 (mean) | 124 | 25 | 6 | NR | Biopsy, imaging and/or clinical course |
| Schuster | 2007 | USA | Retrospective | Fluciclovine | NR | NCE | 6 | 0.0 | 0.0 | NR | NR | NR | NR | 4 | 0 | 0 | NA | Biopsy, imaging and/or clinical course |
| Schuster | 2011 | USA | Prospective | Fluciclovine | 3 | OCE | 48 | 12.0 | 16.0 | No | Yes | 68.3 (mean) (range 50–90) | 6.62 (mean) (range 0.11–44.74) | 37 | 6 | 2 | 0.0% | Biopsy, imaging and/or clinical course |
| Yoshida | 2005 | Japan | Retrospective | Choline | 5 | NR | 8 | 50.0 | 0.0 | No | NR | 68 (range 60–73) | 5.3 (range 1.3–11) | 6 | 0 | NA | NA | Biopsy, imaging and/or clinical course |

one study, 27/319 (8.5%) patients were being primarily staged, but the authors decided to still include this study as the vast majority of patients (91.5%) were being evaluated for BCR [41].

## Risk of bias

All 21 included studies were judged at high risk of bias (Fig. 2). The major potential source of bias in these studies was that the reference standard was not likely to localize metastatic disease with a high degree of accuracy. As mentioned previously, it is neither feasible nor ethical to obtain pathological verification for PET/CT results, especially in the scenario of a negative scan. Therefore, studies used a combination of tissue, further imaging and clinical follow-up (e.g., PSA change ± further therapy) to ascertain the presence of metastatic disease. While this reflects real-world clinical practice, it is unlikely to accurately localize metastatic disease. For example, if a patient with a single positive node that was not amenable to surgery received androgen deprivation therapy, and subsequently, their serum PSA decreased, this would have been classified as a true positive, even though it is possible that there were other areas of metastases that were not detected by PET/CT (i.e., false negative). Moreover, one study classified all negative scans as false negative unless long-term clinical follow-up was completely negative, because they assumed that a rising or persistent PSA following treatment indicated that there was underlying metastatic disease [34]. Furthermore, there was often no pre-specified follow-up protocol in these studies, and therefore, different tests were performed at different schedules for cases within and between studies. This was likely influenced by the results of the PET/CT and is a potential source of bias.

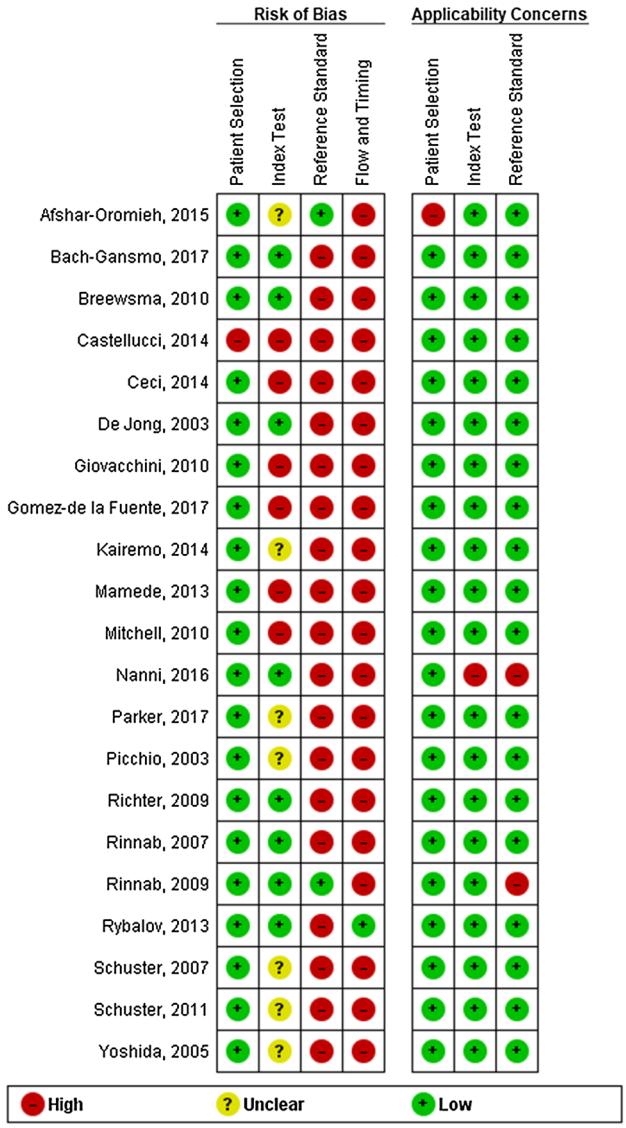


**Fig. 2** Risk of bias

## Diagnostic performance

Sixteen studies reported the diagnostic performance of 11C-choline PET/CT on a per-patient basis with a summary sensitivity and specificity for the detection of metastatic disease of 80.9% (95% CI 70.4–88.3%) and 84.1% (95% CI 70.2–92.2%), respectively (Fig. 3a). The DOR, posLR, and negLR were 25.2, 5.4, and 0.24, respectively.

The summary sensitivity and specificity calculated from the four studies reporting on 18F-FACBC on a per-patient basis was 79.7% (95% CI 51.9–93.4%) and 61.9% (95% CI 41.1–79.0%), respectively (Fig. 3b). The DOR, posLR, and negLR were 8.0, 2.1, and 0.36, respectively. The corresponding measures of performance on a per-lesion basis were 62.7% (95% CI 56.4–68.5%) and 69.8% (95% CI 64.5–74.7%), respectively (Fig. 3c).

The sensitivity and specificity on a per-lesion basis of the one study which investigated 68Ga-PSMA were 76.4% (95% CI 68.3–82.9%) and 99.8% (95% CI 97.5–100%), respectively (Fig. 3d).

Summary receiver operating characteristic (SROC) curve for 11C-choline and 18F-FACBC is shown in Fig. 4. SROC curves were not constructed for per-lesion data because of insufficient studies.

## Detection rate

The pooled detection rate from the 16 studies using 11C-choline as the radiotracer was 62.2% (95% CI 48.9–74.4%). There was significant heterogeneity observed between and within studies ($I^2 = 97.1\%$). In the meta-regression analysis, neither year of publication ($p = 0.44$), median age ($p = 0.31$), nor median PSA ($p = 0.30$) impacted the detection rate of

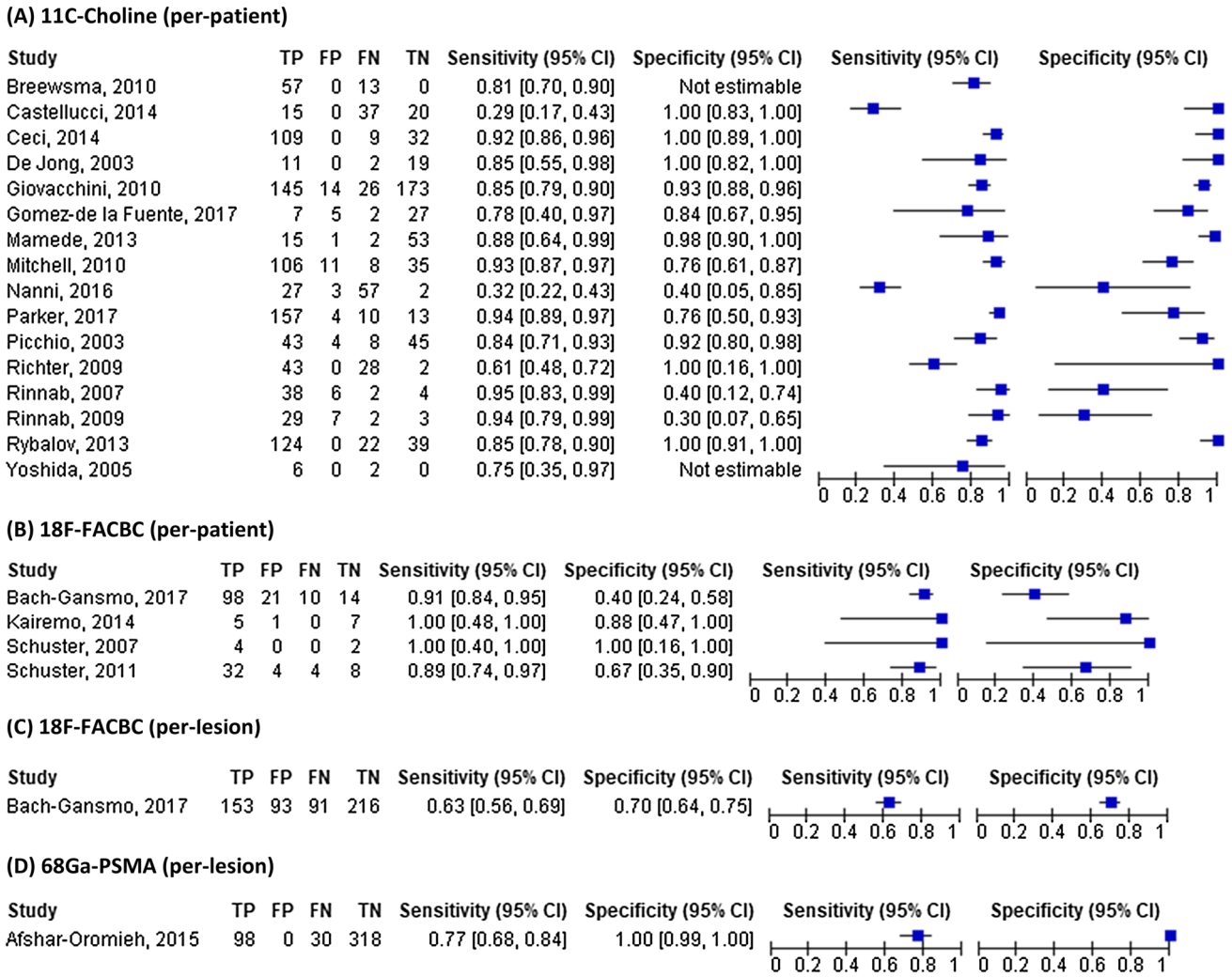


**Fig. 3** Forest plots of test sensitivity and specificity

11C-choline. The summary detection rate for the five studies using 18F-FACBC was 58.6% (95% CI 41.1–875.2%). There was significant heterogeneity observed between and within studies ($I^2 = 88.2\%$). Only one study reported the detection rate using 68Ga-PSMA, 82.8% (95% CI 78.2–86.5%).

## Discussion

Our comprehensive review of the literature of using PET/CT to image men with prostate cancer BCR found that the available evidence is of poor quality and lacks the ability to provide clear insight into the diagnostic ability of these tests. Considering our fairly broad inclusion criteria regarding the reference test, it is somewhat concerning that only 21 studies had adequately verified the PET/CT results. This concern is amplified considering that the pooled specificities of the radiotracers ranged from 61.9 to 84.1% on a per-patient basis and 69.8 to 99.8% by lesion. This issue is still observed in the two studies which histology as the reference standard to verify the results of PET/CT; the false-positive rate for both 11C-choline and 18F-FACBC was 60% [24, 40]. The results seen in our study are supported by a previous meta-analysis with different inclusion criteria which reported the specificity of fluciclovine to be 66% [11]. The impressive diagnostic performance of 68Ga-PSMA is consistent with the meta-analysis by Perera et al., although their estimates were derived from a mixed population of men undergoing primary and secondary staging [42]. Aside from the 68Ga-PSMA study, which reported a high specificity, it is possible that men are receiving inappropriate metastasis-directed treatment due to the relatively high false-positive findings when using 11C-choline or 18F-FACBC in the BCR setting. Not only is this potentially unnecessary, it could also be harmful to patients with salvage radiation therapy and lymph node dissection being associated with substantial morbidity

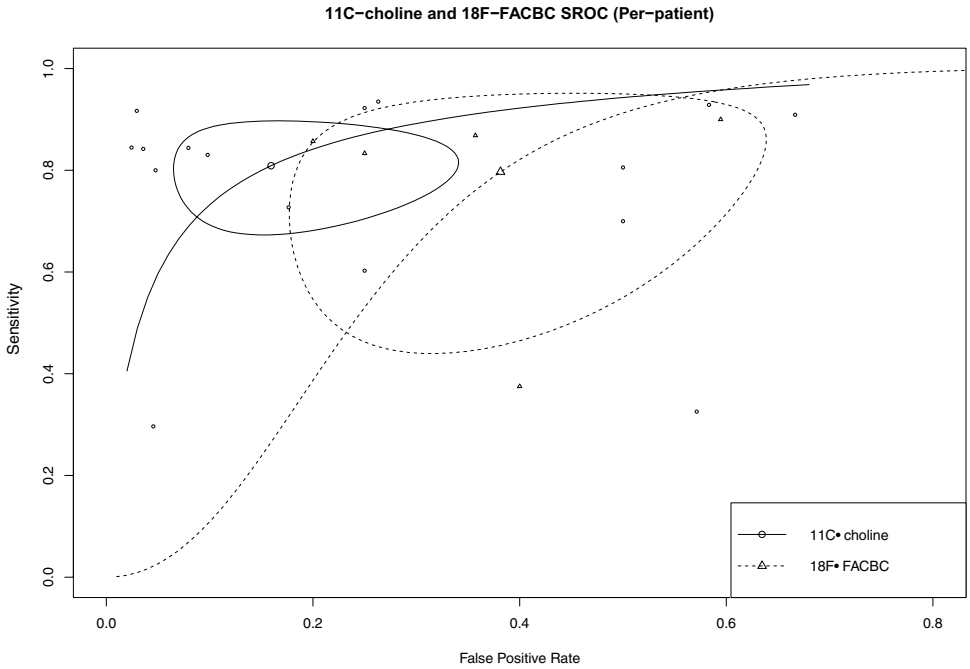


**Fig. 4** Summary receiver operating characteristic (SROC) curve for 11C-choline and 18F-FACBC (per-patient)

[43–45]. This highlights the importance of verifying the findings from PET/CT before initiating further treatment and also conducting well-designed studies that allow clinicians to satisfactorily appraise the diagnostic performance of new technologies.

Despite the above concerns regarding false-positive results, the results from our study allude to the promise of PET-based imaging in the early BCR setting, especially with 68Ga-PSMA. Guidelines have previously recommended against performing conventional imaging in the BCR setting when the PSA is below 20 ng/mL due to poor yield. The detection rate across the three radiotracers ranged from 55.8 to 82.8% in our study even when the median PSA was less than 5 ng/mL in the majority of included studies. These finding are consistent with the literature with detection rates commonly in the 20–45% range and extending up to 67% when PSA is less than 1.0 ng/mL [11]. This has important clinical implications, because salvage therapy is most effective when performed early before disease becomes widely disseminated. There was a delay to BCR, distant metastases, and cancer-specific mortality amongst patients with a pre-salvage PSA $\leq 0.5$ ng/mL compared to those with a serum PSA above this cut-off ($p < 0.001$) [46]. PSA level has been shown to be a predictor of oncological success with salvage lymph node dissection and radiation therapy [47, 48]. The current literature into the efficacy of salvage treatment has predominantly relied on conventional imaging modalities to guide management, and therefore, it can be reasonably assumed that outcomes can be improved using these potentially superior PET-based techniques. Accordingly, the guidelines have been revised to recommend imaging with 68Ga-PSMA if available in the BCR setting or alternatively, 11C-choline.

There were insufficient data and there was substantial heterogeneity between the included studies to determine which of the imaging modalities is the most accurate. A single included study evaluated patients with BCR to both 11C-choline and 18F-FACBC found that the diagnostic performance of fluciclovine was superior to 11C-choline [34]. However, when stratifying patients by PSA level, there was only a difference in sensitivity amongst patients with a PSA less than 1 ng/mL. PSMA is the newest of the radiotracers and appears to be the one with the most promise with the highest absolute sensitivity and specificity amongst the radiotracers included in this study but this estimate was derived from only one study. In a cohort of men undergoing salvage lymph node dissection after both 68Ga-PSMA and 18F-fluoroethylcholine, it was reported that the former imaging modality had a higher sensitivity (86.9 vs 71.2%), specificity (93.1 vs 86.9%), positive predictive value (75.7 vs 67.3%), and negative predictive value (96.6 vs 88.8%) [49]. PET/CT with any of 11C-choline, 18F-FACBC, or 68Ga-PSMA seems to be superior to conventional imaging given the comparatively higher detection rates and the yield of these modalities following negative conventional imaging; hence, these functional modalities should be preferred if accessible to accurately characterize disease and guide management. Similarly, early data suggest that 68Ga-PSMA may be the most accurate, but high-quality comparative studies are required to provide clarity to this space.

There are several limitations of the current study that should be considered. First, estimates of detection rates and

diagnostic performance were mostly derived from small, retrospective, single-institutional studies. This reduces our confidence in the estimates and is reflected by the wide confidence intervals. Furthermore, there was significant heterogeneity observed between the studies regarding population baseline characteristics, imaging protocols, clinician experience, and follow-up, which could all influence the diagnostic performance. However, this may be a more accurate reflection of real-world clinical practice and increases the generalizability of results to different settings.

## Conclusion

PET-based imaging with 11C-choline, 18F-FACBC, and 68Ga-PSMA demonstrates the potential to detect disease in the early BCR setting, where conventional modalities are less useful. There are some concerns regarding false-positive findings especially with 18F-FACBC that should be considered before initiating salvage therapy. Moreover, there is a lack of high-quality studies which validate the findings from PET/CT against a reliable reference standard, and therefore, it is challenging to accurately characterize the diagnostic performance of these tests.

**Author contributions** NJS: protocol, project development, data collection, data analysis, and manuscript writing. MB: protocol, project development, data collection, and manuscript writing. BRK: protocol, project development, and manuscript writing.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

**Research involving human participants and/or animals** For this type of study, formal consent is not required.

**Informed consent** For this type of study, formal consent is not required.

## References

1. Roehl KA, Han M, Ramos CG, Antenor JA, Catalona WJ (2004) Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3478 consecutive patients: long-term results. J Urol 172(3):910–914
2. Uchio EM, Aslan M, Wells CK, Calderone J, Concato J (2010) Impact of biochemical recurrence in prostate cancer among us veterans. Arch Intern Med 170(15):1390–1395
3. Paller CJ, Antonarakis ES (2013) Management of biochemically recurrent prostate cancer after local therapy: evolving standards of care and new directions. Clin Adv Hematol Oncol H&O 11(1):14–23
4. Maurer T, Eiber M, Fanti S, Budäus L, Panebianco V (2016) Imaging for prostate cancer recurrence. Eur Urol Focus 2(2):139–150
5. Rouvière O (2012) Imaging techniques for local recurrence of prostate cancer: for whom, why and how? Diagn Interv Imaging 93(4):279–290
6. Rouviere O, Vitry T, Lyonnet D (2010) Imaging of prostate cancer local recurrences: why and how? Eur Radiol 20(5):1254–1266
7. Kane CJ, Amling CL, Johnstone PA, Pak N, Lance RS, Thrasher JB, Foley JP, Riffenburgh RH, Moul JW (2003) Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy. Urology 61(3):607–611
8. Johnstone PA, Tarman GJ, Riffenburgh R, Rohde DC, Puckett ML, Kane CJ (1997) Yield of imaging and scintigraphy assessing biochemical failure in prostate cancer patients. Urol Oncol 3(4):108–112
9. Gomez P, Manoharan M, Kim SS, Soloway MS (2004) Radionuclide bone scintigraphy in patients with biochemical recurrence after radical prostatectomy: when is it indicated? BJU Int 94(3):299–302
10. Li R, Ravizzini GC, Gorin MA, Maurer T, Eiber M, Cooperberg MR, Alemozzaffar M, Tollefson MK, Delacroix SE, Chapin BF (2018) The use of PET/CT in prostate cancer. Prostate Cancer Prostatic Dis 21(1):4–21
11. Evans JD, Jethwa KR, Ost P, Williams S, Kwon ED, Lowe VJ, Davis BJ (2018) Prostate cancer-specific PET radiotracers: a review on the clinical utility in recurrent disease. Pract Radiat Oncol 8(1):28–39
12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 151(4):W65–W94
13. Leeflang MM, Deeks JJ, Takwoingi Y, Macaskill P (2013) Cochrane diagnostic test accuracy reviews. Syst Rev 2(1):82
14. Sanda MG, Cadeddu JA, Kirkby E, Chen RC, Crispino T, Fontanarosa J, Freedland SJ, Greene K, Klotz LH, Makarov DV et al (2018) Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part II: recommended approaches and details of specific care options. J Urol 199(4):990–997
15. Roach M 3rd, Hanks G, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH, Sandler H (2006) Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 65(4):965–974
16. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 155(8):529–536
17. Doebler P, Holling H (2015) Meta-analysis of diagnostic accuracy with mada. Reterieved at: https://cran.rproject.org/web/packages/mada/vignettes/mada.pdf. Accessed Feb 2018
18. Schwarzer G, Schwarzer MG (2018) Package 'meta'. Meta-Anal R
19. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH (2005) Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol 58(10):982–990
20. Higgins JPT, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560
21. de Jong IJ, Pruim J, Elsinga PH, Vaalburg W, Mensink HJ (2003) 11C-choline positron emission tomography for the evaluation after

treatment of localized prostate cancer. Eur Urol 44(1):32–38 **(discussion 38–39)**
22. Picchio M, Messa C, Landoni C, Gianolli L, Sironi S, Brioschi M, Matarrese M, Matei DV, De Cobelli F, Del Maschio A et al (2003) Value of [11C]choline-positron emission tomography for re-staging prostate cancer: a comparison with [18F]fluorodeoxyglucose-positron emission tomography. J Urol 169(4):1337–1340
23. Yoshida S, Nakagomi K, Goto S, Futatsubashi M, Torizuka T (2005) 11C-choline positron emission tomography in prostate cancer: primary staging and recurrent site staging. Urol Int 74(3):214–220
24. Rinnab L, Mottaghy FM, Blumstein NM, Reske SN, Hautmann RE, Hohl K, Moller P, Wiegel T, Kuefer R, Gschwend JE (2007) Evaluation of [11C]-choline positron-emission/computed tomography in patients with increasing prostate-specific antigen levels after primary treatment for prostate cancer. BJU Int 100(4):786–793
25. Richter JA, Rodriguez M, Rioja J, Penuelas I, Marti-Climent J, Garrastachu P, Quincoces G, Zudaire J, Garcia-Velloso MJ (2010) Dual tracer 11C-choline and FDG-PET in the diagnosis of biochemical prostate cancer relapse after radical treatment. Mol Imaging Biol 12(2):210–217
26. Breeuwsma AJ, Pruim J, van den Bergh AC, Leliveld AM, Nijman RJ, Dierckx RA, de Jong IJ (2010) Detection of local, regional, and distant recurrence in patients with psa relapse after external-beam radiotherapy using (11)C-choline positron emission tomography. Int J Radiat Oncol Biol Phys 77(1):160–164
27. Giovacchini G, Picchio M, Coradeschi E, Bettinardi V, Gianolli L, Scattoni V, Cozzarini C, Di Muzio N, Rigatti P, Fazio F et al (2010) Predictive factors of [(11)C]choline PET/CT in patients with biochemical failure after radical prostatectomy. Eur J Nucl Med Mol Imaging 37(2):301–309
28. Mitchell CR, Lowe VJ, Rangel LJ, Hung JC, Kwon ED, Karnes RJ (2013) Operational characteristics of (11)c-choline positron emission tomography/computerized tomography for prostate cancer with biochemical recurrence after initial treatment. J Urol 189(4):1308–1313
29. Mamede M, Ceci F, Castellucci P, Schiavina R, Fuccio C, Nanni C, Brunocilla E, Fantini L, Costa S, Ferretti A et al (2013) The role of 11C-choline PET imaging in the early detection of recurrence in surgically treated prostate cancer patients with very low PSA level < 0.5 ng/mL. Clin Nucl Med 38(9):e342–e345
30. Rybalov M, Breeuwsma AJ, Leliveld AM, Pruim J, Dierckx RA, de Jong IJ (2013) Impact of total PSA, PSA doubling time and PSA velocity on detection rates of 11C-choline positron emission tomography in recurrent prostate cancer. World J Urol 31(2):319–323
31. Castellucci P, Ceci F, Graziani T, Schiavina R, Brunocilla E, Mazzarotto R, Pettinato C, Celli M, Lodi F, Fanti S (2014) Early biochemical relapse after radical prostatectomy: which prostate cancer patients may benefit from a restaging 11C-choline PET/CT scan before salvage radiation therapy? J Nucl Med 55(9):1424–1429
32. Ceci F, Herrmann K, Castellucci P, Graziani T, Bluemel C, Schiavina R, Vollmer C, Droll S, Brunocilla E, Mazzarotto R et al (2014) Impact of 11C-choline PET/CT on clinical decision making in recurrent prostate cancer: results from a retrospective two-centre trial. Eur J Nucl Med Mol Imaging 41(12):2222–2231
33. Nanni C, Schiavina R, Boschi S, Ambrosini V, Pettinato C, Brunocilla E, Martorana G, Fanti S (2013) Comparison of 18F-FACBC and 11C-choline PET/CT in patients with radically treated prostate cancer and biochemical relapse: preliminary results. Eur J Nucl Med Mol Imaging 40(Suppl 1):S11–S17
34. Nanni C, Zanoni L, Pultrone C, Schiavina R, Brunocilla E, Lodi F, Malizia C, Ferrari M, Rigatti P, Fonti C et al (2016) (18)F-FACBC (anti1-amino-3-(18)F-fluorocyclobutane-1-carboxylic acid) versus (11)C-choline PET/CT in prostate cancer relapse: results of a prospective trial. Eur J Nucl Med Mol Imaging 43(9):1601–1610
35. Gomez-de la Fuente FJ, Martinez-Rodriguez I, de Arcocha-Torres M, Quirce R, Jimenez-Bonilla J, Martinez-Amador N, Banzo I (2017) Contribution of (11)C-choline PET/CT in prostate carcinoma biochemical relapse with serum PSA level below 1 ng/ml. Rev Esp Med Nucl Imagen Mol 37:156–162
36. Parker WP, Davis BJ, Park SS, Olivier KR, Choo R, Nathan MA, Lowe VJ, Welch TJ, Evans JD, Harmsen WS et al (2017) Identification of site-specific recurrence following primary radiation therapy for prostate cancer using C-11 choline positron emission tomography/computed tomography: a nomogram for predicting extrapelvic disease. Eur Urol 71(3):340–348
37. Schuster DM, Votaw JR, Nieh PT, Yu W, Nye JA, Master V, Bowman FD, Issa MM, Goodman MM (2007) Initial experience with the radiotracer anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid with PET/CT in prostate carcinoma. J Nucl Med 48(1):56–63
38. Schuster DM, Savir-Baruch B, Nieh PT, Master VA, Halkar RK, Rossi PJ, Lewis MM, Nye JA, Yu W, Bowman FD et al (2011) Detection of recurrent prostate carcinoma with anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid PET/CT and 111In-capromab pendetide SPECT/CT. Radiology 259(3):852–861
39. Kairemo K, Rasulova N, Partanen K, Joensuu T (2014) Preliminary clinical experience of *trans*-1-amino-3-(18)F-fluorocyclobutanecarboxylic acid (anti-(18)F-FACBC) PET/CT imaging in prostate cancer patients. Biomed Res Int 2014:305182
40. Bach-Gansmo T, Nanni C, Nieh PT, Zanoni L, Bogsrud TV, Sletten H, Korsan KA, Kieboom J, Tade FI, Odewole O et al (2017) Multisite experience of the safety, detection rate and diagnostic performance of fluciclovine ((18)F) positron emission tomography/computerized tomography imaging in the staging of biochemically recurrent prostate cancer. J Urol 197(3 Pt 1):676–683
41. Afshar-Oromieh A, Avtzi E, Giesel FL, Holland-Letz T, Linhart HG, Eder M, Eisenhut M, Boxler S, Hadaschik BA, Kratochwil C et al (2015) The diagnostic value of PET/CT imaging with the (68) Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 42(2):197–209
42. Perera M, Papa N, Christidis D, Wetherell D, Hofman MS, Murphy DG, Bolton D, Lawrentschuk N (2016) Sensitivity, specificity, and predictors of positive (68)Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. Eur Urol 70(6):926–937
43. Cremers RG, van Lin EN, Gerrits WL, van Tol-Geerdink JJ, Kiemeney LA, Vergunst H, Smans AJ, Kaanders JH, Witjes JA (2010) Efficacy and tolerance of salvage radiotherapy after radical prostatectomy, with emphasis on high-risk patients suited for adjuvant radiotherapy. Radiother Oncol 97(3):467–473
44. Hegarty SE, Hyslop T, Dicker AP, Showalter TN (2015) Radiation therapy after radical prostatectomy for prostate cancer: evaluation of complications and influence of radiation timing on outcomes in a large, population-based cohort. PLoS One 10(2):e0118430
45. Rigatti P, Suardi N, Briganti A, Da Pozzo LF, Tutolo M, Villa L, Gallina A, Capitanio U, Abdollah F, Scattoni V et al (2011) Pelvic/retroperitoneal salvage lymph node dissection for patients treated with radical prostatectomy with biochemical recurrence and nodal recurrence detected by [11C]choline positron emission tomography/computed tomography. Eur Urol 60(5):935–943
46. Stish BJ, Pisansky TM, Harmsen WS, Davis BJ, Tzou KS, Choo R, Buskirk SJ (2016) Improved metastasis-free and survival outcomes with early salvage radiotherapy in men with detectable prostate-specific antigen after prostatectomy for prostate cancer. J Clin Oncol 34(32):3864–3871

47. Suardi N, Gandaglia G, Gallina A, Di Trapani E, Scattoni V, Vizziello D, Cucchiara V, Bertini R, Colombo R, Picchio M et al (2015) Long-term outcomes of salvage lymph node dissection for clinically recurrent prostate cancer: results of a single-institution series with a minimum follow-up of 5 years. Eur Urol 67(2):299–309
48. Briganti A, Karnes RJ, Joniau S, Boorjian SA, Cozzarini C, Gandaglia G, Hinkelbein W, Haustermans K, Tombal B, Shariat S et al (2014) Prediction of outcome following early salvage radiotherapy among patients with biochemical recurrence after radical prostatectomy. Eur Urol 66(3):479–486
49. Pfister D, Porres D, Heidenreich A, Heidegger I, Knuechel R, Steib F, Behrendt FF, Verburg FA (2016) Detection of recurrent prostate cancer lesions before salvage lymphadenectomy is more accurate with 68Ga-PSMA-HBED-CC than with 18F-fluoroethylcholine PET/CT. Eur J Nucl Med Mol Imaging 43(8):1410–1417