Am J Nucl Med Mol Imaging 2014;4(6):580-601
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0001396

Original Article

Comparative performance of PET tracers in biochemical recurrence of prostate cancer: a critical analysis of literature

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Received July 12, 2014; Accepted July 21, 2014; Epub September 6, 2014; Published September 15, 2014

Abstract: Positron emission tomography (PET) with a number of tracers targeted to particular biological features of cancer has been explored for the imaging evaluation of patients with biochemical recurrence of prostate cancer after curative primary treatment. However, these reports are often heterogeneous in study design, patient cohorts, standards of reference for the imaging findings, data analysis, and data reporting. The aim of our study was to address these limitations by extracting and re-analyzing the PET detection data only from studies that satisfied pre-defined sets of patient selection criteria and verification standards. Our investigation analyzed the effects of 5 tracers (^{18}F-fluorodeoxyglucose (FDG), ^{11}C-acetate (ACET), ^{11}C- or ^{18}F-choline (CHOL), anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (FACBC), and radiolabeled ligand targeted to prostate-specific membrane antigen (PSMA)), 2 treatment types (radical prostatectomy and radiation therapy), and whether the detected disease was local or metastatic, including lesion type (bone, lymph node, soft tissue). FDG exhibited the lowest detection rate for any suspected disease. ACET tended to be advantageous over CHOL in detecting local recurrence and lymph node lesions, even though the difference was not statistically significant. FACBC had greater likelihood of detecting local recurrence, when compared to CHOL, though this difference was not statistically significant. PSMA tended to show a higher proportion of patients with suspected disease compared to the other four tracers. Patients treated with radiation therapy had greater odds of displaying local recurrence on PET than those treated with radical prostatectomy. We also provide suggestions for future investigations that facilitate communication and the impact of the findings.

Keywords: PET, prostate, cancer, biochemical, recurrence

Introduction

Radical prostatectomy (RP) and radiation therapy (RT) are the two main practices for treating patients diagnosed with clinically localized prostate cancer. While both therapies are associated with relatively high cancer-free and overall survival rates at 5 and 10 years, up to 40% of the patients will develop biochemical recurrence (BCR), evidenced by a rise in serum prostate-specific antigen (PSA) levels, within 10 years after the primary treatment [1-5]. Treatment options for these patients depend on whether the cancer is locally recurrent, has spread to distant sites, or both [6-9]. Imaging ca methylenediphosphonate (Tc-99m MDP) bone scintigraphy (BS) - have limited utility in this regard [10, 11].

Positron emission tomography (PET), which is now commonly used in combination with CT, has demonstrated promising results. This functional imaging technique utilizes radiolabeled biomolecules relevant to cellular processes, including glucose, amino acid, and fatty acid metabolism [12, 13]. ^{18}F-fluorodeoxyglucose is the most common PET tracer in clinical practice, but its utility in re-staging prostate cancer is limited [14-16]. On the other hand, ^{11}C- and ^{18}F-choline demonstrate higher sensitivity and specificity than ^{18}F-fluorodeoxyglucose, and ^{11}C-choline was recently approved by the Food Drug Administration for this clinical setting [17]. Recent studies on ^{11}C-acetate and anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid have also shown comparable detection rates and diagnostic accuracy to radiolabeled choline [18-

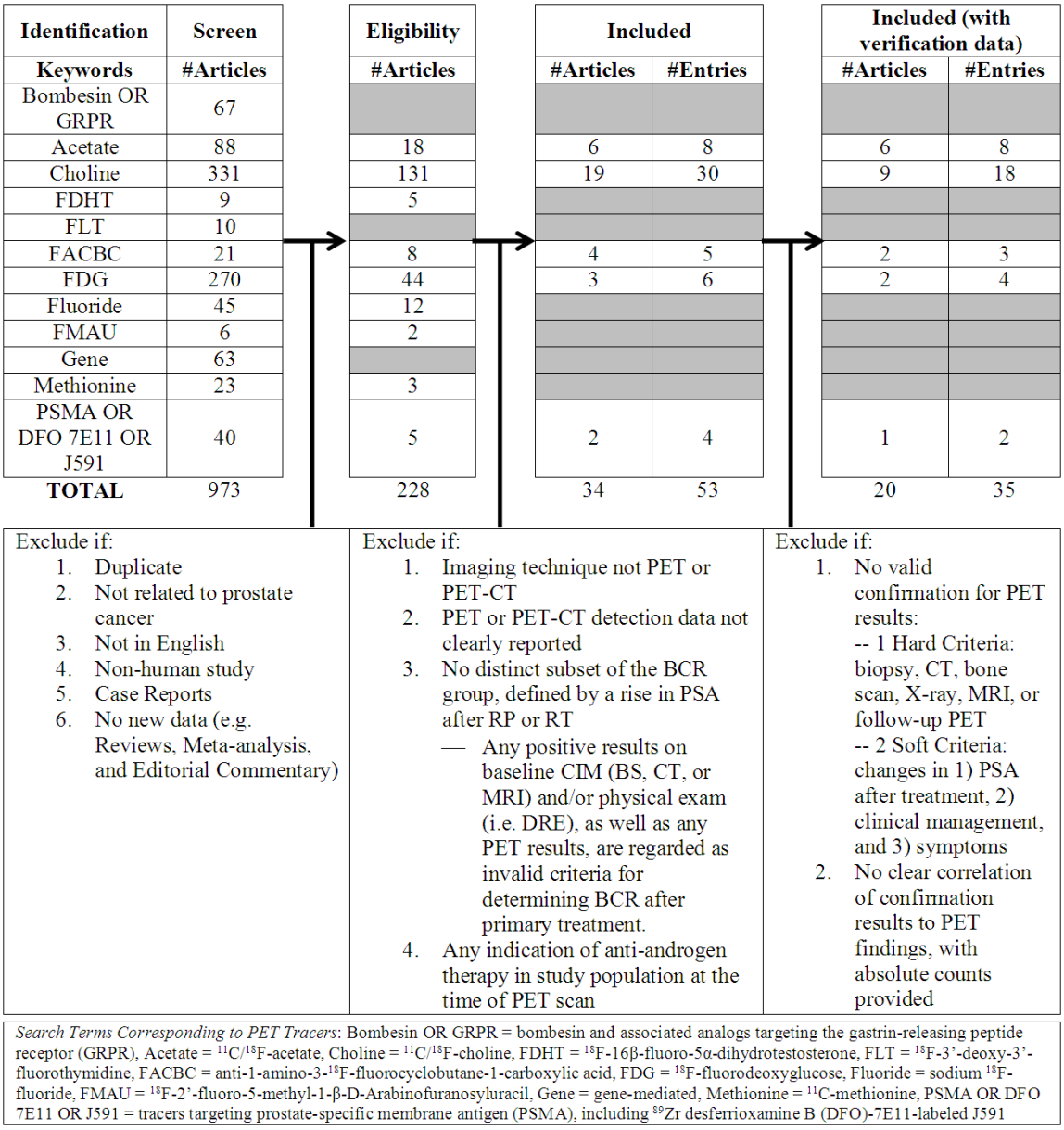

Figure 1. Study Selection - A comprehensive PubMed search was conducted separately on 12 different PET tracers using the indicated keywords followed by "PET prostate" in the keyword phrase. Searches are conducted until the publication year of 2013. The number of articles retrieved in each process is indicated. The PET detection data are divided based on the patient's primary treatment (RP or RT) and the tracer used. The total number of these data subgroups corresponding to the respective tracers is indicated by the number of entries.

20]. There are also other emerging radiotracers, including ^{89}Zr-J591 antibody to prostate-specific membrane antigen, ^{11}C-methionine, and ^{18}F-2'-fluoro-5-methyl-1-b-D-arabinofuranosyluracil, which have not yet had sufficient clinical data to assess their utility in the re-staging context.

Several review articles and few meta-analyses have summarized the data from the published studies to evaluate the efficacy of PET tracers in this clinical setting, but no definitive conclusions have been reached due to several limitations [21-26]. The 3 major limitations that our study has focused on for assessment are:

1. *Heterogeneous study cohorts*: While it is difficult to account for all possible patient characteristics, not many studies have separately analyzed the PET detection data based on pri-

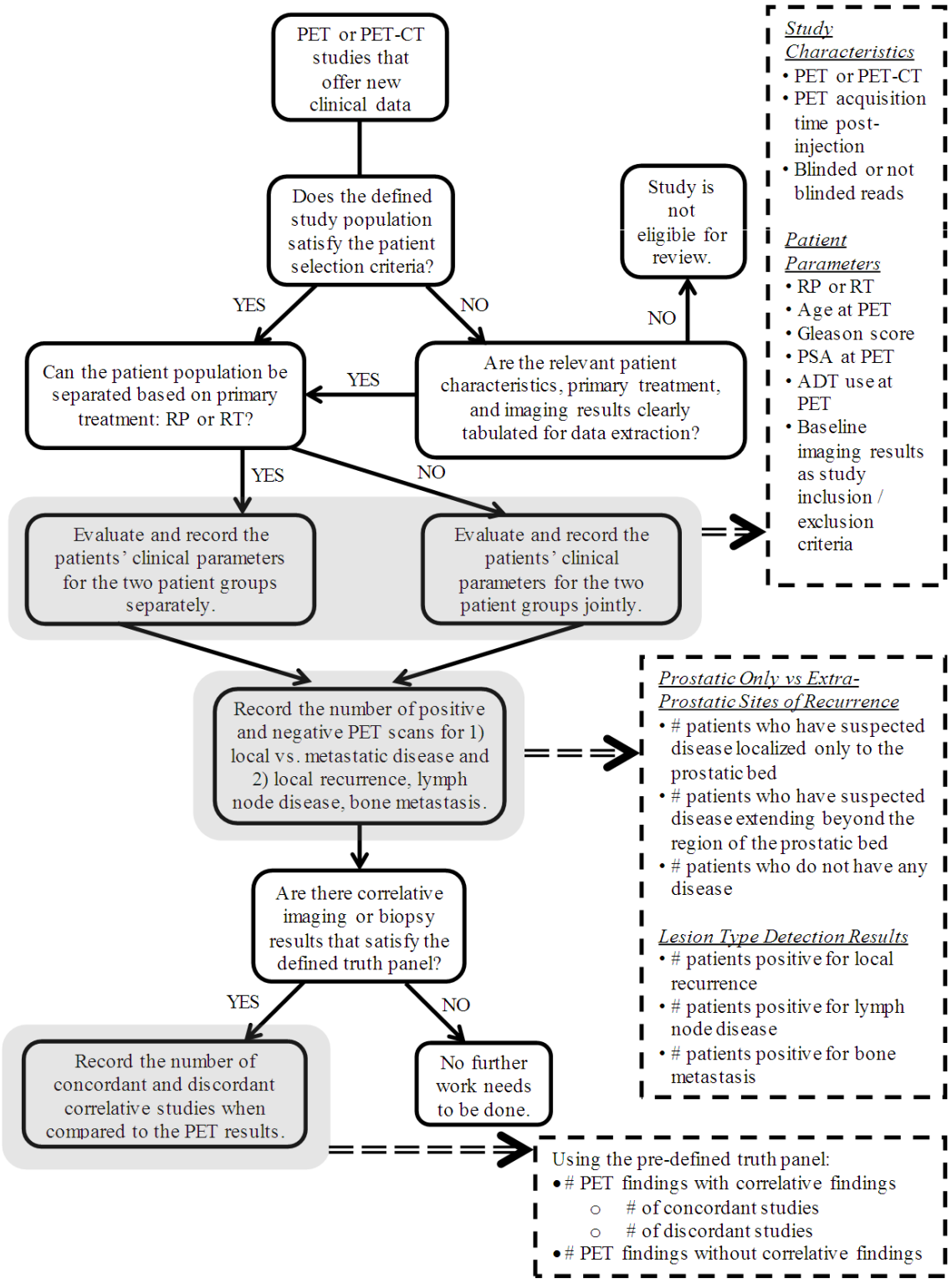

Figure 2. Data collection workflow.

mary treatment (RP and RT). A 2008 study showed that patients who underwent RP or RT differ significantly in various clinical parameters, including age at diagnosis, PSA at diagnosis, Gleason score, and the number of positive prostate biopsies [27]. The same study also

Table 1. Study and patient parameters for selected article entries

ID	Year	Author	Journal	Tr	PET Tech	Acq Time	Blinded	Base-line	No ADT Use	Tx	BCR Def	PSA Roof	#Pt	PSA Mean	PSA SD	PSA Med	PSA Range
1	2006	Wachter et al [48]	J Clin Oncol	ACET	PET-CT	15 min	-	-	-	M	-	-	50	8.1	-	-	.5-24.9
2	2013	Buchegger et al [18]	Eur J Nucl Med Mol Imaging	ACET	PET-CT	5 min	YES	-	NToS	M	-	PSA≤3 for RP and PSA≤5 for RT	23	2.34	1.62	-	<5
3	2002	Kotzerke et al [45]	Eur J Nucl Med Mol Imaging	ACET	PET	5 min	To results of other imaging studies	-	-	RP	-	-	31	15.2	30.2	4.5	.1-150.6
4	2003	Oyama et al [46]	J Nucl Med	ACET	PET	-	To clinical information, aware of selection criteria	-	NToS	RP	DetectablePSA	-	30	4.9	9.5	1.2	.3-47.5
5	2006	Sandblom et al [47]	Adult Urol	ACET	PET	10 min	-	-	-	RP	2xrise	-	20	-	-	2	.5-8.1
6	2007	Albrecht et al [44]	Eur J Nucl Med Mol Imaging	ACET	PET-CT	2 min	-	-	-	RP	-	-	15	1.17	1.52	0.39	.08-4.8
7	2003	Oyama et al [46]	J Nucl Med	ACET	PET	-	To clinical information, aware of selection criteria	-	NToS	RT	3xrise	-	16	5.8	3.3	6.15	.5-11.5
8	2007	Albrecht et al [44]	Eur J Nucl Med Mol Imaging	ACET	PET-CT	2 min	-	-	-	RT	RisePostNadir, confirmed at least once	-	17	10.4	-	6	2.6-30.2
9	2003	Picchio et al [55]	J Urol	CHOL	PET	5 min	-	-	-	M	3xrise	-	100	6.57	-	-	.14-171
10	2011	Casamassima et al [67]	Tumori	CHOL	PET-CT	5 min	-	-	-	M	nadir+2	-	71	-	-	-	-
11	2012	Soyka et al [63]	Eur J Nucl Med Mol Imaging	CHOL	PET-CT	3-4 min	-	-	-	M	-	-	156	-	-	-	-
12	2013	Buchegger et al [18]	Eur J Nucl Med Mol Imaging	CHOL	PET-CT	0 min	YES	-	NToS	M	-	PSA≤3 for RP and PSA≤5 for RT	23	2.34	1.62	-	<5
13	2013	Gacci et al [66]	Scand J Urol	CHOL	PET-CT	4 min	To history of patient	-	-	M	>.2 (2+times, 3moInt) for RP and >.4 Post-Nadir (3+times)	-	103	0.9	0.4	-	-
14	2013	Rybalov et al [62]	World J Urol	CHOL	PET-CT	5 min	To clinical data	-	1 yr	M	3xrisePostNadir	-	185	18.45	-	-	-
15	2003	de Jong et al [52]	Eur Urol	CHOL	PET	5 min	To clinical data	-	6 mo	RP	>.2	-	13	7.2	10.3	4.3	.5-35.7
16	2005	Yoshida et al [59]	Urol Int	CHOL	PET	5 min	-	-	-	RP	>.6	-	5	4.5	2.9	4.9	1.3-8.5
17	2006	Cimitan et al [51]	Eur J Nucl Med Mol Imaging	CHOL	PET-CT	<15 min	To other imaging results	-	NToS	RP	>.1 (2+times)	-	58	5	7.3	1.6	2-38.2
18	2007	Rinnab et al [56]	BJU Int	CHOL	PET-CT	5-10 min	To clinical data and previous imaging	-	NToS	RP	>.2	-	34	3.5	5.7	1.94	.41-33
19	2008	Pelosi et al [54]	Radiol Med	CHOL	PET-CT	60 min	-	-	NToS	RP	DetectablePSA	-	56	4.59	7.87	-	.1-39

20	2009	Castellucci et al [50]	J Nucl Med	CHOL	PET-CT	5 min	-	-	some 3 mo, some NPT	RP	-	-	190	4.2	-	2.1	.2-25.4
21	2010	Giovacchini et al [30]	Eur J Nucl Med Mol Imaging	CHOL	PET-CT	5 min	NO	-	-	RP	>.2 (2+times, 3 moInt)	-	170	3.24	6.11	1.25	.23-48.6
22	2010	Giovacchini et al [53]	J Urol	CHOL	PET-CT	5 min	-	CIM-	NPT	RP	>.2 (2+times, 3 moInt)	-	109	1.31	1.91	0.81	.22-16.76
23	2011	Wurschmidt et al [64]	Radiat Oncol	CHOL	PET-CT	60-90 min	-	-	-	RP	-	-	16	1.7	1.2	1.47	.42-4.8
24	2012	Graute et al [68]	Eur J Nucl Med Mol Imaging	CHOL	PET-CT	60 min	NO	-	AVG 14.5 mo	RP	-	-	82	4.4	5.7	2.4	.03-36
25	2012	Schillaci et al [57]	Eur J Nucl Med Mol Imaging	CHOL	PET-CT	45 min	To clinical data and previous imaging	-	1 yr	RP	DetectablePSA	-	49	4.1	4.6	-	.09-15.51
26	2012	Takesh et al [58]	ISRN Oncol	CHOL	PET-CT	10 min	NO	-	-	RP	-	-	25	4.7	6	1.9	.3-21
27	2013	Hausmann et al [65]	Clin Nucl Med	CHOL	PET-CT	60 min	YES	-	-	RP	>.04	-	32	-	-	-	-
28	2013	Nanni et al [20]	Eur J Nucl Med Mol Imaging	CHOL	PET-CT	3 min	-	-	NToS	RP	3xrise, nadir+2 PostRT, >.3 PostRP	-	15	2.1	2	-	.2-8.48
29	2013	Nanni et al [19]	Clin Genitourin Canc	CHOL	PET-CT	3 min	-	-	6 mo	RP	>.2	-	28	2.9	3.5	1.5	.2-14.6
30	2013b	Afshar-Oromieh et al [81]	Eur J Nucl Med Mol Imaging	CHOL	PET-CT	60 min	-	-	-	RP	-	-	28	7.3	18.7	2.7	.01-100.5
31	2003	de Jong et al [52]	Eur Urol	CHOL	PET	5 min	To clinical data	-	6 mo	RT	3xrisePostNadir	-	9	37.2	43.5	22.8	2.3-120
32	2005	Yoshida et al [59]	Urol Int	CHOL	PET	5 min	-	-	-	RT	3xrisePostNadir	-	3	7.5	4.2	8.7	2.9-11
33	2006	Cimitan et al [51]	Eur J Nucl Med Mol Imaging	CHOL	PET-CT	<15 min	To other imaging results	-	NToS	RT	>.1 (2+times)	-	21	31.1	59.2	5.33	.35-211.3
34	2007	Rinnab et al [56]	BJU Int	CHOL	PET-CT	5-10 min	To clinical data and previous imaging	-	NToS	RT	3xrisePostNadir	-	9	5.3	4	3.4	1-13.1
35	2010	Breeuwsma et al [49]	Int J Radiat Oncol Biol Phys	CHOL	PET	5 min	To clinical data	-	1 yr	RT	3xrisePostNadir	-	70	23.2	-	10.7	.6-54.7
36	2011	Wurschmidt et al [64]	Radiat Oncol	CHOL	PET-CT	60-90 min	-	-	-	RT	-	-	3	6.5, 1.3, n.a (1)	-	-	-
37	2012	Takesh et al [58]	ISRN Oncol	CHOL	PET-CT	10 min	NO	-	-	RT	-	-	4	2.5	1.9	2.6	.3-4.5
38	2013b	Afshar-Oromieh et al [81]	Eur J Nucl Med Mol Imaging	CHOL	PET-CT	60 min	-	-	-	RT	-	-	9	23.1	35.9	11.2	2.6-116
39	2011	Schuster et al [61]	Radiol	FACBC	PET-CT	3 min	NO	BS-	-	RP	3xrise, nadir+2 PostRT, >.3 PostRP	-	9	4.7	6.5	1.14	.11-16.9
40	2013	Nanni et al [20]	Eur J Nucl Med Mol Imaging	FACBC	PET-CT	3 min	-	-	NToS	RP	3xrise, nadir+2 PostRT, >.3 PostRP	-	15	2.1	2	-	.2-8.48
41	2013	Nanni et al [19]	Clin Genitourin Canc	FACBC	PET-CT	3min	-	-	6mo	RP	>.2	-	28	2.9	3.5	1.5	.2-14.6
42	2011	Savir-Baruch et al [60]	Mol Imaging Biol	FACBC	PET-CT	-	-	BS-	6 mo	RT	3xrisePostNadir	-	5	-	-	-	1.1-20.5

43	2011	Schuster et al [61]	Radiol	FACBC	PET-CT	3 min	NO	BS-	-	RT	3xrise, nadir+2 PostRT, >.3 PostRP	-	36	7.2	8.2	5	.4-44.7
44	2003	Chang et al [69]	Urol Int	FDG	PET	30-45 min	To available data	-	NPT	M	>4	-	24	11.4	3.7	10.9	5.2-18.9
45	2003	Jadvar et al [16]	Oncol Rep	FDG	PET	45-60 min	NO	-	-	M	-	-	12	-	-	-	5-206
46	2003	Picchio et al [55]	J Urol	FDG	PET	60 min	-	-	-	M	3xrise	-	100	6.57	-	-	.14-171
47	2003	Oyama et al [46]	J Nucl Med	FDG	PET	-	To clinical information, aware of selection criteria	-	NToS	RP	DetectablePSA	-	30	4.9	9.5	1.2	.3-47.5
48	2005	Schoder et al [15]	Clin Cancer Res	FDG	PET	45-60 min	-	CIM-	NPT*	RP	>.1 in 3x, >2 wksapart	-	91	4.6	8.3	-	.12-49.3
49	2003	Oyama et al [46]	J Nucl Med	FDG	PET	-	To clinical information, aware of selection criteria	-	NToS	RT	3xrise	-	16	5.8	3.3	6.15	.5-11.5
50	2013a	Afshar-Oromieh et al [70]	Eur J Nucl Med Mol Imaging	PSMA	PET-CT	60 min	-	-	-	RP	-	-	16	7.1	17.8	2.3	.51-73.6
51	2013b	Afshar-Oromieh et al [71]	Eur J Nucl Med Mol Imaging	PSMA	PET-CT	60 min	-	-	-	RP	-	-	28	7.3	18.7	2.7	.01-100.5
52	2013a	Afshar-Oromieh et al [70]	Eur J Nucl Med Mol Imaging	PSMA	PET-CT	60 min	-	-	-	RT	-	-	3	26.2	32.4	11.6	3.75-63.3
53	2013b	Afshar-Oromieh et al [71]	Eur J Nucl Med Mol Imaging	PSMA	PET-CT	60 min	-	-	-	RT	-	-	9	23.1	35.9	11.2	2.6-116

The articles are ordered by the following sequence: 1) tracer used in study, 2) primary treatment, 3) year of publication, and 4) the first author's last name. *Note that not all the articles are distinct since we have separated the entries based on the primary treatment and the tracer studied, when applicable. Usually a study will examine a maximum of 2 tracers and 2 treatment groups (RP or RT), meaning that there can be a maximum of 4 entries for any one article. ID=article entry identifier; Year=year of publication; Author=first author's last name in article entry; Journal=journal of the publication of article entry; Tr=radiotracer investigated in the article entries (CHOL=^{11}C- or ^{18}F-Choline; ACET=^{11}C-Acetate; FACBC=anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid; FDG=^{18}F-fluorodeoxyglucose; PSMA=tracers targeting prostate-specific membrane antigen); Acq Time=time PET scan was initiated post-injection; PET Tech=the imaging technique used by study (either PET or PET-CT); Blinded=how the readers were blinded, if at all, during the interpretation of PET scan (YES=readers were blinded but to which information was not clearly stated, NO=readers were not blinded to clinical and/or other imaging data); Baseline=any baseline conventional imaging done in the selecting patients for study (CIM-=negative for disease on some conventional imaging technique, lesion type not specified; BS-=negative for bone disease on bone scan); No ADT Use=whether the articles clearly indicated no ADT use in study, the minimum amount of time of no ADT use is indicated when applicable (NToS=no ADT use at the time of PET scan, NPT=no other treatment given besides RP or RT, NPT*=no other treatment given in the time between primary treatment and PET scan); Tx=primary treatment patient group received (RP=radical prostatectomy, RT=radiation therapy, M=RP or RT, cannot parse out these two groups in study); BCR Def=definition for biochemical recurrence (DetectablePSA=non-zero PSA, 2xrise=rise in PSA on two measurements, 3xrise=rise in PSA on three measurements, RisePostNadir=PSA rise after reaching nadir, nadir+2=PSA rises by at least 2 after reaching nadir, 2+times=PSA measured at least 2 times, 3moInt=PSA levels measured at three-month intervals, 3xrisePostNadir=rise in PSA on three measurements after reaching nadir, 3x, >2wksapart=PSA measurement taken three times at intervals of more than two weeks); PSA roof=the upper bound in PSA value at the time of scan authors may place in the patient selection process; #Pt=total number of patients in the study; SD=standard deviation; -=information is not available or not clearly reported in the study. Article Entries Belonging to Same Study: 33,34; 36,37,38,39; 42,43; 12,13; 14,15; 19,20; 21,22; 23,24; 4,5; 9,10; 29,30; 31,32; 51,52; 44,45; 46,47,48,49.

revealed that the treatment approach differs between RP and RT patients, with a lower percentage of RP patients receiving adjuvant and neo-adjuvant therapies. This observation may be associated with differences in the likelihood of the progression of the disease between these two primary treatment regimens [28, 29].

2. *Heterogeneous standards of reference for PET studies*: Many studies do not have any confirmatory findings for PET-negative scans and label them as false negatives under the assumption that all patients experiencing PSA failure must have true cancer recurrence [15]. Instead of correlating PET findings to other imaging or biopsy results, some studies define true positives as any PSA decrease after treatment or a change in the treatment of the patient [14, 30, 31]. The varying reference standards makes it challenging to interpret the diagnostic performance parameters across multiple studies.

3. *Disparity in having confirmatory results for PET studies*: It is unclear whether there are differences in recurrence detection rates between the PET studies with and without independent verification of results. Even for studies that do have verification results, usually only PET studies positive for disease are evaluated.

The aim of this investigation was to perform a critical re-evaluation of the diagnostic accuracy of PET in the imaging assessment of BCR patients and to examine how the above limitations may have affected the conclusions on the utility of various tracers. More specifically, we compared the effectiveness of PET or PET-CT in 1) detecting any disease, 2) distinguishing locally recurrent from metastatic disease, and 3) detecting the 3 major lesion types (local recurrence, lymph node, and bone) between post-RP and post-RT patients, as well as between verified and unverified PET scans.

Methods

To examine a study population with more comparable background parameters, we separated the PET detection data based on the patient's primary treatment (RP or RT), when possible. We also filtered out any patients who utilized androgen deprivation therapy (ADT) at the time of PET scan. The rationale is that ADT has been shown to influence uptake of some PET tracers, though the effect on the final radiologic assessment may not be statistically significant [32-35]. To address the varying standards of reference for PET studies, we re-examined all the verification data under a pre-defined truth panel to better compare the sensitivity and specificity data across the reviewed studies.

Literature search

Figure 1 summarizes the procedure for identifying and selecting the articles for review. A comprehensive search was done on PubMed on 12 different categories of PET radiotracers that have demonstrated potential in detecting presence of prostate cancer at least in pre-clinical studies [36-38]. These tracers included those radiolabeling bombesin and associated analogs targeting the gastrin-releasing peptide receptor (GRPR), ^{11}C-acetate (ACET), ^{11}C- or ^{18}F-choline (CHOL), ^{18}F-16β-fluoro-5α-dihydrotestosterone (FDHT), ^{18}F-3'-deoxy-3'-fluorothymidine (FLT), anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (FACBC), ^{18}F-fluorodeoxyglucose (FDG), sodium ^{18}F-fluoride (NaF), ^{18}F-2'-fluoro-5-methyl-1-β-D-arabinofuranosyluracil(FMAU), ^{11}C-methionine, and tracers targeting prostate-specific membrane antigen (PSMA) such as ^{89}Zr-desferrioxamine B (DFO)-7E11-labeled J591. The search terms corresponding to these tracers were Bombesin or GRPR, acetate, choline, FDHT, FLT, FACBC, FDG, fluoride, FMAU, methionine, and PSMA, all followed by the key phrase "PET prostate". Searches were conducted for each tracer separately and were performed until publication year 2013.

Article selection

Only non-duplicate articles written in English that presented original data relating to prostate cancer were screened. Articles were then excluded if there were no distinct study population that, 1) was evaluated for prostate cancer recurrence by PET or PET-CT, 2) did not have clearly reported results of PET or PET-CT, 3) did not experience BCR (also termed PSA relapse, PSA failure) after RP or RT, and 4) had no indication of patients undergoing anti-androgen therapy (also referred to as androgen deprivation therapy (ADT) or hormonal therapy) at the time of the PET scan. It should be noted that true definition of BCR requires negative (or indeterminate) conventional imaging [39]. However, many studies include a mixture of patients with

Table 2. Results From Reviewed Studies

ID	#Pt	Distinguishing Disease Status									Detection of Lesion Types																	
ID	#Pt	Pros Dz	Pros Dz T	Pros Dz V	Ex Pros Dz	Ex Pros Dz T	Ex Pros Dz V	No Dz	No Dz T	No Dz V	LR+	LR+ T	LR+ V	LR-	LR- T	LR- V	LN+	LN+ T	LN+ V	LN-	LN- T	LN- V	B+	B+ T	B+ V	B-	B- T	B- V
1	50	UD	UD	UD	UD	UD	UD	5	0	0	19	5	4	31	4	3	14	6	6	36	0	0	11	11	11	39	0	0
2	23	UD	UD	UD	UD	UD	UD	5	0	0	6	4	4	17	0	0	11	0	0	12	0	0	2	2	2	21	0	0
3	31	13	0	0	10	5	5	8	0	0	15	13	13	16	8	5	6	0	0	25	0	0	5	5	5	26	0	0
4	30	0	0	0	6	3	1	24	0	0	1	1	1	19	0	0	10	2	0	20	11	11	2	2	2	28	0	0
5	20	UD	UD	UD	UD	UD	UD	5	0	0	10	10	4	10	0	0	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD
6	15	4	0	0	1	1	0	10	0	0	5	0	0	10	0	0	1	1	0	14	14	14	0	0	0	15	15	15
7	16	2	2	2	6	3	3	8	0	0	2	2	2	14	0	0	6	3	3	10	6	6	2	2	2	14	9	8
8	17	10	0	0	5	5	4	2	0	0	14	5	5	3	1	0	4	3	3	13	13	13	2	2	2	15	15	13
9	100	10	0	0	37	37	33	53	0	0	10	0	0	90	0	0	24	24	21	76	76	76	18	18	17	82	82	82
10	71	3	0	0	36	0	0	32	0	0	3	0	0	68	0	0	25	0	0	46	0	0	11	0	0	60	0	0
11	156	63	0	0	61	0	0	32	0	0	89	0	0	67	0	0	45	0	0	111	0	0	21	0	0	135	0	0
12	23	UD	UD	UD	UD	UD	UD	6	0	0	6	4	4	17	0	0	9	0	0	14	0	0	2	2	2	21	0	0
13	103	15	0	0	45	0	0	43	0	0	15	0	0	88	0	0	19	0	0	84	0	0	26	0	0	77	0	0
14	185	79	0	0	45	0	0	61	0	0	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD
15	13	0	0	0	5	5	5	8	2	2	3	3	3	10	6	6	4	4	4	9	2	2	1	0	0	12	8	8
16	5	2	2	1	1	1	0	2	2	2	2	2	1	3	3	3	0	0	0	5	5	5	1	1	0	4	4	4
17	58	3	0	0	19	16	14	36	10	10	3	0	0	55	18	18	7	4	3	51	14	14	17	14	12	41	24	24
18	34	18	0	0	11	11	8	5	0	0	20	20	17	14	5	3	9	9	6	25	1	1	2	2	2	32	9	9
19	56	4	0	0	20	0	0	32	0	0	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD
20	190	8	0	0	66	66	66	116	0	0	8	8	8	182	0	0	30	30	30	160	0	0	45	45	45	145	0	0
21	170	24	0	0	51	0	0	95	0	0	36	0	0	134	0	0	38	0	0	132	0	0	23	0	0	147	0	0
22	109	4	0	0	8	1	1	97	2	0	4	3	3	105	10	8	8	1	1	101	0	0	0	0	0	109	0	0
23	16	1	0	0	13	0	0	2	0	0	6	0	0	10	0	0	12	0	0	4	0	0	1	0	0	15	0	0
24	82	12	0	0	39	0	0	31	0	0	14	0	0	68	0	0	24	0	0	58	0	0	21	0	0	61	0	0
25	49	4	4	4	29	29	29	16	16	13	6	6	6	43	43	41	21	21	21	28	28	28	13	13	13	36	36	35
26	25	1	1	1	14	14	14	10	10	8	1	1	1	24	24	24	5	5	5	20	20	19	9	9	9	16	16	14
27	32	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD
28	15	UD	UD	UD	UD	UD	UD	12	0	0	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD
29	28	UD	UD	UD	UD	UD	UD	23	0	0	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD
30	28	2	0	0	16	4	4	10	2	0	2	0	0	26	0	0	9	2	2	19	1	0	6	1	1	22	0	0
31	9	4	3	2	3	3	2	2	1	1	6	5	3	3	2	2	1	1	0	8	5	5	2	2	2	7	6	5
32	3	0	0	0	3	3	3	0	0	0	0	0	0	3	3	3	3	3	3	0	0	0	1	1	1	2	2	2
33	21	6	2	1	9	7	4	6	1	0	8	4	1	13	3	3	5	3	1	16	4	4	6	6	3	15	11	10

34	9	9	0	0	0	0	0	0	0	0	9	9	8	0	0	0	0	0	0	9	1	0	0	0	0	9	3	3
35	70	41	15	15	16	15	15	13	13	0	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD
36	3	0	0	0	3	0	0	0	0	0	1	0	0	2	0	0	3	0	0	0	0	0	0	0	0	3	0	0
37	4	0	0	0	2	2	2	2	2	2	0	0	0	4	4	4	0	0	0	4	4	4	2	2	2	2	2	2
38	9	5	0	0	3	0	0	1	0	0	6	1	1	3	0	0	2	0	0	7	0	0	1	0	0	8	0	0
39	9	2	1	1	3	2	2	4	0	0	4	3	2	5	2	2	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD
40	15	UD	UD	UD	UD	UD	UD	9	0	0	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD
41	28	UD	UD	UD	UD	UD	UD	18	0	0	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD
42	5	UD	UD	UD	UD	UD	UD	1	0	0	4	4	4	1	0	0	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD
43	36	22	1	1	7	7	7	7	0	0	29	29	27	7	7	5	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD
44	24	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	12	12	12	12	12	8	UD	UD	UD	UD	UD	UD
45	12	UD	UD	UD	UD	UD	UD	3	3	3	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD	UD
46	100	6	0	0	21	0	0	73	0	0	6	0	0	94	0	0	12	0	0	88	0	0	11	0	0	89	0	0
47	30	0	0	0	2	2	1	28	0	0	0	0	0	30	1	0	1	1	0	29	12	12	1	1	1	29	15	15
48	91	3	0	0	28	0	0	60	0	0	5	0	0	86	0	0	7	0	0	84	0	0	22	0	0	69	0	0
49	16	0	0	0	2	1	1	14	0	0	0	0	0	16	2	0	2	1	1	14	8	6	1	1	1	15	10	8
50	16	0	0	0	13	0	0	3	0	0	0	0	0	16	0	0	8	0	0	8	0	0	4	0	0	12	0	0
51	28	2	0	0	21	6	6	5	0	0	2	0	0	26	0	0	12	3	3	16	0	0	7	1	1	21	0	0
52	3	0	0	0	3	0	0	0	0	0	0	0	0	3	0	0	3	0	0	0	0	0	2	0	0	1	0	0
53	9	5	0	0	4	0	0	0	0	0	6	1	1	3	0	0	3	0	0	6	0	0	1	0	0	8	0	0

ID=article entry identifier; #Pt=total number of patients in the article entry; Pros Dz=number of patients with only suspected local or locoregional disease on PET, without any metastases; Ex Pros Dz=number of patients with suspected extra-prostatic or metastatic disease on PET, with or without local or locoregional disease; No Dz=number of patients without any disease on PET; LR+=number of patients with any local or locoregional lesions on PET, regardless of findings in other lesion types; LR-=number of patients without any local or locoregional lesions on PET, regardless of findings in other lesion types; LN+=number of patients with any lymph node lesions on PET, regardless of findings in other lesion types; LN-=number of patients without any lymph node lesions on PET, regardless of findings in other lesion types; B+=number of patients with any bone lesions on PET, regardless of findings in other lesion types; B-=number of patients without any bone lesions on PET, regardless of findings in other lesion types; T=number of PET studies that have confirmatory findings that satisfy the gold standards established in this study; V=number of confirmatory studies that show results concordant with PET findings; UD=PET results that are not available or not clearly reported; by default, values for T and V are labeled UD if the PET results are labeled UD.

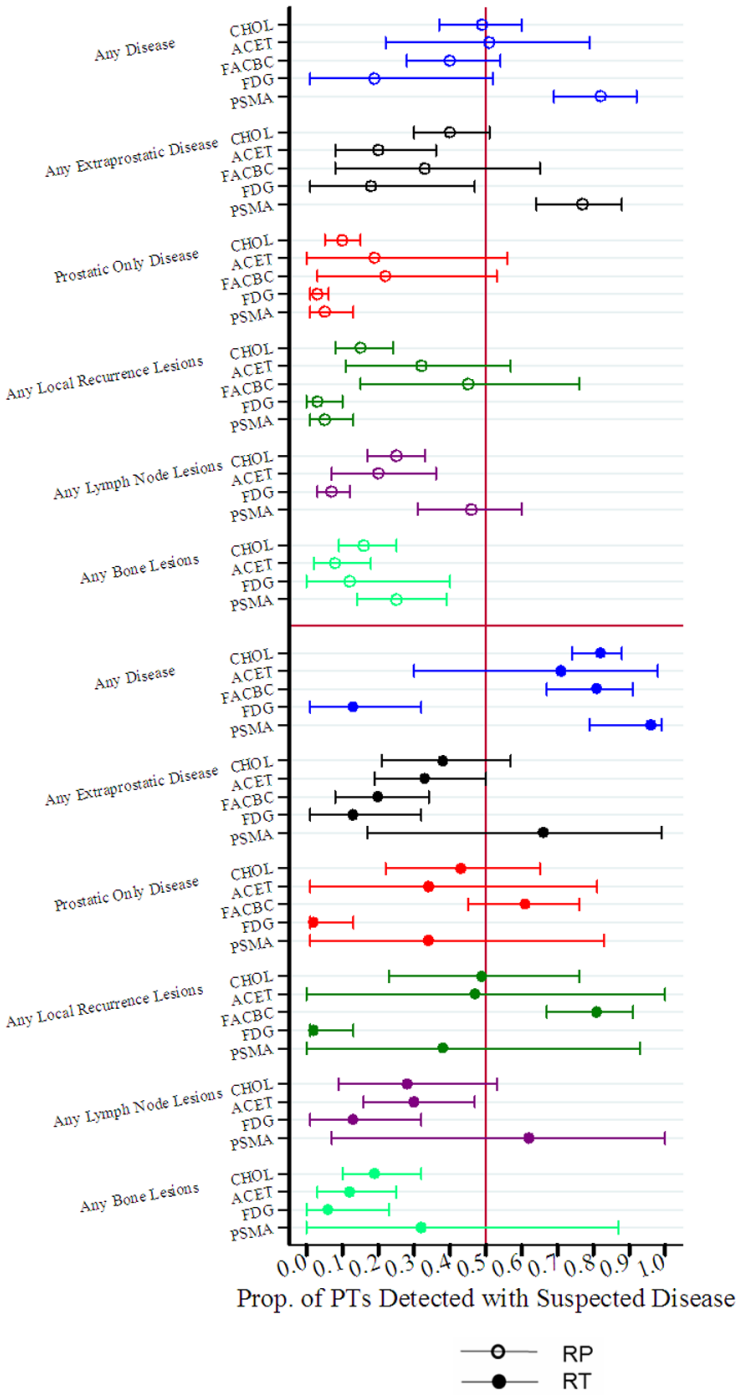

Figure 3. Summarized Proportion of Patients Detected with Suspected Disease. Abbreviations: CHOL=^{11}C- or ^{18}F-Choline; ACET=^{11}C-Acetate; FACBC=anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid; FDG=^{18}F-fluorodeoxyglucose; PSMA=tracers targeting prostate-specific membrane antigen; Prop.=proportion; PTs=patients. Note: The mixed group is not included in this forest plot since the data is difficult to interpret given the unknown composition of patients treated with either RP or RT.

and without positive conventional imaging results. We, therefore, removed the PET detection results for those patients with positive baseline conventional imaging findings.

All available verification data from the selected articles were evaluated under these standards - 1 hard criteria defined by biopsy, CT, bone scan, X-ray, magnetic resonance imaging (MRI), or follow-up PET; and/or 2 soft criteria indicated by changes in PSA after treatment, clinical management, and/or symptoms.

Data extraction

One reviewer (C.Y.Y.) extracted and tabulated the data. For each reviewed study, the study characteristics (author name, journal, year of publication, tracer used, PET or PET-CT imaging technique, PET acquisition time post-injection, and whether the PET interpretation was blinded), study group parameters (RP or RT primary treatment with or without prior ADT, age at PET scan, Gleason score, PSA at time of PET scan, ADT use at time of PET scan, baseline conventional imaging results, the number of positive and negative PET scans (both for distinguishing prostatic only from extra-prostatic sites of recurrence and for detecting the 3 major lesion types: local recurrence, lymph node, and bone lesions), and standards of reference for the PET studies were recorded. The data extraction workflow is summarized in **Figure 2**.

Only patient-based imaging data were considered. Equivocal PET scans were conservatively considered negative. In those studies with multiple PET scans, only the results from the earliest scan were considered. The data were characterized as 1) prostatic only disease: positive

Table 3. Difference in proportion of patients with suspected disease among PET with different tracers and among patients with different prior treatment

Variables	OR[1] (95% CI)	p	Overall p
Suspect of Any Disease			
CHOL	1.0		<0.001
ACET	1.7 (0.88, 3.3)	0.11	
FACBC	1.8 (0.79, 3.9)	0.16	
FDG	0.40 (0.24, 0.66)	<0.001	
PSMA	3.6 (1.3, 10.2)	0.014	
RP[3]	1.0		<0.001
RT[3]	4.1 (2.5, 6.7)	<0.001	
Suspect of Extra-prostatic Disease			
CHOL	1.0		<0.001
ACET	0.75 (0.35, 1.6)	0.48	
FACBC	0.47 (0.11, 2.0)	0.31	
FDG	0.40 (0.24, 0.68)	0.001	
PSMA	3.1 (1.4, 7.1)	0.007	
RP	1.0		0.97
RT	0.95 (0.61, 1.5)	0.81	
Suspect of Prostatic Only Disease			
CHOL	1.0		0.13
ACET	2.4 (0.64, 8.9)	0.19	
FACBC	2.9 (0.32, 26.1)	0.34	
FDG	0.43 (0.17, 1.1)	0.075	
PSMA	0.74 (0.23, 2.3)	0.60	
RP	1.0		<0.001
RT	6.7 (3.8, 12.0)	<0.001	
Suspect of Disease of Local Lesions[2]			
CHOL	1.0		0.031
ACET	2.2 (0.92, 5.0)	0.076	
FACBC	5.0 (0.72, 34.6)	0.10	
FDG	0.41 (0.16, 1.02)	0.055	
PSMA	0.68 (0.23, 2.1)	0.50	
RP	1.0		<0.001
RT	6.7 (3.8, 11.8)	<0.001	
Suspect of Disease of Lymph Node Lesions[2]			
CHOL	1.0		<0.001
ACET	1.3 (0.69, 2.4)	0.43	
FACBC	No observations		
FDG	0.40 (0.23, 0.70)	0.002	
PSMA	2.2 (0.99, 5.1)	0.053	
RP	1.0		0.26
RT	1.3 (0.76, 2.1)	0.37	
Suspect of Disease of Bone Lesions[2]			
CHOL	1.0		0.38
ACET	0.78 (0.36, 1.7)	0.53	
FACBC	No observations		
FDG	0.62 (0.33, 1.2)	0.15	
PSMA	1.5 (0.59, 3.7)	0.40	

for local recurrence and negative for lymph node, bone, and soft tissue lesions; 2) extra-prostatic disease: positive for any lymph node, bone, or soft tissue lesions, with or without local recurrence lesions; and 3) no disease: negative for local recurrence, lymph node, bone, and soft tissue lesions.

For studies that did not have a study population satisfying the patient selection criteria but included tables that detailed pertinent patient clinical information and imaging results, only data from the qualified patient subset were analyzed and reported. In particular, patients whose primary therapies were cryotherapy, high-intensity focused ultrasound, partial prostatectomy, or hormonal therapy were not considered. Those who were receiving hormonal therapy at the time of the PET scan were excluded. In cases where multiple treatments were listed, the primary treatment regimen was assigned based on whether RP or RT appeared first in the list. All reported patient parameters were based on the subset that had been selected for analysis.

RP	1.0		0.90
RT	1.1 (0.63, 2.0)	0.68	

Abbreviations: OR - Odds Ratio; CI - Confidence Interval; CHOL=^{11}C- or ^{18}F-Choline; ACET=^{11}C-Acetate; FACBC=anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid; FDG=^{18}F-fluorodeoxyglucose; PSMA=tracers targeting prostate-specific membrane antigen; [1]Odds ratios were estimated using mixed effects logistic regression models with different studies included as a random effect. [2]The analysis was on difference in the proportions of patients with suspected disease of local lesions, lymph node lesions, or bone lesions, regardless of the disease evaluation of any other lesions. [3]For all analyses on prior treatment, cohorts with mixed treatment were included in the models as separate categories, but ORs were not reported for the mixed group.

Imaging data validation

Validation of all PET studies was evaluated based on the pre-defined truth panel (**Figure 1**) indicated for a particular lesion type (local recurrence, lymph node, bone, and soft tissue) when applicable. Due to the limited soft tissue data across studies, those were not included. A positive PET scan for a lesion type was considered concordant with other correlative imaging studies if at least one of the confirmatory studies was positive, irrespective of whether the extent of a lesion was congruent between the two imaging modalities. A positive PET scan was considered discordant only if all confirmatory studies for that lesion type were negative. Equivocal correlative imaging findings were considered negative. If there were multiple confirmatory studies using the same modality, such as multiple MRI scans conducted at different time points, only the study conducted closest to the time of the PET scan was taken into account.

Standards for confirmation of prostatic only disease are the same as in the lesion-type-based analysis, but correlative imaging studies must have also demonstrated no extra-prostatic or metastatic disease. Metastases were evaluated under the same standards as lymph node, bone, and soft tissue lesions. Positive findings on any of these three lesion types on confirmatory scans verified the presence of metastatic disease. Validation of negative PET studies must have included other imaging studies that were negative for local recurrence, lymph node, bone, and soft tissue lesions, as relevant.

Statistical methods

Using numbers reported in the published papers, six proportions were calculated and compared across the published papers: proportion of patients who, based on PET imaging had 1) any suspected disease, 2) suspected extra-prostatic disease, 3) suspected prostatic only disease, 4) suspected local recurrence lesions regardless of disease evaluation of other lesions, 5) suspected lymph node lesions, and 6) suspected bone lesions. These proportions and their Wilson confidence intervals are presented using forest plots.

Quantitative analyses were performed to estimate the mean proportion of patients with suspected disease, for each tracer (CHOL, ACET, FACBC, FDG, or PSMA) and each patient cohort [40]. Patient cohorts were defined by the prior treatment they received (RP, RT, or mixed). The mixed group represents study cohorts, for which we were unable to separate the PET detection results clearly into the RP and RT groups. Analyses were performed for each of the six proportions tested using the random-effect model, under which the published papers were assumed to be a random sample of the distribution of the proportions. Heterogeneity or inconsistency of the published papers was evaluated, and a p value <0.05 indicated significant inconsistency across the papers. Estimated mean proportions and their 95% confidence intervals (CI) are presented for each of the six proportions, then by tracers and patient cohorts. The means and CI's are presented even though in some cases there was evidence for inconsistency across the published papers, as our intent was to provide a sense of where the average proportion was in each scenario. The proportions reported in the published papers were transformed with the arcsine transformation method before conducting the quantitative analyses [41].

Mixed effects logistic regression analyses were performed to evaluate the effect of tracers on the proportions of patients detected with suspected disease [42]. The proportions were also compared between patient cohorts with different prior treatment (RP vs. RT). In the logistic regression models, different studies were considered as a random effect, and tracers and

prior treatment were considered fixed effects. Odds ratios (OR) and 95% CI calculated from the mixed effects logistic regression models were reported. When analyzing prior treatment, cohorts with mixed treatment were included in the models as separate categories, but ORs were not reported for the mixed group, which has a variable composition of RP- and RT-treated patients.

All *p* values reported were two-sided. Data were analyzed with software STATA version 11 [43].

Results

Study identification

Separate PubMed searches for the 12 selected radiotracers up to and including the publication year of 2013 retrieved a total of 973 articles. The numbers of article entries with an eligible study population were 8 for ACET [18, 44-48], 30 for CHOL [30, 49-59], 5 for FACBC [19, 20, 60-68], 6 for FDG [15, 16, 69], and 4 for PSMA [70, 71]. Among these entries, the numbers of studies that had confirmation results satisfying the pre-defined truth panel were 8 for ACET, 18 for CHOL, 3 for FACBC, 4 for FDG, and 2 for PSMA. These counts do not represent distinct articles, as we subcategorized the PET detection data by primary treatment (RP or RT) and the tracer tested into different article entries, when applicable. For example, a study may have examined 2 tracers and 2 treatment groups (RP or RT) such that a maximum of 4 different article entries would then be available for the given study. In total, 34 distinct articles, subcategorized into 53 entries, were reviewed (**Figure 1**).

Study design and patient parameters

Table 1 summarizes the study characteristics and the relevant patient parameters in the reviewed studies. The article entry number is organized based on the tracer tested, the primary therapy the patients received, the year of publication, and the first author's last name. Among the 53 article entries, 26 (49%) clearly indicated no use of ADT at the time of scan, 34 (64%) stated their definitions for determining biochemical recurrence, 5 (9%) used baseline imaging results as part of their patient selection criteria, and 2 (4%) imposed an upper limit to the PSA values in their study populations.

Counts of patients with suspected disease on PET

Numerical counts of PET positive and negative scans, along with their associated confirmatory study findings, are tabulated in **Table 2**. Two categories of data were extracted: 1) site-based analysis and 2) lesion-based analysis. The site-based analysis aimed to examine the ability of PET to detect any disease and to distinguish disease only localized to from that extending beyond the prostatic bed. The 3 values reported were localized or prostatic only disease (Pros Dz), metastatic or extra-prostatic disease (Extra Pros Dz), and no disease (No Dz) suspected on PET. The number of available confirmatory results satisfying the gold standards defined in this study is indicated in the T column. The number of the confirmatory results that were concordant with the PET findings is indicated in the V column. By default, all PET and confirmatory study results that were not available or were not clearly reported are labeled UD.

The lesion-based analysis aimed to examine the utility of PET in detecting different lesion types: local recurrence (LR), lymph node (LN), and bone (B) lesions. The number of PET findings positive (+) or negative (-) for a particular lesion type was reported irrespective of PET findings for other lesion types. Similar to the results reporting in the site-based analysis, the T column represents the number of available confirmatory studies while the V column represents the number of confirmatory studies that were concordant with the PET findings.

Proportions of patients with suspected disease

Supplemental Figures 1 and 2 present the proportions (and 95% CIs) of patients with 1) any suspected disease, 2) suspected extra-prostatic disease, 3) suspected prostatic only disease, 4) suspected local recurrence lesions regardless of disease evaluation of other lesions, 5) suspected lymph node lesions, and 6) suspected bone lesions. Patient cohorts were grouped by the tracers used, and then sorted by the prior treatment patients received. In Supplemental Figures 1 and 2, patients with mixed treatment (stars) are presented first, followed by patients treated with RP (hollow circles), and then by patients treated with RT (solid dots).

Table 4. Average proportion of patients detected with disease and study heterogeneity

	%Detected	95%CI	Heterogeneity
Suspect of Any Disease			
CHOL			
RP	48%	(37%, 60%)	p<0.001
RT	81%	(74%, 88%)	p=0.45
ACET			
RP	51%	(22%, 79%)	p<0.001
RT	71%	(30%, 98%)	p=0.012
FACBC			
RP	40%	(27%, 54%)	p=0.58
RT	80%	(67%, 91%)	p=0.98
FDG			
RP	19%	(1%, 52%)	p=0.001
RT	12%	(1%, 32%)	Single Pub.[1]
PSMA			
RP	82%	(69%, 92%)	p=0.94
RT	96%	(79%, 99%)	p=0.71
Suspect of Extra-prostatic Disease			
CHOL			
RP	40%	(30%, 50%)	p<0.001
RT	38%	(21%, 57%)	p=0.003
ACET			
RP	20%	(8%, 36%)	p=0.090
RT	33%	(18%, 50%)	p=0.62
FACBC			
RP	33%	(8%, 65%)	Single Pub.
RT	19%	(8%, 34%)	Single Pub.
FDG			
RP	18%	(1%, 47%)	p=0.002
RT	12%	(1%, 32%)	Single Pub.
PSMA			
RP	77%	(64%, 88%)	p=0.63
RT	66%	(17%, 99%)	p=0.10
Suspect of Prostatic Only Disease			
CHOL			
RP	10%	(5%, 15%)	p<0.001
RT	43%	(22%, 65%)	p<0.001
ACET			
RP	18%	(0%, 56%)	p<0.001
RT	34%	(1%, 81%)	p=0.003
FACBC			
RP	22%	(3%, 53%)	Single Pub.
RT	61%	(45%, 76%)	Single Pub.
FDG			
RP	3%	(1%, 6%)	0.39
RT	2%	(1%, 13%)	Single Pub.

The estimated mean proportion of patients detected with suspected disease and the 95% CI are presented in **Figure 3** and **Table 4**. Means and CI's are presented for each of the six types of proportions, then by tracer and patients' primary treatment.

Differences among tracers and among patients with different treatment history

Comparison of the proportions of patients detected with suspected disease among different tracers and among patients with different treatment history is presented in **Table 3**. A significant difference among the tracers was observed in 4 of the 6 proportions tested (please see the overall *p* values in **Table 3**). A general pattern was that FDG tended to show a lower proportion of patients with suspected diseases compared to the other four tracers, while PSMA tended to show a higher proportion of patients with suspected disease compared to the other four tracers. No consistent clear-cut difference was shown for ACET and FACBC compared to CHOL.

Note that the above results were based on a retrospective literature review. Even though PSMA seemed to have a higher proportion of disease detection rate than the other four tracers, this cannot serve as per-

PSMA			
RP	5%	(0%, 13%)	0.35
RT	34%	(1%, 83%)	0.10
Suspect of Disease of Local Lesions			
CHOL			
RP	15%	(8%, 24%)	p<0.001
RT	49%	(23%, 76%)	p<0.001
ACET			
RP	32%	(11%, 57%)	p=0.001
RT	46%	(0%, 100%)	p<0.001
FACBC			
RP	44%	(15%, 76%)	Single Pub.
RT	80%	(67%, 91%)	p=0.98
FDG			
RP	3%	(0%, 10%)	p=0.17
RT	2%	(1%, 13%)	Single Pub.
PSMA			
RP	5%	(0%, 13%)	p=0.35
RT	38%	(0%, 93%)	p=0.047
Suspect of Disease of Lymph Node Lesions			
CHOL			
RP	25%	(17%, 33%)	p<0.001
RT	28%	(9%, 53%)	p=0.002
ACET			
RP	20%	(7%, 36%)	p=0.076
RT	30%	(16%, 47%)	p=0.38
FACBC			
RP	No Data[2]	No Data	No Data
RT	No Data	No Data	No Data
FDG			
RP	6%	(3%, 12%)	p=0.36
RT	12%	(1%, 32%)	Single Pub.
PSMA			
RP	45%	(31%, 60%)	p=0.65
RT	62%	(7%, 100%)	p=0.047
Suspect of Disease of Bone Lesions			
CHOL			
RP	16%	(9%, 25%)	p<0.001
RT	19%	(10%, 32%)	p=0.33
ACET			
RP	8%	(2%, 18%)	p=0.17
RT	12%	(3%, 25%)	p=0.95
FACBC			
RP	No Data	No Data	No Data
RT	No Data	No Data	No Data
FDG			
RP	12%	(0%, 40%)	0.002
RT	6%	(0%, 23%)	Single Pub.
PSMA			

suasive evidence for a better performance of PSMA than the other tracers, since we cannot rule out the possibility that the patient cohorts who used PSMA could have worse disease than the cohorts who used the other tracers or that PSMA was introduced later, when PET imaging techniques had improved overall.

In addition, patients treated with RT seemed to show a higher proportion with suspected diseases than patients treated with RP (**Table 3**). This difference was statistically significant in 3 of the 6 proportions examined (**Table 3**).

Verification of the PET results

In most papers selected for analysis, only a subset of the patients with or without suspected diseases were re-evaluated. Though often only those patients with a suspicious PET lesion were re-evaluated, we used these data to calculate true-positive and false-positive rates. Supplemental Figures 3 and 4 present the proportion of patients with 1) verified extra-prostatic disease, 2) verified prostatic only disease, 3) verified local recurrence lesions regardless of disease evaluation of other lesions, 4) verified lymph node lesions, and 5) verified bone lesions. The number of patients who were re-evaluated was

RP	25%	(13%, 39%)	0.99
RT	32%	(0%, 87%)	0.065

Abbreviations: CHOL=^{11}C- or ^{18}F-Choline; ACET=^{11}C-Acetate; FACBC=anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid; FDG=^{18}F-fluorodeoxyglucose; PSMA=tracers targeting prostate-specific membrane antigen. [1]Heterogeneity for the indicated category cannot be calculated due to the inclusion of only a single article. [2]No data are extracted from the included studies as the reported results do not satisfy the framework established in this study.

usually small. However, based on the limited available data, all the 5 tracers seemed to have reasonable true positive rates.

Discussion

Prior literature reviews have qualitatively and in some cases quantitatively examined the utility of PET in detecting recurrent disease in patients with prostate cancer. However, their analyses were often limited by the heterogeneity in study design, patient cohorts, and standards of reference. Our study attempted to address these limitations by extracting and re-analyzing PET detection data only from studies that satisfied pre-defined sets of patient selection criteria and verification standards.

We re-evaluated the ability of PET to determine whether the patient has 1) any disease, 2) disease localized to or extending beyond the region of the prostatic bed, and 3) any local recurrence, lymph node, and/or bone lesions detected. The first question is important as the patient should not undergo unnecessary treatments if the cancer has not indeed recurred. If there is disease recurrence, the second question concerning the disease status becomes crucial since local recurrence and metastatic disease are treated differently with either local salvage therapies or systemic chemotherapy, respectively. Results from the lesion-type analysis may help in developing an imaging approach using one or a combination of available tracers in re-staging patients experiencing PSA failure.

Our study examined the PET detection data for 5 different tracers (CHOL, ACET, FACBC, FDG, and PSMA) that selectively target cancerous cells through different biological pathways. Both CHOL and ACET are preferentially incorporated into the membranes of prostate tumor cells through increased activity of choline kinase and fatty acid synthase, respectively [72, 73]. FACBC is a synthetic l-leucine analog that has been found to accumulate in prostate cancer cells via a mechanism that has recently been described [74]. FDG uptake into tumor cells, on the other hand, is facilitated by the increased expression of glucose transporter 1 and hexokinase in the tumor cell [75]. PSMA is a transmembrane protein that is specific for and highly expressed in prostate cancer cells [76].

Comparison among the tracers was done through a mixed effects regression analysis. We accounted for randomness among the studies, the tracer studied, and the primary treatment in the model. While multiple studies have suggested that the detection results differ between PET and PET-CT, the PET imaging technique variable had no statistically significant effect on the results of this study (data not shown) [48, 77]. PSA values were also not included in the model since they are often unavailable for individual patients and their reporting was variable.

Results from this model revealed several interesting observations. FDG exhibited the lowest detection rate for any suspected disease among all 4 tracers, as well as for all other proportions examined. This observation agreed with previous findings that FDG may not be a suitable tracer for imaging evaluation of biochemical recurrence [14-16]. Similar to the conclusions drawn by Buchegger et al., there does not seem to be a difference in the detection rate between ACET and CHOL [18]. However, ACET tended to be advantageous over CHOL in detecting local recurrence and lymph node lesions, even though the difference was not statistically significant [46].

We also noticed several observations that may seem contradictory to findings in other studies. In particular, there did not seem to be a difference in the detection rates for any suspected disease between FACBC and CHOL. This observation may be attributed to the difference in the study designs. The two studies by Nanni et al. compared imaging data of the 2 tracers from the same patient cohorts, unlike our study, which treats the 2 groups of data as though they came from 2 separate study popu-

lations [19, 20]. Also, our study compares the average detection rate from multiple studies. While FACBC exhibits greater odds of detecting any disease, this difference is not statistically significant probably due to the lower power from the fewer number of available FACBC studies compared to that for CHOL. While we noticed that FACBC had greater likelihood of detection for local recurrence lesions and prostatic only disease, this difference is not statistically significant.

PSMA seems to have a greater likelihood of detecting extra-prostatic disease, along with lymph node and bone lesions, but the limited data on this tracer prevent us from describing any substantial associations.

In addition to the tracer used, treatment history is another factor that influences the detection rate of recurrence on PET. Notably, patients treated with RT have greater odds of detecting any disease and any local recurrence lesions irrespective of findings in other lesion types. Unlike the complete removal of prostate cancer tissue in RP, RT leaves behind irradiated tissue in the region of the prostatic bed [78]. This may contribute to the greater odds of finding localized disease, as cancer may arise from the irradiated cells or from cells that are left unaffected from the radiation procedure. In spite of the different natures of the 2 treatments, they both have similar biochemical recurrence rates [78]. This observation may explain why we did not observe any statistically significant difference in detecting metastatic disease, lymph node lesions, and bone lesions between the two treatment groups.

Our study also explored the effect of applying a pre-defined set of reference standards to evaluating PET data on the published results. However, the limited number of studies with qualified confirmatory results makes statistical comparison between unverified and verified PET data difficult. Even if there were enough studies to do the analysis, results may still be difficult to interpret because the sensitivity and specificity of each confirmation technique differ [77, 79, 80]. Ideally, histology should be performed for all lesions detected (and not detected) on PET, but this is often not feasible or practical.

Our study has few limitations. Even though our approach to article selection and data extraction addressed several aspects of the heterogeneity across reviewed studies, interpretability of our results is still limited. On patient selection, not all the studies clearly indicated any use of ADT during the time of PET scan and/or distinguished the groups that received RP or RT. Since our analysis evaluated the RP and RT groups separately, some data could have been lost if they were not clearly associated with each patient or either of the two groups. The use of conventional imaging in determining BCR was also variable. In reporting PET detection results, we often had to extrapolate data on distinguishing localized disease from that extending outside the prostatic bed using lesion-type detection results. This might have biased the detection results as extrapolation was not possible for all studies due to unclear reporting. Moreover, we did not account for all the PET data available in studies that conducted multiple PET scans at different time points (early and late) [44, 51, 60]. There were some observed differences in the detection results between early and late scans, but only the early scan was considered.

While our study evaluated PET data under the same standard of reference, there was still heterogeneity in the quality of the reference data. Some studies did not have or did not clearly report their PET and/or confirmatory studies. As such, we made assumptions in interpreting those findings for some studies. When there were confirmatory studies, they were often available or reported only for PET positive lesions. Moreover, our criteria for a true PET-positive scan only required at least one positive confirmatory study while a true PET-negative required all available confirmatory studies to be negative for disease. In addition, we were unable to evaluate PET and PET-CT studies separately due to the small number of studies available for a few tracers. We were also unable to explore differences in PET detection between patients who were experiencing other than the first episode of biochemical recurrence or evaluate the effect of none, prior or current ADT use.

Conclusion

We appraised the published literature and compared the diagnostic utility of 5 PET tracers in

the imaging evaluation of patients with biochemical recurrence of prostate cancer after primary treatments with RP or RT. With the exception of FDG, the other 4 tracers, CHOL, ACET, FACBC, and PSMA, all demonstrated some utility in this clinical setting. Moreover, our systematic approach may serve as a useful model for deciphering the heterogeneous information reported in literature on this and other relevant clinical scenarios. Future studies should strive to avoid the shortcomings that we identified with the current literature in order to enable the medical community to clearly decipher the unique clinical impact of PET with a specific tracer in the imaging evaluation of men with biochemical recurrence of prostate cancer.

Acknowledgements

Supported in part by grants R01-CA111613 and P30-CA014089 from the National Cancer Institute, National Institutes of Health.

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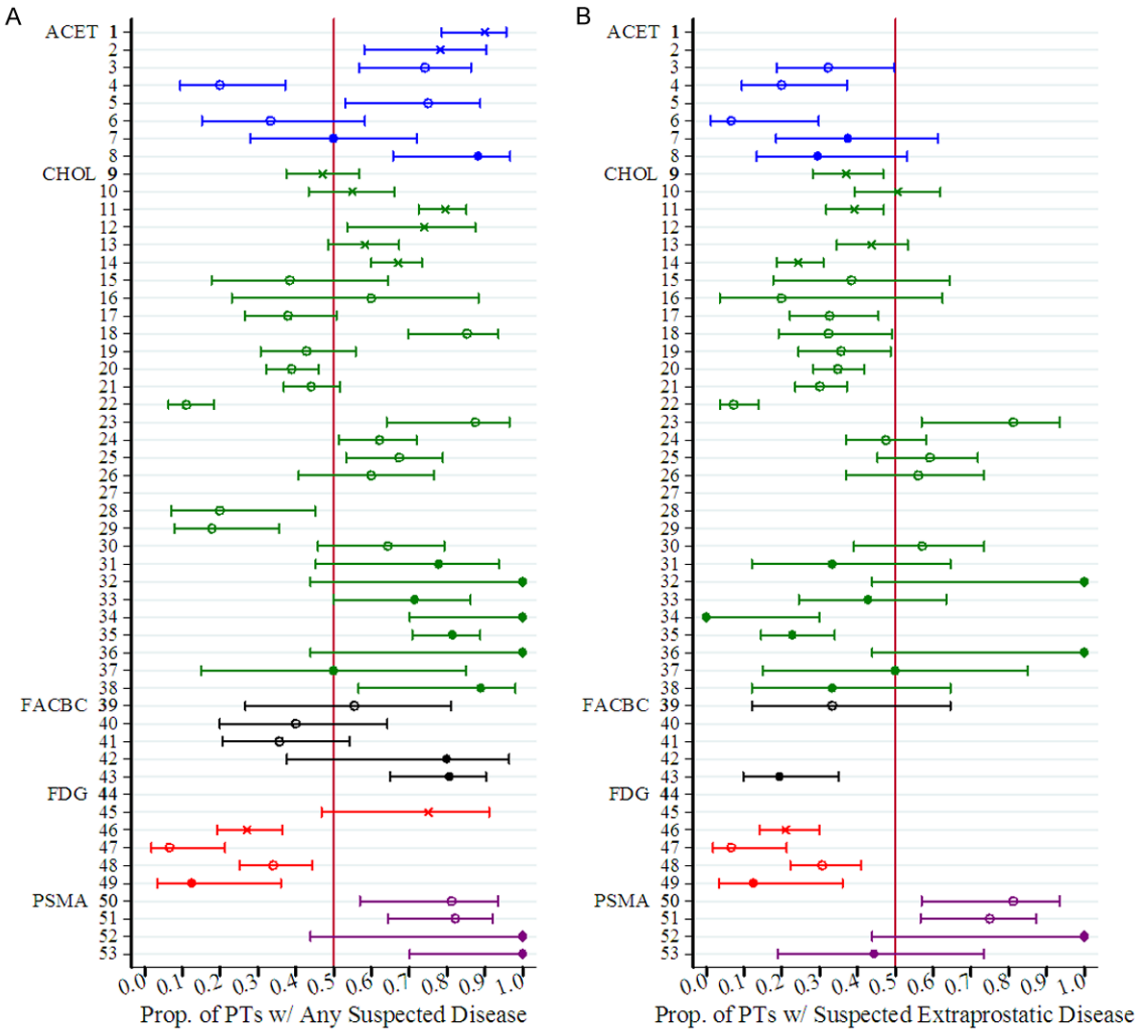
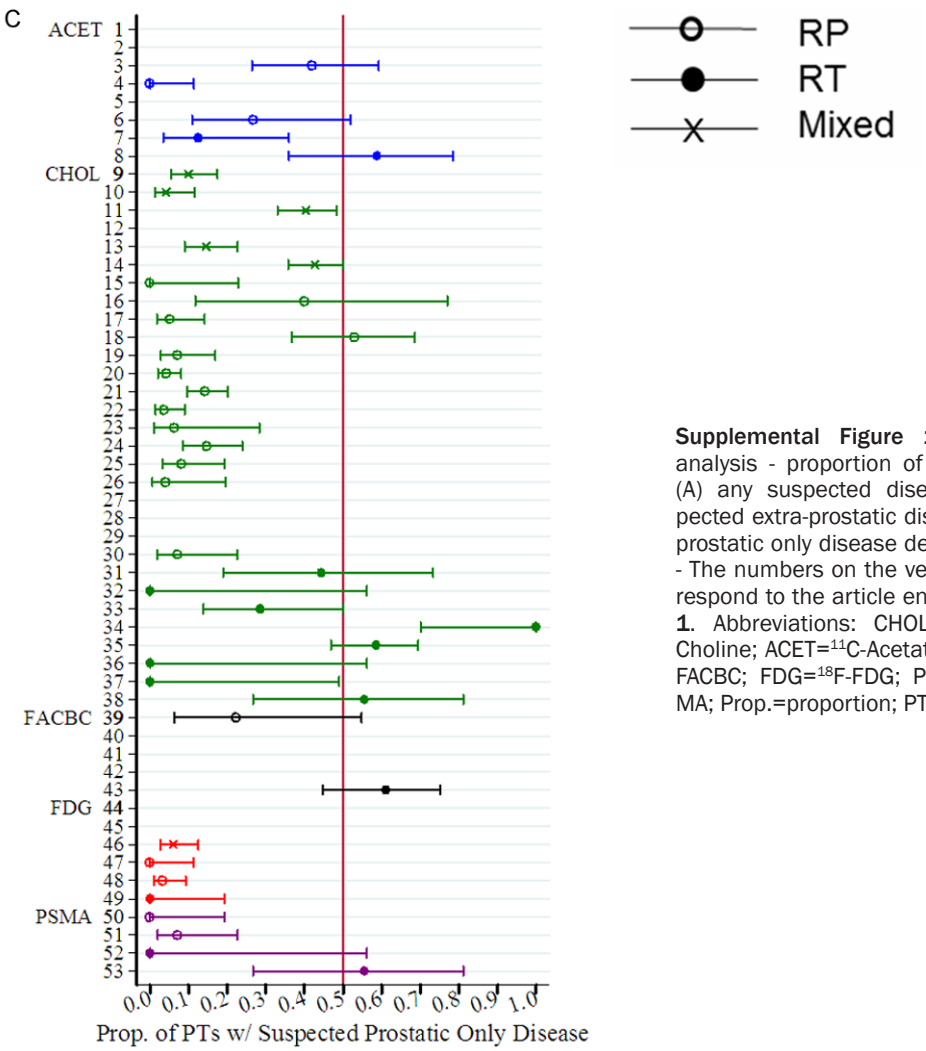
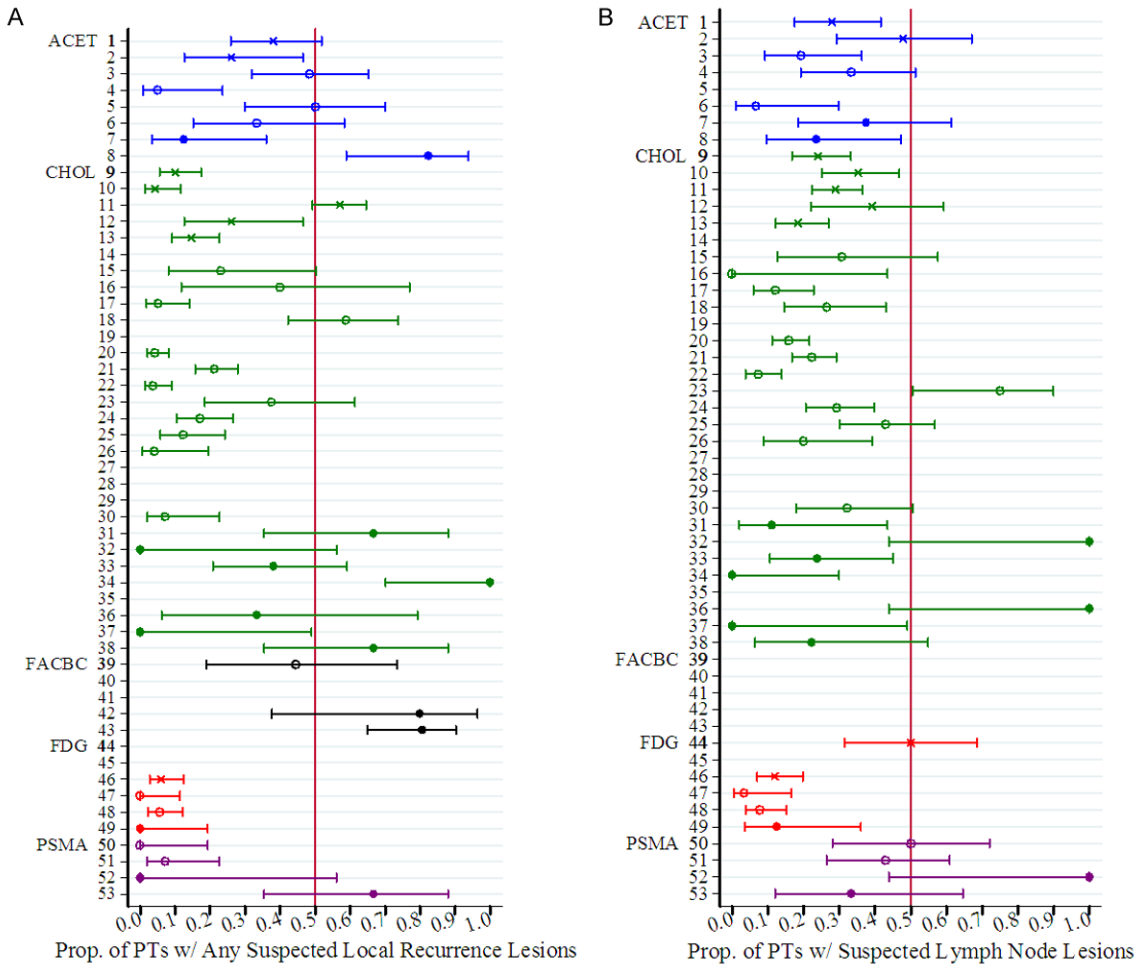
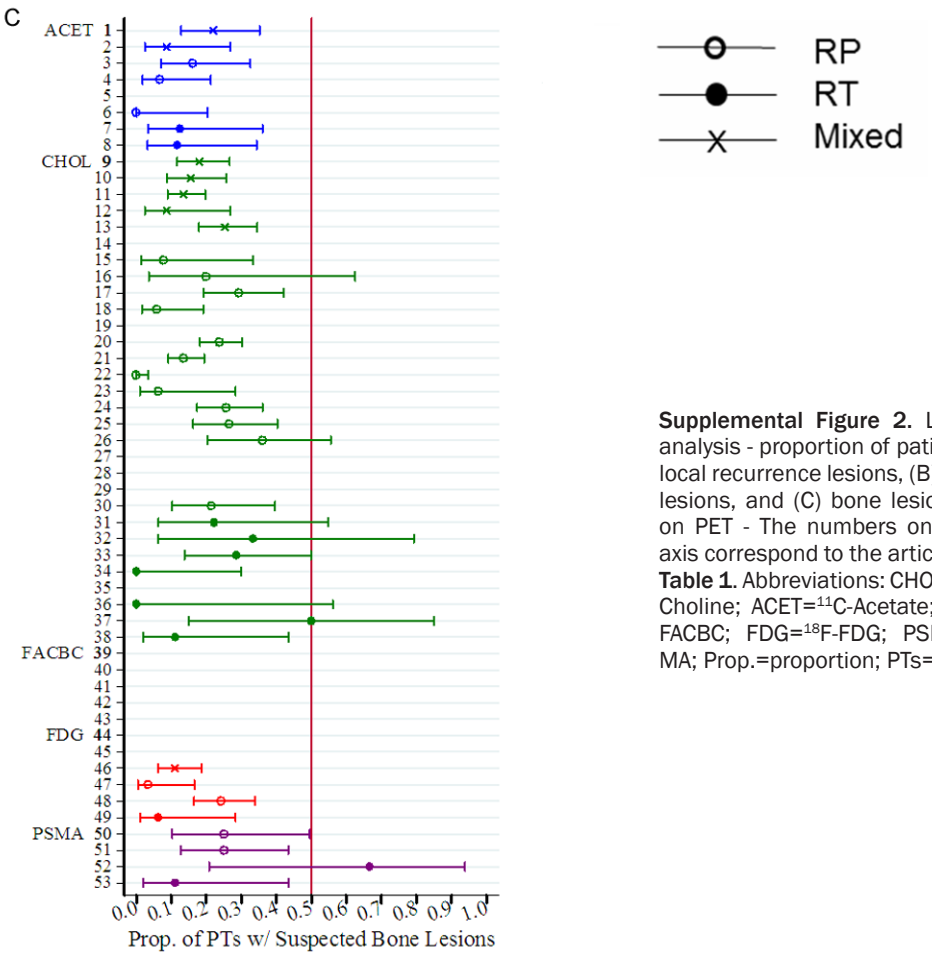
Supporting Information



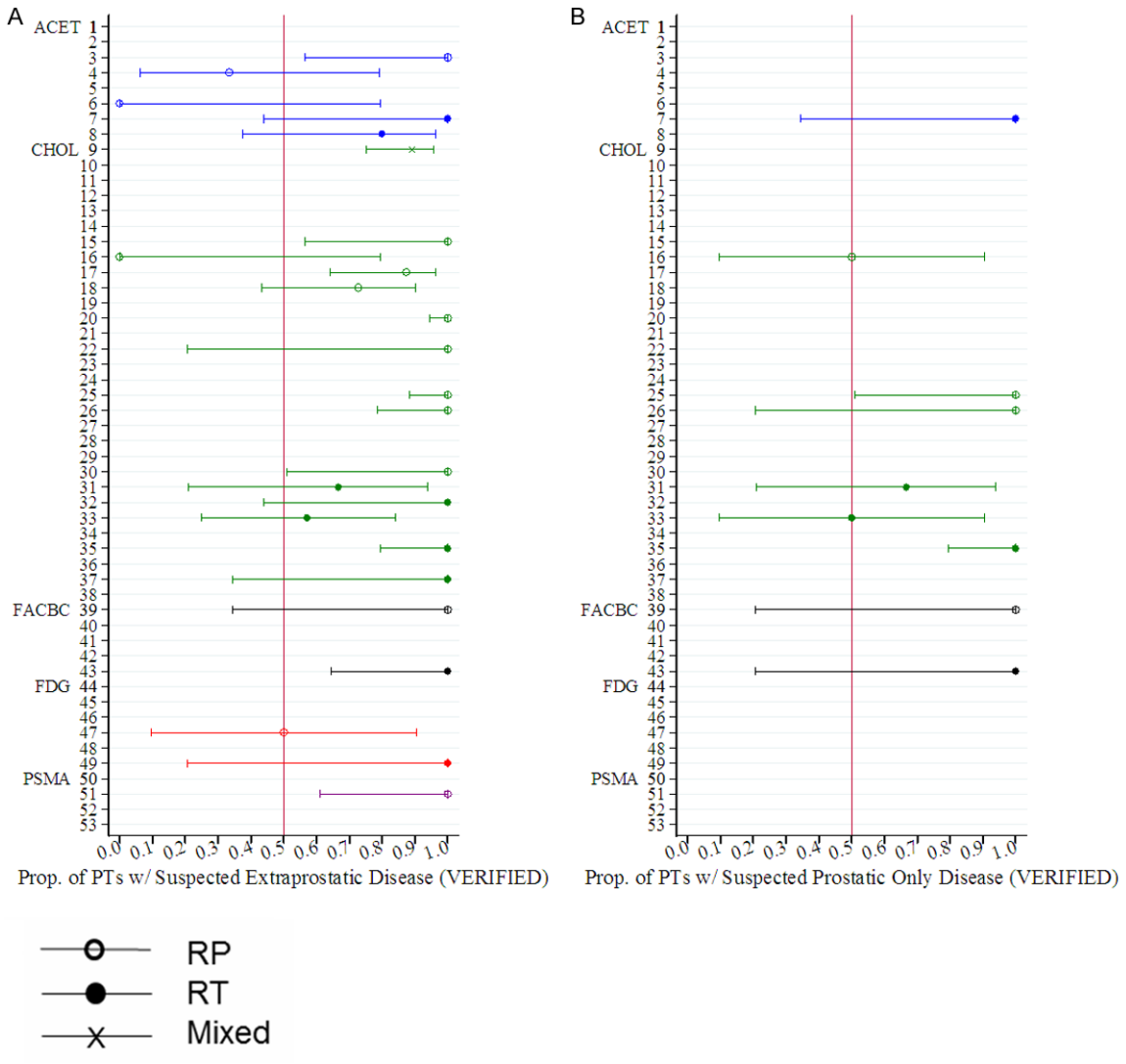


Supplemental Figure 1. Site-based analysis - proportion of patients with (A) any suspected disease, (B) suspected extra-prostatic disease, and (C) prostatic only disease detected on PET - The numbers on the vertical axis correspond to the article entry ID in **Table 1**. Abbreviations: CHOL=^{11}C- or ^{18}F-Choline; ACET=^{11}C-Acetate; FACBC=^{18}F-FACBC; FDG=^{18}F-FDG; PSMA=^{68}Ga-PSMA; Prop.=proportion; PTs=patients.

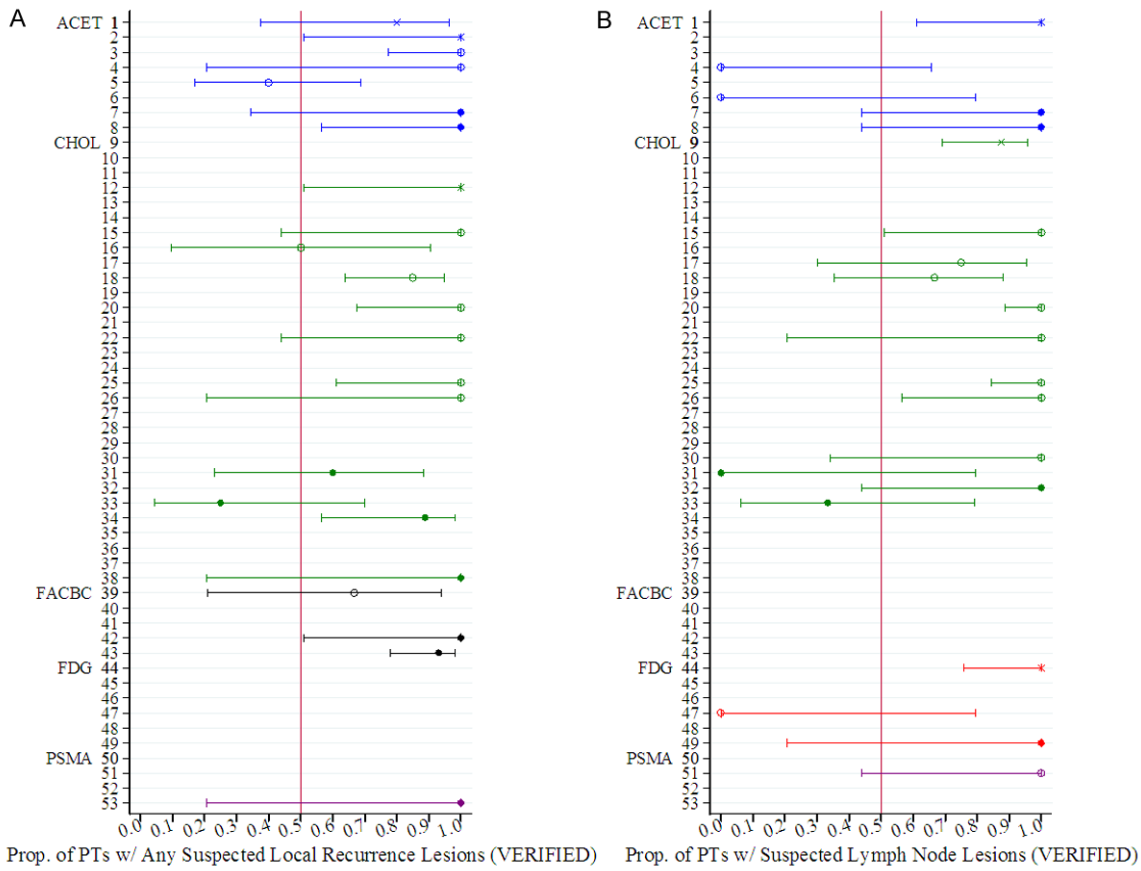

A
ACET
CHOL
FACBC
FDG
PSMA
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Prop. of PTs w/ Any Suspected Local Recurrence Lesions
B
ACET
CHOL
FACBC
FDG
PSMA
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Prop. of PTs w/ Suspected Lymph Node Lesions

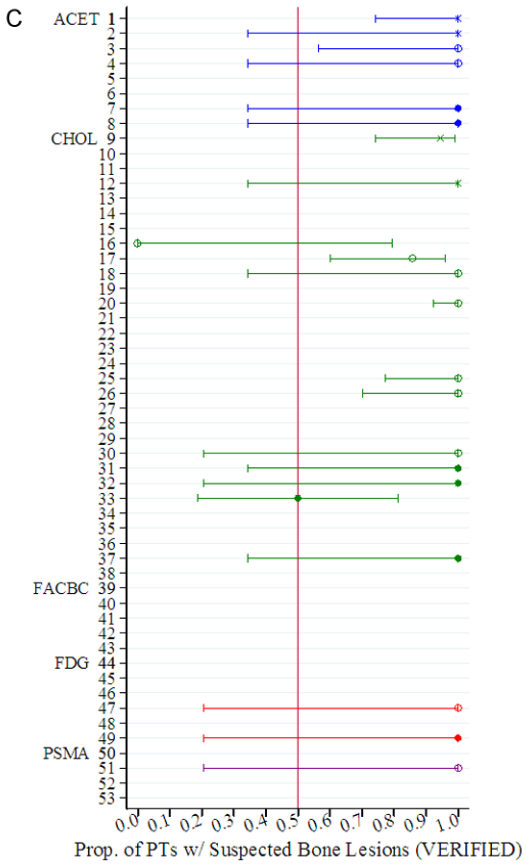


Supplemental Figure 2. Lesion-based analysis - proportion of patients with (A) local recurrence lesions, (B) lymph node lesions, and (C) bone lesions detected on PET - The numbers on the vertical axis correspond to the article entry ID in **Table 1**. Abbreviations: CHOL=^{11}C- or ^{18}F-Choline; ACET=^{11}C-Acetate; FACBC=^{18}F-FACBC; FDG=^{18}F-FDG; PSMA=^{68}Ga-PSMA; Prop.=proportion; PTs=patients.



Supplemental Figure 3. Site-based analysis for verification data - proportion of patients with verified (A) suspected extra-prostatic disease and (B) suspected prostatic only disease detected on PET - The numbers on the vertical axis correspond to the article entry ID in **Table 1.** Abbreviations: CHOL=^{11}C- or ^{18}F-Choline; ACET=^{11}C-Acetate; FACBC=^{18}F-FACBC; FDG=^{18}F-FDG; PSMA=^{68}Ga-PSMA; Prop.=proportion; PTs=patients.


A
ACET
CHOL
FACBC
FDG
PSMA
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Prop. of PTs w/ Any Suspected Local Recurrence Lesions (VERIFIED)
B
ACET
CHOL
FACBC
FDG
PSMA
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Prop. of PTs w/ Suspected Lymph Node Lesions (VERIFIED)



Supplemental Figure 4. Lesion-based analysis for verification data - proportion of patients with verified (A) suspected local recurrence lesions, (B) suspected lymph node lesions, and (C) suspected bone lesions detected on PET - The numbers on the vertical axis correspond to the article entry ID in **Table 1**. Abbreviations: CHOL=^{11}C- or ^{18}F-Choline; ACET=^{11}C-Acetate; FACBC=^{18}F-FACBC; FDG=^{18}F-FDG; PSMA=^{68}Ga-PSMA; Prop.=proportion; PTs=patients.