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Pretreatment PSMA PET in Prostate Cancer Patients without Metastases by Conventional Imaging Changes Primary Stage and Treatment: A Systematic Review and Meta-Analysis

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Abstract

Background: PSMA PET is more sensitive than conventional imaging in patients with Prostate Cancer (PCa) but in patients without metastases by conventional imaging, the change of pretreatment staging and change of treatment is rather limited documented.

Methods: A systematic review and meta-analysis studied publications of patients with PCa localized by conventional imaging for the impact by pretreatment PSMA PET, published between 2016 and January 2025 (INPLASY 2024311004). The team searched for publications in Pubmed, Google Scholar, and reference lists. Forest plots summarized changes of the primary stage and treatment.

Results: 116 publications reported preoperative PSMA PET was used in 19,717 patients with PCa. 131 (1%) patients had low-risk, 5,895 (40%) had intermediate-risk, and 7,247 (59%) had high-risk PCa. PSMA PET downstaged 19% of the patients and upstaged 22%. For 27%, PSMA PET changed the primary treatment.

Conclusion: For a quarter of high-risk patients, pretreatment PSMA PET changed the stage and the primary treatment relative to conventional imaging.

Keywords: Prostate Neoplasms; Prostate Specific Membrane Antigen; Positron Emission Tomography; Staging; Treatment

Introduction

Traditional management of patients with Prostate Cancer (PCa) start with staging with conventional imaging such as ultrasound, CT, and bone scans and a systematic 12 needle diagnostic biopsy. For patients with localized cancer by conventional imaging, primary treatment with a curative intention included Radical Prostatectomy (RP) or External Beam Radiotherapy (EBRT), brachytherapy, or both. After RP, most patients have a fall of PSA to undetectable values, but it is a clinical challenge that a quarter of the responding patients relapse (Biochemical Recurrence (BCR)) [1]. Further, other patients had persisting measurable Prostate Specific Antigen (PSA). Half of the patients who died of PCa initially did not have metastases diagnosed by conventional staging [2]. It was hoped that PSMA PET meets the challenge. In patients with High-Risk PCa (HRPC), pretreatment [^{68}Ga]Ga-PSMA-PET/CT diagnosed metastases better than conventional imaging [3], and some countries recommended that HRPC patients were staged with pretreatment PSMA PET [4]. The Federal Drug Administration of the United States of America (FDA) approved [^{68}Ga]Ga PSMA [3], [^{18}F]F-DCF Pyl PSMA [5], and [^{18}F]F-rh-PSMA 7[6]. Today, half of HRPCa patients are staged with pretreatment PSMA PET [7], and the rate of the pretreatment staging increases.

However, oncologists and international guidelines disagreed on whether changes in the stage diagnosed with pretreatment PSMA PET needed to change the primary treatment [8-11]. Our Systematic Review and Meta-Analysis (SR and MA) aimed to summarize pretreatment PSMA PET for impact on the primary staging and treatment.

Methods

Publications

In August 2024 to January 2025, we undertook a SR according to the Preferred Reporting Items For Systematic Analysis (PRISMA) guidelines [12]. The Pubmed search used the search words ((cohorts) AND (prostate adenocarcinoma OR prostate cancer OR prostate malignancy OR prostate neoplasms) AND (diagnosis OR preoperative OR staging) AND (prostate specific membrane antigen OR PSMA) AND (^{18}Fluoride OR ^{18}F OR ^{68}Gallium OR ^{68}Ga) AND (positron emission tomography OR PET) NOT (abstracts OR case reports OR editorials OR proceedings OR number of patient less than 20 OR publications published before 2016 OR reviews) NOT (biochemical recurrence OR relapse OR restaging)). We searched for publications in Google Scholar and in reference lists of original research publications and reviews. The SR included original research publications reported in English between 2016 and January 2025 including at least 20 patients with localized PCa who had undergone pretreatment PSMA PET. The SR excluded publications that only reported patients with Low-Risk (LRPC) or Intermediate-Risk (IRPC) and Lymph Node Metastases (LNM). The SR was registered in the INPLASY register (2024311004).

Definitions

PCa histology was redefined using the grading of the International Society of Urologic Pathology 2019 (ISUP) [13]. Prostatic lesions with the highest ISUP grade were defined as dominant intraprostatic lesions (DIL). It is the most common site of local failure after radiation therapy for local PCa [14]. Risk groups were defined according to the D'Amico classification [15]. Multiparametric MRI (mpMRI) was defined as the combination of T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast-enhanced imaging. Prostate Imaging Reporting and Data-System (PI-RADS) 4-5, defined as positive mpMRI, had a higher sensitivity and negative predictive value than PI-RADS 1-3, defined as negative or intermediate mpMRI [16].

Lesions diagnosed with conventional imaging in the prostate, lymph nodes, and bones were defined as cT1, cN1, and cM1, respectively. Positive sites on PSMA PET in the prostate, lymph nodes, and bones were defined as miT1, miN1, and miM1, respectively [17].

Activity of the pretreatment PSMA PET was defined as the activity of the PET tracer following intravenous injection. Uptake time of the PET tracer was defined as the interval between injection of the tracer and reading of the uptake. A site was defined as positive, if it had a higher uptake than the liver. The Prostate Cancer Molecular Imaging Standardized Evaluation Framework Including Response Evaluation second version (PROMISE v2) defined how best to perform and report PSMA PET [18].

Statistical Analyses

The findings were registered in an Excel database and transferred to STATA. Rates of findings were summarized in Forest plots by the method by Nyaga [19]. All statistical analyses were carried out in STATA version 14 with updates (Stata Corp., College Station, TX, USA). A p value <0.05 indicated statistical significance.

Results

Pretreatment PSMA PET

Figure 1 shows the selection of publications. (Tables 1A and 1B) summarize findings in 116 original research publications [3,5,20-153]. They reported 19,717 patients. 105 publications reported both IRPC and HRPC patients whereas 11 studies only reported HRPC patients. 131 (1%) patients had LRPC, 5,895 (40%) had IRPC, and 7,247 (59%) patients had HRPC. Meijer [94] and Ingvar [60] found that HRPC patients had more true-positive metastatic sites than IRPC patients. Tables 2A and 2B show PSMA PET methods. Most publications used [^{68}Ga]-Ga-PSMA PET, and some used [^{18}F]-F-PSMA PET. We based the diagnostic performance of pretreatment PSMA PET on publications that used ePLND and histologically confirmed LNM as the gold reference test, shown in Figure 2. Hoffmann [59] and Chandekar [42] found that [^{68}Ga]-Ga PSMA PET and [^{18}F]F-PSMA-1007 were equally effectively to diagnose sites as positive.

The follow-up of findings with [^{18}F]F-PSMA-1007 in patients over time has clarified findings in scapula and in abdominal ganglions showing they are likely to be due to benign and malignant disorders thereby reducing the false-positive readings [154]. PSMA PET could also yield false-negative. For example, PSMA PET did not diagnose most small metastases with a diameter <4 mm, as shown in Figure 3. Patients with small cell and neuroendocrine PCa downregulated PSMA. These patients generally had false-negative PSMA PET. A high ISUP grade and LNM gave a high SUV_{max} on PSMA PET [152,155]. Baas [53] found that pretreatment PSMA PET before RP predicted PSA persistence and BCR. Patients with a negative PSMA PET with no LNM (miN0 pN0) had the lowest rates of PSA persistence and BCR, whereas patients with a positive PSMA PET with LNM (miN1 pN1) had the highest rates.

Year	Author	Reference	Study	Total pts	Clinical characteristics					
					Median age (years)	low risk	interme diate risk	high risk	No with ISUP 4 and 5	Median PSA (ng/mL)
2025	Incesu	[20]	R	333	65	NR	NR	NR	32	7.8
	Madsen	[21]	R	160	72	NR	NR	NR	50	35
2024	Baucknecht	[22]	P	97	67	NR	NR	NR	63	17
	Donswijk	[23]	R	600	68	2	152	436	33	11
	Gautahaman	[24]	P	60	NR	NR	NR	NR	NR	NR
	Heetman	[25]	R	386	70	NR	NR	NR	335	8
	Huebner	[26]	R	108	68	0	32	76	NR	9.25
	Karpinski	[27]	R	244	65	NR	NR	NR	NR	3.6
	Li	[28]	P	86	70	NR	NR	NR	NR	41.2
	Luining ^{68}Ga	[29]	R	939	70	22	602	1535	NR	14.1
	Luining ^{18}F-DCF	[29]	R	839	70	NR	NR	NR	NR	NR
	Luining ^{18}F-1007 ^{68}Ga	[29]	R	264	70	NR	NR	NR	NR	NR
	Luining ^{18}F-JK	[29]	R	161	70	NR	NR	NR	NR	NR
	Madendere	[30]	R	81	64	5	46	30	16	6.8
	Mai	[31]	R	70	67	NR	NR	NR	35	20.4

	Mookerji	[32]	P	134	62	NR	NR	NR	6	7.8
	Patel	[33]	p	30	69	NR	NR	NR	73	11.4
	Prive	[34]	P	75	67	NR	NR	NR	NR	7
	Qiao	[35]	P	120	69.9	NR	NR	NR	49	17.6
	Rajwa	[36]	R	165	66.7	0	0	165	102	24.5
	Shanmug asundaram	[37]	R	667	68.3	NR	NR	NR	594	9.2
	Woo	[38]	R	60	68	NR	NR	NR	20	4.3
2023	Adiyat	[39]	R	165	66.7	0	0	165	102	16.5
	Bodar	[40]	P	74	NR	NR	NR	NR	NR	30.6
	Chaloupka	[41]	P	50	73	0	0	50	38	19
	Chandekar	[42]	P	40	68	0	8	32	17	50.2
	da Silva	[43]	R	35	NR	NR	NR	NR	NR	NR
	Djaileb	[44]	P	240	67	0	46	194	137	11.6
	Du	[45]	R	70	69	NR	NR	NR	17	52
	Hope	[46]	R	167	68.5	NR	NR	NR	78	12.2
	Kubilay	[47]	R	77	66	5	29	43	50	21.5
	Pepe	[48]	R	160	66	NR	NR	NR	44	10
	Seifert	[49]	R	348	70	NR	NR	NR	NR	NR
	Weitzer	[50]	R	100	69.5	9	29	62	42	12
	Zheng	[51]	R	152	68.3	NR	NR	NR	58	12.08
2022	Arslan	[52]	R	39	62	NR	NR	NR	38	9.53
	Baas	[53]	R	213	NR	0	72	141	51	9.3
	Barbosa	[54]	R	91	67	14	25	26	NR	NR
	Bodar	[55]	P	30	69	, 0	16	14	12	7.6
	Erdem	[56]	R	49	64	NR	NR	NR	20	22
	Ferraro	[57]	R	39	65	0	0	39	NR	7.1
	Hermsen	[58]	P	99	68	0	35	64	NR	9.5
	Hoffmann	[59]	R	88	67.5	NR	NR	NR	54	8.8
	Ingvar	[60]	R	104		0	24	80	56	12.6
	Karagiannis	[61]	R	43	70	NR	NR	NR	18	4.34
	Langbein	[62]	R	83	66	0	0	83	18	11

	Lenis	[63]	R	168	66	0	44	124	NR	11.4
	Meissner	[64]	R	25	NR	NR	NR	NR	15	7.3
	Moreira	[65]	R	126	66.8	NR	NR	NR	NR	NR
	Nuo	[66]	R	68	NR	NR	NR	NR	NR	NR
	Parathihasan	[67]	R	65	67	NR	NR	NR	NR	NR
	Roberts	[68]	R	848	66	NR	NR	NR	30	6.0
	Skawran	[69]	R	49	65	0	NR	38	46	9
	Sonni	[70]	P	74	65	0	14	60	NR	11.1
	Szigeti	[71]	P	88	64.5	0	24	57	NR	15.3
	Zacho	[72]	R	48	69	0	0	48	48	13
	Zhang	[73]	R	56	68	NR	NR	NR	31	20.4
2021	Amiel	[74]	R	230	68	0	64	NR	46	NR
	Anttinen	[75]	P	79	70	NR	NR	NR	58	12
	Aydos	[76]	R	302	66.8	NR	NR	NR	152	15
	Bodar	[77]	P	30	68.5	0	10	20	18	11.1
	Chikatamarla	[78]	R	194	70	5	71	118	90	10
	Emmett	[79]	P	291	64	NR	NR	NR	21	5.8
	Esen	[80]	R	96	65	6	50	40	32	8
	Franklin	[81]	R	233	68	NR	NR	NR	50	8.2
	Harsini	[82]	P	25	68.5	NR	NR	NR	12	15.5
	Hope	[83]	P	764	68	8	166	590	450	11.4
	Jansen	[84]	P	117	67	0	43	74	41	10.9
	Jioa	[85]	R	106	NR	NE	NR	NR	30	11,7
	Klingenberg	[86]	R	691	70.4	0	0	691	458	18
	Koerber	[87]	R	335	67	15	101	219	49	11
	Koseoglu	[88]	R	81	67	5	33	43	21	7
	Kwan	[89]	R	72	68	NR	NR	NR	29	8.7
	Liu	[90]	R	52	NR	NR	NR	NR	NR	NR
	Lopci	[91]	P	20	65,5	NR	BR	NR	NR	7
	Malaspina	[92]	P	79	72	NR	NR	NR	58	12
	Margel	[93]	P	99	65	NR	NR	NR	60	6.7

	Meijer	[94]	R	434	68	2	114	318	52	10.7
	Meijer	[95]	R	757	67	NR	NR	NR	446	19.6
	Onal	[96]	R	121	67	0	74	369	224	15.7
	Pienta	[5]	P	268	65	NR	NR	NR	90	9.7
	Prive	[97]	R	53	67	0	11	42	46	12
	Qiu	[98]	R	77	80	NR	NR	NR	29	133
	Scobioala ^{68}Ga	[99]	R	45	68	NR	NR	NR	45	31
	Scobioala ^{18}F	[99]	R	45	68	NR	NR	NR	45	31
	Wondergem	[100]	R	160	71	0	0	160	55	22.8
	Zhang	[101]	P	120	71.1	NR	NR	NR	NR	28.2
2020	Brauchli	[102]	R	100	65.8	NR	NR	NR	61	6.1
	Celen	[103]	P	30	65	2	3	25	36	9.49
	Chandra	[104]	R	64	70	NR	NR	NR	12	13.7
	Chen	[105]	R	54	69	NR	NR	NR	35	13.3
	Cytawa	[106]	R	82	64.9	1	32	39	NR	11
	Donswijk	[107]	R	64	69	0	8	56	56	12
	Frumer	[108]	R	89	67	0	40	49	20	NR
	Gultekin	[109]	R	51	63.5	12	19	20	9	14.6
	Hinsenveld	[110]	R	53	67	0	8	45	32	11
	Hofman	[3]	C	148	69	NR	NR	NR	64	10
	Kopp	[111]	R	90	64.9	0	39	51	30	7.4
	Kroenke	[112]	R	58	68	0	0	58	22	12.2
	Kulkarni	[113]	R	51	65	0	14	37	49	20
	Liu	[114]	R	31	66	NR	NR	NR	NR	20
	Madsen	[115]	R	51	67.2	1	14	32	18	25
	Pallavi	[116]	P	35	62.9	0	NR	NR	26	12.4
	Van Kalmthout	[117]	P	103	69	0	11	92	45	21.8
2019	Abufaraj	[118]	P	65	61	NR	NR	NR	30	9
	Dekalo	[119]	R	59	65	0	30	29	41	13
	Demirci	[120]	R	141	64.6	NR	NR	NR	32	10.1
	Donato	[121]	R	58	65.5	0	45	13	14	7,35

	Dyrberg	[122]	P	55	NR	1	8	28	50	30
	El Hajj	[123]	R	23	69	NR	NR	NR	17	NR
	Muehlematter	[124]	R	40	63	0	8	32	NR	NR
	Nandurkar	[125]	R	142	66	NR	NR	NR	37	9
	Uslu-Besli	[126]	R	28	69	NR	NR	NR	39	8.5
	Van Leeuwen	[127]	R	140	NR	0	30	110	67	9.4
	Yaxley	[128]	R	140	NR	0	30	110	68	9.4
	Yaxley	[129]	R	1257	NR	18	638	597	510	8
	Yilmaz	[130]	R	24	62.8	3	15	6	21	12
2018	Al-Bayati	[131]	R	22	68	NR	NR	NR	6	14.5
	Berger	[132]	R	50	64.9	NR	NR	NR	24	10.6
	Gorin	[133]	R	25	61	NR	NR	NR	13	9.3
	Grubmuller	[134]	P	127	64	NR	NR	NR	57	7.6
	Gupta	[135]	R	97	NR	10	30	57	17	5.7
	Hruby	[136]	R	109	73	NR	NR	NR	95	9.9
	Lengana	[137]	P	113	67	NR	NR	NR	63	23
	Park	[138]	P	33	66.4	0	18	15	15	9.6
	Rogasch	[139]	R	108	NR	2	17	89	53	18
	Taneja	[140]	R	29	65	NR	NR	NR	28	13
	Thalgott	[141]	R	73	68	0	0	73	83	14
2017	Hoffmann	[142]	R	25	67	NR	NR	NR	NR	20.4
	Meyrick	[143]	R	70	67	NR	NR	NR	45	22.4
	Obek	[144]	R	51	NR	NR	NR	NR	NR	NR
	Tulsyan	[145]	P	36	65	0	0	36	NR	8.1
	Uprimny	[146]	R	90	64	NR	NR	NR	38	9.7
	Van Leeuwen	[147]	P	30	65	0	3	27	23	8.1
	Von Klot	[148]	R	21	68	NR	NR	NR	NR	11.9
	Zhang	[149]	R	42	68.9	NR	NR	NR	24	52.3
2016	Budaus	[150]	R	30	62.3	NR	NR	NR	37	8.8
	Eiber	[151]	R	53	66	0	25	28	15	12
	Fendler	[152]	R	21	NR	NR	NR	NR	NR	NR

	Maurer	[153]	R	130	66.5	0	42	88	30	11.6
Total			-	19717	-	131	5895	7247	-	-

Note: C : randomized controlled trial; ^{68}Ga : [^{68}Ga]Ga-PSMA-617 PET; ^{18}F-DCF : [^{18}F]F-DCFPyl-PSMA PET; ^{18}F-1007 : [^{18}F] F-PSMA-1007; ^{18}F JK : [^{18}F]F-PSMA; no : number: NR : not reported; P : prospective study; R : retrospective study.

Table 1A: Clinical characteristics in publications of pretreatment PSMA PET.

Characteristic			Numbers of publications	Patients		
				Number	Median value	IQR
Publications		Retrospective	40			
		Prospective	20			
		RCT	1			
Patients	Age (years)				67	66-68
	Rate of ISUP 4,5 (%)				56	36-66
	PSA (ng/mL)				12	9.5-15.6
	Risk	Low		131		
		Intermediate		5895		
		High		7277		

Table 1B: Summary of characteristics in the publications.

Study			PSMA PET scan				
Year	Author	Reference	PET tracer	CT/MRI	Median activity of PET tracer (MBq)	Median uptake time (min)	Median SUVmean
2025	Incesu	[20]	NR	NR	185	NR	NR
	Madsen	[21]	^{18}F-1007	CT	199	NR	NR
2024	Baucknehl	[22]	^{68}Ga	CT	180	60	NR
	Donswijk	[23]	ALL	CT	NR	NR	NR
	Gauthaman	[24]	^{68}Ga	CT	124	60	NR
	Heetman	[25]	^{68}Ga	CT	145	60	6.5
	Huebner	[26]	^{68}Ga	CT/MRI	NR	NR	NR
	Karpinski	[27]	NR	NR	NR	NR	NR
	Li	[28]	^{18}F-DCF	CT		NR	NR
	Luining 68Ga	[29]	^{68}Ga	CT	135	60	NR
	Luining ^{18}F-DCF	[29]	^{18}F-DCF	CT	300	90	NR
	Luining ^{18}F-1007	[29]	^{18}F-1007	CT	298	90	NR

	Luning 18F-JK-PSMA	[29]	^{18}F-JK	CT	203	69	NR
	Madendere	[30]	^{68}Ga	CT	NR	NR	NR
	Mai	[31]	^{68}Ga	CT	NR	NR	NR
	Mookerji	[32]	^{18}F-1007	CT	360	120	16.9
	Patel	[33]	^{68}Ga	CT	NR	NR	NR
	Prive	[34]	^{18}F-1007	CT	360	86	NR
	Qiao	[35]	^{18}F	MRI	NR	NR	NR
	Rajwa	[36]	^{68}Ga	CT	NR	NR	NR
	Shanmugasundaram	[37]	^{68}Ga	CT	250	30	NR
	Woo	[38]	^{18}F-DCF	CT	250	90	NR
2023	Adiyat	[39]	^{68}Ga	CT	285	118	NR
	Bodar	[40]	^{18}F-DCF	CT	285	118	NR
	Chaloupka	[41]	NR	CT/ MRI	NR	NR	NR
	Chandekar	[42]	^{18}F-1007	CT	NR	NR	NR
	da Silva	[43]	^{68}Ga	CT	NR	NR	NR
	Djaileb	[44]	^{68}Ga	CT	189	60	NR
	Du	[45]	^{68}Ga	CT	180	NR	17.6
	Hope	[46]	NR	NR	NR	NR	NR
	Kubilay	[47]	^{68}Ga	CT	NR	45	NR
	Pepe	[48]	^{68}Ga	CT	NR	NR	NR
	Seifert	[49]	NR	CT	NR	NR	NR
	Weitzer	[50]	^{68}Ga	CT	90	60	NR
	Zheng	[51]	^{18}F-1007	CT	252	90	16.7
2022	Arslan	[52]	^{68}Ga	CT	NR	60	NR
	Baas	[53]	^{18}F-1007	CT	NR	NR	NR
	Barbosa	[54]	^{68}Ga	CT	195	50	NR
	Bodar	[55]	^{18}F-DCF	MRI	310	123	NR
	Erdem	[56]	^{68}Ga	CT	NR	NR	NR
	Ferraro	[57]	^{68}Ga	MRI	85	60	NR
	Hermsen	[58]	^{18}F-1007	CT	252	109	NR
	Hoffmann	[59]	^{18}F-1007	CT	326	60	12.2
	Ingvar	[60]	^{18}F-1007	CT	320	120	NR
	Karagiannis	[61]	^{18}F-1007	CT	250	60	NR

	Langbein	[62]	^{18}F-rh	CT	335	72	13
	Lenis	[63]	NR	CT			
	Meissner	[64]	NR	NR	NR	NR	60.4
	Moreira	[65]	^{68}Ga	CT	180	NR	NR
	Nuo	[66]	^{68}Ga	CT	NR	NR	NR
	Parathihasan	[67]	^{18}F-DCF	CT	250	NR	18.3
	Roberts	[68]	^{68}Ga	CT	NR	53	NR+
	Skawran	[69]	^{68}Ga	MRI	134	60	NR
	Sonni	[70]	^{68}Ga	CT	90	61.5	NR
	Szigeti	[71]	^{68}Ga	CT	189	60	NR
	Zacho	[72]	^{68}Ga	CT	180	60	NR
	Zhang	[73]	^{18}F-DCF	CT	320	53	7.2
2021	Amiel	[74]	^{68}Ga	CT	NR	NR	NR
	Anttinen	[75]	^{18}F-1007	CT	NR	NR	10.5
	Aydos	[76]	^{68}Ga	CT/MRI	137	60	NR
	Bodar	[77]	^{18}F-DCF	CT	312	118	NR
	Chikamatamarla	[78]	^{18}F-1007	CT	250	127	NR
	Emmett	[79]	^{68}Ga	CT	180	60	NR
	Esen	[80]	^{68}Ga	CT	180	45	NR
	Franklin	[81]	^{68}Ga	CT	200	53	NR
	Harsini	[82]	^{68}Ga	CT	170	NR	NR
	Hope	[83]	^{68}Ga	CT/ MRI	185	60	NR
	Jansen	[84]	^{18}F-DCF	CT	331	118	NR
	Jiao	[85]	^{68}Ga	CT	NR	NR	NR
	Klingenberg	[86]	^{68}Ga	CT	189	60	NR
	Koerber	[87]	^{68}Ga	CT	225	115	NR
	Koseoglu	[88]	^{68}Ga	CT	NR	NR	4.8
	Kwan	[89]	^{68}Ga	CT	160	35	NR
	Liu	[90]	^{68}Ga	CT	NR	60	NR
	Lopci	[91]	^{68}Ga	CT	325	NR	4
	Malaspina	[92]	^{18}F-1007	CT	NR	NR	NR
	Margel	[93]	^{68}Ga	MRI	105	NR	NR
	Meijer	[94]	All	CT	NR	NR	NR

	Meijer	[95]	^{68}Ga	CT	299	120	NR
	Onal	[96]	^{68}Ga	CT	160	53	NR
	Pienta	[5]	^{18}F-DCF	CT	330	90	NR
	Prive	[97]	^{18}F-1007	CT	250	90	8.6
	Qiu	[98]	^{68}Ga	CT	NR	NR	NR
	Scobioala 68Ga	[99]	^{68}Ga	MRI	NR	60	NR
	Scobioala 18F	[99]	^{18}F	MRI	NR	120	NR
	Wondergam	[100]	^{18}F-DCF	CT	328	120	NR
	Zhang	[101]	^{68}Ga	CT	145	53	NR
2020	Brauchli	[102]	^{18}F-DCF	CT	304	120	NR
	Celen	[103]	^{68}Ga	CT	185	60	NR
	Chandra	[104]	^{68}Ga	CT	180	60	Detailed
	Chen	[105]	^{68}Ga	CT	132	60	NR
	Cytawa	[106]	^{68}Ga	CT	132	66	Detailed
	Donswijk	[107]	^{68}Ga	CT	100	45	NR
	Frumer	[108]	^{68}Ga	CT	NR	NR	NR
	Gultekin	[109]	^{68}Ga	CT	NR	NR	NR
	Hinsenveld	[110]	^{68}Ga	CT	100	NR	NR
	Hofman	[3]	^{68}Ga	CT	NR	25	NR
	Kopp	[111]	^{68}Ga	CT	170	60	NR
	Kroenke	[112]	18F-rh	CT	337	79.5	NR
	Kulkarni	[113]	^{68}Ga	CT	137	60	11.3
	Liu	[114]	^{68}Ga	CT	206	60	NR
	Madsen	[115]	^{68}Ga	CT	180	60	NR
	Pallawi	[116]	^{68}Ga	CT	185	53	NR
	Van Kalmthout	[117]	^{68}Ga	CT	135	60	NR
2019	Abufaraj	[118]	^{68}Ga	CT/MRI	NR	NR	NR
	Dekalo	[119]	^{68}Ga	CT	156	53	NR
	Demirci	[120]	^{68}Ga	CT	215	53	NR
	Donato	[121]	^{68}Ga	CT	150	60	NR
	Dyrberg	[122]	^{68}Ga	CT	NR	30	NR
	El Hajj	[123]	^{68}Ga	CT	113	60	NR
	Muehlematter	[124]	^{68}Ga	CT	215	53	NR

	Nandurkar	[125]	^{68}Ga	MRI	131	60	NR
	Uslu-Besli	[126]	^{68}Ga	CT	180	60	NR
	Van Leeuwen	[127]	^{68}Ga	CT	116	45	NR
	Yaxley	[128]	^{68}Ga	CT	180	60	NR
	Yaxley	[129]	^{68}Ga	CT	200	60	NR
	Yilmaz	[130]	^{68}Ga	CT	NR	NR	NR
2018	Al-Bayati	[131]	^{68}Ga	CT	175	60	20.7
	Berger	[132]	^{68}Ga	MRI	113	158	NR
	Gorin	[133]	^{68}Ga	CT	NR	60	8.3
	Grubmutter	[134]	^{18}F-DCF	CT	288	60	NR
	Gupta	[135]	^{68}Ga	MRI	NR	NR	NR
	Hruby	[136]	NR	NR	NR	NR	NR
	Lengana	[137]	^{68}Ga	CT	180	45	NR
	Park	[138]	^{68}Ga	CT	118	60	NR
	Rogasch	[139]	^{68}Ga	CT	112	51	NR
	Taneja	[140]	^{68}Ga	CT	192	NR	NR
	Thalgott	[141]	^{68}Ga	MRI	192	NR	NR
2017	Hoffmann	[142]	^{68}Ga	CT	NR	NR	Dec-24
	Meyrick	[143]	^{68}Ga	MRI	138	55	NR
	Obek	[144]	^{68}Ga	CT	180	45	NR
	Tulsyan	[145]	^{68}Ga	CT	80	53	NR
	Uprimny	[146]	^{68}Ga	CT	80	60	NR
	Van Leeuwen	[147]	^{68}Ga	CT	150	60	NR
	Von Klot	[148]	^{68}Ga	CT	98	60	NR
	Zhang	[149]	^{68}Ga	CT	NR	60	NR
2016	Budaus	[150]	^{68}Ga	CT	132	60	7.35
	Eiber	[151]	^{68}Ga	CT	180	60	NR
	Fendler	[152]	^{68}Ga	MRI	141	60	NR
	Maurer	[153]	^{68}Ga	CT	NR	60	NR

Table 2A: Pretreatment PSMA PET.

PET characteristic		Numbers of publications	PSMA PET	
			Median value	(IQR)
Tracer	^{68}Ga	62		
	^{18}F CDF Pyl	5		
	^{18}F 1007	10		
	Other	5		
CT		109		
MRI		11		
CT/MRI		3		
Activity (MBq)			180	135-250
Uptake time (min)			60	60-66

Note: ^{68}Ga : [^{68}Ga]Ga PSMAPET.

Table 2B: Summary of PSMA PET characteristics.

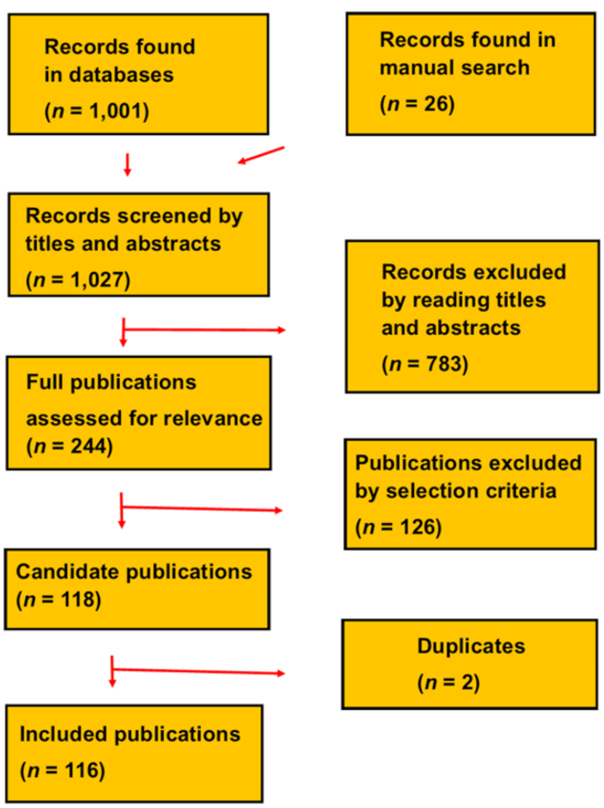

Figure 1: PRISMA flow chart for selection ofthe 116 publications.

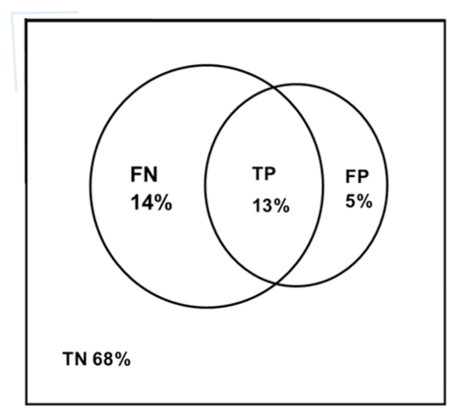

Figure 2: Venn diagram of the diagnostic performance of pretreatment PSMA PET for sites in lymph nodes at initial radical prostatectomy and extensive regional lymph node dissection. The Venn diagram is based on 16 studies with 2051 patients [36,61 ,82,83,110,111,115,124,142,144,147]. The figure shows patient-based analyses. The left circle includes pathology with metastases, and the right circle includes the positive findings on pretreatment PSMA PET.

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Note: TP (true-positive) is positive lesions on PSMA PET confirmed by pathology. FP (false-positive) is positive lesions and PSMA PET not confirmed by pathology. FN (false-negative) is negative lesions on staging PSMA PET in lymph nodes despite pathology is positive. TN (true negative) is negative lesions on staging PSMA PET in lymph nodes confirmed with negative pathology.

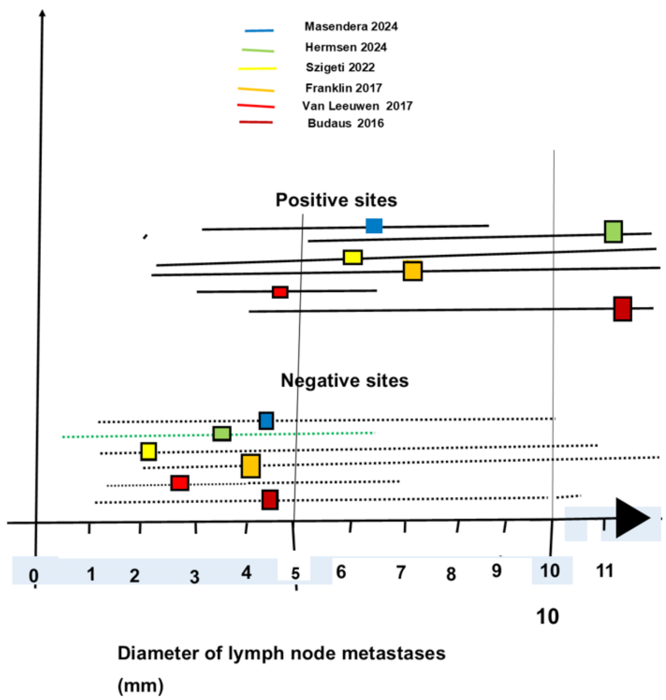


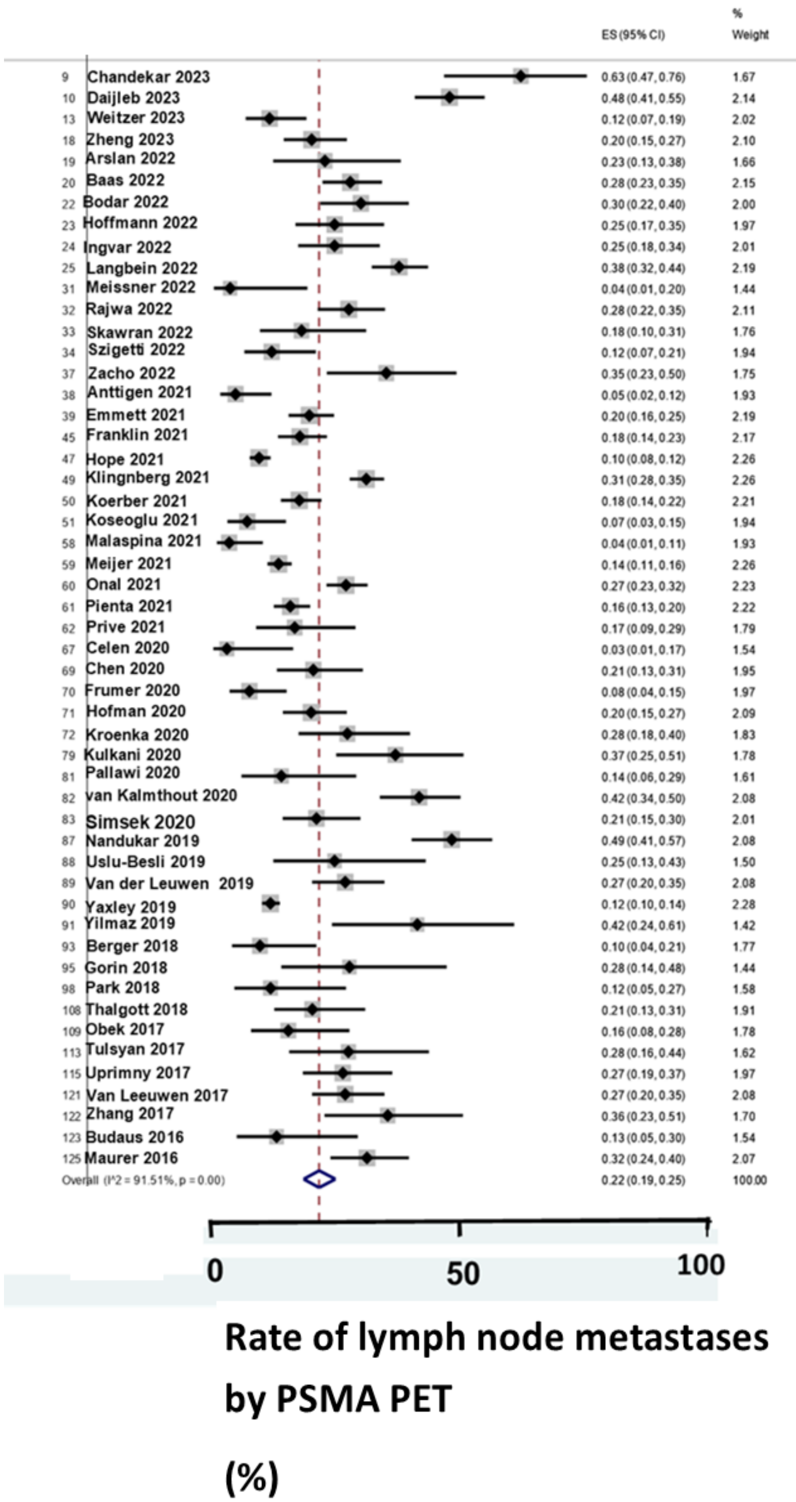
Figure 3: The figure shows six publications that reported the median size of lymph node metastases in patients who underwent extensive pelvic lymph node dissection. PSMA PET-positive lymph node metastases had a greater diameter (median of the median diameter >10 mm) than PSMA PET-negative lymph node metastases (median of the median diameter less than 5 mm).

In contrast to PSMA PET, conventional imaging with CT and bone scans had a low sensitivity to detect metastases. [^{68}Ga]Ga-PSMA PET/CT was better than [^{99}Tc]Tc-Methylene-Diphosphonate (MDP) bone scans. Table 3A shows that pretreatment PSMA was more sensitive to detect metastases than bone scans. Also a previous review [156] summarized six studies with 546 patients. PSMA PET diagnosed bone metastases better than bone scans and whole body mpMRI.

mpMRI is a newer imaging modality than bone scans, but mpMRI had limitations to delineate zones in the prostate. Studies found that pretreatment PSMA PET was better than mpMRI to diagnose extracapsular extension and invasion in seminal vesicles [103]. Pretreatment PSMA PET diagnosed LNM better than mpMRI, as shown in Table 3B.

For patients with local PCa treated with radiation therapy, diagnosis of DIL was more important than diagnosis of clinically significant or insignificant PCa lesions. A combination of mpMRI and pretreatment PSMA was more sensitive to diagnose DIL than mpMRI and pretreatment PSMA PET did separately.

Pretreatment PSMA PET often diagnosed bone metastases in patients with equivocal findings on [^{18}F]-NaF PET/CT [115]. Some HRPC patients who were staged with PSMA PET and mpMRI also underwent bone and [^{18}F]F-NaF PET/CT scans, but these scans did not diagnose significantly more bone metastases [21]. So HRPC patients can be staged adequately with only a combination of pretreatment mpMRI and PSMA PET. Diagnosed with pretreatment PSMA PET, 22% of the patients had LNM and 16% had bone metastases, as shown in Figure 4.



ES (95% CI)
% Weight
9 Chandekar 2023 0.63 (0.47, 0.76) 1.67
10 Daijleb 2023 0.48 (0.41, 0.55) 2.14
13 Weitzer 2023 0.12 (0.07, 0.19) 2.02
18 Zheng 2023 0.20 (0.15, 0.27) 2.10
19 Arslan 2022 0.23 (0.13, 0.38) 1.66
20 Baas 2022 0.28 (0.23, 0.35) 2.15
22 Bodar 2022 0.30 (0.22, 0.40) 2.00
23 Hoffmann 2022 0.25 (0.17, 0.35) 1.97
24 Ingvar 2022 0.25 (0.18, 0.34) 2.01
25 Langbein 2022 0.38 (0.32, 0.44) 2.19
31 Meissner 2022 0.04 (0.01, 0.20) 1.44
32 Rajwa 2022 0.28 (0.22, 0.35) 2.11
33 Skawran 2022 0.18 (0.10, 0.31) 1.76
34 Szigetti 2022 0.12 (0.07, 0.21) 1.94
37 Zacho 2022 0.35 (0.23, 0.50) 1.75
38 Anttigen 2021 0.05 (0.02, 0.12) 1.93
39 Emmett 2021 0.20 (0.16, 0.25) 2.19
45 Franklin 2021 0.18 (0.14, 0.23) 2.17
47 Hope 2021 0.10 (0.08, 0.12) 2.26
49 Klingnberg 2021 0.31 (0.28, 0.35) 2.26
50 Koerber 2021 0.18 (0.14, 0.22) 2.21
51 Koseoglu 2021 0.07 (0.03, 0.15) 1.94
58 Malaspina 2021 0.04 (0.01, 0.11) 1.93
59 Meijer 2021 0.14 (0.11, 0.16) 2.26
60 Onal 2021 0.27 (0.23, 0.32) 2.23
61 Pienta 2021 0.16 (0.13, 0.20) 2.22
62 Prive 2021 0.17 (0.09, 0.29) 1.79
67 Celen 2020 0.03 (0.01, 0.17) 1.54
69 Chen 2020 0.21 (0.13, 0.31) 1.95
70 Frumer 2020 0.08 (0.04, 0.15) 1.97
71 Hofman 2020 0.20 (0.15, 0.27) 2.09
72 Kroenka 2020 0.28 (0.18, 0.40) 1.83
79 Kulkani 2020 0.37 (0.25, 0.51) 1.78
81 Pallawi 2020 0.14 (0.06, 0.29) 1.61
82 van Kalmthout 2020 0.42 (0.34, 0.50) 2.08
83 Simsek 2020 0.21 (0.15, 0.30) 2.01
87 Nandukar 2019 0.49 (0.41, 0.57) 2.08
88 Uslu-Besli 2019 0.25 (0.13, 0.43) 1.50
89 Van der Leuwen 2019 0.27 (0.20, 0.35) 2.08
90 Yaxley 2019 0.12 (0.10, 0.14) 2.28
91 Yilmaz 2019 0.42 (0.24, 0.61) 1.42
93 Berger 2018 0.10 (0.04, 0.21) 1.77
95 Gorin 2018 0.28 (0.14, 0.48) 1.44
98 Park 2018 0.12 (0.05, 0.27) 1.58
108 Thalgott 2018 0.21 (0.13, 0.31) 1.91
109 Obek 2017 0.16 (0.08, 0.28) 1.78
113 Tulsyan 2017 0.28 (0.16, 0.44) 1.62
115 Uprimny 2017 0.27 (0.19, 0.37) 1.97
121 Van Leeuwen 2017 0.27 (0.20, 0.35) 2.08
122 Zhang 2017 0.36 (0.23, 0.51) 1.70
123 Budaus 2016 0.13 (0.05, 0.30) 1.54
125 Maurer 2016 0.32 (0.24, 0.40) 2.07
Overall (I^2 = 91.51%, p = 0.00) 0.22 (0.19, 0.25) 100.00
0
50
100
Rate of lymph node metastases by PSMA PET (%)

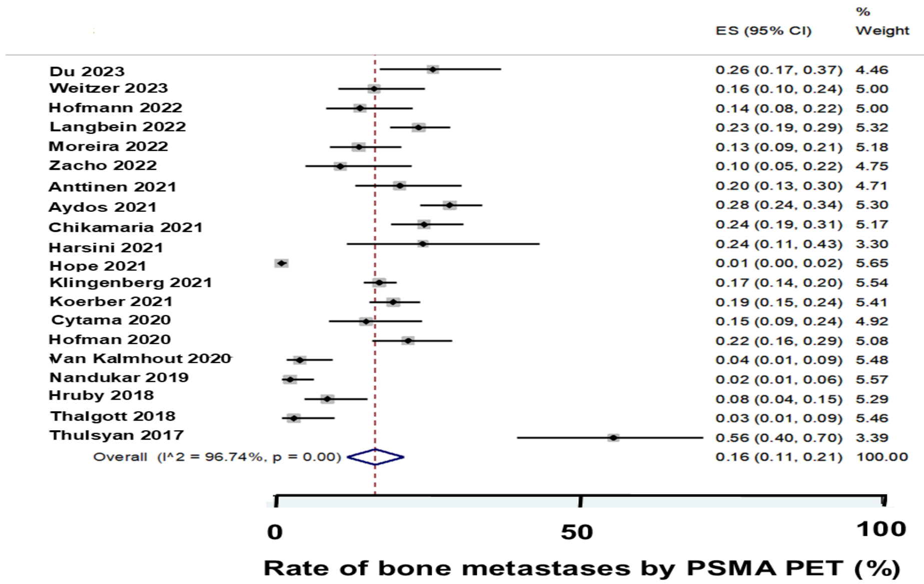


Figure 4: Rate of metastases diagnosed with staging PSMA PET in publications of intermediate and high-risk PCa patients **. A**. Rate of lymph node metastases. B. Rate of bone metastases.

Publication			Total pts	Sensitivity (%)	
Year	Author	Reference		PSMA PET	Bone scans
2024	Qiao	[35]	120	90	43
2024	Shanmugasundaram	[37]	667	10.3	7.9
2023	Hope	[46]	167	17	30
2019	Dyrberg	[122]	77	17	34
2019	Uslu-Besli	[126]	28	90.9	72.7

Table 3A: Comparison of sensitivity with pretreatment PSMA PET and bone scans.

Publication				Total no of pats	Sensitivity (%)	
					PSMA PET	mpMRI
Year	Author	Reference	P/L			
2024	Mai	[31]	P	70	93	NR
	Prive	[35]	P	75	91	95
2022	Arslan	[52]	P	39	18	37
	Bodar	[55]	L	30	50	54
	Ferraro	[57]	P	39	67	61
	Skawran	[68]	P	49	58	61
	Sonni	[69]	L	74	35	35
	Szigeti	[70]	P	81	62	50
2021	Franklin	[80]	P	233	18	9.4
	Malaspina	[91]	P	79	87	45
2020	Celen	[102]	P	30	100	100
2018	Al-Bayati	[131]	P	22	80	59
	Berger	[132]	L	50	100	94
2017	Tulsyan	[145]	P	36	100	66

Note: Some studies reported the sensitivity to diagnose lymph node metastases.

L : lesion- based analysis, NR : not reported, P : patient-based analysis.

Table 3B: Comparison of sensitivity with pretreatment PSMA PET and mpMRI.

Lanfranchi [157] compared oligometastatic PCa diagnosed with [^{18}F]F-fluorocholine PET/CT and [^{68}Ga]Ga-PSMA PET/CT. All patients were treated with Metastasis-Directed Therapy (MDT) for the positive sites on the PET/CT. 26 patients given [^{68}Ga]Ga-PET/CT-guided MDT lived significantly longer without progression than 11 patients given [^{18}F]F-fluorocholine PET/CT-guided MDT. The European Association of Urology (EAU) guidelines for PCa [10] reported that HRPC patients may undergo ePLND as part of the RP. Qiu [98] developed a risk model for the 2-year risk of BCR after the initial treatment. The risk model included the SUV_{max} in PSMA PET.

Many patients with localized advanced PCa were treated with EBRT, brachytherapy, or with both. The FLAME trial [158] showed that EBRT for the whole prostate given with cumulative dose of 77 Gy cured most LRPC patients, whereas most HRPC patients risked recurrence unless the EBRT also included a boost to DIL. mpMRI delineated the DIL, whereas recent publications used pretreatment PSMA PET to delineate the DIL [159].

The HypoFocal trial of dose escalated EBRT of 77 Gy for the whole prostate for PCa patients [159,160] showed that mpMRI and PSMA PET delineated the Gross Tumor Volume (GTV) and the Planned Target Volume (PTV) for the radiation therapy. The ongoing PATRON RCT [161] compares staging with conventional imaging with a combination of both conventional imaging and pretreatment PSMA PET

Change of Stage

Table 4 and Figure 5 show how pretreatment PSMA PET changed the primary staging and treatment. In a previous review, Saad [162] summarized that 30-40% of the patients were upstaged and 20-30% were downstaged relative to conventional imaging. Pretreatment PSMA PET increased diagnosis of LNM with 5 – 30%, and of bone metastases with 10 - 40%.

Klingenberg [163] found of 137 patients staged with conventional imaging that more patients developed BCR compared with 247 staged with PSMA PET (49.6%, versus 25.5%. HR = 0.58, p = 0.004). Bauckneht [22] found that PSMA PET upstaged 27% of the patients and downstaged 6%. da Silva [43] found that PSMA PET changed the stage for more than 60% of the patients: 43% of the patients were downstaged, for instance by not confirming bone metastases, and 23% were upstaged by diagnosis of LNM and bone metastases. Zheng [51] found that PSMA PET upstaged 27% of the patients and downstaged 23%.

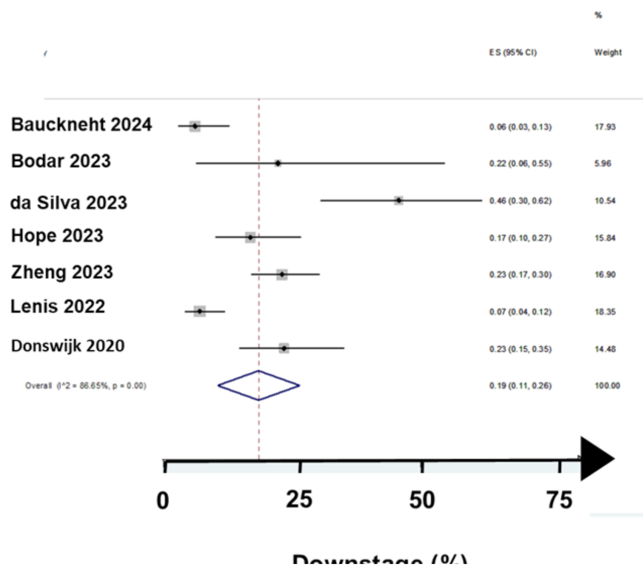


Figure 5A: Downstaging by PSMA PET.

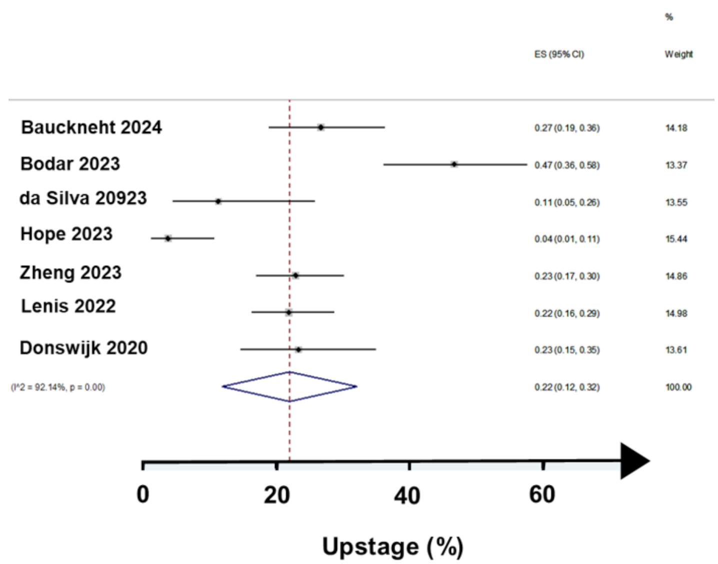


Figure 5B: Upstaging with PSMA PET.

Study			Stage change		No with positive sites		Endpoints	
Year	Author	Reference	Down (%)	Up (%)	LN	Bones	Change of treatment (%)	Rate of BCR (%)
2025	Incesu	[20]	NR	10	10	NR	10	10
	Madsen	[21]	NR	27.5	NR	27.5	NR	NR
2024	Bauckneht	[22]	6	26	NR	NR	0	26.5
	Donswijk	[23]	NR	NR	NR	NR	NR	NR
	Gauthaman	[24]	NR	23	19	9	NR	NR
	Heetman	[25]	NR	NR	NR	NR	NR	NR
	Huebner	[26]	NR	NR	5	NR	NR	7
	Karpinsky	[27]	NR	NR	NR	NR	NR	NR
	Li	[28]	NR	NR	NR	NR	NR	NR
	Luining ^{68}Ga	[29]	NR	NR	NR	NR	NR	NR
	Luining ^{18}F-DCF	[29]	NR	NR	NR	NR	NR	NR
	Luining ^{18F}-1007	[29]	NR	NR	NR	NR	NR	NR
	Luning ^{18}F-JK	[29]	NR	NR	NR	NR	NR	NR
	Madendere	[30]	NR	NR	7	NR	NR	NR
	Mai	[31]	NR	NR	NR	NR	NR	NR
	Mookerji	[32]	NR	NR	NR	NR	NR	NR
	Patel	[33]	NR	NR	NR	NR	NR	NR
	Prive	[34]	NR	NR	NR	NR	NR	NR
	Qiao	[35]	NR	NR	21	37	NR	NR
	Rajwa	[36]	NR	NR	NR	NR	NR	NR
	Shanmugasundaram	[37]	NR	3	NR	67	NR	NR
	Woo	[38]	NR	NR	NR	NR	NR	NR
2023	Adiyat	[39]	NR	NR	NR	NR	NR	MR
	Bodar	[40]	NR	NR	NR	NR	NR	NR
	Chaloupka	[41]	NR	NR	NR	NR	NR	NR
	Chandekar	[42]	NR	NR	NR	NR	NR	NR
	da Silva	[43]	44	37	NR	NR	3	NR
	Djaileb	[44]	NR	NR	60	NR	NR	NR
	Du	[45]	NR	NR	20	18	NR	NR
	Hope	[46]	NR	NR	NR	NR	NR	NR

	Kubilay	[47]	NR	NR	NR	NR	NR	NR
	Pepe	[48]	NR	NR	NR	NR	NR	NR
	Seifert	[49]	NR	NR	NR	NR	NR	NR
	Weitzer	[50]	21	15	13	7	39	NR
	Zheng	[51]	NR	27	90	NR	NR	NR
2022	Arslan	[52]	NR	4	0	NR	NR	NR
	Baas	[53]	NR	NR	60	NR	NR	NR
	Barbosa	[54]	NR	NR	NR	NR	NR	NR
	Bodar	[55]	NR	NR	123	NR	NR	NR
	Erdem	[56]	NR	NR	NR	NR	NR	NR
	Ferraro	[57]	NR	NR	NR	NR	NR	NR
	Hermsen	[58]	NR	NR	23	NR	NR	NR
	Hoffmann	[59]	NR	NR	12	6	NR	NR
	Ingvar	[60]	NR	NR	7	NR	NR	NR
	Karagiannis	[61]	NR	NR	NR	6	29	NR
	Langbein	[62]	NR	NR	52	21	NR	NR
	Lenis	[63]	7,1	22	45	10	NR	NR
	Meissner	[64]	NR	NR	NR	NR	NR	NR
	Moreira	[65]	NR	NR	27	17	NR	NR
	Nuo	[66]	NR	NR	NR	NR	NR	NR
	Parathihasan	[67]	NR	NR	NR	NR	NR	NR
	Roberts	[68]	NR	NR	NR	NR	NR	70
	Skawran	[69]	NR	NR	5	NR	NR	NR
	Sonni	[70]	NR	NR	NR	NR	NR	NR
	Szigeti	[71]	NR	NR	9	NR	NR	NR
	Zacho	[72]	NR	NR	13	5	38	NR
	Zhang	[73]	NR	NR	1	NR	NR	NR
2021	Amiel	[74]	NR	NR	NR	NR	46.5	50.4
	Anttinen	[75]	NR	NR	4	16	NR	NR
	Aydos	[76]	NR	NR	31	86	NR	NR
	Bodar	[77]	NR	NR	NR	NR	NR	NR
	Chikatamarla	[78]	NR	NR	36	40	30	NR
	Emmett	[79]	NR	NR	10	NR	NR	NR

	Esen	[80]	NR	8	9	NR	NR	3
	Franklin	[81]	NR	NR	42	NR	NR	NR
	Harsini	[82]	NR	NR	NR	4	NR	NR
	Hope	[83]	NR	NR	8	5	NR	NR
	Jansen	[84]	NR	NR	NR	NR	NR	NR
	Jiao	[85]	NR	NR	NR	NR	NR	NR
	Klingenberg	[86]	NR	NR	217	116	NR	NR
	Koerber	[87]	NR	NR	81	82	NR	NR
	Koseoglu	[88]	NR	NR	6	NR	NR	NR
	Kwan	[89]	NR	NR	NR	NR	NR	NR
	Liu	[90]	NR	NR	2	NR	NR	NR
	Lopci	[91]	NR	NR	NR	NR	NR	NR
	Malaspina	[92]	NR	NR	27	NR	NR	NR
	Margel	[93]	NR	NR	NR	NR	NR	NR
	Meijer	[94]	NR	NR	58	NR	NR	NR
	Meijer	[95]	NR	NR	104	NR	NR	NR
	Onal	[96]	NR	NR	121	NR	NR	NR
	Pienta	[5]	NR	NR	62	NR	NR	NR
	Prive	[97]	NR	NR	NR	NR	NR	NR
	Qiu	[98]	NR	NR	NR	NR	NR	37.7
	Scobioala ^{68}Ga	[99]	NR	NR	NR	NR	NR	NR
	Scobioala ^{18}F	[99]	NR	NR	NR	NR	NR	NR
	Wondergam	[100]	0	37	81	NR	37	1
	Zhang	[101]	NR	NR	NR	NR	NR	NR
2020	Braucli	[102]	NR	NR	NR	NR	NR	NR
	Celen	[103]	NR	NR	1	NR	NR	NR
	Chandra	[104]	NR	NR	NR	NR	NR	NR
	Chen	[105]	NR	NR	NR	NR	18	NR
	Cytawa	[106]	NR	NR	17	14	NR	NR
	Donswijk	[107]	23	13	NR	NR	22	NR
	Frumer	[108]	NR	NR	5	0	NR	NR
	Gultekin	[109]	NR	NR	NR	NR	NR	NR
	Hinsenveld	[110]	NR	NR	228	NR	NR	NR

	Hofman	[3]	NR	NR	3	32	NR	NR
	Kopp	[111]	NR	NR	7	NR	NR	NR
	Kroenke	[112]	NR	NR	18	NR	NR	NR
	Kulkarni	[113]	NR	NR	9	NR	NR	NR
	Liu	[114]	NR	NR	NR	NR	NR	NR
	Madsen	[115]	NR	NR	NR	NR	NR	NR
	Pallawi	[116]	NR	NR	5	NR	NR	NR
	Van Kalmthout	[117]	0	4	22	4	12.6	NR
2019	Abufaraj	[118]	NR	NR	NR	NR	NR	NR
	Dekalo	[119]	NR	NR	NR	NR	NR	NR
	Demirci	[120]	NR	NR	NR	NR	NR	NR
	Donato	[121]	NR	NR	NR	NR	NR	NR
	Dyrberg	[122]	NR	NR	NR	20	NR	NR
	El Hajj	[123]	NR	NR	NR	NR	NR	NR
	Muehlematter	[124]	NR	NR	NR	NR	NR	NR
	Nandurkar	[125]	NR	NR	15	5	NR	NR
	Uslu-Besli	[126]	NR	NR	6	NR	NR	NR
	Van Leeuwen	[127]	NR	NR	38	NR	NR	27.5
	Yaxley	[128]	NR	NR	107	NR	NR	25.7
	Yaxley	[129]	NR	NR	152	NR	NR	NR
	Yilmaz	[130]	NR	NR	2	NR	NR	NR
2018	Al-Bayati	[131]	NR	NR	NR	NR	NR	NR
	Berger	[132]	NR	NR	6	NR	NR	NR
	Gorin	[133]	NR	NR	7	NR	NR	NR
	Grubmutter	[134]	NR	NR	10	NR	NR	NR
	Gupta	[135]	NR	NR	NR	NR	NR	NR
	Hruby	[136]	NR	NR	25	11	NR	NR
	Lengana	[137]	NR	NR	NR	25	NR	NR
	Park	[138]	NR	NR	5	NR	NR	NR
	Rogasch	[139]	NR	NR	28	19	NR	NR
	Taneja	[140]	NR	NR	NR	NR	NR	0.03
	Thalgott	[141]	NR	NR	15	2	NR	NR
2017	Hoffmann	[142]	NR	NR	3	4	NR	NR

	Meyrick	[143]	NR	NR	12	12	NR	NR
	Obek	[144]	NR	NR	15	NR	NR	NR
	Tulsyan	[145]	0	41	25	20	NR	NR
	Uprimny	[146]	NR	NR	24	NR	NR	NR
	Van Leuwen	[147]	NR	NR	NR	NR	NR	NR
	Von Klot	[148]	NR	NR	NR	NR	NR	NR
	Zhang	[149]	NR	NR	14	NR	NR	NR
2016	Budaus	[150]	NR	NR	12	NR	NR	NR
	Eiber	[151]	NR	NR	NR	NR	NR	NR
	Fendler	[152]	NR	NR	NR	NR	NR	NR
	Maurer	[153]	NR	NR	41	NR	NR	NR

Table 4: Changes after staging PSMA PET.

Change of Treatment

Pretreatment PSMA PET often permitted a change of treatment from what was based on conventional imaging [164]. Also selection of patients for active surveillance may be strengthened if PSMA PET only diagnosed local PCa [165,166]. The FLAME trial [158] showed that increased radiation therapy to DIL improved the survival free of BCR. The same trend was found in three single-armed trials, DELINEATE, 5STAR, and 2SMART [167,168]. The trials studied moderate to ultra-fractionated EBRT radiation therapy that included a boost to the DIL. The three trials also used mpMRI to delineate DIL and pelvic LNM. Another trial used proton radiation for the boost for DIL [169]. Two other trials used a high dose rate brachytherapy boost to DIL [170,171]. New trials of boosting DIL may delineate the DIL by using a combination of pretreatment PSMA PET and mpMRI [159]. An adequate delineation of DIL also helps to de-escalate radiation therapy for the non-DIL zone of the prostate.

For patients undergoing ePLND, a per operative [^{111}In]-In PSMA PET could detect positive sites in regional lymph nodes outside the standard template for the ePLND [172]. The finding motivates a more personalized removal of pelvic lymph nodes. Thus a per operative PSMA PET increased the extent of the primary surgery. In contrast, a study did found that patients did not live longer after ePLND if pelvic lymph nodes were negative for metastases by pretreatment PSMA PET [20].

Corresponding to the changes in staging with pretreatment PSMA PET staging in the da Silva publication [43], 60% of the patients had a changed treatment. Most changes were shifts from a palliative systemic treatment for patients with cM1 to a potentially curative treatment of the primary tumor for patients with miM0. Karagiannis [61] found that PSMA PET changed the planned EBRT for 61% of the patients, as shown in Figure 7. Changes of the EBRT may be regarding both the extent of the target field for the radiation therapy and the radiation dose.

Patients with oligometastatic PCa diagnosed by PSMA PET can be treated with MDT with or without systemic therapy and with or without local treatment [173,174]. An ongoing trial METANOVA (ClinicalTrials NCT06150417) studies radiation therapy for the prostate and up to ten metastatic sites. In the STAMPEDE trial of patients with metastatic PCa [175], local radiation therapy improved OS for patients with low volume-metastatic PCa but not for patients with high volume-metastatic PCa.

In the ORIOLE trial [176], 95% of the patients treated for all positive lesions diagnosed by PSMA PET lived 6 months without progression whereas only 62% of the patients who had at least one untreated lesion lived 6 months without progression (HR = 0.25, p = 0.006). The trial points out that treatment should be based on metastases diagnosed with PSMA PET. Li [28] studied patients with metastatic lesions, and found that a large tumor volume significantly increased the risk of progression. Patients with polymetastatic PCa diagnosed by PSMA PET should be treated with effective systemic therapy [171].

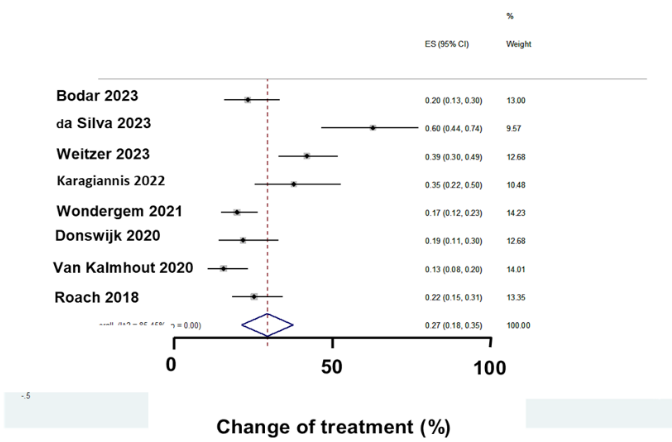


Figure 6: Change of treatment after pretreatment PSMA PET.

Discussion

The pretreatment PSMA PET often results in a change of the initial stage and the primary treatment for many patients with PCa. In the real world, pretreatment PSMA PET is increasingly used for patients with PCa because the scan is a more sensitive imaging modality than conventional imaging. Pretreatment PSMA PET met the challenge both regarding change of stage and change of primary treatment. The changes may have a positive impact on survival.

Pretreatment PSMA can lead to a more personalized primary treatment relative to that based on conventional imaging. The change of treatment after pretreatment PSMA PET is essential for a positive impact on survival. Downstaging to loco-regional PCa makes the patients candidates for primary treatment with a curative intent, and upstaging to metastatic PCa makes the patients candidates for MDT and systemic treatment. But it remains to be shown whether the more sensitive staging and the following adequate modifications of the primary treatment reduce recurrence and deaths of PCa.

Conclusion

Many centers use pretreatment PSMA PET for patients with HRPC. Many ongoing trials study the clinical efficacy of primary treatment that often is changed based on pretreatment PSMA PET.

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