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3 **PSMA PET validates higher rates of metastatic disease for**
4 **European Association of Urology Biochemical Recurrence**
5 **Risk Groups: an international multicentre study**

6
7 **Short title:** EAU risk groups and PSMA PET stage

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39 **ABSTRACT**

40 The European Association of Urology (EAU) Prostate Cancer Guidelines Panel
41 recommends risk groups for biochemically recurrent prostate cancer (BCR) to identify
42 men at high risk of progression or metastatic disease. The rapidly growing availability of
43 PSMA-directed PET imaging (PSMA PET) will impact prostate cancer staging. We
44 determined the rates of local and metastatic disease in recurrent and persistent prostate
45 cancer stratified by EAU BCR risk groups and biochemical persistence (BCP). *Methods:*
46 Patients with BCR/BCP were enrolled under the same prospective clinical trial protocol
47 conducted at three sites (n=1777, 91%; UCLA n=662, NCT02940262; UCSF n=508,
48 NCT03353740; Michigan, n=607, NCT03396874); 183 patients with BCP from
49 Universities of Essen, Bologna, and Munich were included retrospectively. Patients with
50 BCR had to have sufficient data to determine EAU risk score. Multivariate, binomial logistic
51 regression models were applied to assess independent predictors of M1 disease. *Results:*
52 A total of 1960 patients were included. Post-RP EAU BCR low risk, EAU BCR high risk,
53 and BCP groups yield distant metastatic (M1) detection in 43/176 (24%), 342/931 (37%),
54 and 154/386 (40%) of patients. For post-radiotherapy EAU BCR low risk and EAU BCR
55 high risk groups, M1 detection rate was 113/309 (37%) and 110/158 (70%), respectively.
56 BCP, high risk BCR and higher levels of serum PSA were significantly associated with
57 PSMA PET M1 disease in multivariate regression analysis. PSMA-PET revealed no
58 disease in 25% and locoregional only disease in 33% of patients with post-RP or post-
59 radiotherapy EAU BCR high risk. *Conclusion:* Our findings support the new EAU
60 classification; EAU BCR high-risk groups have higher rates of metastatic disease on
61 PSMA PET than the low-risk groups. Discordant subgroups, including metastatic disease
62 in low risk and no disease in high risk patients warrant inclusion of PSMA PET stage to
63 refine risk assessment.

64

65 INTRODUCTION

66 After primary curative-intent treatment for prostate cancer (PCa) with radical
67 prostatectomy (RP) or radiotherapy, approximately one out of four men experience
68 biochemical recurrence (BCR) (1).

69 The incidence and outcomes of BCR are variable. A novel European Association of
70 Urology (EAU) risk-scoring system combines PSA doubling time (PSA-DT), gleason score
71 (GS), and interval from primary therapy to biochemical failure (IBF), to identify patients at
72 high risk for metastases and early disease progression (2). Of note, PSA persistence
73 (BCP), was described as a different pattern of relapse, which is associated with worse
74 oncological outcomes and was therefore not stratified into risk groups (3).

75 Tilki et al. validated the EAU BCR risk score using survival data from an extensive dataset
76 of post-RP patients from their centre. Metastatic progression-free and overall survival
77 were significantly different; However, the prognostic accuracy for metastasis-free survival
78 (c-index 0.67) or disease specific survival (c-index 0.69) was moderate, warranting further
79 refinement of this classification (4).

80 PSMA-targeted positron emission tomography (PSMA PET) has demonstrated
81 high detection rates and accuracy for the localization of prostate cancer metastases (5).
82 The improved accuracy of PSMA PET along with impact on management led to its
83 inclusion in the EAU guidelines as well as FDA approval for imaging primary and recurrent
84 disease (6,7). Several trials evaluating the potential of PSMA PET guided therapy to
85 achieve improved outcome are currently underway or recently published (8,9). PSMA PET
86 disease extent was associated with time to progression in patient candidates for salvage
87 radiotherapy and may thus offer independent prognostic value at BCR and BCP (10).

88 The aim of this study was to assess disease extent in patients with EAU BCR high
89 risk, low risk, and BCP using PSMA PET to identify subgroups of undetectable (T0N0M0),
90 locoregional (Tr/N1), or distant metastatic (M1) disease.

91

92 **METHODS**

93 This is a multicentric, single-arm analysis of Patients with recurrent or persistent
94 PSA after curative treatment of prostate cancer. Biochemical recurrence was defined as
95 a PSA of 0.2 or more ng/mL measured more than 6 weeks after prostatectomy or a PSA
96 of 2 or more ng/mL rise above nadir following radiation therapy. Biochemical persistence
97 was defined as PSA nadir >0.1 ng/ml within 12 weeks after RP. The final database
98 consisted of 1960 patients with either BCR (n=1574) or BCP (n = 386). The majority of
99 patients were enrolled under the same prospective clinical trial protocol conducted at three
100 sites (n=1777, 91%; UCLA n=662, NCT02940262; UCSF n=508, NCT03353740;
101 Michigan, n=607, NCT03396874); 183 patients with BCP from Universities of Essen,
102 Bologna, and Munich were included retrospectively. In total 587/1960 (30%) patients have
103 been reported previously (5,6,11). The study was approved by institutional review boards
104 at each site.

105 Patients were eligible if they had a history of histopathology-proven prostate
106 adenocarcinoma and BCR or BCP after curative-intent radiotherapy or prostatectomy.
107 Further, BCR patients had to have sufficient data to determine risk group: PSA-DT and
108 GS for recurrence after post-prostatectomy, IBF and GS post-radiotherapy. Patients had
109 to have complete reading data. Patients with known metastases prior to PSMA PET, prior
110 salvage treatment or PSMA PET within three months after curative treatment were not
111 eligible for this analysis. A flow chart for patient inclusion is shown in Figure 1.

112 Detailed imaging procedures were reported previously (5) and scans were acquired
113 in accordance with the international guideline (12). In brief, whole-body PET was acquired
114 from skull to mid thighs. PET was performed as hybrid imaging with CT or MRI based on
115 availability and contraindications. For PET/CT, a diagnostic contrast-enhanced CT was
116 obtained before the PET scan. For PET/MRI, an abbreviated pelvis PET/MRI was
117 obtained following a whole-body protocol after the PET scan. PSMA PET findings were
118 interpreted using Prostate Cancer Molecular Imaging Standardized Evaluation
119 (PROMISE) criteria (13).

120 Descriptive statistics were used to report patient characteristics and disease extent.
121 Multivariate, binomial logistic regression models were applied to assess independent
122 predictors of M1 disease. Analyses were performed using R v.3.4.0 (R Foundation for
123 Statistical Computing, Vienna, Austria). Figure parts were created using BioRender
124 Software.

125

126 **RESULTS**

127 Table 1 lists patient characteristics and PSMA PET stage. Median PSA serum level
128 at time of PSMA PET was 1.76 ng/mL (IQR 4.28). PSA values differed post-RP (Median
129 1.0 ng/mL, IQR 2.4) vs. post-radiotherapy (Median 5.1 ng/mL, IQR 6.4). A total of 1493
130 (76%) patients received primary RP and 467 (24%) patients received primary
131 radiotherapy. More than 60% of patients in the post-RP group had PSA <2.0 ng/mL,
132 whereas - also due to different BCR definition - majority of post-radiotherapy patients had
133 PSA \geq 2 ng/mL. Median [IQR] time since initial therapy was longest in the respective EAU
134 low risk groups (post-RP, 9.6 [7.4] months; post-radiotherapy, 7.4 [6.9] months). PSMA

135 PET localized disease in 1515/1960 (77%) patients. Figure 2A shows PSMA PET
136 detected disease extent separate for EAU BCR risk groups and BCP.

137 PSMA PET revealed M1 disease within the post-RP group in 43/176 (24%),
138 342/931 (37%), and 154/386 (40%) of EAU BCR low risk, high risk, and BCP patients,
139 respectively. Within the post-radiotherapy group, M1 disease was detected in 113/309
140 (37%) and 110/158 (70%) of EAU BCR low and high risk patients, respectively. Bone
141 metastases were detected in 19/176 (11%), 201/931 (37%), 88/386 (23%) for post-RP
142 EAU BCR low risk, high risk and BCP subgroups, and in 16/309 (5%) and 15/158 (10%)
143 for post-radiotherapy EAU BCR low and high risk subgroups, respectively. Visceral
144 metastases were detected in 3 to 6% for post-RP subgroups, and 16/309 (5%) as well as
145 15/158 (10%) for post-radiotherapy EAU BCR low and high risk subgroups, respectively.
146 The number of involved regions differed among the different risk groups. Three or more
147 involved metastatic regions were detected in 38/176 (22%), 287/931 (31%), 110/386
148 (29%) of post-RP EAU BCR low risk, high risk and BCP patients, as well as 102/309 (33%)
149 and 92/158 (58%) of post-radiotherapy EAU BCR low and high risk patients, respectively.

150 PSMA PET revealed no disease in 58/176 (33%), 275/931 (30%), and 85/386
151 (22%) of post RP EAU low risk, high risk and BCP subgroups. Post-radiotherapy
152 subgroups were PET negative in 20/309 (7%) low risk patients and 7/158 (4%) EAU BCR
153 high risk, respectively.

154 Figure 2B shows a Forest plot for odds ratios (OR) derived from multivariate
155 regression. Higher PSA levels, EAU BCR high risk (OR 2.91, 95%CI 2.18-3.93), and BCP
156 (OR 3.08, 95%CI 2.12-4.48) were significantly associated with PSMA PET M1 disease,
157 whereas type of initial therapy was not.

158

159 **DISCUSSION**

160 ^{68}Ga -PSMA-11 and ^{18}F -DCFPyL PET were recently approved by FDA based on
161 high accuracy for prostate cancer staging (5,11,14). Approval of PSMA-ligand PET is
162 expected to enable broad availability for staging BCR or BCP in the near future. Our
163 findings present a detailed map of disease extent in the EAU BCR risk groups or BCP.
164 Observed intra- and inter-group heterogeneities for PET stage come with important
165 implications for the EAU classification system.

166 At first, PSMA PET stratified EAU or BCP groups into relevant subgroups with
167 undetectable, locoregional, or distant metastatic disease. After RP, about one third of
168 patients stratified into each of these three subgroups, with somewhat higher rates for
169 metastatic disease in the BCR high risk or BCP patients. We present a single time point
170 assessment; however, PET stage was associated with time to progression in a previous
171 prospective study on BCR (10).

172 Recently, Dong et al. noted in a pooled analysis of 145 patients following
173 prostatectomy or radiotherapy, that EAU BCR high risk group was associated with a
174 higher PSMA-PET positivity rate (15). In this study, we assessed patients following
175 prostatectomy or radiotherapy separately, and found similar rates for PET positivity,
176 however higher rates for metastatic disease in patients with EAU high as compared to low
177 risk. In addition, PSMA PET identified subgroups with discordant findings for EAU risk
178 label versus PET stage: 30% post-RP EAU high risk patients had undetectable disease
179 whereas 24% low risk patients had metastatic disease, including 11% bone and 6%
180 visceral metastases. Discordant findings together with previous evidence by Emmett et al
181 indicate additional prognostic value of PSMA PET to be considered for future risk
182 assessment.

183 Second, disease extent detected by PSMA PET was higher in post-radiotherapy
184 versus RP patients: Post-radiotherapy EAU low risk patients yield PSMA PET M1 rates
185 similar to post-RP high risk or BCP. Strikingly, more than two thirds of post-radiotherapy
186 high risk patients had metastases, including bone metastases in 31.4% and visceral
187 metastases in 14.5%. In patients with EAU high risk, the incidence of M1 post-
188 radiotherapy was nearly twice that of post-RP; the rate of M1 visceral disease was more
189 than two times higher. Due to different BCR definitions, this can be attributed to higher
190 PSA values post-radiotherapy (Median 5.1 ng/mL, IQR 6.4) compared to the post-RP
191 group (Median 1.0 ng/mL, IQR 2.4). Accordingly, initial therapy was not a significant
192 predictor of metastatic disease in multivariate regression analysis with PSA levels
193 included. We assume that heterogeneous PSMA PET disease extent reflect clinical
194 reality, i.e. post-radiotherapy or -RP BCR risk groups will likely present different outcomes
195 despite sharing the same risk label. To account for these differences, PSA level as well
196 as RP/radiotherapy specific risk group nomenclature should be considered for risk
197 assessment. We confirm previously reported association of PSA with PSMA PET M1
198 disease. PSA level was a stronger predictor of the presence of M1 disease than EAU risk
199 groups. BCR or BCP states are defined using PSA kinetics without specific inclusion of
200 individual PSA values. However, in the transition phase with limited availability of PSMA
201 PET, PSA level will help identify patients at high risk who may benefit from PSMA PET
202 staging.

203

204 **CONCLUSION**

205 In summary, we demonstrate that men with high risk BCR according to EAU
206 Prostate Cancer Guidelines Panel and BCP have higher rates of metastatic disease.
207 Discordant subgroups, including metastatic disease in low risk and no disease in high risk
208 patients warrant inclusion of PSMA PET stage to refine risk assessment.

209

210 **DISCLOSURE**

211 JF has received fees from Eisai outside of the submitted work. WPF reports fees
212 from Calyx (consultant), RadioMedix (image review), Bayer (speakers bureau), and
213 Parexel (image review) outside of the submitted work. ME reports personal fees from Blue
214 Earth Diagnostics, Progenics Pharmaceuticals, Amgen, Parexel, Bayer and Point
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216 rhPSMA outside of the submitted work. KH reports personal fees from Bayer, personal
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218 from ABX, personal fees from Adacap, personal fees from Curium, personal fees from
219 Endocyte, grants and personal fees from BTG, personal fees from IPSEN, personal fees
220 from Siemens Healthineers, personal fees from GE Healthcare, personal fees from
221 Amgen, personal fees from Novartis, personal fees from ymabs, outside the submitted
222 work. JC is a cofounder and holds equity in Sofie Biosciences and Trethera Therapeutics.
223 Intellectual property patented by the University of California has been licensed to Sofie
224 Biosciences and Trethera Therapeutics. This intellectual property was not used in the
225 current study. JC is consultant for Blue Earth Diagnostics, Progenics
226 Radiopharmaceuticals, and Radiomedix, outside the submitted work. TAH is on a
227 consultancy or advisory board for Curium and Ipsen; performs research for Clovis

228 Oncology and Philips; and is a trial participant for Novartis and AAA. All others have
229 nothing to disclose.

230

231

232 **KEY POINTS**

233 QUESTION: Does the new EAU Risk classification identify distinct patterns of disease
234 spread in PSMA PET?

235 PERTINENT FINDINGS: In this multicentre, international study, including 1960 men with
236 biochemically recurrent (BCR) or persistent (BCP) prostate cancer, we found that EAU
237 high risk BCR and BCP was significantly associated with a higher risk of metastatic
238 disease in PSMA PET. However, PSMA PET also found patients with discordant patterns,
239 i.e. no detected disease in high risk patients and metastatic disease in low risk patients.

240 IMPLICATIONS FOR PATIENT CARE: PSMA PET validates the novel EAU BCR risk
241 classification. In addition, it may further refine risk assessment in this cohort.

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305 recurrent Prostate Cancer after radical Prostatectomy. *J Nucl Med.* 2021;In press.
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Table 1: Patient characteristics and PSMA PET stages

	Prostatectomy			Radiotherapy	
	EAU low risk (n=176)	EAU high risk (n=931)	Biochemical Persistence (n=386)	EAU low risk (n=309)	EAU high risk (n=158)
Age					
Median [IQR]	71 [9.3]	69 [9.1]	70 [12]	73 [9.6]	72 [9.1]
PSA					
< 0.5 ng/ml	60 (34.1%)	302 (32.4%)	69 (17.9%)	3 (1.0%)	2 (1.3%)
≥0.5 to <1.0 ng/ml	38 (21.6%)	178 (19.1%)	175 (45.3%)	4 (1.3%)	4 (2.5%)
≥1.0 to <2.0 ng/ml	20 (11.4%)	174 (18.7%)	43 (11.1%)	7 (2.3%)	5 (3.2%)
≥2.0 to <5.0 ng/ml	34 (19.3%)	159 (17.1%)	41 (10.6%)	134 (43.4%)	62 (39.2%)
≥5.0 ng/ml	24 (13.6%)	118 (12.7%)	58 (15.0%)	161 (52.1%)	85 (53.8%)
PSADT (months)					
Median [IQR]	20 [18]	4.2 [5.2]	4.5 [5.8]	8.5 [11]	4.1 [5.7]
Gleason Score					
6	30 (17.0%)	42 (4.5%)	17 (4.4%)	97 (31.4%)	2 (1.3%)
7	146 (83.0%)	507 (54.5%)	168 (43.5%)	212 (68.6%)	27 (17.1%)
8	-	168 (18.0%)	79 (20.5%)	-	55 (34.8%)
9-10	-	214 (23.0%)	122 (31.6%)	-	74 (46.8%)
IBF (months)					
Median [IQR]	83 [78]	44 [51]	34 [55]	88 [84]	41 [65]
Adjuvant RT after RP					
Adjuvant RT	50 (28.4%)	368 (39.5%)	78 (20.2%)	-	-
No adjuvant RT	126 (71.6%)	563 (60.5%)	308 (79.8%)	309 (100%)	158 (100%)
PSMA PET stage					
T0N0M0 (no disease)	58 (33.0%)	275 (29.5%)	85 (22.0%)	20 (6.5%)	7 (4.4%)
Tr/N1 M0 (locoregional)	75 (42.6%)	314 (33.7%)	147 (38.1%)	176 (57.0%)	41 (25.9%)
Any M1 (metastatic)	43 (24.4%)	342 (36.7%)	154 (39.9%)	113 (36.6%)	110 (69.6%)
M1 group					
M1a only	13 (7.4%)	102 (11.0%)	53 (13.7%)	49 (15.9%)	30 (19.0%)
Any M1b*	19 (10.8%)	201 (21.6%)	88 (22.8%)	48 (15.5%)	65 (41.1%)
Any M1c	11 (6.2%)	39 (4.2%)	13 (3.4%)	16 (5.2%)	15 (9.5%)
No. M1 regions					
0	133 (75.6%)	589 (63.3%)	232 (60.1%)	196 (63.4%)	48 (30.4%)
1-2	5 (2.8%)	55 (5.9%)	44 (11.4%)	11 (3.6%)	18 (11.4%)
≥3	38 (21.6%)	287 (30.8%)	110 (28.5%)	102 (33.0%)	92 (58.2%)

PSA = prostate specific antigen, IQR = inter quartile range, PSMA stages according to PROMISE criteria (13), * = not including M1c

Figure 1: Study flow chart

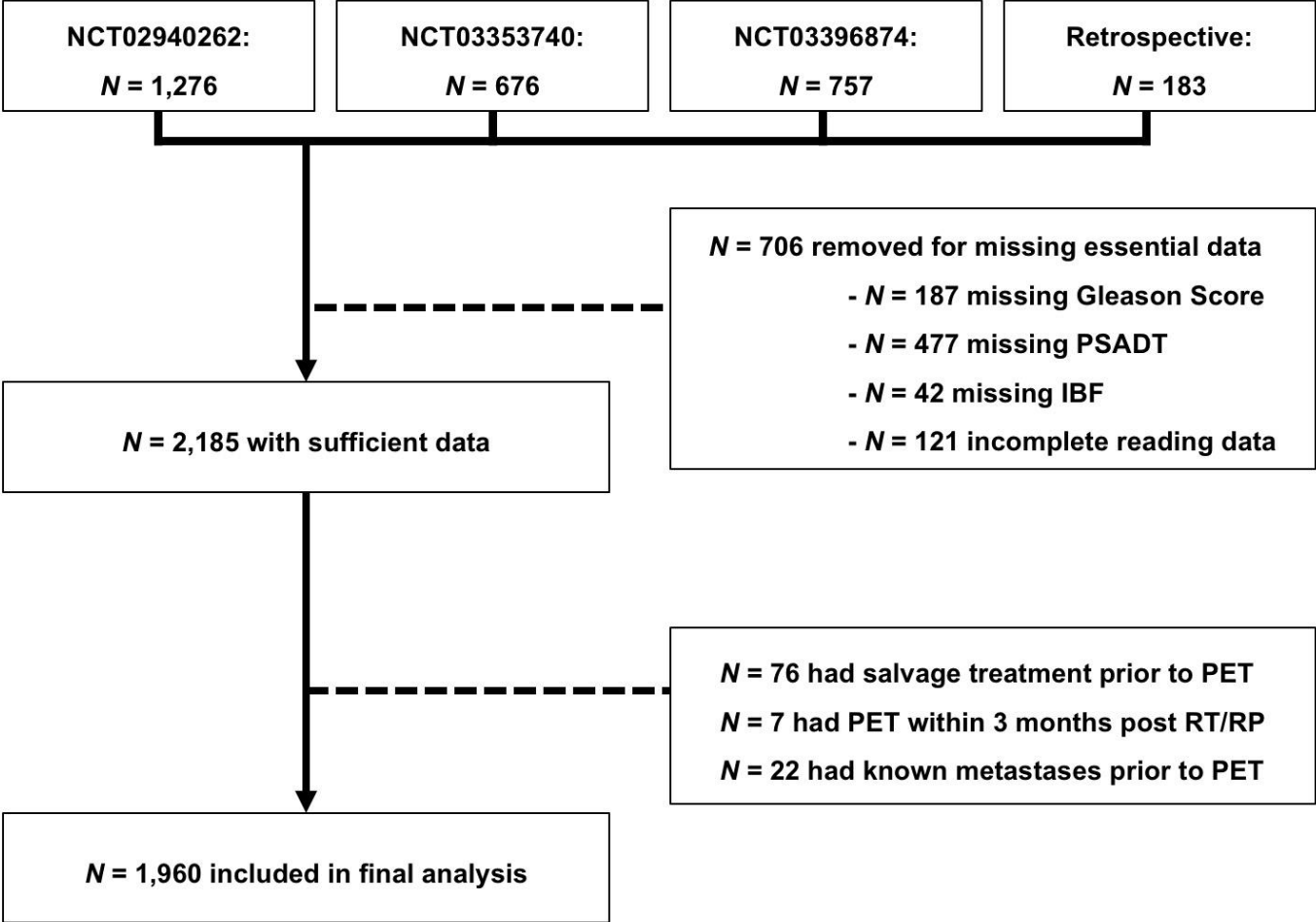
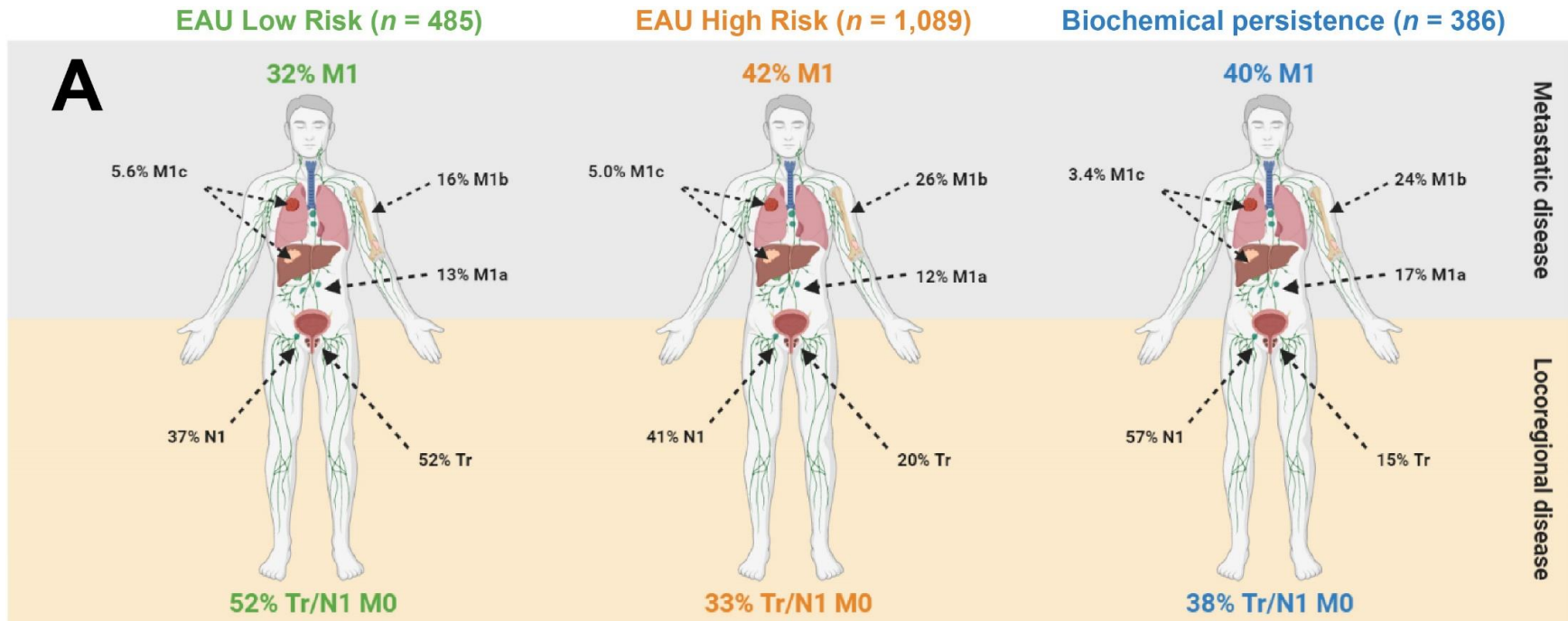
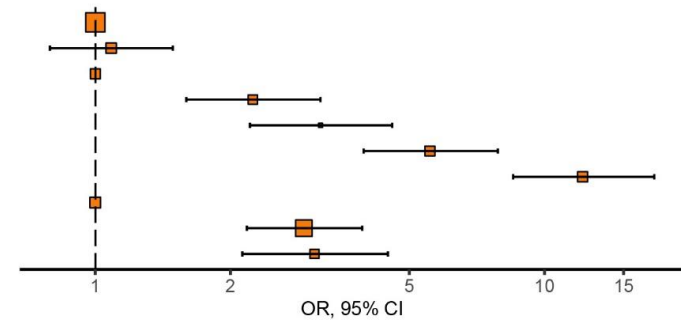


Figure 2: PET disease extent in EAU BCR low risk, high risk and in BCP patients (A) and predictors of PET M1 disease (B)



B

Category	group	no. M0 (%)	no. M1 (%)	OR (CI95)	P
Initial therapy	prostatectomy	954 (79.6)	539 (70.7)		Reference
	radiotherapy	244 (20.4)	223 (29.3)	1.08 (0.79-1.49)	P = 0.612
PSA	< 0.5 ng/ml	366 (30.6)	70 (9.2)		Reference
	≥ 0.5 to < 1.0 ng/ml	276 (23.0)	123 (16.1)	2.24 (1.59-3.17)	P < 0.001
	≥ 1.0 to < 2.0 ng/ml	154 (12.9)	95 (12.5)	3.17 (2.21-4.58)	P < 0.001
	≥ 2.0 to < 5.0 ng/ml	236 (19.7)	194 (25.5)	5.56 (3.96-7.87)	P < 0.001
Risk group	≥ 5.0 ng/ml	166 (13.9)	280 (36.7)	12.16 (8.52-17.55)	P < 0.001
	EAU low risk	329 (27.5)	156 (20.5)		Reference
	EAU high risk	637 (53.2)	452 (59.3)	2.91 (2.18-3.93)	P < 0.001
	Biochemical Persistence	232 (19.4)	154 (20.2)	3.08 (2.12-4.48)	P < 0.001



Graphical Abstract

EAU Low Risk ($n = 485$)

EAU High Risk ($n = 1,089$)

Biochemical persistence ($n = 386$)

