La radiologia medica (2026) 131:158–166
https://doi.org/10.1007/s11547-025-02107-7

RADIOTHERAPY

Oncological outcomes after tailored PSMA-PET-guided treatment in biochemical relapse after prostatectomy (PSICHE Trial—NCT 05022914)

Giulio Francolini[1] · Pietro Garlatti[1] · Vanessa Di Cataldo[1] · Saverio Caini[2] · Mauro Loi[1] · Gabriele Simontacchi[1] · Isacco Desideri[3] · Daniela Greto[1] · Luca Burchini[1] · Ilaria Bonaparte[1] · Giulio Frosini[1] · Sergio Serni[4] · Riccardo Campi[4] · Luca Vaggelli[5] · Niccolò Bertini[1] · Michele Aquilano[6] · Nicola Simoni[7] · Federico Colombo[7] · Ciro Franzese[8] · Marta Scorsetti[8] · Arturo Chiti[9] · Livia Ruffini[10] · Maria Rosaria Raspollini[11] · Mack Roach[12] · Richard K. Valicenti[13] · Lorenzo Livi[3]

Received: 8 April 2025 / Accepted: 20 September 2025 / Published online: 13 October 2025

Abstract

Background Next-generation imaging (NGI) (68 Ga-prostate-specific membrane antigen (PSMA)-PET) represents a cornerstone in biochemical recurrent prostate cancer management. PSICHE is a multicentric prospective study, aimed to assess oncological outcomes of a predefined tailored imaging-guided treatment.

Methods **P**atients with biochemical recurrence (BCR) after surgery (prostate-specific antigen [PSA] > 0.2 ≤ 1 ng/mL) underwent staging with PSMA-PET. A predefined treatment algorithm was proposed to all patients: prostate bed salvage radiotherapy (SRT) in case of negative or positive PET within the prostate bed, stereotactic body radiotherapy (SBRT) if pelvic nodal recurrences or oligometastatic disease were detected, and androgen deprivation therapy (ADT) was proposed in widespread polymetastatic disease. Chi-square test was used to evaluate the relationship between baseline features and the rate of positive PSMA-PET/CT.

Results One hundred and fifty-nine patients were enrolled. One hundred and seven patients had a PSMA negative/positive in the prostate bed; pelvic nodal disease or oligometastatic metastatic disease was detected in 39 and 10 patients, respectively. Three patients had a polymetastatic disease. Seventeen patients underwent observation because of prior postoperative radiotherapy (RT)/treatment refusal. Eighty-eight patients were treated with SRT, and SBRT was performed in 49 patients with pelvic or extrapelvic oligometastatic disease. Stratifying patients according to EAU criteria (low risk: PSA doubling time > 12 months and Gleason score < 8; high risk: PSA doubling time ≤ 12 months or Gleason score ≥ 8) after a median follow-up of 19 months in the overall population, median BRFS and MFS were not significantly different between the two risk subgroups (p = 0.58 and p = 0.21, respectively). Median metastasis-free and ADT-free survival were not reached.

Conclusions A PSMA-targeted treatment strategy led to promising results, avoiding unnecessary toxicity from ADT or standard SRT administered in unselected patients. Analysis after longer follow-up is needed to clarify survival outcomes.

Keywords Prostate cancer · PSMA-PET · SBRT

Introduction

In patients affected by prostate cancer, the rate of biochemical recurrence (BCR), defined as a detectable PSA level ≥ 0.2 ng/mL [1], after radical prostatectomy (RP) at 10 years is between 30 and 40% [2, 3]. Traditionally, treatment for BCR was guided by conventional imaging, and prostate bed salvage radiotherapy (SRT) remained the standard of care following BCR [4, 5]. However, conventional imaging has been associated with a poor detection rate in this scenario [6, 7], potentially leading to an inadequate treatment approach in patients with BCR without correct staging. Next-generation imaging (NGI) has been shown to significantly increase the detection rate in early BCR and may significantly affect treatment in this setting [8–10]. Current guidelines suggest to perform NGI based on prostate-specific membrane antigen (PSMA) or fluciclovine PET/CT,

Extended author information available on the last page of the article

due to their higher positivity rates, but there is no established standard option to tailor curative treatment on the basis of these imaging methods [11]. At the same time, modern treatment approaches based on metastasis-directed therapy (MDT) have been studied in prospective trials, with promising results in terms of oncological outcomes [12]. This highlights the need for prospective data assessing clinical outcomes after treatment approaches based on the integration between currently available imaging methods and MDT in the early BCR setting. For this reason, a prospective trial including BCR patients was designed, aiming to evaluate the use of 68 Ga-PSMA-11 PET/CT (PSMA-PET) within a metastasis-directed treatment framework. The "PSMA Guided Approach for bIoCHEmical Relapse After Prostatectomy-PSICHE" trial (NCT05022914) is a prospective observational trial testing a predefined treatment algorithm including both SRT and MDT via stereotactic body radiotherapy (SBRT) currently ongoing in three Italian centers. In this report, we present early clinical results after enrollment of the complete planned sample size, focusing on toxicity and biochemical outcomes.

Materials and methods

PSICHE (NCT05022914) is a multicenter prospective observational study. The trial oversight has been already published elsewhere [13] [14]. Briefly, patients with BCR after RP, defined as a PSA rise > 0.2 ng/ml, were enrolled in the trial and underwent [68 Ga] Ga-PSMA-11 PET/CT staging. Exclusion criteria consisted of PSA > 1 ng/ml, persistently elevated PSA (> 0.1 ng/ml) within 16 weeks after RP, previous SBRT for pelvic or extrapelvic disease, or ongoing androgen deprivation therapy (ADT) at enrollment. Postoperative ADT was allowed provided that patients were free from ADT for at least 6 months. All patients were treated with a predefined treatment algorithm according to PSMA results. Patients with negative imaging or positive findings within the prostate bed underwent SRT, if not previously received. Treatment intensification was allowed within site-specific study protocols [15, 16] if prostate bed macroscopic recurrence was detected, such as stereotactic SRT (e.g., 35 Gy in 5 fractions). When pelvic nodal recurrences or oligometastatic disease was detected (≤ 3 nodal or bone metastases), SBRT was performed, with doses and fractionations ranging between 24 and 45 Gy in 3–6 fractions [17] [18, 19]. ADT with or without androgen receptor-targeted agent (ARTA) was provided in all cases of widespread metastatic disease (> 3 nodal or bone metastases, presence of visceral disease). For patients who previously received postoperative prostate bed RT, observation and PSMA-PET/CT restaging at further PSA progression was provided in case of negative imaging or positive imaging within the prostate bed. Salvage retreatment (e.g., SBRT for a total dose of 30 Gy in 5 fractions) could be proposed according to clinical decision [20]. After treatment, a biochemical response was defined as a PSA decline > 50% when compared to baseline; a PSA ≤ 0.2 ng/ml was defined as complete biochemical response. Patients were followed with clinical assessment, gastrointestinal (GI) and genitourinary (GU) adverse event reporting and PSA every 3 months after treatment for the first year, and every 6 months thereafter. Biochemical progression is defined as the date in which a PSA increase above 0.2 ng/ml for patients with a PSA nadir ≤ 0.2 ng/ml or two consecutive PSA increases > 25% when compared to nadir in patients with a PSA nadir > 0.2 ng/ml is detected. Patients were re-staged with PSMA-PET/CT when biochemical recurrence was detected. Adverse events were classified according to CTCAE v 4.03. A first interim analysis was planned after reaching the complete sample size enrollment in order to reliably evaluate PSMA detection rate in this cohort and provide data about early biochemical outcomes. Kaplan–Meier analysis was used to compare biochemical relapse-free survival (BRFS) and metastasis-free survival (MFS) in patients affected by low- vs high-risk biochemical recurrence defined according to European Urology Association criteria (low risk: PSA doubling time > 1 year AND ISUP score < 4, high risk: PSA doubling time < 1 year OR ISUP score > 4) [22]. In terms of safety profile, comparing SRT and SBRT, the protocol was approved by local ethical committee (Comitato Etico Area Vasta Centro).

Results

Population

Overall, 159 patients have been enrolled in three Italian centers. Baseline population features are summarized in Table 1.

Staging outcomes and subsequent management

Overall, PSMA-PET was found negative or positive within the prostate bed in 107 patients (67.3%). Pelvic nodal disease or oligometastatic recurrence was found in 39 (24.5%) and 10 (6.3%) patients, respectively. Three patients were found to have polymetastatic disease.

After staging, SRT, observation, or retreatment were proposed in 91 (3 refused), 14, and 2 patients, respectively. SBRT was performed in 49 patients for pelvic or extrapelvic oligometastatic disease. Upfront ADT alone was administered in three patients with widespread metastatic disease

Table 1 Main baseline features

Baseline population features	N (%)
Pts	159
TNM	
pT2	43 (27%)
pT3	111 (70%)
unknown	5 (3%)
pN0	101 (63,5%)
pN1	12 (7,5%)
pNx	46 (29%)
Gleason score at diagnosis	
6	7 (4,4%)
7	89 (56%)
8	32 (20,1%)
9	23 (14,5%)
unknown	8 (5%)
Previous salvage radiotherapy	
Yes	43 (27%)
No	116 (73%)
Median PSA value at BCR (range)	0,49 (0,20—0,27)
Group Risk	
low risk	78 (49%)
high risk	81 (51%)
PET PSMA results	
Negative/positive findings within the prostate bed	107 (67,3%)
Pelvic nodal persistence	39 (24,5%)
Abdominal nodal or bone oligometastatic disease	10 (6,3%)
Abdominal nodal or bone metastatic disease and/or visceral disease	3 (1,9%)
Number of lesions	
0 or prostate bed only	101 (63,5%)
1	43 (27,1%)
2	10 (27,1%)
3	2 (1,2%)
> 3	3 (1,9%)
Lesion site	
None or prostate bed only	108 (67%)
Nodal	40 (25%)
Bone	12 (7,4%)
Visceral	1 (0,6%)
Proposed treatment	
SRT	91 (57,2%)
Retreatment	2 (1,2%)
SBRT	49 (30,8%)
Observation	14 (8,8%)
ADT	3 (1,9%)

BRC: biochemical recurrence; SRT: salvage radiotherapy; stereotactic body radiotherapy; ADT: antiandrogen therapy

(Fig. 1). No ARTA treatment was provided due to limitations in reimbursement within the enrollment period in the treating institutions. Except for three patients refusing SRT, all patients underwent the proposed treatment as per protocol.

Biochemical response and survival outcomes

Only patients who underwent active treatment were included in the analysis of biochemical response rates. Seventeen patients undergoing observation or who refused SRT after staging were excluded from this analysis. After three months, biochemical response and complete biochemical response were detected in 84 and 77 out of 142 patients (59.1% and 54.2%), respectively. Excluding 3 pts who were treated with ADT, the rate of biochemical response and complete biochemical response remained similar (58.2% and 53.2%, respectively). After SRT, biochemical response and complete biochemical response were achieved by 73.9% and 68% of patients receiving treatment. After SBRT, biochemical response and complete biochemical response were reported in 53% and 28.6% of patients treated, respectively. After a median follow-up of 19 months, 53 had a biochemical recurrence, of whom 29 were found positive for new metastatic sites at following PSMA imaging. According to EAU criteria, patients were affected by low- or high-risk BCR in 78 and 81 cases, respectively. Of these, biochemical progression after treatment was reported in 29 and 24 patients, respectively, while metastasis occurrence was detected in 12 and 18 cases. Considering the impact of baseline risk features at biochemical recurrence in the overall population, median BRFS and MFS were not significantly different between low- and high-risk BCR subgroups ($p = 0.58$ and $p = 0.21$, respectively) (Fig. 2 and 3). Fifteen patients started ADT, and 14 received a new course of SBRT for oligoprogressive disease. Median estimated BRFS was 28 months (95% CI 21–63 months). Median metastasis-free survival and ADT-free survival were not reached. Among patients with negative PSMA-PET treated with SRT, median BFRS was 63 months; median MFS and ADT-free survival were not reached. In patients treated with SBRT, median BRFS and metastasis-free survival were 20 and 22 months, and median ADT-free survival was not reached.

Safety

Overall, acute GI and GU adverse events were reported in 13 and 38 patients, respectively. All acute adverse events were G1 except for 4 G2 GU events. Late GI and GU adverse events were reported in 4 and 29 cases, respectively. $G \geq 2$

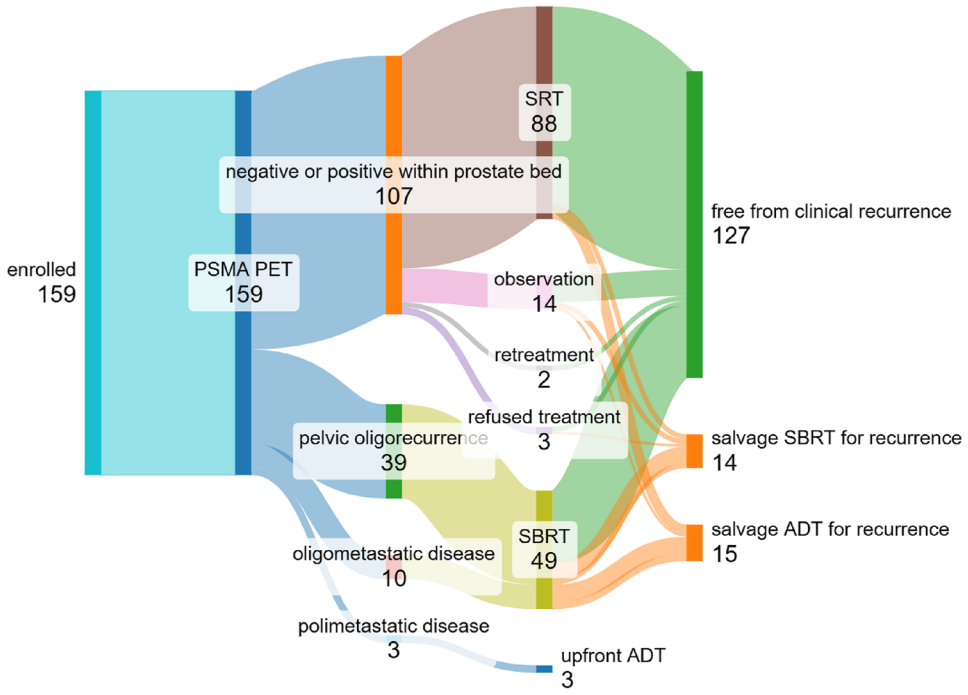

Fig. 1 Sankey diagram depicting diagnostic and treatment workflow of the enrolled population

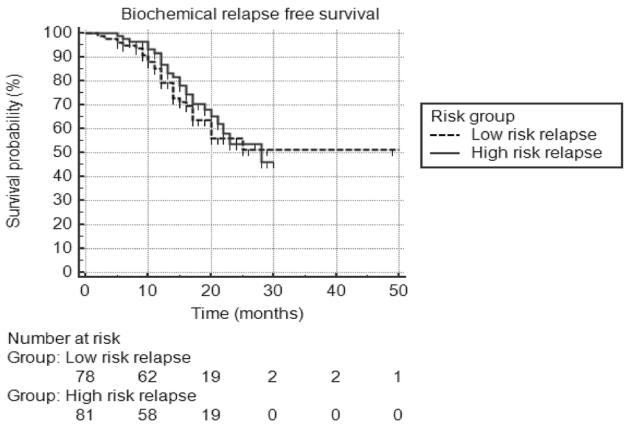

Fig. 2 Biochemical relapse-free survival in low- vs high-risk BCR patients

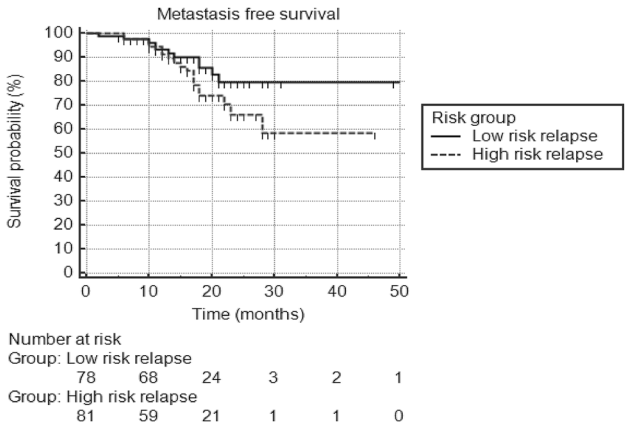

Fig. 3 Metastasis-free survival in low- vs. high-risk BCR patients

late GI and GU toxicity was reported in 1 and 5 cases, respectively. Considering only patients undergoing SRT, 11 and 31 acute GI and GU adverse events were reported (1 and 4 G2, respectively), while 4 and 25 late GI and GU adverse events were reported (1 and 3 G2, respectively). Considering the SBRT population, acute GI and GU adverse events were reported in 2 and 7 patients (all G1), while late toxicity was reported only in two G1 and GU cases. Significant benefit in terms of acute and late GU toxicity was found when comparing SBRT and SRT populations, in favor of SBRT ($p = 0.01$ and $p = 0.005$, respectively), while no significant difference was found for acute or late GI toxicity (Table 2). No G4 or 5 was registered in the overall population; only one late G3 GU event was observed.

In synthesis, PSMA-PET/CT was found positive in 30% of patients affected by early BCR. The predefined treatment algorithm provided promising biochemical outcomes. Moreover, more than half of the population was free from ADT or metastases at the end of follow-up, suggesting a promising clinical benefit of a PSMA tailored approach. Interestingly, BRFS and MFS did not differ between low- and high-risk BCR subgroups, underlining that correct patient selection may counterbalance the negative impact of adverse prognostic features. Finally, safety analysis underscored the potential benefit in

Table 2 Summary of main adverse events reported

Acute Toxicity	Any grade	G1	G2	G3	G4	G5
GI	13	13	0	0	0	0
GU	38	34	4	0	0	0
Late Toxicity	**Any grade**	**G1**	**G2**	**G3**	**G4**	**G5**
GI	4	3	1	0	0	0
GU	29	24	4	1	0	0

GI = gastronintestinal; GU = genitorinary

terms of adverse events of the tested treatment strategy when compared to standard SRT performed in a framework avoiding pretreatment PSMA staging; of note is the favorable GU toxicity profile for the SBRT treatment and the absence of G3 or major adverse events with this therapeutic approach.

Discussion

PSICHE (NCT05022914) is one of the first prospective trials integrating a tailored treatment approach consisting of SRT, SBRT, or ADT according to PSMA-PET/CT imaging results in early BR after RP. First, these patients would have been probably treated with standard SRT with or without ADT in the pre-NGI era, or upfront ADT alone in cases previously managed with postoperative SRT. This underlines how PSMA imaging changed the clinical approach in all those patients undergoing SBRT, observation alone, or retreatment on local macroscopic recurrence in a previously irradiated prostate bed (40.9% of the overall cohort). After tailored treatment, the results of the current analysis show that an early biochemical response is achieved by a consistent percentage of patients after treatment, regardless of ADT prescription. Moreover, clinical outcomes are encouraging, with 81.8% and 88.7% of patients free from metastases and ADT after 19 months of median follow-up. Interestingly, all patients underwent a new PSMA-PET/CT restaging at further PSA recurrence; thus, the results of the current analysis should be considered in light of the sensitivity of imaging performed and do provide important information regarding freedom from clinical recurrence after treatment in the NGI era. At the same time, patients undergoing tailored treatment based on PSMA results (e.g., SBRT on oligorecurrence) spared the toxicity given by ADT and SRT. Of note, clinical outcomes in this series were comparable in patients with low- and high-risk biochemical recurrence. This is of particular interest considering that the EAU prostate guidelines panel recommends stratifying patients in these two risk categories based on the different rates of disease progression on imaging [21] and Tilki et al. further validated this classification, showing that 5 years of MFS was significantly improved in patients with low- vs. high-risk BCR [22]. However, this stratification was proposed outside a NGI-based framework, where high-risk patients may have experienced less benefit from salvage treatment after prostatectomy due to undetected disease. This is recommended by recent guidelines, even if the following management is unclear due to the lack of prospective studies in this scenario [11]. Nonetheless, the EAU classification was recently validated as well in patients undergoing NGI and conventional salvage radiotherapy, underlining its importance even in an actual clinical scenario including modern imaging and confirming its prognostic impact in patients in whom a PSMA conventional SRT was planned [23]. Conversely, patients included in the PSICHE trial had similar treatment outcomes regardless of their baseline EAU risk classification, underlining how a tailored treatment approach may counterbalance the effect of these prognostic features. From this point of view, the predefined treatment algorithm used provided promising results when compared to standard salvage treatment, allowing to integrate the modern imaging and minimally invasive RT and overcome the prognostic effect of EAU risk classification. Of course, these results still have to be validated after longer-term follow-up. In terms of the rate of PSMA-PET/CT positivity, results from the current analysis confirm a larger retrospective dataset published by Zamboglou et al., reporting a similar percentage of patients with PSMA-detected pelvic oligorecurrence at BCR after RP (30.4%) [24]. Interestingly, 38.4% and 31.6% of patients included in that series received elective nodal radiotherapy and concomitant ADT, respectively. However, despite the treatment intensification, pre-SRT-positive PSMA scan persisted as a predictive factor for freedom from biochemical recurrence, prompting the development of tailored treatment strategies for these patients. OLI-P was a trial investigating the role of ablative RT in patients with positive PSMA imaging. Results are consistent with our data and confirm promising outcomes after local treatment, with 20 months of freedom from ADT [25]. Nonetheless, PSICHE and OLI-P are not directly comparable due to the presence of patients with negative PSMA imaging in the present cohort receiving SRT, which may have influenced our results. The role of concurrent ADT and radiotherapy in recurrent PCa is a topic of debate. For patients undergoing SRT, 24 months of ADT showed significant improvement in time to salvage ADT and MFS when compared to short-course ADT within the

RADICALS-HD trial [26]. However, within the three-arm comparison of the same study, patients indicated for SRT derived no significant benefit from no, short-term, or long-term ADT [27]. Consistently with these data, no benefit after the addition of 6 months of ADT was detected in the two-arms comparison (short vs. no ADT) [28]. For these reasons, we believe that a selected cohort of patients with negative postoperative PSA and undergoing systematic NGI staging before treatment could be reasonably managed with SRT only avoiding concomitant ADT within the PSICHE trial.

Regarding the oligometastatic cohort of patients included within this study, RADIOSA trial recently demonstrated that 6 months of ADT added to SBRT in oligometastatic hormone-sensitive Pca improved PFS compared to SBRT alone [29]. Nonetheless, there is still a significant percentage of oligometastatic patients potentially taking advantage from SBRT alone as reported by recent meta-analyses; Miszcyk et al. observed an estimated 2-year local control, ADT-free survival and OS of 97%, 55%, and 97%, respectively [30]. Various pivotal trials have been recently published in the context of non-metastatic biochemical recurrence. EMPIRE-1 is a trial testing the benefit of an NGI-based tailored treatment strategy in this setting. Patients enrolled in EMPIRE trial were randomly assigned in a 1:1 ratio to radiotherapy directed by conventional imaging alone or to conventional imaging plus ^{18}F-fluciclovine-PET/CT. Results suggested a clinical benefit for patients undergoing fluciclovine imaging. However, provided treatment was limited to prostate bed radiotherapy with or without elective nodal treatment according to staging results and did not provide any form of local therapy for oligometastatic patients [29]. In the field of metabolic imaging, other tracers such as choline-PET had a role for assessing patients with BR after prostatectomy with a better accuracy than conventional imaging, but only for higher PSA levels (e.g., > 1,2 ng/ml)[30].

RTOG 0534 trial enrolled patients with a rising PSA below 2 ng/ml post-RP, randomized to prostate bed radiotherapy, prostate bed radiotherapy plus short-course ADT, or prostate bed and elective pelvic radiotherapy plus short-course ADT, after a radiologic conventional staging. NGI was not included. Results of RTOG 0534 trial suggested a significant benefit in terms of progression-free survival for patients receiving elective nodal radiotherapy and short-course ADT [31]. Many advocates for elective nodal treatment could argue that outcomes in the enrolled population may have been improved by providing whole pelvis radiotherapy and short-course ADT in all patients affected by pelvic recurrences, based on RTOG 0534 data. However, it should be noted that the RTOG trial population probably included patients affected by baseline worse prognosis, considering that an early recurrence or postprostatectomy persistence was reported in 26% of cases. Conversely, PSA persistence was one of the formal exclusion criteria of the current series, allowing to select patients with slow-growing, indolent disease that could be effectively treated with metastasis-directed therapy for pelvic recurrence. Moreover, patients included in the RTOG 0534 trial did not undergo NGI, which was the required baseline imaging within the PSICHE trial. Indeed, even if longer follow-up is needed to corroborate present results, 127 out of 159 patients were free from clinical recurrence at the end of the follow-up, and 14 out of 29 clinical recurrences detected could have been safely treated with a new SBRT course. EMBARK trial enrolled patients with BR after definitive treatment, randomized to receive standard ADT, concomitant ADT and enzalutamide, or enzalutamide alone. Overall, patients randomized to experimental treatment regimens containing enzalutamide performed better in terms of metastasis-free survival, indicating that intensified hormonal treatment with ARTA may play an important role in these patients [32]. However, it should be noted that NGI was not provided for patients enrolled in EMBARK trial and that these results are not directly applicable to current clinical practice. Moreover, EMBARK inclusion criteria consisted of a PSA > 1 ng/ml and a PSA doubling time < 9 months in postprostatectomy patients. Again, patients included within the PSICHE trial were affected by biochemical recurrence with more favorable prognostic features and may need a different approach when compared to the intensified treatment proposed (e.g., whole pelvis RT and concomitant short-course ADT or early ARTA administration). Indeed, we advocate for an adequate treatment tailoring based on modern imaging and treatment options, selecting the right candidates for local treatment (e.g., SRT or SBRT for oligometastatic recurrence) or systemic therapy (ADT with or without ARTA for widespread disease). From this point of view, the PSICHE trial is a prospective platform aimed to exploit potential advantage of a hybrid treatment strategy. The predefined treatment algorithm involved conventional SRT for patients with a high likelihood of cure due to PSMA-PET/CT negative imaging, SBRT for oligometastatic patients, and early systemic treatment for those in whom metastasis-directed therapy may have a low likelihood of benefit. In summary, the purpose of the proposed workflow is to maximize all advantages of each available approach. Of note, the correct management of isolated pelvic oligorecurrence is an area of open debate. The comparison between MDT and ENRT in pelvic nodal recurrence is still a matter of discussion. A multi-institutional retrospective analysis by De Bleser et al. found that ENRT provided significant MFS improvement in patients with a single nodal recurrence ($p = 0.009$), while the nodal recurrence rate was increased in the SBRT group ($p < 0.001$). However, no significant differences in bone, prostate, or visceral progression were detected [33]. Recent published

data from the PEACE V-STORM trial, comparing ENRT and MDT in patients with a PET-detected pelvic nodal oligorecurrence, suggested significant MFS improvement with no clinically meaningful differences in terms of acute GI or GU toxicity or in quality-of-life subdomains after ENRT. Of note, more than 90% of patients included within the PEACE V-STORM trial were affected by high-risk BCR, and 29% of SBRT patients could be still managed with a subsequent MDT course after recurrence. Thus, selected pelvic oligorecurrent patients affected by low-risk BCR may still benefit from MDT [34]. Moreover, the overall survival benefit of whole pelvis radiotherapy will be the object of the RTOG 0924 trial, directly comparing patients affected by prostate cancer undergoing definitive prostate radiotherapy with or without elective nodal treatment (NCT01368588). It is interesting to note that, in our cohort, there is no difference in BRFS and MFS between low- and high-risk BCR subgroups, probably due to the limited follow-up; therefore, a longer follow-up will be necessary to be confirmed and compared to previous pivotal trials.

Conclusions

PSICHE trial (NCT05022914) provided important insights about tailored treatment after PSMA imaging in patients affected by early BR. Overall, a tailored treatment strategy seems to provide optimal clinical outcomes avoiding unnecessary toxicity from ADT or standard SRT administered in unselected patients. Longer follow-up of patients enrolled in this trial could confirm the efficacy of a tailored and minimally invasive treatment approach for a selected cohort of patients affected by biochemical recurrence with favorable prognostic features (PSA < 1 ng/ml, absence of PSA persistence after surgery).

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Giulio Francolini, Pietro Garlatti, and Vanessa Di Cataldo. The first draft of the manuscript was written by Giulio Francolini, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Giulio Francolini, Vanessa Di Cataldo, and Lorenzo Livi contributed to conceptualization. Saverio Caini and Giulio Francolini contributed to methodology. Niccolò Bertini, Giulio Frosini, Luca Burchini, and Ilaria Bonaparte contributed to data curation.Saverio Caini contributed to formal analysis and investigation. Pietro Garlatti and Giulio Francolini contributed to writing—original draft preparation. Mauro Loi, Gabriele Simontacchi, Isacco Desideri, and Daniela Greto contributed to validation. Prof. Sergio Serni, Riccardo Campi, Luca Vaggelli, Nicola Simoni, Federico Colombo, Ciro Franzese, Prof. Marta Scorsetti, Arturo Chiti, Livia Ruffini, Maria Rosaria Raspollini contributed to visualization. Prof. Mack Roach III and Prof. Richard K. Valicenti supervised the study.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Declarations

Competing Interests The authors have no relevant financial or non-financial interests to disclose. Prof. Lorenzo Livi and Prof. Isacco Desideri are editors in this Journal.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Comitato Etico Area Vasta Centro Prot.: 6787 del 19/03/2021.

References

1. Pisansky TM, Thompson IM, Valicenti RK, D'Amico AV, Selvarajah S (2019) Adjuvant and salvage radiotherapy after prostatectomy: ASTRO/AUA guideline amendment 2018–2019. J Urol 202(3):533–538. https://doi.org/10.1097/JU.0000000000000295
2. Han M, Partin AW, Pound CR, Epstein JI, Walsh PC. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. *Urol Clin North Am*. 2001;28(3):555–565. https://doi.org/10.1016/s0094-0143(05)70163-4
3. Amling CL, Blute ML, Bergstralh EJ, Seay TM, Slezak J, Zincke H (2000) Long-term hazard of progression after radical prostatectomy for clinically localized prostate cancer: continued risk of biochemical failure after 5 years. J Urol 164(1):101–105
4. Thompson IM, Valicenti RK, Albertsen P et al (2013) Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO guideline. J Urol 190(2):441–449. https://doi.org/10.1016/j.juro.2013.05.032
5. Tendulkar RD, Agrawal S, Gao T et al (2016) Contemporary update of a multi-institutional predictive nomogram for salvage radiotherapy after radical prostatectomy. J Clin Oncol 34(30):3648–3654. https://doi.org/10.1200/JCO.2016.67.9647
6. De Visschere PJL, Standaert C, Fütterer JJ et al (2019) A systematic review on the role of imaging in early recurrent prostate cancer. Eur Urol Oncol 2(1):47–76. https://doi.org/10.1016/j.euo.2018.09.010
7. Miyake M, Tanaka N, Asakawa I et al (2019) The impact of the definition of biochemical recurrence following salvage radiotherapy on outcomes and prognostication in patients with recurrent prostate cancer after radical prostatectomy: a comparative study of three definitions. Prostate Int 7(2):47–53. https://doi.org/10.1016/j.prnil.2018.04.005
8. Hofman MS, Lawrentschuk N, Francis RJ et al (2020) Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 395(10231):1208–1216. https://doi.org/10.1016/S0140-6736(20)30314-7
9. Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al. Diagnostic performance of ^{68}Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients [published correction appears in Eur J Nucl Med Mol Imaging. 2017 Sep;44(10):1781. https://doi.org/10.1007/s00259-017-3763-8]. Eur J Nucl Med Mol Imaging. 2017;44(8):1258–1268. https://doi.org/10.1007/s00259-017-3711-7

10. Calais J, Ceci F, Eiber M, et al. ^{18}F-fluciclovine PET-CT and ^{68}Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial [published correction appears in Lancet Oncol. 2019 Nov;20(11):e613. https://doi.org/10.1016/S1470-2045(19)30593-5] [published correction appears in Lancet Oncol. 2020 Jun;21(6):e304. https://doi.org/10.1016/S1470-2045(20)30279-5]. *Lancet Oncol*. 2019;20(9):1286–1294. https://doi.org/10.1016/S1470-2045(19)30415-2
11. Cornford P, van den Bergh RCN, Briers E et al (2021) EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II-2020 update: treatment of relapsing and metastatic prostate cancer. Eur Urol 79(2):263–282. https://doi.org/10.1016/j.eururo.2020.09.046
12. Deek MP, Van der Eecken K, Sutera P et al (2022) Long-term outcomes and genetic predictors of response to metastasis-directed therapy versus observation in oligometastatic prostate cancer: analysis of STOMP and ORIOLE trials. J Clin Oncol 40(29):3377–3382. https://doi.org/10.1200/JCO.22.00644
13. Francolini G, Banini M, Di Cataldo V et al (2023) PSMA guided approach for biochemical relapse after prostatectomy- (PSICHE) trial (NCT05022914). Detection rate and treatment decision after 68Ga-PSMA PET/CT within a prospective study. Prostate 83(12):1201–1206. https://doi.org/10.1002/pros.24579
14. Francolini G, Ganovelli M, Di Cataldo V et al (2023) Early biochemical outcomes following PSMA guided approach for bIOCHemical relapse after prostatectomy-PSICHE trial (NCT05022914): preliminary results. Clin Exp Metastasis 40(2):197–201. https://doi.org/10.1007/s10585-023-10204-y
15. Francolini G, Jereczek-Fossa BA, Di Cataldo V et al (2022) Stereotactic or conventional radiotherapy for macroscopic prostate bed recurrence: a propensity score analysis. Radiol Med 127(4):449–457. https://doi.org/10.1007/s11547-022-01465-w
16. Francolini G, Jereczek-Fossa BA, Di Cataldo V et al (2020) Stereotactic radiotherapy for prostate bed recurrence after prostatectomy, a multicentric series. BJU Int 125(3):417–425. https://doi.org/10.1111/bju.14924
17. Ost P, Reynders D, Decaestecker K et al (2018) Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. J Clin Oncol 36(5):446–453. https://doi.org/10.1200/JCO.2017.75.4853
18. Phillips R, Shi WY, Deek M et al (2020) Outcomes of observation vs stereotactic ablative radiation for oligometastatic Prostate cancer: the ORIOLE phase 2 randomized clinical trial. JAMA Oncol 6(5):650–659. https://doi.org/10.1001/jamaoncol.2020.0147
19. Zilli T, Achard V et al (2022) Recommendations for radiation therapy in oligometastatic prostate cancer: an ESTRO-ACROP delphi consensus. Radiother Oncol 176:199–207. https://doi.org/10.1016/j.radonc.2022.10.005
20. Francolini G, Loi M, Di Cataldo V et al (2022) Stereotactic re-irradiation in recurrent prostate cancer after previous postoperative or definitive radiotherapy: long-term results after a median follow-up of 4 years. Clin Oncol (R Coll Radiol) 34(1):50–56. https://doi.org/10.1016/j.clon.2021.11.002
21. Van den Broeck T, van den Bergh RCN, Briers E et al (2020) Biochemical recurrence in prostate cancer: the European association of urology prostate cancer guidelines panel recommendations. Eur Urol Focus 6(2):231–234. https://doi.org/10.1016/j.euf.2019.06.004
22. Tilki D, Preisser F, Graefen M, Huland H, Pompe RS (2019) External validation of the European Association of Urology biochemical recurrence risk groups to predict metastasis and mortality after radical prostatectomy in a European cohort. Eur Urol 75(6):896–900. https://doi.org/10.1016/j.eururo.2019.03.016
23. Scharl S, Zamboglou C, Strouthos I et al (2024) European association of urology risk stratification predicts outcome in patients receiving PSMA-PET-planned salvage radiotherapy for biochemical recurrence following radical prostatectomy. Radiother Oncol 194:110215. https://doi.org/10.1016/j.radonc.2024.110215
24. Zamboglou C, Peeken JC, Janbain A et al (2023) Development and validation of a multi-institutional nomogram of outcomes for PSMA-PET-based salvage radiotherapy for recurrent prostate cancer. JAMA Netw Open 6(5):e2314748. https://doi.org/10.1001/jamanetworkopen.2023.14748
25. Hölscher T, Baumann M, Kotzerke J et al (2022) Local control after locally ablative, image-guided radiotherapy of oligometastases identified by Gallium-68-PSMA-positron emission tomography in castration-sensitive prostate cancer patients (OLI-P). Cancers (Basel) 14(9):2073. https://doi.org/10.3390/cancers14092073
26. Parker CC, Amos C et al (2024) Duration of androgen deprivation therapy with postoperative radiotherapy for prostate cancer: a comparison of long-course versus short-course androgen deprivation therapy in the RADICALS-HD randomised trial. Lancet 403(Issue 10442):2416–2425
27. Parker CC, Clarke NW et al (2024) Randomised trial of no, short-term, or long-term androgen deprivation therapy with postoperative radiotherapy after radical prostatectomy: results from the three-way comparison of RADICALS-HD (NCT00541047). Eur Urol 86(5):422–430. https://doi.org/10.1016/j.eururo.2024.07.026
28. Parker CC, Clarke NW et al (2024) Adding 6 months of androgen deprivation therapy to postoperative radiotherapy for prostate cancer: a comparison of short-course versus no androgen deprivation therapy in the RADICALS-HD randomised controlled trial. Lancet 1(10442):2405–2415. https://doi.org/10.1016/S0140-6736(24)00548-8
29. Marvaso G, Corrao G et al (2025) ADT with SBRT versus SBRT alone for hormone-sensitive oligorecurrent prostate cancer (RADIOSA): a randomised, open-label, phase 2 clinical trial. Lancet Oncol 26(3):300–311. https://doi.org/10.1016/S1470-2045(24)00730-7
30. Miszczyk M, Rajwa P et al (2024) The efficacy and safety of metastasis-directed therapy in patients with prostate cancer: a systematic review and meta-analysis of prospective studies. Eur Urol 85(2):125–138. https://doi.org/10.1016/j.eururo.2023.10.012
31. Jani AB, Schreibmann E, Goyal S et al (2021) ^{18}F-fluciclovine-PET/CT imaging versus conventional imaging alone to guide postprostatectomy salvage radiotherapy for prostate cancer (EMPIRE-1): a single centre, open-label, phase 2/3 randomised controlled trial. Lancet 397(10288):1895–1904. https://doi.org/10.1016/S0140-6736(21)00581-X
32. Detti B, Carnevale MG et al (2023) Choline PET/CT in recurrent prostate cancer. Front Oncol 13:1079808. https://doi.org/10.3389/fonc.2023.1079808
33. Pollack A, Karrison TG, Balogh AG et al (2022) The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial. Lancet 399(10338):1886–1901. https://doi.org/10.1016/S0140-6736(21)01790-6
34. Freedland SJ, de Almeida Luz M, De Giorgi U et al (2023) Improved outcomes with enzalutamide in biochemically recurrent prostate cancer. N Engl J Med 389(16):1453–1465. https://doi.org/10.1056/NEJMoa2303974
35. De Bleser E, Jereczek-Fossa BA et al (2019) Metastasis-directed therapy in treating nodal oligorecurrent prostate cancer: a multi-institutional analysis comparing the outcome and toxicity of stereotactic body radiotherapy and elective nodal radiotherapy. Eur Urol 76(6):732–739. https://doi.org/10.1016/j.eururo.2019.07.009
36. Ost P, Siva S et al (2025) Salvage metastasis-directed therapy versus elective nodal radiotherapy for oligorecurrent nodal prostate cancer metastases (PEACE V-STORM): a phase 2, open-label, randomised controlled trial. Lancet Oncol 26(6):695–706. https://doi.org/10.1016/S1470-2045(25)00197-4

Authors and Affiliations

Giulio Francolini[1] · Pietro Garlatti[1] · Vanessa Di Cataldo[1] · Saverio Caini[2] · Mauro Loi[1] · Gabriele Simontacchi[1] · Isacco Desideri[3] · Daniela Greto[1] · Luca Burchini[1] · Ilaria Bonaparte[1] · Giulio Frosini[1] · Sergio Serni[4] · Riccardo Campi[4] · Luca Vaggelli[5] · Niccolò Bertini[1] · Michele Aquilano[6] · Nicola Simoni[7] · Federico Colombo[7] · Ciro Franzese[8] · Marta Scorsetti[8] · Arturo Chiti[9] · Livia Ruffini[10] · Maria Rosaria Raspollini[11] · Mack Roach[12] · Richard K. Valicenti[13] · Lorenzo Livi[3]

✉ Pietro Garlatti
pietro.garlatti@gmail.com

1 Radiation Oncology Unit, Azienda Ospedaliero-Universitaria Careggi, Largo Brambilla, 50134 Florence, Italy

2 Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy

3 Department of Biomedical, Experimental and Clinical Sciences ''Mario Serio'', University of Florence, Florence, Italy

4 Unit of Urological Robotic Surgery and Renal Transplantation, nd Department of Experimental and Clinical Medicine, University of Florence, Careggi Hospital, Florence, Italy

5 Nuclear Medicine Division, Careggi University Hospital, Florence, Italy

6 Cyberknife Center, Istituto Fiorentino Di Cura Ed Assistenza (IFCA), University of Florence, Florence, Italy

7 Radiotherapy Unit, Azienda Ospedaliera Universitaria, Parma, Italy

8 Radiotherapy and Radiosurgery Department, Humanitas Clinical and Research Center, IRCSS, Milan-Rozzano, Italy

9 Nuclear Medicine Department, IRCCS San Raffaele, Milan, Italy

10 Nuclear Medicine Unit, University Hospital of Parma, Parma, Italy

11 Department of Histopathology and Molecular Diagnostics, Careggi University Hospital, Florence, Italy

12 University of California San Francisco, San Francisco, CA, USA

13 Department of Radiation Oncology, UC Davis, Davis, CA, USA