# The role of percentage of PSA reduction after focal therapy using high intensity focused ultrasound for primary localized prostate cancer. Results from a large multinstitutional series

Armando Stabile[1, 2, 5], Clement Orczyk[2, 3], Francesco Giganti[3, 4], Marco Moschini[5, 6], Clare Allen[4], Shonit Punwani[4], Nathalie Cathala[5], Hashim U Ahmed[7, 8], Xavier Cathelineau[5], Francesco Montorsi[1], Mark Emberton[2, 3], Alberto Briganti[1], Rafael Sanchez-Salas[5], Caroline M Moore[2, 3]

[1] Department of Urology and Division of Experimental Oncology, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute, Milan, Italy

[2] Department of Urology, University College London Hospitals NHS Foundation Trust, London, UK

[3] Division of Surgery & Interventional Science, University College London, London, UK

[4] Department of Radiology, University College London Hospitals NHS Foundation Trust, London, UK

[5] Department of Urology, Institut Mutualiste Montsouris and Université Paris Descartes, Paris, France

[6] Klinik für Urologie, Luzerner Kantonsspital, Lucerne, Switzerland

[7] Division of Surgery, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, UK

[8] Imperial Urology, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, UK

**Corresponding author**:
Armando Stabile, MD
Department of Urology and Division of Experimental Oncology
Urological Research Institute, IRCCS San Raffaele Scientific Institute,
Via Olgettina 60, 20132 Milan, Italy
Tel. +39 02 26435663; Fax. +39 02 26437298
E-mail: armando.stabile88@gmail.com

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**Abstract**

Focal therapy (FT) for prostate cancer (PCa) is emerging as a novel therapeutic approach for patients with low to intermediate-risk disease, in order to provide acceptable oncological control, whilst avoiding the side effects of radical treatment. Evidence regarding the ideal follow up strategy, and the significance of PSA kinetics post treatment is needed. In this study we aimed at assessing the value of the percentage of PSA reduction (%PSA reduction) after FT in predicting the likelihood of any additional treatment, or any radical treatment. We retrospectively analysed a multicentre cohort of 688 men receiving FT for PCa. Overall, the rates of any additional treatment, and of any radical treatment rate were 30% and 13%, respectively. Median follow-up was 41 months. The median %PSA reduction after FT was 73%. At Cox multivariable analysis, %PSA reduction was an independent predictor of any additional treatment (hazard ratio [HR]: 0.97; $p<0.001$) and of any radical treatment (HR: 0.96; $p<0.001$) after FT. For %PSA reduction > 90%, the probability of any additional treatment within 5 years was 20%. Conversely, for %PSA reduction < 10% the probability of receiving any additional treatment within 5 years was roughly 70%. This study is the first to assess the role of %PSA reduction in the largest multicenter cohort of men receiving FT for PCa. Given the lack of standardized follow-up strategies in FT field, the use of the %PSA reduction should be considered.

**Patient summary**: The %PSA reduction is a useful tool to assess men following FT. It can assist the urologist in setting up an appropriate follow-up and during post-FT patients counselling.

In the last few years, focal therapy (FT) for prostate cancer (PCa) has emerged as a feasible therapeutic option for patients with localized disease [1–3]. The main purpose of this novel strategy is to offer an approach which may cover the middle ground between active surveillance and radical treatment for patients with low to intermediate-risk PCa in order to avoid the side effects associated with radical treatment [4–6]. Even though the patient selection process for FT has significantly improved, mostly due to the introduction of multiparametric MRI (mpMRI) and targeted biopsies [7], follow-up strategies after FT are not widely agreed [8]. Specifically, there is a lack of consensus regarding the optimal frequency and thresholds for concern for PSA monitoring after FT. The lack of clarity arises due to the intrinsically personalized nature of focal treatment, where a small treatment in a large prostate will have less of an impact on PSA than a hemi-ablation in a small gland. However, PSA kinetics and particularly PSA nadir have been proposed as potential post-operative tools to predict FT failure [9,10], and to tailor the follow up MRI schedule for men. In the current study we sought to determine the relationship of the percentage of PSA reduction (%PSA reduction) after FT using high-intensity focused ultrasound (HIFU) in predicting the risk of for any additional treatment and radical treatment.

We assessed a population of 1225 men treated with focal HIFU for clinically localized PCa as a primary treatment at one of three centres between 2005 and 2018. After exclusion criteria (Supplementary methods) a final population of 688 patients was retrospectively analyzed.

The primary purpose of the analysis was to assess the relationship between %PSA reduction (derived from the ratio between PSA nadir and pre-operative PSA) and the need

for an additional treatment after FT. The secondary outcome was to assess the relationship between %PSA reduction and the likelihood of radical treatment (defined as radical prostatectomy, external beam radiotherapy, hormonal therapy and other whole-gland therapies). Multivariable Cox regression analyses were used to evaluate the relationship between %PSA reduction and the need for any additional treatment and radical treatment. Lastly, the same analysis was used to assess the relationship between %PSA reduction and the presence of PCa and clinically significant prostate cancer (csPCa) at follow-up biopsy after FT. Covariates consisted of age, pre-operative PSA (ng/ml), prostate volume (ml), mpMRI clinical stage (T1 vs T2), Gleason score (3+3 vs 3+4 vs ≥4+3), maximum cancer core length (mm) (MCCL) and ablation template (quadrant- vs hemi-ablation). Cox regression models-derived coefficients with landmark time-point at 5 years, were used to compute the estimated 5-year probability of any additional treatment or any radical treatment. Non parametric local weighted smoother function was used to graphically explore the effect of %PSA reduction on the outcomes, after accounting for the aforementioned confounders. We finally tested the interaction term between %PSA reduction and each individual covariate to explore the effect of %PSA reduction on 5-years any additional treatment probability in different clinical scenarios. Analyses were performed using the RStudio graphical interface v.1.1.383 for R software environment v.3.4.2. All tests were two-sided with a significance level set at $p < 0.05$.

The characteristics of the study population are shown in Table 1. The majority of patients had a Gleason score of 3+4 (62%). The median %PSA reduction was 73% (IQR: 52-85%). The median time to PSA nadir was 5 months (IQR: 3-7). Overall, 30% of men had an additional treatment, with 13% of men having radical treatment over the study period. The

median follow-up was 41 months (IQR: 21-66). Patients' characteristics stratified by centre are described in Supplementary table 1 (Supplementary results). At multivariable Cox regression analysis, %PSA reduction was independently positively associated with a lower risk of having an additional treatment (hazard ratio [HR]: 0.97; 95% confidence interval [CI]: 0.96-0.98; p<0.001; Supplementary table 2a). The %PSA reduction was also positively significantly associated with a lower probability of receiving radical treatment after FT (HR: 0.96; 95% CI: 0.95-0.97; p<0.001; Supplementary table 2b). The 5-year any additional treatment probability appeared linearly associated with %PSA reduction with a steep reduction in the likelihood of additional treatment for %PSA reduction of 80% or more (Figure 1). This probability decreased from 72% to 20% for %PSA reduction of 0% up to close to 100%, respectively. The 5-year radical treatment probability decreased from 43% to 1% for %PSA reduction of 0% up to close to 100%, respectively (Figure 2). It is noteworthy a common pattern of relationship between %PSA reduction and the outcomes tested in both curves (Figure 1, 2). A first phase of downslope of the probability of receiving either an additional treatment or a radical treatment between 0% and 50% of %PSA reduction. In this first phase 5-year any additional treatment probability reduced from 72% to 46% with the 5-year radical treatment probability decreasing from 43% to 17%. A second phase of plateau between 50% and 80% of %PSA reduction where the likelihood of 5-year any additional treatment and 5-year radical treatment remained quite stable until a third phase of steeper downslope beyond the value of 80% of %PSA reduction. Furthermore, the %PSA reduction was independent predictor for the presence of PCa and csPCa (Supplementary results). More specifically, the probability of finding PCa and csPCa within 5 years from treatment decreased for %PSA reduction higher than

70% and 50%, respectively (Supplementary figure 1, 2). The interaction tests for the hypothesis that the impact of %PSA reduction on 5-years any additional treatment varies according to PSA, prostate volume, Gleason score, clinical stage and ablation template were all not statistically significant (all $p>0.05$)(Supplementary results). However, the interaction test was statistically significant between %PSA reduction and MCCL ($p=0.004$), where specifically, the higher the MCCL the stronger the impact of %PSA reduction on 5-years any additional treatment probability (Supplementary Figure 3).

The results of this study provide the first evaluation of the relationship between %PSA reduction and the probability of any additional treatment after FT in a large cohort of men across three centres. Some clinical implications are noteworthy. First, our findings support the use of %PSA reduction as a useful follow-up clinical tool. Considering the median time to PSA nadir being five months, the %PSA reduction can be reliably calculated at the 6 month visit. This will provide useful information regarding the probability of the patient to receive any further treatment within 5 years. Second, a %PSA reduction of at least 50% should be considered as a proxy of good treatment quality and efficacy providing a reduction in the probability of receiving either an additional treatment or a radical treatment within 5 years from treatment that remains stable until %PSA reduction of 80%. On the other hand, a %PSA reduction higher than 80% should be considered as a proxy of excellent treatment quality and efficacy. Patients with a %PSA reduction lower than 40% have high risk of receiving an additional treatment within 5 years from treatment. This subgroup of patients might be served by a more strict follow-up with mandatory biopsy at 12 months after FT. Interestingly, a similar pattern was observed when testing %PSA reduction in predicting the presence of either PCa or csPCa at follow-up biopsy. Third, the

impact of %PSA reduction on the any additional treatment probability is independent in regards to other clinical factors (i.e. Gleason score, clinical stage, PSA and prostate volume). Even though PSA nadir had been proposed as useful post-FT tool [9,10], its value is highly influenced by several factors such as pre-operative PSA, prostate volume and the prostatic tissue ablated during treatment. The use of %PSA reduction allows to overcome all these confounders. Finally, we reported that the relationship between %PSA reduction and 5-years any additional treatment probability has higher impact for men with higher MCCL PCa, underlining the utility of this approach in patients with higher volume lesions. Whilst this study is, to the best of our knowledge, the first to describe the relationship between %PSA reduction and risk of receiving a further treatment after FT in a large multi-institutional cohort, it has some significant limitations. These include the retrospective nature of the study, the lack of data regarding the pre-operative prostate biopsy and eventual use of mpMRI, and variability on the follow up schedule of PSA testing, mpMRI and routine biopsies. In many patients prostate biopsy was performed in response to a rising PSA level or a prostate mpMRI suggestive of residual or recurrent disease, as previously described [2]. In addition, the thresholds for offering additional treatment were not standardized and are likely to be different between the different centres. Nonetheless, this study mirrored the daily clinical practice in three centres.

In conclusion, the %PSA reduction after FT using HIFU for PCa is inversely associated with the need for additional treatment and its use is recommended to provide useful information to both urologist and patient. Men who have a %PSA reduction of <25% could be considered for more intensive post treatment surveillance.

**Figure Legend**

**Figure 1:** Multivariable relationship between percentage of PSA reduction after HIFU and 5-years any additional treatment probability

**Figure 2:** Multivariable relationship between percentage of PSA reduction after HIFU and

5-years radical treatment probability

**Supplementary Figure 1:** Multivariable relationship between percentage of PSA reduction after HIFU and presence of prostate cancer at follow up biopsy within 5 years from treatment

**Supplementary Figure 2:** Multivariable relationship between percentage of PSA reduction after HIFU and presence of clinically significant prostate cancer at follow up biopsy within 5 years from treatment

**Supplementary Figure 3:** Multivariable relationship between percentage of PSA reduction after HIFU and 5-years any additional treatment probability according to MCCL

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