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Predictive value of Prostate Specific Antigen variations in the last week of salvage radiotherapy for biochemical recurrence of prostate cancer after surgery: A practical approach

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Abstract

Background: About a third of patients who underwent radical prostatectomy for prostate cancer (Pca) develop a biochemical failure (BF) within 10 years from surgery, and about a half of them receive salvage radiation therapy (SRT). Factors to predict risk to relapse after SRT are still lacking. Dynamic models, based on the assessment of changes in Prostate Specific Antigen (PSA) postsurgery seem to show good reliability.

Aims: The goal of the study was to identify a simple analytical method for the post-salvage radiation therapy biochemical failure (post-SRTBF) prediction before the end of the SRT, regardless of the PSA value at the beginning of the treatment (PSA start), measuring the PSA values at the start and 1 week before the end of SRT.

Methods: In a series of 83 patients treated with SRT for BF of Pca we measured PSA values at the first day and 1 week before the end of SRT. These values were used to define an analytical method for the post-SRTBF prediction.

Results: PSA value in patients without post-SRTBF show a significant difference in term of difference during the SRT with respect to patients with post-SRTBF. Starting from this difference, we identified a simple and practical analytical method for the post-SRTBF prediction before the end of the SRT. The data corresponds with the model and the analytical method is highly predictive (Sensitivity = 81%, Specificity = 85%, Accuracy = 83%).

Conclusion: This study offers a new tool to early predict Pca relapse overtime and to select patients who can benefit from an early additional systemic treatment.

KEYWORDS
biochemical failure, prostate cancer, PSA, salvage radiation, SRT

1 | INTRODUCTION

The advent of the prostate specific antigen (PSA) test in the last 20 years has led to a higher incidence of early stage Prostate cancer (Pca) diagnosis[1] with an increase from 30% to over 50% of patients undergoing radical prostatectomy.[2]

Nevertheless, a large proportion of prostatectomized patients (30%-50%) will develop a biochemical failure (BF) within 10 years

from surgery and 15%-35% of them will receive a second therapeutic line within 5 years from surgery.[3,4]

After surgery, the PSA value should fall to undetectable levels in about 4 weeks.[5] The threshold used to define a BF after Pca surgery is defined at the cut-off level of 0,2 ng/mL,[6] since more than half of the patients that exceed this threshold will have a progressive increase of the PSA values.[7]

Salvage radiation (SRT) give significant biochemical cure rate results in postsurgery BF patients and today is proposed as a potentially curative treatment in almost half of them.[8-10]

If postsurgical PSA value increase, it is recommended that SRT be administered when the cancer burden is at its lowest, when the value first reaches detectable levels[11,12]; recent studies showed better results in patients with PSA values below the 0.2 ng/mL threshold, ranging between 0.01 and 0.2 ng/mL.[13]

Until now, we still lack radiological imaging that differentiates in this setting local recurrence from systemic progression.[14]

As a consequence, the reported success rate of SRT after RP remain poor, ranging from 10% to 56%.[6,8,15]

In order to select patients with higher probabilities of biochemical control following SRT are used predictive nomograms, dependent on the Gleason Score value, preoperative and postoperative PSA values, Psa Doubling Time (PSADT) and state of surgical margins.[10,16,17]

Three randomized trials[18-20] have shown an improvement in post-SRT biochemical failure (post-SRTBF) by associating hormone therapy (HT), but a recent interim analysis of the RTOG 9601 trial[21] has shown that the advantage in biochemical disease free survival (BDFS) with the addition of HT is largely outweighed by the risk of death from other causes, with an overall survival (OS) reduction in HT patients.

Few non-randomized studies investigated the potential influence of the dose to the prostatic bed and BDFS, with conflicting results.[22,23]

The question is: are we able to discriminate early in the SRT treatment the patients who will do well, for whom no additional therapy is needed, from those who will go badly, for whom it may be advantageous to intensify the treatment with the addition of HT or with dose escalation?

A previous study[24] highlighted that in the salvage setting, a decline in PSA value after at least 45 Gy of SRT dose or a PSA decrease of at least 0.2 ng/mL, compared to the treatment start value, results in a positive prognostic factors for BDFS.

Target of this study was to identify a simple analytical method for the post-SRTBF prediction before the end of the SRT, regardless of the PSA value at the beginning of the treatment (PSA_start), measuring the PSA values at the start and 1 week before the end of SRT.

2 | MATERIAL AND METHOD

2.1 | Clinical data

A total of 83 patients, treated from 2013 to 2017, were retrospectively evaluated. For each patient we measured the PSA on the first day of radiotherapy and 1 week before the end of treatment. These values were used to define the model and the analytical method for the post-SRTBF prediction. Patients in the study had to meet the following criteria:

- Postoperative PSA (measured at 40 days from surgery) not above 0.2 ng/mL
- PSA zenith pre-SRT not above 2 ng/mL and not under 0.2 ng/mL
- At least two consecutive PSA increases, one of which needed to be above 0.2 ng/mL
- Free interval between surgery and BF not shorter than 1 year
- PSA doubling time not under 3 months
- Never hormonally manipulated

The primary end point evaluated if the variation of the PSA value measured during the last week of radiotherapy was related to the probability of BF.

The secondary end points evaluated the correlation of BF with: the progression time-free interval from surgery and the PSADT before SRT.

All patients were irradiated with IMRT rapid arc technique to 66Gray (D50) with 6MV photons; reference OARS constraints were sec. RTOG consensus.[25]

PTV volume was defined according to the EORTC criteria.[26]

For all patients a PSA dosage was performed on the first day of radiation treatment (_PSA_start_) and a second dosage 1 week before the end of SRT (_PSA_end_) at the dose of 56 Gy. The difference between these two values was defined as follows:

$$diffPSA = PSA\_end - PSA\_start \qquad (1)$$

The postradiation PSA values were monitored every 3 months for a minimum of 9 months and a maximum of 42 months in all patients.

The post-SRTBF was defined as:

- Two consecutive increases in PSA over the nadir reached after the end of SRT and above 0.2 ng/mL threshold (in this case the date of BF was backdated to the date of the first increment)
- A single PSA value higher than PSA_start value

A clinical failure was defined as the post-SRTBF with the presence of radiological or pathological evidence of disease relapse.

2.2 | Statistical analysis

Patients with and without postSRTBF were divided in two groups. For each group a linear regression was performed between _diffPSA_ and _PSA_start_. R^2, t Student and significativity were reported.

The procedure to identify an analytical method for the prediction of postSRTBF was tested computing the Pearson chi-square and Sensitivity, Specificity and Accuracy, as follow: Sensitivity = TP/(TP + FN), Specificity = TN/(TN + FP), Accuracy = (TP + TN)/(TP + FN + TN + FP), where TP = true positive, FN = false negative, TF = true false, FP = false positive.

TABLE 1 Patients characteristics

Number patients	83	
Age	50-78 y	Mean 70.4y
pT (surgery)	pT3 = 22	pT2 = 61
Time from surgery	12-173 m	Mean 45.3 m
Gleason Score	5–9	Mean 7
PSA pre SRT	0.21-2 ng/mL	Mean 0.67 ng/mL (SD 0.42)
PSADT pre SRT	3-32.5 m	Mean 8.6 m (SD 6,09)
Radiation dosage	66Gy	
Biochemical failure	28/83	
Clinical failure	12/83	
Follow-up	9-42 months	Mean 28

The secondary end points were achieved comparing the groups of patients with and without BF in terms of PSADT and progression-free interval after surgery. The Leneve test for the analysis of the variance and the relative t Student for independent samples was performed between the two groups. Mean, SD, F value, t value and statistical significance were computed.

3 | RESULTS

The free from BF survival rate in function of time (Kaplan-Meier estimator) suggests a trend comparable with literature[6,8,15] (48% at 39 months).

Patient characteristics are reported in Table 1.

3.1 | Development of an analytical method for the BF prediction

The basic assumption is that the *diffPSA* values follows a different trend in function of the *PSA_start* values with respect to presence or not of post-SRTBF. The *diffPSA* values were plotted in function of the *PSA_start* values, separating patients with and without post-SRTBF. A linear regression was evaluated for the two groups. The group of patients without recurrence is mainly distributed in the left-bottom side of the graph (lower *PSA_start* and lower *diffPSA*, that is, lower *PSA_end* with respect to *PSA_start*). The group of patients with recurrence is mainly distributed in the right-top side of the graph (Figure 1).

Table 2 reports the values of R^2, intercept A, slope B, t Student and statistical significance relatively to the linear regression of the two groups. Results show a good agreement between the data and the linear model for the group of patients without recurrence; for the other group, the high spread of the points limits the accuracy of the fit.

The points distribution highlights a statistical separation between the two groups. Averaging the intercept and slope parameters shown in Table 2, an intermediate line was computed.
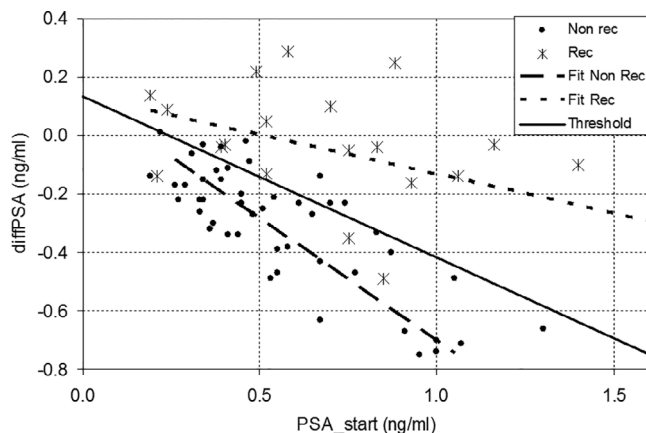

FIGURE 1 The diffPSA values were plotted in function of the PSA_start values, separating patients with and without post-SRTBF. The group of patients without recurrence is mainly distributed in the left-bottom side of the graph (lower PSA_start and lower diffPSA, that is, lower PSA_end with respect to PSA_start). The group of patients with recurrence is mainly distributed in the right-top side of the graph

The *PSA_start – diffPSA* plane (Figure 1) was divided into two parts. Points above or below the line are relative to patients with or without post-SRTBF. The separation line (solid line) was evaluated as follows:

$$diffPSA_{threshold} = 0.136\,ng/mL - 0.553 \times PSA\_start \qquad (2)$$

Starting from Equation (2) we have defined an analytical method for the prediction of the patient's outcome. Once the *PSA_start* is measured, *diffPSA_threshold* can be computed. If the *diffPSA* value measured 1 week before the end of treatment is lower (or higher) than *diffPSA_threshold*, the patient should be included in the group without (or with) post-SRTBF.

Original data were used for a first test for the validity of the method (Table 3).

Results in terms of Sensitivity, Specificity and Accuracy were:

- Sensitivity = 81%
- Specificity = 85%
- Accuracy = 83%

The Pearson chi-square has a value of 17.3 with a significativity less than 0.001.

Moreover, results shown that the higher the distance of a point from the *diffPSA_threshold* line, the higher the probability that the patient was truly with or without post-SRTBF.

3.2 | PSA doubling time and progression-free interval between surgery and biochemical failure

Patients with and without post-SRTBF were compared in terms of PSA doubling time and progression-free interval between surgery and

	R^2	Intercept A	Slope B	t	Sig.
Without recurrence	0.93	0.138	−0.838	−26.7	<0.001
With recurrence	0.21	0.135	−0.267	−1.5	0.167

TABLE 2 fit parameters of linear regressions shown in Figure 1, relative to with and without recurrence groups

TABLE 3 results of the analytical method applied to original data

		True condition	
		With BF	**Without BF**
Predict condition	*Test pos*	22 TP	8 FP
	Test neg	6 FN	47 TN

Note: TP, True Positive; FP, False Positive; FN, False Negative; TN, True Negative.

biochemical failure. The Leneve test was initially performed in order to analyze the variances of the two groups. Both cases show a significativity lower than 0.1., so the *t* test was performed assuming different variances among the patients with and without post-SRTBF groups.

Results shown a statistical difference (*P* = .001; *t* value = 3.96) in terms of PSADT between the groups of patients without post-SRTBF (9.9 ± 6.3 months) and with post-SRTBF (4.4 ± 2.2 months).

No statistical differences were found (*P* = .15; *t* value = 1.46) in terms of free interval from surgery between the groups of patients without post-SRTBF (51 ± 44 months) and with post-SRTBF (33 ± 26 months) .

4 | DISCUSSION AND CONCLUSIONS

The debate between prescribing an adjuvant RT or a salvage treatment at the time of biochemical recurrence is still open. Three recent trials highlighted that SRT at the time of biochemical progression results in similar FFBF rates as adjuvant treatment performed within 6 months from surgery, allowing to avoid pelvic radiation in about half of the patients and reducing the risk of genito-urinary toxicity.[27-29]

Factors to identify, in BF prostatectomized patients, the best chance of disease control with SRT are still lacking.

Diagnostic tests used to identify micro-localizations of PCa below the threshold of 1-1.5 ng/mL are poorly predictive, despite the probability of improving survival increases when the intervention threshold with SRT decreases.[13,15,30]

The PMSA scan test accuracy, using 68Ga citrate ligand, is still under evaluation (trial NCT02282137) with low (about 60%) detection rates in the grey zone from 0.2 to <1 ng/mL PSA values.[31,32]

Basically, the proposed predictive nomograms to select patients that are more suitable for SRT can be considered static (large databases that analyze the pre and postoperative characteristics of the tumor)[10,15] or dynamic (models that study postsurgical tumor dynamics based on PSADT).[33-]

Serum PSA levels measured before the beginning of SRT have proved to be the most important factor to predict SRT results[35] and
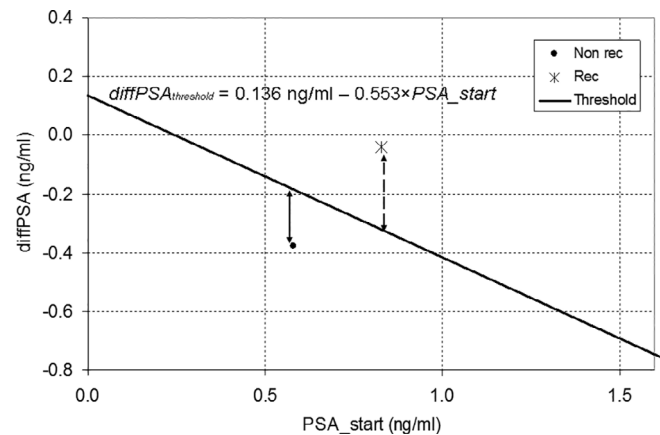

FIGURE 2 In the PSA_start—diffPSA plane, the diffPSA_threshold line ideally splits patients with post-SRTBF (above the line) from patients without post-SRTBF (below the line): the location of a patient in the PSA plane identifies the probability of evolution of his biochemical state

data suggest that more favorable biochemical outcomes are associated with very low PSA values (<0.2 ng/mL).[11-13,16]

While existing nomograms might assist clinicians to identify the best candidates for SRT, we tried to identify a new practical and simple tool to early detection of patients at greatest risk of biochemical failure before the end of SRT, using PSA differences detected during the treatment.

Some authors have reported that PSA changes measured during SRT can be used to predict treatment outcome.[24,36-39]

Our results shown that the combined analysis of the *PSA_start* and *diffPSA* values leads to a greater amount of information; the changes of PSA during the SRT (*diffPSA*) in function of the *PSA_start* are strongly related to the presence or not of post-SRTBF (accuracy of 83%). Conversely, a low *diffPSA* unrelated to the *PSA_start* value may be indicative both of systemic or local failure.

In the *PSA_start - diffPSA* plane (Figure 1), the $diffPSA_{threshold}$ line (Equation (2)) ideally splits patients with post-SRTBF (above the line) from patients without post-SRTBF (below the line): the location of a patient in the PSA plane identifies the probability of evolution of his biochemical state (Figure 2).

Results defined three different evolution scenarios:

- A probable early biochemical escape for distance from $diffPSA_{threshold}$ line greater than +0.2 ng/mL
- A probable prolonged biochemical control for distance from $diffPSA_{threshold}$ line lower than 0.0 ng/mL
- An intermediate prognosis group for distance from $diffPSA_{threshold}$ line in a range between 0.0 ng/mL and + 0.2 ng/mL

The evidence provided by large prospective studies[18-20] recently supported the choice to associate the SRT with HT, but recent analyses of long-term data seems to highlight an increase in toxicity from associated therapy, with negative effects on overall survival.[21]

We are aware that the numerical data that support our evaluation are limited and that the conclusions provided need further clinical validation through prospective studies on large numbers of patients.

At the same time we believe that an early identification of patients who are likely to relapse after SRT compared to those with a low probability of relapse may reserve hormonal treatment for fewer patients, with potential reduction of treatment toxicity and health costs.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethical clearance was obtained from the Ethics Committee of the institute.

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

CONFLICT OF INTEREST

The authors have no conflict of interest to be disclosed related to this work.

AUTHOR CONTRIBUTIONS

Conceptualization: Riccardo Vigna-Taglianti.
Methodology: Riccardo Vigna-Taglianti; Alberto Boriano.
Software: Alberto Boriano; Fabrizio Bergesio.
Validation: Elvio Grazioso Russi; Alberto Boriano, Riccardo Vigna-Taglianti.
Formal Analysis: Alberto Boriano.
Data Curation: Anna Maria Merlotti, Alessia Reali, Antonella Melano.
Supervision: Elvio Grazioso Russi.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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