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Brief Correspondence

Salvage Radiotherapy Following Partial Gland Ablation for Prostate Cancer: Functional and Oncological Outcomes

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Partial gland ablation (PGA) for prostate cancer (PCa) is a minimally invasive treatment modality that has gained traction among patients and clinicians [1]. Short- to medium-term results support its overarching aim of minimizing toxicities; however, clinically significant persistent or recurrent PCa after PGA has been observed in almost half of men managed with this approach [2]. Hence, there is a pressing need to assess outcomes after salvage treatments to provide better information about the role and trade-offs of PGA as an upfront management strategy.

To date, salvage radical prostatectomy and repeated PGA are the salvage options most widely described for recurrent and/or persistent PCa following PGA, with results suggesting comparable oncological and functional outcomes to the primary setting [3]. Radiotherapy remains a mainstay treatment modality for localized PCa and, importantly, it renders a favorable profile of patient-reported quality of life outcomes in sexual and urinary domains [4], in keeping with the priorities of patients and providers when selecting PGA as a primary treatment. Thus, salvage radiotherapy (sRT) seems a highly attractive organ-preserving option for men with recurrent or persistent PCa following PGA, notwithstanding the absence of literature describing outcomes with this approach. The aim of this study was to assess the efficacy and safety of sRT for men with PCa after PGA.

Following institutional review board approval, we performed a review of our prospectively maintained PCa PGA database. We identified patients between 2005 and 2014 who received PGA and subsequently required sRT for persistent or recurrent disease. The primary objective was to describe oncological control including biochemical recurrence (BCR), biopsy-proven recurrence (BPR), and progression to metastatic disease. BCR was defined according to the Phoenix criterion (prostate-specific antigen [PSA] nadir +2 ng/mL). The secondary endpoint was safety in terms of the rate of urinary incontinence (scored as 0, 1, or 2 for no incontinence, use of 1–3 pads, or need for an artificial urinary sphincter, respectively) and Common Terminology Criteria for Adverse Events v4.0 graded toxicity.

Since 2005, patients with stage $\leq$ T2c and International Society of Urological Pathology (ISUP) grade 1–3 PCa have been considered candidates for primary PGA [5]. Staging investigations include multiparametric magnetic resonance imaging (mpMRI) and fusion biopsies (targeted and systematic). Following PGA, patients undergo follow-up with PSA measurement every 3 mo for the first year, and every 6 mo thereafter. mpMRI and targeted biopsies are routinely performed at 6–12 mo and 2 yr after PGA. Patients diagnosed with clinically significant PCa recurrence/persistence (ISUP grade $\geq$2) make a shared decision with the treating urologist on the salvage therapy modality. sRT is predominantly delivered as conventional or moderately hypofractionated image-guided RT (IGRT). RT planning was based on a computed tomography scan of the pelvis and institutional dose constraints to normal tissue from the primary RT setting. Brachytherapy (as monotherapy or a boost to external-beam RT [EBRT]) and combinatorial androgen deprivation therapy (ADT) were prescribed for selected patients at the discretion of the treating oncologist.

We identified 21 patients who underwent sRT following PGA failure between 2005 and 2014 (Table 1). The median age at initial ablation was 67 yr (interquartile range [IQR] 63.2–69.0) and the median baseline PSA was 5.80 ng/mL (IQR 5.00–8.40). PGA consisted of high-intensity focused ultrasound (HIFU; n = 16) and laser ablation (n = 5) comprising zonal ablation in all but three cases. The median time from PGA to BPR was 32 mo (IQR 16.2–60.0) and PSA at BPR was 4.60 ng/mL (IQR 3.30–7.70). The median follow-up from

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Table 1 – Patient demographics and baseline data (*n* = 21).

Parameter	Result
Median age at PGA, yr (interquartile range)	67 (63.2–69)
Type of PGA, *n* (%)	
High-intensity focused ultrasound	16 (76)
Laser	5 (24)
Mean prostate-specific antigen at PGA, ng/mL (standard deviation)	7.5 (4.6)
Missing	1
T stage at PGA, *n* (%)	
T1c	14 (78)
T2a	3 (16)
T2b	1 (5)
Data missing	3
ISUP grade group at PGA, *n* (%)	
1	11 (52)
2	7 (33)
3	3 (14)
Mean prostate-specific antigen at BPR after PGA, ng/mL (standard deviation)	5.5 (3.3)
Data missing	1
T stage at BPR after PGA, *n* (%)	
T1c	16 (80)
T2a	2 (10)
T2b	2 (10)
Data missing	1
ISUP grade group at BPR after PGA, *n* (%)	
1	4 (20)
2	13 (65)
3	1 (5)
4	1 (5)
5	1 (5)
Data missing	1
Location of BPR after PGA *n* (%)	
Same as primary	11 (58)
Different from primary	2 (10)
Same and different	6 (32)
Data missing	2
Median age at salvage RT, yr (interquartile range)	71 (66–74.8)
Type of salvage RT, *n* (%)	
IMRT	16 (80)
LDR brachytherapy monotherapy	3 (15)
IMRT pelvis plus HDR brachytherapy boost	1 (5)
Data missing	1
Salvage RT dose and fractionation, *n* (%)	
IMRT	
70 Gy (2 Gy/fraction)	5 (25)
78 Gy (2 Gy/fraction)	4 (20)
60 Gy (3 Gy/fraction)	7 (35)
Low-dose-rate brachytherapy monotherapy (I-125, 145 Gy)	3 (15)
IMRT (46 Gy, 2 Gy/fraction) pelvis plus high-dose-rate brachytherapy boost (15 Gy)	1 (5)
Data missing	1
Androgen deprivation therapy, *n* (%)	
No	11 (52)
Yes	10 (48)
Androgen deprivation therapy duration, *n*/10 (%)	
3 mo	1 (10)
6 mo	8 (80)
24 mo	1 (10)

BPR = biopsy-proven recurrence; IMRT = intensity-modulated RT; ISUP = International Society of Urological Pathology; PGA = partial gland ablation; RT = radiotherapy.

sRT to the last clinic visit was 3.33 yr (IQR 1.21–6.57). sRT was delivered via IGRT conventional fractionation in nine patients (range 70–78 Gy, 2 Gy/fraction), moderate hypofractionation in seven patients (all cases 60 Gy, 3 Gy/fraction), low-dose-rate brachytherapy in three patients (I-125, 145 Gy), and prostate-pelvis EBRT (46 Gy in 23 fractions) plus a high-dose-rate brachytherapy whole-gland boost (15 Gy) in one patient. ADT was combined with sRT in ten patients (3-, 6- and 24-mo duration in 1, 8, and 1 cases, respectively). At last follow-up, no BCR or metastatic event had been observed (Supplementary Figures 1 and 2), and none of the patients had undergone additional salvage treatments. Two cases of grade 3 acute genitourinary (GU) toxicity occurred (urinary retention), while most patients experienced mild acute GU and/or gastrointestinal (GI) toxicity (grade 0–2). In terms of long-term adverse effects, two patients experienced grade 3 GU toxicity (urethral stricture), and all patients had preserved continence at last follow-up. Subgroup analysis for four patients treated with brachytherapy as monotherapy or boost to EBRT showed no acute or late grade ≥3 GU or GI toxicities. Notably, there were no cases of retrourethral fistula, a significant complication after multiple and mixed ablative technologies. Toxicity and oncological outcomes are summarized in Table 2 and Supplementary Figure 1, respectively.

Table 2 – Safety profile: toxicity graded according to Common Terminology Criteria for Adverse Events v4.0 and continence status scale (*n* = 21).

	Patients, *n* (%)
Acute gastrointestinal toxicity	
Grade 0	13 (68.4)
Grade 1	5 (26.3)
Grade 2	1 (5.3)
Grade ≥3	0 (0)
Missing	2
Acute genitourinary toxicity	
Grade 0	4 (21.1)
Grade 1	7 (36.8)
Grade 2	6 (31.6)
Grade 3	2 (10.5)
Grade ≥4	0 (0)
Missing	2
Late gastrointestinal toxicity	
Grade 0	19 (95)
Grade 1	1 (5)
Grade ≥2	0 (0)
Missing	1
Late genitourinary toxicity	
Grade 0	8 (40)
Grade 1	6 (30)
Grade 2	4 (20)
Grade 3	2 (10)
Grade ≥4	0 (0)
Missing	1
Continence status at baseline	
Grade 0	21 (100)
Grade ≥1	0 (0)
Continence status at last follow-up	
Grade 0	21 (100)
Grade ≥1	0 (0)

Even after PGA failure, an organ-preserving approach would be favored by many patients, in keeping with their initial choice that prioritized quality of life. To the best of our knowledge, this work represents the first characterization of outcomes following sRT for PGA failure. Our results suggest that sRT has a preserved therapeutic index with acceptable oncological and toxicity outcomes, even in the patient subgroup with dose-intensification sRT. Our findings are relevant considering the rising use of PGA with curative intent [3] and the non-negligible rates of persistent/recurrent disease with this approach. The strength of our study is that it is the first to report on outcomes of sRT after PGA with inclusion of various contemporary standardized sRT modalities and dose fractionations. Riviere et al [6] reported the largest series of 100 patients treated with sRT following whole-gland HIFU. Of these, 83 men received sRT without adjuvant ADT; after median follow-up of 36.7 mo the 5-yr progression-free survival rate was 72.5%, with one patient dying due to metastatic disease. However, five cases had grade $\geq$3 toxicities, including one patient requiring urinary diversion (grade 4) and another who died from multiorgan failure after cystectomy for hemorrhagic cystitis (grade 5) [6]. By contrast, crude rates of serious grade 3–5 toxicity events in our study were appreciably lower, even with dose intensification in some cases. In addition, none of the patients developed recurrence after sRT.

Current standard-of-care radical treatments for localized PCa (RP and EBRT) have high cure rates and well-characterized quality-of-life outcomes [7]. More recently it was demonstrated that ultra-hypofractionated RT (eg, 5–7 fractions) is noninferior to conventionally fractionated RT for localized PCa, in terms of both failure-free survival and acute- and long-term toxicity [8]. The high recurrence rate after PGA necessitates the provision of further treatments, translating into additional surveillance burden, costs, and risk of toxicities [2,3]. Therefore, rigorous selection of patients desiring a focal treatment approach and appropriate counseling, including information on potential associated morbidity and mortality of both PGA and potential subsequent therapies, are paramount. Although our study supports the use of sRT for PGA failure as a relatively safe and effective salvage strategy, its outcomes are worse than with primary radical RT, so it seems prudent to consider it an investigational scenario. Further studies, including collaborative larger-scale efforts, seem to be warranted to better characterize the impact of prior PGA on the therapeutic index of curative-intent RT.

The main limitations of our study are its retrospective nature, single-center source of data, small sample size, and short follow-up after sRT. However, this patient population, although increasing, is still infrequently encountered in most centers. It is also worth emphasizing that the data stem from highly selected patients within an active and experienced PGA practice (>10 yr) who opted for a second organ-preserving treatment modality for their persistent/recurrent PCa. In this vein, patients who underwent initial PGA and had unfavorable outcomes may have pursued care at other hospitals and are not captured in this series.

In summary, our study shows that after median follow-up of 3.33 yr, sRT for patients with failure after PGA appears to be safe and effective, but the toxicity rates are higher than with standard-of-care primary RT for localized PCa. The latter in addition to the added costs and need for close surveillance with first-line PGA reinforce the need for its cautious use until comparative randomized data demonstrate therapeutic equipoise with curative-intent radical therapies for localized PCa.

Author contributions: Yazan Qaoud had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Qaoud, Bettoli, Herrera-Caceres, Berjaoui, Fleshner, Berlin.
Drafting of the manuscript: Qaoud, Bettoli, Berlin, Fleshner, Herrera-Caceres.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euros.2020.07.002.

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