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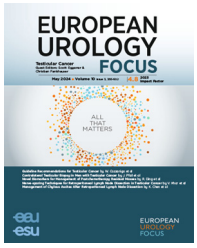

Prostate Cancer

Recurrent Gleason Score 6 Prostate Cancer After Radiotherapy or Ablation: Should We Observe Them All? Results from a Large Multicenter Salvage Radical Prostatectomy Consortium

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Abstract

Background: Salvage radical prostatectomy (sRP) yields poor functional outcomes and relatively high complication rates. Gleason score (GS) 6 prostate cancer (PCa) has genetic and clinical features showing little, if not absent, metastatic potential. However, the behavior of GS 6 PCa recurring after previous PCa treatment including radiotherapy and/or ablation has not been investigated.

Objective: To evaluate the oncological outcomes of sRP for radio- and/or ablation-recurrent GS 6 PCa.

Design, setting, and participants: Retrospective data of sRP for recurrent PCa after local nonsurgical treatment were collected from 14 tertiary referral centers from 2000 to 2021.

Intervention: Prostate biopsy before sRP and sRP.

Outcome measurements and statistical analysis: A survival analysis was performed for pre-sRP biopsy and sRP-proven GS 6. Concordance between PCa at pre-sRP biopsy and sRP histology was assessed.

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Results and limitations: We included GS 6 recurrent PCa at pre-sRP biopsy (n = 142) and at sRP (n = 50), as two cohorts. The majority had primary radiotherapy and/or brachytherapy (83.8% of GS 6 patients at pre-sRP biopsy; 78% of GS 6 patients at sRP) and whole-gland treatments (91% biopsy; 85.1% sRP). Biopsy GS 6 10-yr metastasis, cancer-specific survival (CSS), and overall survival (OS) were 79% (95% confidence interval [CI] 61–89%), 98% (95–99%), and 89% (78–95%), respectively. Upgrading at sRP was 69%, 35.5% had a pT3 stage, and 13.4% had positive nodes. The sRP GS 6 10-yr metastasis-free survival, CSS, and OS were 100%, 100%, and 90% (95% CI 58–98%) respectively; pT3 and pN1 disease were found in 12% and 0%, respectively. Overall complications, high-grade complications, and severe incontinence were experienced by >50%, >10%, and >15% of men, respectively (in both the biopsy and the sRP cohorts). Limitations include the retrospective nature of the study and absence of a centralized pathological review.

Conclusions: GS 6 sRP–proven PCa recurring after nonsurgical primary treatment has almost no metastatic potential, while patients experience relevant morbidity of the procedure. However, a significant proportion of GS 6 cases at pre-sRP biopsy are upgraded at sRP. In the idea not to overtreat, efforts should be made to improve the diagnostic accuracy of pre-sRP biopsy.

Patient summary: We investigated the oncological results of salvage radical prostatectomy for recurrent prostate cancer of Gleason score (GS) 6 category. We found a very low malignant potential of GS 6 confirmed at salvage radical prostatectomy despite surgical complications being relatively high. Nonetheless, biopsy GS 6 was frequently upgraded and had less optimal oncological control. Overtreatment for recurrent GS 6 after nonsurgical first-line treatment should be avoided, and efforts should be made to increase the diagnostic accuracy of biopsies for recurrent disease.

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1. Introduction

Approximately one in four men with newly diagnosed localized prostate cancer (PCa) will undergo nonsurgical primary treatment [1]. In case of primary radiotherapy up to two in three men will have biochemical recurrence (BCR) within 10 yr [2–4]. The number of recurrences after nonsurgical primary treatment is likely to grow further in the coming years due to the expansion of whole-gland and focal ablative strategies [5]. It is hence of primary importance for the urologist to appropriately deal with and manage radio- and ablation-recurrent patients.

While up to 90% of radiorecurrent men used to indiscriminately undergo androgen deprivation therapy [1,6], renewed interests have been recorded in the field of salvage treatments as approximately half of recurrences in case of imaging performed at low prostate-specific antigen (PSA) thresholds are localized to the prostate and may thus achieve cancer-free status [1,6–8]. Salvage radical prostatectomy (sRP) has gained attention as outcomes in the past decade improved compared with historical series [9], making salvage surgery a concrete option for appropriately informed patients. Salvage focal treatments also bear promising outcomes [8,10] and may allow a midground option in selected men, further decreasing the morbidity of salvage therapies [11].

Gleason score (GS) 6 radio- or ablation-recurrent disease is not frequent, but still constitutes 5–10% of cases at final sRP pathology in contemporary series [9]. Currently, European Association of Urology (EAU) guidelines and expert consensus include GS 6 among those who are more likely to benefit from salvage treatments. Weak recommendations allowing monitoring for recurrent disease deemed at low risk according to PSA kinetics and pathology are also present [12,13].

In a first-line setting, active treatment of GS 6 PCa is now strongly discouraged. Long-term outcomes of active surveillance yield excellent results [12,13]. In addition, a low, if not absent, metastatic potential has been shown by a large cohort analysis [14–16] and is further confirmed by the markedly different genetic expressions between low- and high-grade PCa [17,18]. Debate is ongoing, with some groups suggesting that GS 6 should not be labeled as "cancer" anymore [19].

Currently, evidence on radio- or ablation-recurrent PCa is low, not clearly allowing conclusions on whether it mirrors or not untreated primary GS 6, or, on the contrary, previous treatment resulted in resistant and more aggressive disease, possibly benefitting from active removal.

In the attempt to improve patients' quality of life, outcomes of GS 6 recurrent PCa are of paramount importance to confirm not only whether these patients may benefit from treatment, but also, as per primary PCa, whether they may even be spared (over)treatment. This holds even more true in a salvage context, as morbidities, despite recent improvements, are still relevant [9].

Thus, we performed a multicenter study to detail the oncological outcomes of radio- or ablation-recurrent GS 6 PCa patients who underwent sRP.

2. Patients and methods

2.1. Data collection and study criteria

We retrospectively collected data of 1265 men undergoing sRP for recurrent PCa after radiotherapy and/or ablation at 14 tertiary referral centers (from February 2000 to January 2021). We excluded men with pre-sRP castration-resistant prostate cancer (CRPC), metastatic disease before sRP, a follow-up shorter than 6 mo, or insufficient data on sRP pathology.

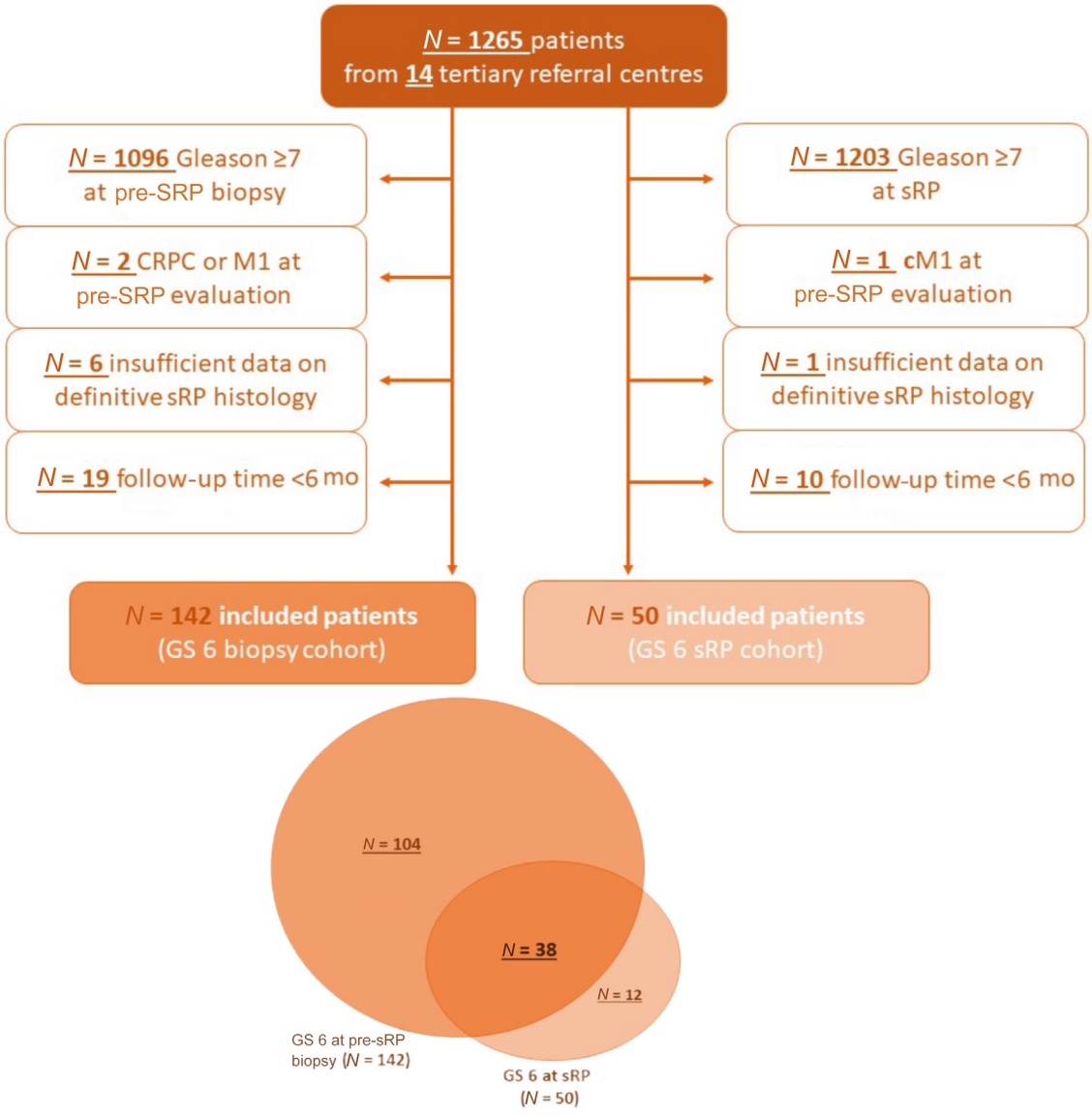

Fig. 1 – Study inclusion flowchart. The Venn diagram in the lower part shows the overlap between the two cohorts included. cM1 = metastatic prostate cancer at pre-sRP imaging; CRPC = castration-resistant prostate cancer; GS 6 = Gleason score 6; sRP = salvage radical prostatectomy.

The study flowchart is provided in Figure 1. Internal review board approval was obtained according to each institution's policy. Data quality review was performed independently by two physicians (G.C. and F. C.). In case of uncertainty or missing information, centers were recontacted for data revision.

2.2. Variable categorization

The following definitions were adopted in terms of oncological outcomes: (1) BCR: postoperative PSA >0.2 ng/ml; (2) CRPC: three consecutive rises in PSA 1 wk apart resulting in two 50% increases over the nadir, and a PSA value of >2 ng/m despite castrate serum testosterone; (3) systemic progression: disease visible on nodal and/or metastatic imaging not present at pre-sRP staging; and (4) persistent PCa was defined as PSA never being below 0.2 ng/ml following sRP [20].

Continence was categorized according to the number of pads used per day: (1) full continence (no pads), (2) mild (one pad per day), (3) moderate (two pads per day), and (4) severe incontinence (three or more pads per day). Erectile function was grouped into (1) spontaneous or phosphodiesterase-5 inhibitors–assisted erections, (2) prostaglandin-E or vacuum-assisted erections, (3) penile prosthesis, and (4) no erections. Both continence and erectile function were evaluated 12 mo following sRP. In case of missing 12-mo values, the 6-mo results were used, if available [21].

Complications were graded using the Clavien-Dindo classification and adhering to the EAU guidelines on reporting complications, considering those with a Clavien grade ≥3 as major complications [22]. Preoperative comorbidity status was recorded using the American Society of Anesthesiologists score, Charlson Comorbidity Index, and Eastern Cooperative Oncology Group performance status.

2.3. Study outcomes

For the purpose of the study, we evaluated two groups of patients: (1) those having a pre-sRP biopsy GS 6 (sRP-biopsy) and (2) those having an sRP pathology GS 6 (sRP-pathology), which was considered the reference standard (true GS 6).

The primary outcome was the rate of systemic progression of GS 6 at sRP pathology. Secondary outcomes included systemic progression for those with GS 6 at sRP-biopsy and other oncological endpoints for both groups (BCR, cancer-specific survival [CSS], and overall survival [OS]). Pathology concordance, upgrading and downgrading of original biopsy at first PCa diagnosis, sRP-biopsy, and sRP-pathology were also assessed.

2.4. Statistical analysis

Comparisons were performed using the Wilcoxon chi-square and Mann-Whitney *U* tests, when appropriate. Kaplan-Meier analyses were plotted for survival and differences assessed through the log rank test. Logistic regression and Cox regression were performed to investigate possible significant regressors. Missing data were treated with pairwise deletion. A statistical analysis was conducted using SPSS version 28.0.1 (IBM SPSS, Armonk, NY, USA).

3. Results

We included 142 sRP-biopsy and 50 sRP-pathology patients; 38 patients, being diagnosed with GS6 PCa both at pre-sRP biopsy and at sRP definitive pathology, were counted in both groups (Fig. 1).

3.1. Salvage RP-biopsy GS 6

Features of men with sRP-biopsy GS 6 are shown in Table 1. The median follow-up was 60 mo (interquartile range [IQR]: 26–121). GS at first-line biopsy was ≥7 in 21.8% (n = 26). The majority had radiotherapy and/or brachytherapy (83.8%) and whole-gland treatments (91%). Only four (2.9%) had cN1 disease before sRP. The median time from first-line treatment to sRP was 48.7 (IQR: 30–83.5) mo. At final pathology GS concordance was low (27.4% confirmed GS 6), while 60.6% were upgraded to GS 7 and 8.5% to GS ≥8; 35.5% had a pT3 stage and 13.4% pathologically positive nodes. Survival analyses are shown in Figure 2 and reported in Supplementary Table 1 with functional outcomes and complications. Ten-year metastasis, CSS, and OS were 79% (95% confidence interval [CI] 61–89%), 98% (95–99%), and 89% (78–95%), respectively. Overall and high-grade complications were experienced by 52.1% and 14.6%, respectively. Severe incontinence was experienced by 18.9%.

Differences among those upgraded and not upgraded at final pathology are detailed in Supplementary Table 2 and Supplementary Figure 1. Among preoperative variables, no predictors of upgrading were found and pre-sRP PSA was the sole significant regressor for metastasis-free survival (p = 0.02, data not shown). Those with upgrading at final pathology had higher pT stage (p < 0.001) and pN stage, but not positive margins (p = 0.11).

3.2. Salvage RP pathology GS 6

Table 2 displays features of patients with sRP GS 6. The median follow-up was 60 (IQR: 24–96) mo. At initial PCa diagnosis, 31% had GS >6, while pre-sRP biopsy detailed 17.4% having GS >6; the majority had radiotherapy and/or brachytherapy as primary treatment (78%) and whole-gland treatment (85.1%). Pathological extracapsular extension was present in 13%. None had pN+ disease.

Table 1 – Baseline features of men with pre–salvage radical prostatectomy biopsy Gleason score 6[a]

First-line treatment	
iPSA (ng/ml), median (IQR)	6.3 (4.5–10)
Gleason score at diagnosis, *n* (%)	
≤6	93 (78.2)
7	23 (19.3)
8	3 (2.5)
Clinical stage at diagnosis, *n* (%)	
cT1	58(60.4)
cT2	32(33.3)
cT3	6 (6.3)
Type, *n* (%)	
Radiotherapy	84 (59.2)
Brachytherapy	31 (21.8)
Cryotherapy	6 (4.2)
HIFU	7 (4.9)
IRE/LIIT	6 (4.2)
Other	4 (2.8)
EBRT + BT	4 (2.8)
Extension, *n* (%)	
Whole gland	121 (91.0)
Focal	12 (9.0)
Salvage radical prostatectomy	
Age (yr), median (IQR)	65 (60.5–69.0)
Pre-sRP PSA (ng/ml), median (IQR)	4.8 (2.5–7.1)
First line to sRP interval (mo), median (IQR)	48.7 (30.0–83.5)
ASA score, *n* (%)	
1	28 (21.9)
2	62 (48.4)
3	38 (29.7)
Date, *n* (%)	
≤2004	23 (16.1)
2005–2012	84 (59.1)
2013–2020	35 (24.8)
Surgical approach, *n* (%)	
Open sRP	107 (75.4)
Laparoscopic sRP	1 (0.7)
Robotic sRP	34 (23.9)
Nerve sparing, *n* (%)	
Not performed	70 (68.0)
Unilateral	11 (10.7)
Bilateral	22 (21.4)
Operation time (min), median (IQR)	180 (150–238)
Pathological features (sRP)	
Gleason score, *n* (%)	
Not evaluable	5 (3.5)
6	39 (27.4)
7	86 (60.6)
≥8	12 (8.5)
pT stage, *n* (%)	
pT0	1 (0.7)
pT2	90 (63.8)
pT3	50 (35.5)
pN stage, *n* (%)	
pN0	106 (74.6)
pN1	19 (13.4)
pNx	17 (12)
Positive surgical margins, *n* (%)	21 (15)

ASA score = American Society of Anesthesiology score; cT stage = clinical tumor stage; EBRT + BT = external beam radiotherapy + brachytherapy; First-line to sRP = time to salvage radical prostatectomy from first-line treatment; HIFU = high-intensity focused ultrasound; iPSA = initial PSA; IQR = interquartile range; IRE/LIIT = irreversible electroporation/laser-induced interstitial thermotherapy; pN stage = pathological nodal stage; PSA = prostate-specific antigen; pT stage = pathological tumor stage; sRP = salvage radical prostatectomy.

[a] Missing data were treated with pairwise deletion.

Survival and complications are detailed in Supplementary Table 3, while Figure 2 shows the Kaplan-Meyer survival analysis. Ten-year metastasis-free survival and CSS were 100%. Ten-year OS and PSA relapse–free survival were 90% (95% CI 58–98%) and 83% (60–93%), respectively. Severe incontinence was experienced by 16.3%, complications by 54.2%, and major complications by 10.6%.

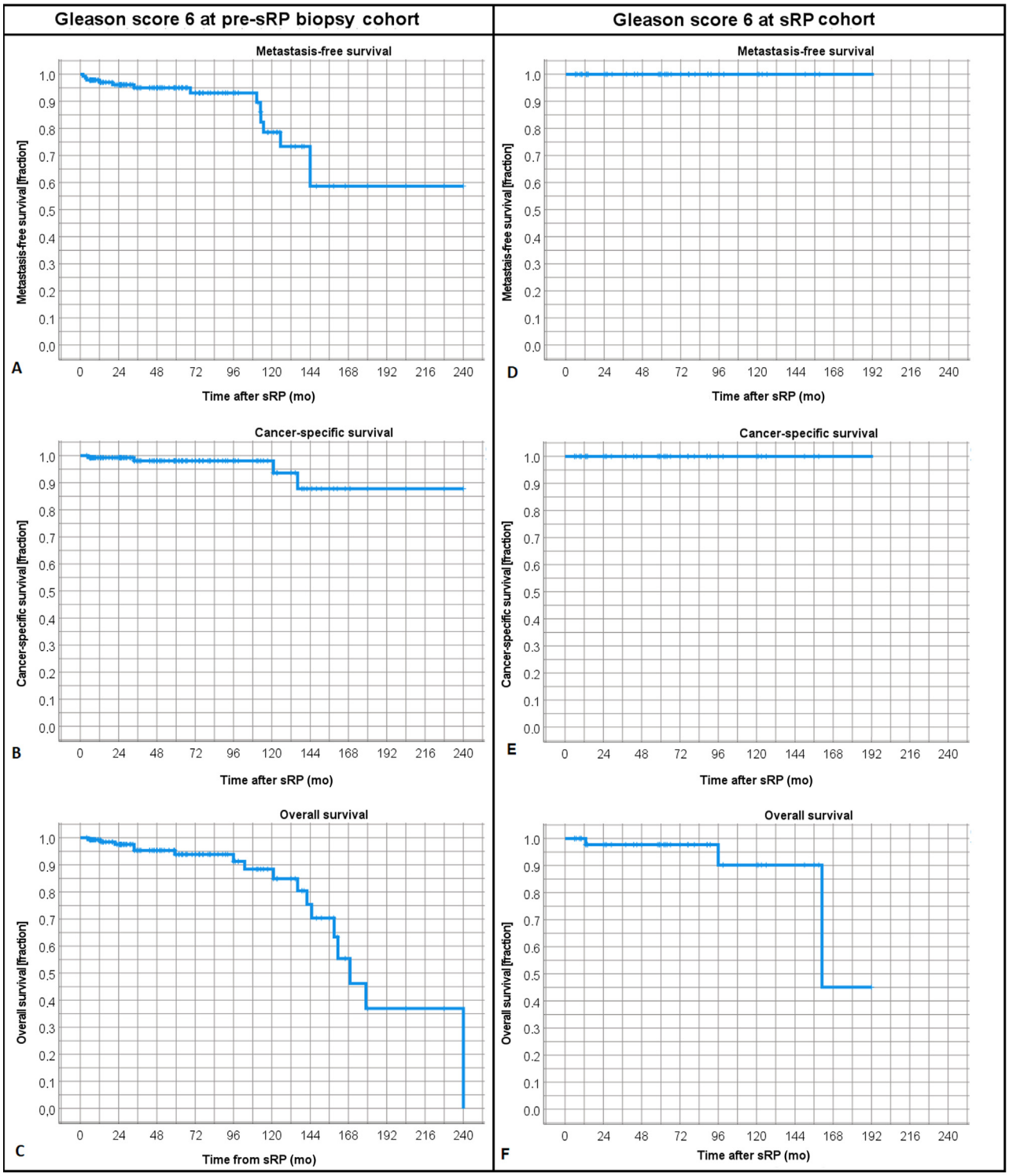

Fig. 2 – Kaplan-Meier survival curves for (A–C) sRP-biopsy and (D–F) sRP-pathology Gleason score 6 patients for metastasis-free, cancer-specific, and overall survival. sRP-biopsy = pre-sRP biopsy Gleason score 6; sRP-pathology = sRP pathology Gleason score 6; sRP = salvage radical prostatectomy.

4. Discussion

In the current study, we report the results of GS 6 radio- or ablation-recurrent PCa treated with sRP. The outcomes of the entire sRP cohort (all GSs) have previously been published [20]. To our knowledge, this study details the largest cohort focusing on GS 6 following primary nonsurgical treatment. We believe that several findings are of interest.

First, true GS 6, when confirmed at sRP pathology, showed no malignant potential. No metastatic progression was recorded at a median of a 5-yr follow-up compared with an average of 20–30% metastatic progression at 5 yr

Table 2 – Baseline features of men with Gleason score 6 at salvage radical prostatectomy[a]

Baseline features at first-line treatment	
iPSA (ng/ml), median (IQR)	5.60 (4.35–8.54)
Gleason score at diagnosis, *n* (%)	
≤6	29 (69.0)
7	12 (28.6)
8	2 (2.4)
Clinical stage at diagnosis, *n* (%)	
cT1	21 (60.0)
cT2	12 (34.3)
cT3	2 (5.7)
Type, *n* (%)	
Radiotherapy	27 (54.0)
Brachytherapy	10 (20.0)
Cryotherapy	4 (8.0)
HIFU	3 (6.0)
Photodynamic therapy	1 (2.0)
IRE/LIIT	3 (6.0)
EBRT + BT	2 (4.0)
Extension, *n* (%)	
Whole gland	40 (85.1)
Focal	7 (14.9)
Salvage radical prostatectomy	
Age (yr), median (IQR)	62.0 (58.8–68.0)
Pre-sRP PSA (ng/ml), median (IQR)	3.98 (2.28–6.30)
Pre-sRP biopsy Gleason score, *n* (%)	
≤6	38 (82.6)
7	7 (15.2)
8	1 (2.2)
First line to sRP interval (mo), median (IQR)	40 (23.5–62.5)
ASA score, *n* (%)	
1	13 (27.0)
2	24 (50.0)
3	11 (22.9)
Date, *n* (%)	
≤2004	5 (10.0)
2005–2012	35 (68.0)
2013–2020	12 (22.0)
Surgical approach, *n* (%)	
Open sRP	37 (74.0)
Robotic sRP	13 (26.0)
Nerve sparing, *n* (%)	
Not performed	22 (68.5)
Bilateral NS	12 (31.5)
Operation time (min), median (IQR)	160.0 (133.0–210.0)
Pathological features	
pT stage, *n* (%)	
pT2	44 (88.0)
pT3	6 (12.0)
pN stage, *n* (%)	
pN0	45 (90.0)
pNx	5 (10.0)
Positive surgical margins, *n* (%)	4 (8.0)

ASA score = American Society of Anesthesiology score; cT stage = clinical tumor stage; EBRT + BT = external beam radiotherapy + brachytherapy; HIFU = high-intensity focused ultrasound; iPSA = initial PSA; IQR = interquartile range; IRE/LIIT = irreversible electroporation/laser-induced interstitial thermotherapy; NS = nerve sparing; pN stage = pathological nodal stage; PSA = prostate-specific antigen; pT stage = pathological tumor stage; sRP = salvage radical prostatectomy.
[a] Missing data were treated with pairwise deletion.

for sRP patients overall [9]. Accordingly, no cancer-related deaths were described. Although our series has a relatively low number of patients, it mirrors the outcomes of treatment-naïve GS 6, where cohorts of over 10 000 men show almost no lymphatic or hematic dissemination ability [14–16].

Second, when GS 6 is found at pre-sRP biopsy, the results are also promising with good medium-term oncological control. However, more than half of the patients reveal a higher grade at final sRP pathology, including a non-negligible proportion of high-risk disease. Not surprisingly, all progressions were detailed in the upgraded cohort only. An important limitation of our work is indeed the low availability of pre-sRP biopsy information. The poor concordance partially reflects the well-known limitation of systematic biopsies, as a significant proportion of cases were performed in the pre–multiparametric MRI (pre-mpMRI) era, together with increased difficulty in interpreting the pathology of non–treatment-naïve cases. Furthermore, recent evidence from the FORECAST study also suggests a relatively low negative predictive value and accuracy of mpMRI in a radiorecurrent setting, which may also partially explain our findings [11].

Third, the incidence of true GS 6 is low, as <5% of men in our sRP multi-institutional cohort revealed GS 6 at final pathology. This is in line with the studies published by others and with the biology of radioresistant PCa, which is generally an aggressive disease [9,23]. Nonetheless, radiorecurrent PCa currently represents the fourth urological malignancy in terms of absolute numbers [6]. An increase in the incidence of GS 6 recurrent disease is also to be expected with the growth of ablation focal and/or whole-gland ablative strategies. Thus, GS 6 is not infrequent, and deserves appropriate attention and optimization of disease understanding and management.

Fourth, salvage radical prostatectomy remains a procedure with significant morbidity, as half of the patients experienced at least one complication, one in ten a major complication, and almost one in two urinary incontinence. Improvements in procedural outcomes compared with historical series make sRP a feasible option to be proposed to selected patients instead of palliative androgen deprivation therapy. On the one hand, the side effects of sRP need to be weighted carefully for those who may not benefit due to high-risk aggressive disease, which will likely not achieve a curative outcome. On the other hand, the same principle of avoiding unnecessary morbidity applies to those who may require no treatment at all, due to a low likelihood of disease progression, as for GS 6 patients.

From a clinical perspective, we provide evidence questioning the appropriateness of sRP for GS 6 radio- or ablation-recurrent PCa due to an overtreatment issue. Furthermore, the benefit-risk ratio seems much worse than a first-line setting; while disease control may be equivalent to treatment-naïve cases, where radical treatment is no longer recommended, surgery in a recurrence setting is more challenging and morbidity is significantly higher. However, although leaving untreated and observing recurrent PCa should be considered initial management, it may not be that straightforward in all cases as bioptic accuracy before sRP seems still far from accurate, as also shown by others [24,25].

From a research perspective, we add evidence claiming the need for improving the criteria to select and treat disease recurring after radiotherapy and/or ablation. While mpMRI has some limitations, prostate-specific membrane antigen (PSMA) positron emission tomography may play an important role in improving pre-sRP biopsy accuracy and potentially complementing mpMRI as detailed in a primary setting [26]. Approximately one in four to five men has prostate-localized PSMA uptake, which could be used

for targeted biopsy. Another interesting use of PSMA could be as a triage test, if it was proved that negative or GS 6 recurrences would constitute the majority of PSMA-negative biopsied patient [7,27]. While evidence on PSMA-uptake patterns when radiation recurrence is suspected is increasing, these studies still lack pathological confirmation, which is indeed essential for changing clinical practice [7,27]. Another compelling argument is the understanding of recurrent PCa biology. The presence of disease after primary radiation generally relates to aggressive genetically resistant clones either selected or induced by treatment. Genetic and epigenetic alterations of recurrent PCa are in the spectrum of those recorded for metastatic disease [28,29]. However, a minority of cases, as in our and others' series, may not bear aggressive features but may more likely relate to inadequate primary treatment dosage or coverage, possibly leaving some tissue not altered and later developing low-risk non–treatment-related disease [9]. This is certainly the case of focal treatments that leaves voluntarily untreated part of the gland. Recurrent PCa genotypic and phenotypic characterization is far from understood and claims further investigation [28,29].

Our work is not devoid of limitations. First, no centralized pathological review was performed. Nonetheless, tertiary referral centers and experienced pathologists were involved. The retrospective nature may have affected data quality and resulted in the exclusion of some cases; in particular, pre-sRP MRI and detailed biopsy data (eg, number of cores, and targeted or systematic approach) were scarcely available (around one out of five included patients) and were not included in our analysis. In this regard, the accrual time window of our cohort trades off a lower MRI use for a longer follow-up. Multiple primary treatments were included, in terms of both treatment type (eg, radiotherapy, brachytherapy, and high-intensity focused ultrasound) and extension (ie, whole- or partial-gland treatment). However, a majority were whole-gland radio- or brachytherapy patients, and thus our cohort is a good representative of this category. Furthermore, it also accounts for the increasing interests in focal energies and thus reflects the trends of recurrences that PCa practitioners have to deal with in the present era [5]. All cases of sRP were carried out by high-volume surgeons, and the results achieved may not fully reflect practice at lower-volume institutions; also, it is known that sRP series are prone to a selection bias, and patient characteristics may not mirror those of all patients recurring after a primary treatment [30]. We acknowledge that, despite having analyzed the largest published sRP cohort, the number of included GS6 patients is limited and may decrease the strength of our conclusions. However, sRP use will likely remain uncommon for low-risk recurrences, due to the associated toxicity and also in light of our results, and larger contemporary series are not expected shortly; this may increase the relevance of our findings.

Outcomes of other and possibly larger series of men recurring after primary nonsurgical treatment and having GS 6 would be of value. However, we feel that the use of sRP for these men should be questioned and other less invasive research methodologies should be preferred to investigate the outcomes of GS 6 recurrent PCa.

5. Conclusions

GS 6 recurrent PCa after nonsurgical treatment showed no metastatic potential in our series. Salvage radical prostatectomy yields significant complications and poor functional outcomes. Nonetheless, a significant proportion of GS 6 cases at pre-sRP biopsy may be upgraded at final sRP pathology. Overtreatment for recurrent GS 6 after nonsurgical treatment should be avoided, especially considering sRP morbidity. In the idea not to overtreat, efforts should be made to improve diagnostic accuracy of pre-sRP biopsy and to refine the selection criteria for salvage surgical treatment. Further studies are urgently awaited to confirm our findings and to increase pre-sRP biopsy accuracy.

***Author contributions*:** Giancarlo Marra and Giorgio Calleris 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.

Study concept and design: Marra, Calleris, Gontero.
Acquisition of data: Marra, Calleris, Conte.
Analysis and interpretation of data: Marra, Calleris, Conte.
Drafting of the manuscript: Marra, Calleris, Gontero.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Calleris.
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Administrative, technical, or material support: None.
Supervision: Gontero.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2023.08.007.

References

[1] Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. J Clin Oncol 2010;28:1117–23.
[2] Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol 2010;11:1066–73.

[3] Stabile A, Orczyk C, Hosking-Jervis F, et al. Medium-term oncological outcomes in a large cohort of men treated with either focal or hemi-ablation using high-intensity focused ultrasonography for primary localized prostate cancer. BJU Int 2019;124:431–40.
[4] Zapatero A, Mínguez R, Nieto S, Martín de Vidales C, García-Vicente F. Post-treatment prostate biopsies in the era of three-dimensional conformal radiotherapy: what can they teach us? Eur Urol 2009;55:902–10.
[5] Marra G, Ploussard G, Ost P, et al. Focal therapy in localised prostate cancer: real-world urological perspective explored in a cross-sectional European survey. Urol Oncol 2018;36:529.e11–e22.
[6] Jones JS. Radiorecurrent prostate cancer: an emerging and largely mismanaged epidemic. Eur Urol 2011;60:411–2.
[7] Smith CP, Xiang M, Armstrong WR, et al. Patterns of failure in men with radiorecurrent prostate cancer: a post-hoc analysis of three prospective Ga-68-PSMA PET/CT imaging trials. Int J Radiat Oncol Biol Phys 2023;116:1079–84.
[8] Marra G, Shah TT, D'Agate D, et al. The SAFE pilot trial—SAlvage Focal Irreversible Electroporation—for recurrent localized prostate cancer: rationale and study protocol. Front Surg 2022;9:900528.
[9] Marra G, Marquis A, Yanagisawa T, Shariat SF. Salvage radical prostatectomy for recurrent prostate cancer after primary nonsurgical treatment : an updated systematic review. Eur Urol Focus 2023;9:251–7.
[10] Marra G, Calleris G, Massari E, et al. Topography of prostate cancer recurrence: a single-centre analysis of salvage radical prostatectomy specimens and implications for focal salvage treatments. Eur Urol Open Sci 2023;47:110–8.
[11] Shah TT, Kanthabalan A, Otieno M, et al. Magnetic resonance imaging and targeted biopsies compared to transperineal mapping biopsies before focal ablation in localised and metastatic recurrent prostate cancer after radiotherapy. Eur Urol 2022;81:598–605.
[12] Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2021;79:243–62.
[13] Gillessen S, Bossi A, Davis ID, et al. Management of patients with advanced prostate cancer. Part I: intermediate-/high-risk and locally advanced disease, biochemical relapse, and side effects of hormonal treatment: report of the Advanced Prostate Cancer Consensus Conference 2022. Eur Urol 2023;83:267–93.
[14] Kweldam CF, Wildhagen MF, Bangma CH, Van Leenders GJLH. Disease-specific death and metastasis do not occur in patients with Gleason score $\leq$6 at radical prostatectomy. BJU Int 2015;116:230–5.
[15] Eggener SE, Scardino PT, Walsh PC, et al. Predicting 15-year prostate cancer specific mortality after radical prostatectomy. J Urol 2011;185:869–75.
[16] Ross HM, Kryvenko ON, Cowan JE, Simko JP, Wheeler TM, Epstein JI. Do adenocarcinomas of the prostate with Gleason score (GS) $\leq$6 have the potential to metastasize to lymph nodes? Am J Surg Pathol 2012;36:1346–52.
[17] Ahmed HU, Arya M, Freeman A, Emberton M. Do low-grade and low-volume prostate cancers bear the hallmarks of malignancy? Lancet Oncol 2012;13:e509–17.
[18] True L, Coleman I, Hawley S, et al. A molecular correlate to the Gleason grading system for prostate adenocarcinoma. Proc Natl Acad Sci U S A 2006;103:10991–6.
[19] Eggener SE, Berlin A, Vickers AJ, Paner GP, Wolinsky H, Cooperberg MR. Low-grade prostate cancer: time to stop calling it cancer. J Clin Oncol 2022;40:3110–4.
[20] Calleris G, Marra G, Benfant N, et al. Salvage radical prostatectomy for recurrent prostate cancer following first-line nonsurgical treatment: validation of the European Association of Urology criteria in a large, multicenter, contemporary cohort. Eur Urol Focus 2023;9:645–9.
[21] Marra G, Karnes RJ, Calleris G, et al. Oncological outcomes of salvage radical prostatectomy for recurrent prostate cancer in the contemporary era: a multicenter retrospective study. Urol Oncol 2021;39:296.e21–e29.
[22] Mitropoulos D, Artibani W, Graefen M, Remzi M, Rouprêt M, Truss M. reporting and grading of complications after urologic surgical procedures: an ad hoc EAU Guidelines Panel assessment and recommendations. Eur Urol 2012;61:341–9.
[23] Philipson RG, Romero T, Wong JK, et al. Patterns of clinical progression in radiorecurrent high-risk prostate cancer. Eur Urol 2021;80:142–6.
[24] Meeks JJ, Walker M, Bernstein M, Kent M, Eastham JA. Accuracy of post-radiotherapy biopsy before salvage radical prostatectomy. BJU Int 2013;112:308–12.
[25] Preisser F, Würnschimmel C, Pose RM, et al. Concordance of biopsy and pathologic ISUP grading in salvage radical prostatectomy patients for recurrent prostate cancer. Prostate 2022;82:254–9.
[26] Emmett L, Buteau J, Papa N, et al. The additive diagnostic value of prostate-specific membrane antigen positron emission tomography computed tomography to multiparametric magnetic resonance imaging triage in the diagnosis of prostate cancer (PRIMARY): a prospective multicentre study. Eur Urol 2021;80:682–9.
[27] Maitre P, Sood S, Pathare P, et al. Timing of Ga68-PSMA PETCT and patterns of recurrence after prostate radiotherapy: implications for potential salvage. Radiother Oncol 2022;169:71–6.
[28] Shah RB, Palsgrove DN, Desai NB, et al. Enrichment of "Cribriform" morphologies (intraductal and cribriform adenocarcinoma) and genomic alterations in radiorecurrent prostate cancer. Mod Pathol 2022;35:1468–74.
[29] Nestler T, Wittersheim M, Schaefer S, et al. Prediction of radioresistant prostate cancer based on differentially expressed proteins. Urol Int 2021;105:316–27.
[30] Philippou Y, Parker RA, Volanis D, Gnanapragasam VJ. Comparative oncologic and toxicity outcomes of salvage radical prostatectomy versus nonsurgical therapies for radiorecurrent prostate cancer: a meta-regression analysis. Eur Urol Focus 2016;2:158–71.