**Salvage Prostatectomy Following Focal Therapy- Functional and Oncological outcomes**

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**Abstract**

Objectives

To report the oncological and functional outcomes of salvage radical prostatectomy (sRP) after focal therapy (FT).

Subjects/patients (or materials) and methods

A retrospective review of all patients who underwent sRP after FT was performed. Clinical and pathological outcomes focused on surgical complications, oncological and functional outcomes.

Results

34 patients were identified. Median age was 61 (IQR 8.25) years. FT modalities included HIFU (n=19), laser ablation (n=13), focal brachytherapy (n= 1) and cryotherapy (n=1). Median time from FT to recurrence was 10.9 (IQR 17.6) months.

There were no rectal or ureteric injuries. 2 (5.9%) patients had iatrogenic cystotomies. 4 (11.8%) patients developed bladder neck contractures. Mean hospital stay was 2.5 days (SD 2.1).

T-stage was pT2 in 14 (41.2%), pT3a in 16 (47.1%) and pT3b in 4 (11.8%) patients. Thirteen (38%) patients had positive surgical margins. Six (17.6%) patients received adjuvant radiotherapy (RT). At a mean follow up of 4.3 years, 7 (20.6%) patients developed a biochemical recurrence (BCR), and of these, 6 (17.6%) patients required salvage RT.

Positive surgical margins were associated with worse BCR-free survival (HR 6.624, 95% CI 2.243 – 19.563, p<0.001)

The median (IQR) preoperative IPSS and IIEF scores were 7 (4.5-9.5) and 23.5 (15.75-25) respectively, while in the final follow up the median (IQR) values were 7 (3.5-11) and 6 (5-12.25), p=0.088 and p< 0.001, respectively.

At last follow up, 31 (91.2%) patients were continent, 2 (5.9%) had moderate (>1 pad/day) incontinence and 1 (2.9%) required an artificial urinary sphincter.

Conclusions

sRP should be considered as an option for patients who have persistent clinically significant PCa or recurrence after FT. Surgical margins should be recognized as a risk for recurrent disease after sRP.

**Key words**: focal therapy; salvage prostatectomy; prostate cancer; recurrence; HIFU

**Introduction**

Focal therapy (FT) is a therapeutic option for highly selected patients with prostate cancer (PCa), with considerably lower rates of sexual, urinary and bowel toxicity compared to primary radical approaches such as surgery or radiotherapy [1]. FT is delivered by a variety of energy modalities, including photothermal ablation, high intensity focused ultrasound (HIFU), cryotherapy, among others [2]. FT has been shown to have acceptable early-term disease free control rates in well-selected patients [3].

Despite the reported success of FT, there is still a significant risk of failure [4], and some patients require additional treatments such as salvage radiotherapy or salvage radical prostatectomy (sRP) [5]. Local recurrence and/or failure are reported in up to 42% of patients following partial gland ablation with HIFU [6]. The available literature regarding the outcome of salvage RP is limited to retrospective case series [7-9]. Our center has been an early adopter of focal therapy, with initial reports in 2006 [10].

The aim of this study was to assess the oncologic and functional outcomes among patients treated with FT who subsequently underwent sRP at our center.

**Subjects/patients (or materials) and methods**

Following institutional review board approval, a retrospective review was performed of our prospectively maintained prostate FT database. We identified all patients who had a sRP after primary FT between 2006 and 2014. We included men who were treated with true focal ablations (trials targeting 8mm margins around the index lesion) and zonal ablations, but excluded hemiablations. All patients who are considered candidates for FT are discussed at a monthly prostate multidisciplinary meeting. Initial FT included HIFU, laser ablation, focal brachytherapy and cryotherapy. The primary outcome was immediate and early outcomes of the surgery, and the secondary was to describe the follow up, biochemical recurrence, rate of incontinence and the need of external beam radiation.

Data collected included age, FT modality, PSA after FT, PSA prior to the surgery, date of biopsy-proven recurrence after FT, biopsy Gleason score, date of surgery, surgical technique, surgical complications (number of events), surgical pathology [11], and postoperative evaluations, including PSA, need of other adjuvant treatments, continence (number of pads per day) and patient-reported erectile function results.

In our center, patients after FT are followed with serum prostate specific antigen (PSA) (every 3 months for the first year and then every 6 months afterwards). All patients undergo a multiparametric magnetic resonance imaging (mpMRI) and subsequent transrectal biopsy within a year of FT.

Salvage treatment (surgery or radiation treatment) is offered if there is clinically significant (Grade group ≥2) PCa detected on biopsy or Grade Group 1 if this results in significant anxiety to the patient. All patients are offered a consultation with a urologic oncologist and radiation oncologist independently. Staging whole body Technetium 99 bone scan and computed tomography were performed to exclude metastatic disease. sRP is offered both robotically and open and the decision is based on a case by case discussion between the urologic oncologist and the patient. A standard template pelvic lymph node dissection was performed where appropriate according to nomogram evaluation. The decision regarding neurovascular bundle preservation was made by the surgeon depending on the risk of local extension based on clinical history, preoperative imaging and/or intraoperative findings. All pathological specimens were reviewed by a dedicated genitourinary pathologist (TvdK).

Adjuvant radiation therapy is offered to patients with a detectable PSA after the surgery, and also patients with positive surgical margins, locally advanced or high risk PCa.

Functional outcomes were measured using the International Prostate Symptom Scale (IPSS) and the International Index of Erectile Function (IIEF) in every visit both preoperative and in the follow up after surgery.

The probability of biochemical recurrence (BCR) was calculated using the Kaplan-Meier method, and difference between treatment groups determined using the log-rank test. Multivariable analysis with Cox Proportional hazards was used to analyse factors associated with PSA persistence and BCR including surgical margin status, T stage and Gleason score in the final biopsy. All statistical tests were two-sided and a p-value $<0.05$ was considered statistically significant. All analyses were conducted using the SPSS software version 23.0 (SPSS Inc., Chicago, IL).

**Results**

A total of 34 patients were identified. Median age of the cohort was 61 (IQR 8.25) years. FT ablative modalities included laser ablation (n=13), HIFU (n=19), brachytherapy (n= 1) and cryotherapy (n=1). Median time from FT to recurrence was 10.9 (IQR 17.6) months. Table 1 show the preoperative characteristics of the patients. Over 90% had ISUP Gleason Grade Group[8] (GGG) 1-2 before FT, but at re-biopsy for local recurrence, 17.6% had GGG upgrading.

sRP was performed through an open incision in 28 patients (82.4%), robotically in 5 patients (14.7%) and laparoscopically in one patient (5.9%). Unilateral nerve sparing was performed in 19 patients (56%), bilateral nerve sparing in 13 patients (38.2%) and non-nerve sparing in 2 patients (5.9%). No rectal injuries were observed, however 2 (5.9%) patients had iatrogenic cystotomies (both in open surgeries). Bladder neck contracture has developed in 4 (11.8%) patients. Dissection difficulties attributed to prior FT were mentioned in the 26 (77%) patient's operative reports. None of the minimally invasive cases were converted to open surgery. Only 1 (2.9%) patient required blood transfusion. Mean hospital stay was 2.5 days (SD 2.1), Table 2.

In terms of oncological outcomes, T-stage distribution was pT2 in 14 (41.2%), pT3a in 16 (47.1%) and pT3b in 4 (11.8%) patients. Nodal status was pNx in 18 (52.9%) and pN0 in 16 (47.1%) patients. Infield only recurrence was noted in 10 (29.4%) patients, out of field only recurrence in 8 (23.5%) patients and both infield and out of field recurrence in 13(38.2%). A positive surgical margin was present in 13 patients (38%) including 4 with pT2 disease and 9 with pT3. GGG upgrading occurred in 8 (23.5%) and downgrade in 6 (17.6%) patients.

Extraprostatic extension was suggested on MRI on only 1 patient prior to FT. The pre FT biopsy showed Gleason 3+3 disease. His post FT MRI showed a satisfcatory intraprostatic ablation zone following HIFU however there remained concern for EPE. The post FT biopsy showed Gleason 3+4 and he underwent a sRP- this demonstrated T3a Gleason 3+4 disease with a negative surgical margin. PSA remains undetectable 10 years later. There were no further cases with concerns for EPE pre or post (1/34- 2.9%) FT .

Post operatively, 6 patients (17.6%) received adjuvant radiotherapy (RT). Follow up information is presented in Table 3.

At a mean follow up of 4.3 years, 7 patients (20.6%) developed a BCR, and 6 (17.6%) of these underwent salvage RT. No patients developed metastases or died. Positive surgical margins (log rank test p=<0.001) were associated with worse BCR-free survival (HR 6.624, 95% CI 2.243 – 19.563), Figure 1.

From a functional outcome perspective, 31 (91.2%) patients were continent (24 were pad free and 7 wore a security pad or <1 pad/day), 2 (5.9%) had moderate (>1 pad/day) incontinence

and 1 (2.9%) required an artificial urinary sphincter, Table 3. Pre sRP, 20(58%) patients had some degree of erectile dysfunction. After the sRP all patients reported a degree of erectile dysfunction but 18 (53%) patients had a response to medical therapy. Preoperative IPSS and IIEF scores were (median, IQR) 7 (4.5-9.5) and 23.5 (15.75-25), while at last follow up the median values were 7 (3.5-11) and 6 (5-12.25), ($p = 0.088$ and $p < 0.001$, respectively).

**Discussion**

FT is increasingly being utilized as an alternative to radical approaches in highly selected patients with localized PCa. One of the key concerns about FT is whether it compromises the quality of subsequent radical approaches [5,7,12,13]. In this study we present the largest single center experience of sRP following FT. There is limited data in the literature regarding sRP and the majority of reports are predominantly robotic series- the majority of the cases in our series were open sRP. Primary RP is a relatively common procedure with known complications, including adjacent organ damage (0.1-1.2%), blood transfusion (0.4-10%), wound infection (2-3%), lymphocele (25-30%), reoperation (0.5-7%) and long term side effects such as erectile dysfunction (40-85%) and incontinence at 1-year (4-31%) [14-16]. It is well established that sRP after RT is a difficult procedure and requires significant experience and skill set [17].

The definition of recurrence after FT is controversial [18], but a positive biopsy for clinically significant PCa is an undeniable sign. In these cases, a secondary treatment must be considered. In our center, all patients undergo a confirmatory biopsy following mpMRI within a year of FT.

In our series most of the patients underwent an open sRP, but as in other series, minimally invasive procedures were feasible [19]. Given that there was explicit notification of difficult dissection associated with the site of previous FT in the majority of operation notes, we support the idea of using the surgical technique in which the surgeon is most experienced with, acknowledging the expected difficulty of these cases. As in primary RP, neurovascular bundle preservation is always desired, but should not be done if oncological efficacy is likely to be compromised. The rate of positive surgical margins (PSM) in our series was close to 40%, which is within the expected rate when compared with sRP after RT, but higher than expected when compared with primary RP [17,20]. However, the PSM rate is higher in our series compared to previous series (15-27%) [5,12] Transfusion rates and hospital stay are both consistent with published series [21,22]. As previous studies have shown, PSM are associated with higher rate of recurrence [23,24].Marconi et al, described the largest series of sRP (n=82), they report a 40% BCR, double that reported in our study [8]. This highlights the need for men to be counselled regarding the potential need for multimodality treatment.

In this study, more than half of the patents had T-stage >pT2, with the majority being pT3a. A similar rate was reported by Lawrenstchuk et al. (10 out of 14 had pT3 disease) [5]. These likely reflect that the patients with lower Gleason scores and lower T-stage are more likely to respond to FT and are thus underrepresented in this salvage series. A multicenter study demonstrating the results of sRP in 15 patients after HIFU (including whole-gland HIFU) was published in 2011 [5]. This study describes a feasible but more complicated surgery compared to primary RP, and recommends the discussion of

this salvage procedure with all patients before undergoing primary HIFU. In another report of robotic assisted sRP in 34 patients (after primary external beam therapy, brachytherapy and HIFU) [19], the authors also state that this procedure is feasible, but with a higher rate of complications compared to primary RP. In this last report, the univariate analysis demonstrated an association between PSA doubling time before the surgery and risk of BCR and also the initial Gleason score and BCR. Similar conclusions, in terms of oncological and functional outcomes compared to primary RP, have been reported in other similar series; and most report higher than expected rate of upstaging in the final pathology [6,7,13].

Most of our patients were completely continent or had minor leakage, using no more than one pad a day in the last follow up. Even though one patient required an artificial urinary sphincter, the overall results in terms of continence and sexual function are acceptable in comparison to primary RP [25].

As imaging techniques advance and become more available- modern imaging techniques such as PSMA PET scans may have a role in the primary staging of prostate cancer. Uprimny et al, demonstrated how Gleason score and PSA level correlated with
the intensity of tracer accumulation in the primary tumours on $^{68}$Ga-PSMA-11 PET/CT [26]. Our group is involved in a prospective trial using a hybrid PET-MRI, a novel scanner which incorporates MRI with molecular imaging will improve the detection rate of clinically significant tumors [27]. It will allow us to hopefully see the clinical utility of PSMA in local staging of prostate cancer with the obvious additional benefit of out-ruling metastatic disease at the outset. Improved detection of clinically significant prostate cancer may enable a tailored, personalized therapeutic approach, decreasing morbidity and potentially improving overall patient outcome.

Furthermore, imaging following FT is a key component in detecting residual or recurrent disease. Punwani et al, demonstrated a sensitivity of up to 87% and specificity up to 82% for detection residual disease following FT [28]. An important consideration in the interpreation is the timing of MRI following FT. Dickinson et al, highlighted the differences between an early (<3 months) and late (>6months) MRI- the former focusing on the extent of the ablation zone and the later at residual or recurrent disease. They demonstrated high negative predictive values (97%) yet low positive predictive values (14-44%) [29]. Our study showed a high rate of pathologic T3 disease which was not detected on MRI- the quality of MRI in our early series is likely a factor here- many pre FT MRIs were performed outside of our institution as currently in Canada- pre biopsy MRI is not covered. All our current trial patients undergo in-house mpMRI.

The main limitation of the study is the retrospective nature of the data. Also, these are all very well selected patients and this represents a single-center experience with experienced urologic

oncologists. The lack of information of PSA dynamics and long term follow up are also limitations of the study, but the objective of the study was to describe the initial complications and functional outcomes of this surgical technique, not the long-term oncological results. The inclusion of surgical results of multiple surgeons and the use of different focal therapy modalities makes this report a real-world experience, but also increases the biases within the data. Despite this, this is a large series to date analyzing outcomes of sRP after FT, although the sample size is still relatively small.

Our study demonstrates that after a mean follow up of 4 years, sRP post FT seems to have reasonable oncological and functional outcomes, although not as favourable as in primary RP. This procedure should be considered as an option for patients who have persistent clinically significant PCa or recurrence after FT, especially in high volume centres. Surgical margins should be recognized as a risk for recurrent disease after sRP. Larger standardized series will be useful to gain better knowledge and offer recommendations for patients with this clinical scenario.

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**Conflicts of Interest**

None

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**Legends to illustrations and tables**

Figure 1. Impact of PSM on the absence of detectable disease after sRP (including PSA persistence and/or BCR)

PSM= positive surgical margins

sRP= salvage radical prostatectomy

BCR= biochemical recurrence

Table 1: Preoperative characteristics

Table 2: Surgical details

Table 3: Follow up details

Table 1: Preoperative characteristics

| | N= 34 |
|---|---|
| **Age at sRP (mean [SD])** | 61.26 (6.66) |
| **PSA Before FT (Median, IQR)** | 4.19, 1,72-15.01 |
| **Gleason Grade/ ISUP Group Before FT** | |
| 3+3/1 | 20 (58.8%) |
| 3+4/2 | 11 (32.4%) |
| 4+3/3 | 2 (5.9%) |
| 4+4/4 | 0 |
| 4+5/5 | 0 |
| NA | 1 (2.9%) |
| **Type of Primary Treatment** | |
| Laser Ablation | 13 (38.2%) |
| HIFU | 19 (55.9%) |
| Cryotherapy | 1 (2.9%) |
| Brachytherapy | 1 (2.9%) |
| **Focal Treatment Site** | |
| Left Base/Mid | 5 (14.7%) |
| Left Apex | 5 (14.7%) |
| Right Apex/Mid | 7 (20.6%) |
| Right Apex | 3 (8.8%) |
| Unspecified | 14 (41.2%) |
| **PSA at Recurrence (Median, IQR)** | 5.38 (2.93-16.98) |
| **Location of recurrence** | |
| Infield only | 10 (29.4%) |
| Out of field only | 8 (23.5%) |
| Both- infield and out of field | 13 (38.2%) |
| Unspecified | 3 (8.8%) |
| **Gleason Grade/ ISUP Group at** | |

| **Biopsy Previous to Surgery** | |
|---|---|
| 3+3/1 | 7 (20.6%) |
| 3+4/2 | 21 (61.8%) |
| 4+3/3 | 2 (5.9%) |
| 4+4/4 | 3 (8.8%) |
| 4+5/5 | 1 (2.9%) |
| **IPSS and IIEF before sRP** | |
| IPSS (mean,IQR) | 7 (4.5-9.5) |
| IIEF (mean,IQR) | 23.5 (15.75-25) |

sRP= salvage radical prostatectomy

FT= focal therapy

ISUP= International Society of Urological Pathology

HIFU= High Frequency Ultrasound

IPSS- International Prostate Symptom Score

IIEF= International index of erectile function

Table 2: Surgical details

| | N= 34 |
|---|---|
| **sRP Approach** | |
| Open | 28 (82.4%) |
| Laparoscopic | 1 (2.9%) |
| Robotic-Assisted | 5 (14.7%) |
| **Nerve sparing** | |
| Unilateral | 19 (56%) |
| Bilateral | 13 (38.2%) |
| None | 2 (5.9%) |
| **Gleason Grade/ ISUP Group After sRP** | |
| 3+3/1 | 7 (20.6%) |
| 3+4/2 | 20 (58.8%) |
| 4+3/3 | 5 (14.7%) |
| 4+4/4 | 0 (0%) |
| 4+5/5 | 2 (5.9%) |
| **Surgical Margin Involvement** | 13 (38.2%) |
| **T Stage** | |
| pT2 | 14 (41.1%) |
| PT3a | 16 (47.1%) |
| pT3b | 4 (11.8%) |
| **N Stage** | |
| Nx | 18 (52.9%) |
| N0 | 16 (47.1%) |
| **Intraoperative Complications** | |
| **Rectal Injury** | 0 (0%) |
| **Cystotomy** | 2 (5.9%) |
| **Ureteric Injury** | 0 (0%) |
| **Blood loss (cc, mean [SD])** | 512 (396) |
| **Length of stay (days, mean [SD])** | 2.45 (2.14) |

| | |
|---|---|
| **Detectable PSA after RP** | 9 (26.5%) |

sRP= salvage radical prostatectomy

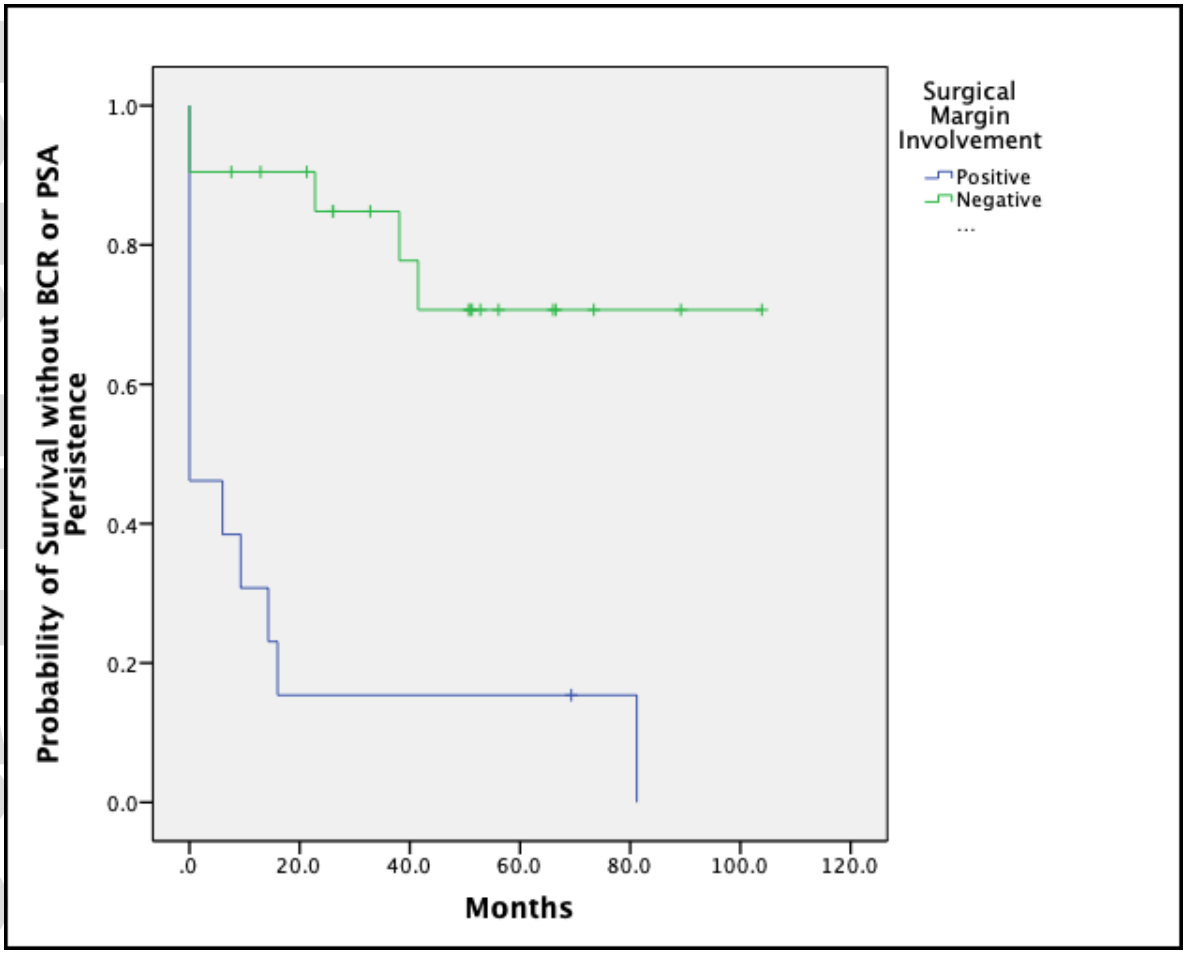
Table 3: Follow up details

| | N= 34 |
|---|---|
| **Follow up in months (Median [Range])** | 52 (7.63-117) |
| **Postoperative Radiation Therapy** | 1 2 (64.7%) |
| Adjuvant | 6 (17.6%) |
| Salvage | 6 (17.6%) |
| **Months to BCR (mean [SD])** | 42.13 (29.23) |
| **Metastasis** | 0 |
| **Continence after sRP** | |
| 1 pad or less | 31 (91.2%) |
| 2 pads or more | 2 (5.9%) |
| Required Artificial Urinary Sphincter | 1 (2.9%) |
| **IPSS and IIEF after sRP** | |
| IPSS (median, IQR) | 7 (3.5-11) |
| IIEF (median, IQR) | 6 (5-12.25) |
| **Bladder Neck Contracture** | 4 (11.8%) |
| **Androgen Deprivation Therapy (with or without radiation therapy)** | 4 (11.8%) |

BCR= biochemical recurrence

sRP= salvage radical prostatectomy

Figure 1. Impact of PSM on the absence of detectable disease after sRP (including PSA persistence and/or BCR)




Abbreviations: PSM, Positive surgical margins; sRP, Salvage radical prostatectomy; PSA, Prostate specific antigen; BCR, Biochemical recurrence