Does adding local salvage ablation therapy provide survival advantage for patients with locally recurrent prostate cancer following radiotherapy?

Whole gland salvage ablation post-radiation failure in prostate cancer

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Abstract

Introduction: Some men who experience prostate cancer recurrence post-radiotherapy may be candidates for local salvage therapy, avoiding and delaying systemic treatments. Our aim was to assess the impact of clinical outcomes of adding salvage local treatment in prostate cancer patients who have failed radiation therapy.

Methods: Following radiation biochemical failure, salvage transperineal cryotherapy (sCT, n=186), transrectal high intensity focused ultrasound ablation (sHIFU, n=113), or no salvage treatment (NST, identified from the pan-Canadian Prostate Cancer Risk Stratification [ProCaRS] database, n=982) were compared with propensity-score matching. Primary endpoints were cancer-specific survival (CSS) and overall survival (OS).

Results: Median followup was 11.6, 25.1, and 14.3 years following NST, sCT, and sHIFU, respectively. Two propensity score-matched analyses were performed: 1) 196 NST vs. 98 sCT; and 2) 177 NST vs. 59 sHIFU. In the first comparison, there were 78 deaths and 49 prostate cancer deaths for NST vs. 80 deaths and 24 prostate cancer deaths for sCT. There were significant benefits in CSS ($p<0.001$) and OS ($p<0.001$) favoring sCT. In the second comparison, there were 52 deaths (31 from prostate cancer) for NST vs. 18 deaths (nine from prostate cancer) for sHIFU. There were no significant differences in CSS or OS possibility attributed to reduced sample size and shorter followup of sHIFU cohort.

Conclusions: In select men with recurrent prostate cancer post-radiation, further local treatment may lead to benefits in CSS. These hypothesis-generating findings should ideally be validated in a prospective clinical trial setting.

Introduction

Localized prostate cancer can be treated with curable intent with radiation therapy. However, a third of the patients fail with biochemical recurrence.[1,2] These patients are usually treated with systemic androgen deprivation therapy (ADT), with its associated comorbidity.[3,4] Some of the patients with localized recurrence post-radiation may be able to avoid or delay systemic therapy with salvage local treatment options. Local ablation options include salvage cryotherapy (sCT) and salvage high intensity focused ultrasound (sHIFU). These ablation techniques may be offered to patients who are averse to the morbidity of salvage radical surgery or are not suitable surgical candidates. sCT has low overall complications and a biochemical cure rate of 39% at 10 years.[5,6] sHIFU and sCT have been shown to have a similar comorbidity profile.[7]

While there are reports on comparing oncological outcomes with ablation technique vs. salvage prostatectomy,[8] there are no reports with local salvage treatment vs. those without salvage therapy (NST). Herein, we performed a propensity score-matched analysis with a large multi-institutional radiation therapy database (where patients received standard of care but did not have salvage local prostate treatment) compared with a prospective single-institution database on salvage local ablative therapies to examine for differences in cancer-specific survival (CSS) and overall survival (OS). Ideally, the findings of this analysis would provide both guidance for clinicians and clinical trialists in the management of this challenging patient population.

Methods

Patient populations

The ablation therapy patient cohorts were selected from a single academic center with a prospectively maintained database. Patients underwent sCT between 1994 and 2004 (n=186) or sHIFU between 2006 and 2018 (n=113) performed by a single surgeon (JC), as previously described.[9,10] All patients had previously received primary radiotherapy (external beam radiation therapy [EBRT] or brachytherapy) and had histologically proven radio-recurrent prostate cancer (all patients had a transrectal ultrasound-guided prostate biopsy post-radiation confirming recurrence). All patients except two had metastatic screening with radionucleotide bone scan and abdominal and pelvic computed tomography (CT). Some patients had been started on ADT prior to their referral for local ablative therapy and were included in the salvage cohorts. However, ADT was discontinued immediately following both sCT and sHIFU.

The NST patient cohort was selected from the Prostate Cancer Risk Stratification (ProCaRS) database consisting of patients from four Canadian institutions, including 3440 prostate cancer patients treated with EBRT between 1994 and 2010, as discussed in detail previously.[11,12] This population was further restricted to patients subsequently developing biochemical failure accordingly to the American Society for Radiation Oncology–Radiation Therapy Oncology Group Phoenix II definition involving a prostate-specific antigen (PSA) rise of ≥2 ng/mL above the nadir PSA (n=982).[13] Research ethics board approval was obtained from Western University for this study (REB #103538).

Treatment

sCT was performed, as previous described,[10] with transperineal placement of cryotherapy probes under three-dimensional transrectal ultrasound guidance. Two freeze-thaw cycles were employed. sHIFU treatment was performed with the Sonablate® 500 device with continuous transrectal monitoring.[9] A suprapubic Foley catheter, placed intraoperatively, was used to divert urine for three weeks for both groups.

Followup

For the ablation group, followup data was obtained from clinical records or by contacting patients directly. Clinical monitoring outside 24 months was at the discretion of the referring urologists.[14] In case of biochemical or clinical failure following local ablative therapy, initiation of ADT was at the discretion of the treating physician.

Endpoints

The primary endpoint was CSS, calculated as time from date of radiotherapy to date of death attributed to prostate cancer or date of last followup, whichever comes first. The secondary endpoint was OS, calculated as time from date of radiotherapy to date of death (any cause) or date of last followup, whichever comes first. As a sensitivity analysis, both endpoints were calculated as time from date of biochemical failure (for NST cohort) or from date of salvage treatment (for sCT and sHIFU cohorts).

Statistical analysis

Patients receiving NST were matched to sCT (match #1) and separately to sHIFU (match #2) using propensity-score matching. Propensity scores were generated using multivariable logistic regression (propensity-score model) predictive of treatment assignment (NST vs. sCT for match #1 and NST vs. sHIFU for match #2) based on: age at radiation; pre-radiation baseline PSA; pre-radiation Gleason score (<6, 6, 7, or 8–10); pre-radiation T-stage (cT1, cT2, cT3, cT4); and pre-radiation ADT (yes, no). The Gleason score of <6 was used as documented by the original pathology reports (which had not conformed to current pathology classifications). Patients were risk-stratified according to the Genitourinary Radiation Oncologists of Canada (GUROC)[12]:

1. Low-risk: T1c–T2a, PSA ≤1 0ng/mL, and Gleason score ≤6
2. Intermediate-risk: T1–T2, PSA ≤20 ng/mL, and Gleason score ≤7, not otherwise low-risk
3. High-risk: T3–T4 or PSA >20 ng/mL, or Gleason score 8–10

All possible interaction terms were examined and retained in final models if significant. Pre-radiation ADT was defined as starting prior to completion of radiation for all cohorts. Twelve possible matching scenarios were examined for each match based on prespecified ratios (1:1 to 1:4) and calipers (0.2 of standard deviation of the logit of the propensity score; 0.10 and 0.15).[15] Standardized differences were calculated to assess for imbalance in baseline characteristics included in the propensity-score model prior to matching and for each match scenario selecting a threshold of >0.10 to indicate statistical imbalance.[16,17] Final optimal matches were selected based on minimizing overall standardized differences across all variables included in match and maximizing power (sample size). Match #1 (NST vs. sCT) was based on a caliper of 0.2 of standard deviation of the logit of the propensity score and Match #2 (NST vs. sHIFU) was based on a caliper of 0.15.

Descriptive statistics were generated for baseline patient characteristics stratified by cohort for all patients prior to matching for Match #1 (NST [n=982] vs. sCT [n=186]) and

Match #2 (NST [n=982] vs. sHIFU [n=113]) and repeated for matched cohorts. Comparisons were made using the Chi-squared test, Fisher's exact test, two-sample T-test or Wilcoxon rank sum test, as appropriate. For variables included in the propensity-score model, comparisons were made using the paired T-test, Wilcoxon signed rank test, or McNemar test, as appropriate, in addition to calculation of standardized differences (discussed previously). Kaplan-Meier estimates were generated for CSS and OS stratified by matched cohorts (Match #1: NST vs. sCT; Match #2: NST vs. sHIFU) and compared using the stratified log-rank test (stratified by matched pair number). All statistical analysis was performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, U.S.), using two-sided statistical testing at the 0.05 significance level.

Results

sCT post-radiation vs. NST

Baseline characteristics comparing sCT and NST are summarized in Table 1. Prior to matching, compared to NST, patients receiving sCT were younger (p<0.001), had more cT2 and fewer cT3 and cT4 disease (p<0.001), and with more Gleason score 6 and fewer Gleason score 7–10 disease (p<0.001). Fewer sCT patients received pre-radiation ADT (p<0.001). The median followup from initial radiation was 11.6 years (95% confidence interval [CI] 11.3–11.9) for NST and 25.1 years (95% CI 24.2–26.1) for the sCT group. Propensity-score matching resulted in final matched cohorts of 98 sCT and 196 NST patients in a 1:2 ratio. Details of final matched cohort selection are summarized in Supplementary Table 1 (available in the Appendix at *cuaj.ca*). Following propensity-score matching, cohorts were comparable in terms of variables included in propensity-score model (age at radiation, pre-radiation baseline PSA, pre-radiation T-stage, pre-radiation Gleason score, and ADT pre-radiation), with no significant differences observed.

In the NST cohort, there were 78 deaths with 49 from prostate cancer (median followup 11.6 years) compared to 80 deaths with 24 from prostate cancer in the sCT cohort (median followup 25.1 years). This translated to a significantly improved CSS (p<0.001) and OS (p<0.001) in patients receiving sCT compared to NST without local salvage therapy (Fig. 1) calculated from date of radiotherapy. Median

Table 1. Baseline patient characteristics stratified by cohort (NST vs. sCT)

Characteristic	All patients (n=1168)					Matched patients (n=294)				
	n	NST (n=982)	sCT (n=186)	p	SD	n	NST (n=196)	sCT (n=98)	p	SD
Age at radiation,[1] mean ± SD, median (IQR)	1168	18.7±22.8 11.9 (7.3, 20.0)	12.9±20.0 7.3 (5.5, 12.2)	**<0.001**	**0.892**	294	67.8±6.5 69.0 (63.0, 73.0)	67.9±4.4 68.4 (65.4, 70.9)	0.788	0.027
Baseline PSA (pre-radiation),[1] mean ± SD, median (IQR)	1133	18.7±22.8 11.9 (7.3, 20.0)	15.8±14.7 11.0 (7.7, 18.9)	0.221	**0.150**	294	16.9±20.3 12.7 (7.0, 18.8)	15.0±12.6 11.0 (7.7, 17.0)	0.459	**0.108**
T stage (pre-radiation),[1] n (%)	1131			**<0.001**		294			0.304	
T1		166 (17.2)	33 (19.8)	0.426	0.065		37 (18.9)	20 (20.4)	0.701	0.039
T2		482 (50.0)	113 (67.7)	**<0.001**	**0.365**		126 (64.3)	61 (62.2)	0.642	0.042
T3		288 (29.9)	21 (12.6)	**<0.001**	**0.433**		33 (16.8)	17 (17.4)	0.879	0.014
T4		28 (2.9)	0 (0)	**0.026**	**0.245**		0 (0)	0 (0)	–	–
Gleason score (pre-radiation),[1] n (%)	1125			**<0.001**		294			0.406	
<6		180 (18.8)	2 (1.2)	**<0.001**	**0.615**		3 (1.5)	2 (2.0)	0.706	0.039
6		212 (22.2)	101 (59.8)	**<0.001**	**0.827**		100 (51.0)	51 (52.0)	0.796	0.020
7		398 (41.6)	54 (32.0)	**0.018**	**0.202**		66 (33.7)	35 (35.7)	0.659	0.043
8–10		166 (17.4)	12 (7.1)	**<0.001**	**0.317**		27 (13.8)	10 (10.2)	0.250	**0.110**
GUROC risk, n (%)	1137			**0.003**	–	294			0.970	–
Low		122 (12.4)	34 (21.9)				33 (16.8)	17 (17.4)		
Intermediate		398 (40.5)	63 (40.7)				89 (45.4)	43 (43.9)		
High		462 (47.1)	58 (37.4)				74 (37.8)	38 (38.8)		
ADT pre-radiation,[1] n (%)	1168	397 (40.4)	33 (17.7)	**<0.001**	**0.516**	294	69 (35.2)	27 (27.6)	0.092	**0.165**
Unknown		29 (6.2)	9 (6.2)				3 (3.9)	4 (5.0)		
Median followup (years),[2] median (95% CI)	1168	11.6 (11.3, 11.9)	25.1 (24.2, 26.1)	**<0.001**	–	294	11.2 (10.5, 11.8)	22.7 (21.4, 24.6)	**<0.001**	–

[1]Included in propensity-score model. [2]Calculated using reverse Kaplan-Meier method. p<0.05 and SD>0.10 shown in BOLD. ADT: androgen deprivation therapy; CI: confidence interval; GUROC: Genitourinary Radiation Oncologists of Canada; IQR: interquartile range; NST: no salvage treatment; PSA: prostate-specific antigen; sCT: salvage transperineal cryotherapy; SD: standardized deviation.

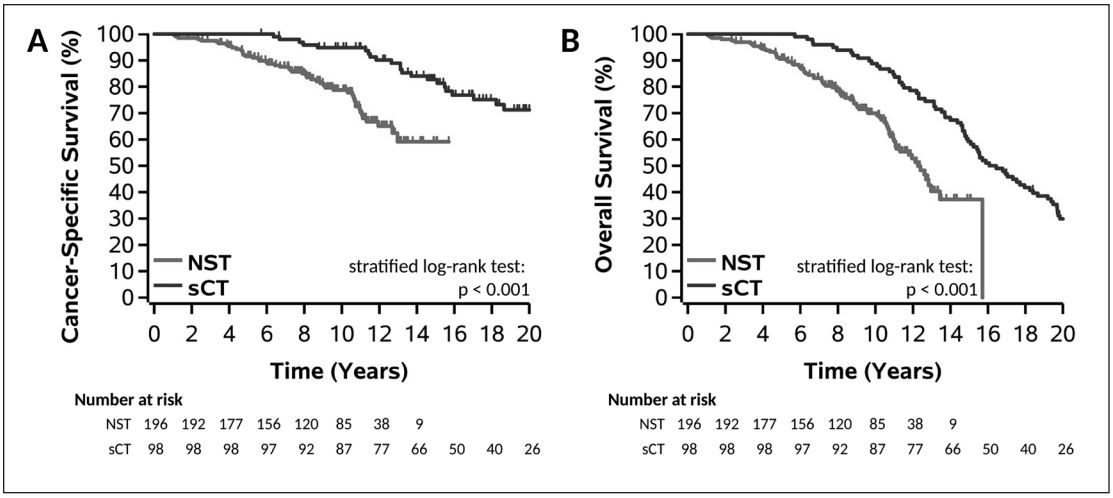

Fig. 1. Kaplan-Meier plot for survival outcomes for matched patients (NST and sCT) from date of radiation therapy. NST: no salvage treatment; sCT: salvage transperineal cryotherapy.

OS was 12.3 years for NST and 16.3 years for sCT (median CSS not reached). This effect was still present following a sensitivity analysis calculated from date of biochemical failure post-radiation (for NST cohort) and from date of salvage ablation treatment (for sCT cohort) for CSS (p=0.003) and OS (p=0.004) (Supplementary Fig. 1; available in the Appendix at *cuaj.ca*). Following sensitivity analysis, median CSS was 11.6 years for NST (not reached for sCT), and median OS was 8.4 years for NST and 11.8 years for sCT.

sHIFU ablation post-radiation vs. NST

Baseline characteristics comparing sHIFU and NST are summarized in Table 2. Similarly, prior to matching compared to NST, patients receiving sHIFU were younger (p<0.001), had more T1 and fewer T3 disease (p<0.001), with more Gleason score 6 and fewer Gleason score 8–10 disease (p<0.001). Fewer sHIFU patients received pre- and post-radiation ADT (p<0.001 and p<0.001, respectively). Median followup from initial radiation was 14.3 years (95% CI 13.3–16.3) for sHIFU patients. Propensity-score matching resulted in final matched cohorts of 59 sHIFU and 177 NST patients in a 1:3 ratio. Details of final matched cohort selection are summarized in Supplementary Table 2 (available in the Appendix at *cuaj.ca*). Following propensity-score matching, cohorts were comparable in terms of variables included in propensity-score model (age at radiation, pre-radiation baseline PSA, pre-radiation T-stage, pre-radiation Gleason score, and ADT pre-radiation), with no significant differences observed.

Fifty-two deaths with 31 from prostate cancer were observed in the NST cohort (median followup 11.6 years) compared with 18 deaths with nine from prostate cancer in the sHIFU cohort (median followup 14.3 years). However, there were no significant differences in CSS (p=0.326) or OS (p=0.182) calculated from date of radiotherapy (Fig. 2). Median OS was 12.8 years for NST and 17.4 years for sHIFU (median CSS not reached). Calculating OS and CSS from date of biochemical failure (for NST cohort) and from date of salvage ablation treatment (for sHIFU cohort) did not result in any significant difference in CSS (p=0.639) or OS (p=0.937) (Supplementary Fig. 2 available in the Appendix at *cuaj.ca*). Median OS was 9.8 years for NST and 10.4 years for sHIFU (median CSS not reached).

Discussion

This study showed that long-term outcomes favour salvage treatment following radiation therapy failure for prostate cancer when compared to NST with no further local treatment. CSS and OS were significantly lower in the NST cohort when compared to the sCT cohort. The low number of events in the smaller sHIFU cohort highlights the need for longer followup for differences in OS and CSS (sHIFU median followup 14.3 years vs. 25.1 years for sCT). The sHIFU cohort findings are, thus relatively exploratory in comparison to the very mature sCT cohort. This study is the first to compare long-term outcomes of salvage local treatment to NST without further local therapy.

The patients who had biochemical failure in the NST group would be treated by systemic ADT at the discretion of their physician. The use of ADT within this cohort of patients is not known, but previous studies have shown 94% of radiation failure patients were treated with only ADT.[4] Some of these patients would have potentially avoided ADT use entirely if the localized recurrence was successfully eradicated. Within the sCT cohort, we have previously shown 58% had delayed biochemical failure, with 51% requiring ADT.[18] Systemic ADT has been linked with increased cardiovascular, metabolic, and bone-related morbidity, which is an important consideration given these patients are already at

Table 2. Baseline patient characteristics stratified by cohort (NST vs. sHIFU)

Characteristic	All patients (n=1095)					Matched patients (n=236)				
	n	NST (n=982)	sHIFU (n=113)	p	SD	n	NST (n=177)	sHIFU (n=59)	p	SD
Age at radiation,[1] mean ± SD, median (IQR)	1095	70.3±6.5 71.0 (67.0, 75.0)	63.3±6.2 63.6 (59.3, 68.3)	**<0.001**	**1.100**	236	67.2±6.1 69.0 (64.0, 71.0)	66.8±4.9 67.6 (63.7, 69.8)	0.449	0.076
Baseline PSA (pre-radiation),[1] mean ± SD, median (IQR)	1077	18.7±22.8 11.9 (7.3, 20.0)	12.9±20.0 7.3 (5.5, 12.2)	**<0.001**	**0.270**	236	12.3±14.9 9.4 (6.2, 14.2)	10.4±7.1 8.5 (5.6, 13.9)	0.362	**0.167**
T stage (pre-radiation),[1] n (%)	1062			**<0.001**		236			0.626	
T1		166 (17.2)	38 (38.8)	**<0.001**	**0.495**		47 (26.6)	18 (30.5)	0.419	0.088
T2		482 (50.0)	52 (53.1)	0.564	0.061		112 (63.3)	34 (57.6)	0.297	**0.116**
T3		288 (29.9)	8 (8.2)	**<0.001**	**0.576**		18 (10.2)	7 (11.9)	0.602	0.054
T4		28 (2.9)	0 (0)	0.101	**0.245**		0 (0)	0 (0)	–	–
Gleason score (pre-radiation),[1] n (%)	1063			**<0.001**		236			0.912	
<6		180 (18.8)	1 (0.9)	**<0.001**	**0.629**		1 (0.6)	1 (1.7)	0.317	**0.107**
6		212 (22.2)	46 (43.0)	**<0.001**	**0.455**		70 (39.6)	22 (37.3)	0.663	0.046
7		398 (41.6)	55 (51.4)	0.053	**0.197**		100 (56.5)	33 (55.9)	0.916	0.011
8–10		166 (17.4)	5 (4.7)	**<0.001**	**0.414**		6 (3.4)	3 (5.1)	0.405	0.084
GUROC risk, n (%)	1083			**<0.001**	–	236			0.750	–
Low		122 (12.4)	31 (30.7)				32 (18.1)	13 (22.0)		
Intermediate		398 (40.5)	49 (48.5)				114 (64.4)	35 (59.3)		
High		462 (47.1)	21 (20.8)				31 (17.5)	11 (18.6)		
ADT pre-radiation,[1] n (%)	1095	397 (40.4)	23 (20.4)	**<0.001**	**0.447**	236	52 (29.4)	15 (25.4)	0.370	0.089
Median followup (years),[2] median (95% CI)	1095	11.6 (11.3, 11.9)	14.3 (13.3, 16.3)	**<0.001**	–	236	10.5 (9.6, 11.1)	13.5 (11.5, 16.7)	**<0.001**	–

[1]Included in propensity-score model. [2]Calculated using reverse Kaplan-Meier method. p<0.05 and SD>0.10 shown in BOLD. ADT: androgen deprivation therapy; CI: confidence interval; GUROC: Genitourinary Radiation Oncologists of Canada; IQR: interquartile range; NST: no salvage treatment; PSA: prostate-specific antigen; SD: standard deviation; sHIFU: salvage transrectal high intensity focused ultrasound.

increased risk on account of their demographics and underlying malignancy.[3,19]

On the other hand, patients undergoing salvage therapies post-radiation may be subjected to significant local adverse effects. Serious complications from sCT include rectourethral fistulas (3%) and severe incontinence (7%).[20] The most common complications are usually manageable endoscopically.[21] Erectile dysfunction is also common with increasing age, comorbidities, and the original local radiation as likely contributing factors.[6] Previously, we have found that sHIFU has an improved morbidity profile when compared to sCT, as the ablation energy can be more precisely targeted to the prostate tissue.[10] Thus, even though the adverse effects can be significant, the incidence is relatively low and most can be managed without significant additional morbidity.

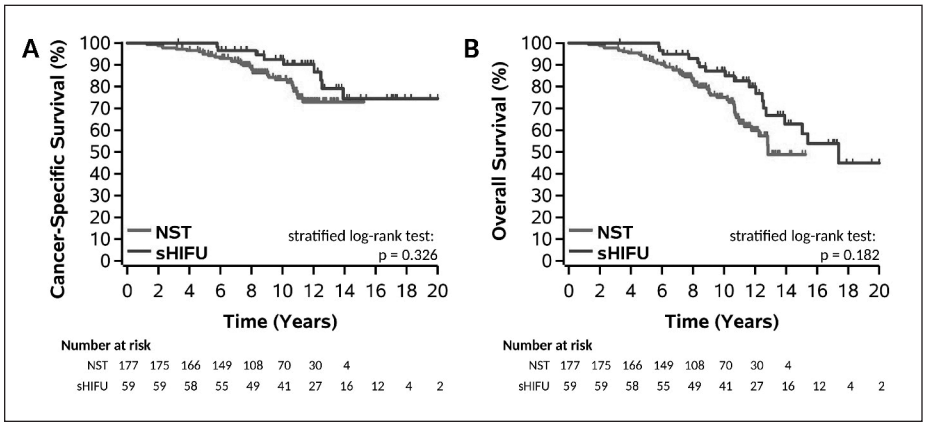

Fig. 2. Kaplan-Meier plot for survival outcomes for matched patients (NST and sHIFU) from date of radiation therapy. NST: no salvage treatment; sHIFU: salvage transrectal high intensity focused ultrasound ablation.

Patients in the ablation group had repeat biopsy within 12 months. Our series had 15% local persistent disease[22] and, in the absence of metastatic disease, were offered repeat ablation. Thus, most of the treatment failures in the ablation group were systemic in nature. Since the salvage ablation cohorts were screened only with computerized axial tomography and radionucleotide bone scans prior to ablation, the systemic failure rate should improve with better staging modalities, such as positron emission tomography (PET), especially

when contemporary radionuclide tracers like prostate-specific membrane antigen (PSMA) are used. Hopefully this can result in further reduction in the detection of occult metastatic disease,[23] thereby refining the patient selection process for local salvage ablative procedures while improving the overall success rate of local salvage therapies.

Selection of an ideal patient who would benefit most from salvage therapies is key to avoid side effects of local ablation while also preventing systemic progression. Previous studies have shown pre-salvage Gleason score and PSA were useful in predicting treatment response to the salvage therapy. Similarly, once salvage cryotherapy treatment was administered, a lower PSA nadir predicted decreased biochemical recurrence.[5,24]

Limitations

There are several limitations to the study. Limitations specific to the NST cohort described previously include heterogeneity within the cohort with regards to treatment regimen.[11] The heterogeneity within the cohort has been highlighted as a concern, especially with one site potentially overclassifying CSS. Likewise, the limitations of salvation ablation group include the retrospective and single-surgeon nature of this study.[10] Furthermore, data on salvage ADT with the NST group were not available. There is a very low chance of the NST group undergoing further local therapy that was not captured; however, salvage ablation was not readily available to our NST population.

Comorbidity data was not available for the NST and not included in the propensity-score model. This would impact the comparisons between the cohorts for the OS. The cohort sizes, followup duration, and treatment time were different. The sCT and sHIFU were done in sequential eras, hence the groups were not merged into a larger single group. Furthermore, the primary analyses compared patients from date of radiation.

Within the ablation group, there could be a selection bias, as some of the patients eligible for ablation may have died prior to selection. This was attempted to be corrected with comparing the groups from date of biochemical failure in the NST group and date of ablation therapy (date of biochemical failure for salvage group was not available for all patients). The analyses results were similar, thus indicating the selection bias as likely having minimal impact.

During the study period from 1994 to present, there have been significant changes in prostate cancer management, including some of the propensity-score matching variables, such as Gleason score, thus making the results hypothesis-generating. To overcome the limitations of the study (vide supra), a prospective external validation is vital. However, recruiting such patients in a timely manner may not be feasible, with both the paucity of appropriate patients and long followup duration required for oncological endpoints to be reached. Furthermore, a prospective study of such duration would be similarly affected by future modifications in prostate cancer management in the NST cohort. Therefore, the authors chose to take advantage of the long followup from our prospectively accrued local salvage cohort and attempted to address some of the deficiencies with propensity-score matching, albeit with the limitations discussed.

Conclusions

In selected men, salvage therapy to the prostate bed following recurrence of prostate cancer may offer improvement in important clinical outcomes compared to current standard of care. These findings would be ideally validated in a prospective, randomized, control trial.

Competing interests: Dr. Nair has participated in a user feasibility study conducted by Profound Medical. Dr. Chin has been an advisor for AbbVie, Astellas, Janssen, Profound Medical, Sanofi-Aventis, and TerSera; has received payment and/or honoraria for consultation and clinical trial participation from AbbVie, Astellas, Profound Medical, Sanofi-Aventis, and TerSera. The remaining authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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