

Outcomes of salvage radiotherapy for recurrent prostate cancer after radical prostatectomy

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ABSTRACT

Introduction: Salvage radiotherapy (SRT) provides effective biochemical control for patients with prostate cancer who have prostate-specific antigen (PSA) failure after radical prostatectomy. However, the effect of SRT on long-term clinical outcomes remains unknown. Therefore, we report the natural history of patients treated with SRT.

Methods: We identified 84 Chinese patients with prostate cancer treated with SRT to the prostatic fossa alone during 2006-2017 at Tuen Mun Hospital, Hong Kong. Survival was calculated using Kaplan-Meier method. Log rank test and Cox regression were used to determine significance of clinical parameters with outcomes.

Results: Median SRT dose given was 70 Gy (range, 64-76 Gy). Median pre-SRT PSA level was 0.4 ng/mL (0.2-7.4 ng/mL). After SRT, 47 (56%) patients had undetectable (<0.1 ng/mL) PSA levels. After median follow-up of 48 months (2 months to 10 years), 25 (30%) patients had further biochemical progression. Subsequently, 12 patients received androgen deprivation therapy and nine (11%) developed distant metastasis. The 5-year biochemical progression-free survival, androgen deprivation therapy-free survival and metastasis-free survival were 62.7%, 83.5% and

86.7%, respectively. Early PSA failure after radical prostatectomy (hazard ratio=7.4), negative surgical margin (hazard ratio=2.7), positive extracapsular extension (hazard ratio=4.6), and detectable PSA levels after SRT (hazard ratio=17.3) were associated with lower biochemical progression-free survival after SRT.

Conclusions: High-dose SRT with intensity-modulated radiotherapy/volumetric modulated arc radiotherapy is an effective local treatment that can prevent distant metastasis and avoid the need for androgen deprivation therapy in Chinese patients who have PSA failure after radical prostatectomy.

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New knowledge added by this study

- Better biochemical progression-free survival after salvage radiotherapy (SRT) can be achieved through higher radiation doses and better selection of patients.
- Patients with prostate-specific antigen (PSA) failure ≤ 24 months after radical prostatectomy, negative surgical margin, positive extracapsular extension, or detectable PSA after SRT are more likely to develop biochemical progression after SRT.

Implications for clinical practice or policy

- Distant metastasis is more likely to occur in patients with extracapsular extension, patients who cannot achieve biochemical complete response, and patients who develop biochemical progression within 1 year of SRT.
- For these patients, close monitoring for distant metastasis may be needed.

Introduction

Prostate cancer (PCa) is the most common non-cutaneous malignancy among men in western countries, and is the third most common cancer among men in Hong Kong.¹ Increasing public awareness in the Chinese community, as well as the common use of prostate-specific antigen (PSA) tests by primary health physicians, have led to detection of PCa at an earlier stage, when it is amenable to either radical surgery or radiotherapy (RT).² Because of recent advancements in operative management,

such as robotic-assisted laparoscopic prostatectomy,³ many patients have found radical prostatectomy (RP) the preferred treatment option. Nevertheless, adjuvant radiotherapy (ART) to the prostatic fossa is indicated postoperatively in cases with positive surgical margin (SM), or residual disease from extracapsular extension (ECE). Alternatively, patients may receive salvage radiotherapy (SRT) when there is PSA failure, defined as any detectable and rising PSA level after RP.

Currently, ART is still being compared

with SRT in three randomised controlled trials (RADICALS, RAVES, GETUG-AFU 17).⁴⁻⁶ While the results of these European and Australasian studies are still pending, the American Society for Radiation Oncology/American Urological Association guidelines recommend that physicians offer SRT to patients with PSA or local recurrence after RP in whom there is no evidence of distant metastasis (DM).⁷ Patients should be advised that SRT should be administered at the earliest sign of PSA recurrence. Approximately 60% of patients who are treated with SRT before the PSA level rises to >0.5 ng/mL will achieve an undetectable PSA level, providing long-term PSA control in nearly half of them.⁸

However, after SRT, some patients may still experience further clinical progression, including DM and cancer-related death. The effect of SRT on the long-term outcomes including metastasis-free survival (MFS) and overall survival—especially in Chinese patients—is not well understood. Herein we report the long-term survival data of patients at a single institution in Hong Kong who received SRT to the prostatic fossa using modern RT techniques.

Methods

Patient selection

Using the MOSAIQ system (version 2.62, IMPAC Medical Systems, Inc.; Sunnyvale [CA], US), we identified 91 Chinese patients treated with postoperative RT to the prostatic fossa at Tuen Mun Hospital, Hong Kong, between 2006 and 2017. The treatment records and clinical data of these patients were reviewed. Two patients who received ART with undetectable PSA were excluded. Patients who had received androgen deprivation therapy (ADT) prior to SRT were also excluded. These selection criteria yielded 84 evaluable individuals who received SRT to the prostatic fossa alone for PSA failure (defined as detection of PSA concentration at 0.2 ng/mL, with a second confirmatory level detected at 0.2 ng/mL) more than 3 months after RP.

Radiation therapy techniques

A planning computed tomographic scan was performed for each patient with 3-mm slice thickness, and the clinical target volume was determined with reference to one of the published consensus guidelines.⁹⁻¹¹ The usual boundaries of the clinical target volume are: inferiorly, 5 mm below the urethral anastomosis; anteriorly, the posterior aspect of the symphysis pubis or the posterior third of the bladder; laterally, the medial border of the obturator internus and levator ani muscles; posteriorly, the anterior mesorectal fascia; and superiorly, 5 mm above the surgical bed. The planning target volume was defined as clinical target volume with a margin of 4 to 5 mm

根治性前列腺切除術後復發的挽救性放射治療結果

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引言：挽救性放射治療（SRT）可為根治性前列腺切除術後前列腺特異性抗原（PSA）失敗的前列腺癌患者提供有效的生化控制。然而，SRT對長期臨床結果的影響仍不清楚。因此，本文報告SRT治療患者的自然病史。

方法：2006年至2017年期間於香港屯門醫院為84位華裔前列腺癌患者進行SRT治療。我們使用Kaplan-Meier方法計算患者經治療後的生存率，並使用log rank檢驗和Cox回歸確定臨床參數與結果的顯著性。

結果：中位SRT劑量為70 Gy（範圍：64-76 Gy）。中位SRT前PSA水平為0.4 ng / mL（0.2-7.4 ng / mL）。SRT後，47名（56%）患者的PSA達不可檢測到的水平（<0.1 ng / mL）。中位隨訪48個月（範圍：2個月至10年）後，25例（30%）患者有進一步的生化惡化進展。12名患者隨後接受雄激素剝奪治療，9名（11%）發生遠處轉移。5年無生化惡化進展生存率、無雄激素剝奪療法生存率，以及無轉移生存率分別為62.7%、83.5%和86.7%。根治性前列腺切除術後早期PSA失敗（危險比7.4）、陰性手術切緣（危險比2.7）、包膜外延伸（危險比4.6），以及SRT後可檢測PSA水平（危險比17.3）與SRT後較低的無生化惡化進展存活率相關。

結論：使用調強放療 / 體積調節弧放療的高劑量SRT是有效的局部治療方法，能夠預防遠處轉移，也避免根治性前列腺切除術後PSA失敗的華裔患者須接受雄激素剝奪治療。

posteriorly and 0.7 to 1 cm in all other directions. Organs at risk, including the rectum, bladder, and bilateral femoral heads were contoured. Conformal radiotherapy or inverse planning techniques with intensity-modulated radiotherapy (IMRT) using seven to nine static beams were used before October 2010. After that, volumetric modulated arc radiotherapy (VMAT) was employed using the Pinnacle treatment planning system (Philips Medical Systems, Fitchburg [WI], US) with treatment delivered through one to two dynamic cone arcs.

Variable definition

Clinical data included age at SRT, time from surgery to RT (≤ 24 months vs > 24 months), SRT dose, pre-SRT PSA level, and post-SRT nadir PSA. Pathological data consisted of pathological T stages (T2a vs T2b vs T2c vs T3a or T3b), ECE, seminal vesicle invasion, SM, and pathological Gleason scores (≤ 7 or ≥ 8).

Outcome definition

After SRT, patients were followed up with PSA level checks every 3 months in the first 2 years, every 6 months from year 3 to year 5, then annually. A complete response was defined as an undetectable nadir PSA (< 0.1 ng/mL). Biochemical progression (PSA failure) was defined as a rise of PSA level by 0.2

ng/mL above the nadir with a second confirmation at least 1 week apart.¹² Biochemical progression-free survival (bPFS) was defined as the date from SRT completion to the first date of biochemical progression. Patients who showed biochemical progression or symptoms suggestive of metastasis received imaging studies at the discretion of the oncologist. Metastasis-free survival was defined as the date from SRT completion to the date of occurrence of metastasis on imaging. Patients who showed biochemical progression with or without metastasis were counselled on the use of ADT; ADT-free survival was defined as the date of SRT completion to the first date of ADT administration.

Statistical analyses

The Kaplan-Meier method was used to estimate bPFS, MFS, and ADT-free survival. Log-rank tests and Cox regression analysis were used to test the association between groups and oncologic outcomes. Covariates consisted of continuous variables, including patient age at SRT, SRT dose, and pre-SRT PSA, and discrete variables including post-SRT nadir PSA (detectable vs undetectable), pathological T stages (T2a vs T2b vs T2c vs T3a vs T3b), pathological Gleason score (≤ 7 vs ≥ 8), SM (negative vs positive), ECE (negative vs positive), seminal vesicle invasion (negative vs positive), and time of SRT (≤ 24 months after RP or >24 months after RP). Only variables that were significantly associated with outcomes on univariate analyses were further tested for association in multivariate analyses.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp, Armonk [NY], US), and numerical data were presented according to Cole.¹³

Results

Patients

The median age of the 84 patients was 68 years (range, 52-79 years) when they received SRT. The patients' median pre-SRT PSA level was 0.4 ng/mL (range, 0.2-7.4 ng/mL). Of the patients, 63 (75%) had positive SM in their prostatectomy specimens. Extracapsular extension was detected in 25 (29.8%) patients. Pelvic lymph nodes of 41 patients were sampled during RP and were all found to be negative for malignancy. These and other pathological characteristics are summarised in Table 1. The median time from surgery to start of SRT was 18.4 months (range, 3.8-121 months).

Treatment delivery

Before October 2010, one patient was treated with conformal RT and 10 patients were treated with IMRT. Subsequently the other 73 patients were treated with VMAT. The median dose given to the

TABLE 1. Patient and RP pathological characteristics (n=84)*

	Data
Age, y	68 (52-79)
Time from RP to start of SRT, months	18.4 (3.8-121)
Pre-SRT PSA, ng/mL	0.4 (0.2-7.4)
Prostatectomy pathology	
pT stage	
Unknown	1 (1.2)
T2a	8 (9.5)
T2b	5 (6.0)
T2	40 (47.6)
T3a	17 (20.2)
T3b	13 (15.5)
pN stage	
pN0	41 (48.8)
pNx	43 (51.2)
Extracapsular extension	
Positive	25 (29.8)
Negative/unknown	59 (70.2)
Seminal vesicle invasion	
Positive	13 (15.5)
Negative/unknown	71 (84.5)
Surgical margin	
Positive	63 (75.0)
Negative/unknown	21 (25.0)
Pathological Gleason score	
≤ 6	28 (33.3)
7	40 (47.6)
≥ 8	16 (19.1)

Abbreviations: PSA = prostate-specific antigen; RP = radical prostatectomy; SRT = salvage radiotherapy

* Data are shown as median (range) or No. (%)

prostatic fossa was 70 Gy (range, 64-76 Gy), with 66 (79%) patients receiving a dose of ≥ 70 Gy. The mean dose delivered using VMAT (69.5 Gy) was slightly higher than that delivered using IMRT/conformal RT (68.1 Gy) [independent-samples *t* test, $t=2.1$; $P=0.028$].

Treatment outcome

Of 84 patients, 47 (56%) had undetectable PSA levels (complete response; <0.1 ng/mL) after SRT. After a median follow-up of 48 months (range, 2-120 months), 25 (30%) patients had biochemical progression with an estimated 5-year bPFS of 62.7% (95% confidence interval [CI], 50.1-75.3%) [Fig 1a]. Among the 25 patients who developed biochemical progression after SRT, seven were found to have DM and subsequently received ADT, and five started ADT in the absence of DM, two of whom

later developed DM and had their disease become castration-resistant. Overall, 12 patients received ADT and nine (11%) patients developed DM. The 5-year ADT-free survival and MFS were 83.5% (95% CI, 73.7-93.3%) and 86.7% (95% CI, 77.7-95.7%), respectively (Fig 1b, c). Notably, only six patients died, all from causes other than PCa.

Biochemical progression-free survival and metastasis-free survival

On univariate analysis, a post-SRT nadir PSA ≥ 0.1 ng/mL, positive ECE, and bPFS ≤ 12 months were significantly associated with a shorter MFS (all $P < 0.001$; Fig 2). Similarly, a post-SRT nadir PSA ≥ 0.1 ng/mL ($P < 0.001$), positive ECE ($P < 0.001$), negative SM ($P = 0.045$), pathological Gleason score ≥ 8 ($P = 0.002$), and time from surgery to SRT ≤ 24 months ($P = 0.008$) were significant predictors of a shorter bPFS (Fig 3). The pre-SRT PSA level, age, and SRT dose were not associated with either MFS or bPFS in this cohort on univariate analysis. On multivariate analysis using the Cox regression method, negative SM (hazard ratio [HR]=2.7; 95% confidence interval [CI], 1.1-6.6), positive ECE (HR=4.6; 95% CI, 1.8-11.7), post-SRT nadir PSA ≥ 0.1 ng/mL (HR=17.3; 95% CI, 5.3-57.0), and time from surgery to SRT ≤ 24 months (HR=7.4; 95% CI, 2.2-24.0) retained significant association with a shorter bPFS (Table 2). There was no variable significantly associated with MFS after multivariate analysis.

Discussion

Most patients who develop biochemical recurrence after RP for localised PCa remain asymptomatic for many years.¹⁴ However, patients with increasing PSA level are at high risk of developing DM. Salvage radiotherapy is effective in terms of biochemical control when it is administered at low PSA level. Stephenson et al¹² reported a 6-year progression-free probability of 32% after SRT. In their multi-institutional retrospective cohort of 1603 consecutive patients from 17 North American tertiary referral centres who received SRT after RP for PSA recurrence between 1987 and 2005, the median dose was only 64.8 Gy (interquartile range, 63-66 Gy) delivered using older techniques. The 5-year bPFS of 62.7% in the present study is similar or better than those reported in western countries.^{12,15,16} This might be due to better selection of patients (most patients started SRT when their PSA level was ≤ 0.5 ng/mL), or the higher dose of SRT to the prostatic fossa (median 70 Gy). In our cohort, all patients but one were treated using IMRT/VMAT. Intensity-modulated radiotherapy was introduced in the 1990s and it has since enabled radiation oncologists to deliver higher doses of radiation to treat patients with PCa—including patients with residual disease

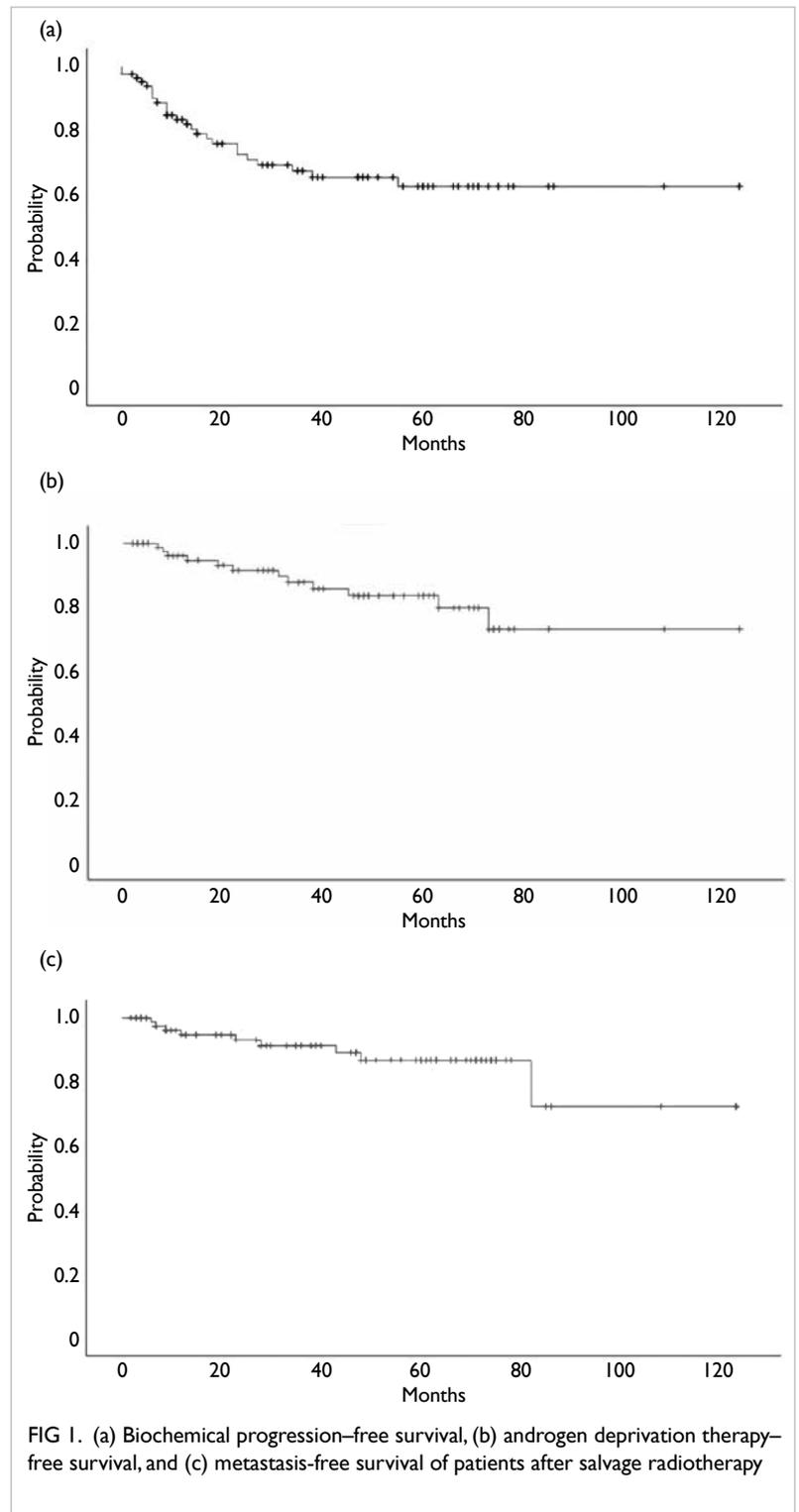
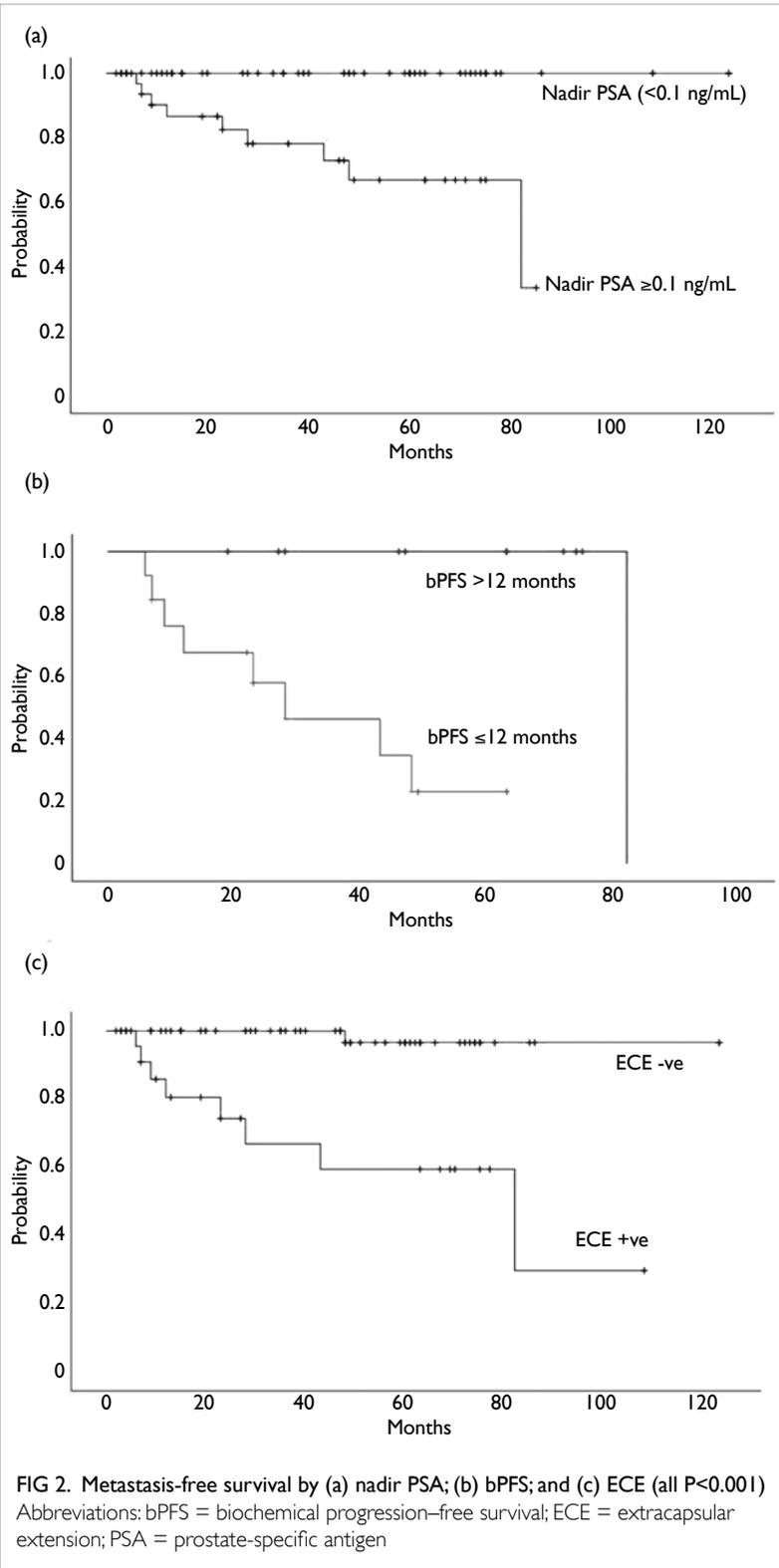


FIG 1. (a) Biochemical progression-free survival, (b) androgen deprivation therapy-free survival, and (c) metastasis-free survival of patients after salvage radiotherapy

at the prostatic fossa—without causing excessive radiation damage to healthy tissue.¹⁷⁻¹⁹ Volumetric modulated arc radiotherapy has recently attracted much interest because it can dynamically deliver a radiation dose during rotation of the gantry; this is also superior to IMRT in terms of its plan qualities and efficiency in the treatment of PCa.^{20,21}

Pisansky et al²² reported that SRT doses of



≥66.0 Gy were associated with reduced cumulative incidence of biochemical progression. A systemic review by King²³ provides level 2a evidence for escalated SRT dose of at least 70 Gy. A 2% improvement in relapse-free survival can be achieved for each additional Gy from 60 Gy to 70 Gy.²³

TABLE 2. Predictive factors of shorter bPFS on multivariate analysis

Predictive factor	Hazard ratio	95% Confidence interval
Post-SRT nadir PSA ≥0.1 ng/mL	17.3	5.3-57.0
Negative surgical margin	2.7	1.1-6.6
Positive extracapsular extension	4.6	1.8-11.7
Time from RP to SRT ≤24 months	7.4	2.2-24.0

Abbreviations: bPFS = biochemical progression-free survival; PSA = prostate-specific antigen; RP = radical prostatectomy; SRT = salvage radiotherapy

However, higher SRT dose was not shown to be associated with better bPFS/MFS in our 84 patients by univariate analysis, because most (79%) had been treated with an SRT dose of ≥70 Gy, and the follow-up time may still be too short to demonstrate any further dose-response relationship. We postulated that such high-dose SRT can be delivered safely with modern techniques using VMAT, therefore our current usual prescribed dose is 70 Gy to the prostatic fossa, unless limited by dose constraints of the organ at risk. We have previously shown the efficiency and low toxicities using VMAT for SRT to the prostatic fossa.²⁴ Longer follow-up is necessary to ensure that late complications are within safety limits.

Despite the success of SRT in biochemical control, some patients may develop further biochemical progression. In our present study, patients whose surgical pathology revealed negative margin and positive ECE had a shorter bPFS (HRs of 2.7 and 4.6, respectively). Patients who start SRT within 2 years of RP may also have a shorter PSA doubling time, leading to earlier detection of recurrence. These patients have a greater than 7-fold higher risk of biochemical regression after SRT than those with later recurrence. Salvage radiotherapy to the prostatic fossa alone cannot eradicate cancer that has spread outside the surgical bed after RP. In fact, negative SM, positive ECE, and shorter PSA doubling time are three of the many adverse factors which predict a shorter bPFS after SRT, using the nomogram proposed by Stephenson et al.²⁵ However, we cannot demonstrate the importance of pre-SRT PSA level in our patient cohort because more than 65% of the patients had started SRT when their PSA level was ≤0.5 ng/mL.

Overall, the role of SRT in improving MFS and overall survival is less certain, because the disease can be indolent and mortality due to causes other than PCa is more likely in older patients. Patients also have other complications related to disease progression, such as painful bone metastasis. Efforts have been made to identify surrogate endpoints that can predict further disease progression, metastasis, and even

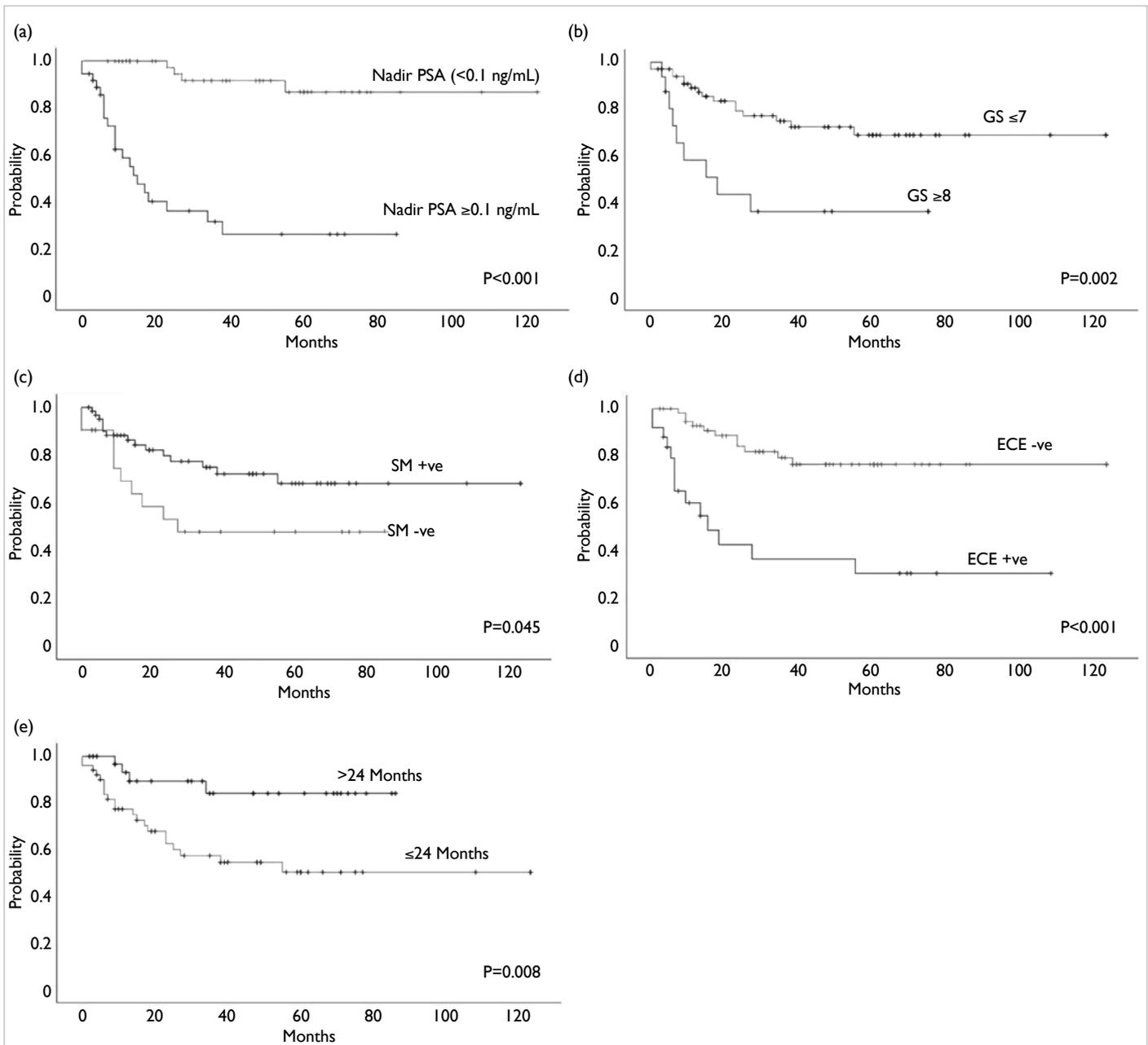


FIG 3. Biochemical progression-free survival by (a) nadir PSA; (b) GS; (c) SM; (d) ECE; and (e) time from RP to SRT
 Abbreviations: ECE = extracapsular extension; GS = Gleason scores; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin; SRT = salvage radiotherapy

cancer-related death after SRT. In a single institution review, Johnson et al²⁶ reported approximately 50% of men experience further biochemical progression after SRT. Those who have a short interval to biochemical progression of ≤18 months after SRT are most likely to experience DM, PCa-specific mortality, and overall mortality. Bartkowiak et al²⁷ reported on the long-term outcomes of patients with a median follow-up of 7 years (maximum, 14 years) after SRT. They found that a post-SRT nadir PSA <0.1 ng/mL was associated with improved bPFS

and overall survival. The results of our univariate analysis support the abovementioned findings²⁷ (Fig 2a, b). On multivariate analysis, we found that undetectable nadir PSA (<0.1 ng/mL) is the most important factor for predicting longer bPFS (Table 2). In the present study, of the 47 patients who achieved biochemical complete response after SRT, none developed DM. In contrast, among the 25 patients who had biochemical progression, nine whose disease progressed within 1 year after SRT eventually developed DM. Although our result

TABLE 3. Pattern of disease progression

Patient No.	PSA when DM detected (ng/mL)	Mode of imaging	Site of DM
1	6.6	Bone scan	Multiple bone
2	9.5 11.1	CT then C11/FDG PET	Bilateral multiple lung
3	5.2	C11/PSMA PET	Mediastinal LNs
4	57	Bone scan	Multiple bone
5	3.5	C11/PSMA PET	Presacral LNs + C7
6	1.4	CT scan	Bilateral multiple lung
7	2.2	C11/PSMA PET	Multiple pelvic LNs + T1 paravertebral node
8	2.7	C11/PSMA PET	C7, L5 + presacral S3 LN + lung
9	9.4	Plain radiography of chest and pelvis	Lung and bone

Abbreviations: C11 = ¹¹C-acetate; CT = computed tomography; DM = distant metastasis; FDG = fluorodeoxyglucose; LN = lymph node; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen

of a 5-year MFS of nearly 90% is encouraging, with the median follow-up of only 4 years, we can hypothesise only that better biochemical control is correlated with improvements in other clinical outcomes. For patients whose PSA level does not become undetectable and rapidly rises within 1 year after SRT (bPFS \leq 12 months), close monitoring for DM may be needed.

The improvement in overall survival and MFS of adjuvant ADT with SRT has been demonstrated by Shipley et al²⁸ in a phase III study. However, ADT is not routinely recommended to our patients because of the known metabolic and cardiovascular toxicities and the negative impact on patients' quality of life. In addition, most of our patients have fewer adverse features than those reported by Shipley et al.²⁸ For patients with biochemical regression alone after SRT, we suggest monitoring for any site of disease recurrence such that further SRT could still be feasible. Nonetheless, we applied positron emission tomography with ⁶⁸Ga-labelled prostate-specific membrane antigen (PET-PSMA) to identify the site of recurrence in four of our patients when their PSA levels increased to \geq 2.2 ng/mL (Table 3). All four patients were found to have DM which was not amenable to further local treatment and ADT had become their only option. It remains unclear whether PET-PSMA or other imaging studies at lower PSA levels are sensitive or useful enough to alter the management decision.²⁹ Further research to study the use of novel radiological examinations in this situation is needed.

Conclusions

This is the first report to demonstrate the therapeutic effects in terms of bPFS and MFS of SRT in Chinese patients in a Hong Kong centre. Salvage radiotherapy is an effective local treatment that can

prevent DM and avoid the need for ADT in most patients who have PSA failure after RP in Chinese patients. Our results appear to be better than those of some studies in western countries, in which older radiotherapy techniques and lower radiation doses were used. The limitations of our study include the retrospective design with lack of evaluation of patients' reported outcome, small sample size, and short duration of follow-up. A multi-institutional study is recommended to collect more local data and experiences.

Author contributions

Concept or design: EKC Lee, Y Tung.
Acquisition of data: EKC Lee, AW Chan.
Analysis or interpretation of data: EKC Lee.
Drafting of the article: EKC Lee, WH Mui, FCS Wong.
Critical revision for important intellectual content: EKC Lee, WH Mui, FCS Wong.

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Declaration

All authors have no conflicts of interest to disclose. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity. An earlier version of this paper was presented as poster presentation at the 9th European Multidisciplinary Meeting on Urological Cancers, 16-19 November 2017, Barcelona, Spain.

Ethical approval

The study was conducted with approval from the New Territories West Cluster Clinical and Research Ethics Committee.

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