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## REVIEW ARTICLE

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# Post-prostatectomy Radiotherapy

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### ABSTRACT

Patients with localised prostate cancer can be cured with radical prostatectomy alone. Nevertheless, many of them may develop local failure due to positive surgical margins or residual disease from extraprostatic extension (pT3), which necessitates post-prostatectomy radiotherapy to the prostatic fossa as either adjuvant radiotherapy (ART) or salvage radiotherapy (SRT). Three randomised studies have addressed the role of ART. The European Organisation for Research and Treatment of Cancer demonstrated the superiority of ART over observation alone, in terms of biochemical progression-free survival, for men with positive margins or pT3 prostate cancer after radical prostatectomy. Subsequently, a German study also showed improvement of biochemical control by about 20% with ART. In North America, the SWOG 8794 trial, which enrolled similar patients, reported an improvement in metastasis-free survival with ART after a median follow-up of 12 years. However, immediate ART may not benefit all patients and can cause serious side-effects. It is uncertain whether ART should be given immediately after surgery or only when there is a rising prostate-specific antigen level after surgery, indicating active cancer. The role of androgen-deprivation therapy (ADT) with SRT/ART also remains unclear. Further randomised controlled trials are under way and their results may provide further information on the optimum timing of SRT and ADT. The challenges of post-prostatectomy radiotherapy include difficulty in determining the clinical target volume, and its close proximity to the rectum and bladder. New radiotherapy techniques such as intensity-modulated radiotherapy and volumetric-modulated arc therapy have been introduced to improve accuracy and efficiency in the delivery of post-prostatectomy radiotherapy. The results of using intensity-modulated radiotherapy as salvage radiotherapy in Tuen Mun Hospital, Hong Kong have been promising in a group of selected patients.

**Key Words:** Prostate-specific antigen; Prostatectomy; Prostatic neoplasms; Radiotherapy adjuvant; Radiotherapy, intensity-modulated

## 中文摘要

### 前列腺切除術後的放射治療

李家齊

單獨使用根治性前列腺切除術可以治癒患有局部性前列腺癌的病人。然而這些病人當中，很多會因手術切除邊緣陽性或前列腺外擴散（pT3）的殘留癌病而出現局部治療失敗，需要於前列腺窩進行前列腺切除術後放射治療，作為輔助放療或挽救性放療。三項隨機試驗研究了輔助放療的角色。EORTC研究證明在根治性前列腺切除術後有邊緣陽性或pT3的前列腺癌男性病人中，輔助放療對病人生化無惡化存活的作用，較單獨採取觀察法為佳。其後一項德國研究亦顯示，採用輔助放療對生化控制有約20%的改善。在北美的SWOG 8794試驗納入了相若的病人，在中位數為12年的跟進後，

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報告表示採用輔助放療對無轉移存活有改善。然而，即時採用輔助放療未必適合所有病人，並可能引致嚴重副作用。目前未能確定應否在手術後立即採用輔助放療，抑或只有在手術後，當前列腺特异性抗原水平上升顯示有活躍癌症時，才採用輔助放療。與挽救性放療 / 輔助放療同時使用雄激素阻斷治療的角色亦未明確。更多隨機對照試驗正在進行中，研究結果可能會提供有關使用挽救性放療與雄激素阻斷治療最佳時機的進一步資料。前列腺切除術後放療所面對的挑戰包括：難以確定臨床目標體積，以及其位置與直腸和膀胱相接近。新的放療技術，例如如強度調控放射治療和體積調控弧形治療已經推出，以改善前列腺切除術後放療的準確性和效率。在屯門醫院一組特選病人中使用強度調控放射治療作挽救性放療的結果令人鼓舞。

## INTRODUCTION

There is a high incidence of prostate cancer in Hong Kong. In 2010, 1491 men were diagnosed with prostate cancer in Hong Kong.<sup>1</sup> In patients with localised disease, radical prostatectomy (RP) alone constitutes a cure. However, treatment failure may occur in patients who have positive surgical margins or residual disease from extraprostatic extension; these patients need postoperative radiotherapy to the prostatic fossa. This can be given in the form of adjuvant radiotherapy (ART) or salvage radiotherapy (SRT). ART is defined as the administration of radiotherapy to post-prostatectomy patients who have a high risk of recurrence due to adverse pathological features prior to evidence of disease recurrence. It is usually administered within 4 to 6 months of RP, when the patient has regained acceptable urinary control. SRT is defined as the administration of radiotherapy to the prostatic bed in a patient with evidence of local recurrence, such as a rising prostate-specific antigen (PSA) level following surgery. This article reviews the clinical evidence supporting the practice of post-prostatectomy radiotherapy to the prostatic fossa in two different clinical situations. The results of using intensity-modulated radiotherapy (IMRT) as SRT in Tuen Mun Hospital, Hong Kong are also presented.

## ADJUVANT RADIOTHERAPY

Bolla et al<sup>2</sup> were the first to report improvement in biochemical and clinical progression-free survival (PFS) with immediate postoperative irradiation in a randomised controlled trial. In the European Organisation for Research and Treatment of Cancer (EORTC) 22911 study, radiotherapy with non-three-dimensional planning was used after RP for prostate cancer. About 1000 patients who had any one of the pathological risk factors (positive margins, capsular penetration, or invasion of the seminal vesicles) in their prostatectomy specimens were randomly assigned to

receive either radiotherapy (60 Gy) to the prostatic fossa within 16 weeks of surgery or to a wait-and-see policy. Updated results at a median follow-up period of 10.6 years showed that ART significantly increased biochemical PFS by about 20% compared with the observation group. However, the between-group difference in clinical PFS was not maintained, and there was no effect on distant metastases or overall survival.<sup>3</sup>

The North American SWOG 8794 study was started in 1988.<sup>4</sup> Over 9 years, 425 patients who had been treated with RP and pelvic lymphadenectomy for prostate cancer were randomised to observation alone or ART to the prostatic fossa (60 - 64 Gy). The inclusion criteria were pT3N0 disease, positive margins, and negative bone scan. An undetectable PSA was not mandatory before randomisation. After more than 12 years of follow-up, patients in the ART arm had longer median metastasis-free survival and overall survival (14.7 years and 15.2 years, respectively) than those randomised to observation (12.9 years and 13.3 years, respectively), despite a greater use of androgen-deprivation therapy in the observation arm.<sup>5</sup> The improvements in metastasis-free survival and overall survival with ART were both statistically and clinically significant ( $p = 0.016$  and  $p = 0.023$ , respectively), as fewer patients suffered or died of complications due to metastatic disease.

In 1996, the German Cancer Society initiated another randomised trial to test the hypothesis that immediate radiotherapy after RP would improve the biochemical 'no evidence of disease' in patients with extraprostatic extension (pT3) tumours and undetectable PSA after prostatectomy, and with high risk of tumour progression.<sup>6</sup> Patients in the study arm underwent three-dimensional treatment planning and received a radiation dose of 60 Gy to the prostatic fossa. At a median follow-up of 54 months, per-protocol analysis showed that the biochemical PFS was longer in the ART arm by about

20% compared with observation alone. Incorporation of the results of the central pathology review suggested that positive surgical margins, PSA levels of >10 ng/ml before prostatectomy, and extraprostatic extension without seminal vesicle invasion were predictors of improved biochemical response to ART.

Overall findings from these three randomised controlled trials confirmed an improvement in biochemical control with postoperative radiotherapy in patients with adverse pathological features. However, only the SWOG study showed an improvement in metastasis-free survival and overall survival. In fact, around 35% of patients in the ART arm had a postoperative PSA level of >0.2 ng/ml, which raised the question of whether survival benefit was actually due to early SRT. While radiotherapy after RP is known to improve outcomes, it is not known whether it should be given immediately after surgery (ART) or only when there are signs of active cancer indicated by rising PSA levels following surgery (SRT). Immediate ART may not benefit all patients, and can cause serious side-effects such as urethral stricture and proctitis. In the SWOG and EORTC studies, patients were treated with older-generation radiotherapy techniques that may have contributed to more adverse outcomes than the current standard of care, which uses three-dimensional conformal radiotherapy or IMRT.

## **SALVAGE RADIOTHERAPY**

Evidence regarding the efficacy of SRT predominantly comes from a large literature base of observational studies. For patients with a rising PSA level after RP, SRT to the prostatic fossa may be curative only if the disease is confined to the prostatic bed, without distant metastasis. Because of the lack of accuracy of current imaging modalities to identify the site of recurrence when patients develop biochemical failure following RP,<sup>7</sup> oncologists can only rely on models that predict the outcome of SRT on the basis of overall characteristics, such as the pre-SRT PSA level, Gleason score, pathological margins, and PSA doubling time. To address this issue, Stephenson et al<sup>8</sup> developed a nomogram to predict the 6-year progression-free probability after SRT. Of the 11 parameters, PSA level before SRT was the most significant predictor of disease progression, with more favourable outcomes noted if SRT was started at low PSA levels. King<sup>9</sup> systematically reviewed 41 published SRT studies involving 5597 patients and found that PSA levels before SRT ( $p < 0.0001$ ) and dose of radiotherapy ( $p = 0.0052$ ) were

significantly and independently associated with relapse-free survival. There was a mean of 2.6% loss of relapse-free survival for each 0.1 ng/ml increment in PSA at the time of SRT. In light of these findings, the American Society for Radiation Oncology recently suggested that SRT should be administered at the earliest sign of PSA recurrence and, ideally, before PSA level reaches 1.0 ng/ml.<sup>10</sup> The Panel also concluded that it was not possible, from the available evidence, to address the question of superiority of ART over SRT. The role of androgen-deprivation therapy in conjunction with SRT also remains unclear. The following three randomised controlled trials are addressing these issues and their results are eagerly awaited.

### (1) Radiotherapy — Adjuvant Versus Early Salvage (RAVES trial, TROG 08.03)<sup>11</sup>

Patients with positive margins and / or pT3 disease will be randomised to ART or active surveillance, with SRT delivered at early relapse. SRT would commence no later than 4 months following the first PSA measurement of  $\geq 0.2$  ng/ml. In both arms, 64 Gy in 32 fractions will be delivered to the prostate bed. The primary outcome measure will be biochemical failure (PSA  $\geq 0.4$  ng/ml, and rising, following radiotherapy).

### (2) Radiotherapy and Androgen Deprivation in Combination after Local Surgery (RADICALS trial MRC PR10, NCIC PR13)<sup>12</sup>

This is a trial with two stages of randomisation; patients may be entered into one or both randomisations. The first randomisation, performed within the first 3 months after RP, is defined as the Radiotherapy Timing Randomization. Patients who have undergone RP, but show uncertainty about the need for immediate radiotherapy (postoperative PSA <0.2 ng/ml, pT3, positive surgical margins at RP, Gleason score >6 or preoperative PSA >10 ng/ml), will be randomised to receive immediate radiotherapy or SRT for PSA control failure. In both arms, 66 Gy in 33 fractions will be delivered to the prostate bed. The second randomisation, performed before the administration of radiotherapy, is defined as the Hormone Duration Randomization. Patients will be randomised to receive either radiotherapy alone, radiotherapy with 6 months of hormonal therapy or radiotherapy with 2 years of hormonal therapy, in the form of either gonadotropin-releasing hormone analogue or bicalutamide 150 mg daily.

### (3) RTOG 9601<sup>13</sup>

This trial, which is now completed, aimed to test

whether long-term anti-androgen therapy combined with SRT would improve overall survival. Patients with a rising PSA level post-RP were randomised to receive SRT (64.8 Gy in 36 fractions) alone or with bicalutamide 150 mg daily, during and after SRT for 2 years. While the full study results are yet to be published, the published abstract indicates that the addition of anti-androgen treatment to SRT can reduce the incidence of metastasis and improve freedom from biochemical progression. However, after a median follow-up of 7.1 years, the number of mortality events that have occurred is too small to allow a statistical comparison of the primary endpoint in both treatment arms.<sup>13</sup>

### Salvage Radiotherapy to Prostatic Fossa using Intensity-modulated Radiotherapy in Tuen Mun Hospital

Since the late 1990s, IMRT has been commonly used to treat prostate cancer. In IMRT, multiple static fields with different beam angles are used and the intensity of each beam is modulated using multi-leaf collimators, enabling the creation of complex, yet highly conformal, dose profiles. Teh et al<sup>14</sup> were the first researchers to report safety data on post-prostatectomy IMRT. In the Tuen Mun Hospital, from January 2006 to October 2010, 14 patients were treated with SRT to the prostatic fossa using IMRT. The patient characteristics are shown in Table 1.

**Table 1.** Patient characteristics (n = 14).

Characteristic	Data*
Age (years)	66 (57-76)
Preoperative PSA (ng/ml)	15.3 (4.5-39.5)
Pre-salvage RT PSA (ng/ml)	0.9 (0.16-2.2)
pT stage	
pT1	2
pT2	6
pT3	6
Gleason score	
3+3	7
3+4	3
4+3	2
4+4	1
3+5	1
Margin/s	
Clear	4
Close / uncertain / involved	10

Abbreviations: PSA = prostate-specific antigen; RT = radiotherapy.  
\* Data are shown as mean (range), or No. of patients.

All patients were simulated and treated in a supine position, with a comfortably full bladder. The usual boundaries of the clinical target volume (CTV) were: inferiorly, at 5 mm below the urethral anastomosis; anteriorly, the posterior aspect of symphysis pubis or 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 (PTV) was defined as CTV with a margin of 5 mm posteriorly, and 1 cm in all other directions. The number of IMRT fields ranged from 6 to 8. The median PTV was 90 cc (range, 27.8-182.8 cc). The prescribed dose to PTV was 1.8 to 2.0 Gy daily (median monitor units, 598) with a total dose of 66 Gy to 70.2 Gy.

All patients completed SRT uneventfully. In one patient whose PSA kept rising during treatment, metastatic disease became evident on bone scan at 6 months after

**Table 2.** Treatment efficacy in terms of prostate-specific antigen control.

Pre-radiotherapy PSA (ng/ml)	Nadir PSA (ng/ml)	PSA at last follow-up (ng/ml)	Follow-up (months)	Remarks
1.3	<0.1	10.1	85.4	BF* at 20 months
0.57	NR	14	77.3	BF during SRT
0.3	<0.1	<0.1	81.3	-
1.5	<0.1	<0.1	81.4	-
1.0	<0.1	<0.1	28.7	-
0.6	<0.1	<0.1	63	-
0.5	0.2	3.7	61	BF at 27 months
0.16	<0.1	<0.1	12.5	Lost to follow-up
0.6	<0.1	<0.1	37.6	-
2.2	<0.1	<0.1	35.3	-
1.4	<0.1	<0.1	37.6	-
0.4	<0.1	<0.1	31.3	-
1.5	0.6	3.5	31	BF at 15 months
0.6	<0.1	<0.1	23.8	-

Abbreviations: BF = biochemical failure; NR = not reached; PSA = prostate-specific antigen; SRT = salvage radiotherapy.  
\* BF = PSA rise of 0.2 ng/ml above the nadir after salvage radiotherapy.

SRT. He continued to receive salvage hormonal therapy at another hospital. All other patients responded to SRT, with PSA becoming undetectable in 11 patients. At a median follow-up of 38 months (range, 12.5-85.4 months), only four patients had PSA progression, defined as a rise in PSA level of 0.2 ng/ml above the nadir after SRT. All other patients have remained progression-free without the need for hormonal therapy (Table 2). To date, there have been no deaths due to prostate cancer in this group. Acute toxicities during and within 1 year of SRT using IMRT were generally mild, and included rectal bleeding (n = 2), rectal urgency (n = 10), urinary frequency (n = 3), dysuria (n = 1), and urinary incontinence (n = 2).

## CONCLUSION

Candidates treated with RP for localised prostate cancer should be seen at a multidisciplinary clinic and informed of the potential for adverse pathological findings post-surgery, which may portend a higher risk of cancer recurrence. Post-prostatectomy radiotherapy to the prostatic fossa may be administered either as ART or SRT. To avoid any toxicities associated with ART in patients who may never show recurrence after surgery alone, a wait-and-see policy with SRT may be the preferred option. However, the optimal timing of SRT remains uncertain and further randomised controlled trials are underway to address this question. Results from the use of newer technologies such as IMRT in our centre have demonstrated promising results for selected patients treated with SRT. Since October 2010, we have further advanced to using volumetric-modulated arc therapy for this indication, which has demonstrated favourable dosimetric and clinical results.<sup>15</sup>

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