# The need for, and utilization of prostate-bed radiotherapy after radical prostatectomy for patients with prostate cancer in British Columbia

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See related article on page 95.

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## Abstract

**Introduction:** Three randomized trials have demonstrated that post-radical prostatectomy (RP) radiotherapy decreases biochemical relapse for those with adverse pathology. Our purpose was to describe the incidence of pathologic risk factors for recurrence in a contemporary series of patients treated with RP and to describe the use of post-RP radiotherapy.

**Methods:** All incident prostate cancers diagnosed between January 2005 and December 2007 were identified from the tumour registry. Cases were then linked to radiotherapy records which included dose and modality (external beam radiotherapy and brachytherapy). The pathology reports in the tumour registry were reviewed for pathologic stage, grade and margin status.

**Results:** We identified 9223 patients with prostate cancer. Overall, 36.3% of patients treated with RP had positive margins, and may have benefited from adjuvant radiotherapy. After RP, 332 (15%) patients had radiotherapy to the prostate bed; of these, only 25 (1.1%) received truly adjuvant radiotherapy (delivered within 6 months with a prostate-specific antigen of <0.2 ng/mL). Of the 2181 patients treated with RP, 270 (12%) were seen by a radiation oncologist within 6 months of RP. Of the 1015 patients (47%) with adverse RP pathology (positive margins, extracapsular extension or seminal vesicle invasion), 230 (23%) were seen by a radiation oncologist within 6 months of RP.

**Conclusion:** Not all patients with adverse prostatectomy pathology were seen by a radiation oncologist post-prostatectomy, and very few received adjuvant radiotherapy despite almost half of them having risk factors for relapse.

## Introduction

Starting in 2004, three randomized trials reported on the role of post prostatectomy radiotherapy for prostate cancer patients with adverse pathology (positive margins, extracapsular extension [ECE] or seminal vesicle invasion [SVI]).[1-3] All three demonstrated a significant reduction in the rate of biochemical relapse with the use of early postoperative radiotherapy compared to initial observation. In 2009, Thompson and colleagues, for the first time, demonstrated that this biochemical disease-free survival advantage translated into an overall survival and disease-specific survival advantage at 10 years.[4] Updates from a subgroup analysis of the European trial and from the German trial suggested that the benefit of postoperative adjuvant radiotherapy may be confined to patients with positive margins.[5,6] In addition, there is debate as to whether early salvage at the time of first detection of prostate-specific antigen (PSA) provides an outcome equivalent to truly adjuvant radiotherapy.[7,8]

On the basis of the initial trial results, the Canadian Genitourinary Radiation Oncology group published two consensus statements on the use of postoperative adjuvant and salvage radiotherapy in the *Canadian Urological Association Journal (CUAJ)*.[9,10] With respect to the role of adjuvant radiotherapy, the consensus statement recommended that "consultation with a radiation oncologist early in the postoperative period is advised to discuss benefits and side effects of adjuvant radiotherapy in those with adverse pathological features at prostatectomy," and that "patients should be offered adjuvant external beam radiotherapy (within 6 months of surgery)."[9,10]

Cancer Care Ontario's Surgical Oncology program recently reported on evidence-based quality indicators for radical prostatectomy (RP) in prostate cancer management.[11] The panel "unanimously determined that the goals for RP are to attain a positive margin rate of <25% for pT2 disease, a mortality rate of <1%."[11]

Our objective was to describe the population-based utilization of RP and to examine the utilization rate of prostate-bed radiotherapy after RP, and factors predicting its use in British Columbia, in the first few years after the aforementioned randomized trials were published.

## Methods

The British Columbia Cancer Agency (BCCA) captures registry and radiotherapy data on all incident cases of prostate cancer diagnosed in British Columbia (BC). All radiotherapy, including brachytherapy and external beam radiotherapy, delivered in BC is delivered at BCCA cancer centres and captured in these databases. All pathology reports from RP specimens with prostate cancer in BC are captured in the BC Cancer Registry (BCCR). For patients referred to the BCCA, pre-treatment clinical stage, initial PSA and biopsy Gleason score are recorded. All medical hormonal therapies (such as nonsteroidal anti-androgens and luteinizing hormone-releasing hormone agonists) are recorded in the BCCA pharmacy database.

All incident prostate cancers diagnosed between January 2005 and December 2007 were identified from the BCCR. Radiotherapy and BCCA stage and demographic records were linked to these incident cases. The pathology records in the BCCR were reviewed for pathologic stage, ECE, SVI, margin status, lymph node status and date of surgery for all cases that potentially could have been treated with RP. The registry files were not reviewed for prostatectomy pathology on patients who presented with clinical M1 disease or were known to have been treated with prostate brachytherapy or dose-escalated radiotherapy above 70 Gy (as they are not prescribed post-prostatectomy in BC). Palliative RPs done in the setting of clinical M1 presentation and salvage post-radiotherapy prostatectomies are not included. No patients were excluded from the analysis; all incident cases diagnosed in the province between January 2005 and December 2007 and captured in the tumour registry are included. All prostatectomy cases, other than those with the above-listed indications, and all post-prostatectomy radiotherapy cases are included. Patients diagnosed in the province, but who left the province for treatment with prostatectomy or radiotherapy would not be captured in the database.

The medical records for cases referred to the BCCA after prostatectomy were reviewed for intent of treatment (i.e., adjuvant or salvage), maximum postoperative PSA pre-radiotherapy, perioperative androgen ablation use, and reasons radiotherapy was not given to patients with risk factors. Postoperative RT was classified as adjuvant for the following reasons: if the radiotherapy was given within 6 months of RP, the postoperative PSA was less than the lab detection limit (typically 0.02 ng/mL), and no androgen ablation was given prior to prostatectomy or prior to the first available postoperative PSA.

We then calculated the proportion of cases treated with radiotherapy after RP or with adjuvant radiotherapy (as defined above). We also determined the proportion of patients with adverse risk factors (ECE, SVI or positive margins). In these patients, we also noted the use of postoperative and adjuvant radiotherapy in patients with adverse risk factors.

Logistic regression analysis was performed to determine factors (including age, ECE status, SVI, margin status, Gleason score, residence within 2 hour drive of a cancer centre) predicting the use of postoperative radiotherapy.

## Results

We identified 9223 incident cases of prostate cancer between 2005 and 2007. Of these patients, initial therapy was hormone therapy alone in 1338 (14%), no therapy in 2840 (31%), RP in 2181 (24%), primary external beam radiotherapy in 2122 (23%) and brachytherapy in 742 (8%) (Table 1). Median ages were 63 years (range: 35-86), 72 years (range: 47-89) and 65 years (range: 45-81) for those treated with RP, external beam radiotherapy and brachytherapy, respectively. Of the men treated with RP, only 1 (0.05%) died within a month of surgery. The pre-treatment Canadian Consensus risk groups were determined based on available pre-treatment stage, PSA and Gleason score.[12] Of the 760 RP cases with known pre-treatment risk, 33% were low risk, 47% were intermediate risk, and 21% were high risk. Of the 728 brachytherapy patients with known pre-treatment risk, 36% were low risk, 57% were intermediate risk, and 7% were high risk. Of the 2007 external beam patients with known pre-treatment risk, 10% were low risk, 42% were intermediate risk, and 48% were high risk.

We compared adverse pathologic factors in RP patients

**Table 1. Summary of treatment received by study population**

| | No. | % of all* |
|---|---|---|
| **Overall cases of prostate cancer in BC** | 9223 | 100% |
| Number referred to BCCA | 5373 | 58% |
| **Primary treatment modality** | | |
| Radical prostatectomy | 2181 | 24% |
| Primary radical external beam RT** | 2122 | 23% |
| Primary prostate brachytherapy | 742 | 8% |
| Hormone therapy alone at diagnosis‡ | 1338 | 14% |
| No treatment within 12 months of diagnosis | 2838 | 31% |
| **Prostatectomy cases** | | **% of RP†** |
| Total cases with adverse pathological features | 1015 | 47% |
| Positive margins | 793 | 36.3% |
| Extracapsular extension | 463 | 21.4% |
| Seminal vesicle involvement | 193 | 9% |
| Missing pathology | 15 | 0.7% |
| **Post-radical prostatectomy RT** | | |
| Salvage RT post-RP** | 307 | 14% |
| Adjuvant RT post-RP** | 25 | 1.1% |

BC: British Columbia; BCCA: British Columbia Cancer Agency; RT: radiotherapy; RP: radical prostatectomy. *Percentage of All, is percentage of all incident cases; †Percentage of RP is percentage of all radical prostatectomy; **Post RP-RT" means post prostatectomy radiotherapy. External beam RT subheading excludes post RP-RT. ‡This refers to cases that were started on androgen ablation within 6 months of diagnosis but did not go on to radical radiotherapy or radical prostatectomy within 12 months of diagnosis.

with reported rates of adverse pathology from the literature (Table 2, Table 3).[13-33] Pathologic stages were unknown in 1%, pT2 in 74%, pT3 in 23% and pT4 in 1%. Overall, 36.3% of patients treated with RP had positive margins, and would potentially benefit from adjuvant radiotherapy based on level I evidence. However, most patients in the trials had pT3 disease, and in our series only 13% had both positive margins and pT3 disease (i.e., 57% had positive margins of the 23% of cases with pT3 disease). Margins were positive in 30% of pT2 and 57% of pT3 patients, and in 49%, 36% and 32% of pre-treatment Canadian Consensus high-, intermediate-, and low-risk groups, respectively.

After RP, 332 (15%) patients had radiotherapy to the prostate bed, of these patients only 25 (1.1%) received adjuvant radiotherapy (according to the definition above). Of the patients with any adverse pathology (ECE positive, margin positive or SVI), 290 (29%) received postoperative radiotherapy, but only 23 (2%) received adjuvant radiotherapy. Of those with positive margins specifically, 244 (31%) received postoperative radiotherapy, and again only 19 (2.4%) received adjuvant radiotherapy. We compared our radiotherapy utilization rates with the literature (Table 4).[34-38]

Of all patients treated with RP, 270 (12%) were seen within 6 months of their RP. Of the patients with adverse RP pathology (positive margins, ECE or SVI), 230 (23%) were seen within 6 months of their RP. Of the 793 patients with positive margins, 198 (25%) were seen within 6 months of their RP; of these patients, 129 (65%) received radiotherapy (15% truly adjuvant and 85% salvage radiotherapy), and 69 (35%) did not. Of the 69 patients seen within 6 months of their RP by an oncologist and did not receive radiotherapy, 50 (72%) were truly eligible for adjuvant radiotherapy (as defined above); of these, 20 (40%) patients were advised against adjuvant radiotherapy by the oncologist.

Logistic regression for factors correlating with the use of postoperative radiotherapy included age (as a categorical variable), ECE status, SVI, positive margin status, Gleason score, and drive time to a cancer centre. A statistical significance ($p < 0.005$) in ECE, margins status, SVI and Gleason score was correlated with use of postoperative radiotherapy. The use of postoperative radiotherapy was higher for patients with higher grades (39% for Gleason 8-10 cases vs. 8% for Gleason 6> cases), SVI (51% with vs. 12% without), ECE (33% with vs. 10% without), and involved margin (31% with vs. 6% without) ($p$ values all <0.0001 with Chi Square tests). Due to the small number of cases receiving truly adjuvant radiotherapy, no regression was performed for adjuvant radiotherapy specifically.

## Discussion

The use of postoperative radiotherapy in our series (15%) is lower than expected based on the prevalence of adverse pathologic factors (47%). This implies that postopera-

**Table 2. Population comparison of adverse pathological features following RP between study population and published data (N>500)**

| Study | Site | No. RP procedures | Positive margin (%) | Positive ECE (%) | Positive SVI (%) |
|---|---|---|---|---|---|
| Schreiber et al. (2010) | SEER | 35642 | 18.3%† | 12.3 | 4.4 |
| Bhojani et al. (2009) | Creteil | 839 | | 28 | 14.5 |
| | Milan | 225 | | 11.1 | 5.3 |
| | Partin | 5730 | | 22 | 3 |
| Bianco et al. (2005) | | 1746 | 12 | 20 | 10 |
| Blute et al. (2001) | | 2518 | 39 | 34 | 15 |
| Boorjian et al. (2008) | | 7591 | 33 | | |
| Eskicorapci et al. (2004) | | 1043 | | 24.2 | 10.3 |
| Karakiewicz et al. (2005) | | 5831 | 26.7 | 34.7 | 11.2 |
| Karakiewicz et al. (2008) | | 1838 | | 26.9 | 5.5 |
| Palisaar et al. (2008) | | 1343 | 19.6 | | |
| Quinn et al. (2001) | | 732 | 45.9 | 42.8* | 13.1 |
| Swanson et al. (2007) | | 715 | 18.0 | 24.10 | 8.80 |
| Swindle et al. (2005) | | 1389 | 12.9 | | |
| Walz et al. (2009) | Hamburg | 2911 | 21.4 | 21.50 | 12.60 |
| | Cleveland | 2875 | 29.3 | 26.3 | 8.6 |
| Ward et al. (2004) | | 7268 | 38.0 | | |
| Wright et al. (2010) | SEER Database | 65633 | 21.2 | | |
| **Average of all studies** | | | 26.4 | 24.8 | 9.8 |
| **BCCA total prostate cases 2005-2007** | | 2181 | 36.3 | 21.6 | 9.0 |

ECE: extracapsular extension; SVI: seminal vesicle invasion; SEER: Surveillance, Epidemiology and End Results; RP: radical prostatectomy; BCCA: British Columbia Cancer Agency. †Estimated positive margin rate, excludes pT4 and pT3b. *Includes focal and extensive ECE.

**Table 3. Comparison of positive surgical margin rate by pathological stage following RP between study population and published data (N>250)**

| Study | No. RP | Positive surgical margins by pathological stage | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | pT2 overall (%) | pT2a (%) | pT2b (%) | pT3 overall (%) | pT3a (%) | pT3b (%) | pT4 (%) |
| Swindle et al. (2005) | 1389 | 6.8 | | | | 23 | | |
| Palisaar et al. (2005) | 1343 | 10.6 | | | 30.5 | 26.7 | 36.7 | 44.4 |
| Guillonneau et al. (2003) | 1000 | 15.5 | 6.9 | 18.6 | 31.5 | 30 | 34 | |
| Orvieto et al. (2006) | 996 | 1.7 | | | 25.3 | 24.2 | 27.1 | |
| Salomon et al. (2003) | 538 | 17.8 | | | | | | |
| Cohn et al. (2002) | 382 | | | | 34.8 | 39 | 12.5 | |
| Martinez-Pineiro et al. (2006) | 604 | 19.2 | | | 53.2 | | | 75 |
| **Average of all studies** | | 11.9 | 6.9 | 18.6 | 35.1 | 28.6 | 27.6 | 59.7 |
| **BCCA total prostate cases 2005-2007** | 2181 | 30 | | | 57 | | | |

RP: radical prostatectomy; BCCA: British Columbia Cancer Agency.

tive radiotherapy, particularly adjuvant radiotherapy, was underutilized in BC during the study era, but was similar to rates of postoperative radiotherapy in other published series (Table 4). This potential under-utilization of adjuvant radiotherapy may reflect a lack of awareness of the data or a perception that the benefit of adjuvant radiotherapy is not worth the additional morbidity. Given the lack of definitive data supporting an overall survival benefit during the era of this study, the latter is most likely the main factor. It is also possible that the use of adjuvant radiotherapy has increased since the additional data on survival was published in 2009.[4] The main use of radiotherapy in our series was salvage for relapse (as opposed to adjuvant radiotherapy), and the main predictors of its use, as expected, were Gleason grade, ECE, SVI and involved margins.

The presence of positive margins is considered one of the main drivers for postoperative adjuvant radiotherapy; therefore, the prevalence of positive margins warrants particular attention. The positive margin rate (36%) in our study was similar to the population-based rate found in Ontario (which ranged from 0-53%).[11] It is difficult to compare these rates to studies that are not population-based, as there may be selection bias, however, the results are within the range of published series (18%-46%, with a mean of 31%) (Table 2). A large population-based series from the Surveillance, Epidemiology and End Results (SEER) registry reported an overall margin positive rate of 21%.[39]

The positive margin rate for pT2 patients in our series (of 30 %) exceeded the 20% threshold held by most Ontario urologists.[11] However, the positive margin rates for pathologic T2 patients in British Columbia are generally comparable to the range of regional rates seen in Ontario (16%-42%),[11] although they are higher than those seen in other jurisdictions (Table 2). The positive margin rate in British Columbia in pT3 cases (57%) are also comparable to the range of regional rates seen in Ontario (42%-83%),[11] and within the ranges of rates reported in the literature (24%-80%).[13-29] In comparison to the recent large SEER series,

**Table 4. Use of both adjuvant and salvage postoperative radiation therapy following RP**

| Study | | Number of RP | Number receiving postoperative RT (%) | |
|---|---|---|---|---|
| Stephenson et al. (2009) | Study (Memorial Sloan-Kettering Cancer Center and Baylor College of Medicine 1987-2005) | 6398 | 115 (2) | |
| | Validation (Cleveland Clinic and University of Michigan) | 6279 | 538 (8) | |
| Berge et al. (2007) | SEER Database | 3940 | Adjuvant (<6 months) | 281 (7.1) |
| | | | Follow-up (6-66 months) | 283 (8.1) |
| Moreira et al. (2009) | Veteran Affairs Medical Centers 1998-2008. | 1975 | Salvage RT (including patients on ADT) | 220 (11) |
| Macdonald et al. (2008) | CaPSURE (1989-2004) | 4563 | Salvage RT (>6 months, detectable PSA) | 237 (5.2) |
| Macdonald et al. (2007) | | 5336 | Adjuvant (<6 months) | 96 (1.8)* |
| Schreiber et al. (2010) | SEER Database | 35642 | Adjuvant (<12 months) | 1186 (11%)† |
| BCCA total prostate cases 2005-2007 | | 2181 | Adjuvant (<6 months, with undetectable PSA) | 23 (2)** |
| | | | Salvage | 267 (26)** |

RP: radical prostatectomy; BCCA: British Columbia Cancer Agency; RT: radiotherapy; ADT: androgen deprivation therapy; PSA: prostate-specific antigen; SEER: Surveillance, Epidemiology and End Results; CaPSURE: Cancer of the Prostate Strategic Urologic. Research Endeavor. *7 cases missing follow-up info. †Adjuvant refers to RT within 12 months of surgery, but no data on Post operative PSA. Percentage refers to the 10,674 cases with ECE or positive margins. ** Expressed as a percentage of 1015 with adverse pathology.

our margin positive rates exceed those reported for SEER (18% for pT2, and 44% for pT3).[39] Unlike the SEER study, which was also population-based, our study detailed patient data on postoperative PSA, which allowed us to distinguish adjuvant and early salvage radiotherapy. The perioperative mortality rate in British Columbia is well within the accepted target described by Cancer Care Ontario (CCO) (< 1 %) and those reported in the literature (0-0.5%).[39]

There are a few caveats and potential limitations in our analysis. Pre-treatment stage and risk groupings were not available for many of the prostatectomy cases, and this limited our ability to estimate the extent to which higher risk patients received RP. Therefore, the margin status findings for the preoperative consensus risk groups may be biased; the referred cases with relapsing PSAs may be over-represented. We also had the potential for missing some cases with the fact that registry ascertainment was not 100% (but this was very minimal). A few cases from eastern regions of British Columbia may get their radiotherapy in Alberta and these patients would not be captured; however, these are sparsely populated regions and would not have a significant impact on the overall radiotherapy utilization rates.

There may be important intraobserver variations in the reporting of positive margins and pathologic stage among pathologists in British Columbia. Only one urologist was performing laparoscopy robotic prostatectomy during this study era, with relatively few cases; therefore, a learning curve related to robotic laparoscopic prostatectomy would not have been a factor. We lack data on patient preferences, decision-making discussions with urologists, and documentation of comorbidities for patients who had a RP and were not referred to a cancer centre. However, we believe that most patients were assessed by a radiation oncologist. In our analysis only patients who received radiotherapy within 6 months of prostatectomy for an undetectable postoperative PSA in the absence of androgen ablation were considered truly adjuvant. This very strict definition of adjuvant radiotherapy may be one reason the proportion of patients receiving it is low. However, even if we extended the time for adjuvant therapy to 12 months post-prostatectomy, the overall adjuvant radiotherapy rate post-prostatectomy was only 1.7 %; for those with positive margins specifically, it was only 3.4%. There is ongoing debate whether the benefit of adjuvant radiotherapy would be as significant in the current era compared to early salvage radiotherapy.

## Conclusion

We encourage all urologists to consider early referral (within 6 months of surgery) to a radiation oncologist for consideration of adjuvant radiotherapy in the setting of high-risk features (ECE, positive margins or SVI) on pathology after RP. Urologists should discuss the risks and benefits of adjuvant radiotherapy and discuss enrolment in the RADICALS (Radiotherapy and Androgen Deprivation In Combination After Local Surgery) trial[40] or other similar trials.

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