Evidence-based Series 3-17 Version 3

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Adjuvant Radiotherapy Following Radical Prostatectomy for Pathologic T3 or Margin-Positive Prostate Cancer

Members of the Genitourinary Cancer Disease Site Group

An assessment conducted in November 2016 deferred the review of Evidence-based Series (EBS) 3-17v3. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

The reviewed EBS report, which is available on the CCO web site (http://www.cancercare.on.ca), consists of the following sections:

Section 1: Guideline Recommendations (ENDORSED)
Section 2: Updated Evidentiary Base
Section 2B: Original Evidentiary Base
Section 3: EBS Development Methods and External Review Process
Section 4: Document Review Summary and Review Tool

Release Date: May 2, 2014

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Phone: 905-527-4322 ext. 42822   Fax: 905-526-6775   E-mail: ccopgi@mcmaster.ca

# Guideline Report History

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Adjuvant Radiotherapy Following Radical Prostatectomy for Pathologic T3 or Margin-Positive Prostate Cancer: Updated Guideline Recommendations 2010


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These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Summary and Review Tool for a summary of updated evidence published between 2006 and 2012, and for details on how this Clinical Practice Guideline was ENDORSED

Report Date: May 2, 2014

QUESTION

Does adjuvant radiotherapy (RT) following radical prostatectomy improve clinically important outcomes in patients with pathologic T3 or margin-positive prostate cancer compared with no adjuvant radiotherapy? The primary outcome of interest is overall survival (OS). Outcomes of secondary interest include prostate cancer-specific survival, metastasis-free survival, biochemical progression-free survival (bPFS), locoregional recurrence-free survival, time to initiation of androgen deprivation therapy (ADT), incidence of acute and late toxicity, and quality of life.

TARGET POPULATION

These recommendations apply to men who have undergone radical prostatectomy for clinically localized prostate cancer and who have been found to have either positive surgical resection margins (R1), tumour extension beyond the prostatic capsule (pT3a), seminal vesicle invasion (pT3b), or more than one of these features.
INTENDED USERS
This guideline is intended for use by clinicians and health care providers involved in the management or referral of men with prostate cancer.

RECOMMENDATIONS
• In patients found at radical prostatectomy to have positive surgical margins, extracapsular extension, or seminal vesicle invasion, early referral to a radiation oncologist is recommended for consideration of adjuvant external beam radiotherapy with the aim of prolonging survival.
• The decision regarding the use of adjuvant radiotherapy should take into account its modest associated genitourinary and rectal toxicity as well as the risk of disease relapse.

QUALIFYING STATEMENTS
• In the trials addressing this question, early referral implied the commencement of adjuvant radiotherapy (if RT was deemed suitable) between six and 18 weeks following prostatectomy.
• The risk of disease relapse is >90% when the post-prostatectomy PSA is rising and is >0.1 ng/mL (1,2).
• The benefits of adjuvant radiotherapy in terms of prolonged biochemical progression-free survival and overall survival are found to extend to patients with any of positive surgical margins, extracapsular extension, or seminal vesicle invasion. However, the completed randomized trials of adjuvant radiotherapy enrolled relatively few patients with organ-confined, margin-positive disease, and therefore further study of this population is warranted.
• The available data from randomized trials do not address:
  o Whether salvage radiotherapy administered at the time of early biochemical failure confers outcomes equivalent to those of adjuvant radiotherapy.
  o Whether androgen deprivation therapy given in conjunction with adjuvant radiotherapy improves outcomes over adjuvant radiotherapy alone.
  o The optimal target volume, technique, or dose-fractionation schedule for adjuvant radiotherapy.
  o The role for post-operative radiotherapy to involved or at-risk pelvic lymph nodes.
• The enrolment of patients at risk for recurrence following radical prostatectomy in clinical trials is encouraged.

MODIFICATIONS FROM ORIGINAL RECOMMENDATIONS
The current recommendations are essentially unchanged from the original recommendations. It is anticipated that the recommendations will be reviewed once mature results are published for the two randomized trials for which only short-term results are currently available.

KEY EVIDENCE
• Three randomized trials (n=1693) were eligible for inclusion in the systematic review of the evidence: SWOG 8794 (3,4), EORTC 22911 (5), and ARO/AUO 96-02 (6,7). In these trials, patients were randomized to either adjuvant external beam radiotherapy in the immediate postoperative period after prostatectomy or to observation with therapies (including radiotherapy, androgen deprivation therapy, and other therapies) held in reserve for salvage. The primary endpoints of interest were biochemical progression-free
survival (two trials) and metastasis-free survival (one trial). Median patient follow-up ranged from 4.5 years (6) to 12.6 years (4).

- Two trials (SWOG 8794 and EORTC 22911) reported data on overall survival. In the only trial with long-term results (SWOG 8794) (4), adjuvant radiotherapy has been found to significantly improve overall survival compared to observation (HR, 0.72; 95% CI, 0.55 to 0.96; p=0.023). Ten-year overall survival was 74% with adjuvant radiotherapy and 66% with observation. Median survival was 15.2 years with adjuvant radiotherapy and 13.3 years with observation. Only short-term results have been published for the EORTC 22911 trial. With a median follow-up of five years, 43 deaths have occurred in the observation arm and 43 deaths in the adjuvant radiotherapy arm. As this represents an event rate for death of only 8.9%, meaningful conclusions cannot yet be drawn on the effect of adjuvant radiotherapy on overall survival in this trial. Longer term results from EORTC 22911 are awaited and they will inform future updates of this guideline.

- An exploratory analysis of SWOG 8794 was presented in which the effect of adjuvant RT on overall survival was assessed in subgroups defined by pathologic characteristics. The overall survival benefit was found to extend to patients with positive surgical margins (HR, 0.68; 95% CI, 0.49 to 0.94), extracapsular extension (HR, 0.62; 95% CI, 0.46 to 0.84), and seminal vesicle invasion (HR, 0.57; 95% CI, 0.35 to 0.93).

- One trial (SWOG 8794) (4) reported data on metastasis-free survival, and adjuvant RT was found to confer a significant improvement in this outcome (HR, 0.71; 95% CI, 0.54 to 0.94; p=0.016).

- All three trials reported data on biochemical progression-free survival and detected statistically significant reductions in biochemical failure with adjuvant radiotherapy compared to observation. A meta-analysis of these data produced a pooled HR of 0.47 (95% CI, 0.40 to 0.56; p<0.00001).

- An exploratory analysis of the three trials was presented in which the effect of adjuvant RT on biochemical progression-free survival was assessed in pathologic subgroups defined by margin status (positive or negative), extracapsular extension (present or absent), and seminal vesicle invasion (present or absent). Adjuvant radiotherapy was found to carry a significant benefit in all subgroups.

- None of the trials provided a time-to-event analysis for locoregional recurrence-free survival. At five years of follow-up, one trial reported that 15.4% (98% CI, 11.2 to 19.6) of those randomized to observation had experienced locoregional failure compared to 5.4% (98% CI, 2.7 to 8.0) of those randomized to adjuvant radiotherapy (p<0.0001) (5).

- All three trials reported on toxicity. Two trials (EORTC 22911 and ARO/AUO 96-02) have provided comparative graded toxicity data and there were no significant differences between arms in major (grade ≥3) gastrointestinal or genitourinary toxicity at latest follow-up. However, a significant excess in minor gastrointestinal and genitourinary toxicity was seen in both trials among patients receiving adjuvant radiotherapy. In the EORTC 22911 trial, the cumulative incidence of grade ≥1 toxicity was significantly greater in the adjuvant radiotherapy arm than the observation arm (64.9% vs. 54.3%, p=0.005). Similarly, in the ARO/AUO 96-02 trial, the cumulative incidence of grade ≥1 gastrointestinal or genitourinary toxicity was 21.9% in the adjuvant radiotherapy arm and 3.7% in the observation arm (p<0.0001).

- A quality of life study (8) was conducted as a companion to SWOG 8794 in approximately half of study participants (n=217). While global health-related quality of life was initially worse in the adjuvant RT arm, by the end of the five-year study period, a greater proportion of patients in the adjuvant RT arm had normal global health-related quality of life than in the observation arm (69% vs. 51%).
FUTURE RESEARCH

The enrolment of patients with R1, pT3a, or pT3b disease following prostatectomy in randomized trials comparing adjuvant radiotherapy with salvage radiotherapy instituted at early biochemical relapse is encouraged. Similarly, enrolment of these patients in trials comparing post-operative radiotherapy alone with post-operative radiotherapy in conjunction with androgen deprivation therapy is encouraged.

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Contact Information

For further information about this report, please contact:

Dr. Andrew Loblaw, Chair, Genitourinary Cancer Disease Site Group
Odette Cancer Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5
Phone: 416-480-4806   Fax: 416-480-1338   E-mail: andrew.loblaw@sunnybrook.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
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REFERENCES


