



Evidence-based Series 3-17 Version 3 ARCHIVED 2017

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 2017 ARCHIVED Evidence-based Series (EBS) 3-17v3. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. 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 [Genitourinary Cancer](#) page, consists of the following sections:

- Section 1: Guideline Recommendations
- 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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ARCHIVED

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version Feb 2008	1980-2008	Full Report	Peer review publication Web publication	NA
Version 2 Jun 2010	2008- 2009	New data added to original report	Updated Web publication	2008 recommendation updated
Version 3 May 2014	2009-2014	New data found in Section 4: Document Summary and Review Tool	Updated Web publication	2010 recommendation ENDORSED

Table of Contents

Section 1: Guideline Recommendations	1
Section 2A: Updated Evidentiary Base	6
Section 2B: Original Evidentiary Base	25
Section 3: Guideline Development and External Review	43
Section 4: Document Review Summary & Review Tool	56

Evidence-based Series 3-17 Version 3: Section 1

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

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

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:
 - Whether salvage radiotherapy administered at the time of early biochemical failure confers outcomes equivalent to those of adjuvant radiotherapy.
 - Whether androgen deprivation therapy given in conjunction with adjuvant radiotherapy improves outcomes over adjuvant radiotherapy alone.
 - The optimal target volume, technique, or dose-fractionation schedule for adjuvant radiotherapy.
 - 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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Evidence-based Series #3-17 Version 3: Section 2A

**Adjuvant Radiotherapy Following Radical Prostatectomy for
Pathologic T3 or Margin-Positive Prostate Cancer:
Updated Evidentiary Base 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: July 22, 2010

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 RT? 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.

INTRODUCTION

A practice guideline report on adjuvant RT following prostatectomy in patients with pT3 or margin-positive prostate cancer was originally completed by the Program in Evidence-Based Care Genitourinary Disease Site Group (PEBC GU DSG) in February 2008. The systematic review, as originally published in February 2008, can be found in Section 2B of this Evidence-based Series. A systematic review manuscript based on that report was published in July 2008 (1). With the availability of new evidence, the GU DSG chose to conduct an update of the

evidence and recommendations in the fall of 2009. A review of the evidence published since February 2008 is presented here, Section 2A, of this report.

METHODS

The evidence-based series guidelines developed by Cancer Care Ontario's PEBC use the methods of the Practice Guidelines Development Cycle (2). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the GU DSG and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on the role of adjuvant RT following prostatectomy in patients with pathologic T3 or margin-positive prostate cancer. The body of evidence in this review is primarily comprised of randomized controlled trial (RCT) data; therefore, recommendations by the DSG are offered. That evidence, along with the original evidence reviewed in Section 2B, forms the basis of a clinical practice guideline developed by the GU DSG found in Section 1 of this evidence-based series. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

Relevant articles published since February 2008 were identified by searches of MEDLINE (2008 - September 2009 week 1), EMBASE (2008 - 2009 week 37), and the Cochrane Library (2009, Issue 4). The updated MEDLINE and EMBASE search strategies are detailed in Appendix 1.

The conference proceedings of the 2008 and 2009 annual meetings of the American Society of Clinical Oncology, the American Society for Radiation Oncology, the American Urological Association, and the European Association of Urology were also searched for relevant trials.

Study Selection Criteria

The study selection criteria used in the original systematic review (See Section 2B) were adopted for the 2010 update. This included RCTs, systematic reviews, or clinical practice guidelines in which adjuvant RT in the immediate postoperative period after radical prostatectomy was compared to observation, with other therapies including RT and ADT held in reserve for salvage. The patients had prostate cancer and were found at prostatectomy to have either extracapsular extension (now more commonly referred to as extraprostatic extension), seminal vesicle invasion, positive surgical resection margins, or more than one of these features.

Synthesizing the Evidence

Assessment of study quality followed the same procedure as in the original systematic review (See Section 2B).

OS, prostate cancer-specific survival, metastasis-free survival, bPFS, locoregional recurrence-free survival, time to initiation of ADT, acute and late toxicity, and quality of life were the outcomes of interest, as in the original systematic review. When data were available on these outcomes from two or more trials, meta-analysis of the trial data was

planned using the Review Manager software (RevMan 5.0.22) provided by the Cochrane Collaboration.¹

RESULTS

Literature Search Results

In the original search, a total of 14 reports (3-16) representing three randomized trials satisfied the eligibility criteria. The main reports of the two trials were published as full articles (6,10) and the other trial was published as an abstract (14).

A literature search update was conducted in September 2009. New reports of two RCTs contributed to the evidence base: longer term follow-up of the Southwest Oncology Group (SWOG) 8794 trial (17), and the full publication of the German Cancer Society ARO 96-02/AUO AP 09/95 trial (18), previously available only as a meeting abstract. Post-hoc analyses of the SWOG trial were also identified (19,20). Three systematic reviews (21-23) and a practice guideline (24) met the selection criteria, but did not contain any new trials. A Cochrane review protocol (25) was identified, but the systematic review is not yet available.

Trial Characteristics

No new results from the European Organization for the Research and Treatment of Cancer (EORTC) 22911 trial (6) have been published since the original version of the systematic review was completed. The GU DSG contacted the EORTC trial committee in October 2009 and at that time there was no definite timeline in place for an updated trial report. While the initial report of SWOG 8794 (10) was based on analysis at a median follow-up of 10.6 years, the updated report published in 2009 (17) extends median follow-up to 12.6 years. The ARO/AUO trial was published in a full report in 2009 (18). Study characteristics in the updated reports remained the same as the original reports. Major characteristics of the three trials (6,17, 18) are summarized in Table 1. The updated trial data are shown in italics.

¹ Review Manager (Revman [Computer program]. Version 5.0.22 for Windows. Oxford (England): The Cochrane Collaboration, 2008.

Table 1. Characteristics of eligible trials.

Trial Descriptors	EORTC 22911	SWOG 8794		German Cancer Society ARO 96-02 and AUO AP 09/95	
	Bolla 2005 (6)	Thompson 2006 (10)	Thompson 2009 (17)	Wiegel 2007 (14)	Wiegel 2009 (18)
Eligibility Criteria	Previously untreated prostate cancer treated with RP	Previously untreated prostate cancer treated with RP	Same	Prostate cancer treated with RP	Same
	At least one of: ECE, SVI, or SM+ (pT2 N0 M0 R1 or pT3 N0 M0 R0-1)	At least one of: ECE, SVI, or SM+ (pT2 N0 M0 R1 or pT3 N0 M0 R0-1)	Same	ECE or SVI with or without SM+ (pT3 N0 R0-1)	Same
	WHO PS 0-1	SWOG PS 0-2	Same	Undetectable PSA following RP	Same
	Age ≤ 75 yrs	Negative pelvic lymphadenectomy*	Same		WHO PS 0-1
				Age <76 yrs	
Median Age	65 yrs	64.9 yrs	Same	NR	64 yrs
Stratification Variables	Institution; ECE status; margin status; SVI status	Tumour extent (presence of ECE or SM+; presence of SVI; presence of SVI and either ECE or SM+); NADT use	Same	Gleason score (2-6 vs. 7-10); margin status; pathologic T-stage (pT3a vs. pT3b); NADT use (3 mo. vs. none)	Same
NADT Use (%)	10%	8.5%	Same	NR	11%
Number Randomized	1005	431	Same	307	388
Number Eligible	968	425	Same	300	307
Time From RP Until Start Adjuvant RT	<16 wks	<18 wks	Same	8-12 wks	6-12 wks
Adjuvant RT Dose-Fractionation	60 Gy in 30 fractions	60-64 Gy in 30-32 fractions	Same	60 Gy in 30 fractions	Same
Treatments Received by Observation Arm (n)	Pelvic RT (113); ADT (45); surgical castration (1); other (4)	Pelvic RT (70); other therapies NR	Same (NR)	NR	NR
RT Volume	Initial phase: 50 Gy to “volume including surgical limits from seminal vesicles to apex with security margin to	Single phase: RT delivered to “prostatic fossa and paraprostatic tissues”	Same	Prostatic fossa and seminal vesicles plus 1 cm margin	Surgical limits from the seminal vesicles, marked with clips intraoperatively, to the apex, with a 1 cm security margin to

Trial Descriptors	EORTC 22911	SWOG 8794		German Cancer Society ARO 96-02 and AUO AP 09/95	
	Bolla 2005 (6)	Thompson 2006 (10)	Thompson 2009 (17)	Wiegel 2007 (14)	Wiegel 2009 (18)
	encompass subclinical disease in periprostatic area” Boost phase: 10 Gy boost to “reduced volume circumscribing the previous landmarks of the prostate with a reduced security margin”				<i>encompass subclinical disease in the periprostatic area</i>
Median Follow-Up	5 yrs	10.6 yrs	12.6 yrs	4.5 yrs	<i>Same</i>
Primary Endpoint	Biochemical progression-free survival	Metastasis-free survival	<i>Same</i>	Biochemical progression-free survival	<i>Same</i>
Definition of Biochemical Progression	An increase of more than 0.2 ng/mL over the postoperative nadir value measured on three occasions at least 2 wks apart	For men with a post-surgical PSA \leq 0.4 ng/mL, the first occurrence of PSA > 0.4 ng/mL.	<i>NR</i>	PSA increase from undetectable to detectable level, with confirmation by further increase at least 3 months later	<i>Two consecutive PSA increases above the detection limit of the respective PSA assay used</i>

Abbreviations: ADT - androgen deprivation therapy; ECE - extracapsular extension; EORTC - European Organization for the Research and Treatment of Cancer; n - number; NADT - neoadjuvant androgen deprivation therapy; NR - not reported; PS - performance status; PSA - prostate specific antigen; RP - radical prostatectomy; RT - radiotherapy; SM+ - positive surgical margin; SVI - seminal vesicle invasion; SWOG - Southwest Oncology Group; vs - versus; WHO - World Health Organization; wks - weeks; yrs - years.

*Towards study end, some patients at very low risk for involved pelvic lymph nodes were not required to undergo lymphadenectomy. Details available in trial report.

Trial Quality

The results of the trial quality assessment are summarized in Table 2. The three trials met all of the trial quality criteria.

Table 2. Methodologic quality of eligible trials.

Trial Characteristic	EORTC 22911	SWOG 8794		German Cancer Society ARO 96-02 and AUO AP 09/95	
	Bolla 2005 (6)	Thompson 2006 (10)	Thompson 2009 (17)	Wiegel 2007 (14)	Wiegel 2009 (18)
Random allocation	Yes	Yes	Same	Yes	Same
Allocation concealment	Yes	Yes	Same	Unclear	Yes
Description of withdrawals	Yes	Yes	Same	Unclear	Yes
Intention-to-treat analysis	Yes	Yes	Same	No	Yes

Outcomes

The updated report on the SWOG trial (17) presented new data for the outcomes of OS and metastasis-free survival. The ARO/AUO trial (18) did not provide new time-to-event analyses beyond those reported in the 2007 abstract. Trial results are summarized in Table 3, and proceeding text only addresses outcomes with updated results.

Table 3. Trial results for outcomes of interest.

Outcome	EORTC 22911	SWOG 8794		ARO 96-02 / AUO AP 09/95	
	Bolla 2005 (6)	Thompson 2006 (10)	Thompson 2009 (17)	Wiegel 2007 (14)	Wiegel 2009 (18)
Overall survival	HR 1.09 (98% CI 0.67 to 1.79)	HR 0.80 (95% CI 0.58 to 1.09) p = 0.16	HR 0.72 (95% CI 0.55 to 0.96) p = 0.023	NR	Deaths at time of reporting: ADJ RT - 3.4% OBS - 5.0% p value NR
Prostate cancer-specific survival	At 5 years: ADJ RT - 98.4% OBS - 97% p value NR	NR	NR	NR	NR
Metastasis-free survival	Distant failures at 5 years: ADJ RT - 3.8% OBS - 3.6% p value NR	HR 0.75 (95% CI 0.55 to 1.02) p = 0.06	HR 0.71 (95% CI 0.54 to 0.94) p = 0.016	NR	Distant failures at time of reporting: ADJ RT - 2.0% OBS - 3.1% p value NR
Biochemical progression-free survival	HR 0.48 (98% CI 0.37 to 0.62)	HR 0.43 [†] (95% CI 0.31 to 0.58) p < 0.001	NR	HR 0.53 [‡] p = 0.0015	Same HR 0.53 (95% CI 0.37 to 0.79) p = 0.0015 [‡]
Locoregional recurrence-free survival	Locoregional failures at 5 years: ADJ RT - 5.4% OBS - 15.4% p < 0.0001	NR	NR	NR	NR
Time to initiation of ADT	NR	HR 0.45 (95% CI 0.29 to 0.68) p < 0.001	NR	NR	NR

Abbreviations: ADJ RT - adjuvant radiotherapy; ADT - androgen deprivation therapy; CI - confidence interval; EORTC - European Organization for the Research and Treatment of Cancer; HR - hazard ratio; NR - not reported; OBS - observation; RT - radiotherapy; SWOG - Southwest Oncology Group

[†]In this trial, biochemical failure was defined as the time of first occurrence of PSA >0.4. Hence only those patients achieving a post-operative PSA ≤0.4 were considered for this outcome (n=347).

[‡]Not derived from an intention-to-treat analysis.

Overall Survival

While the original 2006 report of the SWOG trial (10) showed no difference between treatment groups for OS, the updated report in 2009 (17) showed a significant improvement in overall survival with adjuvant RT (hazard ratio [HR], 0.72; 95% confidence interval [CI], 0.55 to 0.96; p=0.023). At the time of the update, 88 of 214 men randomized to adjuvant RT had died versus 110 of 211 men randomized to observation. Ten-year OS was 74% and 66% for those randomized to adjuvant RT and observation, respectively. Median survival was 15.2 years with adjuvant RT and 13.3 years with observation.

No new results from the EORTC 22911 trial have been published since the initial version of this review was completed. Only short term (five-year) results from the 2005 trial publication are available (6). At the time of publication, 43 deaths had occurred in the observation arm and 46 deaths in the adjuvant RT arm (HR, 1.09; 98% CI, 0.67 to 1.79; p=0.6796). This represents an event rate for death of only 8.9%. In view of the immaturity of these results, the GU DSG felt that inclusion of these data in a meta-analysis was inappropriate and no such meta-analysis has therefore been undertaken. Longer term results from the EORTC trial are awaited and once available will be incorporated into a meta-analysis with the SWOG 8794 results.

Metastasis-Free Survival

Only the SWOG trial (17) provided data on this outcome. In the updated report, adjuvant RT reduced death or metastatic disease by 29% compared with observation (HR, 0.71; 95% CI, 0.54 to 0.94; p=0.016). Ten-year metastasis-free survival was 71% in those randomized to adjuvant RT and 61% in those randomized to observation.

Acute and Late Toxicity

The full report of the ARO/AUO trial (18) did not report early and late toxicity data separately; instead, cumulative rates of toxicity over the entire follow-up period were reported. In the adjuvant RT group, one patient experienced grade 3 GU (bladder) adverse effects, three patients (2%) experienced grade 2 GU adverse events, and two patients (1.4%) experienced grade 2 gastrointestinal adverse effects. No adverse effects ≥ grade 2 were experienced by the observation group. Overall, the cumulative rate of adverse effects for bladder and rectum ≥ grade 1 was 21.9% in the adjuvant RT group and 3.7% in the observation group (p<0.0001). The updated report of the SWOG trial (17) did not include toxicity outcomes.

Subgroup Analyses

The three trials included in this review enrolled patients with positive surgical margins, extracapsular extension, or seminal vesicle invasion. (Strictly speaking, it should be noted that a positive margin alone was not sufficient for entry into the ARO/AUO trial if unaccompanied by pathologic T3 disease.) It is therefore of interest to assess the relative benefit of adjuvant RT in subgroups defined by the presence or absence of these characteristics. Exploratory analyses across these pathologic subgroups have been published for each of the three trials. Two subgroup analyses of the EORTC trial (8,26) were considered in the initial version of this systematic review, and no further analyses have since been

published. The first report (26) included all patients enrolled in the trial and used local pathology data while the second report (8) was limited to approximately half of study patients (n=552) in whom a central pathology review was performed. In each report, bPFS was the outcome of interest and analysis was performed at a median follow-up of five years. Two subgroup analyses of the SWOG trial (one published report considering those patients enrolled in the trial with seminal vesicle invasion (19) and the other an abstract considering those free of seminal vesicle invasion (20)) have appeared since February 2008. Finally, the published ARO/AUO trial report included a subgroup analysis of all trial participants performed at a median follow-up of 4.5 years (18). The outcome of interest was bPFS. The analysis took account of a central pathology review in 85% of cases, while local pathology review was employed for the remaining 15% of cases.

In each of the three trials, randomization was stratified with respect to these pathologic characteristics, whether considered singly or in combination (see Table 1). Hence, the adjuvant RT and observation arms in each trial are likely to be well balanced with respect to these characteristics. In addition, the definitions of bPFS employed across the three trials were similar. In view of this, meta-analysis of the bPFS subgroup data was performed by members of the GU DSG and is to be presented at the 2010 annual meetings of the Canadian Association of Radiation Oncology (27) and the American Society for Radiation Oncology (28). It should be noted that, of the two published post-hoc analyses of the EORTC trial (8,26), results of the one that included all trial patients (26) were included in the meta-analysis. The analysis included previously unpublished data provided by the SWOG trial investigators. These data included subgroup analyses of bPFS and OS by pathologic subgroup. Results of the pooled analysis of bPFS outcomes are summarized in Table 4, with the OS outcome data provided by the SWOG trial investigators.

Table 4. Summary hazard ratios (95% CI) for biochemical progression-free survival across all three trials and hazard ratios (95% CI) for overall survival in SWOG 8794 in subgroups defined by pathologic characteristics.

Pathologic characteristic		Biochemical Progression-Free Survival SWOG, EORTC, ARO/AUO n=1627 Summary HR (95% CI) (27,28)	Overall Survival SWOG 8794 n=416 HR (95% CI) (27,28)
Surgical margin status	Positive	0.45 (0.36-0.57)	0.68 (0.49-0.94)
	Negative	0.61 (0.44-0.85)	0.75 (0.44-1.28)
Extracapsular extension	Present	0.50 (0.41-0.60)	0.62 (0.46-0.84)
	Absent	0.49 (0.31-0.75)	1.32 (0.66-2.63)
Seminal vesicle invasion	Present	0.52 (0.40-0.68)	0.57 (0.35-0.93)
	Absent	0.47 (0.37-0.60)	0.78 (0.55-1.10)

Abbreviations: CI - confidence interval; EORTC - European Organization for the Research and Treatment of Cancer; HR - hazard ratio; NR - not reported; SWOG - Southwest Oncology Group.

It is remarkable that the OS benefit of adjuvant RT observed in the overall SWOG trial population also extends to the subgroup of patients with positive surgical margins (HR, 0.68; 95% CI, 0.49 to 0.94); the subgroup with extracapsular extension (HR, 0.62; 95% CI, 0.46 to 0.84); and the subgroup with seminal vesicle invasion (HR, 0.57; 95% CI, 0.35 to 0.93). Stated alternatively, each of the three constituent pathologic subgroups included in these trials

experienced a significant survival benefit from adjuvant RT that was independent of the others.

An additional comment is necessary regarding the group free of extracapsular extension. This is the only subgroup in which the HR for OS favoured observation. Absence of extracapsular extension in this context should not be assumed to be synonymous with pT2 R1 disease. As pathologic variables were coded independently in the SWOG trial database, the extracapsular extension-absent subgroup is a collection of patients with either pT2 R1 disease or pT3b R0-1 disease without coexisting capsular extension. As such, this is a very heterogeneous group, that is not representative of the population at large with organ-confined, margin-positive disease, and the result is therefore not generalizable to it. It is also a small subgroup (n=85), as evidenced by the broad confidence interval. Finally, the possibility exists that this is a spurious result that has arisen from an exploratory analysis involving multiple comparisons. For these reasons, the GU DSG cautions against overinterpretation of the outlying result seen in this subgroup.

It is noteworthy that in all six subgroups examined (positive and negative surgical margins, presence and absence of extracapsular extension, and presence and absence of seminal vesicle invasion), adjuvant RT conferred a statistically significant benefit in terms of bPFS. The magnitude of benefit was broadly similar across all groups, with the pooled HR ranging from 0.45 (in the case of patients with positive margins) to 0.61 (in the case of patients with negative margins). The finding of benefit across all subgroups conflicts with both the EORTC subgroup analysis based on central pathologic review (8) and the ARO/AUO subgroup analysis (18), in which the margin-negative population did not benefit from adjuvant RT.

It should be acknowledged finally that the population of patients enrolled in these trials with positive surgical margins may not be representative of the general population at large with positive margins following prostatectomy. While a positive margin alone was sufficient for entry into the EORTC and SWOG trials (pT3 disease was a requirement for entry into the ARO/AUO trial), relatively few patients whose only adverse feature was a positive margin were enrolled. For example, in the EORTC trial, 629 of the 1005 enrolled patients possessed positive surgical margins. Among these, in only 163 cases (26%) was the positive margin the only adverse feature present (i.e., pT2 R1 disease), while in the remaining 466 cases (74%) the positive margin occurred in the presence of either extracapsular extension or seminal vesicle invasion (i.e., pT3 R1 disease). Additional study of the impact of adjuvant radiotherapy in patients with organ-confined, margin-positive disease is therefore warranted.

INTERPRETATION AND DISCUSSION

Since the initial publication of this systematic review in 2008, updated results from one of the three included RCTs (17) are now available. At a median follow-up of 12.6 years, adjuvant RT has now been shown to confer a significant benefit in terms of both OS and metastasis-free survival. The significance of these findings warrants re-statement; for the first time, a large-scale RCT has shown that an adjuvant therapy given after prostatectomy improves longevity and reduces distant failure compared to a policy of observation and salvage therapy. The magnitude of the observed benefit is substantial; median survival is prolonged by 1.9 years with adjuvant RT. A number-needed-to-treat analysis reveals that, compared to the observation and salvage strategy employed in the trial, nine courses of adjuvant RT are required to prevent one death by 12.6 years of median follow-up. Placed in context, this is similar to the magnitude of benefit seen with post-mastectomy RT given for node-positive breast cancer (29-31).

Results from the EORTC trial are not sufficiently mature to draw conclusions regarding the effect of adjuvant RT on OS in this trial. At a median follow-up of five years, only 8.9% of

trial participants had died at the time of the most recent report (6). Longer term results from this trial and from the ARO/AUO trial-in which only 4% of patients have died to date-are awaited. Updates of this systematic review, and the clinical practice guideline of which it forms the basis, will be undertaken once new survival data are available.

In terms of pathologic findings, a fairly heterogeneous population of patients was enrolled in each of the three trials. They included men with positive resection margins, capsular breach, or seminal vesicle invasion, and no limitations were placed on Gleason score. The results of subgroup analysis of the SWOG trial with OS as primary endpoint are striking; the benefit in OS conferred by adjuvant RT applies not only to the trial population as a whole, but also to the individual populations of patients with a positive surgical margin, extracapsular extension, or seminal vesicle invasion when considered separately. Further, the pooled subgroup analysis of the three trials with bPFS as primary endpoint demonstrates a clear and statistically significant benefit for adjuvant RT in all subgroups. This is a new finding and is at odds with previously published post-hoc analyses of the EORTC (8) and ARO/AUO (18) trials wherein no significant bPFS benefit was seen in patients with pathologic T3 disease but negative surgical margins. On the basis of the overall trial findings as well as these subgroup analyses, it can be concluded that men found at radical prostatectomy to have any of positive surgical margins, extracapsular extension, or seminal vesicle invasion benefit from adjuvant RT. As noted above, further study of those patients with organ-confined, margin-positive disease is warranted to better define the impact of adjuvant radiotherapy in this setting.

ONGOING TRIALS

While updated results from the SWOG trial (17) indicate the clear superiority of adjuvant RT over the observation and salvage therapy policy employed in the trial, it remains uncertain whether the superiority of adjuvant RT would remain if it were compared to a strict policy of close surveillance with salvage RT initiated at the earliest sign of biochemical recurrence. The latter approach holds the potential advantage of avoiding RT, and its side effects, in those that do not ultimately recur biochemically following surgery. Determining which of these approaches is optimal requires well-designed phase III trials. Fortunately, three such RCTs comparing adjuvant and early salvage approaches to postoperative RT are now underway. Features of these trials, which were identified on a search of the National Cancer Institute trials registry at clinicaltrials.gov, are summarized below. The GU DSG will monitor the progress of the trials and review reported results when they become available.

Protocol ID	Title and details of trial
MRC/NCIC-RADICALS-PR10 NCT00541047	<p>Phase III randomized study of immediate vs. early salvage radiotherapy (RT) and short- vs. long-term androgen deprivation therapy in patients who have undergone local surgery for non-metastatic adenocarcinoma of the prostate.</p> <p>Treatment groups:</p> <p>1) RT timing randomization Arm I - immediate RT; Arm II - early salvage RT in case of PSA failure. In both arms, RT is delivered, according to clinician preference, either to 66 Gy in 33 fractions or 52.5 Gy in 20 fractions to the prostate bed.</p> <p>2) Hormonal therapy during randomization Arm I - 0 months; Arm II - 6 months; Arm III - 24 months. During the pilot phase, patients may elect to be randomized between only 2 of these 3 arms.</p> <p>Target accrual: 6100 Date trial summary last modified: October 3, 2007 Status: active</p>

Protocol ID	Title and details of trial
TROG 08.03 (RAVES) NCT00860652	<p>Radiotherapy - Adjuvant Versus Early Salvage. A Phase III Multi-centre Randomised Trial Comparing Adjuvant Radiotherapy (RT) With Early Salvage RT in Patients With Positive Margins or Extraprostatic Disease Following Radical Prostatectomy</p> <p>Treatment groups: Arm I - Adjuvant RT (ART) commenced within 4 months of radical prostatectomy. 64Gy in 32 fractions to the prostate bed; Arm II - Active surveillance with early salvage RT ((SRT). 64Gy in 32 fractions to the prostate bed. The trigger for SRT is PSA level \geq 0.2ng/ml. RT should commence as soon as possible (no later than 4 months) following the first PSA measurement \geq 0.2ng/mL</p> <p>Target accrual: 470 Date trial summary last modified: Status: active</p>
FNCLCC-GETUG-17/0702 NCT00667069	<p>Randomized, Multicenter Study Comparing the Immediate Adjuvant Radiotherapy Associate With Hormonal Therapy of LH-RH Analogue (Decapeptyl® LP) vs Delayed Radiotherapy Until Biochemical Relapse Associated With Hormonal Therapy of LH-RH Analogue (Decapeptyl® LP) in Patients With Operable Prostate Cancer pT3 R1 pN0 or pNx at Intermediate Risk</p> <p>Arm I - (delayed treatment) Patients receive triptorelin intramuscularly on day 1 and then 3 months later. Patients also undergo conformal radiotherapy daily, 5 days a week, for 7 weeks. Treatment begins at biochemical relapse (PSA is more than 0.2 ng/mL) and before PSA is more than 2 ng/mL Arm II - (immediate treatment) Patients receive treatment as in arm I, but treatment begins within 6 months after surgery</p> <p>Target accrual: 718 Date trial summary last modified: Status: active</p>

CONCLUSIONS

In the only RCT for which long-term follow-up data are available, adjuvant RT following radical prostatectomy in patients with pathologic T3 or margin-positive prostate cancer has been shown to improve OS and reduce distant metastases compared to observation. The OS benefit extends individually to the subgroups with positive surgical margins, extracapsular extension, and seminal vesicle invasion. Longer follow-up from the other two completed RCTs is awaited and this review will be updated once new data become available.

CONFLICT OF INTEREST

There are no known conflicts of interest.

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For a complete list of the Genitourinary Cancer Disease Site Group members, please visit the CCO Web site at <http://www.cancercare.on.ca/>

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Appendix 1: Literature search strategies.

Ovid MEDLINE(R) 1996 to September Week 1 2009

Search run: 15 Sep 2009

#	Searches
1	meta-analysis.mp. or Meta-Analysis/
2	meta-analysis.pt.
3	(meta-analy: or metaanaly: or meta analy:).tw.
4	(systematic adj review).mp. or (systematic adj overview).tw. [mp=title, original title, abstract, name of substance word, subject heading word]
5	exp "Review Literature as Topic"/
6	(cochrane or medline or embase or cancerlit).ab.
7	(hand search or hand-search or manual search or reference list: or bibliograph:).ab.
8	review.pt.
9	(clinical trial or randomized controlled trial).pt.
10	exp Clinical Trial/
11	random allocation.mp. or Random Allocation/
12	double-blind method.mp. or Double-Blind Method/
13	single-blind method.mp. or Single-Blind Method/
14	placebos/ or placebo:.tw. or random:.tw.
15	practice guidelines.mp. or Practice Guideline/
16	practice guideline.pt.
17	(practice guideline or practice parameter).tw.
18	prostatic neoplasms/
19	(prostat: adj3 cancer).tw.
20	(prostat: adj3 carcinoma).tw.
21	(prostat: adj3 adenocarcinoma).tw.
22	prostatectomy/ or prostatectomy.tw.
23	surgery.tw.
24	radiotherapy.mp. or exp Radiotherapy/
25	(adjuvant adj3 (radi: or irradi:)).tw.
26	(postop: adj3 (radi: or irradi:)).tw.
27	(postprostatect: adj3 (radi: or irradi:)).tw.
28	or/1-17
29	or/18-21
30	or/22-23
31	or/24-27
32	28 and 29 and 30 and 31
33	(2008: or 2009:).ed.
34	32 and 33
35	limit 34 to humans

36 limit 35 to english language

EMBASE 1996 to 2009 Week 37 (MEDLINE duplicate citations removed) 184 citations
Search run: 16 Sep 2009

Searches

- 1 meta analysis/
- 2 (meta-analy: or metaanaly: or meta analy:).tw.
- 3 ((systematic adj review) or (systematic adj overview)).tw.
- 4 (cochrane or medline or embase or cancerlit).tw.
- 5 (hand search or hand-search or manual search or reference list: or bibliograph:).tw.
- 6 randomized controlled trial/
- 7 clinical trial/
- 8 random:.tw.
- 9 practice guideline.mp. or exp practice guideline/
- 10 (quantitative overview or quantitative synthes#s).tw.
- 11 exp placebo/ or placebo.mp.
- 12 prostate cancer.mp. or exp prostate cancer/
- 13 (prostat: adj3 cancer).tw.
- 14 (prostat: adj3 carcinoma).tw.
- 15 (prostat: adj3 adenocarcinoma).tw.
- 16 exp prostatectomy/ or prostatectomy.mp.
- 17 (prostatectomy or surgery).tw.
- 18 exp radiotherapy/ or radiotherapy.mp.
- 19 irradiation.mp. or exp irradiation/
- 20 (adjuvant adj3 radiation).tw.
- 21 (adjuvant adj3 irradiation).tw.
- 22 (postoperative adj3 radiation).tw.
- 23 (postoperative adj3 irradiation).tw.
- 24 (postprostatectomy adj3 radiation).tw.
- 25 (postprostatectomy adj3 irradiation).tw.
- 26 or/1-11
- 27 or/12-15
- 28 or/16-17
- 29 or/18-25
- 30 26 and 27 and 28 and 29
- 31 (2008: or 2009:).ew.
- 32 30 and 31
- 33 limit 32 to (human and english language)

Evidence-based Series #3-17 Version 3: Section 2B

**Adjuvant Radiotherapy Following Radical Prostatectomy for
Pathologic T3 or Margin-Positive Prostate Cancer:
Evidentiary Base**

*S. Morgan, T. Waldron, L. Eapen, L. A. Mayhew, E. Winqvist, H. Lukka,
and Members of the Genitourinary Cancer Disease Site Group*

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

The systematic review that makes up Section 2B of this Evidence-based Series was originally completed in February 2008 and contains the relevant data on the topic as of that time. Section 2A of this Evidence-based Series is a systematic review of the relevant data from February 2008 to September 2009, as well as a complete discussion and interpretation of all the relevant data, including the data found here in section 2B.

Report Date: February 21, 2008

QUESTION

Does adjuvant radiotherapy following radical prostatectomy improve clinically important outcomes in patients with pathologic T3 or margin-positive prostate cancer? The primary outcome of interest is overall survival. Outcomes of secondary interest include prostate cancer specific survival, metastasis-free survival, biochemical progression-free survival, locoregional recurrence-free survival, time to initiation of androgen deprivation therapy, incidence of acute and late toxicity, and quality of life.

INTRODUCTION

Prostate cancer is the commonest non-dermatologic malignancy and the third leading cause of cancer death in males in western countries. There were an estimated 22,300 new cases and 4,300 deaths due to prostate cancer in Canada in 2007 [1]. Radical prostatectomy (RP) is the standard definitive surgical management for clinically localized prostate cancer in patients free of serious comorbidities. This procedure confers good long-term disease control in patients who are confirmed pathologically to have localized (pT2) disease. However, results following RP are disappointing in patients who have pathological evidence of cancer

extending beyond the prostatic capsule (pT3 disease) or cancer present at the surgical resection margins (R1). In such patients, the risk of biochemical disease progression is as high as 67% at five years [2]. Despite earlier cancer detection with serum prostate-specific antigen (PSA) screening, approximately 50% of patients who undergo RP today are found to have at least one of these adverse pathologic features [3].

The optimal postoperative management of patients with positive surgical margins or pathologic T3 disease is undefined. Therapeutic alternatives include adjuvant radiotherapy (RT) –that is, radiotherapy to the prostatic bed in the immediate postoperative period—or active surveillance. In the latter approach, the patient is monitored clinically and with frequent PSA testing; radiotherapy and hormonal manipulation are held in reserve for salvage should biochemical failure or clinical disease progression occur. Adjuvant RT continues to be applied inconsistently, and there are no universally accepted indications for its use. Current clinical practice guidelines are also vague on its proper application [4]. In this review, the terms “adjuvant radiotherapy,” “postoperative radiotherapy,” and “postprostatectomy radiotherapy” will be used interchangeably.

Adjuvant RT is a local intervention. Its proximate aim is sterilization of residual tumour cells in the prostate bed following surgery in order to diminish the risk of local and biochemical recurrence. If left untreated, the theory is that these residual cells may give rise to secondary dissemination of the disease with the appearance of distant metastases. By this logic, delaying RT until the time of PSA failure may decrease the probability of secondary cure. Therefore, the ultimate aim of adjuvant RT is improvement in overall survival. One study has shown unequivocally that local treatment with radiotherapy following definitive surgery improves overall survival in node-positive breast cancer [5], and therefore, it is plausible that this result may be generalizable to other disease sites. Additional advantages of an adjuvant rather than a delayed approach for RT include freedom from the systemic toxicity of androgen deprivation therapy (ADT) and preservation of PSA as a marker of disease status.

Chief among the concerns regarding a universal application of postprostatectomy RT is that for many patients it may represent over-treatment. As with any adjuvant therapy, the argument is that many patients will not benefit from RT yet will be exposed to the morbidity from treatment. While modern techniques including three-dimensional conformal radiotherapy and intensity-modulated radiotherapy enable more precise delivery of radiation to the treatment volume, there remains a small risk of acute and long-term rectal and genitourinary toxicity. Consequently, the decision to proceed with an early adjuvant approach or a deferred salvage approach to RT following prostatectomy in patients with pT3 disease or positive surgical margins represents a trade-off in which the likelihood of disease progression and the effectiveness of adjuvant RT in reducing the risk of progression must be weighed against the risks of RT-related toxicity.

Adjuvant RT following RP has been compared to salvage therapy in numerous retrospective studies that have included patients with high-risk pathologic features [6-19]. Overall, the results from those studies support the use of adjuvant RT, with demonstrated improvements in local control. Caution must be used, however, in interpreting and applying these results. For example, retrospective comparisons are prone to the bias that the salvage patients, inasmuch as they have progressed while being monitored, may simply have more aggressive disease characteristics that predispose them to poorer overall outcomes. Prospective randomized controlled trials (RCTs) overcome such biases.

Only in the past three years have RCTs addressing this question appeared in the literature. To date, no systematic review of the randomized data has been published. In view of the uncertain indications for adjuvant RT and emerging evidence from randomized trials, the Genitourinary Cancer Disease Site Group (GU DSG) felt that an evidence-based

guideline was warranted to clarify the benefits and risks of adjuvant RT following prostatectomy for pT3 or margin-positive prostate cancer.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle [20]. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the GU DSG and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on the role of adjuvant RT following prostatectomy in patients with pathologic T3 or margin-positive prostate cancer. The body of evidence in this review is primarily comprised of RCT data; therefore, recommendations by the DSG are offered. That evidence forms the basis of a clinical practice guideline developed by the GU DSG found in Section 1 of this evidence-based series. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

Relevant articles were identified by searches of MEDLINE (1966 - February 2008 week 2), EMBASE (1980 - 2008 week 7), and The Cochrane Library (2007, Issue 4). In MEDLINE, "prostatic neoplasms" (Medical Subject Heading [MeSH]) was combined with "prostatectomy" (MeSH) and "exp radiotherapy" (MeSH). Variations of the following phrases were used as text words: "prostate cancer," "prostate carcinoma," "prostate adenocarcinoma," "prostatectomy," "adjuvant radiation," "postoperative radiation," and "postprostatectomy radiation." These terms were then combined with search terms for the following study designs or publication types: randomized controlled trials, controlled clinical trials, meta-analyses, systematic reviews, and practice guidelines. The EMBASE search was adapted using Excerpta Medica tree terms. The complete MEDLINE and EMBASE search strategies are detailed in Appendix 1.

The conference proceedings of the annual meetings of the American Society of Clinical Oncology (2000-2007), the American Society for Therapeutic Radiology and Oncology (2000-2007), and the American Urological Association (2002-2007) were also searched for relevant trials. Where relevant abstracts were identified, supplementary online resources (i.e., slides from accompanying presentations) were also searched for additional data.

The reference lists of eligible trials were searched for relevant articles. Expert colleagues and collaborators were also asked to identify any relevant unpublished or published trials not otherwise identified.

Study Selection Criteria

Articles were eligible for inclusion in the systematic review if they met the following criteria:

- They were RCTs (published or unpublished, full articles, or abstracts) that compared adjuvant RT in the immediate postoperative period after prostatectomy to observation with therapies (i.e., RT, ADT, or any other therapy) held in reserve for salvage, in patients with prostate cancer with either tumour extension beyond the prostatic capsule (pT3a), seminal vesical invasion (pT3b), positive resection margins (R1), or more than one of these features. No limitations were placed on neoadjuvant ADT.

However, trials in which the adjuvant RT arm included adjuvant treatment modalities in addition to RT (e.g., concurrent ADT) were ineligible.

- They were systematic reviews or evidence-based clinical practice guidelines that addressed the research question.
- They were published in English.

Synthesizing the Evidence

All studies identified by the literature search were assessed against the above selection criteria independently by two reviewers (SM, TW). Discrepancies regarding eligibility were resolved by consensus. Methodologic quality of the eligible studies was assessed by the same two reviewers with respect to the following parameters: whether treatment allocation was genuinely random and concealed from the trialists, whether there was a description of patient withdrawals and dropouts, and whether analyses were performed by intention-to-treat. The criteria were rated as “met,” “unmet,” or “unclear” [21]. Data extraction was performed by a single reviewer using pre-designed forms while a second reviewer acted as an independent auditor to verify accuracy of the data extraction.

Overall survival, prostate cancer-specific survival, metastasis-free survival, biochemical progression-free survival, locoregional recurrence-free survival, time to initiation of ADT, acute and late toxicity, and quality of life were the outcomes of interest. When data were available on these outcomes from two or more trials, meta-analysis of the trial data was planned using the Review Manager software (RevMan 4.2.8) provided by the Cochrane Collaboration (Metaview © Update Software). The hazard ratio (HR) is the preferred statistic for pooling time-to-event outcomes because it incorporates data from the entire Kaplan-Meier curve and allows for censoring. When available, the HR was extracted directly from the most recently reported trial results. The variances of the HR estimates were calculated from the reported confidence intervals (CIs) or p-values using the methods described by Parmar et al [22]. These values were entered directly into RevMan 4.2.8 using the “generic inverse variance” method. A random effects model was used for all pooling as it provides a more conservative effect estimate. Pooled results are expressed as HRs with 95% CI. HRs less than one favour adjuvant RT, whereas HRs greater than one favour observation.

The meta-analysis results were assessed for heterogeneity by visual inspection of the forest plot and by calculating the Chi-square test for heterogeneity and the I^2 percentage. A probability level for the Chi-square statistic of less than or equal to 10% ($p \leq 0.10$) was considered indicative of statistical heterogeneity, and I^2 values of 25%, 50%, and 75% were indicative of low, moderate, and high degrees of heterogeneity, respectively [23]. Sensitivity analyses were performed in the event of heterogeneity or to explore the effects of trial quality on the meta-analysis results.

RESULTS

Literature Search Results

A total of 14 reports [24-37] representing three randomized trials satisfied the eligibility criteria. Two trials were published as full articles [27,31], and the other trial was published as an abstract [35]. A single systematic review without meta-analysis was also identified [38]; however, it was published before the publication of any of the randomized trials. No evidence-based guidelines were identified.

Trial Characteristics

EORTC 22911 [27], a multicentre trial of the European Organization for the Research and Treatment of Cancer, enrolled patients from November 1992 to December 2001. SWOG 8794 [31], a multicentre trial of the Southwest Oncology Group, entered patients from August

1988 to January 1997. ARO 96-02/AUO AP 09/95 [35], a multicentre trial conducted by the German Cancer Society, accrued patients from April 1997 to September 2004. Major characteristics of the three trials are summarized in Table 1. A total of 1,743 patients, 1,693 of whom were found to be eligible, were randomized across these trials. Overall, the trials enrolled patients of similar age, pathologic stage, and performance status. Radiotherapy dose-fractionation and treatment volumes in the adjuvant RT arms were also similar. The trials differed regarding requirements for postoperative PSA nadir. As they were launched early in the PSA era, the SWOG and EORTC trials had no stipulations regarding postoperative PSA. Conversely, in the German Cancer Society trial, only those patients achieving an undetectable PSA postoperatively were randomized to adjuvant RT or observation; all patients failing to meet this requirement were offered adjuvant RT. It should be noted that a substantial proportion (21%) of patients in this trial randomized to the adjuvant RT arm ultimately did not receive it.

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Table 1. Characteristics of eligible trials.

Trial Descriptors	EORTC 22911 [27]	SWOG 8794 [31]	German Cancer Society ARO 96-02 and AUO AP 09/95 [35]
Eligibility Criteria	Previously untreated prostate cancer treated with RP	Previously untreated prostate cancer treated with RP	Prostate cancer treated with RP
	At least one of: extraprostatic extension, seminal vesicle invasion, or positive surgical margins (pT2 N0 M0 R1 or pT3 N0 M0 R0-1)	At least one of: extraprostatic extension, seminal vesicle invasion, or positive surgical margins (pT2 N0 M0 R1 or pT3 N0 M0 R0-1)	Extraprostatic extension or seminal vesicle invasion with or without positive surgical margins (pT3 N0 R0-1)
	WHO PS 0-1	SWOG PS 0-2	Undetectable PSA following RP
	Age ≤ 75 yrs	Negative pelvic lymphadenectomy*	
Median Age	65 yrs	64.9 yrs	NR
Stratification Variables	Institution; pT3a (present vs. absent); R0 vs. R1; pT3b (present vs. absent)	Tumour extent (pT3a or R1 vs. pT3b vs. R1 and pT3b); NADT (present vs. absent)	Gleason score (2-6 vs. 7-10); R0 vs. R1; pT3a vs. pT3b; NADT (present vs. absent)
NADT Use (% of patients)	10%	8.5%	NR
Number Randomized	1005	431	307
Number Eligible	968	425	300
Time From RP Until Start of Adjuvant RT	<16 wks	<18 wks	8-12 wks
Adjuvant RT Dose-Fractionation	60 Gy in 30 fractions	60-64 Gy in 30-32 fractions	60 Gy in 30 fractions
Treatments Received by Observation Arm (n)	Pelvic radiotherapy (113); hormonal treatment (45); surgical castration (1); other (4)	Pelvic radiotherapy (70); other therapies NR	NR
RT Volume	• Initial phase: 50 Gy to	Single phase: RT	Prostatic fossa and

Trial Descriptors	EORTC 22911 [27]	SWOG 8794 [31]	German Cancer Society ARO 96-02 and AUO AP 09/95 [35]
	“volume including surgical limits from seminal vesicles to apex with security margin to encompass subclinical disease in periprostatic area” <ul style="list-style-type: none"> • 10 Gy boost to “reduced volume circumscribing the previous landmarks of the prostate with a reduced security margin” 	delivered to “prostatic fossa and paraprostatic tissues”	seminal vesicles plus 1cm
Median Follow-Up	5 yrs	10.6 yrs	4.5 yrs
Primary Endpoint	Biochemical progression-free survival	Metastasis-free survival	Biochemical progression-free survival
Definition of Biochemical Progression	An increase of more than 0.2 µg/L over the lowest postoperative value measured on three occasions at least 2 weeks apart.	For men with a post-surgical PSA ≤ 0.4 ng/mL, the first occurrence of PSA > 0.4 ng/mL.	PSA increase from undetectable to detectable level, with confirmation by further increase at least 3 months later

Abbreviations: NADT - neoadjuvant androgen deprivation therapy; EORTC - European Organization for the Research and Treatment of Cancer; n - number; NR - not reported; PS - performance status; RP - radical prostatectomy; RT - radiotherapy; SWOG - Southwest Oncology Group; vs. - versus; WHO - World Health Organization; wks - weeks; yrs - years.

*Towards study end, some patients at very low risk for involved pelvic lymph nodes were not required to undergo lymphadenectomy. Details available in trial report.

Trial Quality

The results of the trial quality assessment are summarized in Table 2. The EORTC and SWOG trials met all of the trial quality criteria. In the German Cancer Society trial [35], however, it was unclear whether allocations were concealed from the trialists. Further, inconsistencies in the flow of patients through the trial were identified. In addition, analysis of the primary endpoint was not based on intention-to-treat. Clarification and additional data were sought from the German trial investigators; however, to date no additional information has been forthcoming.

Table 2. Methodologic quality of eligible trials.

Trial Characteristic	EORTC 22911 [27]	SWOG 8794 [31]	German Cancer Society ARO 96-02 and AUO AP 09/95 [35]
Random allocation	Met	Met	Met
Allocation concealment	Met	Met	Unclear
Description of withdrawals	Met	Met	Unclear
Intention-to-treat analysis	Met	Met	Unmet

Outcomes

The primary outcome of interest to this review was overall survival. Outcomes of secondary interest included prostate cancer-specific survival, metastasis-free survival, biochemical progression-free survival, locoregional recurrence-free survival, time to initiation of androgen deprivation therapy, incidence of acute and late toxicity, and quality of life. Trial results for these outcomes are summarized in Table 3 and proceeding text.

Table 3. Trial results for outcomes of interest.

Outcome	EORTC 22911 [27]	SWOG 8794 [31]	ARO 96-02 / AUO AP 09/95 [35]
Overall survival	HR, 1.09 (98% CI 0.67-1.79)	HR, 0.80 (95% CI 0.58-1.09) p=0.16	NR
Prostate cancer-specific survival	At 5 years: ADJ RT - 98.4% OBS - 97% p-value NR	NR	NR
Metastasis-free Survival	Distant failures at 5 years: ADJ RT - 3.8% OBS - 3.6% p-value NR	HR, 0.75 (95% CI 0.55-1.02) p=0.06	NR
Biochemical progression-free survival	HR, 0.48 (98% CI 0.37-0.62)	HR, 0.43 [†] (95% CI 0.31-0.58) p<0.001	HR, 0.53 [‡] p=0.0015
Locoregional recurrence-free survival	Locoregional failures at 5 years: ADJ RT - 5.4% OBS - 15.4% p<0.0001	NR	NR
Time to initiation of ADT	NR	HR, 0.45 (95% CI 0.29-0.68) p<0.001	NR

Abbreviations: ADJ RT - adjuvant radiotherapy; ADT - androgen deprivation therapy; CI - confidence interval; EORTC - European Organization for the Research and Treatment of Cancer; HR - hazard ratio; NR - not reported; OBS - observation; RT - radiotherapy; SWOG - Southwest Oncology Group

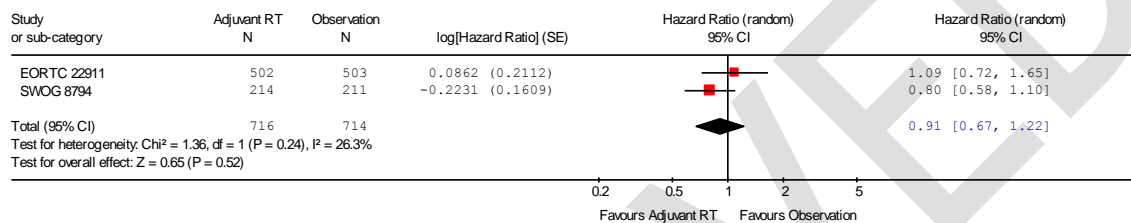
[†]In this trial, biochemical failure was defined as the time of first occurrence of PSA>0.4. Hence only those patients achieving a post-operative PSA≤0.4 were considered for this outcome (n=347).

[‡]Not derived from an intention-to-treat analysis.

Overall Survival

Survival data were available for the EORTC [27] and SWOG trials [31]. Neither trial detected a statistically significant difference in overall survival between adjuvant RT and observation groups. Pooling the mortality data in a meta-analysis (Figure 1) also showed no difference (HR, 0.91; 95% CI, 0.67-1.22; $p=0.52$). Neither the Chi-square nor the I^2 tests indicated statistical heterogeneity. It should be noted that, at the time of reporting, only 89 deaths had occurred in the EORTC trial, representing an event rate of only 8.9%. Consequently, from the point of view of overall survival, data from the EORTC trial are relatively immature.

Figure 1. Meta-analysis of overall mortality using a random effects model. Hazard ratios (95% CI) are shown on a logarithmic scale.



Prostate Cancer-Specific Survival

None of the trials provided a time-to-event analysis of this outcome. After five years of follow-up in the EORTC trial [27], eight deaths (out of 502 patients) due to prostate cancer were observed in the adjuvant RT group compared to 15 deaths (out of 503 patients) in the observation arm; however, the authors noted longer follow-up data are needed to accurately assess this endpoint.

Metastasis-Free Survival

Only the SWOG trial [31] reported on this outcome. Adjuvant RT reduced metastasis-free survival by 25% compared to observation (HR, 0.75; 95% CI, 0.55-1.02; $p=0.06$); however, this result did not reach statistical significance. The EORTC study [27] reported 19 distant failures in the adjuvant RT treatment arm and 18 in the observation group; however, a time-to-event analysis was not provided.

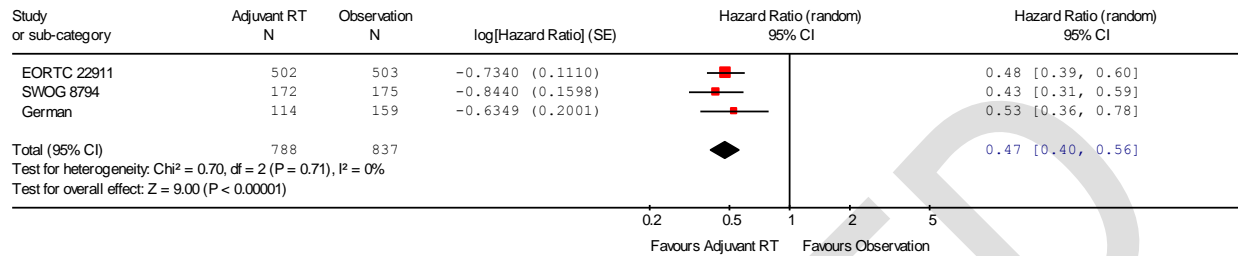
Biochemical Progression-Free Survival

All three trials provided data on this endpoint, and the definitions of biochemical failure used by the trials were similar. All three trials detected longer biochemical progression-free survival with adjuvant RT compared with observation that was statistically significant. Pooling the results of the three trials in a meta-analysis produced an HR of 0.47 (95% CI, 0.40-0.56; $p<0.00001$), which represents a 53% decrease in biochemical progression with adjuvant RT compared to observation.

It is clear from the trial abstract that the German Cancer Society trial [35] did not calculate the reported HR using an intention-to-treat analysis. Instead, the HR calculation was based on patients as they had been treated (i.e., the 34 patients randomized to the adjuvant RT arm who did not ultimately receive RT were excluded from the analysis). It was felt that including the HR from this trial into the meta-analysis might lead to a biased effect estimate. Therefore, to ensure robustness of the estimate, a sensitivity analysis was performed to determine if the meta-analysis result changed with the removal of this trial. The sensitivity analysis showed that the overall meta-analysis results remained the same

without the German trial (HR, 0.46; 95% CI, 0.39-0.55; $p < 0.00001$). In both analyses, neither the Chi-square nor the I^2 tests indicated statistical heterogeneity.

Figure 2. Meta-analysis of biochemical progression using a random effects model. Hazard ratios (95% CI) are shown on a logarithmic scale.



Locoregional Recurrence-Free Survival

None of the three trials provided a time-to-event analysis for this outcome. The EORTC trial [27], however, reported the cumulative incidence of locoregional failure at five years of follow-up: a significantly lower incidence of failure was seen in the adjuvant RT arm (5.4%; 98% CI, 2.7-8.0) than in the observation arm (15.4%; 98% CI, 11.2-19.6; $p < 0.0001$).

Clinical Progression-Free Survival

Although not an outcome of interest to this review, both the EORTC trial [27] and SWOG trial [31] examined clinical progression-free survival. Clinical progression was defined as clinical or imaging evidence of locoregional or distant recurrence irrespective of PSA. Clinical progression-free survival was significantly greater in patients treated with adjuvant RT compared with observation in the EORTC trial (HR, 0.61; 98% CI, 0.43-0.87; $p < 0.0001$) and SWOG trial (HR, 0.62; 95% CI, 0.46-0.82; $p = 0.001$). It should be noted that the SWOG trial refers to this endpoint as “recurrence-free survival.”

Time to Initiation of ADT

This outcome provides a measure of the extent to which patients receiving adjuvant RT are spared the systemic toxicities of ADT. Only the SWOG trial [31] reported on this outcome. A statistically significant reduction in ADT use at five years of follow-up was seen in those randomized to adjuvant RT (10% vs. 21%; HR, 0.45; 95% CI, 0.29-0.68; $p < 0.001$).

Acute and Late Toxicity

The acute and late genitourinary and gastrointestinal toxicities and complications of prostate radiotherapy are well recognized. All three trials reported on these toxicities, however, heterogeneity in reporting complicates interpretation and precluded a pooled analysis of these data.

In the EORTC study [27], 46 episodes of grade 3 acute toxicity and two episodes of grade 4 acute toxicity were observed among the 457 patients randomized to the adjuvant RT arm (who actually received RT). Radiotherapy was interrupted due to toxicity in 14 patients. At five years, the cumulative incidence of grade 3 toxicity was 4.2% (98% CI, 3.4-5.0) in the adjuvant RT arm and 2.6% (98% CI, 0.8-4.4) in the observation arm ($p = 0.073$). The cumulative incidence of any-grade toxicity, however, was significantly greater in the adjuvant RT arm than observation arm (64.9% vs. 54.3%; $p = 0.005$).

Graded acute and late gastrointestinal and genitourinary toxicity data were not included in the SWOG trial report [31]. Instead, rates of complications potentially related to

treatment including urethral stricture, total urinary incontinence, and rectal complications (e.g., proctitis or rectal bleeding), were recorded during follow-up. Considered together, such complications were more common in the adjuvant RT arm (23.8% vs. 11.9%; relative risk [RR]=2.0; 95% CI, 1.3-3.1; p=0.002).

The German Cancer Society trial [36] reported the frequency of acute and late toxicity in the adjuvant RT arm only. Acutely, the rates of grade 3 bladder and grade 2 rectal toxicity were 3% and 12%, respectively. No acute grade 3 rectal toxicity was observed. The rate of late grade 2 and 3 bladder toxicity was 16% and 2%, respectively, while the rate of late grade 2 rectal toxicity was 10%.

Quality of Life

A quality of life study (S8794) was conducted in accompaniment to the SWOG trial and its results were recently published [39]. Two hundred and seventeen of the 425 patients enrolled in the SWOG trial completed health-related quality of life questionnaires at baseline. Subsequent questionnaires were submitted at six weeks, six months, one year, and then annually for a total of five years. Over this period, compliance rates ranged from 67% to 96%. Genitourinary and rectal symptom-specific items were developed. Primary symptom outcomes included tenderness and urgency with bowel movements, urinary frequency, and erectile dysfunction. Global health-related quality of life (GHRQL) was a secondary outcome. Patients randomized to adjuvant RT experienced greater compromise in bowel function for the first two years of follow-up and increased frequency of urination throughout the five-year period compared to those randomized to observation. There was no difference between the two groups with respect to erectile dysfunction. While GHRQL was initially worse in the adjuvant RT arm, by the end of the five-year period a greater proportion of patients in this arm (69%) had normal GHRQL than in the observation arm (51%).

Post hoc Analyses

Two post-hoc analyses have been conducted of the trial data; one examined factors predictive of treatment benefit in the EORTC trial [29], while the other examined patterns of treatment failure in the SWOG trial [34]. The results of these analyses should be interpreted with caution and considered hypothesis generating, as both are subject to the limitations inherent to unplanned subgroup analyses.

In the EORTC trial [29], centrally reviewed prostatectomy specimens were available for approximately half (n=552) of the trial participants. The authors assessed the interaction between the magnitude of benefit from adjuvant RT and five risk factors: surgical margin status, extracapsular extension, seminal vesicle invasion, Gleason score (≤ 6 , 7, or >7), and postprostatectomy PSA level (≤ 0.2 ng/ml vs. >0.2 ng/ml). The endpoint of interest was biochemical progression-free survival. Only surgical margin status was shown to have a significant interaction with treatment effect (heterogeneity, $p < 0.01$). This interaction was such that the benefit from adjuvant RT in patients with negative margins was not statistically significant (HR, 0.87; 95% CI, 0.53-1.46; $p = 0.601$). The benefit from adjuvant RT in patients with positive margins was highly significant (HR, 0.38; 95% CI, 0.26-0.54; $p < 0.0001$). The interaction between treatment effect and surgical margin status remained when patients with postoperative PSA >0.2 ng/ml were excluded. The authors concluded that provided thorough pathology of the prostatectomy is performed, adjuvant RT might not be warranted in patients with negative margins. There are a couple of caveats to consider when interpreting these results. Half of the trial patients were excluded from the analysis because they did not have review pathology. The results may be biased since the omitted patients were found to have a statistically significant poorer prognosis compared to included patients. Secondly, the results were obtained after a centralized pathology review was performed. A preliminary analysis of

the local pathology trial data showed that all pathologic subgroups - including margin-negative patients - had a significant benefit from adjuvant RT in terms of biochemical progression-free survival [40]. This raises concern about generalizability of the results.

In the SWOG trial [34], rates of biochemical failure, local failure, and distant failure in the adjuvant RT and observation arms were compared according to postprostatectomy PSA level: ≤ 0.2 ng/ml, 0.2-1.0 ng/ml, and >1.0 ng/ml. Postoperative PSA data were available for 374 of the 425 trial patients. Adjuvant RT reduced the 10-year risk of PSA treatment failure compared to observation in each PSA group with the exception of the >1.0 ng/ml group. The 10-year biochemical failure rates for adjuvant RT vs. observation for the ≤ 0.2 ng/ml and the 0.2-1.0 ng/ml groups were 42% vs. 72% and 73% vs. 80%, respectively. Patients in the >1.0 ng/ml group fared poorly in both trial arms (100% vs. 94%). No statistical data were provided for these comparisons. Adjuvant RT was also associated with a reduction in the percentage of clinical local treatment failures (8% vs. 22%) and distant metastases (7% vs. 16%) compared to observation, overall, and within each of the PSA subgroups. Again, no statistical data were reported for these comparisons. The authors concluded that treatment failure is primarily local with a low incidence of metastatic failure. Adjuvant RT was recommended standard treatment because it reduced the risk of both biochemical failure and distant metastases at all postoperative levels of PSA.

DISCUSSION

Overall survival is certainly the outcome of greatest importance for any cancer therapy, incorporating the effect of mortality secondary to cancer, the interventions used, and all other causes. Given the relatively indolent natural history of prostate cancer, the expectation is that lengthy follow-up is necessary to assess differences in overall survival, and the results of this review bear this out. Neither the SWOG nor the EORTC trial detected a survival benefit with adjuvant RT; median follow-up times were 10.6 years and five years in each trial, respectively. A meta-analysis of the survival data from these two trials also did not demonstrate a statistically significant result. Follow-up at this time is simply not long enough to accurately determine if adjuvant RT is associated with a survival benefit. Updates of this review and meta-analysis are planned as the data mature and as new trial results become available. It should also be borne in mind that for neither trial was overall survival the primary endpoint; as such, neither trial was specifically powered to detect a difference in overall survival between the two arms. This is of particular relevance to the SWOG trial, in which only 431 patients were randomized.

Biochemical progression is a controversial surrogate marker for other prostate cancer outcomes. The meta-analysis performed of these data unequivocally demonstrates that, compared to observation, adjuvant RT confers a major reduction in the rate of biochemical failure. The magnitude of benefit in this endpoint is remarkably similar across the three included trials. As PSA progression is often a trigger for initiation of ADT, it is not surprising that a reduction in ADT use of similar magnitude was also observed.

While time-to-event analyses for freedom from locoregional recurrence are not available and the sole analysis for freedom from metastasis did not demonstrate a significant benefit from adjuvant RT, two of the trials report an outcome that is a composite of locoregional failure and metastasis - clinical progression-free survival. Both trials reported a significant improvement in this outcome with adjuvant RT. On the basis of these data, adjuvant RT does therefore significantly reduce locoregional and distant recurrences when considered together.

A major shortcoming of the trials included in this review relates to the management of patients in the observation arms of these trials. In short, none of the trials employed a definite protocol as to how and when PSA and clinical failures should be treated. As a

consequence, there was considerable variability in patient management in these arms (Table 1). It may be argued that, in many cases, local intervention with RT was delayed until such time as it was unlikely to be effective. The ongoing RADICALS (Radiotherapy and Androgen Deprivation in Combination After Local Surgery) trial addresses this shortcoming. Once completed, it is hoped that this trial will serve to clarify the optimal timing of RT and the role for ADT following RP in patients with high-risk pathologic features.

Comparing toxicity data across the three trials is made difficult by differences in the reporting of toxicity data. In the SWOG trial, significantly greater rates of urethral stricture, urinary incontinence, and rectal complications were seen in irradiated patients compared to those randomized to observation. Caution must be used, however, in interpreting the toxicity data from the SWOG study. As noted above, toxicity was not recorded using a validated, graded toxicity-scoring instrument. Instead, complications were recorded only if annotated on study flow sheets. Such data are vulnerable to the bias that retrospectively collected unsolicited toxicities are more likely to be reported in the intervention arm. In the EORTC trial, where toxicity was graded prospectively using validated scales, it is clear that there is significantly greater minor (\leq grade 2) acute toxicity in patients who receive adjuvant RT. However, there was no significant excess grade 3 or higher toxicity observed at five years of follow-up. As the late toxicity evaluations performed in the trials only considered genitourinary and gastrointestinal symptoms, the potential benefits of adjuvant RT in terms of sparing the systemic toxicity of ADT could not be assessed.

ONGOING TRIALS

To identify ongoing and recently closed trials of adjuvant RT following prostatectomy in patients with T3 or margin positive prostate cancer, the following electronic databases and trial registries of oncology cooperative groups were searched:

- Clinicaltrials.gov;
- Deutsches Krebsstudien Register (www.studien.de);
- Eastern Cooperative Oncology Group (www.ecog.org);
- EORTC (www.eortc.org);
- Fédération Nationale des Centres de Lutte Contre Le Cancer (www.fnclcc.fr);
- National Cancer Institute Clinical Trials Registry (www.cancer.gov);
- North Central Cancer Treatment Group (www.ncctg.mayo.edu);
- Radiation Therapy Oncology Group (www.rtog.org);
- SWOG (www.swog.org);
- TrialCheck (www.trialcheck.org).

The GU DSG will monitor the progress of the following trial and review reported results when they become available.

Protocol ID	Title and details of trial
MRC-RADICALS-PR10	<p>Phase III randomized study of immediate vs. early salvage radiotherapy (RT) and short- vs. long-term androgen deprivation therapy in patients who have undergone local surgery for non-metastatic adenocarcinoma of the prostate.</p> <p>Treatment groups: Arm I - immediate RT; Arm II - early salvage RT in case of PSA failure; before postoperative RT, patients randomized to one of three hormone therapy (HT) arms: Arm III - no HT; Arm IV - short-term HT; Arm V - long-term HT.</p> <p>Target accrual: 6100 Date trial summary last modified: October 3, 2007 Status: active</p>

CONCLUSIONS

Adjuvant RT following RP in patients with pathologic T3 or margin-positive prostate cancer reduces the risk of biochemical and locoregional failure compared to observation, and prolongs the time to initiation of ADT. Adjuvant RT is associated with a low rate of acute and late major toxicity. To date, an overall survival benefit has not been demonstrated with adjuvant RT. Longer follow-up is needed to ascertain whether such a benefit exists.

CONFLICT OF INTEREST

The members of the GU DSG disclosed potential conflicts of interest relating to this systematic review and none were declared.

JOURNAL REFERENCE

The following systematic review and meta-analysis article has been published by *Radiotherapy and Oncology* (<http://journals.elsevierhealth.com/periodicals/rado>), a peer-reviewed journal, and is available both in print and online:

- Morgan SC, Waldron TS, Eapen L, Mayhew LA, Winquist E, Lukka H; Genitourinary Cancer Disease Site Group of the Cancer Care Ontario Program in Evidence-based Care. Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer: a systematic review and meta-analysis. *Radiother Oncol.* 2008;88:1-9. doi:10.1016/j.radonc.2008.04.013.

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For a complete list of the Genitourinary Cancer Disease Site Group members, please visit the CCO Web site at <http://www.cancercare.on.ca/>

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Appendix 1: Literature search strategies.

MEDLINE

1. prostatic neoplasms/
2. (prostat\$ adj3 cancer).tw.
3. (prostat\$ adj3 carcinoma).tw.
4. (prostat\$ adj3 adenocarcinoma).tw.
5. or/1-4
6. prostatectomy/
7. prostatectomy.tw.
8. or/6-7
9. and/5,8
10. exp radiotherapy/
11. (adjuvant adj3 (radi\$ or irradi\$)).tw.
12. (postoperative adj3 (radi\$ or irradi\$)).tw.
13. (postprostatectomy adj3 (radi\$ or irradi\$)).tw.
14. or/10-13 (90934)
15. randomized controlled trial.pt.
16. controlled clinical trial.pt.
17. randomized controlled trials/
18. randomi#ed controlled trial?.tw.
19. randomi#ed clinical trial?.tw.
20. random allocation/
21. exp meta-analysis/
22. (metaanal\$ or meta-anal\$ or metanal\$ or quantitative overview or quantitative syntheses).tw.
23. (systematic review or systematic overview).tw.
24. practice guidelines/
25. practice guideline.pt.
26. practice guideline.tw.
27. or/15-26
28. and/9,14,27

EMBASE

1. exp prostate cancer/
2. (prostat\$ adj3 cancer).tw.
3. (prostat\$ adj3 carcinoma).tw.
4. (prostat\$ adj3 adenocarcinoma).tw.
5. or/1-4
6. prostatectomy/
7. prostatectomy.tw.
8. or/6-7
9. and/5,8
10. exp radiotherapy/
11. exp irradiation/
12. (adjuvant adj3 (radi\$ or irradi\$)).tw.
13. (postoperative adj3 (radi\$ or irradi\$)).tw.
14. (postprostatectomy adj3 (radi\$ or irradi\$)).tw.
15. or/10-14
16. randomized controlled trial/
17. randomi#ed controlled trial?.tw.
18. randomi#ed clinical trial?.tw.
19. exp meta-analysis/
20. (metaanal\$ or meta-anal\$ or metanal\$ or quantitative overview or quantitative syntheses).tw.
21. (systematic review or systematic overview).tw.
22. exp practice guideline/
23. practice guideline.pt.
24. practice guideline.tw.
25. or/16-24
26. and/9,15,25



Evidence-based Series #3-17 Version 3: Section 3

Adjuvant Radiotherapy Following Radical Prostatectomy for Pathologic T3 or Margin-Positive Prostate Cancer (Update): EBS Development Methods and External Review Process

S.C. Morgan, C. Walker-Dilks, L.J. Eapen, E.W. Winqvist, J.L. Chin, D.A. Loblaw, and Members of the Genitourinary Cancer Disease Site Group

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

Report Date: July 22, 2010

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-Based Series is comprised of three sections.

- *Section 1: Guideline Recommendations.* Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base.* Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process.* Summarizes the EBS development process and the results of the formal external review of the draft version of Section 1: Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THE ORIGINAL EVIDENCE-BASED SERIES - VERSION 1.2008

Development and Internal Review

The original EBS was developed by the GU DSG of CCO's PEBC. The series was a convenient and up-to-date source of the best available evidence on adjuvant radiotherapy for pT3 prostate cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario. The guideline was completed in 2008. A summary of the development and review process of that guideline document follows.

Report Approval Panel

Prior to the submission of this EBS report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the panel included:

1. The panel questioned whether the authors had sufficiently commented on the issue of statistical power with respect to the outcomes analyzed. As background, the authors cited the Whelan meta-analysis, where more than 6000 patients were included. The pooled odds ratio (OR) for locoregional control was 0.69, which “translated” to a survival OR of 0.83. While these data are not directly generalizable to the current question, they do provide an example of the need for an adequate sample size for such an analysis. This point could be indicated in stronger terms.
2. The panel stated that, for the purposes of eventual publication, the authors might wish to contact the authors of the German trial regarding the missing data in Table 2.
3. The panel stated that it was unclear why both the EORTC and SWOG investigators determined “clinical PFS” to be an important secondary outcome, yet the authors of the guideline did not. Is the outcome of potential clinical importance? Is it a valid surrogate for survival?
4. The panel stated that, with respect to the reporting of toxicities, the authors might wish to be more explicit about specific toxicities that play a role in the decision-making process of patients. These specific toxicities would be best known to the authors but might include incontinence and impotence. By summing toxicities under “GU and GI,” details about these specific toxicities are lost.
5. The panel asked whether it would be useful to recommend that time-to-event analyses be included (missing for several secondary outcomes of interest) in future work?
6. The panel questioned the wording of the definition of biochemical progression for the SWOG 8794 trial.

7. The panel commented that the authors had quoted 98% confidence intervals for data from the EORTC study and that these should probably read 95%.
8. The panel stated that, as the authors indicated the follow-up intervals of five years and 10+ years are not long enough for assessing any potential survival benefit, it might be useful to suggest in the document what a relevant interval would be.

GU DSG Response

1. It is true that overall survival was not the primary endpoint of any of the trials considered, and therefore, none of the trials was specifically powered to observe a difference in survival between the two arms. A comment to this effect has been added to the Discussion. However, the authors are of the view that insufficient follow-up in the completed trials, rather than insufficient statistical power, is the chief limiting factor in our analysis.
2. The principal investigator of the German trial was contacted. This is noted on page 6 of Section 2. None of the missing data were forthcoming; however, it is understood that further data has been presented at the 2007 ASCO Annual Meeting. In any case, given the short median follow-up of the German trial at this time, it is doubtful that there would be meaningful data for endpoints such as overall survival and metastasis-free survival as event rates are expected to be very low.
3. Outcomes of interest for the review were established a priori without regard for the outcomes published in the trial reports. Clinical PFS is a composite of locoregional recurrence-free survival and metastasis-free survival. Both of these were considered individually as important secondary outcomes in our review.
4. Two of the three trials report graded toxicities using validated scales. The EORTC trial employed the “Late Radiation Morbidity Scoring Scheme” of the Radiation Therapy Oncology Group and EORTC. This scale is widely used and provides very detailed criteria for the various toxicities relevant to radiotherapy. While the toxicities are listed under the headings of “GI” and “GU,” they refer to specific radiotherapy-related adverse effects and should be well understood by oncologists and urologists.
5. The omission of these data is not unexpected and is a reflection of the short follow-up to date in two of the three the trials. It is anticipated that, with additional follow-up, the data on the secondary outcomes of interest will become available in future reports of the EORTC and German trials. We therefore feel that it is not necessary to make the suggested recommendation.
6. In accordance with the suggestion, the definition has been revised. Biochemical progression in the SWOG trial is now defined: “For men with a post-surgical PSA \leq 0.4 ng/mL, the first occurrence of PSA $>$ 0.4 ng/mL.”
7. The EORTC trial report quoted 98% confidence intervals, not 95% intervals.
8. The median follow-up of all patients included in this systematic review is 6.1 years. To determine what a relevant follow-up period might be, we can refer to another prostate cancer RCT with survival endpoints. The Scandinavian Prostate Cancer Group Study No. 4 randomized 695 men with early prostate cancer to either radical prostatectomy or watchful waiting (3). In the initial analysis performed after 6.2 years of follow-up, there was not a statistically significant reduction in overall mortality with RP. It was only after 10 years of follow-up that a significant reduction was seen (RR=0.74, 95% CI, 0.56-0.99). Thus, given the indolent natural history of prostate cancer, a median follow-up of at least 10 years is likely necessary to ascertain whether an intervention improves survival.

External Review by Ontario Clinicians

Following the review and discussion of [Section 1: Recommendations](#) and [Section 2: Evidentiary Base](#) of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the GU DSG circulated Sections 1 and 2 to external review participants in Ontario for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the GU DSG.

BOX 1:

DRAFT RECOMMENDATIONS (approved for external review April 10, 2007)

To date, adjuvant radiotherapy has not been shown to improve overall survival compared with observation. Longer follow-up from the completed randomized trials is required in order to accurately assess this outcome. On the basis of the available evidence, the Genitourinary Cancer Disease Site Group offers the following recommendations:

- Adjuvant external beam radiotherapy should be offered to patients with the goal of reducing biochemical failure, locoregional failure, and delaying or reducing the need for androgen deprivation therapy.
- Early referral following radical prostatectomy to a radiation oncologist for a discussion around radiotherapy is advisable.
- The decision regarding the use of adjuvant radiotherapy should take into account its modest associated genitourinary and rectal toxicity.

Qualifying Statements

- The available data from randomized trials does not address:
 - Adjuvant radiotherapy following radical prostatectomy versus salvage radiotherapy.
 - Adjuvant radiotherapy combined with androgen deprivation therapy.

Methods

Feedback was obtained through a mailed survey of 104 external review participants in Ontario (73 urologists and 31 radiation oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The survey was mailed out on June 19, 2007. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The GU DSG reviewed the results of the survey.

Results

Fifty responses were received out of the 104 surveys sent (48.1% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the participants who responded, 44 indicated that the report was relevant to their practice or organizational position, and they completed the survey. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to eight items on the feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a guideline, as stated in the “Introduction” section of the report, is clear.	42 (95.5)	1 (2.3)	1 (2.3)
There is a need for a guideline on this topic.	41 (93.1)	2 (4.5)	1 (2.3)
The literature search is relevant and complete.	42 (95.5)	2 (4.5)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	43 (97.8)	1 (2.3)	0
The draft recommendations in the report are clear.	38 (86.4)	4 (9.1)	2 (4.5)
I agree with the draft recommendations as stated.	37 (84.1)	5 (11.4)	2 (4.5)
This report should be approved as a practice guideline.	31 (70.4)	8 (18.2)	4 (9.0)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	39 (88.6)	4 (9.1)	1 (2.3)

Summary of Written Comments

Seventeen respondents (38.6%) provided written comments. The main points contained in the written comments were:

1. Two respondents thought the review lacks the strength of evidence needed to make the draft recommendations a practice guideline. It was suggested more robust data are required before a guideline on this topic is developed.
2. One respondent suggested the review requires a more in depth discussion of the limitations of the randomized trials. Specifically, limitations of the EORTC trial were highlighted:
 - a) 21% of patients in the observation arm of the trial never received salvage therapy.
 - b) 47% of patients in the observation arm received salvage EBRT for a rising PSA while the remainder of patients only received salvage when there was clinical evidence of a decrease.

These limitations will have an impact on progression-free survival, an outcome in which a statistical difference was found.
3. One respondent disagreed with the statement that “no statistically significant difference in metastases-free-survival was observed” and requested it be rephrased. The respondent felt that most would agree that the trial did in fact demonstrate an improvement in this outcome; it just failed to meet a significance p-value of 0.05 (0.06).
4. One respondent thought the guideline was vague and failed to address the following important clinical questions:
 - a) If there is a unifocal positive margin (T3a) is it reasonable to omit radiation?
 - b) Is it applicable to men with significant disease (T3b) that predicts micrometastases?
 - c) What is the minimum dose of EBRT? What technique (field arrangement) should be used?
 - d) If few lymph nodes are sampled should they be treated as well?

- e) Should any of these men receive hormones?
5. One respondent requested clarification on whether the guideline is appropriate for both margin-positive and margin-negative T3 patients. It was also suggested that the guideline would be improved with a discussion of optimal radiation dose and volume.
6. One respondent provided specific comments to several different sections of the review:
 - a) On p.2 it suggests IMRT and 3DCRT enable more precise delivery, however, it is difficult to know if there is any value in this setting as the correct CTV is unknown.
 - b) On p.4 random effects is suggested as giving a more conservative effect estimate. While this may be true, the largest difference between random and fixed effects models is that random effects leads to larger confidence intervals, making type 1 error less likely.
 - c) On p.4 it says heterogeneity testing was performed but with only three trials; is this valid?
 - d) The introduction of the review suggests the need for adjuvant RT may be high due to the number of patients, yet all three trials took at least 10 years to accrue patients (p.4 under trial characteristics). This suggests the situation is not very common or the study patients represent a small proportion of patients, which raises issues of external validity.
 - e) On p.5 (Table 1), would it be worthwhile to report on radiated volume even though these studies did a poor job of reporting this information.
 - f) On p.10 “avoidance of the anxiety of PSA failure” is a bogus benefit to PSA control; patient education is cheaper with fewer side effects and quite likely as good as radiation.
7. One respondent commented that standardization of pathological reporting will be extremely important in implementing the draft recommendations.
8. Three respondents thought the guideline was well written and suggested it be reviewed and followed by radiation oncologists.

Modifications/Actions

1. The draft recommendations are based on the data available from randomized trials. Unfortunately, the current state of the data does not inform about the most important outcomes of cancer-specific and overall survival. The GU DSG recommendations are preceded by a statement that reflects the current state of the evidence.
2. The limitations cited by the respondent apply to all three trials included in the review, and have to do with the fact that none of the trials employed a prescribed protocol on how to handle PSA failures. In some cases, salvage RT in the observation arm may have been unduly delayed or omitted entirely. This limitation may have led to an overestimate of the benefit reported in the trials in biochemical progression-free survival and other outcomes with adjuvant RT. Mention of this issue has been added to the Discussion of Section 2 of the report.
3. The statement regarding metastasis-free survival (p. 8) has been rephrased and reads as follows: “Adjuvant RT reduced metastasis-free survival by 25% compared to observation (HR, 0.75; 95% CI, 0.55-1.02; $p=0.06$); however, this result did not reach statistical significance”.
4. Unfortunately, although important, the clinical issues raised by the respondent cannot be answered by the randomized trials. In order to highlight that these issues are not addressed in the guideline, additional qualifying statements have been added to Section 1 of the report.
5. Addressed in (4).

6. The respondents comments were handled as follows:
 - a) This issue is now addressed in a qualifying statement in Section 1 of the report.
 - b) This statement is redundant; a random effects model produces larger confidence intervals, which infers a more conservative effect estimate.
 - c) The power of the Chi-square test for heterogeneity increases with the total information available rather than simply the number of trials included in the meta-analysis (4). It is also true that power decreases if one trial comprises a large proportion of the total information (as is the case here with the EORTC trial). Owing to the shortcomings of the test, additional methods were used to assess heterogeneity including the I^2 percentage and visual inspection of the forest plot. In Figure 2, the I^2 percentage indicates no heterogeneity present (0%) and visual inspection of the forest plot clearly shows a consistent treatment effect.
 - d) Patient accrual is dependent on numerous factors. Slow patient accrual does not necessarily indicate that this patient population is rare and represents a small proportion of patients with prostate cancer. In modern series, approximately 50% of patients are found to have at least one adverse pathologic feature postprostatectomy (5).
 - e) Information on radiated volume was added to Table 1.
 - f) The GU DSG agrees with the respondent's comment; this sentence has been removed from the review.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the GU DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES - VERSION 2.2010

Development and Internal Review

An updated EBS was initiated by the GU DSG of the CCO PEBC in 2009 and completed in 2010. The series is a convenient and up-to-date source of the best available evidence on adjuvant radiotherapy for pT3 prostate cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario. The original systematic review from February 2008 has been retained in Section 2B of the new series, while new evidence from February 2008 to January 2010 is presented in Section 2A. The updated Guideline Recommendations are presented in Section 1.

Disease Site Group Consensus Process

The members of the GU DSG reviewed the new evidence contained in Section 2A via email and also at a meeting held in March 2010. A rearrangement of the recommendations was suggested so that a recommendation that adjuvant RT should be used with the aim of prolonging survival in all patients found at prostatectomy to have positive surgical margins, extracapsular extension, or seminal vesicle invasion and a recommendation for early referral to a radiation oncologist following radical prostatectomy were combined to state that early referral to a radiation oncologist is recommended for consideration of adjuvant RT. A statement about the risk of disease relapse and genitourinary and rectal toxicity was added. A statement about revisiting the recommendations when mature results of two of the three RCTs are published was moved to qualifying statements. Qualifying statements were added to define early referral as commencing between six and 18 weeks following prostatectomy, and to quantify risk of disease relapse being >90% when the post-prostatectomy PSA is rising and is

>0.1 ng/mL. A qualifying statement encouraging participation in clinical trials for patients at risk was also added.

Report Approval Panel

Prior to the submission of this EBS report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including the PEBC director and an oncologist with expertise in methodology issues. Key issues raised by the panel included:

- The authors should add a statement about key differences with the original recommendations.
- In a discussion of the subgroup analysis, it is shown that 5 of 6 subgroups in the SWOG trial benefit with adjuvant RT. In the subgroup that does not benefit, the authors conclude *“As such, the subgroup of patients without extracapsular extension is not necessarily representative of the population at large with organ-confined, margin-positive disease and therefore this finding may not be generalizable to this population.”* This qualifying statement is at odds with the powerful nature of the other data. The authors should consider a stronger statement about the exploratory nature of this analysis, the limited statistical power, the issue of multiple comparisons and that, from a policy level, these data are insufficient for separate policy recommendations; the recommendations determined by assessing all patients also apply to this subset. While the analysis they report is of potential interest for developing hypotheses, it is insufficient for policy. The above comment is not at odds with the authors’ final recommendations. While the authors speculate that this subgroup may be clinically unique, it is also possible that they are seeing random variation.

Modifications/Actions

The following modifications and responses were made to address key issues made by the Report Approval Panel:

- A statement was added to the guideline recommendations describing the differences between the original recommendations and the updated recommendations.
- The discussion surrounding the subgroup of patients without extracapsular extension was revised to emphasize the heterogeneity of the subgroup and the possibility that it is a spurious result arising from exploratory analysis.

External Review by Ontario Clinicians

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the GU DSG circulated Sections 1 and 2 to external review participants in Ontario for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the GU DSG.

BOX 1:

DRAFT RECOMMENDATIONS (approved for external review May 10, 2010)

- 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.

DRAFT QUALIFYING STATEMENTS

- In the trials addressing this question, early referral was variably defined as commencing between 6 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:
 - Whether salvage radiotherapy administered at the time of early biochemical failure confers outcomes equivalent to those of adjuvant radiotherapy.
 - Whether androgen deprivation therapy given in conjunction with adjuvant radiotherapy improves outcomes over adjuvant radiotherapy alone.
 - The optimal target volume, technique, or dose-fractionation schedule for adjuvant radiotherapy.
 - 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.

Methods

Targeted Peer Review: During the guideline development process, four targeted peer reviewers from Ontario, Quebec, Alberta, and British Columbia considered to be clinical experts on the topic were identified by the GU DSG. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on February 26, 2010.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Medical and radiation oncologists and surgeons working in the field of genitourinary cancer in Ontario were identified from the PEBC database and were contacted by email to inform them of the guideline and to solicit their feedback. Participants could participate using a web survey tool or by hardcopy through regular mail or fax. They were provided with access to the questionnaire, the guideline recommendations (Section 1), and a link to the evidentiary base (Section 2). Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. The invitations to participate were sent out May 26, 2010. The consultation period ended on July 5, 2010. The authors reviewed the results of the survey.

Results

Targeted Peer Review: Three responses were received from three reviewers. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods. (Consider: The appropriate stakeholders were involved in the development of the guideline. The evidentiary base was developed systematically. Recommendations were consistent with the literature. Consideration of alternatives, health benefits, harms, risks, and costs were made.)				1	2
2. Rate the guideline presentation. (Consider: The guideline is well organized. The recommendations were easy to find.)				2	1
3. Rate the guideline recommendations. (Consider: The recommendations are clinically sound. The recommendations are appropriate for the intended patients.)				2	1
4. Rate the completeness of reporting. (Consider: The guideline development process was transparent and reproducible. How complete was the information to inform decision making?)					3
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	1	1
6. What are the barriers or enablers to the implementation of this guideline report? Responses are compiled in the comments section below.					
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
7. Rate the overall quality of the guideline report.				2	1
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
8. I would make use of this guideline in my professional decisions.			1	1	1
9. I would recommend this guideline for use in practice.			1	1	1

Summary of Written Comments

The targeted reviewers highly rated the guideline development methods, presentation, and completeness of reporting. One reviewer suggested that heterogeneity testing of the SWOG

study subgroups would be valuable to show whether there was significant heterogeneity of treatment effect. One reviewer noted that the term “early referral” in the recommendation was somewhat vague and should be defined more precisely.

The barriers to implementation suggested were:

- Possible reluctance by urologists to refer patients as they feel they can adequately counsel patients on the role of postoperative RT
- The fact that so far only 1 RCT shows a survival difference and the meta-analyzed biochemical surrogate endpoints are insufficient to persuade a change of treatment policy at the provincial level.
- The remaining unanswered question of whether salvage at the time of biochemical recurrence would be as effective and reduce the burden of treatment in patients not destined to recur.

Modifications/Actions

- Meta-analysis of the pathological subgroups depends on unpublished data from SWOG. The guideline developers maintain that analysis with unpublished data is not recommended in a practice guideline. The authors have submitted meeting abstracts on the subgroup analyses.
- The qualifying statement regarding early referral has been clarified to indicate the commencement of adjuvant radiotherapy between 6 and 18 weeks following prostatectomy.
- The authors acknowledge that the available evidence does not address whether salvage radiotherapy administered at the time of early biochemical failure confers outcomes similar to those of adjuvant radiotherapy. Ongoing RCTs comparing these two approaches are identified.

Professional Consultation: 60 responses were received. Key results of the feedback survey are summarized in Table 2.

Table 2. Responses to three items on the professional consultation survey.

General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	1	1	4	32	22
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.		3	6	21	29
3. I would recommend this guideline for use in practice.		3	8	24	25

Summary of Written Comments

The comments tended to echo those of the targeted reviewers. The main barriers to implementation indicated by respondents were:

- Data are not mature enough; only 1 RCT with long-term follow-up
- Reluctance of urologists to refer patients for RT
- Unresolved issue of adjuvant RT versus early salvage RT

- Concerns regarding the toxicity of adjuvant RT
- No clear evidence on positive margins

Modifications/Actions

- The authors acknowledge the paucity of long-term data on this topic and that only one of the three relevant RCTs has reported updated results. Nevertheless, with the long-term follow-up from the SWOG study, it has now been shown that adjuvant radiotherapy confers a significant benefit after radical prostatectomy and this finding warrants incorporation in a practice guideline. The recommendations will be reviewed once mature results are published for the two randomized trials for which only short-term results are currently available.
- The RCTs included relatively few patients with organ-confined, margin-positive disease and it is unclear whether the overall results should apply to these patients.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the GU DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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

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1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol.* 1995;13:502-12.
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Evidence-based Series 3-17 Version 3: Section 4

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**

Guideline Review Summary

S.C. Morgan, C. Agbassi and Members of the Genitourinary Cancer Disease Site Group

Review Date: May 2, 2014

The 2010 guideline recommendations are

ENDORSED

*This means that the recommendations are still current and
relevant for decision making.*

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2008 and updated in 2010. In November 2013, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (CA) conducted an updated search of the literature. A clinical expert (SM) reviewed and interpreted the new eligible evidence and proposed the existing recommendations be endorsed. The Genitourinary Cancer Disease Site Group endorsed the recommendations found in Section 1 (Clinical Practice Guideline) in May 2014.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question(s) Considered

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.

Literature Search and New Evidence

The new search (Sept 2009 to Jan 2014) yielded three relevant publications of two RCTs comparing adjuvant radiotherapy to no adjuvant radiotherapy in prostate cancer. The longer-term results of EORTC 22911 and ARO 96-02/AUO 09/95 that have emerged since the 2010 guideline update are at odds with the mature results from SWOG 8794 with respect to the effect of adjuvant radiotherapy on overall survival. While it would be important to update the evidentiary base of the guideline document such that the latest results from the EORTC and ARO trials are included, it is not anticipated that new recommendations would be necessary.

An additional search for ongoing studies on Clinicaltrials.gov yielded two potentially relevant ongoing RCTs. Brief results of these searches are shown in the Document Review Tool below.

Impact on Guidelines and Its Recommendations

The new data support existing recommendations. Considering the evidence from the three completed randomized trials, the existing principle guideline recommendation on early referral to a radiation oncologist remains valid even in the light of these new data. Although the overall survival was not shown to be significantly different between arms, the Genitourinary Cancer DSG decided to endorse the 2010 recommendations on adjuvant radiotherapy following radical prostatectomy for pathologic T3 margin-positive prostate cancer. This guideline will be assessed annually to determine if it needs to be updated.

Document Review Tool

Number and title of document under review	3-17 Adjuvant radiotherapy following radical prostatectomy for pathologic T3 margin-positive prostate cancer
Current Report Date	July 22, 2010
Clinical Expert	Scott Morgan
Research Coordinator	Chika Agbassi
Assessment Date	November 2013
Approval Date and Review Outcome (once completed)	May 2 2014 [ENDORSED]

Original Question(s):

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.

Study Selection Criteria:

The study selection criteria used in the original systematic review (See Section 2B) were adopted for the 2010 update. This included RCTs, systematic reviews, or clinical practice guidelines in which adjuvant RT in the immediate postoperative period after radical prostatectomy was compared to observation, with other therapies including RT and ADT held in reserve for salvage. The patients had prostate cancer and were found at prostatectomy to have either extracapsular extension (now more commonly referred to as extraprostatic extension), seminal vesicle invasion, positive surgical resection margins, or more than one of these features.

Search Details:

- Sept 2009 to Jan 2014 (Medline week 3 and Embase week 3)
- Sept 2009 to Jan 2014 (ASCO Annual Meeting)
- Sept 2009 to Jan 2014 (Clinicaltrial.gov)

Brief Summary/Discussion of New Evidence:

Of 297 total hits from Medline + Embase and 13 abstracts from ASCO, two references representing two RCTs were found evaluating adjuvant radiotherapy or wait and see.

Interventions	Name of RCT (med F/U)	Population (n)	Outcomes	Brief results	References
ART (60Gy for 6W) vs. Wait and see	EORTC trial 22911 (10.6yrs)	Untreated cT0-3 WHO PS = 0-1 Age ≤75 (n =1005)	bPFS	After a 10yr follow-up, bPFS remained significantly better in patients that had ART compared with those that did not; HR=0.49 (95%CI 0.4-0.59) p<0.0001 but the rate of late adverse effect was significantly higher in the ART arm; 70.8% (95%CI66.6-75.0) vs. 59.7% (95%CI55.3-64.1) p=0.001. The significance of clinical PFS at 5yrs was not maintained at 10yrs follow-up	Bolla et al 2012
ART (60Gy for 6W) vs. Wait and see	ARO 96-02/AUO 09/95 (9.4 yrs.)	pT3-4 with ±ve surgical margin. Undetectable PSA following RP WHO PS = 0-1 (n = 385)	bPFS	At 5yr follow-up, ART significantly improved the bPFS; 72% (95% CI; 45%-63%) against 54% (95% CI 65%-81%) in WS; HR=0.53 (95% CI; 0.37-0.79 p=0.0015) At 10yrs follow-up, biochemical control increased to 56% in ART and 35% in WS (HR= 0.51; p=0.00002). OS and MFS were not significantly different between arms.	Wiegel et al 2013 [ABSTRACT] Wiegel et al 2009

On Going Trials

Retrieved from www.clinicaltrial.gov

Interventions	Official title	Status	Protocol ID	Last Updated
ART (64Gy) vs. Active surveillance	Radiotherapy - Adjuvant Versus Early Salvage. A Phase III Multi-centre Randomised Trial Comparing Adjuvant Radiotherapy (RT) With Early Salvage RT in Patients With Positive Margins or Extraprostatic Disease Following Radical Prostatectomy	Recruiting	NCT00860652 RAVES	February 13, 2013
Immediate RT plus (short HT, Long HT or no NT) vs. Delayed RT	RADICALS - Radiotherapy and Androgen Deprivation In Combination After Local Surgery	Unknown	NCT00541047 RADICALS	February 19, 2012

ART = Adjuvant radiotherapy; bPFS = biochemical progression free survival; HT= Hormone therapy; MFS = Metastasis free survival; n = number recruited; OS = Overall survival; PS = Performance status; WS = wait and see.

Clinical Expert Interest Declaration:

The clinical expert (SM) derives a proportion of his billings from the planning of post-prostatectomy radiotherapy. He has published two commentaries on the use of adjuvant and salvage radiotherapy after prostatectomy in the past five years.

Instructions: For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.	
1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?	NO
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?	a. YES b. YES
3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	NO
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?	N/A
Review Outcome	ENDORSED
DSG/GDG Approval Date	2 May 2014
DSG/GDG Commentary	

New References Identified (alphabetical order):

1. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet*. 2012;380(9858):2018-27. PubMed PMID: 23084481.
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Literature Search Strategy:

MEDLINE

1. exp prostate cancer/
2. (prostat\$ adj3 cancer).tw.
3. (prostat\$ adj3 carcinoma).tw.
4. (prostat\$ adj3 adenocarcinoma).tw.
5. or/1-4
6. prostatectomy/
7. prostatectomy.tw.
8. or/6-7
9. and/5,8
10. exp radiotherapy/
11. (adjuvant adj3 (radi\$ or irradi\$)).tw.
12. (postoperative adj3 (radi\$ or irradi\$)).tw.
13. (postprostatectomy adj3 (radi\$ or irradi\$)).tw.
14. or/10-13
15. randomized controlled trial.pt.
16. controlled clinical trial.pt.
17. randomized controlled trials/
18. randomi#ed controlled trial?.tw.
19. randomi#ed clinical trial?.tw.
20. random allocation/
21. exp meta-analysis/
22. (metaanal\$ or meta-anal\$ or metanal\$ or quantitative overview or quantitative synthes#s).tw.
23. (systematic review or systematic overview).tw.
24. practice guidelines/
25. practice guideline.pt.
26. practice guideline.tw.
27. or/15-26
28. and/9,14,27
29. (200909\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$ or "201401").ed.
30. 28 and 29

EMBASE

1. exp prostate cancer/
2. (prostat\$ adj3 cancer).tw.
3. (prostat\$ adj3 carcinoma).tw.
4. (prostat\$ adj3 adenocarcinoma).tw.
5. or/1-4
6. prostatectomy/
7. prostatectomy.tw.
8. or/6-7
9. and/5,8
10. exp radiotherapy/
11. exp irradiation/
12. (adjuvant adj3 (radi\$ or irradi\$)).tw.
13. (postoperative adj3 (radi\$ or irradi\$)).tw.
14. (postprostatectomy adj3 (radi\$ or irradi\$)).tw.
15. or/10-14
16. randomized controlled trial/
17. randomi#ed controlled trial?.tw.
18. randomi#ed clinical trial?.tw.
19. exp meta-analysis/
20. (metaanal\$ or meta-anal\$ or metanal\$ or quantitative overview or quantitative synthes#s).tw.
21. (systematic review or systematic overview).tw.
22. exp practice guideline/
23. practice guideline.pt.
24. practice guideline.tw.
25. or/16-24
26. and/9,15,25
27. (200901\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$ or "201403").ew.
28. 26 and 27

OUTCOMES DEFINITION

1. **ARCHIVED** - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the word “ARCHIVED”.
2. **ENDORSED** - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.
3. **DELAY** - A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.
4. **UPDATE** - An update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.