Purpose: The purpose of this guideline is to provide a clinical framework for the use of radiotherapy after prostatectomy in patients with and without evidence of prostate cancer recurrence.

Methods: A systematic review of the literature using the Pubmed, Embase, and Cochrane databases (search dates 1/1/90-12/15/12) was conducted to identify peer-reviewed publications relevant to the use of radiotherapy after prostatectomy. The review yielded an evidence base of 301 articles after application of inclusion/exclusion criteria. These publications were used to create the guideline statements. When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high quality evidence; high certainty), B (moderate quality evidence; moderate certainty), or C (low quality evidence; low certainty) and evidence-based statements of Standard, Recommendation, or Option were developed. Additional information is provided as Clinical Principles and Expert Opinion when insufficient evidence existed. See text for definitions and detailed information.

Guideline Statements:

1. **CLINICAL PRINCIPLE.** Patients who are being considered for management of localized prostate cancer with radical prostatectomy should be informed of the potential for adverse pathologic findings that portend a higher risk of cancer recurrence and that these findings may suggest a benefit of additional therapy after surgery.

2. **CLINICAL PRINCIPLE.** Patients with adverse pathologic findings including seminal vesicle invasion, positive surgical margins, and extracapsular extension should be informed that adjuvant radiotherapy, compared to observation, reduces the risk of biochemical (PSA) recurrence, local recurrence, and clinical progression of cancer. They should also be informed that the impact of adjuvant radiation on subsequent metastases and overall survival is less clear; one of two randomized controlled trials that addressed these outcomes indicated a benefit but the other trial findings were equivocal.

3. **STANDARD.** Physicians should offer adjuvant radiotherapy to patients with adverse pathologic findings at prostatectomy including seminal vesicle invasion, positive surgical margins, or extraprostatic extension. (Body of Evidence Strength Grade A)

4. **CLINICAL PRINCIPLE.** Patients should be informed that the development of a PSA recurrence after surgery is associated with a higher risk of development of metastatic prostate cancer or death from the disease. Congruent with this clinical principle, physicians should regularly monitor PSA after radical prostatectomy to enable early administration of salvage therapies if appropriate.
5. **RECOMMENDATION.** Clinicians should define biochemical recurrence as a detectable or rising PSA value after surgery that is ≥ 0.2 ng/ml with a second confirmatory level ≥ 0.2 ng/ml or as a consistently rising serum PSA level.

6. **OPTION.** A restaging evaluation in the patient with a PSA recurrence may be considered.

7. **RECOMMENDATION.** Physicians should offer salvage radiotherapy to patients with PSA or local recurrence after radical prostatectomy in whom there is no evidence of metastatic disease. (Body of Evidence Strength Grade C)

8. **CLINICAL PRINCIPLE.** Patients should be informed that the effectiveness of radiotherapy for PSA recurrence is greatest when given at lower levels of PSA.

9. **CLINICAL PRINCIPLE.** Patients should be informed of the possible short-term and long-term urinary, bowel, and sexual side effects of radiotherapy as well as of the potential benefits of controlling disease recurrence.
INTRODUCTION

Purpose

This guideline’s purpose is to provide direction to clinicians and patients regarding the use of radiotherapy after prostatectomy in patients with and without evidence of prostate cancer recurrence. The strategies and approaches recommended in this document were derived from evidence-based and consensus-based processes. This document constitutes a clinical strategy and is not intended to be interpreted rigidly. The most effective approach for a particular patient is best determined by the individual clinician faced with a particular patient. As the science relevant to the use of radiotherapy after prostatectomy evolves and improves, the strategies presented here will require amendment to remain consistent with the highest standards of clinical care.

Methodology

A systematic review was conducted to identify published articles relevant to the use of radiotherapy (RT) after prostatectomy, including its efficacy in patients with detectable and undetectable prostatic specific antigen (PSA) levels, its toxicity and quality of life (QoL) impact, and optimal imaging strategies to determine the appropriateness of RT use in patients suspected of recurrence. Literature searches were performed on English-language publications using the Pubmed, Embase, and Cochrane databases from 1/1/1990 to 12/15/2012. Data from studies published after the literature search cut-off will be incorporated into the next version of this guideline. Preclinical studies (e.g., animal models), commentary, and editorials were excluded. Only studies in which PSA data were provided for 75% or more patients were included. Review article references were checked to ensure inclusion of all possibly relevant studies. Multiple reports on the same patient group were carefully examined to ensure inclusion of only nonredundant information. The review yielded an evidence base of 301 articles from which to construct a clinical framework for the use of radiotherapy after prostatectomy.

Quality of Individual Studies and Determination of Evidence Strength.

Quality of individual studies that were randomized controlled trials (RCTs) or controlled clinical trials (CCTs) was assessed using the Cochrane Risk of Bias tool (Higgins 2007). Case-control studies and comparative observational studies were rated using the Newcastle-Ottawa Quality (NOQ) Assessment Scale (Wells 2009). Because there is no widely-agreed upon quality assessment tool for single cohort observational studies, the quality of these studies was not assessed except in the case of diagnostic accuracy studies. Diagnostic accuracy studies were rated using the QUADAS (Whiting et al., 2003, 2004).
The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes consideration of study design, individual study quality, consistency of findings across studies, adequacy of sample sizes, and generalizability of samples, settings, and treatments for the purposes of the guideline. The AUA categorizes body of evidence strength (ES) as Grade A (well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty (Faraday, Hubbard et al., 2009).

For some clinical issues, there was little or no evidence from which to construct evidence-based statements. Where gaps in the evidence existed, the Panel provides guidance in the form of Clinical Principles or Expert Opinion with consensus achieved using a modified Delphi technique if differences of opinion emerged (Hsu and Sandford 2007). A Clinical Principle is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. Expert Opinion refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence.

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, and the Panel’s judgment regarding the balance between benefits and risks/burdens (Faraday, Hubbard et al. 2009). Standards are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade A (high quality; high certainty) or Grade B (moderate quality; moderate certainty) evidence. Recommendations are directive...
statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade C (low level of certainty) evidence. **Options** are non-directive statements that leave the decision to take an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears relatively equal or appears unclear; **Options** may be supported by Grade A (high certainty), B (moderate certainty), or C (low certainty) evidence.

**Limitations of the Literature.** The Panel proceeded with full awareness of the limitations of the radiotherapy after prostatectomy literature. A major limitation of this literature is the lack of a large number of randomized controlled trials (RCTs) to guide decision-making in patients with and without evidence of recurrence and to indicate the appropriate use of androgen deprivation therapies in these patients. Further, a major limitation of all randomized trials in localized prostate cancer with long-term follow-up is the change in characteristics of contemporary patients; because of increased prostate cancer screening via prostatic specific antigen (PSA) testing and consequent detection of disease and initiation of therapy at earlier disease stages, patients recruited into trials decades ago have a greater risk of adverse outcomes than do contemporary patients. However, the Panel is fully aware that these issues will always be present in trials of therapies for localized prostate cancer because disease events (e.g., metastases and death) generally occur one to two decades after treatment. Additional limitations include: the preponderance of non-randomized studies; poorly-defined or heterogeneous patient groups; in studies that compared RT administered to patients with and without recurrence, the lack of group equivalence in terms of pathological risk factors; variability in PSA assay sensitivity and in failure criteria across studies and over time; the paucity of studies with follow-up duration longer than 60 mos; and, the overwhelming focus of the literature on biochemical recurrence with less information available regarding metastatic recurrence, cancer-specific survival, and overall survival. In addition, relatively few studies focused on quality of life outcomes that are of critical importance to patients, such as erectile function.

**Process.** The Radiotherapy after Prostatectomy Panel was created in 2011 by the American Urological Association Education and Research, Inc. (AUA) and the American Society for Radiation Oncology (ASTRO). The AUA Practice Guidelines Committee (PGC) and the ASTRO Guidelines Committee (GC) selected the Panel Chairs and the additional panel members with specific expertise in this area.

AUA and ASTRO conducted a thorough peer review process. The draft guidelines document was distributed to 73 peer reviewers, of which XX reviewers provided comments. The panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC and the ASTRO GC. Then it was submitted to the AUA and ASTRO Boards of Directors for final approval. Funding of the panel was provided by the AUA and ASTRO; panel members received no remuneration for their work.
BACKGROUND

General Background.

In 2012, an estimated 241,740 men were diagnosed with prostate cancer (American Cancer Society 2012). The most common primary treatment for localized disease is radical prostatectomy (Miller 2006). In approximately two-thirds of men, prostatectomy constitutes a cure but within 10 years up to one-third of patients will present with recurrent disease (Amling 2000; Chun 2006; Han 2001; Bianco 2005). Recurrence after prostatectomy is thought to result from residual subclinical disease in the operative site that later manifests as a rising prostatic-specific antigen (PSA) level, a local tumor recurrence, or metastatic disease. The risk of recurrence is greater among men with adverse pathology such as positive margins, seminal vesicle invasion (SVI), extracapsular extension (ECE), and higher Gleason scores (e.g., Stephenson 2006; Swindler 2005; Hawkins 1995; Kupelian 1997; Epstein 1993; Zietman 1994; Lee 2004; Ohori 1995; Lowe 1997; Pound 1999; Catalona 1994).

Clinicians, therefore, frequently face two scenarios in the patient for whom prostatectomy is the primary prostate cancer treatment. In the high-risk patient, revealed to have adverse pathological features at prostatectomy, clinicians and patients face the question of whether an adjuvant therapy should be considered to prevent possible future recurrence. In the post-prostatectomy patient who later presents with a detectable PSA level, appropriate salvage therapies may be considered.

This guideline focuses on the evidence for use of radiotherapy (RT) in the adjuvant and salvage contexts. Adjuvant radiotherapy (ART) is defined as the administration of radiotherapy to post-prostatectomy patients at a higher risk of recurrence because of adverse pathological features prior to evidence of disease recurrence. Salvage radiotherapy (SRT) is defined as the administration of radiotherapy to the prostatic bed in the patient with a PSA recurrence after surgery but no evidence of metastatic disease. Biochemical (PSA) recurrence after surgery is defined as a detectable or rising PSA level $> 0.2$ ng/mL with a second confirmatory level $> 0.2$ ng/mL or a consistently rising PSA.

The most commonly-reported post-prostatectomy outcome in the peer-reviewed literature is biochemical (PSA) recurrence and biochemical recurrence-free survival (bRFS). Other reported outcomes include local recurrence and local recurrence-free survival, metastatic recurrence and metastatic recurrence-free survival (mRFS), clinical progression-free survival (no evidence of local or metastatic progression, excluding evidence of biochemical recurrence), cancer-specific survival, and overall survival. Clinicians generally use regularly-obtained PSA levels over time in post-RP patients to detect recurrence, to trigger the administration of additional therapies, and/or to guide further diagnostic evaluations.
Adjuvant radiotherapy (ART). The highest-quality evidence that addresses the use of radiotherapy after prostatectomy is provided by three randomized controlled trials (RCTs) that have examined the effect of radiotherapy delivered primarily in an adjuvant context. Findings from the three trials are reviewed below and in Table 2.

Overall Findings. Biochemical recurrence. Three RCTs (SWOG 8794, EORTC 22911, and ARO 96-02), two with more than 10 years of follow-up, documented significant improvements in biochemical recurrence-free survival (bRFS) among patients with adverse pathological features (i.e., seminal vesicle invasion, positive surgical margins, and/or extraprostatic extension) with the use of adjuvant RT in comparison with observation only post-prostatectomy (Thompson 2006; Bolla 2012; Wiegel 2009). A meta-analysis of biochemical recurrence data performed as part of the literature review yielded a pooled hazard ratio of 0.48 (95% confidence interval: 0.42 – 0.56; p <0.00001; random effects model; see Figure 1 below).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolla 2012</td>
<td>-0.713</td>
<td>0.093</td>
<td>65.0%</td>
<td>0.49 [0.41, 0.59]</td>
</tr>
<tr>
<td>Thompson 2009</td>
<td>-0.844</td>
<td>0.164</td>
<td>20.9%</td>
<td>0.43 [0.31, 0.59]</td>
</tr>
<tr>
<td>Wiegel 2009</td>
<td>-0.635</td>
<td>0.2</td>
<td>14.1%</td>
<td>0.53 [0.36, 0.78]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.48 [0.42, 0.56]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 9.73 (P < 0.00001)

Figure 1: Meta-analysis of biochemical recurrence data from SWOG 8794 (Thompson 2009), EORTC 22911 (Bolla 2012), and ARO 96-02 (Wiegel 2009).

Locoregional recurrence. Two RCTs demonstrated a reduction in locoregional failure in ART patients compared to RP only patients; ARO 96-02 did not assess locoregional failure. This difference was statistically significant in EORTC 22911 (Bolla 2012) at median 10.6 years of follow-up with 8.4% of ART patients having locoregional failure compared to 17.3% of RP only patients. In SWOG 8794, also at 10.6 years of follow-up, locoregional recurrence was 8% in the ART group and 22% in the RP only group (Thompson 2006). A p level was not presented but the proportions are similar to those reported in EORTC 22911.

Hormonal-therapy free survival. SWOG 8794 also reported a statistically significant improvement in hormonal therapy-free survival in ART patients compared to RP only patients with approximately 84% of ART patients remaining hormone-therapy free at 10 years compared to approximately 66% of RP only patients. EORTC 22911 reported that by year 10, 21.8% of patients in the ART group had started an active salvage treatment (including salvage...
radiotherapy or ADT) compared to 47.5% of patients in the RP only group -- a statistically significant difference.

Clinical progression. SWOG 8794 and EORTC 22911 also both demonstrated improved clinical progression-free survival (defined as clinical or imaging evidence of recurrence or death but not including biochemical progression) in patients who had ART compared to those who had RP only. This difference was statistically significant in SWOG 8794 at median 10.6 years of follow up and borderline significant (p = 0.054) in EORTC 22911 at the same follow-up point. The weaker effect in EORTC 22911 may have been the result of the higher rate of non-prostate cancer mortality among the ART group (17.1%) compared to the RP only group (12.3%) or possibly because salvage treatments in the RP only group were initiated at lower PSA levels than in the ART group.

Metastatic recurrence and overall survival. Only SWOG 8794 demonstrated significantly improved overall survival (74% in ART patients compared to 66% for RP only patients) and significantly improved metastatic recurrence-free survival (43.5% for ART patients compared to 54% for RP only patients) with the use of ART compared to RP only at more than 12 years of follow-up (Thompson 2009). These findings did not replicate in EORTC 22911 at median 10.6 years of follow-up (Bolla 2012). There are several differences between the two trials that may be relevant to the disparate findings. These include the fact that the overall survival rate of the RP only group in SWOG 8794 was much lower (66.0%) than the RP only group in EORTC 22911 (80.7%); the reason for the lower survival rate in SWOG 8794 is not clear. The trials used identical patient selection criteria. Patient demographics were reported differently in the two trials, making it somewhat difficult to compare recruited patient characteristics that might be relevant to the disparate findings. The proportion of patients administered preoperative hormonal therapies was similar, however (SWOG 8794 – 8% of Observation group, 9% of ART group; EORTC 22911 – 10% of each group). More patients had SVI in EORTC 22911 (approximately 25% of each group) than in SWOG 8794 (10-11% of each group). In SWOG 8794, 68% of the Observation group and 67% of the ART group had ECE or positive margins. EORTC 22911 reported that 78.9% of the Observation group and 75.1% of the ART group had ECE and 63% of the Observation group and 62.2% of the ART group had positive margins. The proportion of patients with post-RP PSA values ≤ 0.2 ng/ml also was relatively similar across trials (SWOG 8794 – 68% of Observation group, 65% of ART group; EORTC 22911 – 68.6% of Observation group, 70.3% of ART group). None of these patient-level differences, however, clearly explain the outcome differences. It also is possible that salvage treatments in SWOG 8794 were not used as extensively as in EORTC 22911; the trials had similar rates of salvage treatment despite higher relapse rates in SWOG 8794. A definitive answer has yet to be identified.

Subgroup Findings. The three RCTs also reported outcomes for various patient subgroups (see Table 3). Not all trials reported on all subgroups and subgroup analyses were

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not performed for all outcomes. These analyses are summarized below. The Panel notes that the trials did not stratify randomization by subgroups and that these comparisons were unplanned, internal analyses for which the trials did not necessarily have sufficient statistical power. Subgroup analyses, therefore, should be interpreted with caution and their utility is primarily to guide new research directions.

Positive surgical margins: All three trials reported a statistically significant improvement in biochemical RFS among patients with positive surgical margins who received radiotherapy compared to patients who did not. In addition, both SWOG 8794 and EORTC 22911 reported a significant improvement in clinical RFS among patients who received radiotherapy (this outcome was not addressed by ARO 96-02). Only EORTC 22911 reported overall survival data for this subgroup; there were no differences in overall survival between patients who did or did not receive radiotherapy.

Patients with positive surgical margins comprised the majority in EORTC 22911 (62.2% of the ART group; 63% of the RP only group) and in ARO 96-02 (68% of the ART group; 61% of the RP only group). SWOG 8794 did not report the number of patients with positive margins separately but reported that 67% of patients in the ART group and 68% in the RP only group had disease that extended beyond the capsule or had positive margins.

Negative surgical margins: Among patients with negative surgical margins, EORTC 22911 reported that the use of radiotherapy did not improve clinical RFS rates and significantly decreased overall survival (HR 1.68; 95% CI 1.10-2.56). Although EORTC 22911 reported a significant improvement in biochemical RFS with radiotherapy in this subgroup, ARO 96-02 reported no improvement with radiotherapy. SWOG 8794 did not address outcomes among patients with negative margins.

Seminal vesicle invasion (SVI): In patients with SVI, SWOG 8794 and EORTC 22911 reported significantly improved bRFS with radiotherapy. However, RT did not improve clinical RFS in either trial, metastatic RFS in SWOG 8794, or overall survival in EORTC 22911. Further, ARO 96-02 reported no difference in bRFS with RT among patients with SVI.

Absence of SVI: Only EORTC 22911 reported on patients without SVI and the findings are exactly the same as for patients with SVI – improved bRFS but no difference in clinical RFS or overall survival.

Extracapsular extension (ECE): EORTC 22911 and ARO 96-02 reported significantly improved biochemical RFS with use of RT among patients with ECE. EORTC 22911 reported no differences, however, in clinical recurrence-free survival or overall survival. SWOG 8794 did not report on this subgroup.
Absence of ECE: Only EORTC 22911 reported on outcomes among patients without ECE. Similar to patients with ECE, use of RT among patients without ECE significantly improved bRFS but not clinical recurrence-free survival or overall survival.

Gleason score subgroups: Gleason 2-6. EORTC 22911 and ARO 96-02 both reported significantly improved biochemical RFS with use of RT among Gleason 2-6 patients. SWOG 8794 reported no differences, however, in metastatic RFS with use of RT in this subgroup.

Gleason 7-10. ARO 96-02 reported significant improvement in bRFS with use of RT among Gleason 7-10 patients. EORTC 22911 reported improved bRFS among Gleason 7 patients that did not reach statistical significance and no difference with RT among Gleason 8-10 patients. SWOG 8794 reported a statistically significant improvement in metastatic RFS with RT, however, among Gleason 7-10 patients.

Patient age. EORTC 22911 reported on outcomes for patients younger than age 65 years, age 65 to 69 years, and age 70 years and older. In patients younger than age 65 years, the use of RT resulted in significant improvements in biochemical RFS and clinical RFS. Among patients aged 65 to 69 years, the use of RT resulted in significant improvements in bRFS but not clinical RFS. Among patients aged 70 years and older, the use of RT did not improve bRFS or clinical RFS and, in fact, appeared to worsen overall survival (HR 2.94; CI 1.75-4.93, p<0.05).

Observational studies also have evaluated the use of ART; because of the confounds to interpretation and to causal attribution inherent in designs that lack randomization and other controls for bias, the Panel based its judgments regarding ART primarily on the findings from the RCTs.

Interpretation. The Panel interpreted the findings from the RCTs to indicate that adjuvant radiotherapy after prostatectomy may benefit patients with high-risk pathological features. The most consistent findings were an improvement in biochemical RFS across all three trials and improvements in locoregional and clinical RFS in the two trials that reported these outcomes, with less consistent findings across trials for other outcomes. The most consistent finding for subgroup benefit was for positive margin patients with all three trials reporting improved outcomes with RT.

The Panel is fully aware that the apparent benefits associated with RT are the result, in part, of a subset of patients treated with RT who never would have presented with recurrence. It is the nature of adjuvant therapies to treat high-risk patients with full knowledge that this decision will result in some patients who are over-treated. It should be noted that primary therapy for localized prostate cancer (e.g., radical prostatectomy) also is employed for the benefit of an unknown minority of patients with the understanding that this strategy will result
in over-treatment of a large number of men who never would have experienced an adverse event from their tumor.

To put these issues in context, it is useful to consider the efficacy of radical prostatectomy compared to watchful waiting relative to the efficacy of prostatectomy in combination with ART compared to prostatectomy only. The number needed to treat (NNT) is a helpful statistic for this purpose; the lower the NNT, the more effective the treatment in preventing the designated outcome.

With regard to prostatectomy compared to watchful waiting, Bill-Axelson (2011; SPCG-4 trial) reported that at 15 years post-RP, the NNT for overall survival was 15. That is, approximately 15 men would have to undergo prostatectomy in order to prevent one death from any cause compared to watchful waiting. Using data from approximately 45,000 patients from the SEER database, Abdollah (2012) stratified patients into high-risk (pT2c or Gleason 8-10) vs. low-intermediate risk (all other patients) and reported an NNT at 10 years of follow-up of 13 for death from prostate cancer for high-risk patients and an NNT of 42 for low-intermediate risk patients.

With regard to RP plus ART compared to RP only, SWOG 8794 reported an NNT of 9.1 for overall survival, indicating that approximately 9 men would need to be treated with RP+ART compared to RP only to prevent one death from any cause at median 12.6 years of follow up (Thompson 2009). With regard to preventing metastatic disease, SWOG 8794 reported an NNT of 12.2. EORTC 22911 did not replicate these findings and reported a higher overall death rate among RP+ART patients (25.9%) compared to RP only patients (22.9%) – these data yield a negative NNT, indicating a lack of benefit for the active treatment. With regard to cancer-specific survival, for which EORTC 22911 also did not document a treatment benefit, the NNT calculated from the raw data provided in Table 2 (Bolla 2012) is 55.6, indicating that approximately 56 men would need to be treated with RP+ART to prevent one case of death from prostate cancer at 10.6 years of follow-up compared to RP only (the other two trials did not report cancer-specific data). As a point of comparison, a pooled NNT for preventing biochemical recurrence derived from combining SWOG 8794 and EORTC 22911 (which each had follow-up durations >10 years) is 4.2. Combining local recurrence data from SWOG 8794 and

Note that NNTs from papers that compared RP to watchful waiting appear to have been calculated using cumulative incidence rates whereas the NNTs from SWOG 8794 reported in Thompson (2009) and calculated from data provided in EORTC 22911 (Bolla 2012) and ARO 96-02 (Wiegel 2009) for purposes of comparison were calculated using raw event data; these different calculation methods will yield somewhat different NNTs because they use different denominators (use of cumulative incidence rates will lead to higher NNTs). As an example, using raw event data from Bolla (2012) yielded an NNT of 55.6 for cancer-specific survival; using cumulative incidence data provided in the text of the same paper yielded an NNT of 66.7 for cancer-specific survival.

Given the findings from the RCTs, the nature of adjuvant treatments to inevitably result in over-treatment for some patients, and the contextual information provided by NNTs, the Panel emphasizes that ART should be offered to all patients at high risk of recurrence because of adverse pathological features. The offering of ART should occur in the context of a thorough discussion of the potential benefits and risks/burdens associated with ART (see Guideline Statements 2 and 3). Ultimately, whether ART is likely to benefit a particular patient and should be administered is a decision best made by the multidisciplinary treatment team and the patient with full consideration of the patient’s history, values, and preferences.
Table 2: Outcomes from Randomized Controlled Trials
(yellow highlighting = statistically significant comparison; green highlighting = borderline significant comparison)

<table>
<thead>
<tr>
<th>Study</th>
<th>SWOG 8794</th>
<th>EORTC 22911</th>
<th>ARO 96-02</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biochemical recurrence and Biochemical recurrence-free survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWOG 8794</td>
<td>60/172 (34.9%) recurrence</td>
<td>112/175 (64%) recurrence</td>
<td>198/502 (39.4%) recurrence</td>
</tr>
<tr>
<td></td>
<td>5 y bRFS: 71.0%</td>
<td>5 y bRFS: 44.0%</td>
<td>5 y bRFS: 74.0%</td>
</tr>
<tr>
<td></td>
<td>10 y bRFS: 53.0%</td>
<td>10 y bRFS: 60.6%</td>
<td>10 y bRFS: 41.1%</td>
</tr>
<tr>
<td>Comparison: HR = 0.43 (95% CI: 0.31-0.58; p&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC 22911</td>
<td>38/148 (25.7%) recurrence</td>
<td>311/503 (61.8%) recurrence</td>
<td>67/159 (42.1%) recurrence</td>
</tr>
<tr>
<td></td>
<td>5 year bRFS: 72%</td>
<td>5 year bRFS: 54%</td>
<td>5 year bRFS: 54%</td>
</tr>
<tr>
<td><strong>Local recurrence, local recurrence-free survival, cumulative local relapse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWOG 8794</td>
<td>15/190 (8%) local recurrence at median 10.6 y</td>
<td>40/184 (22%) local recurrence at median 10.6 y</td>
<td>4/148 (2.7%) local recurrence at median 4.5 y</td>
</tr>
<tr>
<td></td>
<td>5 y hTFS: 90.0%</td>
<td>5 y hTFS: 79.0%</td>
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<td></td>
<td>10 y hTFS: 84.0%</td>
<td>10 y hTFS: 66.0%</td>
<td>10 y hTFS: 66.0%</td>
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<tr>
<td>Comparison: HR = 0.45 (95% CI: 0.29-0.68; p&lt;0.001)</td>
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<tr>
<td>EORTC 22911</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>ARO 96-02</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td><strong>Metastases, Metastases-free survival (mRFS), cumulative metastatic rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWOG 8794</td>
<td>93/214 (43.5%) had metastases or died of any cause</td>
<td>114/211 (54%) had metastases or died of any cause</td>
<td>55/502 (11.0%) had distant metastases</td>
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<tr>
<td></td>
<td>20/214 (9.3%) had metastases</td>
<td>37/211 (17.5%) had metastases</td>
<td>57/503 (11.3%) had distant metastases</td>
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<tr>
<td></td>
<td>5 y mRFS: 88%</td>
<td>5 y mRFS: 84%</td>
<td>10 y mRFS: 61%</td>
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<td>10 y mRFS: 71%</td>
<td>10 y mRFS: 61%</td>
<td>10 y mRFS: 61%</td>
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<td>Comparison: HR = 0.71 (95% CI: 0.54-0.94; p=0.016)</td>
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<tr>
<td>EORTC 22911</td>
<td>Comparison: HR = 0.99 (95% CI: 0.67-1.44; p=0.94)</td>
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<tr>
<td></td>
<td>NR</td>
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<tr>
<td>ARO 96-02</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td><strong>Clinical progression and clinical progression-free survival (cPFS); does not include bRFS</strong></td>
<td></td>
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<tr>
<td>SWOG 8794</td>
<td>84/214 (39.3%) clinical progression or death at median 10.6 y</td>
<td>111/211 (52.6%) clinical progression or death at median 10.6 y</td>
<td>25/502 (5.0%) deaths from prostate cancer</td>
</tr>
<tr>
<td></td>
<td>10 y cPFS: 70%</td>
<td>10 y cPFS: 49%</td>
<td>10 y cPFS: 49%</td>
</tr>
<tr>
<td>Comparison: HR = 0.62 (95% CI: 0.46-0.82; p=0.001)</td>
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<tr>
<td>EORTC 22911</td>
<td>Comparison: HR = 0.81 (95% CI: 0.65-1.01; p=0.054)</td>
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<tr>
<td></td>
<td>NR</td>
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<td>NR</td>
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<tr>
<td>ARO 96-02</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td><strong>Deaths from cancer and cancer-specific survival</strong></td>
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<tr>
<td>SWOG 8794</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>25/502 (5.0%) deaths from prostate cancer</td>
<td>34/503 (6.8%) deaths from prostate cancer</td>
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</tr>
<tr>
<td></td>
<td>10 y cumulative prostate cancer mortality rate: 3.9% (95% CI: 2.0-5.7%)</td>
<td>10 y cumulative prostate cancer mortality rate: 5.4% (95% CI: 3.2-7.5%)</td>
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<td></td>
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<tr>
<td>EORTC 22911</td>
<td>Comparison: HR = 0.78 (95% CI: 0.46-1.33; p=0.34)</td>
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<tr>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>ARO 96-02</td>
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<tr>
<td><strong>Overall survival (OS)</strong></td>
<td></td>
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<tr>
<td>SWOG 8794</td>
<td>88/214 (41.1%) deaths at median 12.7 y</td>
<td>110/211 (52.1%) deaths at median 12.5 y</td>
<td>5/148 (3.4%) deaths at median 4.5 y</td>
</tr>
<tr>
<td></td>
<td>110/211 (52.1%) deaths at median 12.5 y</td>
<td>130/502 (25.9%) deaths at median 10.6 y</td>
<td>5/148 (3.4%) deaths at median 4.5 y</td>
</tr>
<tr>
<td></td>
<td>115/503 (22.9%) deaths at median 10.6 y</td>
<td>115/503 (22.9%) deaths at median 10.6 y</td>
<td>115/503 (22.9%) deaths at median 10.6 y</td>
</tr>
<tr>
<td></td>
<td>8/159 (5.0%) deaths at median 4.5 y</td>
<td>8/159 (5.0%) deaths at median 4.5 y</td>
<td>8/159 (5.0%) deaths at median 4.5 y</td>
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<table>
<thead>
<tr>
<th>10 y OS estimate:</th>
<th>10 y OS estimate:</th>
<th>10 y OS estimate:</th>
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<tr>
<td>74.0%</td>
<td>66.0%</td>
<td>76.9%</td>
<td>80.7%</td>
</tr>
<tr>
<td>Comparison: HR = 0.72 (95% CI: 0.55 – 0.96; p=0.023)</td>
<td>Comparison: HR = 1.18 (95% CI: 0.91 – 1.53; p=0.20)</td>
<td>NR</td>
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</table>
### Table 3: Risk Factor Subgroup Findings from RCTs
(all comparisons statistically significant unless otherwise noted)

<table>
<thead>
<tr>
<th></th>
<th>SWOG 8794</th>
<th>EORTC 22911</th>
<th>ARO 96-02</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gleason 2-6</strong></td>
<td><strong>Met RFS</strong>: Obs. = RT(^2) (HR approx. 0.90, CI 0.55-1.50)</td>
<td><strong>Biochem RFS</strong>: Obs &lt; RT(^4) (HR approx. 0.44; CI 0.26-0.82)</td>
<td><strong>Biochem RFS</strong>: Obs &lt; RT(^5) (HR 0.42, CI 0.20-0.89)</td>
</tr>
<tr>
<td><strong>Gleason 7-10</strong></td>
<td><strong>Met RFS</strong>: Obs. &lt; RT(^5) (HR approx. 0.58, CI 0.35-0.92)</td>
<td><strong>Biochem RFS</strong>: -Gleason 7: Obs &lt; RT(^4) but dif n.s. (HR approx. 0.63; CI 0.38-1.00) -Gleason 8-10: Obs &lt; RT(^4) but dif n.s. (HR approx. 0.52; CI 0.26-1.20)</td>
<td><strong>Biochem RFS</strong>: Obs &lt; RT(^5) (HR 0.59, CI 0.37-0.95)</td>
</tr>
<tr>
<td><strong>No SVI</strong></td>
<td><strong>Not reported</strong></td>
<td><strong>Biochem RFS</strong>: Obs. &lt; RT(^1) (HR 0.43, CI 0.35-0.54) <strong>Clin RFS</strong>: Obs. = RT(^1) (HR 0.8; CI 0.61-1.04) <strong>Overall survival</strong>: Obs. = RT(^1) (HR 1.30, CI 0.95-1.77)</td>
<td><strong>Not reported</strong></td>
</tr>
<tr>
<td><strong>SVI</strong></td>
<td><strong>Biochem RFS</strong>: Obs &lt; RT(^1) (HR 0.23, CI 0.06 to 0.84) <strong>Met RFS</strong>: Obs. &lt; RT(^5) but dif ns (HR approx. 0.68, CI 0.42-1.07) <strong>Clin RFS</strong>: Obs = RT(^1) (HR 0.76, CI 0.33 to 1.74)</td>
<td><strong>Biochem RFS</strong>: Obs. &lt; RT(^1) (HR 0.60, CI 0.44-0.82) <strong>Clin RFS</strong>: Obs. = RT(^1) (HR 0.82; CI 0.58-1.16) <strong>Overall survival</strong>: Obs. = RT(^1) (HR 1.00, CI 0.66-1.52)</td>
<td><strong>Biochem RFS</strong>: Obs = RT(^5) but dif n.s. (pT3c: HR 0.77, CI 0.42-1.40)</td>
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<tr>
<td><strong>Negative margins</strong></td>
<td><strong>Not reported</strong></td>
<td><strong>Biochem RFS</strong>: Obs. &lt; RT(^1) (HR 0.61, CI 0.45-0.81) <strong>Clin RFS</strong>: Obs. = RT(^1) (HR 1.08; CI 0.78-1.55) <strong>Overall survival</strong>: Obs. &gt; RT(^1) (HR 1.68, CI 1.10-2.56)</td>
<td><strong>Biochem RFS</strong>: Obs = RT(^5) (HR 0.95, CI 0.47-1.93)</td>
</tr>
<tr>
<td><strong>Positive margins</strong></td>
<td><strong>Biochem RFS</strong>: Obs. &lt; RT(^1) (HR 0.44, CI 0.35 to 0.65) <strong>Clin RFS</strong>: Obs &lt; RT(^1) (HR 0.64, CI 0.45 to 0.93)</td>
<td><strong>Biochem RFS</strong>: Obs. &lt; RT(^1) (HR 0.44, CI 0.35-0.75) <strong>Clin RFS</strong>: Obs. &lt; RT(^3) (HR 0.69; CI 0.53-0.91) <strong>Overall survival</strong>: Obs. = RT(^1) (HR 0.98, CI 0.72-1.34)</td>
<td><strong>Biochem RFS</strong>: Obs &lt; RT(^5) (HR 0.41, CI 0.25-0.66)</td>
</tr>
<tr>
<td><strong>No ECE</strong></td>
<td><strong>Not reported</strong></td>
<td><strong>Biochem RFS</strong>: Obs. &lt; RT(^1) (HR 0.51, CI 0.35-0.75) <strong>Clin RFS</strong>: Obs. = RT(^1) (HR 0.78; CI 0.49-1.24) <strong>Overall survival</strong>: Obs. = RT(^1) (HR 1.21, CI 0.70-2.08)</td>
<td><strong>Not reported</strong></td>
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<tr>
<td><strong>ECE</strong></td>
<td><strong>Not reported</strong></td>
<td><strong>Biochem RFS</strong>: Obs. &lt; RT(^1) (HR 0.49, CI 0.40-0.60) <strong>Clin RFS</strong>: Obs. = RT(^1) (HR 0.83; CI 0.65-1.05)</td>
<td><strong>Biochem RFS</strong>: Obs &lt; RT(^5) (pT3a/b: HR 0.34, CI 0.19-0.64)</td>
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<tr>
<td>Factor</td>
<td>Effect Size</td>
<td>Statistic</td>
<td>Notes</td>
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<tr>
<td><strong>Overall survival</strong></td>
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<tr>
<td>Obs. = RT</td>
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<tr>
<td><strong>ECE or Positive margins</strong></td>
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<tr>
<td>Met RFS: Obs. &lt; RT but dif n.s. (HR approx. 0.73, CI 0.52-1.08)</td>
<td>Not reported</td>
<td>Not reported</td>
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<tr>
<td><strong>SVI and Positive margins</strong></td>
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<tr>
<td>Biochem RFS: Obs &lt; RT (HR 0.40, CI 0.20-0.77)</td>
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<td>Not reported</td>
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<tr>
<td>Clin RFS: Obs &lt; RT (HR 0.47, CI 0.27-0.81)</td>
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<td>Not reported</td>
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<tr>
<td><strong>Age</strong></td>
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<tr>
<td>Biochem RFS:</td>
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<tr>
<td>&lt;65 y: Obs. &lt; RT (HR 0.43, CI 0.33-0.56)</td>
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<td>Not reported</td>
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<tr>
<td>65-69 y: Obs. &lt; RT (HR 0.46, CI 0.34-0.61)</td>
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<td>Not reported</td>
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<tr>
<td>≥70 y: Obs. &lt; RT but dif n.s. (HR 0.75, CI 0.52-1.08)</td>
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<td>Not reported</td>
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<tr>
<td>Clin RFS:</td>
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<tr>
<td>&lt;65 y: Obs. = RT (HR 0.57, CI 0.40-0.79)</td>
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<td>65-69 y: Obs. = RT (HR 0.81, CI 0.57-1.15)</td>
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<tr>
<td>≥70 y: Obs. &gt; RT (HR 1.78, CI 1.14-2.78)</td>
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<td>Not reported</td>
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<tr>
<td><strong>Overall survival</strong></td>
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<tr>
<td>&lt;65 y: Obs. = RT (HR 0.91, CI 0.60-1.39)</td>
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<td>65-69 y: Obs. = RT (HR 0.97, CI 0.65-1.44)</td>
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<td>Not reported</td>
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<tr>
<td>≥70 y: Obs. &lt; RT (HR 2.94, CI 1.75-4.93)</td>
<td>Not reported</td>
<td>Not reported</td>
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</tbody>
</table>

1 Thompson 2006; median 10.6 years follow-up; all bRFS analyses conducted in patient subset of 348 who had post-RP PSA ≤ 0.4 ng/ml
2 Thompson 2009; median 12.7 years follow-up for RT group; median 12.5 years follow-up for Observ group; all bRFS analyses conducted in patient subset of 348 who had post-RP PSA ≤ 0.4 ng/ml
3 Bolla 2012; median 10.6 years follow-up
4 Van der Kwast 2007; patient subset (n=552) of total eligible sample (n=972) who had central pathology review; included here are data from Fig. 2 which consists of only patient with post-RP PSA ≤ 0.2 ng/ml
5 Wiegel 2009; median 4.5 years follow-up; 1992 AJCC – pT3a/b – ECE; pT3c - SVI

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Salvage radiotherapy (SRT). Evidence regarding the efficacy of SRT in the post-RP patient is available in the form of a large literature composed of observational studies; however, only a few studies compared patients who received SRT to RP only patients with PSA or local recurrence who did not receive further therapy (e.g., Boorjian 2009; Trock 2008). Generally, these studies indicate that SRT improves outcomes compared to RP only patients but the benefits may be specific to certain risk groups (see Discussion under Guideline Statement 7). In addition, two of the three RCTs (SWOG 8794 and EORTC 22911) enrolled patients with detectable PSA levels post-RP – salvage patients by definition. These two trials also generally revealed better outcomes among SRT patients compared to RP only patients with evidence of PSA recurrence (see Discussion under Guideline Statement 7).

ART vs. SRT. One of the most pressing clinical questions regarding the care of the post-RP patient is whether it is better to administer RT before evidence of recurrence – RT as adjuvant therapy – or to wait until recurrence manifests and then administer RT – RT as salvage therapy. It is acknowledged that the use of ART may involve irradiation of some patients who never would have had recurrent cancer, thus exposing them unnecessarily to the risks, toxicity, and quality of life impact of RT. Waiting to administer RT as a salvage therapy limits its use to patients with recurrence but, particularly in patients with high-risk disease, could be less effective and could allow the emergence of metastatic disease.

The literature review attempted to address this issue by examining the large number of observational studies that reported outcomes for ART and SRT patients in the PSA era. Study arms were categorized as adjuvant if post-RP patients administered RT had no evidence of recurrence based on the PSA failure threshold used by the authors. Study arms were categorized as salvage if post-RP patients had evidence of PSA or local recurrence at the time of RT administration. A third group of studies in which outcomes for ART and SRT patients were combined also was retrieved. Mixed studies were considered with regard to toxicity and quality of life outcomes (see below) but not for efficacy outcomes.

When this literature is examined as a whole, it appears that ART patients generally have better outcomes compared to SRT patients. For example, when the percentage of patients who had biochemical recurrence are plotted against follow-up duration post-RT for all observational studies that reported this outcome, the ART study arms generally report lower rates of biochemical recurrence\(^3\) and metastatic recurrence than do SRT study arms (see Figures 2 and 3).

Patterns with regard to cancer-specific survival and overall survival are less clear because few ART studies reported these outcomes (data not shown).

Overall, the interpretation that ART leads to superior outcomes is difficult to make with certainty in the absence of randomization and given that SRT studies focus only on patients

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\(^2\) Multiple reports on the same patient group were extracted as a composite report. Some publications contributed more than one study arm.

\(^3\) It should be noted that authors varied considerably in how biochemical recurrence was defined, including what constituted a detectable PSA level, whether one or more than one detectable values were required, whether values had to be rising, and/or whether values were evaluated with reference to the post-RT nadir.
who have already relapsed, making direct comparisons with ART studies problematic. ART and SRT studies also differ across numerous factors, any of which potentially confound interpretation. These include differences in patient characteristics (e.g., ART patients generally have more adverse pathological profiles), RT protocols (e.g., SRT studies often used higher RT doses than ART studies), failure definitions, follow-up durations, and in other key factors. In addition, most of the published literature reports findings from the use of older RT techniques (e.g., EBRT protocols), making it unclear whether newer techniques might result in fewer apparent differences between ART and SRT outcomes.

Given these issues, the Panel concluded that it is not possible from the available evidence to address the question of the superiority of ART vs. SRT. Currently, two RCTs are actively accruing patients to address this important question – the RADICALS trial (MRC PR10, NCIC PR13) and the RAVES trial (TROG 08.03) (see more detailed discussion in Research Needs and Future Directions).

Radiotherapy techniques and protocols in the post-prostatectomy patient.

The Panel’s literature review attempted to address the question of which radiotherapy techniques and doses produced optimal outcomes in the adjuvant and salvage context. It was not possible to answer these questions, however, from the available data.

Specifically, approximately one-third of the ART and SRT observational studies treated patients with conventional external beam modalities which have since been replaced by more sophisticated approaches using three-dimensional conformal radiation therapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) methods. The published literature has lagged well behind the implementation of these newer methods, with only one-quarter of the reviewed studies reporting use of 3D-CRT techniques and less than 5 percent reporting use of IMRT techniques. The remaining studies used either a mix of techniques, without separating...
patient outcomes based on technique, or did not report enough information to determine the type of RT used. The lack of studies using newer RT methods made it difficult to definitively address the question of optimal methods in general and whether these might differ in the adjuvant vs. salvage contexts.

With regard to the randomized controlled trials of ART, the men treated in SWOG 8794 and EORTC 22911 were administered RT using EBRT techniques (Thompson 2006; Bolla 2009); patients in ARO 96-02 were administered 3D-CRT (Wiegel 2009). Although there were no clear differences in toxicity, biochemical recurrence, or local recurrence among the three RCTs, a broader literature suggests that patients treated with 3D-CRT and IMRT would be expected to experience less treatment-related toxicity and better biochemical and local control compared to men irradiated with traditional techniques (e.g., Zelefsky 1998; Ost 2009).

Among the observational studies, the RT dosages varied from 50 to 78 Gy with most studies administering doses in the 60 to 70 Gy range and with SRT studies administering somewhat higher radiation dosages than ART studies (median ART dose – 61 Gy; median SRT dose – 65 Gy). Although RT dose-escalation has been shown in multiple randomized trials to improve freedom from biochemical relapse when used as primary treatment for localized prostate cancer, the optimal post-prostatectomy radiation dose is less clear and has never been tested in a prospective fashion. However, the clinical data suggest that doses above 65 Gy can be safely delivered and may lead to improved tumor control as determined by a reduction in biochemical progression (e.g., Bernard 2010; Cozzarini 2009; King & Spiotto 2008; Siegmann 2011). In the three RCTs, the majority of patients were treated with radiation doses of 60 Gy, which was lower than the dose used in most observational studies.

Given the difficulties in interpreting findings from the observational studies and the lack of high-quality evidence regarding optimal RT dosing and protocols in the adjuvant and salvage contexts, it is not possible at this time to identify the best RT strategies for these patients.

**Use of androgen-deprivation therapies in conjunction with RT in the post-RP patient.**

One of the questions faced by the clinician and post-prostatectomy patient is whether, when, for how long, and in what form androgen-deprivation therapy (ADT) should be administered. The systematic review attempted to address these questions by retrieving the literature that focused on the use of ADT in patients who underwent prostatectomy and then adjuvant or salvage radiotherapy. The Panel’s conclusion after reviewing the available evidence (see brief review below) was that, given the methodological weaknesses of this literature, it is not possible at this time to provide guidance regarding the use of ADT in conjunction with adjuvant or salvage radiotherapy. These weaknesses include: observational, non-randomized study designs; small sample sizes and consequent lack of statistical power to reliably detect differences between RT only and RT+ADT groups; lack of equivalence of RT and RT+ADT groups.
on pathological risk factors; large differences in ADT protocols, including when it was administered (e.g., pre-RP, pre-RT, during RT, post-RT) and for how long (e.g., weeks vs. months vs. years); and, other differences across studies that may be relevant to efficacy such as differences in RT techniques, targets, and total Gy administered.

Randomized controlled trials are needed to provide definitive evidence regarding these issues. At the time of this writing, RTOG 9601 was examining the effects of salvage RT with and without 24 mos of bicalutamide in patients with biochemical failure who had pT3N0 or pT2N0 disease with positive margins; to-date, findings from this trial had been reported only in abstract form. At median follow-up 7.1 years, patients who received SRT plus ADT had significantly improved freedom from biochemical progression and significantly fewer metastases (Shipley 2011). These findings are promising; publication of full trial results is awaited to provide more detailed guidance regarding the use of ADT in combination with salvage RT. In addition, currently RTOG 0534 is actively recruiting patients post-RP with a rising PSA to participate in a trial of short-term ADT with pelvic lymph node or prostate bed only RT. Findings from this trial, once mature, also will help to answer these important questions.

ADT in the adjuvant setting. Only four observational studies compared RP patients who received adjuvant radiotherapy to those who received ART in combination with some form of ADT (Bastide 2011; Ost 2009; Ost, de Troyer 2011; Pai 2009). Although all four studies reported findings suggesting that patients who received ADT in combination with ART had better outcomes, only one study reported a statistically significant difference between groups. Specifically, Bastide (2011) reported at median follow-up 60.3 mos that the ART+ADT group had significantly higher biochemical recurrence-free survival (bRFS) rates at five and seven years than did the ART only group (82.8% vs. 44.4%, respectively, at 5 years; 62.1% vs. 28.6%, respectively, at 7 years). bRFS rates for two additional comparison groups (patients who had RP only and patients who had RP+ADT but did not have ART) were similar to rates for the ART only group. All patients in this study had SVI but the distribution of other risk factors (i.e., Gleason scores, positive margins) differed somewhat across groups. The ADT administered was an LHRH analog; it was initiated on the first day of RT with median duration 12 mos. These findings require replication in a randomized trial.

ADT in the salvage setting. Twenty-one observational studies evaluated RP patients who received salvage RT compared to those who received SRT in combination with some form of ADT. Overall, this literature arrived at mixed conclusions. Six studies documented statistically significantly better outcomes for SRT+ADT patients compared to SRT only patients (De La Taille 2002; King Presti 2008; Pai 2009; Spiotto 2007; Stephenson 2007; Taylor 2003). The Panel notes that findings from the study with the largest sample size (Stephenson 2007; 1325 SRT patients; 214 SRT+ADT patients) derived from a multi-institutional retrospective cohort are particularly promising. Stephenson and colleagues (2007) used the sample to develop an SRT nomogram and demonstrated a significant advantage in progression-free
survival for patients who had SRT+ADT compared to SRT only patients. ADT (type not specified) was administered either before RT or during RT for median 4.1 months.

Seven studies reported that SRT+ADT patients had better outcomes than SRT only patients but either did not report a p level or the comparison did not reach statistical significance (De Meerleer 2008; Katz 2003; Liauw 2008; Monti 2006; Ost, de Troyer 2011; Trock 2008; Wadasaki 2007). Eight studies indicated that SRT only patients had better outcomes than did SRT+ADT patients or that the outcomes were indistinguishable (Anscher 2000; Buskirk 2006; Do 1998; Neuhof 2007; Ost, Lumen 2011; Song 2002; Stephenson 2004; Yoshida 2011).

Although the majority of studies suggested better outcomes for patients who had SRT in combination with some type of ADT, studies differed in when ADT was administered (pre-RT only, pre- and during RT, post-RT only; during RT only; during and post-RT), for how long (weeks, months, years), and in ADT type. In addition, studies varied in patient risk factors, RT protocols, and follow-up durations. Overall, the Panel’s conclusion was that, in the absence of randomized trials, the role of ADT in the ART or SRT context remains unclear.

Toxicity and quality of life (QoL) impact of RT post-prostatectomy.

A key concern of clinicians and patients when adjuvant or salvage RT is contemplated is the toxicity and quality of life effects of RT in patients who have already undergone prostatectomy. The Panel’s systematic review retrieved the literature relevant to these issues; findings are reviewed below. In addition to ART and SRT studies, studies that reported on mixed groups of ART and SRT patients were included given the importance of understanding toxicity effects. It was not possible to delineate differences in RT toxicity and QoL effects between ART and SRT studies given the many confounds to interpretation. These included: the absence of pre-RP information regarding genitourinary (GU), gastrointestinal (GI), and sexual functioning; large differences in the RP to RT interval, with consequent differential recovery from prostatectomy in ART vs SRT patients; the greater incidence of adverse pathology among ART patients; the use of somewhat higher radiation doses in SRT studies; and, the paucity of published studies using newer radiotherapy delivery modes such as 3D-CRT and IMRT that might minimize toxicity.

Toxicity. The most commonly-used measures to report toxicity information were the Radiation Therapy Oncology Group (RTOG) measure for acute effects (through day 90) and the RTOG/European Organisation for Research and Treatment of Cancer (EORTC) measure for late RT effects (persisting beyond day 90 or developing after day 90). The second most commonly-used measure was the Common Toxicity Criteria Adverse Event (CTCAE) measure which uses the same time frames. Both systems use a rating system of 0 to 5: a score of 0 indicates no change in function; 1 indicates a minor change in function that generally does not require any clinical action; 2 indicates a moderate change in function that may require medication; 3

**Acute toxicity.** Of the 94 study arms that reported any toxicity information, 30 reported at least one measure of acute genitourinary (GU) toxicity (4 ART arms, 12 SRT study arms, and 14 mixed study arms) and 28 reported at least one measure of acute gastrointestinal toxicity (2 ART arms, 13 SRT arms, 13 mixed arms).

**Acute GU toxicity symptoms** include:
- **Grade 1** – presence of the following symptoms without the requirement for medications - urinary frequency or nocturia that is twice pre-treatment levels, dysuria, urgency;
- **Grade 2** – urinary frequency or nocturia that is <1/hour, dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium);
- **Grade 3** – urinary frequency with urgency and nocturia hourly or more frequently with dysuria, pelvis pain or bladder spasm requiring regular frequency narcotics or gross hematuria with/without clot passage;
- **Grade 4** – hematuria requiring transfusion, acute bladder obstruction not secondary to clot passage; ulceration or necrosis

**Acute GI toxicity symptoms** include:
- **Grade 1** – presence of the following symptoms without the requirement for medications - anorexia with ≤5% weight loss; nausea, abdominal discomfort, increased frequency or change in bowel habits, rectal discomfort;
- **Grade 2** – anorexia with ≤15% weight loss, nausea and/or vomiting or abdominal pain requiring medication, diarrhea requiring parasympatholytics, mucus discharge not requiring sanitary pads, rectal/abdominal pain requiring analgesics;
- **Grade 3** – anorexia with >15% weight loss or nausea/vomiting or diarrhea requiring nasogastric (NG) tube or parenteral support; abdominal pain that is severe despite

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medications, hematemesis or melena, abdominal distension; severe mucus/blood discharge requiring sanitary pads; - Grade 4 – ileus, subacute or acute obstruction, fistula, perforation, GI bleeding requiring transfusion, abdominal pain requiring tube decompression or bowel diversion.

The ranges for proportions of patients experiencing Grade 1-2 and Grade 3-4 acute toxicities are presented in Table 4; no grade 5 toxicities were reported. Grade 1-2 acute toxicities were characterized by extremely wide ranges, with a great deal of variability across studies, and high percentages in many study arms, suggesting that these effects are relatively common. Grade 3-4 toxicities, however, were relatively uncommon.

Table 4: Acute Toxicity Effects of Radiotherapy After Prostatectomy
(Ranges based on RTOG or CTCAE Grading Systems)

<table>
<thead>
<tr>
<th>Study Arm Type</th>
<th>Genitourinary</th>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>10.5 - 26%</td>
<td>2.0 - 7.0%</td>
</tr>
<tr>
<td>Salvage</td>
<td>3.0 - 82.0%</td>
<td>0.0 – 3.8%</td>
</tr>
<tr>
<td>Mixed</td>
<td>5.0 – 92.0%</td>
<td>0.0 - 2.3%</td>
</tr>
</tbody>
</table>

With regard to acute GU effects, two studies compared patients treated with 3D-CRT to patients treated with IMRT (Alongi 2009; Goenka 2011). Both studies reported that use of 3D-CRT resulted in higher rates of grade 2 or greater toxicities (12.3% and 20.8%, respectively) compared to IMRT (6.6% and 13.4%, respectively).

Additional acute GU toxicity information was reported by Bolla (2005), one of the three RCTs that evaluated adjuvant RT, using the World Health Organization (WHO) scale for acute effects. The WHO scale breaks down functioning into 0 – no change, 1 – slight disturbance, 2 – greater disturbance but without influence on daily life; 3 – toxicities requiring treatment, and 4 - severe toxicities requiring vigorous treatment or hospitalization. Grade 1 and 2 frequency symptoms (44.9% and 17.3%, respectively), were the most frequently reported acute GU toxicities. Grade 3 frequency was uncommon (3.3%) and grade 4 frequency was rare (0.4%). Grade 1 and 2 dysuria occurred in 37.9% and 10.3% of patients, respectively, with only 1.1% reporting grade 3 dysuria and no reports of grade 4. Hematuria was uncommon, with 3.7% of patients exhibiting grade 1, 0.9% exhibiting grade 2, and no patients exhibiting the higher grades.

With regard to acute GI effects, Goenka (2011) reported that 3D-CRT patients had higher levels of grade 2 or greater toxicities (13.2%) compared to IMRT patients (7.6%). Alongi (2009) divided toxicities into lower and upper GI and reported that patients treated with 3D-CRT.
CRT had higher lower GI toxicity rates (8.6%) and higher upper GI toxicity rates (22.2%) than did patients treated with IMRT (lower: 3.3%; upper: 6.6%).

Using the WHO scale, Bolla (2005) reported that rates of diarrhea were grade 1 – 38.3%, grade 2 – 17.7%, grade 3 – 5.3%, and grade 4 – 0%. Nausea/vomiting symptoms were uncommon, with grade 1 levels manifested in 4.2% of patients, grade 2 in 0.2%, and no patients exhibiting grade 3 or 4.

**Late toxicity.** Of the total 94 study arms that reported any toxicity information, 40 reported at least one measure of late genitourinary (GU) toxicity (6 ART arms, 23 SRT study arms, and 11 mixed study arms) and 32 reported at least one measure of late gastrointestinal (GI) toxicity (2 ART arms, 20 SRT arms, 10 mixed arms).

**Late GU toxicity symptoms** include:
- **Grade 1** – slight bladder epithelial atrophy, minor telangiectasia (microscopic hematuria)
- **Grade 2** – moderate frequency, generalized telangiectasia, intermittent macroscopic hematuria
- **Grade 3** – Severe frequency and dysuria, severe generalized telangiectasia (often with petechiae), frequent hematuria, reduction in bladder capacity (<150 cc)
- **Grade 4** – Necrosis, contracted bladder (capacity <100 cc), severe hemorrhage, cystitis

**Late GI toxicity symptoms** include:
- **Grade 1** – mild diarrhea, mild cramping, bowel movement 5/day, slight rectal discharge or bleeding
- **Grade 2** – moderate diarrhea and colic, bowel movement >5/day, excessive mucus or intermittent bleeding
- **Grade 3** – Obstruction or bleeding requiring surgery
- **Grade 4** – Necrosis, perforation, fistula

The ranges for proportions of patients experiencing Grade 1-2 and Grade 3-4 late toxicities are presented in Table 5; no grade 5 toxicities were reported. Similar to acute toxicity data, Grade 1-2 late toxicities were characterized by extremely wide ranges, with a great deal of variability across studies (except for ART study arms for which only 2 values were available), and high percentages in many study arms, suggesting that these effects are relatively common. Grade 3-4 toxicities, however, were relatively uncommon.
Late toxicity over time. In contrast to acute toxicities, late toxicities may manifest cumulatively for several years post-RT and persist for many years.

Ost Lumen (2011) noted that the probability of late grade 2-3 GU toxicity rose from 12% at 24 mos post-SRT to 22% at 60 mos post-SRT. Pearse (2008) reported a similar pattern with 13% of patients manifesting grade 2 or higher GU toxicity at 12 mos post-SRT, rising to 28% at 48 mos post-SRT, and remaining at 28% at 60 mos post-SRT. Feng (2007) reported in a mixed group of patients that grade 2 or higher toxicities occurred in 4% of patients at 12 mos post-RT rising to 12% at 60 mos post-RT. Goenka (2011) reported on patients who were administered 3D-CRT or IMRT and noted that the probability of late grade 2 or higher toxicities for 3D-CRT patients ranged from 5% at 24 mos post-SRT to 25% at 96 mos post-SRT. For IMRT, 9% of patients exhibited grade 2 or higher toxicities at 24 mos post-SRT with the proportion rising to 16.8% at 60 mos post-SRT and remaining at 16.8% through 120 mos of post-SRT follow-up.

Late GI toxic effects are less common. Ost Lumen (2011) also reported that the probability of late grade 2-3 GI toxicity rose from 3% at 24 mos post-SRT to 8% at 48 mos post RT and remaining at 8% at 60 mos post-SRT. Pearse (2008) reported a similar pattern with 3% of patients manifesting grade 2 or higher GU toxicity at 12 mos post-SRT, rising to 7% at 36 mos post-SRT, and remaining at 7% at 60 mos post-SRT. Feng (2007) reported in a mixed group of patients that grade 2 or higher toxicities occurred in 2% of patients at 12 mos post-RT rising to 4% at 60 mos post-RT. Goenka (2011) reported on patients who were administered 3D-CRT or IMRT and noted that the probability of late grade 2 or higher toxicities for 3D-CRT patients ranged from 4.5% at 24 mos post-SRT to 10.2% at 96 mos post-SRT. For IMRT, 1% of patients exhibited grade 2 or higher toxicities at 24 mos post-SRT with the proportion rising to 4.0% at 72 mos post-SRT and remaining at 4.0% through 120 mos of post-SRT follow-up.

Additional late toxicity information is provided by Thompson (2006), one of the three RCTs (SWOG 8794). At median 127 mos follow-up, urethral stricture was more common among RT patients (17.8%) than among RP only patients (9.5%). Proctitis also was more common among RT patients (3.3%) than among RP only patients (0%). Moinpour (2008) reported on frequency symptoms defined as >8 voids/day among a subset of patients from SWOG 8794. Before RT, rates of frequency were similar between groups (21% of patients who then received RT; 22% of RP only patients). Frequency rates rose post-RT for RT patients (12 mos – 27.5%; 24 mos – 23%; 36 mos – 26%; 48 mos – 28%) but decreased for RP only patients (12 mos – 14%; 24

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mos – 12%; 36 mos – 13%; 48 mos – 15%). By 60 mos post-RT, however, the two groups had similar frequency rates that were indistinguishable from pre-RT values (RT – 22%; RP only – 19.5%). Rates of bowel movement tenderness, although similar between groups post-RP and pre-RT, became elevated among RT patients post RT and remained elevated through 60 mos of follow up (6 mos post-RT/RP: RT – 18%; RP only – 5%; 60 mos post RT/RP: RT – 18.5%; RP only 11%).

**Urinary incontinence.** To understand the impact of RT on urinary incontinence (UI) post prostatectomy, the Panel focused on studies that provided either pre-RT baseline information and/or reported findings for a comparison group.

Five ART studies reported in six papers provided information on urinary incontinence (Choo 2002; Formenti 1996, 2000; Hoffman 2003; Van Cangh 1998; Thompson 2006). One study provided pre-RT information (25 of 69 patients with UI) and reported at median 50.4 mos follow-up that one additional patient had developed UI (Choo 2002). Three reports compared ART patients to RP only patients; at follow-up durations ranging from one to three years, ART and RP only patients had indistinguishable and low rates of UI and pad use (ART: 12-23%; RP only: 14 – 19%) (Formenti 1996, 2000; Hoffman 2003). Two reports focused on patients from the RCTs (Van Cangh 1998 – EORTC 22911; Thompson 2006 – SWOG 8794). Van Cangh (1998) noted that among patients from the Belgian arm of EORTC 22911, there were no statistically significant differences between ART and RP only patients in Grade 2-3 UI (grade 2 – use of 1-4 pads soaked; grade 3 – more than 4 pads) pre-RP (ART 8.3%; RP only 9.6%) or at 24 mos post RP/RT (ART – 8.3%; RP only 2%). Thompson (2006) reported a non-significant difference in total UI between ART patients (6.5%) and RP only patients (2.8%) at median 127 mos follow up.

Seven SRT studies that included pre-RT baseline information and/or a comparison group reported information regarding UI (Borg 2006; Chawla 2002; Choo 2005; Duchesne 2003; Hagan 2004; Katz 2003; Pearse 2008). As a group, these studies reported either isolated cases of new onset UI and/or mild worsening of UI in small numbers of patients (usually one or two patients).

**Quality of Life (QoL).** Few studies focused on the QoL impact of urinary and GI symptoms and on overall QoL post-RT. No ART studies and only two SRT studies reported urinary and GI-related QoL information using a validated measure. Using the EPIC (score range 0-100 with higher scores indicating better QoL), Pinkawa (2008) reported that pre-RT, SRT patients had urinary-related function and bother scores that ranged from 75 to 87. Although urinary function and bother scores worsened immediately after RT, scores returned to pre-RT levels by 2 mos post-RT and remained at those levels at >1 year post-RT. Pre-RT, mean bowel function score was 92 and bowel bother score was 94. Post-RT, there was a significant decrease in function and bother scores (indicating worse QoL) that did not recover to pre-RT levels until 1 year post-RT. Similar patterns were evident for individual symptoms of rectal urgency, fecal incontinence, painful bowel movements, and having a moderate/big problem
from bowel dysfunction. Hu (2006) reported responses to the UCLA Prostate Cancer Index in SRT patients and noted that urinary and bowel function and bother scores did not change from pre-RT to 12-18 mos post-RT.

One ART study reported overall quality of life data. Moinpour (2008; data subset from SWOG 8794) reported that pre-RT, similar proportions of ART patients (47%) and RP only patients (52%) reported having a normal health-related quality of life. These proportions increased over time for the ART group, with 69% of patients reporting a normal quality of life at 60 mos post-RT. In contrast, for the RP only patients, the proportions remained the same, with 51% reporting a normal quality of life at 60 mos post-RP. For up to 36 mos post-RT, ART patients had higher symptom distress scores than did RP only patients but by 48 and 60 mos post-RT, ART patients had lower distress scores than RP only patients. For the RAND Medical Outcomes subscales (Physical Function, Emotional Function, Social Function, and Role Function), the groups were indistinguishable throughout follow-up.

One SRT study reported overall QoL data (Hu 2006). SRT patient scores on the RAND physical component summary and mental component summary did not change from pre-RT to 12-18 mos post-RT. The population mean on these scales is 50; SRT patient mean scores ranged from 46.0 to 54.0.

Erectile Function. ART studies. Five studies reported information in six publications regarding erectile function in ART patients (Choo 2002; MacDonald Lee 2007; Do 2002; Formenti 1996, 2000; Moinpour 2008). Given the limited number of studies, the lack of validated measures, the absence of key data over time (particularly pre-RP baseline data), and potential confounding variables such as unequal use of ADT across patient groups and lack of full recovery from RP (RP to RT interval < 6 mos), it is not possible to determine the impact of RT on erectile function when given for adjuvant purposes to post-RP patients. It is noteworthy that the percentages of patients who had intact erectile function post-RP but pre-RT were low, ranging from 7% to 33.3% with the most rigorous data from SWOG 8794 (Moinpour 2008) indicating that only 7% of men had intact function pre-RT.

SRT studies. The impact of salvage RT on erectile function also is difficult to determine. Thirteen studies reported erectile function information in SRT patients (Bastach 2002; Borg 2006; Buskirk 1996; Do 2002; Duchesne 2003; Petroski 2004; Wilder 2000; Wu 1995; Zelefsky 1997; Cremers 2010; Hu 2006; Goenka 2011; Pinkawa 2008). Nine of these studies reported only proportions of patients with ED at various time points and provide contradictory information (three studies reported no change post-RT and six reported increased proportions of patients with ED post-RT). In most of these studies: sample sizes were extremely small (<50); pre-RP functioning was not reported; the type of RP was not reported or varied (some patients had nerve-sparing procedures and others did not); the RP to RT interval was less than 2 years, making it unclear whether erectile function had fully recovered post-RP; patients were followed
for less than 2 years; and data were obtained from physician chart notes rather than patient-reported. Four studies used some type of validated measure. Although the sample sizes were larger, many of the same potential confounds remain. Three of these studies reported no changes over time from the post-RP/pre-RT measurement point throughout follow-up; one reported increased ED rates.

In addition, similar to the ART studies, post-RP patients who presented for salvage RT had very low rates of adequate erectile function (3.8% to 35.7%; most studies reported that <10% patients had full potency post-RP but pre-RT) and low scores on QoL measures of sexual function/bother. The only study that included pre-RP data (Petroski 2004) reported that 74 of 110 patients (73%) were fully potent pre-RT, 9 (9%) were partially potent, and 18 (18%) were impotent. Post-RP/Pre-RT, 7 of 74 previously potent patients remained potent (9.5%); 14 of 74 previously potent patients became partially potent (19%); 53 of 74 previously potent patients became impotent (71.6%); in addition, all 9 patients who were partially potent pre-RT became impotent. Post-RT (minimum follow-up 60 mos), of the 21 patients who were potent or partially potent post-RT, 9 (43%) became impotent, 10 (47.6%) became or remained partially potent, and 2 (9.4%) retained full potency; 1 of the 9 patients who lost partial potency post-RP regained partial potency during follow-up.

Overall, given the paucity of available data and the potential confounds to interpretation, the Panel interpreted these data to indicate that the impact of RT on erectile function given in either the adjuvant or salvage context is not currently known.

**Secondary malignancies.** Findings from studies carried out to investigate the risk of secondary malignancies resulting from the use of radiotherapy post-prostatectomy are contradictory as pointed out by Guedea (2010). Specifically, Bhojani (2010) estimated that the hazard ratio of developing a rectal tumour at 120 months was 2.2 in patients treated with radiotherapy compared with the general population. In contrast, a Canadian study evaluated all prostate cancer cases treated in British Columbia from 1984 to 2000 and found no significant difference between observed and expected second cancer rates, regardless of whether treatment included radiotherapy (Pickles 2002). In addition, none of the trials that focused on ART or SRT have reported secondary malignancy data. Further, post-prostatectomy men may not be an accurate control group for estimating the risk of secondary malignancies post-RT because there is evidence that they have a lower risk of second cancers than the general population (Eifler 2012). Finally, the risk of secondary cancers also may be related to co-existing factors such as the presence of past or current smoking (e.g., van Leeuwen 1995; Koivisto-Korander 2012; Zelefsky 2012). The Panel concluded that at this time the risk of a secondary malignancy as a result of the administration of RT in the adjuvant or salvage context is not known.

**Guideline Statement 1.**
Patients who are being considered for management of localized prostate cancer with radical prostatectomy should be informed of the potential for adverse pathologic findings that portend a higher risk of cancer recurrence and that these findings may suggest a potential benefit of additional therapy after surgery. \textit{Clinical Principle}

\textbf{Discussion.} Patients should be counseled before radical prostatectomy that certain pathology findings at prostatectomy are associated with higher risks for cancer recurrence. These findings include positive surgical margins, the presence of seminal vesicle invasion (SVI), and extracapsular extension (ECE). Rates of recurrence in post-RP patients with adverse pathological features may be greater than 60\% at 5 years post-RP in case series (e.g., Stephenson 2006; Swindler 2005; Epstein 1993; Zietman 1994; Lee 2004; Ohori 1995; Lowe 1997; Pound 1999; Catalona 1994; Karakiewicz 2005; Han 2001, 2003). In addition, two randomized controlled trials with more than 10 years of follow-up reported recurrence rates of >60\% in high-risk patients who had RP only (Thompson 2009; Bolla 2012).

The most definitive evidence for an increased probability of disease recurrence associated with specific high-risk pathologic features is provided by a recent report on approximately 4,400 radical prostatectomies with median follow-up of 10 years (and follow-up of up to 29 years in subset of patients) (Mullins 2012). Approximately 3,300 of these patients were treated during the PSA era (from 1992 to 2011). These data reveal reduced rates of biochemical recurrence-free survival and reduced rates of metastases-free survival at 15 years post-RP in men with a variety of pathological risk factors (see Tables 6 and 7).

Patients also should be informed that if these adverse pathological features are detected, then additional therapy after surgery, such as radiotherapy, may be beneficial.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Pathology Finding} & \textbf{Pathological Gleason Score} & \textbf{3 + 3} & \textbf{3 + 4} & \textbf{\geq 4 + 3} \\
\hline
Organ-confined & 99 & 86 & 79 \\
No ECE; Margin + & 94 & 75 & 67 \\
ECE; Margin - & 89 & 72 & 41 \\
ECE; Margin + & 75 & 45 & 27 (at 14 years) \\
SVI & 39 & 39 & 15 \\
\hline
\end{tabular}
\caption{15-Year Biochemical Recurrence-Free Survival (%) in Men Treated with Radical Prostatectomy in the PSA era (adapted from Mullins 2012)}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Pathology Finding} & \textbf{Pathological Gleason Score} & \textbf{3 + 3} & \textbf{3 + 4} & \textbf{\geq 4 + 3} \\
\hline
Organ-confined & 100 & 98 & 92 \\
No ECE; Margin + & 100 & 100 & 50 \\
ECE; Margin - & 100 & 97 & 75 \\
ECE; Margin + & 100 & 88 & 73 \\
\hline
\end{tabular}
\caption{15-Year Metastatic Recurrence-Free Survival (%) in Men Treated with Radical Prostatectomy in the PSA era (adapted from Mullins 2012)}
\end{table}
Guideline Statement 2.

Patients with adverse pathologic findings including seminal vesicle invasion, positive surgical margins, and extracapsular extension should be informed that adjuvant radiotherapy, compared to observation, reduces the risk of biochemical (PSA) recurrence, local recurrence, and clinical progression of cancer. They should also be informed that the impact of adjuvant radiation on subsequent metastases and overall survival is less clear; one of two randomized controlled trials that addressed these outcomes indicated a benefit but the other trial findings were equivocal. **Clinical Principle**

**Discussion.** Patients with adverse pathologic findings at prostatectomy should be counseled regarding the most up-to-date findings from the randomized controlled trials that have evaluated the use of ART. This counseling should emphasize that high-quality evidence indicates that the use of ART in patients with adverse pathological findings reduces the risk of biochemical recurrence, local recurrence, and clinical progression of cancer. Patients also should be informed that the impact of ART on subsequent metastases and overall survival is less clear, with benefits reported in one of two trials with long-term data on these outcomes. Clinicians also should counsel patients regarding the potential benefits and risks/burdens of the available treatment alternatives if biochemical recurrence, local recurrence, and/or clinical progression occur.

Guideline Statement 3.

Physicians should offer adjuvant radiotherapy to patients with adverse pathologic findings at prostatectomy including seminal vesicle invasion, positive surgical margins, or extraprostatic extension. **Standard**

**Discussion.** (*Evidence strength – Grade A; Benefits outweigh risks/burdens*). Three randomized controlled trials (SWOG 8794, EORTC 22911, and ARO 96-02), two with more than 10 years of follow-up, evaluated the effects of ART on outcomes among patients with adverse pathologic features at prostatectomy [Thompson 2006, 2009; Bolla 2012; Wiegel 2009; for detailed discussion of RCT findings, see **Adjuvant Radiotherapy (ART)** section in **General Background**]. All three trials documented significant improvements in biochemical recurrence-free survival (bRFS) with use of ART compared to RP only (pooled hazard ratio of 0.48; 95% CI 0.42 – 0.56; p <0.00001; see Figure 1 above). The Panel notes that prevention of biochemical...
progression is an important clinical endpoint because biochemical progression may trigger salvage therapy, with its associated toxicities and quality of life impact. In addition, patients with biochemical recurrence are more likely to manifest metastatic recurrence. Therapies for metastatic recurrence, such as androgen deprivation therapies, can have profound quality of life impact and their efficacy has not yet been convincingly demonstrated.

The two RCTs that evaluated locoregional failure (SWOG 8794; EORTC 22911) demonstrated a reduction in failure in ART patients compared to RP only patients at more than 10 years of follow-up. This difference was statistically significant in EORTC 22911 (Bolla 2012; locoregional failure in 8.4% of ART patients compared to 17.3% of RP only patients) and similar in magnitude in SWOG 8794 (Thompson 2006; locoregional failure in 8% of ART patients compared to 22% in RP only patients; no p value reported). The Panel viewed reduction of locoregional failure as another important clinical endpoint because the occurrence of local failure also triggers the use of salvage therapies, with associated toxicities, and increases the probability of subsequent metastatic failure.

Both SWOG 8794 and EORTC 22911 also reported statistically significant reductions in the use of subsequent salvage therapies with ART compared to RP only at approximately 10 years of follow up. SWOG 8794 reported improvement in hormonal therapy-free survival in ART patients (84%) compared to RP only patients (66%). EORTC 22911 reported that fewer ART patients (21.8%) had started an active salvage treatment (including salvage radiotherapy or ADT) compared to RP only patients (47.5%). The Panel viewed reduction in initiation of salvage therapies as a result of ART as another important clinical endpoint because of the avoidance of the negative consequences of these therapies.

SWOG 8794 and EORTC 22911 also both demonstrated improved clinical progression-free survival (defined as clinical or imaging evidence of recurrence or death but not including biochemical progression) at more than 10 years of follow up in ART patients compared to RP only patients. This difference was statistically significant in SWOG 8794 and borderline significant (p = 0.054) in EORTC 22911. The Panel also judged improved clinical progression-free survival as an important endpoint because it reflects lower rates of local and distant failure as well as lower death rates associated with the use of ART.

Two of the trials – SWOG 8794 and EORTC 22911 -- assessed metastatic recurrence and overall survival. Only SWOG 8794 demonstrated significantly improved metastatic recurrence-free survival (43.5% for ART patients; 54% for RP only patients) and overall survival (74% in ART patients; 66% in RP only patients) at more than 12 years of follow-up (Thompson 2009). Several possible explanations for the discrepant findings across trials have been offered. These include the fact that the overall survival rate of the RP only group in SWOG 8794 was much lower (66.0%) than the RP only group in EORTC 22911 (80.7%); the reason for the lower survival rate in SWOG 8794 is not clear. It also is possible that salvage treatments in SWOG 8794 were
not used as extensively as in EORTC 22911; the trials had similar rates of salvage treatment despite higher relapse rates in SWOG 8794. Therefore, in the context of offering ART to patients, it should be emphasized that there is less certainty regarding potential benefits in terms of preventing metastatic recurrence and improving overall survival.

Given the consistency of findings across trials regarding other clinically-important endpoints of reduced biochemical and locoregional failure, clinical progression, and the reduction in the need for initiation of salvage therapies in patients administered ART, the Panel concluded that patients with high-risk pathological features should be offered ART.

The Panel also notes that RT should be offered to patients with adverse pathology detected at prostatectomy who have a persistent post-prostatectomy PSA level. Although by the definitions used in the guideline this is a salvage context for RT, two of the trials (SWOG 8794 and EORTC 22911) enrolled some patients with a detectable PSA in the early post-RP period (< 18 weeks). EORTC 22911 reported that RT improved biochemical recurrence-free point estimates similarly in patients with undetectable post-RP PSA levels (<0.2 ng/ml) and with detectable post-RP PSA levels (≥0.2 ng/ml) (Bolla 2012). SWOG 8794 reported that RT improved metastases-free survival point estimates similarly in patients with undetectable (< 0.2 ng/ml) and detectable (≥ 0.2 ng/ml) post-RP PSA (Thompson 2009). It is important to note that in SWOG 8794, although the point estimate of benefit was similar, the Kaplan-Meier survival analysis revealed that men with a detectable PSA post-RP who received RT were more likely over time to develop metastases or to die than were men who had an undetectable PSA and received RT.

The Panel is fully aware that the apparent benefits associated with ART are the result, in part, of a subset of patients treated who never would have presented with recurrence. For this reason, the Panel emphasizes that ART should be offered to all patients at high risk of recurrence because of adverse pathological features. Whether ART is likely to benefit a particular patient and should be administered is a decision best made by the multidisciplinary treatment team and the patient with full and thoughtful consideration of the patient’s history, current functional status, values, and preferences, and his tolerance for the potential toxicities and quality of life effects of radiotherapy.

Guideline Statement 4.

Patients should be informed that the development of a PSA recurrence after surgery is associated with a higher risk of development of metastatic prostate cancer or death from the disease. Congruent with this clinical principle, physicians should regularly monitor PSA after radical prostatectomy to enable early administration of salvage therapies if appropriate.

Clinical Principle
**Discussion.** Prostate specific antigen (PSA) levels drawn following a radical prostatectomy should be undetectable. An increasing PSA level suggests the presence of residual disease and frequently heralds the eventual development of symptomatic metastases and death from prostate cancer. Pound et al (1999) were among the first to describe the time course of disease progression. They followed 1997 consecutive men undergoing radical prostatectomy at the Johns Hopkins Hospital and demonstrated that no man experienced either distant or local recurrence without also demonstrating a rising PSA level. Among 304 men who developed detectable PSA values following surgery, the median time to the development of metastases was 8 years. Men with Gleason score 8-10 disease in the surgical specimen developed metastases more rapidly, usually within five years, while men with Gleason score 5-7 disease developed metastases more slowly, usually within ten years.

Early PSA rise was associated with more rapid development of metastases. Specifically, men who developed a rise in their PSA value within 2 years of surgery developed metastases more rapidly -- usually within five years; men who developed a rise in their PSA values more than two years post surgery, however, developed metastases later, many more than ten to fifteen years later. The median PSA doubling time provided the most statistically significant prediction of time to distant progression. Men with a PSA doubling time less than 10 months usually developed metastases within five years of surgery, while men with a PSA doubling time greater than 10 months developed metastases much later. Men who developed metastatic disease usually died at median five years later (range two to twelve years later).

Albertsen et al (2004) reported similar findings from a population based sample. They reported outcomes of 1136 men who underwent treatment in community practice following diagnosis of localized disease between 1990 and 1992. Among the 516 men who underwent surgery, the majority of men had post treatment PSA levels that remained undetectable or at a low, constant detectable level. For the remaining patients PSA levels increased immediately after surgery or after a time delay. Among the patients who did NOT die of prostate cancer within ten years of follow up, 40% showed no increase in post treatment PSA values, whereas 10% had a PSA doubling time of six to seven months or longer. A doubling time of approximately twelve months provided the maximum separation between patients who died of prostate cancer within ten years of surgery and those who did not. PSA doubling times were correlated with patients’ biopsy Gleason score and their pretreatment PSA level.

Overall, these data indicate that men with an increasing PSA after surgery are at risk for developing metastases and subsequently dying from their disease; this risk is particularly high among men with rapid PSA doubling times. Half of all men with PSA values doubling faster than every 10 to 12 months after surgery are dead from their disease within 10 to 13 years. Patients should be informed of the relationship between PSA recurrence post-surgery and the probability of metastatic recurrence and death from prostate cancer.
Guideline Statement 5.

Clinicians should define biochemical recurrence as a detectable or rising PSA value after surgery that is $\geq 0.2$ ng/ml with a second confirmatory level $\geq 0.2$ ng/ml or as a consistently rising serum PSA level. **Recommendation**

**Discussion. (Evidence strength – Grade C; Benefits outweigh risks/burdens).**

The vast majority of the published literature assessing the efficacy of radical prostatectomy uses a PSA threshold value of 0.2 ng/mL to define recurrence although some authors have advocated for the use of higher values (Amling 2001). Many adjuvant studies, including the three RCTs reviewed in detail in this guideline, and many salvage radiotherapy studies also use a PSA threshold of 0.2 ng/ml to define recurrence. Patients who have had a prostatectomy should be informed that a PSA value of 0.2 ng/ml or higher that has been confirmed by a second elevated PSA value constitutes evidence of a biochemical recurrence. The presence of a biochemical recurrence necessitates a thorough discussion of the available alternatives for salvage therapy, including the use of radiotherapy and other types of therapy.

The Panel notes that recurrences can be identified earlier and at much lower PSA levels (e.g., 0.07 ng/mL or less) using ultra-sensitive PSA assays (Pruthi 1997; Malik 2011). In addition, even more sensitive assays may add further clarity as to whether patients are at increased risk for clinical failure (Sarno 2012; Moul 2012). Data from retrospective and prospective trials tend to support the notion that more favorable biochemical outcomes are associated with very low PSA values at the time radiotherapy is offered (Swanson 2007). The salvage literature also generally reports that patients who receive radiotherapy at lower PSA levels have better outcomes than do patients who receive radiotherapy at higher PSA levels (see Discussion under Guideline Statement 8). However, a small percentage of patients may have detectable but stable PSAs for 10 years or more without evidence of clinical failure, which may reflect the presence of benign prostate glands in the surgical bed (Shinghal 2003). Currently, therefore, it is not clear whether the use of more sensitive assays would translate into improved outcomes for most patients or, alternatively, would result in an increase in unnecessary treatments (Malik 2011; Eisenberg 2010; Chang 2010). Given the lack of evidence regarding the use of ultrasensitive PSA assays to guide care, the Panel judged that the use of the 0.2 ng/ml threshold value with a second confirmatory value to document recurrence or treatment initiated by a clearly rising PSA value is the optimal strategy currently.

Body of evidence strength is Grade C because the majority of the relevant literature is composed of observational studies and no randomized trials have focused on the impact of different PSA thresholds on outcomes.

Guideline Statement 6.
A restaging evaluation in the patient with a PSA recurrence may be considered. **Option**

**Discussion. (Evidence strength – Grade C; Balance between benefits and risks/burdens uncertain).** In the patient with evidence of recurrence manifested as a detectable or rising PSA, determining the site of recurrence (local vs. metastatic) may be relevant to select an appropriate salvage strategy. The guideline systematic review included retrieval of the literature regarding imaging strategies to detect recurrence location in the post-RP patient who has biochemical evidence of recurrence.

The Panel grappled with numerous challenges in interpreting this literature. The most difficult issue was the lack of a reliable and relatively error-free reference standard with which to evaluate new modalities. In many studies no recurrence location could be identified in a subset of patients with biochemical failure by either the reference standard or the modality under evaluation, making the true performance of the evaluated modality unclear. Other problems included the use of different reference standards within and across studies, failure to administer the reference standard to all patients, lack of independence of the reference standard from the evaluated modality, and lack of blinding for test interpreters. In addition, the majority of studies assessed relatively small sample sizes (<50 for the majority of study arms). For these reasons, body of evidence strength for this literature is Grade C.

**Local recurrence.** Thirty-one studies comprised of 51 study arms reported on the diagnostic performance of 19 modalities for local recurrence detection. The modalities evaluated included digital rectal exam (DRE; Abi-Aad 1992; Casciani 2008; Scattoni 2003), transrectal ultrasound (TRUS; Abi-Aad 1993; Drudi 2006; Foster 1993; Kapoor 1993; Leventis 2001; Salomon 1993; Scattoni 2003; Sudakoff 1996), color Doppler TRUS (Sudakoff 1996), color power Doppler TRUS (Drudi 2006; Tamsel 2006), contrast-enhanced (CE) color power Doppler TRUS (Drudi 2006), body coil MRI (Huch Boni 1996), endorectal coil MRI without contrast (Casciani 2008; Cirillo 2009; Huch Boni 1996; Sella 2004), endorectal coil MRI with contrast (Cirillo 2009; Huch Boni 1996; Silverman 1997), $^{11}$C acetate PET/CT (Albrecht 2007), $^{11}$C choline PET/CT (Castelluci 2011; Reske 2008), $^{18}$FDG PET (Haseman 1996; Schoder 2005), $^{18}$FCH PET/CT (Panebianco 2012; Schillaci 2012), dynamic contrast-enhanced (DCE) MRI (Boonsirikamchai 2012; Casciani 2008; Scirra 2008), diffusion-weighted MRI with contrast (Giannanarini 2012), $^{1}$H-MRSI (Scirra 2008), $^{1}$H-MRSI with DCE MRI (Panebianco 2012; Scirra 2008), CT with contrast (Kramer 1997), Prostascint (Haseman 1996; Kahn 1998; Koontz 2008; Nagda 2007; Texter 1998; Wilkinson 2004), and Prostascint fused with MRI or CT (Schettino 2004). For more than half of the modalities evaluated, only one or two study arms reported findings; the lack of a sufficient number of studies on each modality limited the interpretability of findings. In addition, many modalities exhibited highly variable sensitivities and specificities across studies; this lack of consistency further limited interpretability of the performance of specific modalities.
Overall, endorectal coil MRI with contrast, DCE-MRI, $^1$H-MRSI, and $^1$H-MRSI with DCE MRI yielded the highest and most consistent sensitivities and specificities for the detection of local recurrence. Sensitivities were all above 70% and endorectal coil MRI with contrast and $^1$H-MRSI with DCE-MRI had sensitivities above 80%. The same set of modalities also yielded high specificities with all values above 70% except for one endorectal coil MRI with contrast study that reported a specificity of 66.7% (Huch Boni 1996). Specificities for $^1$H-MRSI were above 80% and those for DCE-MRI were above 85%. Two published systematic reviews on this topic came to similar conclusions (Beresford 2010; Martino 2011).

Other modalities exhibited excellent sensitivity but poor or variable specificity or vice versa. For example, nine study arms that evaluated TRUS reported sensitivities that ranged from 75% to 95.5% but specificities that ranged from 0 to 83.3%. Digital rectal exam (DRE), color power Doppler TRUS, and $^{11}$C choline PET/CT all exhibited specificities of 75% or higher but sensitivities that ranged from 32 to 50% for DRE, 41.6 to 93.3% for color power Doppler TRUS, and 53.8 to 69.7% for $^{11}$C choline PET/CT.

Overall, the decision regarding which modality to use to determine the presence or absence of local recurrence will depend on the availability of specific modalities and on the clinician’s goals for imaging.

Recurrence in nodes. Five studies reported on the diagnostic performance of $^{11}$C choline PET/CT (Rinnab 2008; Scattoni 2007; Schilling 2008; Winter 2010) and $^{18}$FDG PET/CT (Chang 2003) to detect recurrence in lymph nodes. The sensitivity of $^{11}$C choline PET/CT was 100% across studies; three studies reported data per patient and one study reported data per node (Winter 2010). Scattoni (2007) also reported data per node with a sensitivity of 64%. The single $^{18}$FDG PET/CT study reported a sensitivity of 75%. In contrast to high sensitivity values, specificities were more variable; values for $^{11}$C choline PET/CT ranged from 0 to 100% and the single $^{18}$FDG PET/CT study reported a value of 100%.

Two additional studies reported on the use of MRI with lymphotropic superparamagnetic nanoparticles (LSN). One study was conducted in patients who had not yet undergone prostatectomy and reported values for sensitivity and specificity above 90% (Harisinghani 2003). The only study retrieved that used this modality in post-RP patients with biochemical failure did not biopsy sufficient patients so that diagnostic performance could be calculated (Ross 2009).

Overall, the Panel concluded that insufficient data are available to recommend specific techniques for the detection of recurrence in nodes.

Recurrence in bone. Four studies comprised of ten study arms reported on the use of bone scan with or without SPECT (Even-Sapir 2006; Kane 2003), $^{11}$C choline PET/CT (Fuccio...
2010; Luboldt 2008), $^{18}$F fluoride PET (Even-Sapir 2006), $^{18}$F fluoride PET/CT (Even-Sapir 2006), DWE MRI with contrast (Luboldt 2008), conventional MRI-STIR (Luboldt 2008), and conventional MRI –T1 weighted (Luboldt 2008). It is difficult to draw firm conclusions from this literature given that most modalities were evaluated in only one study arm and that nine of ten study arms evaluated 25 or fewer patients. The sensitivities across techniques ranged from 66.7% to 100% with five studies reporting values of 100% (MRI-STIR, DW-MRI with contrast, $^{18}$F fluoride PET, $^{18}$F fluoride PET/CT, and bone scan without SPECT). Two studies reported values above 90% (MRI-T1 weighted and bone scan with SPECT). Only six study arms provided specificity information; these values ranged from 64% to 100% with four of five study arms reporting values above 80% (bone scan with and without SPECT, $^{11}$C choline PET/CT, $^{18}$F fluoride PET, and $^{18}$F fluoride PET/CT).

An additional set of studies focused on bone scan findings in patients with various PSA-related characteristics. This group of studies reported that scans were more likely to be positive among patients with higher PSA levels, shorter PSA doubling times (PSADTs), and faster PSA velocities (Cher1998; Choueiri 2008; Dotan 2005; Gomez 2004; Okotie 2004). For example, at PSA levels less than 10 ng/ml, less than 5% of patients had a positive bone scan (Dotan 2005). For PSADT greater than 6 mos, the probability of a positive bone scan was 3% (Okotie 2004). The yield of bone scans, given that most patients manifest biochemical failure at PSA values <1.0 ng/ml, will be low.

Metastatic recurrence. Six studies provided information regarding the detection of metastases outside of the prostate bed. Three studies reported on the use of ProstaScint (Raj 2001; Kahn 1998; Nagda 2007). One study each focused on $^{11}$C choline PET/CT (Castelluci 2011), $^{18}$FDG PET (Schoder 2005), and $^{18}$FCH PET/CT (Schillaci 2012). Sensitivity values for ProstaScint ranged from 30% to 100%. The other three scanning modalities had sensitivities above 95%. Specificities ranged from 0% to 58% for the ProstaScint studies and were above 95% for the other modalities. In the absence of multiple studies assessing each modality, definitive conclusions regarding the best imaging strategy to detect metastatic recurrence are not possible, but these data suggest that $^{11}$C choline PET/CT, $^{18}$FDG PET, and $^{18}$FCH PET/CT are promising.

Recurrence at all sites. Twenty-one studies provided diagnostic performance information regarding the detection of disease recurrence anywhere in the body using seven different imaging techniques (Kotzerke 2002; Sandblom 2006; De Jong 2003; Picchio 2003; Castelluci 2011; Garcia 2009; Giovacchini Picchio Coradeschi 2010; Richter 2010; Rinnab 2007, 2009; Yoshida 2005; Schoder 2005; Seltzer 1999; Pelosi 2008; Climent 2006; Heinsch 2006; Husarik 2008; Schillacci 2012; Proano 2006; Raj 2001; Mitchell 2012). A wide range of reference standards were employed including: other imaging modalities; biopsies of the prostate bed, nodes, and/or bone; PSA responses to salvage RT; and follow-up. In most cases, only a few study arms examined the same modality, making it difficult to arrive at definitive
conclusions. Eight study arms reported findings from the use of $^{11}$C choline PET/CT, however. All sensitivities were above 60% and six of the eight study arms reported sensitivities at 80% or higher. Specificity was provided in five of the eight study arms and ranged from 36% to 100%. In three of the five arms, specificity was above 75% (Mitchell 2012; Castelluci 2011; Giovachinni Pichhio Coradeschi 2010); the lower specificity values occurred in studies from the same institution in which a single reference standard (biopsy) was used (Rinnab 2007, 2009). Mitchell (2012) summarized the recent Mayo Clinic experience with $^{11}$C-choline PET/CT in 176 patients who had biochemical recurrence (most patients had RP as primary treatment) and concluded that $^{11}$C-choline PET/CT not only performed well but substantially enhanced the rate of prostate cancer lesion detection by approximately 32% beyond what could be identified using conventional imaging technologies. This enhanced rate of cancer detection allowed decisions regarding appropriate care that were not possible with conventional imaging and included observation, surgical resection, anatomically targeted therapies, and systematic therapies. Given the body of data on $^{11}$C choline PET/CT, this imaging strategy appears promising.

Guideline Statement 7.

Physicians should offer salvage radiotherapy to patients with PSA or local recurrence after radical prostatectomy in whom there is no evidence of metastatic disease. Recommendation

Discussion. (Evidence strength – Grade C; Benefits outweigh risks/burdens). Two of the RCTs included a subgroup of patients who had detectable PSA levels post-RP – patients that could be categorized as salvage patients. Subgroup analyses of these patients suggest a benefit of RT. In SWOG 8794, RT significantly reduced metastatic recurrence rates among patients with detectable PSA post-RP (Thompson 2009). In EORTC 22911, RT significantly reduced rates of biochemical failure among patients with detectable PSA post-RP; rates of clinical progression were lower among this group than among patients with detectable PSA post-RP who were observed but the difference was not significant (HR = 0.75; 95% CI: 0.52-1.08; Bolla 2012).

This statement also is supported by two observational studies that reported outcomes for patients who had SRT vs. post-RP patients with detectable PSA and/or local recurrence who did not have SRT. Boorjian (2009) reported on a cohort of 2,657 patients with biochemical failure post-RP; 856 of these patients had salvage RT. Median follow-up post-RP was 11.5 years; median follow-up post biochemical failure was 6.9 years. SRT patients were followed for median 5.9 years post-RT. SRT significantly reduced the risk of local recurrence (by almost 90%) and systemic progression (by 75%) and delayed the need for ADT administration; these differences were present even after controlling for differences between groups in clinical and pathological features. No overall survival difference was documented, however. Trock (2008) reported outcomes for post-RP patients with biochemical failure and/or local recurrence who
received no salvage treatment (n=397), received SRT alone (n=160), or who received SRT in
combination with ADT (n= 78). At median follow-up of 6 years after recurrence and 9 years
after RP, 22% of men who received no salvage therapy had died from prostate cancer – a
significantly higher rate than men who had SRT (11% deaths from prostate cancer) and men
who had SRT with ADT (12% deaths from prostate cancer); there were no differences between
the two SRT groups. The authors note that the cancer-specific survival advantage associated
with SRT (with or without ADT) was specific to certain clinical subgroups. These included men
with a PSA doubling time of <6 mos with a recurrence to RT interval of <2 years. Men with a
PSA level ≤ 2 ng/ml at the time of RT also had increased survival; however, among men with
PSADT of <6 mos, SRT significantly increased survival regardless of PSA level at time of RT. SRT
also significantly improved survival among men whose PSA became undetectable in response to
RT but not in men whose PSA remained detectable. Overall, in men with PSADT <6 mos, 10-
year cancer-specific survival rates were significantly higher for men who received SRT
compared to those who did not regardless of surgical margin status or Gleason score. For men
with PSADT >6 mos, the cancer-specific survival advantage associated with RT was only evident
among patients with positive margins and Gleason scores 8-10. Overall survival in men with
pT3 cancer was significantly increased by SRT but only in men with PSADT <6 mos.

In the context of administering SRT, clinicians should be aware that a large number of
observational studies have reported that patients in certain high-risk groups have poorer
outcomes than patients without these risk factors or in lower risk groups. As a group, these
studies focused primarily on biochemical recurrence-free survival. Generally, although all
comparisons were not statistically significant, studies indicate that poorer bRFS is present in
patients with higher Gleason scores, higher pT stages, with SVI, and with ECE compared to
lower risk subgroups (Borg 2006; Buskirk 2006; Chawla 2002; Cremers 2010; De La Taille 2002; De Meerleer
2008; Do 1998; Garg 1993; Jacinto 2007; King 2004; King Presti 2008; Kruser 2011; Lee
McBain 2004; Leventis 2001; Liauw 2008; MacDonald 2004; Monti 2006; Mosbacher 2002; Nagda 2007; Neuhof
1996; Song 2002; Song 2009; Stephenson 2004; Swanson 2011; Symon 2006; Taylor 2003; Tomita 2009; Tsien
2003; Wiegel 2009; Yoshida 2011; Youssef 2002).

Body of evidence strength was Grade C because the analyses from the RCTS were
internal subgroup analyses and because the remaining evidence was derived from
observational studies.
Guideline Statement 8.

Patients should be informed that the effectiveness of radiotherapy for PSA recurrence is greatest when given at lower levels of PSA. **Clinical Principle**

**Discussion.** Forty-five observational studies compared biochemical recurrence-free survival rates for salvage radiotherapy patients at lower vs. higher pre-RT PSA levels (Bernard 2010; Buskirk 1996; Catton 2001; Chawla 2002; Cheung 2005; Cremers 2010; De La Taille 2002; De Meerleer 2008; Do 1998; Forman 1997; Garg 1998; Hugen 2010; Jacinto 2007; King & Spiotto 2008; King Presti 2008; Leventis 2001; Liauw 2008; Loeb 2008; MacDonald 2004; Maier 2004; Monti 2006; Nagda 2007; Neuhof 2007; Nudell 1999; Ost De Troyer 2011; Ost Lumen 2011; Pai 2009; Pazona 2005; Perez 2003; Petroski 2004; Pisansky 2000; Rogers 1998; Schild Buskirk 1996; Song 2002; Stephenson 2004; Stephenson 2007; Swanson 2011; Symon 2006; Taylor 2003; Terai 2005; Tomita 2009; Vanuytsel 2001; Wiegel 2009; Wilder 2000; Youssef 2002). Thirty-nine studies used cut-off values to divide the low and higher groups of approximately 1.0 ng/ml or less.

All but one study reported that patients with lower pre-RT PSA levels had higher bRFS rates over time compared to patients with higher pre-RT PSA levels although the differences between groups were not always statistically significant. The exception was Tomita (2009), which divided patients into those with pre-RT PSA <0.25 ng/ml or ≥0.25 ng/ml – an extremely low threshold. This is the only study in which values for the low and high groups were reversed, with 51% of the pre-RT PSA <0.25 ng/ml free of biochemical recurrence at 36 mos compared to 59% of the pre-RT PSA ≥0.25 ng/ml group – a non-significant difference.

Confirmatory subgroup analyses from SWOG 8794 presented in Swanson (2007) indicate that among patients with detectable PSA at the time of radiotherapy, those with PSA values ≤1.0 ng/ml had higher 5- and 10-year bRFS rates than those with pre-RT PSA values >1.0 ng/ml.

Therefore, patients should be advised that if recurrence is detected without evidence of metastases, then radiotherapy should be administered at the earliest sign of PSA recurrence and, ideally, before PSA rises to 1.0 ng/ml.

Guideline Statement 9.

Patients should be informed of the possible short-term and long-term urinary, bowel, and sexual side effects of radiotherapy as well as of the as well as of the potential benefits of controlling disease recurrence. **Clinical Principle**

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**Discussion.** Patient counseling regarding the potential toxicity and quality of life (QoL) impact of radiotherapy is important to ensure that patients make informed treatment decisions and have appropriate expectations regarding the course and consequences of radiotherapy. Counseling should include the fact that the evidence base for toxicity and QoL effects of RT is based mostly on reports using older RT techniques; newer techniques appear to have fewer toxic effects.

**Acute toxicity.** Patients should be informed that during radiotherapy and in the immediate post-RT period of 2-3 mos, mild to moderate genitourinary and gastrointestinal effects that may require the use of medication for management have been frequently reported, with over 90% of patients experiencing these effects in some studies. Serious toxicity effects of radiotherapy, including those requiring aggressive medication management, outpatient procedures, or hospitalization, however, are uncommon or rare, with most studies reporting rates of 5% or less. The lowest acute toxicity rates have been reported with use of IMRT radiotherapy techniques (Alongi 2009; Goenka 2011).

**Late toxicity.** Patients should be informed that, similar to acute toxicities, mild to moderate late toxicities occurring more than 90 days post-RT are commonly reported with some studies reporting rates as high as 79%. Serious late toxicities, however, are relatively uncommon, with most studies reporting rates of 10% or less. Patients also should be told that in a small proportion of patients, late toxicities that are moderate to major may emerge for up to four to five years post-RT and may persist beyond that point. These toxicities are more likely to include GU symptoms (up to 28% of patients; Ost Lumen 2011) than to include GI symptoms (up to 10.2% of patients; Goenka 2011). The use of newer RT techniques such as IMRT, however, is associated with lower cumulative rates of late GU (up to 16.8% of patients) and GI (4.0% of patients) toxicities (Goenka 2011).

**Urinary incontinence.** Patients should be informed that rates and severity of urinary incontinence in patients who have had RP and then adjuvant RT are generally similar to rates for patients who have had RP only. Studies of SRT patients indicate possible mild worsening of UI in small numbers of patients and isolated cases of new onset UI. Overall, the Panel interpreted these data to indicate that RT is unlikely to have a major impact on UI.

**Sexual function.** Patients with intact erectile function post-RP should be informed that the impact of RT on erectile function in men who have already had a prostatectomy is not clear. This uncertainty derives from the fact that few studies have addressed the impact of RT on erectile function in post-RP patients and also from the fact that most men post-RP do not have intact erectile function, making it difficult to determine whether RT results in further loss of function.
Adjuvant RT may reduce the need for salvage therapies. Patients also should be informed that the use of ART, because it is associated with improved biochemical recurrence-free survival compared to RP only, is likely to reduce the need for subsequent salvage therapies. Salvage therapies such as androgen deprivation can have debilitating side effects and also present increased risks for osteoporosis, cardiovascular disease, and other health problems.

Secondary malignancies. Clinicians should advise patients that the potential for developing secondary malignancies exists when postoperative radiotherapy is given, but that studies investigating the risk of developing secondary malignancies in men undergoing prostate cancer radiotherapy are contradictory (Bhojani 2010; Pickles 2002). Furthermore, in clinical trials of adjuvant and salvage radiotherapy no data have been reported on secondary malignancies. Finally, the risk of secondary cancers may be related to co-existing behavioral factors such as the presence of past or current smoking (e.g., van Leeuwen 1995; Koivisto-Korander 2012; Zelefsky 2012). Therefore, the Panel concluded that at this time the risk of developing a secondary malignancy as a result of ART or SRT administration is not known.
Research Needs and Future Directions

**Ongoing Clinical Trials.** Several ongoing clinical trials will help to clarify the magnitude and impact of adjuvant or salvage radiotherapy, the relative value of combining RT with hormonal and other therapies, and potentially make clear which patients are more likely to benefit from specific therapies, therapy combinations, and therapeutic contexts.

- **RTOG 0534** is randomizing post-prostatectomy patients (pT2N0/Nx or pT3N0/Nx) with Gleason scores ≤9, with or without positive margins, and with post-RP PSA of ≥ 0.1 ng/ml to < 2.0 ng/ml to prostate bed radiotherapy, prostate bed radiotherapy plus short-term androgen deprivation (4-6 mos) therapy, or pelvic lymph node RT plus prostate bed RT plus short-term ADT. Patients are stratified by SV status, Gleason score ≤7 or 8-9, pre-RT PSA of ≥0.1 to 1.0 ng/ml or >1.0 to <2.0 ng/ml, and pT2 with negative margins vs. all other patients. The trial includes assessments of biomarkers, quality of life, neurocognitive function, and urinary function. 3D-CRT or IMRT methods are used with 64.8-70.2 Gy administered to the prostate bed and 45 Gy administered to pelvic lymph nodes.

- **RTOG 9601** is examining the effects of radiotherapy with or without long-term androgen deprivation in men post-prostatectomy with pT3N0 disease or pT2N0 disease with a positive margin or positive prostate fossa/anastomosis biopsy with PSA ≥ 0.2 ng/ml to 4 ng/ml. Radiation doses were 64.8 Gy to the prostate bed and anti-androgen therapy consisted of 24 months of bicalutamide (150 mg daily) monotherapy. While not yet published, results reported in abstract form indicate that the addition of 24 months of bicalutamide during and after RT significantly improved freedom from biochemical progression and reduced the incidence of metastatic disease without adding significantly to radiation related toxicity. There were no differences in overall survival with a median followup of 7.1 years (Shipley 2011). Implementation of these preliminary findings into clinical care awaits publication of the full trial results.

- **The RADICALS** trial is a 3,000-subject study taking place in the UK, Canada, Denmark and Republic of Ireland recruiting post-prostatectomy patients who are within 22 weeks of RP with post-RP PSA ≤0.2 ng/ml with one or more of the following characteristics: pT3 or pT4 disease; Gleason score 7-10; preoperative PSA ≥ 10 ng/ml; and/or positive margins. This trial is addressing two critical questions in post-prostatectomy patients. The first question is the comparative efficacy of the ART vs SRT approach. Patients are randomized to either immediate adjuvant RT or to regular PSA testing and salvage RT if PSA becomes detectable. The second, concurrent randomization addresses the question of the role of androgen deprivation therapy. Patients receiving radiation (either ART or SRT) are further randomized to three treatment arms: radiation alone, radiation plus 6 months of hormonal therapy or radiation plus two years of hormonal
therapy. This study will address perhaps the most contentious of issues regarding radiation after surgery: whether salvage radiation when PSA becomes detectable is equivalent to early adjuvant radiation.

- The RAVES trial (TROG 08.03) is a phase III multi-center trial taking place in Australia and New Zealand comparing adjuvant RT with early salvage RT in patients with positive margins or ECE. The primary trial aim is to determine whether surveillance with early salvage RT results in equivalent biochemical control and improved quality of life when compared with adjuvant RT. Secondary outcomes include quality of life, toxicity, anxiety/depression, biochemical recurrence-free survival, overall survival, cancer-specific survival, time to distant failure, time to local failure, time to initiation of ADT, quality adjusted life years, and cost-utility. This trial is actively recruiting.

Improved imaging techniques. A major question among patients who are undergoing treatment for localized, higher-risk prostate cancer is the true extent of disease. For example, patients with high-volume, high-grade disease whose staging studies (generally bone and CT scans) are negative are those who are most likely to exhibit an immediate PSA relapse, demonstrating pre-existing disease beyond the prostate at the time of diagnosis and treatment. Another challenging class of patients is those who have locally-extraprostatic (e.g., positive margins or seminal vesicle invasion) disease or microscopic nodal disease. In both groups of patients, improved imaging techniques would help to better define appropriate therapies or modifications to existing therapies. Knowing the true extent of disease could lead to more rational nerve-sparing at the time of surgery or could lead to the extension of radiation to include nodal groups or replacement of local therapy (radiation or surgery) with systemic therapy for patients with occult distant metastases. In the realm of adjuvant or salvage radiation, better imaging could allow confirmation that residual disease is confined to the pelvis before embarking on therapy. A significant challenge will be the design of clinical trials to confirm the sensitivity and specificity of such imaging techniques as these studies are confounded by the very long natural history of the disease and the fact that in almost all cases, histologic confirmation that scans are true positive or true negative is lacking. Advances in this field are most likely to be achieved by study designs with clinically-practical outcomes.

New PET imaging tracers appear more accurate in the assessment of prostate cancer than conventional $^{18}$F deoxyglucose PET imaging. Further research in $^{11}$C or $^{18}$F Choline or $^{11}$C acetate for assessment of local and regional disease is required to validate their utility in the postoperative setting. Similarly, improved bone metastases imaging with $^{18}$F sodium fluoride will allow clinicians to avoid futile local therapy in men with documented metastatic disease. Improved MRI imaging with dynamic contrast enhancement (DCE) or MR spectroscopy will define sites of local recurrence and improve salvage radiation therapy targeting and the need to
add adjuvant therapies such as androgen deprivation in patients with bulky recurrences not expected to be eradicated with conventional doses of radiation therapy.

**Biomarkers of prognosis.** A significant need in the arena of adjuvant therapies of prostate cancer are biomarkers of prognosis. To illustrate this point simply requires an examination of SWOG 8794, the only clinical trial finding a survival benefit to adjuvant radiation (Thompson 2009). With a median followup of 12.6 years and up to 20 years of followup overall, metastases (the primary outcome) were reported in only 37 of 211 patients in the RP only group and in 20 of 214 patients in the ART group. Although a high-risk population, most men did not develop metastases nor die from their cancer; nonetheless, the number needed to treat with radiation to prevent 1 case of metastatic disease at a median followup of 12.6 years was 12.2.

Ideally, adjuvant or salvage radiation should be given only to the patient who will ultimately develop an adverse outcome (e.g., metastases or death from cancer) and in whom treatment will prevent that outcome. The advantage of patients undergoing prostatectomy is that both blood-based biomarkers as well as tissue biomarkers from the entire prostate are available for analysis. A host of new markers have been identified which may be linked with disease prognosis. It is possible to embed these biomarkers within trials such as RADICALS as secondary objectives to validate their utility in discriminating the patient who is most likely to benefit from adjuvant or salvage therapy.

**Quality of life.** A major challenge with all prostate cancer therapies is the impact of therapy on Quality of Life (QOL) including sexual, urinary, and GI systems. The generally unanswered question in high-risk patients who are candidates for adjuvant or salvage therapy is how QOL is modulated by such therapies and how this compares and balances with the impact of therapy on survival outcomes. A major problem in most prostate cancer clinical trials (and clinical trials in general) is that QOL studies are underresourced and often undervalued with the primary focus on disease control. Clinical trials of salvage or adjuvant therapy should be designed in such a fashion so as to monitor disease and therapy-related QOL outcomes and to have a pre-planned analysis that integrates both survival and QOL outcomes to allow future patients and physicians to weigh the outcomes to reach a treatment decision for an individual patient.

Clinical trials are being conducted to evaluate the postoperative rehabilitation of men undergoing radical prostatectomy. Biofeedback, physical nerve stimulation and pharmaceutical intervention with phosphodiesterase inhibitors may lessen the impact of surgery on urinary and sexual dysfunction. Improved radiation therapy targeting may also lessen the adverse consequences of treatment for men receiving either adjuvant or salvage radiation therapy.
Combination or alternative therapies. For some patients who undergo adjuvant or salvage radiation, such treatment is not sufficient to control the disease. In SWOG 8794, 20 of 214 patients developed metastatic disease despite early adjuvant RT (Thompson 2009). In these men, either alternative systemic therapy or combination therapy may have prevented this outcome. The major questions for these highest-risk men are (a) can early identification of men most likely to exhibit disease progression be accomplished (i.e., with prognostic markers), and (b) what are optimal therapies for these men (e.g., other therapies such as hormone therapies in combination with radiotherapy or alternate therapies that replace radiotherapy)?

Some evidence to suggest that combination/alternative therapy may be beneficial comes from early results of SWOG 9921. This trial randomized high-risk patients post-prostatectomy to two years of adjuvant androgen deprivation therapy with or without chemotherapy (Dorff 2011). In this study, the surgery plus hormonal therapy arm included some patients who had received radiation due to pT3 disease and, with early followup, higher-than-expected disease-free survival results were encountered. Prospective clinical trials are needed to examine prospectively the utility of systemic therapies in combination with radiation and other local therapies for such high risk disease.

Comorbidities. An issue that pervades the management of prostate cancer is how patient comorbidities affect treatment decision-making. Most patients are older and, in many, death due to other causes is far more frequent than death or complications from disease progression. Methods to better predict the chronology of disease relapse and progression as well as life expectancy will enhance the selection of patients most likely to benefit from adjuvant or salvage therapy. Additionally, as radiation does have side effects, the prediction of men more likely to have these complications would help better select patients for treatment. Some comorbidities such as diabetes, hypertension, and vascular disease may increase the risk of radiation-related toxicity. Predictors for such outcomes could be based on functional (e.g., validated measures of erectile, urinary, or GI function) or biologic (e.g., DNA repair mutations) measures.
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