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 to 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 294 articles after the application of inclusion/exclusion criteria. These publications were used to create the guideline statements. If sufficient evidence existed, then 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. 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. (Clinical Principle)

2. Patients with adverse pathologic findings including seminal vesicle invasion, positive surgical margins, and extraprostatic extension should be informed that adjuvant radiotherapy, compared to radical prostatectomy only, reduces the risk of biochemical (PSA) recurrence, local recurrence, and clinical progression of cancer. They should also be informed that the impact of adjuvant radiotherapy 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 did not demonstrate a benefit. However, the other trial was not powered to test the benefit regarding metastases and overall survival. (Clinical Principle)

3. Physicians should offer adjuvant radiotherapy to patients with adverse pathologic findings at prostatectomy including seminal vesicle invasion, positive surgical margins, or extraprostatic extension because of demonstrated reductions in biochemical recurrence, local recurrence, and clinical progression. (Standard; Evidence Strength: Grade A)

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)

5. Clinicians should define biochemical recurrence as a detectable or rising PSA value after surgery that is \( \geq 0.2 \text{ ng/ml} \) with a second confirmatory level \( \geq 0.2 \text{ ng/ml} \). (Recommendation; Evidence Strength: Grade C)

6. A restaging evaluation in the patient with a PSA recurrence may be considered.
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7. Physicians should offer salvage radiotherapy to patients with PSA or local recurrence after radical prostatectomy in whom there is no evidence of distant metastatic disease. (Recommendation; Evidence Strength: Grade C)

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

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 potential benefits of controlling disease recurrence. (Clinical Principle)
INTRODUCTION

This guideline’s purpose is to provide direction to clinicians and patients regarding the use of radiotherapy (RT) 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 discussions among the multidisciplinary team of physicians, the patient, and his family. As the science relevant to the use of RT 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 RT after prostatectomy, including its efficacy in patients with detectable and undetectable prostate 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 294 articles from which to construct a clinical framework for the use of RT 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.1 Case-control studies and comparative observational studies were rated using the Newcastle-Ottawa Quality (NOQ) Assessment Scale.2 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 QUADAS3,4

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.5

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.6 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.5 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 level of certainty) or Grade B (moderate level of 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 RT 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; the lack of group equivalence in terms of pathological risk factors in studies that compared RT administered to patients with and without recurrence; variability in PSA assay sensitivity and in failure criteria across studies and over time; heterogeneity of cumulative radiation dose, dose schedules, methods of administering radiation and treatment planning protocols; the paucity of studies with follow-up duration longer than 60 months; 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 QOL outcomes that are of critical importance to patients, such as voiding and 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 75 peer reviewers, of which 44 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.
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BACKGROUND

In 2012 an estimated 241,740 men were diagnosed with prostate cancer. The most common primary treatment for localized disease is radical prostatectomy (RP). 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. Recurrence after prostatectomy is thought to result from residual subclinical disease in the operative site that later manifests as a rising prostate-specific antigen (PSA) level, a local tumor recurrence, metastatic disease or occult metastatic disease that was present at the time of the prostatectomy. The risk of recurrence is greater among men with adverse pathological features prior to evidence of disease recurrence. 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 RT in the adjuvant and salvage contexts.

Adjuvant radiotherapy (ART) is defined as the administration of RT to post-prostatectomy patients at a higher risk of recurrence because of adverse pathological features prior to evidence of disease recurrence (i.e., with an undetectable PSA). There is no evidence that addresses the timing of the first PSA test post-prostatectomy to determine a patient’s disease status; in the Panel’s clinical experience the first PSA generally should be obtained two to three months post-RP. ART is usually administered within four to six months following RP. Generally, RT is initiated after the return of acceptable urinary control. As sexual function can require one to two years before a full return of function is observed, return of erections is not a requirement before initiation of adjuvant radiation.

Salvage radiotherapy (SRT) is defined as the administration of RT to the prostatic bed and possibly to the surrounding tissues, including lymph nodes, in the patient with a PSA recurrence after surgery but no evidence of distant metastatic disease. Biochemical (PSA) recurrence after surgery is defined as a detectable PSA level ≥ 0.2 ng/mL with a second confirmatory level ≥ 0.2 ng/mL.

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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 RT after prostatectomy is provided by three randomized controlled trials (RCTs) that have examined the effect of RT delivered primarily in an adjuvant context. Findings from the three trials are reviewed below and in Appendices B and C. It is important to note that the three trials were powered for different primary outcomes. The primary outcome for SWOG 8794 was metastases-free survival, defined as time to first evidence of metastatic disease or death due to any cause. The primary outcome for EORTC 22911 was initially local control but changed in March 1995 to clinical progression-free survival. The primary outcome in ARO 96-02 was biochemical progression-free survival. Further, the majority of patients in the RT arms of these three trials were treated with 60 Gy – a dose somewhat lower than currently used.

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 ART in comparison with observation only post-prostatectomy. 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 Appendix A). ARO 96-02 trial is the only trial in which all patients had an undetectable PSA at the time of RT.

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 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 (p < 0.01).26

**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 SRT or ADT) compared to 47.5% of patients in the RP only group -- a statistically significant difference. It should be noted that the use of salvage therapies was at physician discretion and not prescribed by trial protocols.

**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 (defined as evidence of metastases or death from any cause; 71% for ART patients compared to 61% for RP only patients) with the use of ART compared to RP only at more than 12 years of follow-up.26,27 These findings did not replicate in EORTC 22911 at median 10.6 years of follow-up.24

There are several differences between the two trials that may be relevant to the disparate findings. 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 (SWOG 8794 – 8% of RP only 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% to 11% of each group). In SWOG 8794, 68% of the RP only group and 67% of the ART group had EPE or positive margins. EORTC 22911 reported that 78.9% of the RP only group and 75.1% of the ART group had EPE and 63% of the RP only 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 RP only group, 65% of ART group; EORTC 22911 – 68.6% of RP only group, 70.3% of ART group). It is noteworthy that the median age of the SWOG 8794 RP only group was 1.7 years older (65.8 years) than the median age of the ART group (64.1 years). Median overall survival for the RP only group (13.3 years) was 1.9 years less than for the ART group (15.2 years), raising the possibility that the survival difference between the arms might be the result of the older age at enrollment of the RP only group. In the other two trials, there was no age difference between the two groups. 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. An additional possibility has to do with the fact that the number of deaths from prostate cancer in EORTC 22911 was extremely low – making it unlikely that ART would result in a survival advantage. A definitive answer has yet to be identified.

**Subgroup Findings**

The three RCTs also reported outcomes for various patient subgroups (see Appendix C). The Panel is fully aware of the clinical need for evidence-based risk stratification to inform decision-making regarding the use of ART in patients with specific pathological findings. However, after reviewing the subgroup findings from the best evidence available – the three RCTs – the Panel could not come to definitive conclusions. There are inconsistencies across trials in terms of which subgroups were selected for analysis and inconsistencies in the findings across subgroups. In addition, subgroup analyses were not performed for all outcomes. Further, 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 generate hypotheses and guide new research directions – not to test hypotheses. These analyses are summarized below.

**Positive surgical margins.** All three trials reported a statistically significant improvement in biochemical RFS among patients with positive surgical margins who received RT 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 RT (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 RT.

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 RT 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 RT in this subgroup, ARO 96-02 reported no improvement with RT. 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 RT. 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 outcomes among 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.

Extraprostatic extension (EPE). EORTC 22911 and ARO 96-02 reported significantly improved biochemical RFS with use of RT among patients with EPE. EORTC 22911 reported no differences, however, in clinical recurrence-free survival or overall survival. SWOG 8794 did not report on this subgroup.

Absence of EPE. Only EORTC 22911 reported on outcomes among patients without EPE. Similar to patients with EPE, use of RT among patients without EPE 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 patients. SWOG 8794 reported a statistically significant improvement in metastatic RFS with RT, however, among Gleason 7-10 patients.
European Randomized Study of Screening for Prostate Cancer (ERSPC) followed men randomly assigned to a PSA screening group compared to a control group not offered screening. At median 11 years of follow-up the authors reported that 1,055 men would need to be invited for screening and 37 cancers would need to be detected in order to prevent one death from prostate cancer.

With regard to prostatectomy compared to watchful waiting, Bill-Axelson 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 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. 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 Appendix B 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 EORTC 22911 yields an NNT of 9.8. Combining clinical progression data from SWOG 8794 and EORTC 22911 yields an NNT of 13.8.

Given the findings from the RCTs, the nature of adjuvant treatments to inevitably result in overtreatment of 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.

**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 post-RP patients with PSA or local recurrence who received SRT to patients with PSA or local recurrence post-RP who did not receive further therapy. 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).

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 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 progression to 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. The 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 and calculated from data provided in EORTC 22911 and ARO 96-02 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 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.
Radiotherapy techniques and protocols in the post-

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Background

-prostatectomy patient. The Panel’s literature review
attempted to address the question of which RT
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 that have since
been replaced by more sophisticated approaches using
three-dimensional conformal RT (3D-CRT) or intensity-
modulated radiotherapy (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% reporting use of IMRT techniques.
The remaining studies used either a mix of techniques,
without separating patient outcomes based on

When this literature is examined as a whole, it appears
that ART patients generally have better outcomes
compared to SRT patients. For example, ART study
arms generally report lower rates of biochemical
recurrence and metastatic recurrence than do SRT
study arms at similar post-RP follow-up durations. Patterns with regard to cancer-specific survival and
overall survival are less clear because few ART studies
reported these outcomes.

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 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
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. A recent
propensity score-matched, multi-institutional analysis
has attempted to address this issue, reporting no
difference in biochemical recurrence-free survival rates
at 60 months between pT3N0 patients administered RT
adjuvantly compared to those observed and treated
with early SRT (with PSA ≤ 0.5 ng/ml).

In this analysis, however, the follow-up duration for the
observed group was considerably shorter (median 30
months) than the follow-up duration for the ART group
(median 67 months). 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).

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 section below) but not for
efficacy outcomes.

The search yielded 48 ART study arms reporting
outcomes for 4,043 patients. The search
yielded 137 SRT study arms reporting outcomes for
13,549 patients.

When this literature is examined as a whole, it appears
that ART patients generally have better outcomes
compared to SRT patients. For example, ART study
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and the RAVES trial (TROG 08.03; see more detailed
discussion in Research Needs and Future Directions).
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patient’s functional status, history, and tolerance for toxicity. The Panel is aware that there is controversy in the field regarding appropriate RT targets and field size. This issue was beyond the scope of this guideline; however, guidance can be found in Michalski (see http://www.rtog.org/CoreLab/ContouringAtlases/ProstatePostOp.aspx for atlas), Sidhom, Wiltshire and Poortmans.

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 ART or SRT. 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 how long (e.g., weeks vs. months vs. years); primary focus on biochemical recurrence with relatively few reports that focused on local recurrence, metastatic recurrence, cancer-specific survival and overall survival; 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 months of bicalutamide (150 mg qd) 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. 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. Further, the RADICALS trial is addressing the use of ADT and its duration (6 months v. 24 months) in both the ART and SRT contexts. Findings from these trials, once mature, also will help to answer these important questions.

ADT in the adjuvant setting. Only five observational studies compared RP patients who received adjuvant radiotherapy to those who received ART in combination with some form of ADT. 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 reported at median follow-up 60.3 months 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 months. These findings require replication in a randomized trial such as the ongoing RADICALS trial. Ost did not detect a difference in bRFS at seven years (ART only – 86%; ART + ADT – 79%) or clinical RFS (ART only – 90%; ART + ADT – 83%) on univariate analysis but on multivariate analysis the use of ADT resulted in a significant hazard ratio of 0.4 for bRFS and 0.1 for cRFS. However, the two groups exhibited significant imbalances in pathologic risk factors, emphasizing the need for appropriately stratified randomized studies. Additional information is provided by DaPozza which reported that ART+ADT significantly improved bRFS and cancer-specific survival on multivariate analyses (but not univariate analysis) compared to patients who received ART only (all patients in this study had positive nodes); however, there was no ART only comparison group in this study.

ADT in the salvage setting. Twenty-three 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. Seven studies documented statistically significantly better outcomes for SRT+ADT patients compared to SRT only patients. Findings from the study with the largest sample size (1325 SRT patients; 214
Radiotherapy after Prostatectomy

Background

SRT+ADT patients) derived from a multi-institutional retrospective cohort were used 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.

Eight 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. 

In one study, although the overall comparison was not significant, a significant advantage in progression-free survival was observed in high-risk patients (defined as pT3 or higher, Gleason score 8 to 10, or PSA of 20 ng/ml or higher at RP). Eight studies indicated that SRT only patients had better outcomes than did SRT+ADT patients or that the outcomes were indistinguishable. 

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 v. SRT patients; the use of somewhat higher radiation doses in SRT studies; and, the paucity of published studies using newer RT delivery modes such as 3D-CRT and IMRT that might minimize toxicity. In particular, among the three RCTs, only ARO 96-02 used newer RT methods. Toxicity overall, therefore, may be somewhat less than the majority of the published literature reports.

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; authors who reported toxicity data using this measure specified the same time frames. Both measures 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 indicates a major change in function sufficient to require more aggressive medication use or outpatient procedures; 4 indicates severe symptoms requiring hospitalization and surgical procedures; and, 5 indicates death (see Appendix D). A total of 107 study arms reported at least one measure of toxicity; these arms included 13 ART study arms reporting on a total of 1,735 patients, 58 SRT study arms reporting on a total of 5,574 patients and 36 mixed ART-SRT study arms reporting on a total of 4,838 patients.

Acute toxicity. Of the 107 study arms that reported any toxicity information, 38 reported at least one measure of acute GU toxicity (5 ART arms, 13 SRT study arms, and 20 mixed study arms) and 34 reported at least one measure of acute gastrointestinal toxicity (2 ART arms, 13 SRT arms, 19 mixed arms).

The ranges for proportions of patients experiencing Grade 1-2 and Grade 3-4 acute toxicities are presented in Appendix E; no grade 5 toxicities (deaths) 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.

With regard to acute GU effects, two studies compared patients treated with 3D-CRT to patients treated with IMRT. 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). One study compared patients treated with EBRT to patients treated with 3D-CRT. Patients treated with EBRT had higher rates of grade 2 or 3 acute GI toxicity (83%) compared to patients treated with 3D-CRT (61%). Rates of grade 2 or 3 acute GU toxicity were statistically similar (EBRT – 22%; 3D-CRT – 30%). There were no grade 4 events in either group. In contrast, Eldredge reported that patients treated with EBRT or with cone-beam CT-guided 3D-CRT had similar rates of acute Grade 2 GU.
Additional acute GU toxicity information was reported by Bolla\(^\text{164}\) 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\(^\text{99}\) reported that 3D-CRT patients had higher levels of grade 2 or greater toxicities (13.2%) compared to IMRT patients (7.6%). Along\(^\text{174}\) divided toxicities into lower and upper GI and reported that patients treated with 3D-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\(^\text{164}\) 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 107 study arms that reported any toxicity information, 51 reported at least one measure of late genitourinary (GU) toxicity (9 ART arms, 26 SRT study arms, and 16 mixed study arms) and 41 reported at least one measure of late gastrointestinal (GI) toxicity (4 ART arms, 22 SRT arms, 15 mixed arms). It is important to note that commonly, cumulative rates of late toxicities are reported; these rates do not take into account the fact that many of these patients ultimately have resolution of their symptoms.

The ranges for proportions of patients experiencing Grade 1-2 and Grade 3-4 late toxicities are presented in Appendix F; no grade 5 toxicities (deaths) 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 GI toxicity in ART study arms for which only 4 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\(^\text{129}\) noted that the probability of late grade 2-3 GU toxicity rose from 12% at 24 months post-SRT to 22% at 60 months post-SRT. Pearse\(^\text{192}\) reported a similar pattern with 13% of patients manifesting grade 2 or higher GU toxicity at 12 months post-SRT, rising to 28% at 48 months post-SRT, and remaining at 28% at 60 months post-SRT. Feng\(^\text{185}\) reported in a mixed group of patients that grade 2 or higher toxicities occurred in 4% of patients at 12 months post-RT rising to 12% at 60 months post-RT. Goenka\(^\text{99}\) reported on patients who were administered 3D-CRT or IMRT and noted that the probability of late grade 2 or higher toxicities for IMRT patients ranged from 5% at 24 months post-SRT to 25% at 96 months post-SRT. For IMRT, 9% of patients exhibited grade 2 or higher toxicities at 24 months post-SRT with the proportion rising to 16.8% at 60 months post-SRT and remaining at 16.8% through 120 months of post-SRT follow-up. Iyengar\(^\text{188}\) reported at median five years follow-up that statistically similar proportions of EBRT (19%) and 3D-CRT (16%) patients had grade 2 or higher late GU toxicities. The most common symptoms were urinary frequency (14.6%) and bleeding (8.6%). Incontinence as the only late GU symptom was almost twice as common among patients treated with EBRT (7.5%) compared to patients treated with 3D-CRT (4%).

Cozzarini\(^\text{182}\) assessed toxicity rates in an ART cohort (n=556) compared to an SRT cohort (n = 186) at median 8 years of follow-up post-RT (either EBRT or 3D-CRT). These authors reported statistically indistinguishable probabilities of late Grade 3 GU effects of 12.2% among ART patients and 10% among SRT patients. The ART and SRT groups had similar rates of urethral stricture requiring dilation (ART - 5%; SRT - 3%), of grade 3 bleeding (ART – 2%; SRT – 1%), and of severe incontinence (ART – 7%; SRT – 6%). Each group had only one case of Grade 4 toxicity (necessitating radical cystectomy in both cases).

Late GI toxic effects are less common. Ost Lumen\(^\text{129}\) also reported that the probability of late grade 2-3 GI toxicity rose from 3% at 24 months post-SRT to 8% at 48 months post RT and remaining at 8% at 60 months post-SRT. Pearse\(^\text{192}\) reported a similar pattern with 3% of patients manifesting grade 2 or higher GU toxicity at 12 months post-SRT, rising to 7% at 36 months post-SRT, and remaining at 7% at 60 months post-SRT. Feng\(^\text{185}\) reported in a mixed group of patients that grade 2 or higher toxicities occurred in 2% of patients at 12 months post-RT rising to 4% at 60 months post-RT. Goenka\(^\text{99}\) 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 months post-SRT to 10.2% at 96 months post-SRT. For IMRT, 1% of patients exhibited grade 2 or higher toxicities at 24 months post-SRT with the proportion rising to 4.0% at 72 months post-SRT and remaining at 4.0% through 120 months of post-SRT follow-up. Iyengar reported at median five years follow-up that statistically similar proportions of EBRT (13.7%) and 3D-CRT (14%) patients had grade 2 or higher late GI toxicities. The most common symptoms were rectal bleeding (12%) and frequency (4.3%). Rectal bleeding as the only late GI symptom, however, was twice as likely among 3D-CRT-treated patients (17%) compared to EBRT-treated patients (8.2%).

In addition, both Cozzarini and Tramacere reported that the presence of acute toxicity was a significant predictor of late toxicities.

Additional late toxicity information is provided by Thompson, one of the three RCTs (SWOG 8794). At median 127 months 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%). Moiopoulos 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 months – 27.5%; 24 months – 23%; 36 months – 26%; 48 months – 28%) but decreased for RP only patients (12 months – 14%; 24 months – 12%; 36 months – 13%; 48 months – 15%). By 60 months 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 months of follow up (six months post-RT/RP: RT – 18%; RP only – 5%; 60 months 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. One study provided pre-RT information (25 of 69 patients with UI) and reported at median 50.4 months follow-up that one additional patient had developed UI. 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%). Two reports focused on patients from the RCTs (EORTC 22911; SWOG 8794). Van Cangh 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 months post RP/RT (ART – 8.3%; RP only 2%). Thompson reported a non-significant difference in total UI between ART patients (6.5%) and RP only patients (2.8%) at median 127 months follow up.

Seven SRT studies that included pre-RT baseline information and/or a comparison group reported information regarding UI. 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, two SRT studies, and one mixed study 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 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 two months 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 an significant decrease in function and bother scores (indicating worse QOL) that did not recover to pre-RT levels until one 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 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 months post-RT. In a group of 78 mixed patients treated with IMRT, Corbin reported after administering the EPIC-26 and the International Prostate Symptom Index (IPSS) at 2-, 6-, 12-, 18-, and 24-month intervals post-RT that there were no declines in urinary continence or gastrointestinal quality of life outcomes.

One ART study reported overall quality of life data. Moiopoulos (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 QOL. These proportions increased over time for the ART group, with 69% of patients reporting a normal quality of life at 60 months post-RT. In contrast, for the RP only patients, the proportions remained the same, with 51% reporting a normal quality of life.
quality of life at 60 months post-RP. For up to 36 months post-RT, ART patients had higher symptom distress scores than did RP only patients, but by 48 and 60 months 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. SRT patient scores on the RAND physical component summary and mental component summary did not change from pre-RT to 12-18 months 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. 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 months), 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 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. 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-RT 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 two years, making it unclear whether erectile function had fully recovered post-RP; patients were followed for less than two 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-RT/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-RT data reported that 74 of 110 patients (73%) were fully potent post-RP, 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 months), of the 21 patients who were potent or partially potent post-RP, 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.

**Mixed studies.** One mixed study reported poor erectile function in 62% of men post-RP but pre-RT and in 66% of men 24 months post-RT. There were no differences over time in the proportions of men reporting problems with erectile strength or with sexual performance or reporting difficulty with orgasm.

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 RT post-prostatectomy are contradictory as pointed out by Guedea. Specifically, Bhojani estimated that the hazard ratio of developing a rectal tumour at 120 months was 2.2 in patients treated with RT 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 secondary cancer rates, regardless of whether treatment included RT. 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 secondary cancers than the general population. Finally, the risk of secondary cancers also may be related to co-existing factors such as the presence of past or current smoking. 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 STATEMENTS

Guideline Statement 1.

Patients who are being considered for management of localized prostate cancer with RP 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. *(Clinical Principle)*

**Discussion:** Patients should be counseled before RP 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 extraprostatic extension (EPE). Rates of recurrence in post-RP patients with adverse pathological features may be greater than 60% at five years post-RP in case series. 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.

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). 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 Appendices G and H).

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

Guideline Statement 2.

Patients with adverse pathologic findings including seminal vesicle invasion, positive surgical margins, and extraprostatic extension should be informed that adjuvant radiotherapy, compared to RP only, reduces the risk of biochemical (PSA) recurrence, local recurrence, and clinical progression of cancer. They should also be informed that the impact of adjuvant radiotherapy 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 did not demonstrate a benefit. However, the other trial was not powered to test the benefit regarding metastases and overall survival. *(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 because of demonstrated reductions in biochemical recurrence, local recurrence and clinical progression. *(Standard; Evidence Strength: Grade A)*

**Discussion:** 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. By “offered,” the Panel means that the patient, his family and the multi-disciplinary treatment team should engage in a shared decision-making process in which the patient is advised to consider the possibility of additional treatment (i.e., RT). 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 RT.

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 for detailed discussion of RCT findings, see Adjuvant Radiotherapy (ART) section in 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 Appendix A). The Panel notes that prevention of biochemical progression is an important clinical endpoint because biochemical progression may trigger
Clinical success of salvage therapies, (i.e., ADT), 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.

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 (locoregional failure in 8.4% of ART patients compared to 17.3% of RP only patients) and similar in magnitude in SWOG 8794 (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 improved 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. 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). 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. 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.

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 RP 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. were among the first to describe the time course of disease progression. They followed 1997 consecutive men undergoing RP 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 eight 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 two 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 10 to 15 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. 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 scores and their pretreatment PSA levels.

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 ≥ 0.2 ng/ml with a second confirmatory level ≥ 0.2 ng/ml. *(Recommendation; Evidence Strength: Grade C)*

**Discussion:** The vast majority of the published literature assessing the efficacy of RP uses a PSA threshold value of 0.2 ng/mL to define recurrence although some authors have advocated for the use of higher values. 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. This definition also is consistent with the Prostate-Specific Antigen Best Practice Statement: 2009 Update of the AUA (http://www.auanet.org/education/best-practice-statements.cfm). 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 RT and other types of therapy, and is sufficient to trigger the administration of salvage therapies. The Panel further notes that there is no evidence to suggest a threshold above which RT is ineffective.

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. In addition, even more sensitive assays may add further clarity as to whether patients are at increased risk for clinical failure. 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 RT is offered. The salvage literature also generally reports that patients who receive RT at lower PSA levels have better outcomes than do patients who receive RT at higher PSA levels (see Discussion under Guideline Statement 8). However, a small percentage of patients (8.8% of patients with biochemical recurrence) 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. 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. In addition, calculation of PSA doubling time (PSADT) using data derived from ultra-sensitive assays may yield markedly different PSADT...
values compared to using data derived from higher-threshold assays, how these differences should be interpreted is unclear. 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 is the optimal strategy currently. The Panel notes, however, that the decision to initiate salvage therapies is best made by the clinician who has full knowledge of a specific patient’s pathology findings, risk factors, family history, preferences and values in consultation with that patient and with full discussion of the potential benefits and risks of treatment. In the era of ultrasensitive PSA assays, a detectable PSA that is confirmed and rising may be an appropriate trigger for salvage therapy, particularly in patients who are at high risk for recurrence and/or who have other evidence of potential progression.

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; Evidence Strength: Grade C)

Discussion: In the patient with evidence of recurrence manifested as a detectable or rising PSA, determining the site of recurrence (local v. 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. Clinicians should be aware that the yield of some modalities (e.g., bone scan) is extremely low in patients with PSA values below 10 ng/mL (see literature review below).

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-three studies comprised of 53 study arms reported on the diagnostic performance of 19 modalities for local recurrence detection. The modalities evaluated included digital rectal exam (DRE), transrectal ultrasound (TRUS), color Doppler TRUS, color power Doppler TRUS, contrast-enhanced (CE) color power Doppler TRUS, body coil MRI, endorectal coil MRI without contrast, endorectal coil MRI with contrast, 11C-acetate PET/CT, 11C-choline PET/CT, 18FDG PET, 18FCH PET/CT, 18FDG PET/CT, dynamic contrast-enhanced (DCE) MRI, diffusion-weighted MRI with contrast, 1H-MRSI, 1H-MRSI with DCE MRI, CT with contrast, and Prostascint and Prostascint fused with MRI or CT. 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, 1H-MRSI, and 1H-MRSI with DCE MRI yielded the highest and most consistent sensitivities and specificities for the detection of local recurrence. Sensitivities were all above 70% (except for Rischke in which sensitivity was 67%); endorectal coil MRI with contrast and 1H-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%. Specificities for 1H-MRSI were above 80% and those for DCE-MRI were above 85%. Two published systematic reviews on this topic come to similar conclusions.

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%. DRE, color power Doppler TRUS, and 11C-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 45.5 to 69.7% for 11C-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 11C-choline PET/CT and 18FDG PET/CT to detect recurrence in lymph nodes. The sensitivity of 11C-choline PET/CT was 100% across

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studies; three studies reported data per patient and one study reported data per node.\textsuperscript{268} Scattoni\textsuperscript{266} also reported data per node with a sensitivity of 64\%. The single 18FDG PET/CT study reported a sensitivity of 75\%. In contrast to high sensitivity values, specificities were more variable; values for 11C-choline PET/CT ranged from 0 to 100\% and the single 18FDG PET/CT study reported a value of 100\%.

Two additional studies reported on the use of MRI with lymhotropic superparamagnetic nanoparticles (LSN). One study was conducted in patients who had not yet undergone prostatectomy and reported values for sensitivity and specificity above 90\%.\textsuperscript{270} Two studies used this modality in post-RP patients with biochemical failure.\textsuperscript{271-2} In Ross\textsuperscript{271} insufficient patients were biopsied; diagnostic performance could not be calculated. None of the patients in Meijer\textsuperscript{272} were biopsied, but findings correlated well with Stephenson nomogram predictions regarding which patients would benefit from SRT. Fortuin\textsuperscript{272} reported in 29 patients that more lymph nodes were detected by MR lymphography (738 nodes) than by 11C-choline PET/CT (132 nodes) and more suspicious nodes were detected by MR lymphography (151 of 738 nodes) than by PET/CT (34 of 132 nodes). However, this study also lacked a reference standard, making it unclear how many of the suspicious nodes constituted true metastases. The Panel notes that the MR lymphography data are promising but there is a need for more methodologically rigorous studies.

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

Recurrence in bone. Five studies comprised of eleven study arms reported on the use of bone scan with or without SPECT,\textsuperscript{274-5} 11C-choline PET/CT,\textsuperscript{276-8} 18F-fluoride PET,\textsuperscript{274} 18F-fluoride PET/CT,\textsuperscript{274} DWE MRI with contrast,\textsuperscript{278} conventional MRI-STIR,\textsuperscript{276} and conventional MRI –T1 weighted.\textsuperscript{278} 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, 18F fluorde PET, 18F fluorde 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, 11C-choline PET/CT, 18F-fluoride PET and 18F-fluoride PET/CT). Additional information is provided by Fuccio\textsuperscript{277} who used 11C-choline PET/CT to evaluate 123 post-RP patients with rising PSA, all of whom had a negative bone scan; 11C-choline PET/CT detected bone lesions not apparent on bone scan in 18 patients.

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.\textsuperscript{279-283} For example, at PSA levels less than 10 ng/ml, less than 5\% of patients had a positive bone scan.\textsuperscript{281} For PSADT greater than six months, the probability of a positive bone scan was 3\%.\textsuperscript{283} The yield of bone scans, given that most patients manifest biochemical failure at PSA values <1.0 ng/ml, will be low.

Metastatic recurrence. Seven studies provided information regarding the detection of metastases outside of the prostate bed. Three studies reported on the use of ProstaScint,\textsuperscript{126, 258, 284} One study each focused on 11C-choline PET/CT,\textsuperscript{246} 18FDG PET,\textsuperscript{250} 18F-FDG PET/CT,\textsuperscript{285} 18F-NaF PET/CT,\textsuperscript{285} and 18FCH PET/CT.\textsuperscript{252} Sensitivities for ProstaScint ranged from 30\% to 100\%. The other scanning modalities had sensitivities above 95\% except for the 18F-FDG PET/CT and 18F-NaF PET/CT study that focused on patients who had already had negative conventional imaging.\textsuperscript{285} In this study, 18F-NaF PET/CT detected metastatic lesions in six of 26 post-RP patients not identified on conventional imaging. 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 11C-choline PET/CT, 18FDG PET and 18FCH PET/CT are promising.

Recurrence at all sites. Twenty-two studies provided diagnostic performance information regarding the detection of disease recurrence anywhere in the body using seven different imaging techniques.\textsuperscript{250, 252, 284, 286, 304} 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 11C-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\%;\textsuperscript{291, 293} the lower specificity values occurred in studies from the same institution in which a single reference standard (biopsy) was used.\textsuperscript{295-6} Mitchell\textsuperscript{304} summarized the recent Mayo Clinic experience with 11C-choline PET/CT in 176 patients who had biochemical
recurrence (most patients had RP as primary treatment) and concluded that 11C-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 systemic therapies. Given the body of data on 11C-choline PET/CT, this imaging strategy appears promising.

The probability of a positive scan, however, may depend on PSA level and PSA dynamics. Using 11C-choline PET/CT, several authors reported that the proportion of positive scans increased as PSA level increased,29, 291, 305 as PSA velocities increased,291, 306-7 and as PSADTs decreased.306-7 Using 18F-fluorocholine PET/CT, Kwee387 reported that the percentages of positive scans also increased with higher PSA levels; ROC analysis indicated that the ideal cut-off for scanning was a PSA level of 1.1 ng/ml.

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 distant metastatic disease. (Recommendation; Evidence Strength: Grade C)

Discussion: 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.25 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).44

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. Boorjian31 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. Trock32 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 months 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 months, SRT significantly increased survival regardless of PSA level at time of RT. SRT also significantly improved survival among men with PSA that became undetectable in response to RT but not in men whose PSA remained detectable. Overall, in men with PSADT <6 months, 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 months, 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 months.

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 EPE compared to lower risk subgroups.59, 63, 67, 78, 82, 84, 90-2, 94, 97, 103, 107-109, 111, 113-5, 119, 124-7, 129, 133-6, 138, 142-3, 146, 149-150, 153, 158, 162-3

The panel notes that many considerations are important in the decision to administer SRT. As PSA recurrence may be noted years after RP, patients with limited life expectancy and a low or slowly-increasing PSA may have limited benefit from SRT. Other considerations may include sexual, gastrointestinal or urinary function at the time of biochemical recurrence.

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-seven observational studies compared biochemical recurrence-free survival rates for salvage radiotherapy patients at lower v. higher pre-RT PSA levels. Reports from the American Urological Association Education and Research, Inc.®

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 potential benefits of controlling disease recurrence. (Clinical Principle)

Discussion. Patient counseling regarding the potential toxicity and QOL impact of RT is important to ensure that patients make informed treatment decisions and have appropriate expectations regarding the course and consequences of RT. 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 RT and in the immediate post-RT period of two to three months, 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 RT, 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 RT techniques.

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) than to include GI symptoms (up to 10.2% of patients). 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.

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 RT is given, but that studies investigating the risk of developing secondary malignancies in men undergoing prostate cancer RT are contradictory.\(^{209-10}\) 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.\(^{212-14}\) 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.
Patients receiving radiation (either ART or SRT) are often asked about the role of androgen deprivation therapy. 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 RT, prostate bed RT plus short-term androgen deprivation therapy (four to six months) plus pelvic lymph node RT, or pelvic lymph node RT alone, radiation plus six 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 multicenter trial taking place in Australia and New Zealand comparing adjuvant RT with early salvage RT in patients with positive margins or EPE. 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, 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 18F deoxyglucose PET imaging. Further research in 11C-or 18F-choline or 11C-acetate for assessment of local and regional disease is required to validate their utility in...
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the postoperative setting. Similarly, improved bone metastases imaging with 18F-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.26 With a median follow-up of 12.6 years and up to 20 years of follow-up 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 one case of metastatic disease at a median follow-up 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 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 RP. 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 systemic 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.26 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 RT or alternate therapies that replace RT)?

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.309 In this study, the surgery plus hormonal therapy arm included some patients who had received radiation due to pT3 disease and, with early follow-up, 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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CONFLICT OF INTEREST DISCLOSURES

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