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American Society for Radiation Oncology (ASTRO)/American Urological Association (AUA)

Adjuvant and Salvage Radiotherapy after Prostatectomy: ASTRO/AUA Guideline

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Note to the Reader:

This document was amended in October 2018 to reflect new Level 1 literature that was released since the original publication of the guideline in April 2013 related to the use of hormone therapy with salvage radiation therapy. In addition, new long-term data from the ARO 96-02 trial of adjuvant radiotherapy was incorporated to update the existing evidence base. The role of genomic classifiers on post-prostatectomy treatment assignment and its potential for predicting therapeutic outcomes is also discussed in this amended guideline.

Purpose: The purpose of this guideline is to provide direction to clinicians and patients regarding the use of radiotherapy after radical prostatectomy in the adjuvant or salvage setting. The strategies and approaches recommended in the guideline were derived from evidence-based and consensus-based processes. This document constitutes a clinical strategy; therefore, the most effective treatment approach for a particular patient is best determined by the patient, his family, and a multi-disciplinary team of providers using the shared decision-making model. This guideline amendment incorporates newly-published literature into the original ASTRO/AUA Adjuvant and Salvage Radiotherapy after Prostatectomy Guideline and to provide an updated clinical framework for clinicians.

Methodology: 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. In April 2018, the guideline underwent its first amendment, which incorporated evidence from three randomized controlled trials into the evidence base. A new evidence-based statement was also developed to discuss the use of hormone therapy in the salvage radiotherapy setting.

Guideline Statements

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

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 radical prostatectomy only, reduces the risk of biochemical 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 three randomized controlled trials that addressed these outcomes indicated a benefit but the other two trials did not demonstrate a benefit. However, these two trials were not designed to identify a significant reduction in metastasis or death with adjuvant radiotherapy. (Clinical Principle)

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)

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)

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)

Guideline Statement 6. A restaging evaluation in the patient with a PSA recurrence may be considered. (Option; Evidence Strength: Grade C)

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)

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)

Guideline Statement 9. Clinicians should offer hormone therapy to patients treated with salvage radiotherapy (postoperative PSA ≥0.20 ng/mL) Ongoing research may someday allow personalized selection of hormone or other therapies within patient subsets. (Standard; Evidence Strength: Grade A)

Guideline Statement 10. 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 radical prostatectomy (RP) 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 RP 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 RP, including its efficacy in patients with detectable and undetectable prostatic specific antigen (PSA) levels, its toxicity and quality of life (QoL) impact and optimal imaging strategies to determine the appropriateness of RT use in patients suspected of recurrence. Literature searches were performed on English-language publications using the PubMed, Embase and Cochrane databases from 1/1/1990 to 12/15/2012. 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 was assessed using the Cochrane Risk of Bias tool.[1] Case-control studies and comparative observational studies were rated using the Newcastle-Ottawa Quality 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 Quality Assessment Tool for Diagnostic Studies.[3, 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 American Urological Association (AUA) categorizes body of evidence strength 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 RP literature. A major limitation of this literature is the lack of a large number of RCTs to guide decision-making in patients with and without evidence of recurrence. Further, a major limitation of all RCTs in localized prostate cancer with long-term follow-up is the change in characteristics of contemporary patients; because of increased prostate cancer screening via 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 (CSS) and overall survival (OS). 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 AUA and the American Society for Radiation Oncology (ASTRO). The AUA Practice Guidelines Committee and the ASTRO Guidelines Committee 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 original version of 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 Practice Guidelines Committee and the ASTRO Guidelines Committee. 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.

Guideline Amendment. In October 2018, the guideline was amended to maintain currency through a process in which newly published high quality literature was identified, reviewed, and integrated into the original 2013 guideline. The original search strategy, with two differences, was re-implemented by an experienced medical librarian. It was limited to publication dates from September 2012 to December 2017, and it added the MeSH heading "Radiotherapy, Adjuvant" that

Table 1: AUA Nomenclature
Standard: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/ burdens outweigh benefits) be taken based on Grade A (high quality; high certainty) or B (moderate quality; moderate certainty) evidence.
Recommendation: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade C (low quality; low certainty) evidence.
Option: Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/ burdens appears equal or appears uncertain based on Grade A (high quality; high certainty), B (moderate quality; moderate certainty), or C (low quality; low certainty) evidence.
Clinical Principle: 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: 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.

was deliberately excluded from the search strategy used during the production of the original guideline. The Panel had also added two new key questions to explore during this timeframe search. The new key questions concerned (a) the use of genomic classifiers to predict treatment outcomes in the radiation after prostatectomy setting, and (b) the treatment of oligo-metastases with radiation post-prostatectomy. A new search strategy was developed to identify literature relevant to the two new key questions. This search was conducted from January 1990 to December 2017 to ensure uniformity with the search period used to explore the questions from the original guideline. These searches yielded a total of 2,516 references of which 2,361 were excluded after de-duplication and title and abstract review. Full texts were retrieved for 155 references for more detailed review. Using methodological criteria employed in the original guideline and the best evidence approach, synthesis of new, relevant evidence was focused on the recent publication of three randomized controlled trials with 60 or more months of follow-up. Two of these trials formed the crux of this amended guideline by providing evidence on the use of hormone therapy among men who received salvage radiotherapy (SRT) after primary RP, a patient population who until now, have lacked Level 1 evidence-based recommendations. In addition, long-term data from the ARO 96-02 trial comparing adjuvant radiotherapy (ART) to wait-and-see was incorporated to update Guideline Statement 2. No relevant studies were found to directly address the two new key questions concerning the predictive ability of genomic classifiers and treatment of oligo-metastases in the radiation after prostatectomy setting.

Background

In 2018, an estimated 174,650 men were diagnosed with prostate cancer.[7] The most common primary treatment for localized disease is RP.[8] 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.[9-12] Recurrence after prostatectomy is thought to result from residual subclinical disease in the operative site that later manifests as a rising 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 pathology, such as positive surgical margins, seminal vesicle invasion (SVI), extraprostatic extension (EPE) and higher Gleason scores.[13-22]

Clinicians, therefore, frequently face two scenarios in the patient for whom RP 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 ART should be considered to prevent possible future recurrence. In the post -RP 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.

Definitions

ART is defined as the administration of RT to post-RP 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 examines the timing of the first PSA test post-RP 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.

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 recurrence after surgery is defined as a detectable PSA level $\geq$ 0.2 ng/mL with a second confirmatory level $\geq$ 0.2 ng/mL.

The most commonly-reported post-prostatectomy outcome in the peer-reviewed literature is biochemical recurrence and biochemical recurrence-free survival (bRFS). Other reported outcomes include local recurrence and local recurrence-free survival (RFS), metastatic recurrence and metastatic recurrence-free survival (mRFS), clinical progression-free survival (cPFS): defined as no evidence of local or metastatic progression, excluding evidence of biochemical recurrence), CSS and OS. 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.

FINDINGS

ART. The highest-quality evidence that addresses the use of RT after RP is provided by three RCTs that have examined the effect of RT delivered primarily in an adjuvant context. Findings from the three trials are reviewed below. It is important to note that the three trials were powered for different primary outcomes. The primary outcome for Southwest Oncology Group (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 European Organisation for Research and Treatment of Cancer (EORTC) 22911 was initially local control, but changed in March 1995 to cPFS. 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 Gray (Gy), a dose somewhat lower than currently used.

Biochemical recurrence. Three RCTs (SWOG 8794, EORTC 22911 and ARO 96-02), all with more than 10 years of follow-up, documented significant improvements in bRFS among patients with adverse pathological features (i.e., SVI, positive surgical margins and/or EPE) with the use of ART in comparison with observation only post-prostatectomy.[23-27] A meta-analysis of biochemical recurrence data performed as part of the literature review yielded a pooled hazard ratio of 0.47 (95% CI=0.40 – 0.56; p<0.001; random effects model; see Appendix A). ARO 96-02 is the only trial in which all participants were required to have undetectable PSA (<0.5 ng/ml) to be included in the study; based on the detection limit of the assay used in the trial, all participants in ARO 96-02 were reported to achieve a PSA of <0.1 ng/ml prior to commencing the ART or the wait-and-see protocol.

Locoregional recurrence. SWOG 8794 and EORTC 22911 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[25] 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).[24]

Hormone-therapy free survival. SWOG 8794 also reported a statistically significant improvement in hormone therapy-free survival in ART patients compared to RP-only patients with approximately 84% of ART patients remaining hormone-therapy free compared to approximately 66% of RP only patients at 10 years. EORTC 22911 reported that by year 10, 21.8% of patients in the ART group had started an active salvage treatment (including SRT or hormone therapy) 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 cPFS (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 OS. Only SWOG 8794 demonstrated significantly improved OS (74% in ART patients compared to 66% for RP only patients) and significantly improved mRFS (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.[24, 28] These findings did not replicate in EORTC 22911 at median 10.6 years of follow-up.[25]

There are several differences between the two trials that may be relevant to the disparate findings. The OS 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 hormone 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 OS 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 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 for table of subgroup findings). 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 bRFS 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 recurrence-free survival (cRFS) among patients who received RT (this outcome was not addressed by ARO 96-02). Only EORTC 22911 reported OS data for this subgroup; there were no differences in OS 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 cRFS rates and significantly decreased OS (HR=1.68; 95% CI=1.10-2.56). Although EORTC 22911 reported a significant improvement in bRFS with RT in this subgroup, ARO 96-02 reported no improvement with RT. SWOG 8794 did not address outcomes among patients with negative margins.

SVI. In patients with SVI, SWOG 8794 and EORTC 22911 reported significantly improved bRFS with RT. However, RT did not improve cRFS in either trial, mRFS in SWOG 8794 or OS in EORTC 22911. Further, ARO 96-02 reported no difference in bRFS with RT among patients with SVI.

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

EPE. EORTC 22911 and ARO 96-02 reported significantly improved bRFS with use of RT among patients with EPE. EORTC 22911 reported no differences, however, in cRFS or OS. 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 cRFS or OS.

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

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

Patient age. EORTC 22911 reported on outcomes for patients younger than age 65 years, age 65 to 69 years and age 70 years and older. In patients younger than age 65 years, the use of RT resulted in significant improvements in bRFS and cRFS. Among patients aged 65 to 69 years, the use of RT resulted in significant improvements in bRFS but not cRFS. Among patients aged 70 years and older, the use of RT did not improve bRFS or cRFS and, in fact, appeared to worsen OS (HR=2.94; 95% CI=1.75-4.93, $p<0.05$). Whether worsened OS was the result of an unrecognized detrimental effect of RT in elderly men is not clear.

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

Interpretation

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

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

The number needed to treat (NNT) is a helpful statistic to put these issues in context; the lower the NNT, the more effective the treatment or intervention in preventing the designated outcome. For example, the European Randomized Study of Screening for Prostate Cancer followed men randomly assigned to a PSA screening group compared to a control group not offered screening.[29] 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[30] reported that at 15 years post-RP, the NNT for OS 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[31] 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 OS, 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.[24] ** 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%).

**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[24] and calculated from data provided in EORTC 22911[25] and ARO 96-02[26,27] 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[24] 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.

These data yield a negative NNT, indicating a lack of benefit for the active treatment. With regard to CSS, for which EORTC 22911 also did not document a treatment benefit, the NNT calculated from the raw data provided in Appendix B[25] 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, EORTC 22911 and ARO 96-02 is 4.4. 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 over-treatment 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.

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.[32, 33] Generally, these studies indicate that SRT improves outcomes compared to RP-only patients but the benefits may be specific to certain risk groups (see Discussion under Guideline Statement 7). In addition, two of the three RCTs (SWOG 8794 and EORTC 22911) enrolled patients with detectable PSA levels post-RP salvage patients by definition. These two trials also generally revealed better outcomes among SRT patients compared to RP-only patients with evidence of PSA recurrence (see Discussion under Guideline Statement 7).

ART vs. SRT. One of the most pressing clinical questions regarding the care of the post-RP patient is whether it is better to administer RT before evidence of recurrence (i.e. 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 QoL 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 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.[18, 32, 34-75] The search yielded 137 SRT study arms reporting outcomes for 13,549 patients.[18, 32, 33, 37-40, 44-47, 51, 52, 54, 56-62, 64, 66, 68-70, 73-164]

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 CSS and OS 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., external beam radiation therapy [EBRT] protocols), making it unclear whether newer techniques might result in fewer apparent differences between ART and SRT outcomes.

Given these issues, the Panel concluded that it is not possible from the available evidence to address the question of the superiority of ART vs. SRT. A recent propensity score-matched, multi-institutional analysis has attempted to address this issue, reporting no difference in bRFS 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).[37] 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, the Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) trial (MRC PR10, NCIC PR13) is actively accruing patients to address this important question. The Radiotherapy - Adjuvant Versus Early Salvage (RAVES) trial (TROG 08.03) closed prematurely because the rate of participant accrual diminished over time; see more detailed discussion in Research Needs and Future Directions.

Radiotherapy techniques and protocols in the post-prostatectomy patient. The Panel's literature review attempted to address the question of which 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 technique or did not report enough information to determine the type of RT used. The lack of studies using newer RT methods made it difficult to definitively address the question of optimal methods in general and whether these might differ in the adjuvant v. salvage contexts.

With regard to the randomized controlled trials of ART, the men treated in SWOG 8794 and EORTC 22911 were administered RT using EBRT techniques;[23, 165] patients in ARO 96-02 were administered 3D-CRT.[26] Although there were no clear differences in toxicity among the RT arms of the three RCTs, a broader literature suggests that patients treated with 3D-CRT and IMRT would be expected to experience less treatment-related toxicity and better biochemical and local control compared to men irradiated with traditional techniques.[55, 166]

Among the observational studies, the RT dosages varied from 50 to 78 Gy with most studies administering doses in the 60 to 70 Gy range and with SRT studies administering somewhat higher radiation dosages than ART studies (median ART dose: 61 Gy; median SRT dose: 65 Gy). Although

RT dose-escalation has been shown in multiple randomized trials to improve freedom from biochemical relapse when used as primary treatment for localized prostate cancer, the optimal post-prostatectomy radiation dose is less clear and has never been tested in a prospective fashion. However, the clinical data suggest that doses above 65 Gy can be safely delivered and may lead to improved tumor control as determined by a reduction in biochemical progression.[43, 108, 141, 167] In the three RCTs, the majority of patients were treated with radiation doses of 60 Gy, which was lower than the dose used in most observational studies.

In the Panel's view, 64-65 Gy is the minimum dose that should be delivered in the post-RP setting but decisions regarding dose should always be made by the treating physician who has full knowledge of a particular 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,[168] Sidhom,[169] Wiltshire[170] and Poortmans.[171]

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 hormone therapy in conjunction with RT in the post-RP patient. One of the questions faced by the clinician and post-RP patient is whether, when, for how long and in what form hormone therapy should be administered. The original systematic review attempted to address these questions by retrieving literature that focused on the use of hormone therapy in patients who underwent prostatectomy and then ART or SRT. The Panel's conclusion after reviewing the available evidence (see brief review below) in 2013 was that, given the methodological weaknesses of this literature, it was not possible to provide guidance regarding the use of hormone therapy in conjunction with ART or SRT. 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+hormone therapy groups; lack of equivalence of RT and RT+hormone therapy groups on pathological risk factors; large differences in hormone therapy protocols, including when it was administered (e.g., pre-RP, pre-RT, during RT, post-RT) and for how long (e.g., weeks vs. months vs. years); primary focus on biochemical recurrence with relatively few reports that focused on local recurrence, metastatic recurrence, CSS and OS; and, other differences across studies that may be relevant to efficacy such as differences in RT techniques, targets, and total dose administered.

When the original guideline was published, the Radiation Therapy Oncology Group (RTOG) 9601 trial of SRT with or without 24 months of bicalutamide (150 mg daily) had been presented in abstract form only. At median follow-up of 7.1 years, patients who received SRT with bicalutamide had significantly improved freedom from biochemical progression and significantly fewer metastases.[172] The Panel viewed these findings as promising, but awaited full publication to provide more detailed guidance regarding bicalutamide use with SRT. During the writing of this amendment, 13-year follow-up data from the trial was published (n=384 bicalutamide and n=376 placebo).[173] In addition, 5-year follow up data from the GETUG-AFU 16 trial that examined the effects of SRT with (n=369) or without (n=374) subcutaneous goserelin acetate (10.8 mg given on the first day of RT and again 3 months later) had been published.[174] These two randomized controlled trials provide the Level 1 evidence required to properly validate the treatment effect of hormone therapy with SRT.

A third such trial, RTOG 0534, completed recruitment of 1,792 participants in March 2015; it is a 3-arm randomized controlled trial with assignment to prostate bed SRT with or without 4 - to 6-month duration hormone therapy, or to the same hormone therapy with pelvic nodal and

prostate bed RT in men with rising PSA after prostatectomy. Another trial, RADICALS, is addressing the use of hormone therapy (bicalutamide, goserelin and leuprolide) and its duration (6 months vs. 24 months) in the ART and SRT context.[172] Mature results from these trials, once reported, will help answer important additional questions regarding hormone therapy use, its duration, and RT field size requirements.

Hormone therapy in the adjuvant setting. Only five observational studies compared RP patients who received ART to those who received ART in combination with some form of hormone therapy.[36, 55, 56, 58, 173] Although all four studies reported findings suggesting that patients who received hormone therapy in combination with ART had better outcomes, only one study reported a statistically significant difference between groups. Specifically, Bastide[36] reported at median follow-up 60.3 months that the ART+hormone therapy group had significantly higher 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+hormone therapy 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 hormone therapy administered was an luteinizing hormone-releasing hormone 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[173] did not detect a difference in bRFS at seven years (ART only – 86%; ART + hormone therapy – 79%) or cRFS (ART only – 90%; ART + hormone therapy – 83%) on univariate analysis but on multivariate analysis the use of hormone therapy 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[174] which reported that ART+hormone therapy significantly improved bRFS and CSS on multivariate analyses (but not univariate analysis) compared to patients who received hormone therapy-only (all patients in this study had positive nodes); however, there was no ART only comparison group in this study. Without data from RCTs in the adjuvant RT setting, the Panel concluded that the role of hormone therapy in this context remains uncertain until the reporting of the RADICALS trial.

Hormone therapy in the salvage setting. At the time of publication of the original guideline in 2013, there were no RCTs with published data to evaluate the use of hormone therapy in the SRT setting. Based on the evaluation of 23 observational studies evaluating RP patients who received SRT alone compared to those selected to receive SRT in combination with some form of hormone therapy, most studies suggested better outcomes for patients selected for SRT in combination with hormone therapy. [33, 56, 58, 64, 75, 76, 83, 92, 93, 95, 100, 106, 110, 116, 125, 128, 130, 143, 145-148, 163]

However, these studies included heterogeneous patient groups, various RT and hormone therapy regimens, and varying follow-up durations. The type, sequencing, and duration of hormone therapy was not uniform, and the risk of bias and other confounders was substantial. The Panel concluded at that time that the role of hormone therapy in the SRT setting was unclear, because outcomes from RCTs were lacking.

Results from the RTOG 9601[175] and GETUG-AFU 16[176] trials had been published at the time of this amendment (see Appendix D). Both trials examined the use of hormone therapy in the SRT setting. However, there are inherent differences of particular note between the trials apart from disparate follow-up durations (13 years versus five years). The type and duration of hormone therapy was different between trials. RTOG 9601 used the oral anti-androgen bicalutamide at high-dose (150 mg daily), while GETUG-AFU 16 used the Gonadotropin Releasing Hormone (GnRH) receptor agonist goserelin subcutaneously.

GETUG-AFU 16 specified short-term, six-month duration hormone therapy during SRT compared to long-term, 24-month duration anti-androgen in RTOG 9601. In addition, the trials were designed to examine different primary outcomes; OS in RTOG 9601, and progression-free survival (biochemical or clinical progression, or all-cause mortality) in GETUG-AFU 16. The inclusion criteria and characteristics of the overall study populations were also somewhat different. RTOG 9601 enrolled men with pT2 disease and positive surgical margins or pT3 disease, all of whom had no pathologic evidence of nodal involvement, as every participant had undergone RP and pelvic lymphadenectomy. GETUG-AFU 16 included men with pT2-pT4a disease who may or may not have had nodal involvement, in that 26% had not undergone pelvic lymphadenectomy. Men in GETUG-AFU 16 were required to have undetectable PSA (<0.1 ng/mL) for at least 6 months post-prostatectomy, and 80% had PSA <0.5 ng/mL and 94% had PSA <1.0 ng/mL at trial entry. In contrast, the proportion of participants with undetectable PSA before SRT is not known from the publication of RTOG 9601, although a PSA nadir ≥0.5 ng/mL after prostatectomy was reported in 12% of patients. Pelvic nodal RT was not given in RTOG 9601, but 61% of participants who did not undergo pelvic nodal lymphadenectomy in the GETUG-AFU 16 trial received elective pelvic RT. Median age was similar in both trials, and men were enrolled only if their life expectancy was more than 10 years. Men in GETUG-AFU 16 had a better risk profile compared to RTOG 9601: pT3 disease: 46% vs. 67%; positive surgical margins: 50% vs. 75%; Gleason score ≥8 – 11% vs. 17%; persistently elevated PSA post-prostatectomy ≥0.5 ng/mL: 0% vs. 12%; and median PSA at trial entry: 0.3 ng/mL vs. 0.6 ng/mL.

After a median follow-up of 13 years, RTOG 9601 reported a reduction in the 12-year incidence of biochemical recurrence (HR=0.48; 95% CI=0.40-0.58; p<0.001), distant metastasis (HR=0.63; 95% CI=0.46-0.87; p=0.005) and prostate cancer-specific mortality (HR=0.49; 95% CI=0.32-0.74; p<0.001), and improved OS (HR=0.77; 95% CI=0.59-0.99; p=0.04) with assignment to bicalutamide (compared with placebo) and SRT. Survival was improved with bicalutamide in most reported subgroups, and was statistically significantly so in those with Gleason score 7, trial entry PSA 0.7-4.0 ng/mL, or positive surgical margins.

In the GETUG-AFU 16 trial, improved progression-free survival (biochemical or clinical progression, or all-cause mortality) was reported with addition of goserelin to SRT (HR=0.50; 95% CI=0.38-0.66; p<0.0001) at 5 years follow-up; subgroup analyses favored goserelin use in all age, risk, pre-prostatectomy and pre-SRT PSA, and pre-SRT PSA doubling time (PSADT) groups. There were more local and metastatic progression events in the group assigned SRT alone (tests of significance not done), and also more deaths attributed to prostate cancer and from any cause. Between-group comparison awaits the 10-year pre-specified survival analysis plan.

In general, both trials reported limited data on early adverse events, and had used different reporting tools. However, some similarities are apparent. For example, similar rates of genitourinary (GU) and gastrointestinal (GI) adverse events were reported in both arms of both studies, and these were primarily mild. Most importantly, when discussing hormone therapy, an emphasis on examining its adverse effects becomes relevant. GETUG-AFU 16 reported higher rates of hot flashes (46% vs. <1%) and sweating (13% vs. 0%) with goserelin vs SRT alone, but these were overwhelmingly mild-to-moderate (grade 1-2) in severity. No difference in hot flashes was reported in RTOG 9601, but mild-to-moderate (grade 1-2) gynecomastia was reported in 67% of men assigned to high-dose (150 mg daily) bicalutamide versus 11% who received placebo; 4% of men had severe gynecomastia with bicalutamide. Gynecomastia with six-month duration goserelin was very rare (<1%) in the GETUG-AFU 16 trial.

Given the findings from the RCTs, taking note of the differences between the trials and possible limitations, the Panel concluded that there was

sufficiently strong evidence overall to encourage clinicians to inform patients and offer the option to add hormone therapy to SRT. The Panel recognized that neither trial was designed to identify specific patients within the overall targeted population in whom a hormone therapy benefit could be excluded. The offering of hormone therapy therefore should be accompanied by a thorough discussion of the potential benefits and risks/burdens associated with its use in the SRT setting (see Guideline Statement 9). Shared decision-making that considers the patient's values, preferences, and history is encouraged.

More high quality evidence will be required to identify subgroups that would and would not benefit from the addition of hormone therapy to SRT, and to provide specific recommendations on the type and optimal duration of such.

Toxicity and QoL impact of RT post-prostatectomy. A key concern of clinicians and patients when ART or SRT is contemplated is the toxicity and QoL 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 GU, 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 RTOG measure for acute effects (through day 90) and the 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 E). 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.[18, 26, 39, 40, 42-44, 46, 47, 50, 55-57, 60, 63, 65, 67, 68, 72, 75, 76, 79, 80, 82, 83, 85, 87, 88, 90-93, 97, 100, 104-106, 112-114, 122, 123, 125, 128-130, 133-136, 138, 140-143, 149, 151, 152, 154, 155, 158-161, 163, 165, 166, 173, 177-203]

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 GI 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 F; 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.[100, 177] 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.[191] 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[187] reported that patients treated with EBRT or with cone-beam computed tomography (CT)-guided 3D-CRT had similar rates of acute grade 2 GU (13% in both groups) and GI toxicities (EBRT: 15%; 3D-CRT: 13%).

Additional acute GU toxicity information was reported by Bolla[165] 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[100] reported that 3D-CRT patients had higher levels of grade 2 or greater toxicities (13.2%) compared to IMRT patients (7.6%). Alongi[177] 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[165] 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 GU toxicity (9 ART arms, 26 SRT study arms, and 16 mixed study arms) and 41 reported at least one measure of late 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 G; 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[130] 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[195] 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[188] 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[100] reported on patients who were administered 3D-CRT or IMRT and noted that the probability of late grade 2 or higher toxicities for 3D-CRT patients ranged from 5% at 24 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[191] 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[185] 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[130] 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[195] 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[188] 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[100] 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[191] 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[185] and Tramacere[67] reported that the presence of acute toxicity was a significant predictor of late toxicities.

Additional late toxicity information is provided by Thompson,[23] 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%). Moinpour[204] 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:

18%; post-RP only: 5%; 60 months post-RT:18.5%; post-RP only: 11%).

Urinary incontinence. To understand the impact of RT on urinary incontinence (UI) post RP, 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 UI.[23, 42, 205-208] 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.[42] 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%).[205-207] Two reports focused on patients from the RCTs[23, 208] (EORTC 22911; SWOG 8794). Van Cangh[208] 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[23] 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.[46, 79, 85, 87, 106, 186, 195] 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).

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[198] 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 a 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[209] 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[210] reported after administering the EPIC-26 and the International Prostate Symptom Index at 2-, 6-, 12-, 18-, and 24-month intervals post-RT that there were no declines in urinary continence or gastrointestinal QoL outcomes.

One ART study reported overall quality of life data. Moinpour[204] (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 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.[209] 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.[42, 44, 50, 204-206] 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 hormone therapy 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[204] indicating that only 7% of men had intact function pre-RT.

SRT studies. The impact of SRT on erectile function also is difficult to determine. Thirteen studies reported erectile function information in SRT patients.[44, 60, 79, 82, 91, 100, 160, 161, 166, 179, 186, 198, 209] Nine of these studies reported only proportions of patients with erectile dysfunction (ED) at various time points and provide contradictory information (three studies reported no change post-RT and six reported increased proportions of patients with ED post-RT). In most of these studies sample sizes were extremely small (<50); pre-RP functioning was not reported; the type of RP was not reported or varied (some patients had nerve-sparing procedures and others did not); the RP to RT interval was less than 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 confounders remain. Three of these studies reported no changes over time from the post-RP/ pre-RT measurement point throughout follow-up; one reported increased ED rates.

In addition, similar to the ART studies, post-RP patients who presented for SRT had very low rates of adequate erectile function (3.8% to 35.7%; most studies reported that <10% patients had full potency post-RP but pre-RT) and low scores on QoL measures of sexual function/ bother. The only study that included pre-RP data[60] reported that 74 of 110 patients (73%) were fully potent pre-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-RP 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.[210]

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-RP are contradictory as pointed out by Guedea.[211] Specifically, Bhojani[212] 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.[213] In addition, none of the trials that focused on ART or SRT have reported secondary malignancy data. Further, post-RP 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.[214] Finally, the risk of secondary cancers also may be related to co-existing factors such as the presence of past or current smoking.[215-217] 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.

GUIDELINES STATEMENTS

Guideline Statement 1: *Patients who are being considered for management of localized prostate cancer with radical prostatectomy should be informed of the potential for adverse pathologic findings that portend a higher risk of cancer recurrence and that these findings may suggest a potential benefit of additional therapy after surgery. (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 SVI, and 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.[11, 13, 14, 16, 18-22, 218-220] 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.[24, 25]

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 RP with median follow-up of 10 years (and follow-up of up to 29 years in subset of patients).[221] Approximately 3,300 of these patients were treated during the PSA era (from 1992 to 2011). These data reveal reduced rates of bRFS 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 radical prostatectomy only, reduces the risk of biochemical 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 three randomized controlled trials that addressed these outcomes indicated a benefit but the other two trials did not demonstrate a benefit. However, these two trials were not designed to identify a significant reduction in metastasis or death with adjuvant radiotherapy. (Clinical Principle)*

Discussion: Patients with adverse pathologic findings at prostatectomy should be counseled regarding the most up-to-date findings from the RCTs 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 OS is less clear, with benefits reported in one of three 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 QoL effects of RT.

Three RCTs (SWOG 8794, EORTC 22911, and ARO 96-02), all with more than 10 years of follow-up, evaluated the effects of ART on outcomes among patients with adverse pathologic features at prostatectomy[23-27] [for detailed discussion of RCT findings, see ART section in Background]. All three trials documented significant improvements in bRFS with use of ART compared to RP-only. The Panel notes that prevention of biochemical progression is an important clinical endpoint because biochemical progression may trigger salvage therapy (i.e., hormone therapy), with its associated toxicities and QoL impact. In addition, patients with biochemical recurrence are more likely to manifest metastatic recurrence. Therapies for metastatic recurrence, such as hormone therapies, can have profound QoL 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[25] (locoregional failure in 8.4% of ART patients compared to 17.3% of RP-only patients) and similar in magnitude in SWOG 8794[23, 24] (locoregional failure in 8% of ART patients compared to 22% in RP-only patients; no p-value reported). The Panel viewed reduction of locoregional failure as another important clinical endpoint because the occurrence of local failure also triggers the use of salvage therapies, with associated toxicities and increases the probability of subsequent metastatic failure.

Both SWOG 8794 and EORTC 22911 also reported statistically significant reductions in the use of subsequent salvage therapies with ART compared to RP-only at approximately 10 years of follow up. SWOG 8794 reported improvement in hormone 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 SRT or hormone therapy) 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 cPFS (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 cPFS 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 OS. Only SWOG 8794 demonstrated significantly improved

mRFS (43.5% for ART patients; 54% for RP-only patients) and OS (74% in ART patients; 66% in RP-only patients) at more than 12 years of follow-up.[24] Several possible explanations for the discrepant findings across trials have been offered. These include the fact that the OS 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 OS.

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 bRFS 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).[25] 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.[24] 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: 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.[21] 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 PSADT provided the most statistically significant prediction of time to distant progression. Men with a PSADT less than 10 months usually developed metastases within five years of surgery, while men with a PSADT 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.[222] 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 PSADT of six to seven months or longer. A PSADT 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. PSADT 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 PSADT. 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.[223] Many adjuvant studies, including the three RCTs reviewed in detail in this guideline, and many SRT 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.[224, 225] In addition, even more sensitive assays may add further clarity as to whether patients are at increased risk for clinical failure.[226, 227] 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.[228] The SRT 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.[229] 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.[225, 230, 231] In addition, calculation of PSADT using data derived from ultra-sensitive assays may yield markedly different PSADT values compared to using data derived from higher-

threshold assays;[232] 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 SRT 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 SRT, 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[233-235] (DRE), transrectal ultrasound[235-242] (TRUS), color Doppler TRUS,[242] color power Doppler TRUS,[237, 243] contrast-enhanced color power Doppler TRUS,[237] body coil magnetic resonance imaging (MRI),[244] endorectal coil MRI without contrast,[234, 244-246] endorectal coil MRI with contrast,[244, 245, 247] 11C-acetate positron emission tomography (PET)/ CT,[248] 11C-choline PET/CT,[249-251] 18FDG PET,[252-263] 18FCH PET/CT,[254, 255] dynamic contrast-enhanced (DCE) MRI,[234, 256-258] diffusion-weighted MRI with contrast,[259] 1H-magnetic resonance spectroscopic imaging (MRSI),[257] 1H-MRSI with DCE MRI,[254, 257] CT with contrast,[260] Prostascint[127, 252, 261-264] and Prostascint fused with MRI or CT.[265] 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[258] 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%.[244] 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.[266, 267]

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[268-271] and 18FDG PET/CT[272] to detect recurrence in lymph nodes. The sensitivity of 11C -choline PET/CT was 100% across studies; three studies reported data per patient and one study reported data per node.[271] Scattoni[269] 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 lymphotropic superparamagnetic nanoparticles. One study was conducted in patients who had not yet undergone RP and reported values for sensitivity and specificity above 90%.[273] Two studies used this modality in post-RP patients with biochemical failure.[274, 275] In Ross[274] insufficient patients were biopsied; diagnostic performance could not be calculated. None of the patients in Meijer[275] were biopsied, but findings correlated well with Stephenson nomogram predictions regarding which patients would benefit from SRT. Fortuin[276] reported in 29 patients that more lymph nodes were detected by MR lymphography (MRL) than by 11C-choline PET/CT (738 vs. 132 nodes respectively) and more suspicious nodes were detected by MRL (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 MRL 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 single-photon emission computerized tomography (SPECT),[277, 278] 11C-choline PET/CT,[279-281] 18F-fluoride PET,[277] 18F-fluoride PET/CT[277] DWE-MRI with contrast,[281] conventional MRI-STIR[281] and conventional MRI–T1 weighted.[281] 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, DWE -MRI with contrast, 18F fluoride PET, 18F fluoride PET/CT, and bone scan without SPECT). Two studies reported values above 90% (MRI-T1 weighted and bone scan with SPECT). Only six study arms provided specificity information; these values ranged from 64% to 100% with four of five study arms reporting values above 80% (bone scan with and without SPECT, 11C-choline PET/CT, 18F-fluoride PET and 18F-fluoride PET/CT). Additional information is provided by Fuccio[280]

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 PSADTs and faster PSA velocities.[282-286] For example, at PSA levels less than 10 ng/ml, less than 5% of patients had a positive bone scan.[284] For PSADT greater than six months, the probability of a positive bone scan was 3%.[286] 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.[127, 261, 287] One study each focused on 11C-choline PET/CT,[249] 18FDG PET,[253] 18F-FDG PET/CT,[288] 18F-NaF PET/CT[288] and 18FCH PET/CT.[255] Sensitivity values 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.[288] 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.[253, 255, 287, 289-307] A wide range of reference standards were employed including: other imaging modalities; biopsies of the prostate bed, nodes and/or bone; PSA responses to SRT; 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%;[294, 296, 307] the lower specificity values occurred in studies from the same institution in which a single reference standard (biopsy) was used.[298, 299] Mitchell[307] summarized the recent Mayo Clinic experience with11C-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 systematic 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,[294, 296, 308] as PSA velocities increased[294, 309, 310] and as PSADTs decreased.[309, 310] Using 18F-fluorocholine PET/CT, Kwee[290] 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.[24] 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).[25]

This statement also is supported by two observational studies that reported outcomes for patients who had SRT vs. post-RP patients with detectable PSA and/or local recurrence who did not have SRT. Boorjian[32] reported on a cohort of 2,657 patients with biochemical failure post-RP; 856 of these patients had SRT. 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 hormone therapy administration; these differences were present even after controlling for differences between groups in clinical and pathological features. No OS difference was documented, however. Trock[33] reported outcomes for post-RP patients with biochemical failure and/or local recurrence who did not receive SRT (n=397), received SRT alone (n=160), or who received SRT in combination with hormone therapy (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 hormone therapy (12% deaths from prostate cancer); there were no differences between the two SRT groups. The authors note that the CSS advantage associated with SRT (with or without hormone therapy) was specific to certain clinical subgroups. These included men with a PSADT 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 CSS 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 CSS 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 bRFS. 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.[60, 64, 68, 79, 83, 85, 91-93, 95, 98, 104, 108-110, 112, 114-116, 120, 125-128, 130, 134-137, 139, 143, 144, 147, 150, 151, 154, 159, 163, 164]

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, GI, 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 SRT patients at lower v. higher pre-RT PSA levels.[40, 54, 56, 58, 60, 64, 78, 82, 85, 86, 91-93, 95, 97, 98, 103, 104, 108, 110, 115-117, 120, 122, 125, 127, 128, 130, 132, 133, 135, 137, 139, 142, 143, 147, 148, 150, 151, 153-155, 157, 159, 160, 164]

Forty-one studies used cut-off values to divide the low and higher groups of approximately 1.0 ng/ml or less.

All but one study reported that patients with lower pre-RT PSA levels had higher bRFS rates over time compared to patients with higher pre-RT PSA levels although the differences between groups were not always statistically significant. The exception was Tomita,[154] which divided patients into those with pre-RT PSA <0.25 ng/ml or ≥0.25 ng/ml – an extremely low threshold. This is the only study in which values for the low and high groups were reversed, with 51% of the pre-RT PSA <0.25 ng/ml free of biochemical recurrence at 36 months compared to 59% of the pre-RT PSA ≥0.25 ng/ml group – a non-significant difference. The relevance of pre-SRT PSA level was confirmed by a recent systematic review of 41 selected SRT studies.[311] These authors reported that PSA level before SRT was significantly associated with relapse-free survival with an average 2.6% loss of relapse-free survival for each 0.1 ng/ml PSA increment at the time of SRT. In addition, a meta -regression performed on a selected group of 25 SRT studies indicated that pre-RT PSA levels were significantly associated with five-year progression -free survival levels such that progression-free survival rates dropped by 18.1% for every 1 ng/ml increase in pre-RT PSA.[167]

Confirmatory subgroup analyses from SWOG 8794 presented in Swanson[29] indicate that among patients with detectable PSA at the time of RT, those with PSA values ≤1.0 ng/ml had higher five - and 10-year bRFS rates than those with pre-RT PSA values >1.0 ng/ml.

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

Guideline Statement 9: *Clinicians should offer hormone therapy to patients treated with salvage radiotherapy (postoperative PSA ≥0.2 ng/mL). Ongoing research may someday allow personalized selection of hormone or other therapies within patient subsets. (Standard; Evidence Strength: Grade A);*

Discussion: Two randomized controlled trials (RTOG 9601[175] and GETUG-AFU 16[176]) evaluated the effects of hormone therapy on OS, and on biochemical and clinical progression among patients who received SRT after prostatectomy. See detailed discussion of the study characteristics, limitations and differences between the two in the Background section under the heading "Hormone therapy in the salvage setting". RTOG 9601 reported longer term outcomes, and thus provided the opportunity to observe a significant advantage in OS at 12 years follow-up with 24-month duration, high-dose (150 mg daily) bicalutamide. The trial also reported reductions in the cumulative incidences of distant metastasis, biochemical recurrence, and death attributed to prostate cancer. GETUG-AFU 16 had a primary outcome of progression-free survival, mainly a bRFS endpoint, and documented significant improvements in freedom from disease progression, which was observed in all prognostic subgroups; there was no difference in OS at 5 years, but the study was not designed to detect any difference until ten years follow-up. When RTOG 9601 reported its seven-year follow up data in an abstract in 2010, patients who received bicalutamide with SRT had improved biochemical and clinical progression (distant metastasis), but there was no difference in OS. Similar to RTOG 9601, longer follow-up from GETUG-AFU 16 may provide more insights into the effect of six-month

duration hormone therapy on OS. Statistically significant improved survival outcomes were observed in certain subgroups in RTOG 9601, namely in patients with higher Gleason score, trial entry PSA 0.7 ng/mL – 4.0 ng/mL, and those with positive surgical margins. However, RTOG 9601 was not designed to test the effect of bicalutamide in prespecified subgroups, so it is unknown whether there is lack of benefit in other subgroups.

Both trials reported SRT-attributed adverse events in keeping with prior publications, and these were not affected by the addition of hormone therapy. Adverse events attributed to hormone therapy were mainly mild-to-moderate, but they differed because of the distinct type of hormone therapy used in the two trials. Hot flashes (46% of participants), including sweats (13%), were expected and common with use of a GnRH receptor agonist in the GETUG-AFU 16 trial, but the rate of hot flashes with bicalutamide anti-androgen therapy (22%) was similar to that of placebo (17%) in RTOG 9601. In contrast, gynecomastia in RTOG 9601 was recorded in 70% of participants assigned to bicalutamide (150 mg daily for 24 months) versus placebo (11%), but gynecomastia (1%) and breast pain (1%) were uncommonly reported in the GETUG-AFU 16 trial.

Based on findings from these two RCTs, the Panel recommends that clinicians offer hormone therapy to candidates for SRT, namely patients with postoperative PSA ≥0.2 ng/mL and no distant metastasis. There is insufficient evidence for such in patients with lower (<0.2 ng/mL) PSA levels. When offered, the clinician must provide information about benefits and harms associated with this therapy, particularly discussing the improved freedom from disease progression documented in both trials, and improved OS reported in RTOG 9601. The Panel recognized the statistical limitations of *post hoc* subgroup analyses wherein reductions in distant metastasis and all-cause mortality was statistically significant in only some subgroups.[173] Nonetheless, these risks were also less in other subgroups,[173] but without statistical significance, in which the number of patients was limited. The decision of which particular patient would benefit most from this therapy will be best achieved through a multi-disciplinary care team and through shared decision-making accounting for each patient's history, values and preferences.

Guideline Statement 10: *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 GU and GI 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.[101, 178]

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)[130] than to include GI symptoms (up to 10.2% of patients).[100] 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.[100]

UI. Patients should be informed that rates and severity of UI in patients who have had RP and then ART 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.

ART may reduce the need for salvage therapies. Patients also should be informed that the use of ART, because it is associated with improved bRFS 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.[212, 213] Furthermore, in clinical trials of ART and SRT 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.[215-217] Therefore, the Panel concluded that at this time the risk of developing a secondary malignancy as a result of ART or SRT administration is not known.

RESEARCH NEEDS AND FUTURE DIRECTIONS

Ongoing Clinical Trials. Several ongoing clinical trials will help to clarify the magnitude and impact of ART or SRT, the relative value of combining RT with hormone 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 ADT (four to six months) or pelvic lymph node RT plus prostate bed RT plus short-term ADT. Patients are stratified by SVI status, Gleason score ≤7 or 8-9, pre-RT PSA of ≥0.1 to 1.0 ng/mL or >1.0 to <2.0 ng/mL and pT2 with negative margins vs. all other patients. The trial includes assessments of biomarkers, QoL, neurocognitive function and urinary function. 3D-CRT or IMRT methods are used with 64.8-70.2 Gy administered to the prostate bed and 45 Gy administered to pelvic lymph nodes.

The RADICALS trial is a 3,000-subject study taking place in the UK, Canada, Denmark and Republic of Ireland recruiting post-prostatectomy patients who are within 22 weeks of RP with post-RP PSA ≤0.2 ng/mL with one or more of the following characteristics: pT3 or pT4 disease; Gleason score 7-10; preoperative PSA ≥ 10 ng/mL; and/or positive margins. This trial is addressing two critical questions in post-RP patients. The first question is the comparative efficacy of the ART vs. SRT approach. Patients are randomized to either immediate adjuvant RT or to regular PSA testing and SRT if PSA becomes detectable. The second, concurrent randomization addresses the question of the role of hormone therapy. Patients receiving radiation

(either ART or SRT) are further randomized to three treatment arms: radiation alone, radiation plus six months of hormone therapy or radiation plus two years of hormone therapy. This study will address perhaps the most contentious of issues regarding radiation after surgery: whether SRT when PSA becomes detectable is equivalent to early ART.

The RAVES trial (TROG 08.03) was a phase III multi-center trial taking place in Australia and New Zealand comparing ART with early SRT in patients with positive margins or EPE. The primary trial aim was to determine whether surveillance with early SRT results in equivalent biochemical control and improved QoL when compared with ART. Secondary outcomes include QoL, toxicity, anxiety/depression, bRFS, OS, CSS, time to distant failure, time to local failure, time to initiation of hormone therapy, quality adjusted life years, and cost-utility. The rate of participant accrual diminished over time, and the trial closed prematurely with entry of 333 of the 470 patients planned.

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 SVI) 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 ART or SRT, 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 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 DCE or magnetic resonance spectroscopy will define sites of local recurrence and improve SRT targeting and the need to add adjuvant therapies, such as hormone therapy 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.[24] 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, ART or SRT 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 ART or SRT.

Genomic classifiers as predictors of treatment effectiveness. Tissue microarray analysis of prostatectomy samples can describe the gene expression profile of the prostate cancer phenotype. The Decipher™ genomics resource information database has been recently used to link genomic findings with clinical outcomes, as have other methods. Development and validation of the Decipher™ genomic classifier uses a cluster of 22 transcriptome signature biomarkers (Decipher™ - POSTOP) as a prognostic risk stratification tool to identify patients with significantly different outcomes following ART or SRT after radical prostatectomy.[312, 313] At the time of this amendment, six retrospective studies and one Markov decision analysis using the Decipher™ - POSTOP classifier had been published, demonstrating its prognostic association with disease progression, focusing particularly on distant metastases, after radical prostatectomy.[314-320] A 24-gene post-operative RT outcomes score (PORTOS) profile has been described also,[326] as has a 50-gene (PAM50) molecular subtyping of basal and luminal cell lineage.[327] Although prognostic, further study is needed to determine whether genomic classifiers are predictive of outcome in a yet to be treated patient, and whether it is predictive for efficacy of a particular treatment (RT, hormone therapy, or chemotherapy). A genomic classifier as a predictive marker will identify individuals in whom the effectiveness of a controlled treatment method varies as a direct result of the marker, and as it relates to a particular outcome (for example, metastasis-free survival). At present, there is ongoing recruitment to a RCT conducted by NRG Oncology (GU002) that uses Decipher™ - POSTOP as a pre-randomization stratification factor with participants categorized into low/ intermediate genomic classifier score and high genomic classifier score. Participants are then randomized to receive either SRT with hormone therapy or the same with chemotherapy. Treatment response by genomically-defined subsets of patients will be used to assess whether the genomic classifier predicted response to chemotherapy. NRG Oncology (GU006) incorporates PAM50 molecular subtyping in a similar manner, seeking to determine whether it is predictive of response to the next-generation anti-androgen apalutamide. The present level of evidence cannot discern whether such genomic classifiers predict the efficacy, or lack thereof, of ART or SRT after prostatectomy. The timing (ART, early SRT, late SRT), type, targeted volume, and dosage of RT, and the use and duration of hormone therapy are confounding variables that limit certainty in the interpretation of the current literature.

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 ART or SRT 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 SRT or ART 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 RT targeting may also lessen the adverse consequences of treatment for men receiving either ART or SRT.

Combination or systemic therapies. For some patients who undergo ART or SRT, such treatment is not sufficient to control the disease. In SWOG 8794, 20 of 214 patients developed metastatic disease despite early ART.[24] 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-RP to two years of adjuvant ADT with or without chemotherapy.[321] In this study, the surgery plus hormone therapy arm included some patients who had received RT 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 RT 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 ART or SRT. 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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Abbreviations

3D-CRT	Three-dimensional conformal radiotherapy
ART	Adjuvant radiotherapy
ASTRO	American Society for Radiation Oncology
AUA	American Urological Association
bRFS	Biochemical recurrence-free survival
cRFS	Clinical recurrence-free survival
CI	Confidence interval
cPFS	Clinical progression-free survival
CSS	Cancer-specific survival
CT	Computed tomography
CTCAE	Common toxicity criteria adverse event
DCE	Dynamic contrast-enhanced
DRE	Digital rectal exam
DWE	Diffusion weighted
EBRT	Dxternal beam radiotherapy
ED	Erectile dysfunction
EORTC	European organisation for research and treatment of cancer
EPE1	Extraprostatic extension
GI	Gastrointestinal
GU	Genitourinary
Gy	Gray
HR	Hazard ratio
IMRT	Intensity-modulated radiotherapy
mRFS	Metastatic recurrence-free survival
ml	Milliliter
MRI	Magnetic resonance imaging
MRSI	Magnetic resonance spectroscopic imaging
MRL	MR lymphography
ng	Nanogram
NNT	Number needed to treat
OS	Overall survival
PET	Positron emission tomography
PSA	Prostatic specific antigen
PSADT	PSA doubling time
QoL	Quality of life
RADICALS	Radiotherapy and androgen deprivation in combination after local surgery
RAVES	Radiotherapy - adjuvant versus early salvage
RCT	Randomized controlled trial
RFS	Recurrence-free survival
RP	Radical prostatectomy
RT	Radiotherapy
RTOG	Radiation therapy oncology group
SPECT	Single-photon emission computerized tomography
SRT	Salvage radiotherapy
STIR	Short T1 inversion recovery
SVI	Seminal vesicle invasion
SWOG	Southwest oncology group
TRUS	Transrectal ultrasonography
UI	Urinary incontinence
WHO	World Health Organization

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Conflict of Interest Disclosures
All panel members completed COI disclosures during the development of the original guideline in 2013. Relationships that have expired (more than one year old) since the panel's initial meeting, are listed. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received.

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