Adjuvant and Salvage Radiation Therapy After Prostatectomy: American Society for Radiation Oncology/American Urological Association Guidelines

Richard K. Valicenti, MD, MBA,* Ian Thompson Jr., MD,† Peter Albertsen, MD, MS,‡ Brian J. Davis, MD, PhD,§ S. Larry Goldenberg, MD,¶ J. Stuart Wolf, MD,¶¶ Oliver Sartor, MD,# Eric Klein, MD,** Carol Hahn, MD,†† Jeff Michalski, MD, MBA,†‡ Mack Roach III, MD,§§ and Martha M. Faraday, PhD

*Department of Radiation Oncology, University of California, Davis School of Medicine, Davis, California; †Department of Urology, University of Texas Health Science Center at San Antonio, San Antonio, Texas; ‡Division of Urology, University of Connecticut Health Center, Farmington, Connecticut; §Department of Radiation Oncology, Mayo Medical School, Rochester, Minnesota; ¶Department of Urologic Sciences, University of British Columbia, Vancouver, British Columbia, Canada; ¶¶Department of Urology, University of Michigan, Ann Arbor, Michigan; #Department of Medicine and Urology, Tulane Medical School, New Orleans, Louisiana; **Glickman Urological Kidney Institute, Cleveland Clinic, Cleveland, Ohio; ††Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina; †‡Department of Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri; §§Department of Radiation Oncology, University of California, San Francisco, San Francisco, California; and †§ Four Oaks, Inc.

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Purpose: The purpose of this guideline was to provide a clinical framework for the use of radiation therapy after radical prostatectomy as adjuvant or salvage therapy.

Methods and Materials: A systematic literature review using PubMed, Embase, and Cochrane database was conducted to identify peer-reviewed publications relevant to the use of radiation therapy after prostatectomy. The review yielded 294 articles; these publications were used to create the evidence-based guideline statements. Additional guidance is provided as Clinical Principles when insufficient evidence existed.

Results: Guideline statements are provided for patient counseling, use of radiation therapy in the adjuvant and salvage contexts, defining biochemical recurrence, and conducting a restaging evaluation.

Conclusions: Physicians should offer adjuvant radiation therapy to patients with adverse pathologic findings at prostatectomy (ie, seminal vesicle invasion, positive surgical margins, extraprostatic extension) and salvage radiation therapy to patients with
Purpose

This guideline’s purpose is to provide direction to clinicians and patients regarding the use of radiation therapy (RT) after prostatectomy as adjuvant or salvage therapy.

Methodology

A systematic review identified articles relevant to the use of RT after prostatectomy as adjuvant or salvage therapy. Literature searches were performed using PubMed, Embase, and Cochrane database from January 1, 1990, to December 15, 2012. The review yielded an evidence base of 294 articles.

The American Urological Association (AUA) nomenclature system links statement type to body of evidence strength and the Panel’s judgment regarding the balance between benefits and risks/burdens. For discussion of this system, see the unabridged guideline.

Limitations of the literature

Limitations of the literature included few randomized controlled trials (RCTs); lack of group equivalence in pathological risk factors in observational studies; variability in prostate-specific antigen (PSA) assay sensitivity and failure criteria; heterogeneity of radiation dose and methods; a paucity of studies with follow-up duration longer than 60 months; and, the overwhelming focus of the literature on biochemical recurrence with less information available regarding metastatic recurrence, cancer-specific survival, and overall survival. In addition, few studies focused on important quality of life (QoL) outcomes such as voiding and erectile function.

Background

Prevalence

In 2012, an estimated 241,740 men were diagnosed with prostate cancer (1). In approximately two-thirds of men, radical prostatectomy (RP) constituted a cure, but within 10 years, up to one-third of patients manifested recurrent disease (2-5). Recurrence risk is greater among men with adverse pathology such as positive surgical margins, seminal vesicle invasion (SVI), extraprostatic extension (EPE), and higher Gleason scores (6-12).

Definitions

Adjuvant RT (ART) is the administration of RT postprostatectomy to patients at a higher risk of recurrence because of adverse pathological features prior to evidence of disease recurrence (ie, with an undetectable PSA). Salvage RT (SRT) is the administration of RT to the prostatic bed and possibly to the surrounding tissues, including lymph nodes, in the patient with a PSA recurrence after surgery but no evidence of distant metastatic disease. Biochemical (PSA) recurrence after surgery is defined as detection of PSA concentration at ≥0.2 ng/mL, with a second confirmatory level detected at ≥0.2 ng/mL.

ART

The highest quality evidence that addresses the use of RT after prostatectomy is provided by three RCTs that examined the effect of RT delivered primarily as ART.

ART Versus SRT

A pressing clinical question is whether it is better post-RP to administer RT adjuvantly (before recurrence) or as a salvage therapy (after recurrence). The use of ART involves irradiation of some patients who never would have had recurrent cancer, exposing them unnecessarily to RT side effects. Administering RT as a salvage therapy limits its use to patients with recurrence but, particularly in patients with high-risk disease, could allow progression to metastatic disease.

The Panel attempted to address this issue by examining the observational studies that reported outcomes for ART and SRT patients. These studies lack randomization and differ in patient characteristics, RT protocols, failure definitions, and follow-up durations. In addition, most of the published literature reports findings from the use of older RT techniques (eg, external beam RT [EBRT]), making it unclear whether newer techniques might result in fewer apparent differences between ART and SRT outcomes. Overall, the existing literature cannot answer this question.

RT techniques

The Panel attempted to determine which RT techniques and doses produced optimal outcomes in the adjuvant and salvage contexts. It was not possible to answer these questions from the available data.

Specifically, approximately one-third of the ART and SRT observational studies treated patients with conventional external beam modalities, which have since been replaced by three-dimensional conformal RT (3D-CRT) or intensity modulated RT (IMRT). The published literature does not reflect implementation
of these newer methods, and only one-quarter of the reviewed studies reported use of 3D-CRT techniques, and less than 5% reported use of IMRT techniques. With regard to the RCTs of ART, Southwest Oncology Group (SWOG) protocol 8794 and European Organization for Research and Treatment of Cancer (EORTC) 22911 protocol administered RT using EBRT techniques (13, 14); and the ARO 96-02 study administered RT using 3D-CRT (15). The lack of studies using newer RT methods made it difficult to definitively address the question of optimal methods and whether these might differ in the adjuvant versus salvage context.

Among observational studies, RT doses ranged from 50-78 Gy; SRT studies administered somewhat higher dosages than ART studies. Although RT dose escalation improves freedom from biochemical relapse when used as primary treatment for localized prostate cancer, the optimal postprostatectomy radiation dose has never been tested. Clinical data suggest that doses above 65 Gy can be safely delivered and may lead to improved tumor control (16-20). In the three RCTs, most patients were treated with 60 Gy.

In the Panel’s view, 64-65 Gy is the minimum dose that should be delivered post-RP, but decisions regarding dose should be made by the treating physician who has full knowledge of the patient’s functional status, history, and toxicity tolerance. The Panel notes that there is controversy regarding RT targets and field size (for guidance see http://www.rtog.org/CoreLab/ContouringAtlases/ProstatePostOp.aspx) (21-24).

Use of androgen deprivation therapies

Key questions are whether, when, for how long, and in what form androgen deprivation therapy (ADT) should be administered. The literature review attempted to address these questions by examining studies that focused on the use of ADT in patients who underwent prostatectomy and then ART or SRT. The Panel’s conclusion was that, given the methodological weaknesses of this literature, it is not possible to provide guidance regarding the use of ADT in conjunction with RT. These weaknesses include non-randomized study designs; small sample sizes and lack of statistical power; lack of group equivalence on pathological risk factors; large differences in ADT protocols, including when it was administered and for how long; primary focus on biochemical recurrence; and other differences relevant to efficacy such as differences in RT techniques, targets, and total Gy administered. Randomized controlled trials are needed to provide definitive evidence.

Guideline statement 1

Patients who are being considered for management of localized prostate cancer with RP should be informed of the potential for adverse pathologic findings that portend a higher risk of cancer recurrence and that these findings may suggest a potential benefit of additional therapy after surgery (Clinical Principle). Patients should be counseled before RP that certain pathology findings are associated with higher risks for cancer recurrence. These findings include positive surgical margins, SVI, and EPE. Recurrence rates in post-RP patients with adverse pathology may be greater than 60% at 5 years. Two RCTs with more than 10 years of follow-up reported recurrence rates of >60% in high-risk patients who underwent RP only (25, 26). Patients also should be informed that if adverse pathology is detected, then additional therapy after surgery, such as RT, may be beneficial.

Guideline statement 2

Patients with adverse pathologic findings including SVI, positive surgical margins, and EPE should be informed that adjuvant RT, compared to RP only, reduces the risk of biochemical (PSA) recurrence, local recurrence, and clinical progression of cancer. They should also be informed that the impact of adjuvant RT on subsequent metastases and overall survival is less clear; one of two RCTs that addressed these outcomes indicated a benefit, but the other trial did not demonstrate a benefit. However, the other trial was not powered to test the benefit regarding metastases and overall survival (Clinical Principle).

Patients should be counseled that high-quality evidence indicates that use of ART in patients with adverse pathology reduces the risk of biochemical recurrence, local recurrence, and clinical cancer progression. Patients should be informed that the impact of ART on metastases and overall survival is less clear, with benefits reported in one of two trials with long-term data for these outcomes.

Guideline statement 3

Physicians should offer adjuvant RT to patients with adverse pathologic findings at prostatectomy, including SVI, positive surgical margins, or EPE because of demonstrated reductions in biochemical recurrence, local recurrence, and clinical progression (Standard; Evidence Strength Grade A).

The Panel notes that the apparent benefits associated with ART are partially the result of a patient subset that was treated who never would have presented with recurrence. The Panel emphasizes that ART should be offered to all patients at high recurrence risk because of adverse pathology. By “offered,” the Panel means that the patient, his family, and the multidisciplinary treatment team should engage in a shared decision making process in which the patient is advised to consider the possibility of additional treatment (ie, RT). Whether ART should be administered is a decision best made by the multidisciplinary treatment team and the patient with consideration of the patient’s history, 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), two with more than 10 years of follow-up, evaluated the effects of ART among patients with adverse pathology (13, 15, 25, 26). All trials documented significant improvements in biochemical recurrence-free survival (bRFS) with use of ART compared to use of RP only (Fig. 1, meta-analysis). Two RCTs evaluated locoregional failure (SWOG 8794 and EORTC 22911) and reported failure reductions in patients who underwent ART compared to those who underwent RP only (EORTC 22911: 8.4% ART patients; 17.3% RP only patients; P<.05; SWOG 8794: 8% ART patients; 22% RP only patients; no P value reported).

SWOG 8794 and EORTC 22911 also reported statistically significant reductions in the use of salvage therapy with ART compared to RP only. 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 ADT) than RP only patients (47.5%).
SWOG 8794 and EORTC 22911 also demonstrated improved clinical progression-free survival (defined as clinical or imaging evidence of recurrence or death but not including biochemical progression) in ART compared to RP only patients. This difference was statistically significant in SWOG 8794 and borderline significant ($P = .054$) in EORTC 22911.

Prevention of biochemical progression and locoregional recurrence are important clinical endpoints because these events may trigger salvage therapy with associated toxicities and QoL impact and are predictive of metastatic progression. Improved clinical progression-free survival is an important endpoint because it reflects lower rates of local and distant failure and lower death rates. Reduction in salvage therapy initiation is another important clinical endpoint because of the avoidance of the negative consequences of these therapies.

Two of the trials, SWOG 8794 and EORTC 22911, assessed metastatic recurrence and overall survival. SWOG 8794, but not EORTC 22911, demonstrated significantly improved metastatic recurrence-free survival (43.5% for ART patients; 54% for RP only patients) and overall survival (74% in ART patients; 66% in RP only patients) at more than 12 years of follow-up (26). Only SWOG 8794, however, was designed and powered to test these outcomes. Therefore, it should be emphasized to patients that, regarding benefits, there is less certainty that ART will prevent metastatic recurrence and improve overall survival.

The Panel also notes that RT should be offered to patients with adverse pathology with a persistent detectable postprostatectomy PSA level. This is a salvage context for RT; two of the trials (SWOG 8794 and EORTC 22911) enrolled some patients with detectable PSA in the early post-RP period (<18 weeks). EORTC 22911 reported that RT improved biochemical recurrence-free point estimates similarly in patients with undetectable post-RP PSA levels (<0.2 ng/mL) and with detectable post-RP PSA levels (≥0.2 ng/mL) (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 (26).

**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 RP to enable early administration of salvage therapies if appropriate (Clinical Principle).

PSA levels post-RP should be undetectable. An increasing PSA level suggests the presence of residual disease and frequently heralds metastases development and death from prostate cancer. This risk is particularly high among men with rapid PSA doubling times. Half of all men with PSA values doubling faster than every 10 to 12 months after surgery will die from their disease within 10-13 years (12, 27). Patients should be informed of the relationship between PSA recurrence 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 of ≥0.2 ng/mL (Recommendation; Evidence Strength Grade C).

Most studies assessing the efficacy of RP used a PSA threshold of 0.2 ng/mL to define recurrence. Many ART and SRT studies, including the three RCTs, also used a PSA threshold of 0.2 ng/mL to define recurrence. This definition is consistent with the prostate-specific antigen best practice statement: 2009 update of the AUA (http://www.auanet.org/education/guidelines/prostate-specific-antigen.cfm).

Patients who have had a prostatectomy should be informed that a PSA value of ≥0.2 ng/mL that has been confirmed by a second elevated PSA value constitutes evidence of recurrence. Detection of biochemical recurrence necessitates a thorough discussion of salvage therapies and is sufficient to trigger salvage therapy administration.

Data suggest that more favorable biochemical outcomes are associated with very low PSA values at the time RT is offered (28). The salvage literature also generally reports that patients who receive RT at lower PSA levels have better outcomes than do patients who receive RT at higher PSA levels. However, a small percentage of patients (8.8% of patients with biochemical recurrence) may have detectable but stable PSA levels for 10 years or more without evidence of clinical failure (29).

Therefore, the decision to initiate salvage therapy is best made by the clinician who has full knowledge of the patient’s pathology findings, risk factors, family history, preferences and values in consultation with that patient and with full discussion of potential treatment benefits and risks. In the era of ultrasensitive PSA assays, a detectable PSA that is confirmed and rising may be an appropriate trigger for salvage therapy, particularly in patients who are at high risk for recurrence and/or who have other evidence of potential progression.

**Guideline statement 6**

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

In the patient with evidence of PSA recurrence, determining the site of recurrence (local vs metastatic) may be relevant to select an appropriate salvage strategy. Physicians should be aware...
that the yield of some modalities (eg, bone scan) is extremely low in patients with PSA values below 10 ng/mL (30).

**Guideline statement 7**

Physicians should offer SRT to patients with PSA or local recurrence after RP in whom there is no evidence of distant metastatic disease (Recommendation; Evidence Strength Grade C).

Two of the RCTs included a patient subgroup that had detectable PSA levels post-RP salvage patients. In SWOG 8794, RT significantly reduced metastatic recurrence rates among patients with detectable PSA post-RP (26). 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 (hazard ratio [HR] = 0.75; 95% confidence interval [CI]: 0.52-1.08) (25).

Two observational studies compared outcomes for SRT patients with those for RP-only patients with detectable PSA or local recurrence. At median 11.5 years post-RP, SRT significantly reduced local recurrence risk (by almost 90%) and systemic progression (by 75%) and delayed the need for ADT administration; these differences were present even after controlling for group differences in clinical and pathological features (31). No overall survival difference was documented, however. At median 9 years post-RP, 22% of men who received no salvage therapy had died from prostate cancer, a significantly higher rate than that for men who had SRT (11% deaths from prostate cancer) (32). This survival advantage was most marked in certain clinical subgroups (see full guideline).

In the context of administering SRT, many observational studies have reported that patients in certain high-risk groups have poorer outcomes than patients without these risk factors or who are in lower risk groups. 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 and higher pT stages, and in those with SVI and EPE than in those in lower risk subgroups.

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

**Guideline statement 8**

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

The majority of observational studies that compared bRFS for SRT patients at lower versus higher pre-RT PSA levels reported that patients with lower pre-RT PSA levels had higher bRFS rates than patients with higher pre-RT PSA levels (differences were not always statistically significant). The relevance of pre-SRT PSA level was confirmed by a recent systematic review (33). 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 metaregression performed in a selected group of SRT studies indicated that pre-RT PSA levels were significantly associated with 5-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 patients (34).

Confirmatory subgroup analyses from SWOG 8794 indicate that among patients with detectable PSA at the time of RT, those with PSA values of ≤1.0 ng/mL had higher 5- and 10-year bRFS rates than those with pre-RT PSA values of >1.0 ng/mL (28).

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.

**Guideline statement 9**

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

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 note that the evidence base for RT toxicity and QoL effects is based mostly on reports using older RT techniques; newer techniques appear to have lower toxicity. The measures most commonly used to report toxicity information were the Radiation Therapy Oncology Group (RTOG) measure for acute effects (through day 90), the RTOG/EORTC measure for late RT effects (persisting beyond day 90 or developing after day 90), and the Common Toxicity Criteria Adverse Event (CTCAE) measure using the same time frames. These measures use a rating system of 0-5, where 0 is no change in function; 1 is minor change in function; 2 is moderate change in function that may require medication; 3 is major change in function sufficient to require more aggressive medication use or outpatient procedures; 4 is severe symptoms requiring hospitalization and surgical procedures; and 5 is death.

**Acute toxicity**

Patients should be informed that during RT and in the immediate post-RT period of 2-3 months, mild to moderate genitourinary and gastrointestinal effects that may require the use of medication for management have been reported frequently, with over 90% of patients experiencing these effects in some studies (Table 1). 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%. The lowest acute toxicity rates have been reported with use of IMRT techniques (35, 36).

<table>
<thead>
<tr>
<th>Study arm type</th>
<th>Genitourinary Grades 1-2</th>
<th>Genitourinary Grades 3-4</th>
<th>Gastrointestinal Grades 1-2</th>
<th>Gastrointestinal Grades 3-4</th>
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<tr>
<td>Adjuvant</td>
<td>10.5%-26%</td>
<td>2.0%-8.0%</td>
<td>22.0%-25.0%</td>
<td>0.0%-2.0%</td>
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<td>Salvage</td>
<td>3.0%-82.0%</td>
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<td>2.9%-96.0%</td>
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</tr>
<tr>
<td>Mixed</td>
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<td>0.0%-3.0%</td>
<td>4.3%-87.0%</td>
<td>0.0%-1.3%</td>
</tr>
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Late toxicity
Patients should be informed that mild to moderate late toxicities occurring more than 90 days post-RT are commonly reported and some studies report rates as high as 79% (Table 2). Serious late toxicities, however, are relatively uncommon, and most studies report 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 4-5 years post-RT and may persist beyond that point. These toxicities are more likely to include genitourinary (GU) symptoms (up to 28% of patients) (37) than gastrointestinal (GI) symptoms (up to 10.2% of patients) (36). 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 (36).

Urinary incontinence
Patients should be informed that rates and severity of urinary incontinence in patients who have had RP and then ART are generally similar to rates for patients who have had RP only.

Sexual function
Patients with intact erectile function post-RP should be informed that the impact of RT on erectile function in men who are post-RP is not clear; studies indicate that most men who present for RT post-RP already have compromised erectile function.

Adjuvant RT may reduce the need for salvage therapies
Patients 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.

Secondary malignancies
Clinicians should advise patients that the potential for developing secondary malignancies exists when RT is given, but that studies investigating the risk of developing secondary malignancies in post-RP men undergoing prostate cancer RT are inconclusive.

Research Needs and Future Directions

Ongoing clinical trials
Ongoing clinical trials (eg, RTOG 0534, RTOG 9601, RADI-CALS, RAVES) will help to clarify the role of ART or SRT, the value of combining RT with other therapies, and potentially make clear which patients are more likely to benefit from specific therapeutic approaches.

Improved imaging techniques
Patients with high-volume, high-grade disease with negative staging studies are most likely to exhibit an immediate PSA relapse, demonstrating preexisting extraprostatic disease at the time of treatment. Another challenging class of patients are those who have locally extraprostatic disease or microscopic nodal disease. Improved imaging techniques would help to better define appropriate therapies.

Prognostic biomarkers
Prognostic biomarkers are greatly needed. In SWOG 8794, the only RCT finding a survival benefit to ART, at median follow-up of 12.6 years and up to 20 years of follow-up overall, metastases were reported in only 37 of 211 RP-only patients and in 20 of 214 ART patients (26). Although a high-risk population, most men did not develop metastases nor die from cancer.

Ideally, ART or SRT should be given only to patients who will develop adverse outcomes and in whom treatment will prevent those outcomes. With prostatectomy, blood- and tissue-based biomarkers can be obtained. New markers have been identified which may be linked with disease prognosis; the utility of these markers requires evaluation in clinical trials.

Quality of life
A major challenge with all prostate cancer therapies is the impact of therapy on QoL. The generally unanswered question in high-risk patients who are candidates for ART or SRT is how QoL outcomes can be integrated with the impact of therapy on survival outcomes. Clinical trials are needed that accomplish this integration.

Combination or systemic therapies
For some patients, RT is insufficient to control disease. The major issues for these highest-risk patients are whether early identification of men most likely to exhibit disease progression can be accomplished and identification of optimal therapies.

Comorbidities
A pervasive issue in prostate cancer management is how patient comorbidities should affect treatment decision making. Most patients are older and, in many, death from other causes is more likely than death or complications from disease progression. Better prediction of relapse chronology, progression, and life expectancy will enhance the selection of patients most likely to benefit from ART or SRT. Some comorbidities (eg, diabetes, hypertension, vascular disease) may increase the risk of radiation-related toxicity; better understanding of this issue also would improve patient selection procedures.

References


