Adjuvant and Salvage Radiotherapy After Prostatectomy: AUA/ASTRO Guideline

Ian M. Thompson,* Richard K. Valicenti,* Peter Albertsen, Brian J. Davis, S. Larry Goldenberg, Carol Hahn, Eric Klein, Jeff Michalski, Mack Roach, Oliver Sartor, J. Stuart Wolf, Jr. and Martha M. Faraday

From the American Urological Association Education and Research, Inc., Linthicum, Maryland, and the American Society for Radiation Oncology, Fairfax, Virginia

Purpose: The purpose of this guideline is to provide a clinical framework for the use of radiotherapy after radical prostatectomy as adjuvant or salvage therapy.
Materials and Methods: A systematic literature review using the PubMed®, Embase, and Cochrane databases was conducted to identify peer-reviewed publications relevant to the use of radiotherapy 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, the use of radiotherapy in the adjuvant and salvage contexts, defining biochemical recurrence, and conducting a re-staging evaluation.
Conclusions: Physicians should offer adjuvant radiotherapy to patients with adverse pathologic findings at prostatectomy (i.e., seminal vesicle invasion, positive surgical margins, extraprostatic extension) and should offer salvage radiotherapy to patients with prostatic specific antigen or local recurrence after prostatectomy in whom there is no evidence of distant metastatic disease. The offer of radiotherapy should be made in the context of a thoughtful discussion of possible short- and long-term side effects of radiotherapy as well as the potential benefits of preventing recurrence. The decision to administer radiotherapy should be made by the patient and the multi-disciplinary treatment team with full consideration of the patient's history, values, preferences, quality of life, and functional status. Please visit the ASTRO and AUA websites (http://www.redjournal.org/webfiles/images/journals/rob/RAP%20Guideline.pdf and http://www.auanet.org/education/guidelines/radiation-after-prostatectomy.cfm) to view this guideline in its entirety, including the full literature review.

Key Words: prostatic neoplasms, radiotherapy, postoperative period, prostatectomy

Abbreviations and Acronyms

3D-CRT = 3-dimensional conformal radiotherapy
ADT = androgen deprivation therapy
ARO = Arbeitsgemeinschaft Radiologische Onkologie
ART = adjuvant radiotherapy
ASTRO = American Society for Radiation Oncology
AUA = American Urological Association
bRFS = biochemical recurrence-free survival
CTCAE = common toxicity criteria adverse event
EBRT = external beam radiotherapy
EORTC = European Organization for Research and Treatment of Cancer
EPE = extraprostatic extension
GI = gastrointestinal
GU = genitourinary
IMRT = intensity-modulated radiotherapy
OS = overall survival
PIVOT = Prostate Cancer Versus Observation Trial
PSA = prostate specific antigen
QoL = quality of life
RCT = randomized controlled trial
RFS = recurrence-free survival
RP = radical prostatectomy
RT = radiotherapy
RTOG = Radiation Therapy Oncology Group
SRT = salvage radiotherapy
SVI = seminal vesicle invasion
SWOG = Southwest Oncology Group

The complete guideline is available at http://www.auanet.org/education/guidelines/radiation-after-prostatectomy.cfm and http://www.redjournal.org/webfiles/images/journals/rob/RAP%20Guideline.pdf.

This document is being printed as submitted without independent editorial or peer review by the Editors of *The Journal of Urology*®.

* Equal author contribution.

INTRODUCTION

The purpose of this guideline is to provide direction to clinicians and patients regarding the use of radiotherapy 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 the PubMed, Embase and Cochrane databases from 1/1/1990 to 12/15/2012. The

0022-5347/13/1902-0441/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2013.05.032
Vol. 190, 441-449, August 2013
Printed in U.S.A.

review yielded an evidence base of 294 articles. The 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; lack of group equivalence in pathological risk factors in observational studies; variability in PSA assay sensitivity and failure criteria; heterogeneity of radiation dose and methods; 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 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 constitutes a cure but within 10 years up to one-third of patients manifest recurrent disease.[2–5] Recurrence risk is greater among men with adverse pathology such as positive surgical margins, seminal vesicle invasion, extraprostatic extension and higher Gleason scores.[6–12]

Definitions

Adjuvant radiotherapy is the administration of radiotherapy post-prostatectomy to patients at a higher risk of recurrence because of adverse pathological features prior to evidence of disease recurrence (i.e., with an undetectable PSA). Salvage radiotherapy is the administration of radiotherapy to the prostatic bed and possibly to the surrounding tissues, including lymph nodes, in the patient with a PSA recurrence after surgery but no evidence of distant metastatic disease. Biochemical (PSA) recurrence after surgery is defined as a detectable PSA level >0.2 ng/ml with a second confirmatory level >0.2 ng/ml.

Adjuvant radiotherapy

The highest quality evidence that addresses the use of radiotherapy after prostatectomy is provided by three RCTs that examined the effect of radiotherapy delivered primarily as ART. 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 (e.g., 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.

Radiotherapy techniques

The Panel attempted to determine which radiotherapy 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 radiotherapy or intensity-modulated radiotherapy. The published literature does not reflect implementation of these newer methods, with only one-quarter of the reviewed studies reporting use of 3D-CRT techniques and less than five percent reporting use of IMRT techniques. With regard to the RCTs of ART, SWOG 8794 and EORTC 22911 administered RT using EBRT techniques,[13,14] and ARO 96-02 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 vs. salvage contexts.

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 post-prostatectomy 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, the majority of 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.[21–24]

A key question is 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.

GUIDELINES STATEMENTS

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

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 had RP only.[25,26] Patients also should be informed that if adverse pathology is detected, then additional therapy after surgery, such as radiotherapy, may be beneficial.

2. Patients with adverse pathologic findings including seminal vesicle invasion, positive surgical margins, and extraprostatic extension should be informed that adjuvant radiotherapy, compared to radical prostatectomy only, reduces the risk of biochemical (PSA) recurrence, local recurrence, and clinical progression of cancer. They should also be informed that the impact of adjuvant radiotherapy on subsequent metastases and overall survival is less clear; one of two randomized controlled trials that addressed these outcomes indicated a benefit but the other trial did not demonstrate a benefit. (*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 on these outcomes.

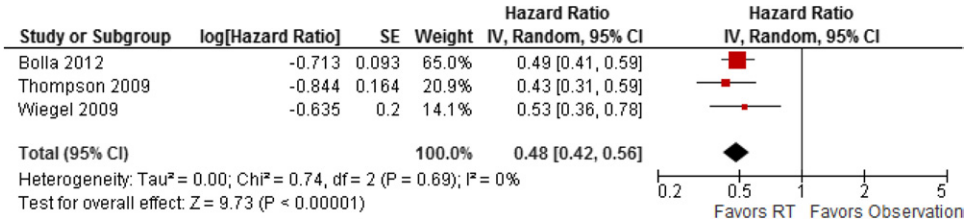
3. Physicians should offer adjuvant radiotherapy to patients with adverse pathologic findings at prostatectomy including seminal vesicle invasion, positive surgical margins, or extraprostatic extension because of demonstrated reductions in biochemical recurrence, local recurrence, and clinical progression.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

The Panel notes that the apparent benefits associated with ART are partially the result of a patient subset 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 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. radiotherapy). 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, preferences and tolerance for the potential toxicities and QoL effects of radiotherapy.

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 with use of ART compared to RP only (see figure). Two RCTs evaluated locoregional failure (SWOG 8794, EORTC 22911) and reported failure reductions in ART compared to RP only patients (EORTC 22911: ART 8.4%, RP only 17.3%, $p < 0.05$; SWOG 8794: ART 8%, RP only 22%, no p value reported).

SWOG 8794 and EORTC 22911 also reported statistically significant reductions in salvage therapy use with ART compared to RP only. SWOG 8794 reported improvement in hormonal therapy-free survival in ART patients (84%) compared to RP only patients (66%). EORTC 22911 reported that fewer ART patients (21.8%) had started an active salvage treatment (including salvage radiotherapy or ADT) compared to RP only patients (47.5%).

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



Meta-analysis of biochemical recurrence data from SWOG 8794,[26] EORTC 22911[25] and ARO 96–02[15]

difference was statistically significant in SWOG 8794 and borderline significant (p = 0.054) in EORTC 22911.

Prevention of biochemical progression and prevention of locoregional recurrence are important clinical endpoints because these events may trigger salvage therapy with associated toxicities and quality of life 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.

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 there is less certainty regarding benefits of ART to 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 post-prostatectomy PSA level. This is a salvage context for RT; SWOG 8794 and EORTC 22911 enrolled some patients with detectable PSA in the early post-RP period (<8 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]

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)*

Prostate specific antigen 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 are dead from their disease within 10 to 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.

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)*

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/content/media/psa09.pdf).

Patients who have had a prostatectomy should be informed that a PSA value ≥0.2 ng/ml that has been confirmed by a second elevated PSA value constitutes evidence of a 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 radiotherapy is offered.[28] The salvage literature also generally reports that patients who receive radiotherapy at lower PSA levels have better outcomes than do patients who receive radiotherapy at higher PSA levels. 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.[29]

Therefore, the decision to initiate salvage therapies 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.

6. A re-staging 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. 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.[30]

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)*

Two of the RCTs included a patient subgroup that had detectable PSA levels post-RP, i.e. 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 (HR = 0.75, 95% CI 0.52–1.08).[25]

Two observational studies reported outcomes for SRT patients vs. 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 of prostate cancer, a significantly higher rate than men who had SRT (11% deaths from prostate cancer).[32] This survival advantage was most marked in certain clinical subgroups (see complete 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 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, higher pT stages, with SVI and with EPE compared to 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.

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

The overwhelming majority of observational studies that compared bRFS for SRT patients at lower vs. higher pre-RT PSA levels reported that patients with lower pre-RT PSA levels had higher bRFS rates compared to patients with higher pre-RT PSA levels (differences 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 meta-regression performed on 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.[34]

Confirmatory subgroup analyses from SWOG 8794 indicate that among patients with detectable PSA at the time of radiotherapy, those with PSA values $\leq$1.0 ng/ml had higher 5 and 10-year bRFS rates than those with pre-RT PSA values $>$1.0 ng/ml.[28]

Therefore, patients should be advised that if recurrence is detected without evidence of distant metastases, then radiotherapy should be administered at the earliest sign of PSA recurrence.

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

Patient counseling regarding the potential toxicity and quality of life impact of radiotherapy is important to ensure that patients make informed treatment decisions and have appropriate expectations regarding the course and consequences of radiotherapy. Counseling should 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 most

Table 1. *Acute toxicity effects of radiotherapy after prostatectomy*

Study arm type	% Genitourinary		% Gastrointestinal	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Adjuvant	10.5–26	2.0–8.0	22.0–25.0	0.0–2.0
Salvage	3.0–82.0	0.0–6.0	2.9–96.0	0.0–2.2
Mixed	5.0–92.0	0.0–3.0	4.3–87.0	0.0–1.3

Ranges based on RTOG or CTCAE grading systems.

commonly used measures to report toxicity information were the Radiation Therapy Oncology Group measure for acute effects (through day 90), the RTOG/European Organization for Research and Treatment of Cancer measure for late RT effects (persisting beyond day 90 or developing after day 90) and the Common Toxicity Criteria Adverse Event measure using the same time frames. These measures use a rating system of 0 to 5: 0—no change in function, 1—minor change in function, 2—moderate change in function that may require medication, 3—major change in function sufficient to require more aggressive medication use or outpatient procedures, 4—severe symptoms requiring hospitalization and surgical procedures, and 5—death.

Acute Toxicity (table 1). Patients should be informed that during radiotherapy 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 frequently reported, with over 90% of patients experiencing these effects in some studies. Serious toxicity effects of radiotherapy, including those requiring aggressive medication management, outpatient procedures, or hospitalization, however, are uncommon or rare, with most studies reporting rates of <5%. The lowest acute toxicity rates have been reported with use of IMRT radiotherapy techniques.[35,36]

Late Toxicity (table 2). Patients should be informed that 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 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)[37] than to include 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 adjuvant RT 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 the majority of 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 radiotherapy is given, but that studies investigating the risk of developing secondary malignancies in post-RP men undergoing prostate cancer radiotherapy are inconclusive.

FUTURE DIRECTIONS

Ongoing Clinical Trials

Ongoing clinical trials (e.g. RTOG 0534, RTOG 9601, RADICALS, RAVES) will help to clarify the role of ART or SRT and 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 is 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

Table 2. *Late toxicity effects of radiotherapy after prostatectomy*

Study arm type	% Genitourinary		% Gastrointestinal	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Adjuvant	2.0–22.0	0.0–10.6	1.0–12.7	0.0–6.7
Salvage	1.0–49.0	0.0–6.0	0.0–66.0	0.0–18.0
Mixed	1.3–79.0	0.0–17.0	2.0–59.0	0.0–4.3

Ranges based on RTOG/EORTC or CTCAE grading systems.

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 or die of 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 quality of life. 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 (e.g. diabetes, hypertension, vascular disease) may increase the risk of radiation-related toxicity; better understanding of this issue also would improve patient selection procedures.

Conflict of Interest Disclosures

All panel members completed COI disclosures. 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.**Consultant/Advisor: Ian Thompson**, Ferring (C) (Expired), Cancer Prevention and Research Institute of Texas (C); **Peter Albertsen**, American Board of Urology (C) (Expired), Blue Cross/ Blue Shield (C), Dendreon (C), Fallon Medical Corporation (C) (expired), Johnson & Johnson (C) (Expired), National Cancer Institute (C) (expired), National Institutes of Health (C)(Expired), Oxford University (C) (Expired), Glaxo Smith Kline (C)(Expired); **Mack Roach**, Algeta (C) (Expired), Arista (C), Astellas (C), Astra-Zeneca (C), Bayer (C), CareCore (C) (Expired), Centocor Ortho Biotech (C) (Expired), Ferring (C), GE (C) (Expired), Molecular Insights (C), (Expired), Myriad (C) (Expired), Nihon Medi-Physics (C), Novartis (C) (Expired), Quest Labs, (C), Takeda (C), Trofex (C) (Expired), University of Pennsylvania (C) (Expired); A. **Oliver Sartor**, Algeta(C), Ausio (C) (Expired), Bayer (C), Bellicum (C), Celgene Corporations (C), (Expired), Dendreon (C), Enzon (C) (Expired), Exelixis (C), GSK (C) (Expired), GTX (C) (Expired), Johnson & Johnson (C), Medivation Neurology (C), Oncogenex (C), Pfizer (C) (Expired), Sanofi-Aventis (C), Tolmar Therapeutics (C) (Expired), Viamet (C) (Expired). **Health Publishing: Mack Roach**, Elsevier (C) (Expired), Springer (C), (Expired). **Leadership Position: Ian Thompson**, NCI, Early Detection Research (U), American Board of Urology (C) SWOG (U), Cancer Prevention and Research Institute of Texas (C),), UTHSCSA, CTRC (U); **Peter Albertsen**, Hartford County Medical Association (C), National Children's Cancer Society (U); **Brian Davis**, American Brachytherapy Society (U); **S. Larry Goldenberg**, Genyous Biomed (C); **Eric Klein**, Society of Urologic Oncology (U); **Jeff Michalski**, American Society of Radiation Oncology (U), Radiation Therapy Oncology Group (U); **Mack Roach**, American Cancer Society (U) (Expired). **Meeting Participant or Lecturer: Ian Thompson**, American Association for Cancer Research (C), American Society of Clinical Oncology (C), Canary Foundation (C), Columbia University (C), Cornell University (C), Doctors Hospital Renaissance (C), Ireland Urologic Society (C), Loredo Medical Center (C), Texas Urological Society (C), Urologic Society of Australia (C); **Peter Albertsen**, Cornell Medical Center (C), European Association of Urology (C) (Expired), International Robotic Conference (C), National Cancer Institute (C), New York University (C), Rigshospitalet (C) (Expired), Steba Pharmaceutical (C), University of Alabama (C) (Expired); **Brian Davis**, American Brachytherapy Society (C)(Expired); **Jeff Michalski**, Augmenix, Inc. (U) (Expired), Elekta, Inc. (U) (Expired), Viewrary, Inc. (C) (Expired); **Mack Roach**, Astra-Zeneca (C), Dendreon (C), (Expired), Ferring (C), GE (C) (Expired), Nihon Medi-Physics Co. (C), Siemens (C) (Expired). **Scientific Study or Trial: Ian Thompson**, National Cancer Institute-SWOG (C); **Peter Albertsen**, Sanofi Aventis (U) (Expired); **Brian Davis**, Mayo Clinic - Prostate SPORE program (U) (Expired); **Eric Klein**, Genomic Health (C), (Expired); **Jeff Michalski**, ATC (C) (Expired), NCCF (C) (Expired), National Institute of Health (C) Radiation Therapy Oncology Group (C) (Expired), SCC (C) (Expired); **Mack**

Roach, Focus Surgery (C) (Expired), Glaxo Smith Klein (C) (Expired), Molecular Insight, Trofex (C) (Expired); **Oliver Sartor**, Algeta (C), Astra-Zeneca (C) (Expired), Bayer (C), Cougar (C) (Expired), Exelixis (C), Johnson & Johnson (C), Millennium (C) (Expired), Sanofi-Aventis (C). **Investment Interest: Peter Albertsen**, Abbott Labs, Becton Dickinson, Bristol Myers Squibb, General Electric Co., Johnson & Johnson, Medco Health Solutions, Merck & Company, Pfizer Inc., Sanofi Aventis, Schering Plough Corp, TomoTherapy, Walgreens, WellPoint Inc.; **Brian Davis**, Pfizer; **Eric Klein**, Exelixis; **Oliver Sartor**, Glaxo Smith Klein, Johnson & Johnson, Lilly, Novartis. **Other, Patent license: Eric Klein**, Abbott Diagnostics (C); **Mack Roach**, Elsevier (C), Springer (C), Up -to Date(C).

Guidelines Disclaimer

This document was written by the Prostate Guidelines Panel of the American Society of Radiation Oncology and the American Urological Association Education and Research, Inc. Both the Guidelines Committee of ASTRO and the Practice Guidelines Committee of the AUA selected the respective committee chair. Panel members were selected by both panel chairs. Membership of the committee included urologists, radiation oncologists, and a medical oncologist, with specific expertise on this disorder. The mission of the committee was to develop recommendations that are analysis-based or consensus-based, depending on Panel processes and available data, for optimal clinical practices in the diagnosis and treatment of prostate cancer. Funding of the committee was provided by ASTRO and the AUA. Committee members received no remuneration for their work. Each member of the committee provides an ongoing conflict of interest disclosure to ASTRO and the AUA. **While these guidelines do not necessarily establish the standard of care, ASTRO/AUA seek to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated.** As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. Furthermore, this Guideline should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment and propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases. Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ("off label") that are not approved by the Food and Drug Administration, or about medications or substances not subject to the FDA approval process. ASTRO/AUA urge strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not intended to provide legal advice about use and misuse of these substances. ASTRO/AUA assume no liability for the information, conclusions, and findings contained in the Guideline. Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited and are prepared on the basis of information available at the time the panel was conducting its research on this topic. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices. For this reason, ASTRO/AUA does not regard technologies or management which are too new to be addressed by this Guideline as necessarily experimental or investigational. In addition, this Guideline cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment are needed or are being explored. This Guideline presents scientific, health, and safety information and may to some extent reflect scientific or medical opinion. It is made available to ASTRO and AUA members, and to the public, for educational and informational purposes only. Any commercial use of any content in this Guideline without the prior written consent of ASTRO or AUA is strictly prohibited.

REFERENCES

1. American Cancer Society: Prostate cancer key statistics. 2009; Available at http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics. Accessed November 3, 2012.

2. Amling CL, Blute ML, Bergstralh EJ et al: Long-term hazard of progression after radical prosta-

tectomy for clinically localized prostate cancer: continued risk of biochemical failure after 5 years. J Urol 2000; **164:** 101.

3. Chun FK, Graefen M, Zacharias M et al: Anatomic radical retropubic prostatectomy – long-term recurrence-free survival rates for localized prostate cancer. World J Urol 2005; **24:** 273.
4. Han M, Partin AW, Pound CR et al: Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy: the 15-year Johns Hopkins experience. Urol Clin North Am 2001; **28:** 555.
5. Bianco FJ Jr, Scardino PT and Eastham JA: Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). Urology 2005; **66:** 83.
6. Stephenson AJ, Scardino PT, Eastham JA et al: Preoperative nomogram predicting for the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Natl Cancer Inst 2006; **98:** 715.
7. Swindler P, Eastham JA, Ohori M et al: Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. J Urol 2005; **174:** 903.
8. Kupelian PA, Katcher J, Levin HS et al: Stage T1–2 prostate cancer: a multivariate analysis of factors affecting biochemical and clinical failures after radical prostatectomy. Int J Radiat Oncol Biol Phys 1997; **377:** 1043.
9. Lee HM, Solan MJ, Lupinacci P et al: Long-term outcome of patients with prostate cancer and pathologic seminal vesicle invasion (pT3b): Effect of adjuvant radiotherapy. Urology 2004; **64:** 84.
10. Ohori M, Wheeler TM, Kattan MW et al: Prognostic significance of surgical margins in radical prostatectomy specimens. J Urol 1995; **154:** 1818.
11. Lowe BA and Lieberman SF: Disease recurrence and progression in unrelated pathologic stage T3 prostate cancer: selecting the patient for adjuvant therapy. J Urol 1997; **158:** 1452.
12. Pound CR, Partin AW, Eisenberger MA et al: Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999; **281:** 1591.
13. Thompson IM Jr, Tangen CM, Paradelo J et al: Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA 2006; **296:** 2329.
14. Bolla M, van Poppel H, Collette L et al: Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet 2005; **366:** 572.
15. Wiegel T, Bottke D, Steiner U et al: Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol 2009; **27:** 292.
16. Bernard JR Jr, Buskirk SJ, Heckman MG et al: Salvage radiotherapy for rising prostate-specific antigen levels after radical prostatectomy for prostate cancer: dose-response analysis. Int J Radiat Oncol Biol Phys 2010; **76:** 735.
17. Cozzarini C, Montorsi F, Fiorino C at al: Need for high radiation dose (> or = 70 gy) in early postoperative irradiation after radical prostatectomy: a single-institution analysis of 334 high-risk, node-negative patients. Int J Radiat Oncol Biol Phys 2009; **75:** 966.
18. King CR and Spiotto MT: Improved outcomes with higher doses for salvage radiotherapy after prostatectomy. Int J Radiat Oncol Biol Phys 2008; **71:** 23.
19. Siegmann A, Bottke D, Faehndrich J et al: Dose escalation for patients with decreasing PSA during radiotherapy for elevated PSA after radical prostatectomy improves biochemical progression-free survival: results of a retrospective study. Strahlenther Onkol 2011; **187:** 467.
20. Ohri N, Dicker A, Trabulsi E et al: Can early implementation of salvage radiotherapy for prostate cancer improve the therapeutic ratio? A systematic review and regression meta-analysis with radiobiological modeling. Eur J Cancer 2012; **48:** 837.
21. Michalski JM, Lawton C, El Naqa I et al: Development of RTOG consensus guidelines for the definition of the clinical target volume for postoperative conformal radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2010; **76:** 361 (see http://www.rtog.org/CoreLab/ContouringAtlases/ProstatePostOp.aspx for atlas).
22. Sidhom MA, Kneebone AB, Lehman M et al: Post-prostatectomy radiation therapy: consensus guidelines of the Australian and New Zealand Radiation Oncology Genito-Urinary Group. Radiother Oncol 2008; **88:** 10.
23. Wiltshire KL, Brock KK, Haider MA et al: Anatomic boundaries of the clinical target volume (prostate bed) after radical prostatectomy. Int J Radiat Oncol Biol Phys 2007; **69:** 1090.
24. Poortmans P, Bossi A, Vandeputte K et al: Guidelines for target volume definition in post-operative radiotherapy for prostate cancer, on behalf of the EORTC Radiation Oncology Group. Radiother Oncol 2007; **84:** 121.
25. Bolla M, van Poppel H, Tombal B et al: Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomized controlled trial (EORTC trial 22911). Lancet 2012; **380:** 2018.
26. Thompson IM, Tangen CM, Paradelo J et al: Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term follow-up of a randomized clinical trial. J Urol 2009; **181:** 956.
27. Albertsen PC, Hanley JA, Penson DF et al: Validation of increasing prostate specific antigen as a predictor of prostate cancer death after treatment of localized prostate cancer with surgery or radiation. J Urol 2004; **171:** 2221.
28. Swanson GP, Hussey MA, Tangen CM et al: Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. J Clin Oncol 2007; **25:** 2225.
29. Shinghal R, Yemoto C, McNeal JE et al: Biochemical recurrence without PSA progression characterizes a subset of patients after radical prostatectomy. Prostate-specific antigen. Urology 2003; **61:** 380.
30. Dotan ZA, Bianco FJ Jr, Rabbani F et al: Pattern of prostate-specific antigen (PSA) failure dictates the probability of a positive bone scan in patients with an increasing PSA after radical prostatectomy. J Clin Oncol 2005; **23:** 1962.
31. Boorjian SA, Karnes RJ, Crispen PL et al: Radiation therapy after radical prostatectomy: impact on metastasis and survival. J Urol 2009; **182:** 2708.
32. Trock BJ, Han M, Freedland SJ et al: Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA 2008; **299:** 2760.
33. King CR: The timing of salvage radiotherapy after radical prostatectomy: a systematic review. Int J Radiat Oncol Biol Phys 2012; **84:** 104.
34. Ohri N, Dicker A, Trabulsi E et al: Can early implementation of salvage radiotherapy for prostate cancer improve the therapeutic ratio? A systematic review and regression meta-analysis with radiobiological modeling. Eur J Cancer 2012; **48:** 837.
35. Alongi F, Fiorino C, Cozzarini C et al: IMRT significantly reduces acute toxicity of whole-pelvis irradiation in patients treated with post-operative adjuvant or salvage radiotherapy after radical prostatectomy. Radiother Oncol 2009; **93:** 207.
36. Goenka A, Magsanoc JM, Pei Xet al: Improved toxicity profile following high-dose postprostatectomy salvage radiation therapy with intensity-modulated radiation therapy. Eur Urol 2011; **60:** 1142.
37. Ost P, Lumen N, Goessaert AS et al: High-dose salvage intensity-modulated radiotherapy with or without androgen deprivation after radical prostatectomy for rising or persisting prostate-specific antigen: 5-Year results. Eur Urol 2011; **60:** 842.