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ADJUVANT AND SALVAGE RADIOTHERAPY AFTER PROSTATECTOMY: AUA/ASTRO Guideline AMENDMENT 2018–2019

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Abstract

Purpose: The purpose of this amendment is to incorporate newly-published literature into the original ASTRO/AUA Adjuvant and Salvage Radiotherapy after Prostatectomy Guideline and to provide an updated clinical framework for clinicians.

Materials and Methods: The original systematic review yielded 294 studies published between January 1990 and December 2012. In April 2018, the guideline underwent an amendment and incorporated 155 references that were published from January 1990 through December 2017. Two new key questions were added. One on the use of genomic classifiers and the other on the treatment of oligo-metastases with radiation post-radical prostatectomy.

Results: A new statement on the use of hormone therapy with salvage radiotherapy after radical prostatectomy was added and long-term data was used to update an existing statement on adjuvant radiotherapy. The balance of the guideline statements were re-affirmed and references were added to the existing literature base. A discussion on the use of genomic classifiers as a risk stratification tool was added to the future research discussion. No relevant data on oligo-metastases was found.

Conclusions: Hormone therapy should be offered to patients who have had radical prostatectomy and who are candidates for salvage radiotherapy. The clinician should discuss possible short- and long-term side effects with the patient as well as the potential benefits of preventing recurrence. The decision to use hormone therapy should be made by the patient and a multi-disciplinary team of providers with full consideration of the patient's history, values, preferences, quality of life, and functional status.

PANEL DISCLOSURES

Consultant/Advisor: Ian Thompson, Threshold, Harvard University, Rapamycin Holdings

Scientific Study or Trial: Ian Thompson, SWOG, MagForce, Exosome Diagnostics

Keywords

radiotherapy; postoperative period; prostatectomy

INTRODUCTION

Guideline Purpose.

The purpose of this guideline is to provide direction to clinicians and patients regarding the use of radiotherapy (RT) after radical prostatectomy (RP) 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.

Methodology.

For the original 2013 guideline, literature searches were performed on English-language publications using the PubMed, Embase and the Cochrane database for Systematic Reviews from January 1990 to December 2012. Preclinical studies (e.g., animal models), commentaries and, editorials were excluded. Only studies in which prostate-specific antigen (PSA) data were provided for 75% or more of patients were included. References from review articles 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 non-redundant information. The original systematic review yielded an evidence base of 294 articles from which to construct a clinical framework for the use of RT after RP. In April 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. For this amendment, an identical approach was implemented to examine peer-reviewed articles published and indexed between September 2012 and December 2017. The Panel also added two new key questions. One concerned the use of genomic classifiers to predict treatment outcomes in the RT after RP setting. The second focused on the treatment of oligo-metastases with RT post-RP (no relevant data on oligo-metastases was found). A new search strategy was developed to identify literature relevant to these 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. Both 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 the best evidence approach, three randomized controlled trials (RCT) were evaluated in detail to produce this amendment.

For a complete discussion of the methodology and evidence grading, please refer to the unabridged guideline available at www.AUAnet.org.

Limitations of the Literature.

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

BACKGROUND

Prevalence.

In 2018, an estimated 164,690 men were diagnosed with prostate cancer.[1] RP constitutes a cure in approximately two-thirds of such men, but up to one-third of patients manifest recurrent disease within 10 years.[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 RT (ART) is the administration of RT post-RP 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 RT (SRT) is the administration of RT to the prostatic bed and possibly to the surrounding tissues, including lymph nodes, in the patient with PSA recurrence after surgery but no evidence of distant metastatic disease. Biochemical recurrence after surgery is defined as a detectable PSA level ≥ 0.2 ng/mL with a second confirmatory level > 0.2 ng/mL.

ART.

The highest-quality evidence that addresses the use of RT after RP is provided by three RCTs with ten years of follow-up data that examined the effect of RT delivered primarily as ART. However, it is important to note that all three RCTs were powered for different primary outcomes. The primary outcome for the Southwest Oncology Group (SWOG) 8794 trial was metastases-free survival; the European Organisation for Research and Treatment of Cancer (EORTC) 22911 used clinical progression-free survival as the primary outcome; and biochemical progression-free survival was the primary endpoint in the ARO 96–02 trial.[13–16]

ART vs. SRT.

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

The Panel attempted to address this issue by examining 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, making it unclear whether newer techniques might result in fewer apparent differences between ART and SRT outcomes. Overall, the existing literature could not answer this question.

Radiotherapy techniques.

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

Approximately one-third of the ART and SRT observational studies looked at patients treated with two-dimensional “conventional” methods, which have since been replaced by three-dimensional conformal RT (3D-CRT) or intensity-modulated RT. The published literature does not reflect implementation of these newer methods adequately. With regard to the RCTs of ART, SWOG 8794 and EORTC 22911 administered RT using “conventional” techniques;[13, 14] ARO 96–02 administered RT using 3D-CRT.[15, 16] The lack of high quality studies using newer RT methods made it difficult to definitively address the question of optimal methods and whether these might differ in the ART vs. SRT settings.

Among observational studies, RT doses ranged from 50–78 gray (Gy) where SRT studies administered somewhat higher dosages than ART studies. Although RT dose-escalation improves freedom from biochemical and (possibly) distant metastatic relapse when used as primary treatment for localized prostate cancer, RCTs have not reported the optimal post-RP RT dose. Clinical data suggest that doses above 65 Gy can be safely delivered and may lead to improved tumor control.[17–21] In the SWOG 8794, EORTC 22911, and ARO 96–02 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.[22–25]

Use of hormone therapy.

A key question is whether, when, for how long, and in what form hormone therapy should be administered. The literature review attempted to address these questions by examining studies that focused on the use of hormone therapy in patients who underwent RP and then ART or SRT. Two RCTs evaluated the effects of hormone therapy on OS, and on biochemical and clinical progression-free survival among participants who received SRT after RP. The Radiation Therapy Oncology Group (RTOG) 9601 trial of SRT with or without 24 months of bicalutamide (150 mg daily) had 13 years of follow-up, while the GETUG-AFU 16 trial examined the effects of SRT with or without 10.8 mg subcutaneous goserelin acetate given on the first day of RT, and again 3 months later, had 5 years of follow-up.[26, 27] Together, the Panel concluded that these provided sufficient evidence to develop a new statement (see Guideline Statement 9).

The Panel could not provide guidance on the use of hormone therapy in the ART setting given the methodological weaknesses of this literature. These weaknesses include non-randomized study designs, small sample sizes, lack of group equivalence on pathological risk factors, large variations in hormonal therapy protocols, primary focus on biochemical recurrence, and other differences relevant to efficacy such as differences in RT techniques, targets, and total dosage administered. RCTs in this area will be needed to provide definitive evidence.

Genomic classifiers to predict treatment effectiveness.

For this amendment, the Panel examined a new question to determine if there are genomic classifiers that could predict treatment effectiveness in this patient population. There were six retrospective studies and one Markov decision analysis using the Decipher™ classifier demonstrating its prognostic association with disease progression, focusing particularly on distant metastases after RP.[28–34] A 24-gene post-operative RT outcomes score (PORTOS) profile has also been described, as has a 50-gene (PAM50) molecular subtyping of basal and luminal cell lineage.[35, 36] Further evaluation is needed to determine whether genomic classifiers are predictive of a particular treatment effect in a yet-to-be-treated patient, and the Panel concluded that the present level of evidence cannot discern whether genomic classifiers can predict the efficacy, or lack thereof, of ART or SRT after RP. The timing (ART, early SRT, late SRT), type, targeted volume, and dosage of RT, and the use and duration of hormonal therapy are confounding variables that limit certainty in the interpretation of the current literature.

GUIDELINE AMENDMENTS

The 2018 amendment literature search did not uncover additional information that would alter Statement 1, Statements 3– 8, and Statement 10 (formerly Statement 9). They remain unchanged from the 2013 publication of this guideline; all new references have been added to the evidence base. The amended guideline focuses on Statement 2, which was revised to reflect the presence of 10-year data from ARO 96–02; only 5-year data was available from this trial during the publication of the original guideline. In addition, evidence from the RTOG 9601 and the GETUG-AFU 16 trials formed the evidence base to write a new guideline statement on the use of hormone therapy in patients receiving SRT after RP. A discussion on the use of genomic classifiers as a risk stratification tool was added to the future research discussion.

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)

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 progression. Three RCTs (SWOG 8794, EORTC 22911, and ARO 96–02) with more than 10 years of follow-up evaluated the effects of ART among patients with adverse pathology. All trials documented significant improvements in biochemical recurrence-free survival with the use of ART compared to RP only (See Figure 1). Patients should be informed that the impact of ART on metastases and OS is less clear, with benefits reported only in one of the three trials with long-term data on these outcomes.

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 hormonal or other therapies within patient subsets. (Standard; Evidence Strength: Grade A).

Two RCTs (RTOG 9601 and GETUG-AFU 16) evaluated the effects of hormone therapy on OS and on biochemical and clinical progression among patients who received SRT after RP.[26,27] RTOG 9601 reported longer term outcomes, and provided the opportunity to observe a significant advantage in OS at 12 years follow-up with 24-month duration of 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. Improved survival outcomes were also 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.

GETUG-AFU 16 had a primary outcome of progression-free survival, mainly a biochemical recurrence-free survival endpoint, and documented significant improvements in freedom from disease progression, which was observed in all prognostic subgroups. There was however no difference in OS at five years, but the study was not designed to detect any difference until ten years of follow-up.

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. When hormone therapy is offered, the clinician should discuss possible short- and long-term side effects with the patient as well as the potential benefits of preventing recurrence. The decision to use hormone therapy should be made by the patient and a multi-disciplinary team of providers using the shared decision-making model, taking into account the patient’s history, values, preferences, quality of life, and functional status.

FUTURE DIRECTIONS

Genomic classifiers.

The Decipher™ genomics resource information database has been recently used to link genomic findings with clinical outcomes, as have other methods. 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. At present, there is ongoing recruitment to a RCT conducted by NRG Oncology (GU002) that uses Decipher™ 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 hormonal 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.

DISCLAIMER

This document was written by the Prostate Guidelines Panel of the America Society of Radiation Oncology (ASTRO) and the American Urological Association Education and Research, Inc. (AUA). Both the Guidelines Committee of ASTRO and the Practice Guidelines Committee of the AUA selected the panel. 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 Food and Drug Administration 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.

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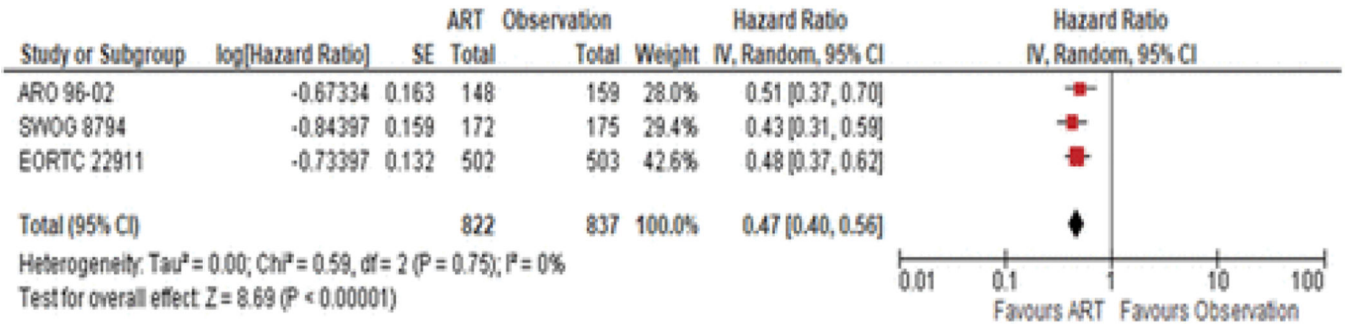

Figure 1.

Meta-analysis of biochemical recurrence data from SWOG 8794, EORTC 22911, and ARO 96–02