AMENDMENT SUMMARY

Adjuvant and Salvage Radiotherapy after Prostatectomy: ASTRO/AUA Guideline

Amendment Panel

Dr. Ian Thompson, MD (Co-Chair); Dr. Richard Valicenti, MD (Co-Chair); Dr. Thomas Pisansky, MD; Dr. Anthony D'Amico, MD

Purpose: This guideline's purpose is to provide direction to clinicians and patients regarding the use of radiotherapy (RT) after radical prostatectomy (RP) in patients with and without evidence of prostate cancer recurrence.

Updated Methodology

A systematic review was conducted to identify published articles relevant to the use of RT after RP, including its efficacy in patients with detectable and undetectable prostatic specific antigen (PSA) levels, its toxicity and quality of life (QoL) impact and optimal imaging strategies to determine the appropriateness of RT use in patients suspected of recurrence. Literature searches were performed on English-language publications using the PubMed, Embase and Cochrane databases from 1/1/1990 to 12/15/2012. Preclinical studies (e.g., animal models), commentary, and editorials were excluded. Only studies in which PSA data were provided for 75% or more patients were included. Review article references were checked to ensure inclusion of all possibly relevant studies. Multiple reports on the same patient group were carefully examined to ensure inclusion of only nonredundant information. The review yielded an evidence base of 294 articles from which to construct a clinical framework for the use of RT after prostatectomy.

In October 2018, the guideline was amended to maintain currency through a process in which newly published high quality literature was identified, reviewed, and integrated into the original 2013 guideline. The original search strategy, with two differences, was re-implemented by an experienced medical librarian. It was limited to publication dates from September 2012 to December 2017, and it added the MeSH heading "Radiotherapy, Adjuvant" that was deliberately excluded from the search strategy used during the production of the original guideline. The Panel had also added two new key questions to explore during this timeframe search. The new key questions concerned (a) the use of genomic classifiers to predict treatment outcomes in the radiation after prostatectomy setting, and (b) the treatment of oligo-metastases with radiation post-prostatectomy. A new search strategy was developed to identify literature relevant to the two new key questions. This search was conducted from January 1990 to December 2017 to ensure uniformity with the search period used to explore the questions from the original guideline. These searches yielded a total of 2,516 references of which 2,361 were excluded after de-duplication and title and abstract review. Full texts were retrieved for 155 references for more

detailed review. Using methodological criteria employed in the original guideline and the best evidence approach, synthesis of new, relevant evidence was focused on the recent publication of three randomized controlled trials with 60 or more months of follow-up. Two of these trials formed the crux of this amended guideline by providing evidence on the use of hormone therapy among men who received salvage radiotherapy (SRT) after primary RP, a patient population who until now, have lacked Level 1 evidence-based recommendations. In addition, long-term data from the ARO 96-02 trial comparing adjuvant radiotherapy (ART) to wait-and-see was incorporated to update Guideline Statement 2. No relevant studies were found to directly address the two new key questions concerning the predictive ability of genomic classifiers and treatment of oligo-metastases in the radiation after prostatectomy setting.

Peer Review and Approval: The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts in the use of adjuvant and salvage radiotherapy after prostatectomy. In addition to reviewers from the AUA Practice Guidelines Committee (PGC), Science and Quality Council (SQC), and Board of Directors (BOD), the document was reviewed by representatives from ASTRO as well as external content experts. The guideline was also sent to the Urology Care Foundation to open the document further to the patient perspective. The draft guideline document was distributed to 21 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 20 reviewers provided comments. At the end of the peer review process, a total of 73 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC, SQC and BOD as well as the governing body of ASTRO for final approval.

Summary of Guideline Changes

Guideline Statement 2: Patients with adverse pathologic findings including seminal vesicle invasion, positive surgical margins, and extraprostatic extension should be informed that adjuvant radiotherapy, compared to RP only, reduces the risk of biochemical (PSA) recurrence, local recurrence, and clinical progression of cancer. They should also be informed that the impact of adjuvant radiotherapy on subsequent metastases and overall survival is less clear; one of three randomized controlled trials that addressed these outcomes indicated a benefit but the other two trials did not demonstrate a benefit. However, these two trials were not designed to identify a significant reduction in metastasis or death with adjuvant radiotherapy. (Clinical Principle)

Guideline Statement 9: Clinicians should offer hormonal therapy with radiotherapy to patients who are candidates for salvage radiation therapy. (Standard; Evidence Strength: Grade A)

Research Needs and Future Directions
Genomic classifiers as predictors of treatment effectiveness. Tissue microarray analysis of prostatectomy samples can describe the gene expression profile of the prostate cancer phenotype.

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

Updated References

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