ADJUVANT AND SALVAGE RADIOTHERAPY AFTER PROSTATECTOMY: ASTRO/AUA GUIDELINE

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Purpose: The purpose of this guideline is to provide a clinical framework for the use of radiotherapy after prostatectomy in patients with and without evidence of prostate cancer recurrence.

Methods: A systematic review of the literature using the Pubmed, Embase and Cochrane databases (search dates 1/1/90 to 12/15/12) was conducted to identify peer-reviewed publications relevant to the use of radiotherapy after prostatectomy. The review yielded an evidence base of 294 articles after the application of inclusion/exclusion criteria. These publications were used to create the guideline statements. If sufficient evidence existed, then the body of evidence for a particular treatment was assigned a strength rating of A (high quality evidence; high certainty), B (moderate quality evidence; moderate certainty) or C (low quality evidence; low certainty) and evidence-based statements of Standard, Recommendation or Option were developed. Additional information is provided as Clinical Principles and Expert Opinion when insufficient evidence existed. See text for definitions and detailed information.

GUIDELINE 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)
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. However, the other trial was not powered to test the benefit regarding metastases and overall survival. (Clinical Principle)
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)
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)
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)
6. A restaging evaluation in the patient with a PSA recurrence may be considered.

(Option; Evidence Strength: Grade C)

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

INTRODUCTION

This guideline's purpose is to provide direction to clinicians and patients regarding the use of radiotherapy (RT) after prostatectomy in patients with and without evidence of prostate cancer recurrence. The strategies and approaches recommended in this document were derived from evidence-based and consensus-based processes. This document constitutes a clinical strategy and is not intended to be interpreted rigidly. The most effective approach for a particular patient is best determined by discussions among the multidisciplinary team of physicians, the patient, and his family. As the science relevant to the use of RT after prostatectomy evolves and improves, the strategies presented here will require amendment to remain consistent with the highest standards of clinical care.

METHODOLOGY

A systematic review was conducted to identify published articles relevant to the use of RT after prostatectomy, 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. Data from studies published after the literature search cut-off will be incorporated into the next version of this guideline. Preclinical studies (e.g., animal models), commentary and editorials were excluded. Only studies in which PSA data were provided for 75% or more patients were included. Review article references were checked to ensure inclusion of all possibly relevant studies. Multiple reports on the same patient group were carefully examined to ensure inclusion of only nonredundant information. The review yielded an evidence base of 294 articles from which to construct a clinical framework for the use of RT after prostatectomy.

Quality of Individual Studies and Determination of Evidence Strength. Quality of individual studies that were randomized controlled trials (RCTs) or controlled clinical trials (CCTs) was assessed using the Cochrane Risk of Bias tool.[1] Case-control studies and comparative observational studies were rated using the Newcastle-Ottawa Quality (NOQ) Assessment Scale.[2] Because there is no widely-agreed upon quality assessment tool for single cohort observational studies, the quality of these studies was not assessed except in the case of diagnostic accuracy studies. Diagnostic accuracy studies were rated using the QUADAS.[3,4]

The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes consideration of study design, individual study quality, consistency of findings across studies, adequacy of sample sizes and generalizability of samples, settings, and treatments for the purposes of the guideline. The AUA categorizes body of evidence strength (ES) as Grade A (well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings) or Grade C (observational studies that are inconsistent, have small sample sizes or have other problems that potentially confound interpretation of data). By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.[5]

For some clinical issues, there was little or no evidence from which to construct evidence-based statements. Where gaps in the evidence existed, the Panel provides guidance in the form of *Clinical Principles* or *Expert Opinion* with consensus achieved using a modified Delphi technique if differences of opinion emerged.[6] A *Clinical Principle* is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. *Expert Opinion* refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge and judgment for which there is no evidence.

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty and the Panel's judgment regarding the balance between benefits and risks/burdens.[5] ***Standards*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade A (high level of certainty) or Grade B (moderate level of certainty) evidence. ***Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade C (low level of certainty) evidence. ***Options*** are non-directive statements that leave the decision to take an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears relatively equal or appears unclear; ***Options*** may be supported by Grade A (high certainty), B (moderate certainty), or C (low certainty) evidence.

Limitations of the Literature. The Panel proceeded with full awareness of the limitations of the RT after prostatectomy literature. A major limitation of this literature is the lack of a large number of randomized controlled trials (RCTs) to guide decision-making in patients with and without evidence of recurrence and to indicate the appropriate use of androgen deprivation therapies in these patients. Further, a major limitation of all randomized trials in localized prostate cancer with long-term follow-up is the change in characteristics of contemporary patients; because of increased prostate cancer screening via prostatic specific antigen (PSA) testing and consequent detection of disease and initiation of therapy at earlier disease stages, patients recruited into trials decades ago have a greater risk of adverse outcomes than do contemporary patients. However, the Panel is fully aware that these issues will always be present in trials of therapies for localized prostate cancer because disease events (e.g., metastases and death) generally occur one to two decades after treatment.

Additional limitations include the preponderance of non-randomized studies; poorly-defined or heterogeneous patient groups; the lack of group equivalence in terms of pathological risk factors in studies that compared RT administered to patients with and without recurrence; variability in PSA assay sensitivity and in failure criteria across studies and over time; heterogeneity of cumulative radiation dose, dose schedules, methods of administering radiation and treatment planning protocols; the paucity of studies with follow-up duration longer than 60 months; and the overwhelming focus of the literature on biochemical recurrence with less information available regarding metastatic recurrence, cancer-specific survival and overall survival. In addition, relatively few studies focused on QOL outcomes that are of critical importance to patients, such as voiding and erectile function.

Process. The Radiotherapy after Prostatectomy Panel was created in 2011 by the American Urological Association Education and Research, Inc. (AUA) and the American Society for Radiation Oncology (ASTRO). The AUA Practice Guidelines Committee (PGC) and the ASTRO Guidelines Committee (GC) selected the Panel Chairs and the additional panel members with specific expertise in this area.

AUA and ASTRO conducted a thorough peer review process. The draft guidelines document was distributed to 75 peer reviewers, of which 44 reviewers provided comments. The panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC and the ASTRO GC. Then it was submitted to the AUA and ASTRO Boards of Directors for final approval. Funding of the panel was provided by the AUA and ASTRO; panel members received no remuneration for their work.

Table 1: AUA Nomenclature

Linking Statement Type to Level of Certainty and Evidence Strength

Standard: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A (high quality; high certainty) or B (moderate quality; moderate certainty) evidence
Recommendation: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade C (low quality; low certainty) evidence
Option: Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears equal or appears uncertain based on Grade A (high quality; high certainty), B (moderate quality; moderate certainty), or C (low quality; low certainty) evidence
Clinical Principle: a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature
Expert Opinion: a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence

BACKGROUND

In 2012 an estimated 241,740 men were diagnosed with prostate cancer.[7] The most common primary treatment for localized disease is radical prostatectomy (RP).[8] In approximately two-thirds of men, prostatectomy constitutes a cure, but within 10 years up to one-third of patients will present with recurrent disease.[9-12] Recurrence after prostatectomy is thought to result from residual subclinical disease in the operative site that later manifests as a rising prostate-specific antigen (PSA) level, a local tumor recurrence, metastatic disease or occult metastatic disease that was present at the time of the prostatectomy. The risk of recurrence is greater among men with adverse pathology, such as positive surgical margins, seminal vesicle invasion (SVI), extraprostatic extension (EPE) and higher Gleason scores.[13-22]

Clinicians, therefore, frequently face two scenarios in the patient for whom prostatectomy is the primary prostate cancer treatment. In the high-risk patient, revealed to have adverse pathological features at prostatectomy, clinicians and patients face the question of whether an adjuvant therapy should be considered to prevent possible future recurrence. In the post-prostatectomy patient who later presents with a detectable PSA level, appropriate salvage therapies may be considered. This guideline focuses on the evidence for use of RT in the adjuvant and salvage contexts.

Adjuvant radiotherapy (ART) is defined as the administration of RT to post-prostatectomy patients at a higher risk of recurrence because of adverse pathological features prior to evidence of disease recurrence (i.e., with an undetectable PSA). There is no evidence that addresses the timing of the first PSA test post-prostatectomy to determine a patient's disease status; in the Panel's clinical experience the first PSA generally should be obtained two to three months post-RP. ART is usually administered within four to six months following RP. Generally, RT is initiated after the return of acceptable urinary control. As sexual function can require one to two years before a full return of function is observed, return of erections is not a requirement before initiation of adjuvant radiation.

Salvage radiotherapy (SRT) is defined as the administration of RT to the prostatic bed and possibly to the surrounding tissues, including lymph nodes, in the patient with a PSA recurrence after surgery but no evidence of distant metastatic disease. *Biochemical (PSA) recurrence after surgery* is defined as a detectable PSA level $\geq$ 0.2 ng/mL with a second confirmatory level $\geq$ 0.2 ng/mL.

The most commonly-reported post-prostatectomy outcome in the peer-reviewed literature is biochemical (PSA) recurrence and biochemical recurrence-free survival (bRFS). Other reported outcomes include local recurrence and local recurrence-free survival, metastatic recurrence and metastatic recurrence-free survival (mRFS), clinical progression-free survival (no evidence of local or metastatic progression, excluding evidence of biochemical recurrence), cancer-specific survival and overall survival. Clinicians generally use regularly-obtained PSA levels over time in post-RP patients to detect recurrence, to trigger the administration of additional therapies and/or to guide further diagnostic evaluations.

Adjuvant radiotherapy (ART). The highest-quality evidence that addresses the use of RT after prostatectomy is provided by three randomized controlled trials (RCTs) that have examined the effect of RT delivered primarily in an adjuvant context. Findings from the three trials are reviewed below and in Appendices B and C. It is important to note that the three trials were powered for different primary outcomes. The primary outcome for SWOG 8794 was metastases-free survival, defined as time to first evidence of metastatic disease or death due to any cause. The primary outcome for EORTC 22911 was initially local control but changed in March 1995 to clinical progression-free survival. The primary outcome in ARO 96-02 was biochemical progression-free survival. Further, the majority of patients in the RT arms of these three trials were treated with 60 Gy – a dose somewhat lower than currently used.

Overall Findings

Biochemical recurrence. Three RCTs (SWOG 8794, EORTC 22911 and ARO 96-02), two with more than 10 years of follow-up, documented significant improvements in biochemical recurrence-free survival (bRFS) among patients with adverse pathological features (i.e., seminal vesicle invasion, positive surgical margins and/or extraprostatic extension) with the use of ART in comparison with observation only post-prostatectomy.[23-25] A meta-analysis of biochemical recurrence data performed as part of the literature review yielded a pooled hazard ratio of 0.48 (95% confidence interval: 0.42 – 0.56; p <0.00001; random effects model; see Appendix A). ARO 96-02 trial is the only trial in which all patients had an undetectable PSA at the time of RT.

Locoregional recurrence. Two RCTs demonstrated a reduction in locoregional failure in ART patients compared to RP only patients; ARO 96-02 did not assess locoregional failure. This difference was statistically significant in EORTC 22911[24] at median 10.6 years of follow-up with 8.4% of ART patients having locoregional failure compared to 17.3% of RP only patients. In SWOG 8794, also at 10.6 years of

follow-up, locoregional recurrence was 8% in the ART group and 22% in the RP only group ($p< 0.01$).[26]

Hormonal-therapy free survival. SWOG 8794 also reported a statistically significant improvement in hormonal therapy-free survival in ART patients compared to RP, only patients with approximately 84% of ART patients remaining hormone-therapy free at 10 years compared to approximately 66% of RP only patients. EORTC 22911 reported that by year 10, 21.8% of patients in the ART group had started an active salvage treatment (including SRT or ADT) compared to 47.5% of patients in the RP only group -- a statistically significant difference. It should be noted that the use of salvage therapies was at physician discretion and not prescribed by trial protocols.

Clinical progression. SWOG 8794 and EORTC 22911 also both demonstrated improved clinical progression-free survival (defined as clinical or imaging evidence of recurrence or death but not including biochemical progression) in patients who had ART compared to those who had RP only. This difference was statistically significant in SWOG 8794 at median 10.6 years of follow-up and borderline significant ($p = 0.054$) in EORTC 22911 at the same follow-up point. The weaker effect in EORTC 22911 may have been the result of the higher rate of non-prostate cancer mortality among the ART group (17.1%) compared to the RP only group (12.3%) or possibly because salvage treatments in the RP only group were initiated at lower PSA levels than in the ART group.

Metastatic recurrence and overall survival. Only SWOG 8794 demonstrated significantly improved overall survival (74% in ART patients compared to 66% for RP only patients) and significantly improved metastatic recurrence-free survival (defined as evidence of metastases or death from any cause; 71% for ART patients compared to 61% for RP only patients) with the use of ART compared to RP only at more than 12 years of follow-up.[26,27] These findings did not replicate in EORTC 22911 at median 10.6 years of follow-up.[24]

There are several differences between the two trials that may be relevant to the disparate findings. The overall survival rate of the RP only group in SWOG 8794 was much lower (66.0%) than the RP only group in EORTC 22911 (80.7%); the reason for the lower survival rate in SWOG 8794 is not clear. The trials used identical patient selection criteria. Patient demographics were reported differently in the two trials, making it somewhat difficult to compare recruited patient characteristics that might be relevant to the disparate findings. The proportion of patients administered preoperative hormonal therapies was similar (SWOG 8794 – 8% of RP only group, 9% of ART group; EORTC 22911 – 10% of each group). More patients had SVI in EORTC 22911 (approximately 25% of each group) than in SWOG 8794 (10% to 11% of each group). In SWOG 8794, 68% of the RP only group and 67% of the ART group had EPE or positive margins. EORTC 22911 reported that 78.9% of the RP only group and 75.1% of the ART group had EPE and 63% of the RP only group and 62.2% of the ART group had positive margins. The proportion of patients with post-RP PSA values ≤ 0.2 ng/ml also was relatively similar across trials (SWOG 8794 – 68% of RP only group, 65% of ART group; EORTC 22911 – 68.6% of RP only group, 70.3% of ART group). It is noteworthy that the median age of the SWOG 8794 RP only group was 1.7 years older (65.8 years) than the median age of the ART group (64.1 years). Median overall survival for the RP only group (13.3 years) was 1.9 years less than for the ART group (15.2 years), raising the possibility that the survival difference between the arms might be the result of the older age at enrollment of the RP only group. In the other two trials, there was no age difference between the two groups. None of these patient-level differences, however, clearly explain the outcome differences. It also is possible that salvage treatments in SWOG 8794 were not used as extensively as in EORTC 22911; the trials had similar rates of salvage treatment despite higher relapse rates in SWOG 8794. An additional possibility has to do with the fact that the number of deaths from prostate cancer in EORTC 22911 was extremely low – making it unlikely that ART would result in a survival advantage. A definitive answer has yet to be identified.

Subgroup Findings

The three RCTs also reported outcomes for various patient subgroups (see Appendix C). The Panel is fully aware of the clinical need for evidence-based risk stratification to inform decision-making regarding the use of ART in patients with specific pathological findings. However, after reviewing the subgroup findings from the best evidence available – the three RCTs – the Panel could not come to definitive conclusions. There are inconsistencies across trials in terms of which subgroups were selected for analysis and inconsistencies in the findings across subgroups. In addition, subgroup analyses were not performed for all outcomes. Further, the Panel notes that the trials did not stratify randomization by subgroups and that these comparisons were unplanned, internal analyses for which the trials did not necessarily have sufficient statistical power. Subgroup analyses, therefore, should be interpreted with caution and their utility is primarily to generate hypotheses and guide new research directions – not to test hypotheses. These analyses are summarized below.

Positive surgical margins. All three trials reported a statistically significant improvement in biochemical RFS among patients with positive surgical margins who received RT compared to patients who did not. In

addition, both SWOG 8794 and EORTC 22911 reported a significant improvement in clinical RFS among patients who received RT (this outcome was not addressed by ARO 96-02). Only EORTC 22911 reported overall survival data for this subgroup; there were no differences in overall survival between patients who did or did not receive RT.

Patients with positive surgical margins comprised the majority in EORTC 22911 (62.2% of the ART group; 63% of the RP only group) and in ARO 96-02 (68% of the ART group; 61% of the RP only group). SWOG 8794 did not report the number of patients with positive margins separately but reported that 67% of patients in the ART group and 68% in the RP only group had disease that extended beyond the capsule or had positive margins.

Negative surgical margins. Among patients with negative surgical margins, EORTC 22911 reported that the use of RT did not improve clinical RFS rates and significantly decreased overall survival (HR 1.68; 95% CI 1.10-2.56). Although EORTC 22911 reported a significant improvement in biochemical RFS with RT in this subgroup, ARO 96-02 reported no improvement with RT. SWOG 8794 did not address outcomes among patients with negative margins.

Seminal vesicle invasion (SVI). In patients with SVI, SWOG 8794 and EORTC 22911 reported significantly improved bRFS with RT. However, RT did not improve clinical RFS in either trial, metastatic RFS in SWOG 8794 or overall survival in EORTC 22911. Further, ARO 96-02 reported no difference in bRFS with RT among patients with SVI.

Absence of SVI. Only EORTC 22911 reported on patients without SVI and the findings are exactly the same as for patients with SVI – improved bRFS but no difference in clinical RFS or overall survival.

Extraprostatic extension (EPE). EORTC 22911 and ARO 96-02 reported significantly improved biochemical RFS with use of RT among patients with EPE. EORTC 22911 reported no differences, however, in clinical recurrence-free survival or overall survival. SWOG 8794 did not report on this subgroup.

Absence of EPE. Only EORTC 22911 reported on outcomes among patients without EPE. Similar to patients with EPE, use of RT among patients without EPE significantly improved bRFS but not clinical recurrence-free survival or overall survival.

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

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

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

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

Interpretation

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

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

The number needed to treat (NNT) is a helpful statistic to put these issues in context; the lower the NNT, the more effective the treatment or intervention in preventing the designated outcome. For example, the

European Randomized Study of Screening for Prostate Cancer (ERSPC) followed men randomly assigned to a PSA screening group compared to a control group not offered screening.[28] At median 11 years of follow-up the authors reported that 1,055 men would need to be invited for screening and 37 cancers would need to be detected in order to prevent one death from prostate cancer.

With regard to prostatectomy compared to watchful waiting, Bill-Axelson[29] reported that at 15 years post-RP, the NNT for overall survival was 15. That is, approximately 15 men would have to undergo prostatectomy in order to prevent one death from any cause compared to watchful waiting. Using data from approximately 45,000 patients from the SEER database, Abdollah[30] stratified patients into high-risk (pT2c or Gleason 8-10) vs. low-intermediate risk (all other patients) and reported an NNT at 10 years of follow-up of 13 for death from prostate cancer for high-risk patients and an NNT of 42 for low-intermediate risk patients.

With regard to RP plus ART compared to RP only, SWOG 8794 reported an NNT of 9.1 for overall survival, indicating that approximately 9 men would need to be treated with RP+ART compared to RP only to prevent one death from any cause at median 12.6 years of follow up.[26] With regard to preventing metastatic disease, SWOG 8794 reported an NNT of 12.2. EORTC 22911 did not replicate these findings and reported a higher overall death rate among RP+ART patients (25.9%) compared to RP only patients (22.9%) – these data yield a negative NNT, indicating a lack of benefit for the active treatment. With regard to cancer-specific survival, for which EORTC 22911 also did not document a treatment benefit, the NNT calculated from the raw data provided in Appendix B[24] is 55.6, indicating that approximately 56 men would need to be treated with RP+ART to prevent one case of death from prostate cancer at 10.6 years of follow-up compared to RP only (the other two trials did not report cancer-specific data). As a point of comparison, a pooled NNT for preventing biochemical recurrence derived from combining SWOG 8794 and EORTC 22911 (which each had follow-up durations >10 years) is 4.2. Combining local recurrence data from SWOG 8794 and EORTC 22911 yields an NNT of 9.8. Combining clinical progression data from SWOG 8794 and EORTC 22911 yields an NNT of 13.8.

Given the findings from the RCTs, the nature of adjuvant treatments to inevitably result in over-treatment of some patients, and the contextual information provided by NNTs, the Panel emphasizes that ART should be offered to all patients at high risk of recurrence because of adverse pathological features. The offering of ART should occur in the context of a thorough discussion of the potential benefits and risks/ burdens associated with ART (see Guideline Statements 2 and 3). Ultimately, whether ART is likely to benefit a particular patient and should be administered is a decision best made by the multidisciplinary treatment team and the patient with full consideration of the patient's history, values and preferences.

Salvage radiotherapy (SRT). Evidence regarding the efficacy of SRT in the post-RP patient is available in the form of a large literature composed of observational studies; however, only a few studies compared post-RP patients with PSA or local recurrence who received SRT to patients with PSA or local recurrence post-RP who did not receive further therapy.[31, 32] Generally, these studies indicate that SRT improves outcomes compared to RP only patients but the benefits may be specific to certain risk groups (see Discussion under Guideline Statement 7). In addition, two of the three RCTs (SWOG 8794 and EORTC 22911) enrolled patients with detectable PSA levels post-RP – salvage patients by definition. These two trials also generally revealed better outcomes among SRT patients compared to RP only patients with evidence of PSA recurrence (see Discussion under Guideline Statement 7).

ART vs. SRT. One of the most pressing clinical questions regarding the care of the post-RP patient is whether it is better to administer RT before evidence of recurrence – RT as adjuvant therapy – or to wait until recurrence manifests and then administer RT as salvage therapy. It is acknowledged that the use of ART may involve irradiation of some patients who never would have had recurrent cancer, thus exposing them unnecessarily to the risks, toxicity, and quality of life impact of RT. Waiting to administer RT as a salvage therapy limits its use to patients with recurrence but, particularly in patients with high-risk disease, could be less effective and could allow the progression to metastatic disease.

The literature review attempted to address this issue by examining the large number of observational studies that reported outcomes for ART and SRT patients in the PSA era. Study arms were categorized as adjuvant if post-RP patients administered RT had no evidence of recurrence based on the PSA failure threshold used by the authors. Study arms were categorized as salvage if post-RP patients had evidence of PSA or local

[i] NNTs from papers that compared RP to watchful waiting appear to have been calculated using cumulative incidence rates whereas the NNTs from SWOG 8794 reported in Thompson[26] and calculated from data provided in EORTC 22911[24] and ARO 96-02[25] for purposes of comparison were calculated using raw event data; these different calculation methods will yield somewhat different NNTs because they use different denominators (use of cumulative incidence rates will lead to higher NNTs). As an example, using raw event data from Bolla[24] yielded an NNT of 55.6 for cancer-specific survival; using cumulative incidence data provided in the text of the same paper yielded an NNT of 66.7 for cancer-specific survival.

recurrence at the time of RT administration. A third group of studies in which outcomes for ART and SRT patients were combined also was retrieved. Mixed studies were considered with regard to toxicity and quality of life outcomes (see section below) but not for efficacy outcomes.

The search yielded 48 ART study arms reporting outcomes for 4,043 patients.[18, 31, 33-74] The search yielded 137 SRT study arms reporting outcomes for 13,549 patients.[18, 31-2, 36-39, 43-46, 50-1, 53, 55-61, 63, 65, 67-9, 72-163]

When this literature is examined as a whole, it appears that ART patients generally have better outcomes compared to SRT patients. For example, ART study arms generally report lower rates of biochemical recurrence and metastatic recurrence than do SRT study arms at similar post-RP follow-up durations. Patterns with regard to cancer-specific survival and overall survival are less clear because few ART studies reported these outcomes.

Overall, the interpretation that ART leads to superior outcomes is difficult to make with certainty in the absence of randomization and given that SRT studies focus only on patients who have already relapsed, making direct comparisons with ART studies problematic. ART and SRT studies also differ across numerous factors, any of which potentially confound interpretation. These include differences in patient characteristics (e.g., ART patients generally have more adverse pathological profiles), RT protocols (e.g., SRT studies often used higher RT doses than ART studies), failure definitions, follow-up durations, and in other key factors. In addition, most of the published literature reports findings from the use of older RT techniques (e.g., EBRT protocols), making it unclear whether newer techniques might result in fewer apparent differences between ART and SRT outcomes.

Given these issues, the Panel concluded that it is not possible from the available evidence to address the question of the superiority of ART vs. SRT. A recent propensity score-matched, multi-institutional analysis has attempted to address this issue, reporting no difference in biochemical recurrence-free survival rates at 60 months between pT3N0 patients administered RT adjuvantly compared to those observed and treated with early SRT (with PSA ≤ 0.5 ng/ml).[36] In this analysis, however, the follow-up duration for the observed group was considerably shorter (median 30 months) than the follow-up duration for the ART group (median 67 months). Currently, two RCTs are actively accruing patients to address this important question – the RADICALS trial (MRC PR10, NCIC PR13) and the RAVES trial (TROG 08.03; see more detailed discussion in Research Needs and Future Directions).

Radiotherapy techniques and protocols in the post-prostatectomy patient. The Panel's literature review attempted to address the question of which RT techniques and doses produced optimal outcomes in the adjuvant and salvage context. It was not possible to answer these questions, however, from the available data.

Specifically, approximately one-third of the ART and SRT observational studies treated patients with conventional external beam modalities that have since been replaced by more sophisticated approaches using three-dimensional conformal RT (3D-CRT) or intensity-modulated radiotherapy (IMRT) methods. The published literature has lagged well behind the implementation of these newer methods, with only one-quarter of the reviewed studies reporting use of 3D-CRT techniques and less than 5% reporting use of IMRT techniques. The remaining studies used either a mix of techniques, without separating patient outcomes based on technique or did not report enough information to determine the type of RT used. The lack of studies using newer RT methods made it difficult to definitively address the question of optimal methods in general and whether these might differ in the adjuvant v. salvage contexts.

With regard to the randomized controlled trials of ART, the men treated in SWOG 8794 and EORTC 22911 were administered RT using EBRT techniques;[23, 164] patients in ARO 96-02 were administered 3D-CRT.[25] Although there were no clear differences in toxicity among the RT arms of the three RCTs, a broader literature suggests that patients treated with 3D-CRT and IMRT would be expected to experience less treatment-related toxicity and better biochemical and local control compared to men irradiated with traditional techniques.[54, 165]

Among the observational studies, the RT dosages varied from 50 to 78 Gy with most studies administering doses in the 60 to 70 Gy range and with SRT studies administering somewhat higher radiation dosages than ART studies (median ART dose – 61 Gy; median SRT dose – 65 Gy). Although RT dose-escalation has been shown in multiple randomized trials to improve freedom from biochemical relapse when used as primary treatment for localized prostate cancer, the optimal post-prostatectomy radiation dose is less clear and has never been tested in a prospective fashion. However, the clinical data suggest that doses above 65 Gy can be safely delivered and may lead to improved tumor control as determined by a reduction in biochemical progression.[7, 42, 107, 140, 166] In the three RCTs, the majority of patients were treated with radiation doses of 60 Gy, which was lower than the dose used in most observational studies.

In the Panel's view, 64-65 Gy is the minimum dose that should be delivered in the post-RP setting but decisions regarding dose should always be made by the treating physician who has full knowledge of a particular

patient's functional status, history, and tolerance for toxicity. The Panel is aware that there is controversy in the field regarding appropriate RT targets and field size. This issue was beyond the scope of this guideline; however, guidance can be found in Michalski[167] (see http://www.rtog.org/CoreLab/ContouringAtlases/ProstatePostOp.aspx for atlas), Sidhom,[168] Wiltshire[169] and Poortmans.[170]

Given the difficulties in interpreting findings from the observational studies and the lack of high-quality evidence regarding optimal RT dosing and protocols in the adjuvant and salvage contexts, it is not possible at this time to identify the best RT strategies for these patients.

Use of androgen-deprivation therapies in conjunction with RT in the post-RP patient. One of the questions faced by the clinician and post-prostatectomy patient is whether, when, for how long and in what form androgen-deprivation therapy (ADT) should be administered. The systematic review attempted to address these questions by retrieving the literature that focused on the use of ADT in patients who underwent prostatectomy and then ART or SRT. The Panel's conclusion after reviewing the available evidence (see brief review below) was that, given the methodological weaknesses of this literature, it is not possible at this time to provide guidance regarding the use of ADT in conjunction with adjuvant or salvage radiotherapy. These weaknesses include observational, non-randomized study designs; small sample sizes and consequent lack of statistical power to reliably detect differences between RT only and RT+ADT groups; lack of equivalence of RT and RT+ADT groups on pathological risk factors; large differences in ADT protocols, including when it was administered (e.g., pre -RP, pre-RT, during RT, post-RT) and for how long (e.g., weeks vs. months vs. years); primary focus on biochemical recurrence with relatively few reports that focused on local recurrence, metastatic recurrence, cancer-specific survival and overall survival; and, other differences across studies that may be relevant to efficacy such as differences in RT techniques, targets and total Gy administered.

Randomized controlled trials are needed to provide definitive evidence regarding these issues. At the time of this writing, RTOG 9601 was examining the effects of salvage RT with and without 24 months of bicalutamide (150 mg qd) in patients with biochemical failure who had pT3N0 or pT2N0 disease with positive margins; to-date, findings from this trial had been reported only in abstract form. At median follow-up 7.1 years, patients who received SRT plus ADT had significantly improved freedom from biochemical progression and significantly fewer metastases.[171] These findings are promising; publication of full trial results is awaited to provide more detailed guidance regarding the use of ADT in combination with salvage RT. In addition, currently RTOG 0534 is actively recruiting patients post-RP with a rising PSA to participate in a trial of short-term ADT with pelvic lymph node or prostate bed only RT. Further, the RADICALS trial is addressing the use of ADT and its duration (6 months v. 24 months) in both the ART and SRT contexts. Findings from these trials, once mature, also will help to answer these important questions.

ADT in the adjuvant setting. Only five observational studies compared RP patients who received adjuvant radiotherapy to those who received ART in combination with some form of ADT.[35, 54, 55, 57, 172] Although all four studies reported findings suggesting that patients who received ADT in combination with ART had better outcomes, only one study reported a statistically significant difference between groups. Specifically, Bastide[35] reported at median follow-up 60.3 months that the ART+ADT group had significantly higher biochemical recurrence-free survival (bRFS) rates at five and seven years than did the ART only group (82.8% vs. 44.4%, respectively, at 5 years; 62.1% vs. 28.6%, respectively, at 7 years). bRFS rates for two additional comparison groups (patients who had RP only and patients who had RP+ADT but did not have ART) were similar to rates for the ART only group. All patients in this study had SVI but the distribution of other risk factors (i.e., Gleason scores, positive margins) differed somewhat across groups. The ADT administered was an LHRH analog; it was initiated on the first day of RT with median duration 12 months. These findings require replication in a randomized trial such as the ongoing RADICALS trial. Ost[172] did not detect a difference in bRFS at seven years (ART only – 86%; ART + ADT – 79%) or clinical RFS (ART only – 90%; ART + ADT – 83%) on univariate analysis but on multivariate analysis the use of ADT resulted in a significant hazard ratio of 0.4 for bRFS and 0.1 for cRFS. However, the two groups exhibited significant imbalances in pathologic risk factors, emphasizing the need for appropriately stratified randomized studies. Additional information is provided by DaPozza[173] which reported that ART+ADT significantly improved bRFS and cancer-specific survival on multivariate analyses (but not univariate analysis) compared to patients who received ADT only (all patients in this study had positive nodes); however, there was no ART only comparison group in this study.

ADT in the salvage setting. Twenty-three observational studies evaluated RP patients who received salvage RT compared to those who received SRT in combination with some form of ADT. Overall, this literature arrived at mixed conclusions. Seven studies documented statistically significantly better outcomes for SRT+ADT patients compared to SRT only patients.[57, 63, 91, 99, 109, 145, 147] Findings from the study with the largest sample size[147] (1325 SRT patients; 214

SRT+ADT patients) derived from a multi-institutional retrospective cohort were used to develop an SRT nomogram and demonstrated a significant advantage in progression-free survival for patients who had SRT+ADT compared to SRT only patients. ADT (type not specified) was administered either before RT or during RT for median 4.1 months.

Eight studies reported that SRT+ADT patients had better outcomes than SRT only patients but either did not report a p level or the comparison did not reach statistical significance.[32, 55, 74, 92, 105, 115, 124, 144] In one study, although the overall comparison was not significant, a significant advantage in progression-free survival was observed in high-risk patients (defined as pT3 or higher, Gleason score 8 to 10, or PSA of 20 ng/ml or higher at RP).[144] Eight studies indicated that SRT only patients had better outcomes than did SRT+ADT patients or that the outcomes were indistinguishable.[75, 82, 94, 127, 129, 142, 146, 162]

Although the majority of studies suggested better outcomes for patients who had SRT in combination with some type of ADT, studies differed in when ADT was administered (pre-RT only, pre- and during RT, post-RT only; during RT only; during and post-RT), for how long (weeks, months, years) and in ADT type. In addition, studies varied in patient risk factors, RT protocols and follow-up durations. Overall, the Panel's conclusion was that, in the absence of randomized trials, the role of ADT in the ART or SRT context remains unclear.

Toxicity and quality of life (QOL) impact of RT post-prostatectomy. A key concern of clinicians and patients when adjuvant or salvage RT is contemplated is the toxicity and quality of life effects of RT in patients who have already undergone prostatectomy. The Panel's systematic review retrieved the literature relevant to these issues; findings are reviewed below. In addition to ART and SRT studies, studies that reported on mixed groups of ART and SRT patients were included given the importance of understanding toxicity effects. It was not possible to delineate differences in RT toxicity and QOL effects between ART and SRT studies given the many confounds to interpretation. These included: the absence of pre-RP information regarding genitourinary (GU), gastrointestinal (GI), and sexual functioning; large differences in the RP to RT interval, with consequent differential recovery from prostatectomy in ART v. SRT patients; the use of somewhat higher radiation doses in SRT studies; and, the paucity of published studies using newer RT delivery modes such as 3D-CRT and IMRT that might minimize toxicity. In particular, among the three RCTs, only ARO 96-02 used newer RT methods. Toxicity overall, therefore, may be somewhat less than the majority of the published literature reports.

Toxicity. The most commonly-used measures to report toxicity information were the Radiation Therapy Oncology Group (RTOG) measure for acute effects (through day 90) and the RTOG/European Organisation for Research and Treatment of Cancer (EORTC) measure for late RT effects (persisting beyond day 90 or developing after day 90). The second most commonly-used measure was the Common Toxicity Criteria Adverse Event (CTCAE) measure; authors who reported toxicity data using this measure specified the same time frames. Both measures use a rating system of 0 to 5: a score of 0 indicates no change in function; 1 indicates a minor change in function that generally does not require any clinical action; 2 indicates a moderate change in function that may require medication; 3 indicates a major change in function sufficient to require more aggressive medication use or outpatient procedures; 4 indicates severe symptoms requiring hospitalization and surgical procedures; and, 5 indicates death (see Appendix D). A total of 107 study arms reported at least one measure of toxicity; these arms included 13 ART study arms reporting on a total of 1,735 patients, 58 SRT study arms reporting on a total of 5,574 patients and 36 mixed ART-SRT study arms reporting on a total of 4,838 patients.[18, 25, 38, 39,41-43, 45,46, 49, 54-6, 59, 62, 64, 66,67, 71,74,75,78,79,81,82, 84,86,87,89,90-2, 96, 99, 103-5, 111-3, 121, 122, 124, 127-129, 132-5, 137,139-142, 148, 150-1, 153-4, 157-160, 162, 164,165, 172, 174-200]

Acute toxicity. Of the 107 study arms that reported any toxicity information, 38 reported at least one measure of acute GU toxicity (5 ART arms, 13 SRT study arms, and 20 mixed study arms) and 34 reported at least one measure of acute gastrointestinal toxicity (2 ART arms, 13 SRT arms, 19 mixed arms).

The ranges for proportions of patients experiencing Grade 1-2 and Grade 3-4 acute toxicities are presented in Appendix E; no grade 5 toxicities (deaths) were reported. Grade 1-2 acute toxicities were characterized by extremely wide ranges, with a great deal of variability across studies, and high percentages in many study arms, suggesting that these effects are relatively common. Grade 3-4 toxicities, however, were relatively uncommon.

With regard to acute GU effects, two studies compared patients treated with 3D-CRT to patients treated with IMRT.[99, 174] Both studies reported that use of 3D-CRT resulted in higher rates of grade 2 or greater toxicities (12.3% and 20.8%, respectively) compared to IMRT (6.6% and 13.4%, respectively). One study compared patients treated with EBRT to patients treated with 3D-CRT.[188] Patients treated with EBRT had higher rates of grade 2 or 3 acute GI toxicity (83%) compared to patients treated with 3D-CRT (61%). Rates of grade 2 or 3 acute GU toxicity were statistically similar (EBRT – 22%; 3D-CRT – 30%). There were no grade 4 events in either group. In contrast, Eldredge[184] reported that patients treated with EBRT or with cone-beam CT-guided 3D-CRT had similar rates of acute Grade 2 GU

(13% in both groups) and GI toxicities (EBRT – 15%; 3D-CRT – 13%).

Additional acute GU toxicity information was reported by Bolla[164] one of the three RCTs that evaluated adjuvant RT, using the World Health Organization (WHO) scale for acute effects. The WHO scale breaks down functioning into 0 – no change, 1 – slight disturbance, 2 – greater disturbance but without influence on daily life; 3 – toxicities requiring treatment, and 4 - severe toxicities requiring vigorous treatment or hospitalization. Grade 1 and 2 frequency symptoms (44.9% and 17.3%, respectively), were the most frequently reported acute GU toxicities. Grade 3 frequency was uncommon (3.3%) and grade 4 frequency was rare (0.4%). Grade 1 and 2 dysuria occurred in 37.9% and 10.3% of patients, respectively, with only 1.1% reporting grade 3 dysuria and no reports of grade 4. Hematuria was uncommon, with 3.7% of patients exhibiting grade 1, 0.9% exhibiting grade 2 and no patients exhibiting the higher grades.

With regard to acute GI effects, Goenka[99] reported that 3D-CRT patients had higher levels of grade 2 or greater toxicities (13.2%) compared to IMRT patients (7.6%). Alongi[174] divided toxicities into lower and upper GI and reported that patients treated with 3D-CRT had higher lower GI toxicity rates (8.6%) and higher upper GI toxicity rates (22.2%) than did patients treated with IMRT (lower: 3.3%; upper: 6.6%).

Using the WHO scale, Bolla[164] reported that rates of diarrhea were grade 1 – 38.3%, grade 2 – 17.7%, grade 3 – 5.3%, and grade 4 – 0%. Nausea/vomiting symptoms were uncommon, with grade 1 levels manifested in 4.2% of patients, grade 2 in 0.2%, and no patients exhibiting grade 3 or 4.

Late toxicity. Of the total 107 study arms that reported any toxicity information, 51 reported at least one measure of late genitourinary (GU) toxicity (9 ART arms, 26 SRT study arms, and 16 mixed study arms) and 41 reported at least one measure of late gastrointestinal (GI) toxicity (4 ART arms, 22 SRT arms, 15 mixed arms). It is important to note that commonly cumulative rates of late toxicities are reported; these rates do not take into account the fact that many of these patients ultimately have resolution of their symptoms.

The ranges for proportions of patients experiencing Grade 1-2 and Grade 3-4 late toxicities are presented in Appendix F; no grade 5 toxicities (deaths) were reported. Similar to acute toxicity data, Grade 1-2 late toxicities were characterized by extremely wide ranges, with a great deal of variability across studies (except for GI toxicity in ART study arms for which only 4 values were available), and high percentages in many study arms, suggesting that these effects are relatively common. Grade 3-4 toxicities, however, were relatively uncommon.

Late toxicity over time. In contrast to acute toxicities, late toxicities may manifest cumulatively for several years post-RT and persist for many years.

Ost Lumen[129] noted that the probability of late grade 2-3 GU toxicity rose from 12% at 24 months post-SRT to 22% at 60 months post-SRT. Pearse[192] reported a similar pattern with 13% of patients manifesting grade 2 or higher GU toxicity at 12 months post-SRT, rising to 28% at 48 months post-SRT, and remaining at 28% at 60 months post-SRT. Feng[185] reported in a mixed group of patients that grade 2 or higher toxicities occurred in 4% of patients at 12 months post-RT rising to 12% at 60 months post-RT. Goenka[99] reported on patients who were administered 3D-CRT or IMRT and noted that the probability of late grade 2 or higher toxicities for 3D-CRT patients ranged from 5% at 24 months post-SRT to 25% at 96 months post-SRT. For IMRT, 9% of patients exhibited grade 2 or higher toxicities at 24 months post-SRT with the proportion rising to 16.8% at 60 months post-SRT and remaining at 16.8% through 120 months of post-SRT follow-up. Iyengar[188] reported at median five years follow-up that statistically similar proportions of EBRT (19%) and 3D-CRT (16%) patients had grade 2 or higher late GU toxicities. The most common symptoms were urinary frequency (14.6%) and bleeding (8.6%). Incontinence as the only late GU symptom was almost twice as common among patients treated with EBRT (7.5%) compared to patients treated with 3D-CRT (4%).

Cozzarini[182] assessed toxicity rates in an ART cohort (n=556) compared to an SRT cohort (n = 186) at median 8 years of follow-up post-RT (either EBRT or 3D -CRT). These authors reported statistically indistinguishable probabilities of late Grade 3 GU effects of 12.2% among ART patients and 10% among SRT patients. The ART and SRT groups had similar rates of urethral stricture requiring dilation (ART - 5%; SRT - 3%), of grade 3 bleeding (ART – 2%; SRT – 1%), and of severe incontinence (ART – 7%; SRT – 6%). Each group had only one case of Grade 4 toxicity (necessitating radical cystectomy in both cases).

Late GI toxic effects are less common. Ost Lumen[129] also reported that the probability of late grade 2-3 GI toxicity rose from 3% at 24 months post-SRT to 8% at 48 months post RT and remaining at 8% at 60 months post-SRT. Pearse[192] reported a similar pattern with 3% of patients manifesting grade 2 or higher GU toxicity at 12 months post-SRT, rising to 7% at 36 months post-SRT, and remaining at 7% at 60 months post-SRT. Feng[185] reported in a mixed group of patients that grade 2 or higher toxicities occurred in 2% of patients at 12 months post-RT rising to 4% at 60 months post-RT. Goenka[99] reported on patients who were administered 3D-CRT or IMRT and noted that the probability of late grade 2 or higher toxicities for 3D-

CRT patients ranged from 4.5% at 24 months post-SRT to 10.2% at 96 months post-SRT. For IMRT, 1% of patients exhibited grade 2 or higher toxicities at 24 months post-SRT with the proportion rising to 4.0% at 72 months post-SRT and remaining at 4.0% through 120 months of post-SRT follow-up. Iyengar[188] reported at median five years follow-up that statistically similar proportions of EBRT (13.7%) and 3D-CRT (14%) patients had grade 2 or higher late GI toxicities. The most common symptoms were rectal bleeding (12%) and frequency (4.3%). Rectal bleeding as the only late GI symptom, however, was twice as likely among 3D-CRT-treated patients (17%) compared to EBRT-treated patients (8.2%).

In addition, both Cozzarini [182] and Tramacere[66] reported that the presence of acute toxicity was a significant predictor of late toxicities.

Additional late toxicity information is provided by Thompson,[23] one of the three RCTs (SWOG 8794). At median 127 months follow-up, urethral stricture was more common among RT patients (17.8%) than among RP only patients (9.5%). Proctitis also was more common among RT patients (3.3%) than among RP only patients (0%). Moinpour[201] reported on frequency symptoms defined as >8 voids/day among a subset of patients from SWOG 8794. Before RT, rates of frequency were similar between groups (21% of patients who then received RT; 22% of RP only patients). Frequency rates rose post-RT for RT patients (12 months – 27.5%; 24 months – 23%; 36 months – 26%; 48 months – 28%) but decreased for RP only patients (12 months – 14%; 24 months – 12%; 36 months – 13%; 48 months – 15%). By 60 months post -RT, however, the two groups had similar frequency rates that were indistinguishable from pre-RT values (RT – 22%; RP only – 19.5%). Rates of bowel movement tenderness, although similar between groups post-RP and pre-RT, became elevated among RT patients post RT and remained elevated through 60 months of follow up (six months post-RT/RP: RT – 18%; RP only – 5%; 60 months post RT/RP: RT – 18.5%; RP only 11%).

Urinary incontinence. To understand the impact of RT on urinary incontinence (UI) post prostatectomy, the Panel focused on studies that provided either pre-RT baseline information and/or reported findings for a comparison group.

Five ART studies reported in six papers provided information on urinary incontinence.[23, 41, 202-5] One study provided pre-RT information (25 of 69 patients with UI) and reported at median 50.4 months follow-up that one additional patient had developed UI.[41] Three reports compared ART patients to RP only patients; at follow-up durations ranging from one to three years, ART and RP only patients had indistinguishable and low rates of UI and pad use (ART: 12-23%; RP only: 14 – 19%).[202-4] Two reports focused on patients from the RCTs[23, 205] (EORTC 22911; SWOG 8794). Van Cangh[205] noted that among patients from the Belgian arm of EORTC 22911, there were no statistically significant differences between ART and RP only patients in Grade 2-3 UI (grade 2 – use of 1-4 pads soaked; grade 3 – more than 4 pads) pre-RP (ART 8.3%; RP only 9.6%) or at 24 months post RP/RT (ART – 8.3%; RP only 2%). Thompson[23] reported a non-significant difference in total UI between ART patients (6.5%) and RP only patients (2.8%) at median 127 months follow up.

Seven SRT studies that included pre-RT baseline information and/or a comparison group reported information regarding UI.[45, 78, 84, 86, 105, 183, 192] As a group, these studies reported either isolated cases of new onset UI and/or mild worsening of UI in small numbers of patients (usually one or two patients).

Quality of Life (QOL). Few studies focused on the QOL impact of urinary and GI symptoms and on overall QOL post-RT. No ART studies, two SRT studies, and one mixed study reported urinary and GI-related QOL information using a validated measure. Using the EPIC (score range 0-100 with higher scores indicating better QOL), Pinkawa[195] reported that pre-RT, SRT patients had urinary-related function and bother scores that ranged from 75 to 87. Although urinary function and bother scores worsened immediately after RT, scores returned to pre-RT levels by two months post-RT and remained at those levels at >1 year post-RT. Pre-RT, mean bowel function score was 92 and bowel bother score was 94. Post-RT, there was a significant decrease in function and bother scores (indicating worse QOL) that did not recover to pre-RT levels until one year post-RT. Similar patterns were evident for individual symptoms of rectal urgency, fecal incontinence, painful bowel movements, and having a moderate/big problem from bowel dysfunction. Hu[206] reported responses to the UCLA Prostate Cancer Index in SRT patients and noted that urinary and bowel function and bother scores did not change from pre-RT to 12-18 months post-RT. In a group of 78 mixed patients treated with IMRT, Corbin[207] reported after administering the EPIC-26 and the International Prostate Symptom Index (IPSS) at 2-, 6-, 12-, 18-, and 24-month intervals post-RT that there were no declines in urinary continence or gastrointestinal quality of life outcomes.

One ART study reported overall quality of life data. Moinpour[201] (data subset from SWOG 8794) reported that pre-RT, similar proportions of ART patients (47%) and RP only patients (52%) reported having a normal health-related QOL. These proportions increased over time for the ART group, with 69% of patients reporting a normal quality of life at 60 months post-RT. In contrast, for the RP only patients, the proportions remained the same, with 51% reporting a normal

quality of life at 60 months post-RP. For up to 36 months post-RT, ART patients had higher symptom distress scores than did RP only patients, but by 48 and 60 months post-RT, ART patients had lower distress scores than RP only patients. For the RAND Medical Outcomes subscales (Physical Function, Emotional Function, Social Function, and Role Function), the groups were indistinguishable throughout follow-up.

One SRT study reported overall QOL data.[206] SRT patient scores on the RAND physical component summary and mental component summary did not change from pre-RT to 12-18 months post-RT. The population mean on these scales is 50; SRT patient mean scores ranged from 46.0 to 54.0.

Erectile Function

ART studies. Five studies reported information in six publications regarding erectile function in ART patients.[41, 43, 49, 201-3] Given the limited number of studies, the lack of validated measures, the absence of key data over time (particularly pre-RP baseline data) and potential confounding variables, such as unequal use of ADT across patient groups and lack of full recovery from RP (RP to RT interval < 6 months), it is not possible to determine the impact of RT on erectile function when given for adjuvant purposes to post-RP patients. It is noteworthy that the percentages of patients who had intact erectile function post-RP but pre-RT were low, ranging from 7% to 33.3% with the most rigorous data from SWOG 8794[201] indicating that only 7% of men had intact function pre-RT.

SRT studies. The impact of salvage RT on erectile function also is difficult to determine. Thirteen studies reported erectile function information in SRT patients.[43, 59, 78, 81, 90, 99, 159,160,165, 176, 183, 195, 206] Nine of these studies reported only proportions of patients with ED at various time points and provide contradictory information (three studies reported no change post-RT and six reported increased proportions of patients with ED post-RT). In most of these studies sample sizes were extremely small (<50); pre-RP functioning was not reported; the type of RP was not reported or varied (some patients had nerve-sparing procedures and others did not); the RP to RT interval was less than two years, making it unclear whether erectile function had fully recovered post-RP; patients were followed for less than two years; and data were obtained from physician chart notes rather than patient-reported. Four studies used some type of validated measure. Although the sample sizes were larger, many of the same potential confounds remain. Three of these studies reported no changes over time from the post-RP/pre-RT measurement point throughout follow-up; one reported increased ED rates.

In addition, similar to the ART studies, post-RP patients who presented for salvage RT had very low rates of adequate erectile function (3.8% to 35.7%; most studies reported that <10% patients had full potency post-RP but pre-RT) and low scores on QOL measures of sexual function/bother. The only study that included pre-RP data[59] reported that 74 of 110 patients (73%) were fully potent pre-RP, 9 (9%) were partially potent, and 18 (18%) were impotent. Post-RP/Pre-RT, 7 of 74 previously potent patients remained potent (9.5%); 14 of 74 previously potent patients became partially potent (19%); 53 of 74 previously potent patients became impotent (71.6%); in addition, all 9 patients who were partially potent pre-RP became impotent. Post-RT (minimum follow-up 60 months), of the 21 patients who were potent or partially potent post-RP, 9 (43%) became impotent, 10 (47.6%) became or remained partially potent, and 2 (9.4%) retained full potency; 1 of the 9 patients who lost partial potency post-RP regained partial potency during follow-up.

Mixed studies. One mixed study reported poor erectile function in 62% of men post-RP but pre-RT and in 66% of men 24 months post-RT. There were no differences over time in the proportions of men reporting problems with erectile strength or with sexual performance or reporting difficulty with orgasm.[207]

Overall, given the paucity of available data and the potential confounds to interpretation, the Panel interpreted these data to indicate that the impact of RT on erectile function given in either the adjuvant or salvage context is not currently known.

Secondary malignancies. Findings from studies carried out to investigate the risk of secondary malignancies resulting from the use of RT post-prostatectomy are contradictory as pointed out by Guedea.[208] Specifically, Bhojani[209] estimated that the hazard ratio of developing a rectal tumour at 120 months was 2.2 in patients treated with RT compared with the general population. In contrast, a Canadian study evaluated all prostate cancer cases treated in British Columbia from 1984 to 2000 and found no significant difference between observed and expected secondary cancer rates, regardless of whether treatment included RT.[210] In addition, none of the trials that focused on ART or SRT have reported secondary malignancy data. Further, post-prostatectomy men may not be an accurate control group for estimating the risk of secondary malignancies post-RT because there is evidence that they have a lower risk of secondary cancers than the general population.[211] Finally, the risk of secondary cancers also may be related to co-existing factors such as the presence of past or current smoking.[212-14] The Panel concluded that at this time the risk of a secondary malignancy as a result of the administration of RT in the adjuvant or salvage context is not known.

GUIDELINE STATEMENTS

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)*

Discussion: Patients should be counseled before RP that certain pathology findings at prostatectomy are associated with higher risks for cancer recurrence. These findings include positive surgical margins, the presence of seminal vesicle invasion (SVI), and extraprostatic extension (EPE). Rates of recurrence in post-RP patients with adverse pathological features may be greater than 60% at five years post-RP in case series.[11, 13, 14, 16, 18-22, 215-17] In addition, two randomized controlled trials with more than 10 years of follow-up reported recurrence rates of >60% in high-risk patients who had RP only.[24, 26]

The most definitive evidence for an increased probability of disease recurrence associated with specific high-risk pathologic features is provided by a recent report on approximately 4,400 radical prostatectomies with median follow-up of 10 years (and follow-up of up to 29 years in subset of patients).[218] Approximately 3,300 of these patients were treated during the PSA era (from 1992 to 2011). These data reveal reduced rates of biochemical recurrence-free survival and reduced rates of metastases-free survival at 15 years post-RP in men with a variety of pathological risk factors (see Appendicies G and H).

Patients also should be informed that if these adverse pathological features are detected, then additional therapy after surgery, such as RT, may be beneficial.

Guideline Statement 2.

Patients with adverse pathologic findings including seminal vesicle invasion, positive surgical margins, and extraprostatic extension should be informed that adjuvant radiotherapy, compared to 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 two randomized controlled trials 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*)

Discussion: Patients with adverse pathologic findings at prostatectomy should be counseled regarding the most up-to-date findings from the randomized controlled trials that have evaluated the use of ART. This counseling should emphasize that high-quality evidence indicates that the use of ART in patients with adverse pathological findings reduces the risk of biochemical recurrence, local recurrence, and clinical progression of cancer. Patients also should be informed that the impact of ART on subsequent metastases and overall survival is less clear, with benefits reported in one of two trials with long-term data on these outcomes. Clinicians also should counsel patients regarding the potential benefits and risks/burdens of the available treatment alternatives if biochemical recurrence, local recurrence, and/or clinical progression occur.

Guideline Statement 3.

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

Discussion: The Panel is fully aware that the apparent benefits associated with ART are the result, in part, of a subset of patients treated who never would have presented with recurrence. For this reason, the Panel emphasizes that ART should be offered to all patients at high risk of recurrence because of adverse pathological features. By "offered," the Panel means that the patient, his family and the multi-disciplinary treatment team should engage in a shared decision-making process in which the patient is advised to consider the possibility of additional treatment (i.e., RT). Whether ART is likely to benefit a particular patient and should be administered is a decision best made by the multidisciplinary treatment team and the patient with full and thoughtful consideration of the patient's history, current functional status, values, and preferences, and his tolerance for the potential toxicities and quality of life effects of RT.

Three randomized controlled trials (SWOG 8794, EORTC 22911, and ARO 96-02), two with more than 10 years of follow-up, evaluated the effects of ART on outcomes among patients with adverse pathologic features at prostatectomy[23-6] [for detailed discussion of RCT findings, see Adjuvant Radiotherapy (ART) section in Background]. All three trials documented significant improvements in biochemical recurrence-free survival (bRFS) with use of ART compared to RP only (pooled hazard ratio of 0.48; 95% CI 0.42 – 0.56; p <0.00001; see Appendix A). The Panel notes that prevention of biochemical progression is an important clinical endpoint because biochemical progression may trigger

salvage therapy (i.e., ADT), with its associated toxicities and quality of life impact. In addition, patients with biochemical recurrence are more likely to manifest metastatic recurrence. Therapies for metastatic recurrence, such as androgen deprivation therapies, can have profound quality of life impact.

The two RCTs that evaluated locoregional failure (SWOG 8794; EORTC 22911) demonstrated a reduction in failure in ART patients compared to RP only patients at more than 10 years of follow-up. This difference was statistically significant in EORTC 22911[24] (locoregional failure in 8.4% of ART patients compared to 17.3% of RP only patients) and similar in magnitude in SWOG 8794[23] (locoregional failure in 8% of ART patients compared to 22% in RP only patients; no p value reported). The Panel viewed reduction of locoregional failure as another important clinical endpoint because the occurrence of local failure also triggers the use of salvage therapies, with associated toxicities and increases the probability of subsequent metastatic failure.

Both SWOG 8794 and EORTC 22911 also reported statistically significant reductions in the use of subsequent salvage therapies with ART compared to RP only at approximately 10 years of follow up. SWOG 8794 reported improvement in 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%). The Panel viewed reduction in initiation of salvage therapies as a result of ART as another important clinical endpoint because of the avoidance of the negative consequences of these therapies.

SWOG 8794 and EORTC 22911 also both demonstrated improved clinical progression-free survival (defined as clinical or imaging evidence of recurrence or death but not including biochemical progression) at more than 10 years of follow up in ART patients compared to RP only patients. This difference was statistically significant in SWOG 8794 and borderline significant ($p = 0.054$) in EORTC 22911. The Panel also judged improved clinical progression-free survival as an important endpoint because it reflects lower rates of local and distant failure as well as lower death rates associated with the use of ART.

Two of the trials – SWOG 8794 and EORTC 22911 -- assessed metastatic recurrence and overall survival. Only SWOG 8794 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] Several possible explanations for the discrepant findings across trials have been offered. These include the fact that the overall survival rate of the RP only group in SWOG 8794 was much lower (66.0%) than the RP only group in EORTC 22911 (80.7%); the reason for the lower survival rate in SWOG 8794 is not clear. It also is possible that salvage treatments in SWOG 8794 were not used as extensively as in EORTC 22911; the trials had similar rates of salvage treatment despite higher relapse rates in SWOG 8794. Therefore, in the context of offering ART to patients, it should be emphasized that there is less certainty regarding potential benefits in terms of preventing metastatic recurrence and improving overall survival.

Given the consistency of findings across trials regarding other clinically-important endpoints of reduced biochemical and locoregional failure, clinical progression, and the reduction in the need for initiation of salvage therapies in patients administered ART, the Panel concluded that patients with high-risk pathological features should be offered ART.

The Panel also notes that RT should be offered to patients with adverse pathology detected at prostatectomy who have a persistent post-prostatectomy PSA level. Although by the definitions used in the guideline this is a salvage context for RT, two of the trials (SWOG 8794 and EORTC 22911) enrolled some patients with a detectable PSA in the early post-RP period (< 18 weeks). EORTC 22911 reported that RT improved 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).[24] 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] It is important to note that in SWOG 8794, although the point estimate of benefit was similar, the Kaplan-Meier survival analysis revealed that men with a detectable PSA post-RP who received RT were more likely over time to develop metastases or to die than were men who had an undetectable PSA and received RT.

Guideline Statement 4.

Patients should be informed that the development of a PSA recurrence after surgery is associated with a higher risk of development of metastatic prostate cancer or death from the disease. Congruent with this clinical principle, physicians should regularly monitor PSA after radical prostatectomy to enable early administration of salvage therapies if appropriate. (*Clinical Principle*)

Discussion: Prostate specific antigen (PSA) levels drawn following a RP should be undetectable. An increasing PSA level suggests the presence of residual disease and frequently heralds the eventual

development of symptomatic metastases and death from prostate cancer. Pound et al.[21] were among the first to describe the time course of disease progression. They followed 1997 consecutive men undergoing RP at the Johns Hopkins Hospital and demonstrated that no man experienced either distant or local recurrence without also demonstrating a rising PSA level. Among 304 men who developed detectable PSA values following surgery, the median time to the development of metastases was eight years. Men with Gleason score 8-10 disease in the surgical specimen developed metastases more rapidly, usually within five years, while men with Gleason score 5-7 disease developed metastases more slowly, usually within ten years.

Early PSA rise was associated with more rapid development of metastases. Specifically, men who developed a rise in their PSA value within two years of surgery developed metastases more rapidly -- usually within five years; men who developed a rise in their PSA values more than two years post-surgery, however, developed metastases later, many more than 10 to 15 years later. The median PSA doubling time provided the most statistically significant prediction of time to distant progression. Men with a PSA doubling time less than 10 months usually developed metastases within five years of surgery, while men with a PSA doubling time greater than 10 months developed metastases much later. Men who developed metastatic disease usually died at median five years later (range two to twelve years later).

Albertsen et al.[219] reported similar findings from a population based sample. They reported outcomes of 1136 men who underwent treatment in community practice following diagnosis of localized disease between 1990 and 1992. Among the 516 men who underwent surgery, the majority of men had post treatment PSA levels that remained undetectable or at a low, constant detectable level. For the remaining patients PSA levels increased immediately after surgery or after a time delay. Among the patients who did NOT die of prostate cancer within ten years of follow up, 40% showed no increase in post treatment PSA values, whereas 10% had a PSA doubling time of six to seven months or longer. A doubling time of approximately twelve months provided the maximum separation between patients who died of prostate cancer within ten years of surgery and those who did not. PSA doubling times were correlated with patients' biopsy Gleason scores and their pretreatment PSA levels.

Overall, these data indicate that men with an increasing PSA after surgery are at risk for developing metastases and subsequently dying from their disease; this risk is particularly high among men with rapid 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. Patients should be informed of the relationship between PSA recurrence post-surgery and the probability of metastatic recurrence and death from prostate cancer.

Guideline Statement 5.

Clinicians should define biochemical recurrence as a detectable or rising PSA value after surgery that is ≥ 0.2 ng/ml with a second confirmatory level ≥ 0.2 ng/ml. (*Recommendation*; Evidence Strength: Grade C)

Discussion: The vast majority of the published literature assessing the efficacy of RP uses a PSA threshold value of 0.2 ng/mL to define recurrence although some authors have advocated for the use of higher values[220]. Many adjuvant studies, including the three RCTs reviewed in detail in this guideline, and many salvage radiotherapy studies also use a PSA threshold of 0.2 ng/ml to define recurrence. This definition also is consistent with the Prostate-Specific Antigen Best Practice Statement: 2009 Update of the AUA (http://www.auanet.org/education/best-practice-statements.cfm). Patients who have had a prostatectomy should be informed that a PSA value of 0.2 ng/ml or higher that has been confirmed by a second elevated PSA value constitutes evidence of a biochemical recurrence. The presence of a biochemical recurrence necessitates a thorough discussion of the available alternatives for salvage therapy, including the use of RT and other types of therapy, and is sufficient to trigger the administration of salvage therapies. The Panel further notes that there is no evidence to suggest a threshold above which RT is ineffective.

The Panel notes that recurrences can be identified earlier and at much lower PSA levels (e.g., 0.07 ng/mL or less) using ultra-sensitive PSA assays.[221-2] In addition, even more sensitive assays may add further clarity as to whether patients are at increased risk for clinical failure.[223-4] Data from retrospective and prospective trials tend to support the notion that more favorable biochemical outcomes are associated with very low PSA values at the time RT is offered.[225] 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 (see Discussion under Guideline Statement 8). However, a small percentage of patients (8.8% of patients with biochemical recurrence) may have detectable but stable PSAs for 10 years or more without evidence of clinical failure, which may reflect the presence of benign prostate glands in the surgical bed.[226] Currently, therefore, it is not clear whether the use of more sensitive assays would translate into improved outcomes for most patients or, alternatively, would result in an increase in unnecessary treatments.[222, 227-8] In addition, calculation of PSA doubling time (PSADT) using data derived from ultra-sensitive assays may yield markedly different PSADT

values compared to using data derived from higher-threshold assays;[229] how these differences should be interpreted is unclear. Given the lack of evidence regarding the use of ultrasensitive PSA assays to guide care, the Panel judged that the use of the 0.2 ng/ml threshold value with a second confirmatory value to document recurrence is the optimal strategy currently. The Panel notes, however, that the decision to initiate salvage therapies is best made by the clinician who has full knowledge of a specific patient's pathology findings, risk factors, family history, preferences and values in consultation with that patient and with full discussion of the potential benefits and risks of treatment. In the era of ultrasensitive PSA assays, a detectable PSA that is confirmed and rising may be an appropriate trigger for salvage therapy, particularly in patients who are at high risk for recurrence and/or who have other evidence of potential progression.

Body of evidence strength is Grade C because the majority of the relevant literature is composed of observational studies and no randomized trials have focused on the impact of different PSA thresholds on outcomes.

Guideline Statement 6.

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

Discussion: In the patient with evidence of recurrence manifested as a detectable or rising PSA, determining the site of recurrence (local v. metastatic) may be relevant to select an appropriate salvage strategy. The guideline systematic review included retrieval of the literature regarding imaging strategies to detect recurrence location in the post-RP patient who has biochemical evidence of recurrence. Clinicians should be aware that the yield of some modalities (e.g., bone scan) is extremely low in patients with PSA values below 10 ng/ml (see literature review below).

The Panel grappled with numerous challenges in interpreting this literature. The most difficult issue was the lack of a reliable and relatively error-free reference standard with which to evaluate new modalities. In many studies no recurrence location could be identified in a subset of patients with biochemical failure by either the reference standard or the modality under evaluation, making the true performance of the evaluated modality unclear. Other problems included the use of different reference standards within and across studies, failure to administer the reference standard to all patients, lack of independence of the reference standard from the evaluated modality, and lack of blinding for test interpreters. In addition, the majority of studies assessed relatively small sample sizes (<50 for the majority of study arms). For these reasons, body of evidence strength for this literature is Grade C.

Local recurrence. Thirty-three studies comprised of 53 study arms reported on the diagnostic performance of 19 modalities for local recurrence detection. The modalities evaluated included digital rectal exam[230-2] (DRE), transrectal ultrasound[232-239] (TRUS), color Doppler TRUS,[239] color power Doppler TRUS,[234, 240] contrast-enhanced (CE) color power Doppler TRUS,[234] body coil MRI,[241] endorectal coil MRI without contrast,[231, 241-3] endorectal coil MRI with contrast,[241-2, 244] 11C-acetate PET/CT,[245] 11C-choline PET/CT,[246-8] 18FDG PET,[249-260] 18FCH PET/CT,[251-2] dynamic contrast-enhanced (DCE) MRI,[231, 253-5] diffusion-weighted MRI with contrast,[256] 1H-MRSI,[254] 1H-MRSI with DCE MRI,[251, 254] CT with contrast,[257] Prostascint[126, 249, 258-61] and Prostascint fused with MRI or CT.[262] For more than half of the modalities evaluated, only one or two study arms reported findings; the lack of a sufficient number of studies on each modality limited the interpretability of findings. In addition, many modalities exhibited highly variable sensitivities and specificities across studies; this lack of consistency further limited interpretability of the performance of specific modalities.

Overall, endorectal coil MRI with contrast, DCE-MRI, 1H -MRSI, and 1H-MRSI with DCE MRI yielded the highest and most consistent sensitivities and specificities for the detection of local recurrence. Sensitivities were all above 70% (except for Rischke[255] in which sensitivity was 67%); endorectal coil MRI with contrast and 1H-MRSI with DCE-MRI had sensitivities above 80%. The same set of modalities also yielded high specificities with all values above 70% except for one endorectal coil MRI with contrast study that reported a specificity of 66.7%.[241] Specificities for 1H-MRSI were above 80% and those for DCE-MRI were above 85%. Two published systematic reviews on this topic come to similar conclusions.[263-4]

Other modalities exhibited excellent sensitivity but poor or variable specificity or vice versa. For example, nine study arms that evaluated TRUS reported sensitivities that ranged from 75% to 95.5% but specificities that ranged from 0 to 83.3%. DRE, color power Doppler TRUS, and 11C-choline PET/CT all exhibited specificities of 75% or higher but sensitivities that ranged from 32 to 50% for DRE, 41.6 to 93.3% for color power Doppler TRUS, and 45.5 to 69.7% for 11C-choline PET/CT.

Overall, the decision regarding which modality to use to determine the presence or absence of local recurrence will depend on the availability of specific modalities and on the clinician's goals for imaging.

Recurrence in nodes. Five studies reported on the diagnostic performance of 11C-choline PET/CT[265-8] and 18FDG PET/CT[269] to detect recurrence in lymph nodes. The sensitivity of 11C-choline PET/CT was 100% across

studies; three studies reported data per patient and one study reported data per node.[268] Scattoni[266] also reported data per node with a sensitivity of 64%. The single 18FDG PET/CT study reported a sensitivity of 75%. In contrast to high sensitivity values, specificities were more variable; values for 11C-choline PET/CT ranged from 0 to 100% and the single 18FDG PET/CT study reported a value of 100%.

Two additional studies reported on the use of MRI with lymphotropic superparamagnetic nanoparticles (LSN). One study was conducted in patients who had not yet undergone prostatectomy and reported values for sensitivity and specificity above 90%.[270] Two studies used this modality in post-RP patients with biochemical failure.[271-2] In Ross[271] insufficient patients were biopsied; diagnostic performance could not be calculated. None of the patients in Meijer[272] were biopsied, but findings correlated well with Stephenson nomogram predictions regarding which patients would benefit from SRT. Fortuin[273] reported in 29 patients that more lymph nodes were detected by MR lymphography (738 nodes) than by 11C-choline PET/CT (132 nodes) and more suspicious nodes were detected by MR lymphography (151 of 738 nodes) than by PET/CT (34 of 132 nodes). However, this study also lacked a reference standard, making it unclear how many of the suspicious nodes constituted true metastases. The Panel notes that the MR lymphography data are promising but there is a need for more methodologically rigorous studies.

Overall, the Panel concluded that insufficient data are available to recommend specific techniques for the detection of recurrence in nodes.

Recurrence in bone. Five studies comprised of eleven study arms reported on the use of bone scan with or without SPECT,[274-5] 11C-choline PET/CT,[276-8] 18F-fluoride PET,[274] 18F-fluoride PET/CT[274] DWE MRI with contrast,[278] conventional MRI-STIR[278] and conventional MRI –T1 weighted.[278] It is difficult to draw firm conclusions from this literature given that most modalities were evaluated in only one study arm and that nine of ten study arms evaluated 25 or fewer patients. The sensitivities across techniques ranged from 66.7% to 100% with five studies reporting values of 100% (MRI-STIR, DW-MRI with contrast, 18F fluoride PET, 18F fluoride PET/CT, and bone scan without SPECT). Two studies reported values above 90% (MRI-T1 weighted and bone scan with SPECT). Only six study arms provided specificity information; these values ranged from 64% to 100% with four of five study arms reporting values above 80% (bone scan with and without SPECT, 11C-choline PET/CT, 18F-fluoride PET and 18F-fluoride PET/CT). Additional information is provided by Fuccio[277] who used 11C-choline PET/CT to evaluate 123 post-RP patients with rising PSA, all of whom had a negative bone scan; 11C-choline PET/CT detected bone lesions not apparent on bone scan in 18 patients.

An additional set of studies focused on bone scan findings in patients with various PSA-related characteristics. This group of studies reported that scans were more likely to be positive among patients with higher PSA levels, shorter PSA doubling times (PSADTs) and faster PSA velocities.[279-283] For example, at PSA levels less than 10 ng/ml, less than 5% of patients had a positive bone scan.[281] For PSADT greater than six months, the probability of a positive bone scan was 3%.[283] The yield of bone scans, given that most patients manifest biochemical failure at PSA values <1.0 ng/ml, will be low.

Metastatic recurrence. Seven studies provided information regarding the detection of metastases outside of the prostate bed. Three studies reported on the use of ProstaScint.[126, 258, 284] One study each focused on 11C-choline PET/CT,[246] 18FDG PET,[250] 18F-FDG PET/CT,[285] 18F-NaF PET/CT[285] and 18FCH PET/CT.[252] Sensitivity values for ProstaScint ranged from 30% to 100%. The other scanning modalities had sensitivities above 95% except for the 18F-FDG PET/CT and 18F-NaF PET/CT study that focused on patients who had already had negative conventional imaging.[285] In this study, 18F-NaF PET/CT detected metastatic lesions in six of 26 post-RP patients not identified on conventional imaging. Specificities ranged from 0% to 58% for the ProstaScint studies and were above 95% for the other modalities. In the absence of multiple studies assessing each modality, definitive conclusions regarding the best imaging strategy to detect metastatic recurrence are not possible, but these data suggest that 11C-choline PET/CT, 18FDG PET and 18FCH PET/CT are promising.

Recurrence at all sites. Twenty-two studies provided diagnostic performance information regarding the detection of disease recurrence anywhere in the body using seven different imaging techniques.[250, 252, 284, 286-304] A wide range of reference standards were employed including: other imaging modalities; biopsies of the prostate bed, nodes and/or bone; PSA responses to salvage RT; and follow-up. In most cases, only a few study arms examined the same modality, making it difficult to arrive at definitive conclusions. Eight study arms reported findings from the use of 11C-choline PET/CT, however. All sensitivities were above 60%, and six of the eight study arms reported sensitivities at 80% or higher. Specificity was provided in five of the eight study arms and ranged from 36% to 100%. In three of the five arms, specificity was above 75%;[291, 293, 304] the lower specificity values occurred in studies from the same institution in which a single reference standard (biopsy) was used.[295-6] Mitchell[304] summarized the recent Mayo Clinic experience with11C-choline PET/CT in 176 patients who had biochemical

recurrence (most patients had RP as primary treatment) and concluded that 11C-choline PET/CT not only performed well but substantially enhanced the rate of prostate cancer lesion detection by approximately 32% beyond what could be identified using conventional imaging technologies. This enhanced rate of cancer detection allowed decisions regarding appropriate care that were not possible with conventional imaging and included observation, surgical resection, anatomically targeted therapies and systematic therapies. Given the body of data on 11C-choline PET/CT, this imaging strategy appears promising.

The probability of a positive scan, however, may depend on PSA level and PSA dynamics. Using 11C-choline PET/CT, several authors reported that the proportion of positive scans increased as PSA level increased,[291, 293, 305] as PSA velocities increased[291, 306-7] and as PSADTs decreased.[306-7] Using 18F-fluorocholine PET/CT, Kwee[287] reported that the percentages of positive scans also increased with higher PSA levels; ROC analysis indicated that the ideal cut-off for scanning was a PSA level of 1.1 ng/ml.

Guideline Statement 7.

Physicians should offer salvage radiotherapy to patients with PSA or local recurrence after radical prostatectomy in whom there is no evidence of distant metastatic disease. (*Recommendation*; Evidence Strength: Grade C)

Discussion: Two of the RCTs included a subgroup of patients who had detectable PSA levels post-RP – patients that could be categorized as salvage patients. Subgroup analyses of these patients suggest a benefit of RT. In SWOG 8794, RT significantly reduced metastatic recurrence rates among patients with detectable PSA post-RP.[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).[24]

This statement also is supported by two observational studies that reported outcomes for patients who had SRT vs. post-RP patients with detectable PSA and/or local recurrence who did not have SRT. Boorjian[31] reported on a cohort of 2,657 patients with biochemical failure post-RP; 856 of these patients had salvage RT. Median follow-up post-RP was 11.5 years; median follow-up post biochemical failure was 6.9 years. SRT patients were followed for median 5.9 years post-RT. SRT significantly reduced the risk of local recurrence (by almost 90%) and systemic progression (by 75%) and delayed the need for ADT administration; these differences were present even after controlling for differences between groups in clinical and pathological features. No overall survival difference was documented, however. Trock[32] reported outcomes for post-RP patients with biochemical failure and/or local recurrence who received no salvage treatment (n=397), received SRT alone (n=160), or who received SRT in combination with ADT (n= 78). At median follow-up of 6 years after recurrence and 9 years after RP, 22% of men who received no salvage therapy had died from prostate cancer – a significantly higher rate than men who had SRT (11% deaths from prostate cancer) and men who had SRT with ADT (12% deaths from prostate cancer); there were no differences between the two SRT groups. The authors note that the cancer-specific survival advantage associated with SRT (with or without ADT) was specific to certain clinical subgroups. These included men with a PSA doubling time of <6 months with a recurrence to RT interval of <2 years. Men with a PSA level ≤ 2 ng/ml at the time of RT also had increased survival; however, among men with PSADT of <6 months, SRT significantly increased survival regardless of PSA level at time of RT. SRT also significantly improved survival among men with PSA that became undetectable in response to RT but not in men whose PSA remained detectable. Overall, in men with PSADT <6 months, 10 -year cancer-specific survival rates were significantly higher for men who received SRT compared to those who did not regardless of surgical margin status or Gleason score. For men with PSADT >6 months, the cancer-specific survival advantage associated with RT was only evident among patients with positive margins and Gleason scores 8-10. Overall survival in men with pT3 cancer was significantly increased by SRT but only in men with PSADT <6 months.

In the context of administering SRT, clinicians should be aware that a large number of observational studies have reported that patients in certain high-risk groups have poorer outcomes than patients without these risk factors or in lower risk groups. As a group, these studies focused primarily on biochemical recurrence-free survival. 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.[59, 63, 67, 78, 82, 84, 90-2, 94, 97, 103, 107-109, 111, 113-5, 119, 124-7, 129, 133-6, 138, 142-3, 146, 149-150, 153, 158, 162-3]

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

Body of evidence strength was Grade C because the analyses from the RCTS were internal subgroup

analyses and because the remaining evidence was derived from observational studies.

Guideline Statement 8.

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

Discussion. Forty-seven observational studies compared biochemical recurrence-free survival rates for salvage radiotherapy patients at lower v. higher pre-RT PSA levels.[39, 53, 55, 57, 59, 63, 77, 81, 84-5, 90-2, 94, 96-7, 102-3, 107, 109, 114-117, 121 , 124, 126-7, 129, 131-2, 134, 136, 138, 141-2, 146-7, 149-150, 152-4, 156, 158-159, 163] Forty-one studies used cut-off values to divide the low and higher groups of approximately 1.0 ng/ml or less.

All but one study reported that patients with lower pre-RT PSA levels had higher bRFS rates over time compared to patients with higher pre-RT PSA levels although the differences between groups were not always statistically significant. The exception was Tomita,[153] which divided patients into those with pre-RT PSA <0.25 ng/ml or ≥0.25 ng/ml – an extremely low threshold. This is the only study in which values for the low and high groups were reversed, with 51% of the pre-RT PSA <0.25 ng/ml free of biochemical recurrence at 36 months compared to 59% of the pre-RT PSA ≥0.25 ng/ml group – a non-significant difference. The relevance of pre-SRT PSA level was confirmed by a recent systematic review of 41 selected SRT studies.[308] These authors reported that PSA level before SRT was significantly associated with relapse-free survival with an average 2.6% loss of relapse-free survival for each 0.1 ng/ml PSA increment at the time of SRT. In addition, a meta-regression performed on a selected group of 25 SRT studies indicated that pre-RT PSA levels were significantly associated with five-year progression-free survival levels such that progression-free survival rates dropped by 18.1% for every 1 ng/ml increase in pre-RT PSA.[166]

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

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

Guideline Statement 9.

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

Discussion. Patient counseling regarding the potential toxicity and QOL impact of RT is important to ensure that patients make informed treatment decisions and have appropriate expectations regarding the course and consequences of RT. Counseling should include the fact that the evidence base for toxicity and QOL effects of RT is based mostly on reports using older RT techniques; newer techniques appear to have fewer toxic effects.

Acute toxicity. Patients should be informed that during RT and in the immediate post-RT period of two to three months, mild to moderate 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 RT, including those requiring aggressive medication management, outpatient procedures, or hospitalization, however, are uncommon or rare, with most studies reporting rates of 5% or less. The lowest acute toxicity rates have been reported with use of IMRT RT techniques.[100, 175]

Late toxicity. Patients should be informed that, similar to acute toxicities, mild to moderate late toxicities occurring more than 90 days post-RT are commonly reported with some studies reporting rates as high as 79%. Serious late toxicities, however, are relatively uncommon, with most studies reporting rates of 10% or less. Patients also should be told that in a small proportion of patients, late toxicities that are moderate to major may emerge for up to four to five years post-RT and may persist beyond that point. These toxicities are more likely to include GU symptoms (up to 28% of patients)[129] than to include GI symptoms (up to 10.2% of patients).[99] 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.[99]

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. Studies of SRT patients indicate possible mild worsening of UI in small numbers of patients and isolated cases of new onset UI. Overall, the Panel interpreted these data to indicate that RT is unlikely to have a major impact on UI.

Sexual function. Patients with intact erectile function post-RP should be informed that the impact of RT on erectile function in men who have already had a prostatectomy is not clear. This uncertainty derives from the fact that few studies have addressed the impact of RT on erectile function in post-RP patients and also from the fact that most men post-RP do not

have intact erectile function, making it difficult to determine whether RT results in further loss of function.

Adjuvant RT may reduce the need for salvage therapies. Patients also should be informed that the use of ART, because it is associated with improved biochemical recurrence-free survival compared to RP only, is likely to reduce the need for subsequent salvage therapies. Salvage therapies such as androgen deprivation can have debilitating side effects and also present increased risks for osteoporosis, cardiovascular disease and other health problems.

Secondary malignancies. Clinicians should advise patients that the potential for developing secondary malignancies exists when postoperative RT is given, but that studies investigating the risk of developing secondary malignancies in men undergoing prostate cancer RT are contradictory.[209-10] Furthermore, in clinical trials of adjuvant and salvage radiotherapy no data have been reported on secondary malignancies. Finally, the risk of secondary cancers may be related to co-existing behavioral factors such as the presence of past or current smoking.[212-14] Therefore, the Panel concluded that at this time the risk of developing a secondary malignancy as a result of ART or SRT administration is not known.

RESEARCH NEEDS AND FUTURE DIRECTIONS

Ongoing Clinical Trials. Several ongoing clinical trials will help to clarify the magnitude and impact of adjuvant or salvage radiotherapy, the relative value of combining RT with hormonal and other therapies, and potentially make clear which patients are more likely to benefit from specific therapies, therapy combinations, and therapeutic contexts.

RTOG 0534 is randomizing post-prostatectomy patients (pT2N0/Nx or pT3N0/Nx) with Gleason scores ≤9, with or without positive margins, and with post-RP PSA of ≥ 0.1 ng/ml to < 2.0 ng/ml to prostate bed RT, prostate bed RT plus short-term androgen deprivation (four to six months) therapy or pelvic lymph node RT plus prostate bed RT plus short-term ADT. Patients are stratified by SV status, Gleason score ≤7 or 8-9, pre-RT PSA of ≥0.1 to 1.0 ng/ml or >1.0 to <2.0 ng/ml and pT2 with negative margins v. all other patients. The trial includes assessments of biomarkers, quality of life, neurocognitive function and urinary function. 3D-CRT or IMRT methods are used with 64.8-70.2 Gy administered to the prostate bed and 45 Gy administered to pelvic lymph nodes.

RTOG 9601 is examining the effects of RT with or without long-term androgen deprivation in men post-prostatectomy with pT3N0 disease or pT2N0 disease with a positive margin or positive prostate fossa/ anastomosis biopsy with PSA ≥ 0.2 ng/ml to 4 ng/ml. Radiation doses were 64.8 Gy to the prostate bed and anti-androgen therapy consisted of 24 months of bicalutamide (150 mg daily) monotherapy. While not yet published, results reported in abstract form indicate that the addition of 24 months of bicalutamide during and after RT significantly improved freedom from biochemical progression and reduced the incidence of metastatic disease without adding significantly to radiation related toxicity. There were no differences in overall survival with a median follow-up of 7.1 years.[171] Implementation of these preliminary findings into clinical care awaits publication of the full trial results.

The RADICALS trial is a 3,000-subject study taking place in the UK, Canada, Denmark and Republic of Ireland recruiting post-prostatectomy patients who are within 22 weeks of RP with post-RP PSA ≤0.2 ng/ml with one or more of the following characteristics: pT3 or pT4 disease; Gleason score 7-10; preoperative PSA ≥ 10 ng/ml; and/or positive margins. This trial is addressing two critical questions in post-prostatectomy patients. The first question is the comparative efficacy of the ART v. SRT approach. Patients are randomized to either immediate adjuvant RT or to regular PSA testing and salvage RT if PSA becomes detectable. The second, concurrent randomization addresses the question of the role of androgen deprivation therapy. Patients receiving radiation (either ART or SRT) are further randomized to three treatment arms: radiation alone, radiation plus six months of hormonal therapy or radiation plus two years of hormonal therapy. This study will address perhaps the most contentious of issues regarding radiation after surgery: whether salvage radiation when PSA becomes detectable is equivalent to early adjuvant radiation.

The RAVES trial (TROG 08.03) is a phase III multi-center trial taking place in Australia and New Zealand comparing adjuvant RT with early salvage RT in patients with positive margins or EPE. The primary trial aim is to determine whether surveillance with early salvage RT results in equivalent biochemical control and improved quality of life when compared with adjuvant RT. Secondary outcomes include quality of life, toxicity, anxiety/depression, biochemical recurrence-free survival, overall survival, cancer-specific survival, time to distant failure, time to local failure, time to initiation of ADT, quality adjusted life years and cost-utility. This trial is actively recruiting.

Improved imaging techniques. A major question among patients who are undergoing treatment for localized, higher-risk prostate cancer is the true extent of disease. For example, patients with high-volume, high-grade disease whose staging studies (generally bone and CT scans) are negative are those who are most likely to exhibit an immediate PSA relapse, demonstrating pre-existing disease beyond the prostate at the time of diagnosis and treatment. Another challenging class of patients is those who have locally-extraprostatic (e.g., positive margins or seminal vesicle invasion) disease or microscopic nodal disease. In both groups of patients, improved imaging techniques would help to better define appropriate therapies or modifications to existing therapies. Knowing the true extent of disease could lead to more rational nerve-sparing at the time of surgery or could lead to the extension of radiation to include nodal groups or replacement of local therapy (radiation or surgery) with systemic therapy for patients with occult distant metastases. In the realm of adjuvant or salvage radiation, better imaging could allow confirmation that residual disease is confined to the pelvis before embarking on therapy. A significant challenge will be the design of clinical trials to confirm the sensitivity and specificity of such imaging techniques as these studies are confounded by the very long natural history of the disease and the fact that in almost all cases, histologic confirmation that scans are true positive or true negative is lacking. Advances in this field are most likely to be achieved by study designs with clinically-practical outcomes.

New PET imaging tracers appear more accurate in the assessment of prostate cancer than conventional 18F deoxyglucose PET imaging. Further research in 11C-or 18F-choline or 11C-acetate for assessment of local and regional disease is required to validate their utility in

the postoperative setting. Similarly, improved bone metastases imaging with 18F-sodium fluoride will allow clinicians to avoid futile local therapy in men with documented metastatic disease. Improved MRI imaging with dynamic contrast enhancement (DCE) or MR spectroscopy will define sites of local recurrence and improve salvage radiation therapy targeting and the need to add adjuvant therapies, such as androgen deprivation in patients with bulky recurrences not expected to be eradicated with conventional doses of radiation therapy.

Biomarkers of prognosis. A significant need in the arena of adjuvant therapies of prostate cancer are biomarkers of prognosis. To illustrate this point simply requires an examination of SWOG 8794, the only clinical trial finding a survival benefit to adjuvant radiation.[26] With a median follow-up of 12.6 years and up to 20 years of follow-up overall, metastases (the primary outcome) were reported in only 37 of 211 patients in the RP only group and in 20 of 214 patients in the ART group. Although a high-risk population, most men did not develop metastases nor die from their cancer; nonetheless, the number needed to treat with radiation to prevent one case of metastatic disease at a median follow-up of 12.6 years was 12.2.

Ideally, adjuvant or salvage radiation should be given only to the patient who will ultimately develop an adverse outcome (e.g., metastases or death from cancer) and in whom treatment will prevent that outcome. The advantage of patients undergoing prostatectomy is that both blood-based biomarkers as well as tissue biomarkers from the entire prostate are available for analysis. A host of new markers have been identified which may be linked with disease prognosis. It is possible to embed these biomarkers within trials such as RADICALS as secondary objectives to validate their utility in discriminating the patient who is most likely to benefit from adjuvant or salvage therapy.

Quality of life. A major challenge with all prostate cancer therapies is the impact of therapy on QOL including sexual, urinary and GI systems. The generally unanswered question in high-risk patients who are candidates for adjuvant or salvage therapy is how QOL is modulated by such therapies and how this compares and balances with the impact of therapy on survival outcomes. A major problem in most prostate cancer clinical trials (and clinical trials in general) is that QOL studies are underresourced and often undervalued with the primary focus on disease control. Clinical trials of salvage or adjuvant therapy should be designed in such a fashion so as to monitor disease and therapy-related QOL outcomes and to have a pre-planned analysis that integrates both survival and QOL outcomes to allow future patients and physicians to weigh the outcomes to reach a treatment decision for an individual patient.

Clinical trials are being conducted to evaluate the postoperative rehabilitation of men undergoing RP. Biofeedback, physical nerve stimulation and pharmaceutical intervention with phosphodiesterase inhibitors may lessen the impact of surgery on urinary and sexual dysfunction. Improved radiation therapy targeting may also lessen the adverse consequences of treatment for men receiving either adjuvant or salvage radiation therapy.

Combination or systemic therapies. For some patients who undergo adjuvant or salvage radiation, such treatment is not sufficient to control the disease. In SWOG 8794, 20 of 214 patients developed metastatic disease despite early adjuvant RT.[26] In these men, either alternative systemic therapy or combination therapy may have prevented this outcome. The major questions for these highest-risk men are (a) can early identification of men most likely to exhibit disease progression be accomplished (i.e., with prognostic markers), and (b) what are optimal therapies for these men (e.g., other therapies such as hormone therapies in combination with RT or alternate therapies that replace RT)?

Some evidence to suggest that combination/alternative therapy may be beneficial comes from early results of SWOG 9921. This trial randomized high-risk patients post-prostatectomy to two years of adjuvant androgen deprivation therapy with or without chemotherapy.[309] In this study, the surgery plus hormonal therapy arm included some patients who had received radiation due to pT3 disease and, with early follow-up, higher-than-expected disease-free survival results were encountered. Prospective clinical trials are needed to examine prospectively the utility of systemic therapies in combination with radiation and other local therapies for such high risk disease.

Comorbidities. An issue that pervades the management of prostate cancer is how patient comorbidities affect treatment decision-making. Most patients are older and, in many, death due to other causes is far more frequent than death or complications from disease progression. Methods to better predict the chronology of disease relapse and progression as well as life expectancy will enhance the selection of patients most likely to benefit from adjuvant or salvage therapy. Additionally, as radiation does have side effects, the prediction of men more likely to have these complications would help better select patients for treatment. Some comorbidities such as diabetes, hypertension, and vascular disease may increase the risk of radiation-related toxicity. Predictors for such outcomes could be based on functional (e.g., validated measures of erectile, urinary or GI function) or biologic (e.g., DNA repair mutations) measures.

REFERENCES

1 Higgins JDA: Assessing quality of included studies in Cochrane Reviews. The Cochrane Collaboration Methods Groups Newsletter 2007; 11.

2 Wells GA, Shea B, O'Connell D, et al: The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. http://www.ohrica/programs/clinical_epidemiology/oxfordhtm 2009; Available from: URL:http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.

3 Whiting P, Rutjes AW, Reitsma J.B, et al: The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodology 2003 Nov; 10: 25.

4 Whiting P, Rutjes AW, Dinnes J, et al: Development and validation of methods for assessing the quality of diagnostic accuracy studies. Health Technol Assess. 2004 Jun; 8(3): 1-234.

5 Faraday M, Hubbard H, Kosiak B et al: Staying at the cutting edge: a review and analysis of evidence reporting and grading; the recommendations of the American Urological Association. BJU Intl 2009; 104: 294.

6 Hsu CC, Sandford BA: The Delphi Technique: Making Sense of consensus. Practical Assessment, Research and Evaluation 2007; 12(10): 1-8.

7 American Cancer Society: Prostate cancer key statistics. 2009; Available from: http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics; downloaded 11/3/2012.

8 Miller D, Gruber S, Hollenbeck B et al: Incidence of initial local therapy among men with lower-risk prostate cancer in the United States. J. Natl Cancer Inst. 2006; 98: 1134-41.

9 Amling CL, Blute ML, Bergstralh EJ et al: Long-term hazard of progression after radical prostatectomy for clinically localized prostate cancer: continued risk of biochemical failure after 5 years. J Urol 2000; 164: 101-5.

10 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: 273-80.

11 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: 555-565.

12 Bianco FJ Jr, Scardino PT, Eastham JA: Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ('trifecta'). Urology 2005; 66: 83-94.

13 Stephenson AJ, Scardino PT, Eastham JA et al: Preoperative nomogram predicting for the 10-year probability of prostate cancer recurrence after radical prostatectomy. J. Nat Cancer Inst 2006; 98(10): 715-717.

14 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(3): 903-907.

15 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: 1043-1052.

16 Epstein JI, Pizov G, Walsh PC: Correlation of pathological findings with progression after radical retropubic prostatectomy. Cancer 1993; 71(11): 3582-3593.

17 Zeitman AL, Edelstein RA, Coen JJ et al: Radical prostatectomy of the prostate: the influence of preoperative and pathological findings on biochemical disease-free outcome. Urology 1994; 43(6): 828-833.

18 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 Jul; 64(1): 84-89.

19 Ohori M, Wheeler TM, Kattan MW et al: Prognostic significance of surgical margins in radical prostatectomy specimens. J. Urol 1995; 154(5): 1818-1824.

20 Lowe BA, Lieberman SF: Disease recurrence and progression in unrelated pathologic stage T3 prostate cancer: selecting the patient for adjuvant therapy. J. Urol 1997; 158(4): 1452-1456.

21 Pound CR, Partin AW, Eisenberger MA et al: Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999; 281 (17): 1591-1597.

22 Catalona WJ, Smith DS: 5-year tumor recurrence rates after anatomic radical retropubic prostatectomy for prostate cancer. J. Urol 1994; 152: 1837-1842.

23 Thompson IM Jr, Tangen CM, Paradelo J, et al: Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA 2006 Nov 15; 296(19): 2329-35

24 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). The Lancet 2012; 380: 2018 -2027.

25 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 Jun; 27(18): 2924-2930.

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: 956-962.

27 Swanson GP, Thompson IM: Adjuvant radiotherapy for high-risk patients following radical prostatectomy. Urologica Oncology: Seminars and Oncologic Investigators 2007; 25: 515-519.

28 Schroder F, Hugosson J, Roobol M, et al: Prostate-Cancer Mortality at 11 years of follow-up. NEJM 2012; 366: 981-990.

29 Bill-Axelson A, Holmberg L, Ruutu M, et al: Radical prostatectomy versus watchful waiting in early prostate cancer. NEJM 2011; 364: 1709-1717.

30 Abdollah F, Sun M, Schmitges J, et al: Survival benefit of radical prostatectomy in patients with localized prostate cancer: Estimations of the number needed to treat according to tumor and patient characteristics. J. Urol. 2012; 188: 73-83.

31 Boorjian SA, Karnes RJ, Crispen PL, et al: Radiation Therapy After Radical Prostatectomy: Impact on Metastasis and Survival. J Urol 2009 Dec; 182(6): 2708-2715.

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(23): 2760-9.

33 Abdollah F, Suardi N, Cozzarini C et al: Selecting the optimal candidate for adjuvant radiotherapy after radical prostatectomy for prostate cancer: A long-term survival analysis. European Urology 2012. [Epub ahead of print]

34 Arcangeli G, Strigari L, Arcangeli S, et al: Retrospective Comparison of External Beam Radiotherapy and Radical Prostatectomy in High-Risk, Clinically Localized Prostate Cancer. Int J Radiat Oncol 2009 Nov; 75(4): 975-982.

35 Bastide C, Rossi D, Lechevallier E, et al: Seminal vesicle invasion: What is the best adjuvant treatment after radical prostatectomy?. BJU Int 2011 Aug; doi: 10.1111/j.1464-410X.2011.10332.x. [Epub ahead of print]

36 Briganti A, Wiegel T, Joniau S et al: Early salvage radiation therapy does not compromise cancer control in patients with pT3N0 prostate cancer after radical prostatectomy: Results of a match-controlled multi-institutional analysis. European Urol 2012; 62: 472-487.

37 Budiharto T, Perneel C, Haustermans K, et al. A multi-institutional analysis comparing adjuvant and salvage radiation therapy for high-risk prostate cancer patients with undetectable PSA after prostatectomy. Radiother Oncol. 2010 Dec; 97(3):474-9.

38 Caraffini B, De Stefani A, Vitali E, at al: Postoperative radiotherapy after radical prostatectomy for prostate carcinoma: the

experience of the Brescia Radium Institute. Radiol Med (Torino) 2006 Aug; 111(5): 741-7.

39 Catton, C, Gospodarowicz, M, Warde, P, et al: Adjuvant and salvage radiation therapy after radical prostatectomy for adenocarcinoma of the prostate. Radiother Oncol 2001 Apr; 59(1): 51-60.

40 Cheng WS, Frydenberg M, Bergstralh EJ, et al: Radical prostatectomy for pathologic Stage C prostate cancer: Influence of pathologic variables and adjuvant treatment on disease outcome. Urology 1993; 42(3): 283-291.

41 Choo R, Hruby G, Hong J, et al: Positive resection margin and/or pathologic T3 adenocarcinoma of prostate with undetectable postoperative prostate-specific antigen after radical prostatectomy: To irradiate or not?. Int J Radiat Oncol 2002 Mar; 52 (3): 674-680.

42 Cozzarini C, Montorsi F, Fiorino C, at al: Need for High Radiation Dose ((greater-than or equal to)70 Gy) in Early Postoperative Irradiation After Radical Prostatectomy: A Single-Institution Analysis of 334 High-Risk, Node-Negative Patients. Int J Radiat Oncol 2009 Nov; 75(4): 966-974.

43 Do LV, Do TM, Smith R, et al: Postoperative radiotherapy for carcinoma of the prostate: Impact on both local control and distant disease-free survival. Am J Clin Oncol 2002; 25(1): 1-8.

44 Eggener SE, Roehl KA, Smith ND, at al: Contemporary survival results and the role of radiation therapy in patients with node negative seminal vesicle invasion following radical prostatectomy. J Urol 2005 Apr; 173(4): 1150-1155.

45 Hagan M, Zlotecki R, Medina C, at al: Comparison of adjuvant versus salvage radiotherapy policies for postprostatectomy radiotherapy. Int J Radiat Oncol Biol Phys 2004 Jun 1; 59(2): 329-40.

46 Kalapurakal JA, Huang C-F, Neriamparampil MM, et al: Biochemical disease-free survival following adjuvant and salvage irradiation after radical prostatectomy. Int J Radiat Oncol 2002 Nov; 54 (4): 1047-1054.

47 Kamat AM, Babaian K, Cheung MR, et al: Identification of factors predicting response to adjuvant radiation therapy in patients with positive margins after radical prostatectomy. J Urol 2003 Nov; 170(5) 1860-1863.

48 Leibovich BC, Engen DE, Patterson DE, et al: Benefit of adjuvant radiation therapy for localized prostate cancer with a positive surgical margin. J Urol 2000 Apr; 163(4): 1178-1182.

49 Macdonald OK, Lee RJ, Snow G, et al: Prostate-Specific Antigen Control with Low-Dose Adjuvant Radiotherapy for High-Risk Prostate Cancer. Urology 2007 Feb; 69(2): 295-299.

50 Mayer R, Pummer K, Quehenberger F, at al: Postprostatectomy radiotherapy for high-risk prostate cancer. Urology 2002; 59(5): 732-739.

51 McCarthy JF, Catalona WJ, Hudson MA: Effect of radiation therapy on detectable serum prostate specific antigen levels following radical prostatectomy: Early versus delayed treatment. J Urol 1994; 151(6): 1575-1578.

52 Neulander EZ, Wajsman Z, Greene GF: Radical prostatectomy and postoperative radiation in patients with adenocarcinoma of prostate of intermediate and high risk for recurrence. J Ark Med Soc 2005 Mar; 101(9): 276-80.

53 Nudell DM, Grossfeld GD, Weinberg VK, at al: Radiotherapy after radical prostatectomy: treatment outcomes and failure patterns.. Urology 1999 Dec; 54(6): 1049-1057.

54 Ost P, Fonteyne V, Villeirs G, et al: Adjuvant High-Dose Intensity-Modulated Radiotherapy after Radical Prostatectomy for Prostate Cancer: Clinical Results in 104 Patients. Eur Urol 2009 Oct; 56(4): 669-677.

55 Ost P, De Troyer B, Fonteyne V, et al: A matched control analysis of adjuvant and salvage high-dose postoperative intensity-modulated radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2011; 80(5): 1316-22.

56 Pacholke HD, Wajsman Z, Algood CB, et al: Postoperative adjuvant and salvage radiotherapy for prostate cancer: Impact on freedom from biochemical relapse and survival. Urology 2004 Nov; 64(5): 982-986.

57 Pai HH, Eldridge B, Bishop D, et al: Does neoadjuvant hormone therapy improve outcome in

prostate cancer patients receiving radiotherapy after radical prostatectomy? Can J Urol 2009 Apr; 16(2): 4541-4552.

58 Peschel RE, Robnett TJ, Hesse D, et al: PSA based review of adjuvant and salvage radiation therapy vs. observation in postoperative prostate cancer patients. Int J Cancer 2000 Feb 20; 90(1): 29-36.

59 Petroski RA, Warlick WB, Herring J, et al: External beam radiation therapy after radical prostatectomy: Efficacy and impact on urinary continence. Prostate Cancer Prostatic Dis 2004; 7 (2): 170-177.

60 Schaefer U, Witt F, Schueller P, et al: Prostate-specific antigen (PSA) in the monitoring of prostate cancer after radical prostatectomy and external beam radiation. Anticancer Res 2000 Nov-Dec; 20 (6D): 4989-92.

61 Schafer U, Witt F, Micke O, et al: Adjuvant radiotherapy in locally confined prostate cancer. Anticancer Res 2003 Mar-Apr; 23(2A): 983-5.

62 Schild SE, Pisansky TM: The role of radiotherapy after radical prostatectomy. Urol Clin North Am 2001 Aug; 28(3): 629-37.

63 Taylor N, Kelly JF, Kuban DA, et al: Adjuvant and salvage radiotherapy after radical prostatectomy for prostate cancer. Int J Radiat Oncol Biol Phys 2003 Jul 1; 56(3): 755-63.

64 Teh BS, Bastasch MD, Mai WY, et al: Long-term benefits of elective radiotherapy after prostatectomy for patients with positive surgical margins. J Urol 2006 Jun; 175(6): 2097-2101.

65 Trabulsi EJ, Valicenti RK, Hanlon AL, at al: A Multi-Institutional Matched-Control Analysis of Adjuvant and Salvage Postoperative Radiation Therapy for pT3-4N0 Prostate Cancer. Urology 2008 Dec; 72 (6): 1298-1302.

66 Tramacere F, Gianicolo E, Pignatelli A, et al: High-dose 3D-CRT in the radical and postoperative setting for prostate cancer. Analysis of survival and late rectal and urinary toxicity. Tumori 2012; 98: 337-343.

67 Tsien C, Griffith KA, Sandler HM, et al: Long-term results of three-dimensional conformal adjuvant and salvage radiotherapy after radical prostatectomy. Urology 2003 Jul; 62(1): 93-98.

68 Valicenti RK, Gomella LG, Ismail M, et al: Pathologic seminal vesicle invasion after radical prostatectomy for patients with prostate carcinoma: Effect of early adjuvant radiation therapy on biochemical control. Cancer 1998 May; 82(10): 1909-1914.

69 Valicenti RK, Gomella LG, Ismail M, et al: Effect of higher radiation dose on biochemical control after radical prostatectomy for PT3N0 prostate cancer. Int J Radiat Oncol Biol Phys 1998; 42(3): 501-6.

70 Valicenti RK, Gomella LG, Ismail M, at al: The efficacy of early adjuvant radiation therapy for pT3N0 prostate cancer: A matched-pair analysis. Int J Radiat Oncol 1999 Aug; 45(1): 53-58.

71 Valicenti RK, Chervoneva I, Gomella LG: Importance of margin extent as a predictor of outcome after adjuvant radiotherapy for Gleason score 7 pT3N0 prostate cancer. Int J Radiat Oncol Biol Phys 2004 Mar 15; 58(4): 1093-7.

72 Vargas C, Kestin LL, Weed DW, et al: Improved biochemical outcome with adjuvant radiotherapy after radical prostatectomy for prostate cancer with poor pathologic features. Int J Radiat Oncol Biol Phys 2005 Mar 1; 61(3): 714-24.

73 Vicini FA, Ziaja EL, Kestin LL, et al: Treatment outcome with adjuvant and salvage irradiation after radical prostatectomy for prostate cancer. Urology 1999 Jul; 54(1): 111-117.

74 Wadasaki K, Kaneyasu Y, Kenjo M, et al: Treatment results of adjuvant radiotherapy and salvage radiotherapy after radical prostatectomy for prostate cancer. Int J Clin Oncol; 4(2): 87–89.

75 Anscher MS, Clough R, Dodge R: Radiotherapy for a rising prostate-specific antigen after radical prostatectomy: the first 10 years. Int J Radiat Oncol Biol Phys 2000; 48(2): 369-75.

76 Bastide C, Savage C, Cronin A, et al: Location and number of positive surgical margins as prognostic factors of biochemical recurrence after salvage radiation therapy after radical prostatectomy. BJU Int 2010; 106(10): 1454-7.

77 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(3): 735-40.

78 Borg M, Sutherland P, Stapleton A, et al: Outcome of post-prostatectomy radiotherapy in one institution. Australas Radiol 2006 Oct; 50(5): 475-480

79 Brodak M, Kosina J, Holub L, et al: Radical prostatectomy in high-grade prostate cancer, salvage and adjuvant radiotherapy. Urol Int 2011 Mar; 86(2): 146-151.

80 Brooks JP, Albert PS, O'Connell J, et al: Lymphovascular invasion in prostate cancer: prognostic significance in patients treated with radiotherapy after radical prostatectomy. Cancer 2006 Apr 1; 106(7): 1521-6.

81 Buskirk SJ, Schild SE, Durr ED, et al: Evaluation of serum prostate-specific antigen levels after postoperative radiation therapy for pathologic stage T3, N0 prostate cancer. Mayo Clin Proc 1996; 71(3): 242-8.

82 Buskirk SJ, Pisansky TM, Schild, SE, et al: Salvage radiotherapy for isolated prostate specific antigen increase after radical prostatectomy: evaluation of prognostic factors and creation of a prognostic scoring system. J Urol 2006 Sep; 176(3): 985-90.

83 Cadeddu JA, Partin AW, DeWeese TL et al: Long-term results of radiation therapy for prostate cance recurrence following radical prostatectomy. J. Urol; 1998; 159: 173-178.

84 Chawla AK, Thakral HK, Zietman AL, et al: Salvage radiotherapy after radical prostatectomy for prostate adenocarcinoma: analysis of efficacy and prognostic factors. Urology 2002 May; 59(5): 726-31.

85 Cheung R, Kamat AM, de Crevoisier R, et al:Outcome of salvage radiotherapy for biochemical failure after radical prostatectomy with or without hormonal therapy. Int J Radiat Oncol Biol Phys 2005 Sep 1; 63(1): 134-40.

86 Choo R, Morton G, Danjoux C, et al: Limited efficacy of salvage radiotherapy for biopsy confirmed or clinically palpable local recurrence of prostate carcinoma after surgery. Radiother Oncol 2005 Feb; 74(2): 163-7.

87 Choo R, Hruby G, Hong J, et al: (IN)-efficacy of salvage radiotherapy for rising PSA or clinically isolated local recurrence after radical prostatectomy. Int J Radiat Oncol Biol Phys 2002 Jun 1; 53(2): 269-76.

88 Coetzee LJ, Hars V, Paulson DF: Postoperative prostate-specific antigen as a prognostic indicator in patients with margin-positive prostate cancer, undergoing adjuvant radiotherapy after radical prostatectomy. Urology 1996; 47(2): 232-235.

89 Cozzarini C, Bolognesi A, Ceresoli GL, et al: Role of postoperative radiotherapy after pelvic lymphadenectomy and radical retropubic prostatectomy: a single institute experience of 415 patients. Int J Radiat Oncol Biol Phys 2004 Jul 1; 59.

90 Cremers RGHM, Van Lin ENJT, Gerrits WLJ, et al: Efficacy and tolerance of salvage radiotherapy after radical prostatectomy, with emphasis on high -risk patients suited for adjuvant radiotherapy. Radiother Oncol 2010 Dec; 97(3): 467-473.

91 De La Taille A, Flam TA, Thiounn N, et al: Predictive factors of radiation therapy for patients with prostate specific antigen recurrence after radical prostatectomy. BJU Int 2002 Dec; 90(9): 887-892.

92 De Meerleer G, Fonteyne V, Meersschout S, et al: Salvage intensity-modulated radiotherapy for rising PSA after radical prostatectomy. Radiother Oncol 2008; 89(2): 205-13.

93 Delongchamps NB, Zerbib M, Mejean A et al: Conformal radiotherapy for detectable PSA following radical prostatectomy: efficacy and predictive factors of recurrence. Can J Urol 2009 Oct; 16(5): 4813-9.

94 Do T, Parker RG, Do C, et al: Salvage radiotherapy for biochemical and clinical failures following radical prostatectomy. Cancer J Sci Am 1998; 4 (5): 324-330.

95 Do T, Dave G, Parker R, et al: Serum PSA evaluations during salvage radiotherapy for post-prostatectomy biochemical failures as prognosticators for treatment outcomes. Int J Radiat Oncol Biol Phys 2001 Aug 1; 50(5): 1220-5.

96 Forman JD, Meetze K, Pontes E, et al: Therapeutic

irradiation for patients with an elevated post-prostatectomy prostate specific antigen level. J Urol 1997; 158(4): 1436-9; discussion 1439-40.

97 Garg MK, Tekyi-Mensah S, Bolton S, et al: Impact of postprostatectomy prostate-specific antigen nadir on outcomes following salvage radiotherapy. Urology 1998; 51(6): 998-1002.

98 Geinitz H, Riegel MG, Thamm R, et al: Outcome after conformal salvage radiotherapy in patients with rising prostate-specific antigen levels after radical prostatectomy. Int J Radiat Oncol Biol Phys. 2012 Apr 1; 82(5):1930-7.

99 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(6): 1142-8.

100 Haab F, Meulemans A, Boccon-Gibod L, et al: Effect of radiation therapy after radical prostatectomy on serum prostate- specific antigen measured by an ultrasensitive assay. Urology 1995; 45(6): 1022-1027.

101 Hayashi S, Hayashi K, Yoshimura R et al: Salvage radiotherapy after radical prostatectomy: Outcomes and prognostic factors especially focusing on pathological findings. J. Radiation Research 2012; 53:727-734.

102 Hugen CM, Polcari AJ, Quek ML, et al: Long-term outcomes of salvage radiotherapy for PSA-recurrent prostate cancer: validation of the Stephenson nomogram. World J Urol 2010; 28(6): 741-4.

103 Jacinto AA, Fede AB, Fagundes LA, et al: Salvage radiotherapy for biochemical relapse after complete PSA response following radical prostatectomy: outcome and prognostic factors for patients who have never received hormonal therapy. Radiat Oncol 2007; 2: 8.

104 Jereczek-Fossa BA, Zerini D, Vavassori A, et al: Sooner or later? Outcome analysis of 431 prostate cancer patients treated with postoperative or salvage radiotherapy. Int J Radiat Oncol Biol Phys 2009; 74(1): 115-25.

105 Katz MS, Zelefsky MJ, Venkatraman ES, et al: Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer. J Clin Oncol 2003 Feb; 21(3): 483-489.

106 Kim BS, Lashkari A, Vongtama R, et al: Effect of pelvic lymph node irradiation in salvage therapy for patients with prostate cancer with a biochemical relapse following radical prostatectomy. Clin Prostate Cancer 2004 Sep; 3 (2): 93-7.

107 King CR, Spiotto MT: Improved outcomes with higher doses for salvage radiotherapy after prostatectomy. Int J Radiat Oncol Biol Phys 2008; 71(1): 23-7.

108 King CR, Presti JC Jr, Gill H, et al: Radiotherapy after radical prostatectomy: does transient androgen suppression improve outcomes? Int J Radiat Oncol Biol Phys 2004 Jun 1; 59(2): 341-7.

109 King CR, Presti JC, Brooks JD, et al: Postoperative prostate-specific antigen velocity independently predicts for failure of salvage radiotherapy after prostatectomy. Int J Radiat Oncol Biol Phys 2008; 70(5): 1472-7.

110 Koppie TM, Grossfeld GD, Nudell DM, et al: Is anastomotic biopsy necessary before radiotherapy after radical prostatectomy?. J Urol 2001; 166(1): 111-115.

111 Kruser TJ, Jarrard DF, Graf AK, et al: Early hypofractionated salvage radiotherapy for postprostatectomy biochemical recurrence. Cancer 2011; 117(12): 2629-36.

112 Kundel Y, Pfeffer R, Lauffer M, et al: Salvage prostatic fossa radiation therapy for biochemical failure after radical prostatectomy: the Sheba experience. Isr Med Assoc J 2004 Jun; 6(6): 329-31.

113 Lee LW, McBain CA, Swindell R, et al: Hypofractionated radiotherapy as salvage for rising prostate-specific antigen after radical prostatectomy. Clin Oncol (R Coll Radiol) 2004 Dec; 16(8): 517-22.

114 Leventis AK, Shariat SF, Kattan MW, et al: Prediction of response to salvage radiation therapy in patients with prostate cancer recurrence after radical prostatectomy. J Clin Oncol 2001 Feb 15; 19(4): 1030-9.

References

115 Liauw SL, Weichselbaum RR, Zagaja GP, et al: Salvage radiotherapy after postprostatectomy biochemical failure: does pretreatment radioimmunoscintigraphy help select patients with locally confined disease?. Int J Radiat Oncol Biol Phys 2008 41122; 71(5): 1316-21.

116 Loeb S, Roehl KA, Viprakasit DP, et al: Long-Term Rates of Undetectable PSA with Initial Observation and Delayed Salvage Radiotherapy after Radical Prostatectomy. Eur Urol 2008 Jul; 54(1): 88-96.

117 Macdonald OK, Schild SE, Vora SAet al: Salvage radiotherapy for palpable, locally recurrent prostate cancer after radical prostatectomy. Int J Radiat Oncol Biol Phys 2004 Apr 1; 58(5): 1530-5.

118 Macdonald OK, Schild SE, Vora SAet al: Radiotherapy for men with isolated increase in serum prostate specific antigen after radical prostatectomy. J Urol 2003 Nov; 170(5): 1833-7.

119 MacDonald OK, Schild SE, Vora S, et al: Salvage radiotherapy for men with isolated rising PSA or locally palpable recurrence after radical prostatectomy: do outcomes differ?. Urology 2004 Oct; 64(4): 760-4.

120 Macdonald OK, D'Amico AV, Sadetsky N, Shrieve DC, Carroll PR: Predicting PSA failure following salvage radiotherapy for a rising PSA post-prostatectomy: from the CaPSURE database. Urol Oncol 2008; 26(3): 271-5.

121 Maier J, Forman J, Tekyi-Mensah S, et al: Salvage radiation for a rising PSA following radical prostatectomy. Urol Oncol 2004 Jan-Feb; 22(1): 50-6.

122 Matsui Y, Ichioka K, Terada N, Yoshimura K, et al: Impact of volume weighted mean nuclear volume on outcomes following salvage radiation therapy after radical prostatectomy. J Urol 2004 Feb; 171 (2 Pt 1): 687-91.

123 Medini E, Medini I, Reddy PK, et al: Delayed/ salvage radiation therapy in patients with elevated prostate specific antigen levels after radical prostatectomy. A long term follow-up. Cancer 1996; 78(6): 1254-9.

124 Monti CR, Nakamura RA, Ferrigno R, et al: Salvage conformal radiotherapy for biochemical recurrent prostate cancer after radical prostatectomy. Int Braz J Urol 2006 Jul-Aug; 32(4): 416- 26; 427.

125 Mosbacher MR, Schiff PB, Otoole KM, et al: Postprostatectomy salvage radiation therapy for prostate cancer: impact of pathological and biochemical variables and prostate fossa biopsy. Cancer J 2002 May-Jun; 8(3): 242-6.

126 Nagda SN, Mohideen N, Lo SS, et al : Long-term follow-up of 111In-capromab pendetide (ProstaScint) scan as pretreatment assessment in patients who undergo salvage radiotherapy for rising prostate-specific antigen after radical prostatectomy for prostate cancer. Int J Radiat Oncol Biol Phys 2007 Mar 1; 67(3): 834-40.

127 Neuhof D, Hentschel T, Bischof M, Sroka-Perez G, et al: Long-term results and predictive factors of three-dimensional conformal salvage radiotherapy for biochemical relapse after prostatectomy. Int J Radiat Oncol Biol Phys 2007 Apr 1; 67(5): 1411-7.

128 Numata K, Azuma K, Hashine K, et al: Predictor of response to salvage radiotherapy in patients with PSA recurrence after radical prostatectomy: the usefulness of PSA doubling time. Jpn J Clin Oncol 2005 May; 35(5): 256-9.

129 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 (4): 842-849.

130 Patel R, Lepor H, Thiel RP, et al: Prostate-specific antigen velocity accurately predicts response to salvage radiotherapy in men with biochemical relapse after radical prostatectomy. Urology 2005 May; 65(5): 942-6.

131 Pazona JF, Han M, Hawkins SA, et al: Salvage radiation therapy for prostate specific antigen progression following radical prostatectomy: 10-year outcome estimates. J Urol 2005 Oct; 174(4 Pt 1): 1282-6.

132 Perez CA, Michalski JM, Baglan K, et al: Radiation therapy for increasing prostate-specific antigen levels after radical prostatectomy. Clin Prostate Cancer 2003; 1(4): 235-41.

133 Peyromaure M, Allouch M, Eschwege F, et al: Salvage radiotherapy for biochemical recurrence

after radical prostatectomy: a study of 62 patients. Urology 2003 Sep; 62(3): 503-7.

134 Pisansky TM, Kozelsky TF, Myers RP, et al: Radiotherapy for isolated serum prostate specific antigen elevation after prostatectomy for prostate cancer. J Urol 2000; 163(3): 845-50.

135 Quero L, Mongiat-Artus P, Ravery V, et al: Salvage radiotherapy for patients with PSA relapse after radical prostatectomy: a single institution experience. BMC Cancer 2008; 8: 26.

136 Rogers R, Grossfeld GD, Roach M III, et al: Radiation therapy for the management of biopsy proved local recurrence after radical prostatectomy. J Urol 1998; 160(5): 1748-53.

137 Sasaki T, Nakamura K, Shioyama Y, et al: Low pre -radiotherapy prostate-specific antigen level is a significant predictor of treatment success for postoperative radiotherapy in patients with prostate cancer. Anticancer Res 2006 May-Jun; 26 (3B): 2367-74.

138 Schild SE, Buskirk SJ, Robinow JS, et al: The results of radiotherapy for isolated elevation of serum PSA levels following radical prostatectomy. Int J Radiat Oncol Biol Phys 1992 ; 23(1): 141-5.

139 Schwarz R, Krull A, Tribius S, et al: Results of three dimensional conformal radiotherapy and hormonal therapy for local recurrence after radical prostatectomy. Strahlenther Onkol 2005 Jul; 181 (7): 442-447.

140 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(8): 467-72.

141 Siegmann A, Bottke D, Faehndrich J, et al: Salvage radiotherapy after prostatectomy: What is the best time to treat? Radiotherapy and Oncology; 2012; 103: 239-243.

142 Song DY, Thompson TL, Ramakrishnan V, et al: Salvage radiotherapy for rising or persistent PSA after radical prostatectomy. Urology 2002 Aug; 60 (2): 281-7.

143 Song C, Kim YS, Hong JH, et al: Treatment failure and clinical progression after salvage therapy in men with biochemical recurrence after radical prostatectomy: Radiotherapy vs androgen deprivation. BJU Int 2009; 106(2): 188-193.

144 Soto D, Passarelli M, Daignault S et al: Concurrent androgen deprivation therapy during salvage prostate radiotherapy improves treatment outcomes in high-risk patients. Int J Radiation Oncology Biol Phys, 2012; 82: 1227-1232.

145 Spiotto MT, Hancock SL, King CR: Radiotherapy after prostatectomy: improved biochemical relapse -free survival with whole pelvic compared with prostate bed only for high-risk patients. Int J Radiat Oncol Biol Phys 2007 Sep 1; 69(1): 54-61.

146 Stephenson A J, Shariat SF, Zelefsky MJ, et al: Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA 2004 Mar 17; 291(11): 1325-32.

147 Stephenson AJ, Scardino PT, Kattan MW, et al: Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 2007 May 20; 25(15): 2035-41.

148 Stockdale AD, Vakkalanka BK, Fahmy A, et al: Management of biochemical failure following radical prostatectomy: salvage radiotherapy - a case series. Prostate Cancer Prostatic Dis 2007; 10 (2): 205-9.

149 Swanson GP, Du F, Michalek JE, et al: Long-term follow-up and risk of cancer death after radiation for post-prostatectomy rising prostate-specific antigen. Int J Radiat Oncol Biol Phys 2011; 80(1): 62-8.

150 Symon Z, Kundel Y, Sadetzki S, et al: Radiation rescue for biochemical failure after surgery for prostate cancer: predictive parameters and an assessment of contemporary predictive models. Am J Clin Oncol 2006 Oct; 29(5): 446-50.

151 Tefilli MV, Gheiler EL, Tiguert R, et al : Quality of life in patients undergoing salvage procedures for locally recurrent prostate cancer. J Surg Oncol 1998; 69(3): 156-61.

152 Terai A, Matsui Y, Yoshimura K, et al: Salvage radiotherapy for biochemical recurrence after radical prostatectomy. BJU Int 2005 Nov; 96(7):

1009-13.

153 Tomita N, Kodaira T, Furutani K, et al: Early salvage radiotherapy for patients with PSA relapse after radical prostatectomy. J Cancer Res Clin Oncol 2009; 135(11): 1561-7.

154 Umezawa R, Ariga H, Ogawa Y, et al. Impact of pathological tumor stage for salvage radiotherapy after radical prostatectomy in patients with prostate-specific antigen < 1.0 ng/ml. Radiation Oncology, 2011; 6: 150.

155 Van Der Poel HG, Moonen L, Horenblas S: Sequential treatment for recurrent localized prostate cancer. J Surg Oncol 2008; 97(5): 377-82.

156 Vanuytsel L, Janssens G, Van Poppel H, et al: Radiotherapy for PSA recurrence after radical prostatectomy. Eur Urol 2001 Apr; 39(4): 425-9.

157 Ward JF, Zincke H, Bergstralh EJ, et al: Prostate specific antigen doubling time subsequent to radical prostatectomy as a prognosticator of outcome following salvage radiotherapy. J Urol 2004 Dec; 172: 6(Pt 1): 2244-8.

158 Wiegel T, Lohm G, Bottke D, et al: Achieving an undetectable PSA after radiotherapy for biochemical progression after radical prostatectomy is an independent predictor of biochemical outcome--results of a retrospective study. Int J Radiat Oncol Biol Phys 2009; 73(4): 1009-16.

159 Wilder RB, Hsiang JY, Ji M, et al: Preliminary results of three-dimensional conformal radiotherapy as salvage treatment for a rising prostate-specific antigen level postprostatectomy. Am J Clin Oncol 2000 Apr; 23(2): 176-80.

160 Wu JJ, King SC, Montana GS, et al: The efficacy of postprostatectomy radiotherapy in patients with an isolated elevation of serum prostate-specific antigen. Int J Radiat Oncol Biol Phys 1995; 32(2): 317-23.

161 Xu Y, Liu R, Zhang Z, et al: Variables which might predict the response to salvage radiotherapy in Chinese patients with biochemical failure after radical prostatectomy. Urol Int 2006 Nov; 77(3): 205-210.

162 Yoshida T, Nakayama M, Suzuki O, et al: Salvage radiotherapy for prostate-specific antigen relapse after radical prostatectomy for prostate cancer: a single-center. Jpn J Clin Oncol 2011; 41(8): 1031-6.

163 Youssef E, Forman JD, Tekyi-Mensah S, et al: Therapeutic postprostatectomy irradiation. Clin Prostate Cancer 2002 Jun; 1(1): 31-6.

164 Bolla M, van Poppel H, Collette L, et al: Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet 2005 Aug 13-19; 366 (9485): 572-8.

165 Zelefsky M, Leibel S, Kutcher G. et al: Three-dimensional conformal radiotherapy and dose escalation: Where do we stand? Seminars in Radiation Oncology; 1998; 8(2): 107-114.

166 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. European J of Cancer; 2012; 48: 837-844.

167 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: 361-368.

168 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. Radiotherapy and Oncology 2008; 88: 10-19.

169 Wiltshire KL, Brock KK, Haider MA et al. Anatomic boundaries of the clinical target volume (prostate bed) after radical prostatectomy. Int J Radiation Oncology Biol Phys 2007; 69: 1090-1099.

170 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. Radiotherapy and Oncology 2007; 84: 121-127.

171 Shipley W, Hunt D, Lukka P, et al: Initial report of RTOG 9601, a phase III trial in prostate cancer:

Effect of anti-androgen therapy (AAT) with bicalutamide during and after radiation therapy (RT) on freedom from progression and incidence of metastatic disease in patients following radical prostatectomy (RP) with pT2-3, N0 disease and elevated PSA levels. J. Clin Oncol 2011; 29(suppl 7: abstr 1).

172 Ost P, Cozzarini C, Meerleer G et al: High-dose adjuvant radiotherapy after radical prostatectomy with or without androgen deprivation therapy. In J Radiation Oncol Biol Phys 2012; 83: 960-965.

173 Da Pozzo LF, Cozzarini C, Briganti A, et al: Long-term follow-up of patients with prostate cancer and nodal metastases treated by pelvic lymphadenectomy and radical prostatectomy: the positive impact of adjuvant radiotherapy. European Urology 2009; 55: 1003-1011.

174 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 Nov; 93(2): 207-212.

175 Azelie C, Gauther M, Mirjolet C et al: Exclusive image guided IMRT vs. radical prostatectomy followed by postoperative IMRT for localized prostate cancer: A matched-pair analysis based on risk-groups. Radiation Oncology 2012; 7(158).

176 Bastasch MD, Teh BS, Mai WY, et al: Post-nerve-sparing prostatectomy, dose-escalated intensity-modulated radiotherapy: effect on erectile function. Int J Radiat Oncol Biol Phys 2002 Sep 1; 54(1): 101-6.

177 Bellavita R, Massetti M, Abraha I, et al. Conformal postoperative radiotherapy in patients with positive resection margins and/or pT3-4 prostate adenocarcinoma. Radiation Oncoloy 2012; 84: e299-e304.

178 Brooks JP, Albert PS, Wilder RB, et al: Long-term salvage radiotherapy outcome after radical prostatectomy and relapse predictors. J Urol 2005 Dec; 174(6): 2204-8.

179 Cheng J, Schultheiss T, Nguyen KH et al: Acute toxicity in definitive versus postprostatectomy image-guided radiotherapy for prostate cancer. In J Radiation Oncology Biol Phys 2008; 71: 351-357.

180 Choo R, Pearse M, Danjoux C, et al: Analysis of gastrointestinal and genitourinary morbidity of postoperative radiotherapy for pathologic T3 disease or positive surgical margins after radical prostatectomy using national cancer institute expanded common toxicity criteria. Int J Radiat Oncol Biol Phys 2008; 72(4): 989-95.

181 Cozzarini C, Fiorino C, Ceresoli GL, et al: Significant correlation between rectal DVH and late bleeding in patients treated after radical prostatectomy with conformal or conventional radiotherapy (66.6-70.2 Gy). Int J Radiat Oncol 2003 Mar; 55(3): 688-694.

182 Cozzarini C, Fiorino C, Da Pozzo LF et al: Clinical factors predicting late severe urinary toxicity after postoperative radiotherapy for prostate carcinoma: A single-institute analysis of 742 patients. Int J Radiation Oncology Biol Phys 2012; 82: 191-199.

183 Duchesne GM, Dowling C, Frydenberg M, et al: Outcome, morbidity, and prognostic factors in post-prostatectomy radiotherapy: an Australian multicenter study. Urology 2003 Jan; 61(1): 179-83.

184 Eldredge H, Studenski M, Keith S, et al: Post-prostatectomy image-guided radiation therapy: Evaluation of toxicity and inter-fracation variation using online cone-beam CT. Journal of Medical Imaging and Radiation Oncology; 2011; 58: 507-515.

185 Feng M, Hanlon AL, Pisansky TM, et al: Predictive factors for late genitourinary and gastrointestinal toxicity in patients with prostate cancer treated with adjuvant or salvage radiotherapy. Int J Radiat Oncol Biol Phys 2007 Aug 1; 68(5): 1417-23.

186 Fontaine E, Mouelli BS, Thomas L, et al: Urinary continence after salvage radiation therapy following radical prostatectomy, assessed by a self-administered questionnaire: a prospective study. BJU Int 2004 Sep; 94(4): 521-3.

187 Goldner G, Pötter R: Radiotherapy in lymph node-positive prostate cancer patients - a potential cure? Single institutional experience regarding outcome and side effects. Front Radiat Ther Oncol 2008; 41: 68-76.

References

188 Iyengar P, Levy L, Choi S et al: Toxicity associated with postoperative radiation therapy for prostate cancer. Am J Clin Oncol 2011; 34: 611-618.

189 Jung C, Cookson MS, Chang SS, et al: Toxicity following high-dose salvage radiotherapy after radical prostatectomy. BJU Int 2007 Mar; 99(3): 529-33.

190 Macdonald OK, D'Amico AV, Sadetsky N, et al: Adjuvant radiotherapy in prostate cancer: predictors of prostate-specific antigen recurrence from the CaPSURE database. Urology 2007 Jul; 70 (1): 106-10.

191 Nath SK, Sandhu AP, Rose BS, Set al: Toxicity analysis of postoperative image-guided intensity-modulated radiotherapy for prostate cancer. Int J Radiat Oncol 2010 Oct; 78(2): 435-441.

192 Pearse M, Choo R, Danjoux C, et al: Prospective assessment of gastrointestinal and genitourinary toxicity of salvage radiotherapy for patients with prostate-specific antigen relapse or local recurrence after radical prostatectomy. Int J Radiat Oncol Biol Phys 2008 41214; 72(3): 792-8.

193 Perna L, Alongi F, Fiorino C, et al: Predictors of acute bowel toxicity in patients treated with IMRT whole pelvis irradiation after prostatectomy. Radiother Oncol 2010; 97(1): 71-5.

194 Peterson JL, Buskirk SJ, Heckman MG, et al: Late toxicity after postprostatectomy salvage radiation therapy. Radiother Oncol 2009 Nov; 93(2): 203-206.

195 Pinkawa M, Fischedick K, Asadpour B, et al: Health -related quality of life after adjuvant and salvage postoperative radiotherapy for prostate cancer - a prospective analysis. Radiother Oncol 2008; 88(1): 135-9.

196 Riou O, Laliberte B, Azria D et al: Implementing intensity modulated radiotherapy to the prostate bed: Dosemetric study and early clinical results. Medical Dosimetry 2012; 38(2):117-121.

197 Schild SE, Buskirk SJ, Wong WW, et al: The use of radiotherapy for patients with isolated elevation of serum prostate specific antigen following radical prostatectomy. J Urol 1996 Nov; 156(5): 1725-9.

198 Sharma R, Chuba PJ, Duclos M, et al: Differences in dosimetry and toxicity between definitive and postprostatectomy radiation therapy. Radiology 1997; 204(1): 211-2.

199 Suzuki K, Nakano K, Morita T: Outcome of adjuvant radiotherapy after radical prostatectomy for prostate cancer patients. Urol Int 2010; 84:382 –387.

200 Valicenti RK, Gomella LG, Ismail M, et al: Durable efficacy of early postoperative radiation therapy for high-risk pT3N0 prostate cancer: the importance of radiation dose. Urology 1998; 52: 6.

201 Moinpour CM, Hayden KA, Unger JM, et al: Health-related quality of life results in pathologic stage C prostate cancer from a Southwest Oncology Group trial comparing radical prostatectomy alone with radical prostatectomy plus radiation therapy. J Clin Oncol 2008 Jan; 26(1): 112-120.

202 Formenti SC, Lieskovsky G, Simoneau AR, et al: Impact of moderate dose of postoperative radiation on urinary continence and potency in patients with prostate cancer treated with nerve sparing prostatectomy. J Urol 1996; 155(2): 616-9.

203 Formenti SC, Lieskovsky G, Skinner D, et al: Update on impact of moderate dose of adjuvant radiation on urinary continence and sexual potency in prostate cancer patients treated with nerve-sparing prostatectomy. Urology 2000 Sep 1; 56 (3): 453-8.

204 Hofmann T, Gaensheimer S, Buchner A, et al: An unrandomized prospective comparison of urinary continence, bowel symptoms and the need for further procedures in patients with and with no adjuvant radiation after radical prostatectomy. BJU Int 2003 Sep; 92(4): 360-364.

205 Van Cangh PJ, Richard F, Lorge F, et al: Adjuvant radiation therapy does not cause urinary incontinence after radical prostatectomy: Results of a prospective randomized study. J Urol 1998 Jan; 159(1): 164-166.

206 Hu JC, Elkin EP, Krupski TL, et al: The effect of postprostatectomy external beam radiotherapy on quality of life: Results from the cancer of the prostate strategic urologic research endeavor.

Cancer 2006 Jul; 107(2): 281-288.

207 Corbin K, Kunnavakkam R, Eggener S, et al: Intensity modulated radiation therapy after radical prostatectomy: Early results show no decline inurinary continence, gastrointestinal, or sexual quality of life. Practical Radiation Oncology 2012: Practical Radiation Oncology; 3(2): 138-144.

208 Guedea F, Davis BJ: Treatment of localised prostate cancer with radiation therapy: evidence versus opinion. Clin Transl Oncol. 2010; 12:315-317.

209 Bhojani N, Capitanio U, Suardi N et al: Therape of secondary malignancies after radical prostatectomy versus external beam radiation therapy for localized prostate cancer: a population -basedstudy on 17,845 patients. Int J Radiat Oncol BiolPhys 2010; 76: 342–348.

210 Pickles T, Phillips N: The risk of secondmalignancy in men with prostate cancer treated with or without radiation in British Columbia,1984–2000. Radiother Oncol 2002; 65: 145–151.

211 Eifler JB, Humphreys EB, Agro M, et al: Causes of death after radical prostatectomy at a large tertiary center. J. Urol. 2012; 188: 798-802.

212 Van Leeuwen FE, Klokman WJ, Stovall M, et al: Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. J. Natl Cancer Inst 1995; 87: 1530-7.

213 Koivisto-Korander R, Scelo G, Ferro G, et al: Second primary malignancies among women with uterine sarcoma. Gynecologic Oncology 2012; 126: 30-35.

214 Zelefsky MJ, Pei X, Teslova T, et al: Secondary cancers after intensity-modulated radiotherapy, brachytherapy and radical prostatectomy for the treatment of prostate cancer: incidence and cause-specific survival outcomes according to the initial treatment intervention. BJU Int 2012; 110: 1696-1701.

215 Zietman AL, Coen JJ, Shipley WU, et al: Adjuvant irradiation after radical prostatectomy for adenocarcinoma of prostate: Analysis of freedom from PSA failure. Urology 1993; 42(3): 292-299.

216 Karakiewicz P, Eastham J, Graefen M et al: Prognostic impact of positive surgical margins in surgically treated prostate cancer: Multi-institutional assessment of 5831 patients. Urology 2005; 66: 1245-50.

217 Han M, Partin AW, Zahurak M, et al: Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol. 2003 Feb; 169 (2):517-23.

218 Mullins JK, Feng Z, Trock BJ, et al: The impact of anatomical radical retropubic prostatectomy on cancer control: the 30-year anniversary. J Urol. 2012 Dec; 188(6):2219-24.

219 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; 171:2221-2225.

220 Amling CL, Bergstralh EJ, Blute ML, et al: Defining prostate specific antigen progression after radical prostatectomy: what is the most appropriate cut point? J Urol 2001; 165:1146-51.

221 Pruthi RS, Haese A, Huland E, et al: Use of serum concentration techniques to enhance early detection of recurrent prostate cancer after radical prostatectomy. Urology 1997; 49: 404-10.

222 Malik RD, Goldberg JD, Hochman T, et al: Three-year postoperative ultrasensitive prostate-specific antigen following open radical retropubic prostatectomy is a predictor for delayed biochemical recurrence. Eur Urol 2011; 60: 548-53.

223 Sarno MJ, Davis CS: Robustness of ProsVue linear slope for prognostic identification of patients at reduced risk for prostate cancer recurrence: Simulation studies on effects of analytical imprecision and sampling time variation. Clin Biochem 2012; 45:1479-84.

224 Moul JW, Lilja H, Semmes OJ, et al: NADiA ProsVue Prostate-specific Antigen Slope Is an Independent Prognostic Marker for Identifying Men at Reduced Risk of Clinical Recurrence of Prostate Cancer After Radical Prostatectomy. Urology 2012; 80: 1319-27.

References

225 Swanson, G.P. 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.

226 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: 380-5.

227 Eisenberg ML, Davies BJ, Cooperberg MR, et al: Prognostic implications of an undetectable ultrasensitive prostate-specific antigen level after radical prostatectomy. Eur Urol 2012; 57: 622-9.

228 Chang SL, Freedland SJ, Terris MK, et al: Freedom from a detectable ultrasensitive prostate-specific antigen at two years after radical prostatectomy predicts a favorable clinical outcome: analysis of the SEARCH database. Urology 2012; 75:439-44.

229 Reese A, Fradet V, Whitson J et al. Poor agreement of prostate specific antigen doubling times calculated using ultrasensitive versus standard prostate specific antigen values: Important impact on risk assessment. J. Urol 2011; 186: 2228-2232.

230 Abi-Aad AS, Macfarlane MT, Stein A et al: Detection of local recurrence after radical prostatectomy by prostate specific antigen and transrectal ultrasound. J Urol 1992 Mar; 147(3 Pt 2): 952-5.

231 Casciani E, Polettini E, Carmenini E, et al: Endorectal and dynamic contrast-enhanced MRI for detection of local recurrence after radical prostatectomy. AJR Am J Roentgenol 2008 May; 190(5): 1187-92.

232 Scattoni V, Roscigno M, Raber M, et al: Multiple vesico-urethral biopsies following radical prostatectomy: the predictive roles of TRUS, DRE, PSA and the pathological stage. Eur Urol 2003 Oct; 44(4): 407-14.

233 Macfarlane MT, Abi-Aad A, Stein, A, et al: Neoadjuvant hormonal deprivation in patients with locally advanced prostate cancer. J Urol 1993 Jul; 150(1): 132-4.

234 Drudi FM, Giovagnorio F, Carbone A, et al: Transrectal colour Doppler contrast sonography in the diagnosis of local recurrence after radical prostatectomy--comparison with MRI. Ultraschall Med 2006 Apr; 27(2): 146-51.

235 Foster LS, Jajodia P, Fournier G, et al: The value of prostate specific antigen and transrectal ultrasound guided biopsy in detecting prostatic fossa recurrences following radical prostatectomy. J Urol 1993 May; 149(5): 1024-8.

236 Kapoor DA, Wasserman NF, Zhang G: Value of transrectal ultrasound in identifying local disease after radical prostatectomy. Urology 1993 Jun; 41 (6): 594-7.

237 Leventis AK, Shariat SF, Slawin KM: Local recurrence after radical prostatectomy: correlation of US features with prostatic fossa biopsy findings. Radiology 2001 May; 219(2): 432-9.

238 Salomon CG, Flisak ME, Olson MC, et al: Radical prostatectomy: transrectal sonographic evaluation to assess for local recurrence. Radiology 1993 Dec; 189(3): 713-9.

239 Sudakoff GS, Smith R, Vogelzang NJ, et al: Color Doppler imaging and transrectal sonography of the prostatic fossa after radical prostatectomy: early experience. AJR Am J Roentgenol 1996 Oct; 167 (4): 883-8.

240 Tamsel S, Killi R, Apaydin E, et al: The potential value of power Doppler ultrasound imaging compared with grey-scale ultrasound findings in the diagnosis of local recurrence after radical prostatectomy. Clin Radiol 2006 Apr; 61(4): 323-30.

241 Huch Böni RA, Meyenberger C, Pok Lundquist J, et al: Value of endorectal coil versus body coil MRI for diagnosis of recurrent pelvic malignancies. Abdominal Imaging 1996; 21(4): 345-352.

242 Cirillo S, Petracchini M, Scotti L, et al: Endorectal magnetic resonance imaging at 1.5 Tesla to assess local recurrence following radical prostatectomy using T2-weighted and contrast-enhanced imaging. Eur Radiol 2009 Mar; 19(3): 761-9.

243 Sella T, Schwartz LH, Swindle PW, et al: Suspected local recurrence after radical prostatectomy: endorectal coil MR imaging. Radiology 2004 May; 231(2): 379-85.

244 Silverman JM, Krebs TL: MR imaging evaluation with a transrectal surface coil of local recurrence of prostatic cancer in men who have undergone radical prostatectomy. AJR Am J Roentgenol 1997 Feb; 168: 2.

245 Albrecht S, Buchegger F, Soloviev D, et al: (11)C-acetate PET in the early evaluation of prostate cancer recurrence. Eur J Nucl Med Mol Imaging 2007; 34(2): 185-96.

246 Castellucci P, Fuccio C, Rubello D, et al: Is there a role for (1)(1)C-choline PET/CT in the early detection of metastatic disease in surgically treated prostate cancer patients with a mild PSA increase <1.5 ng/ml?. Eur J Nucl Med Mol Imaging 2011 Jan; 38(1): 55-63.

247 Reske SN, Blumstein NM, Glatting G: [11C]choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy. Eur J Nucl Med Mol Imaging 2008 Jan; 35(1): 9-17.

248 Reske SN, Moritz S, Kull T:[11C]Choline-PET/CT for outcome prediction of salvage radiotherapy of local relapsing prostate carcinoma. Q J Nucl Med Mol Imaging. 2012 Oct; 56(5): 430-9.

249 Haseman MK, Reed NL, Rosenthal SA: Monoclonal antibody imaging of occult prostate cancer in patients with elevated prostate-specific antigen: Positron emission tomography and biopsy correlation. Clin Nucl Med 1996 ; 21(9): 704-713.

250 Schoder H, Herrmann K, Gonen M, et al: 2-[18F] fluoro-2-deoxyglucose positron emission tomography for the detection of disease in patients with prostate-specific antigen relapse after radical prostatectomy. Clin Cancer Res 2005; 11(13): 4761–4769.

251 Panebianco V, Sciarra A, Lisi D, et al: Prostate cancer: 1HMRS-DCEMR at 3T versus [(18)F] choline PET/CT in the detection of local prostate cancer recurrence in men with biochemical progression after radical retropubic prostatectomy (RRP). Eur J Radiol 2012; 81: 700-708.

252 Schillaci O, Calabria F, Tavolozza M, et al: Influence of PSA, PSA velocity and PSA doubling time on contrast-enhanced (18)F-choline PET/CT detection rate in patients with rising PSA after radical prostatectomy. Eur J Nucl Med Mol Imaging 2012 Apr; 39(4): 589-96.

253 Boonsirikamchai P, Kaur H, Kuban DA, et al: Use of maximum slope images generated from dynamic contrast-enhanced MRI to detect locally recurrent prostate carcinoma after prostatectomy: a practical approach. AJR Am J Roentgenol 2012 Mar; 198(3): W228-36.

254 Sciarra A, Panebianco V, Salciccia S, et al: Role of dynamic contrast-enhanced magnetic resonance (MR) imaging and proton MR spectroscopic imaging in the detection of local recurrence after radical prostatectomy for prostate cancer. European Urology 2008; 54: 589-600.

255 Rischke H, Schafer A, Nestle U et al: Detection of local recurrent prostate cancer after radical prostatectomy in terms of salvage radiotherapy using dynamic contrast enhanced-MRI without endorectal coil. Radiation Oncology 2012; 7: 185.

256 Giannarini G, Nguyen DP, Thalmann GN, et al: Diffusion-weighted magnetic resonance imaging detects local recurrence after radical prostatectomy: initial experience. Eur Urol 2012 Mar; 61(3): 616-20.

257 Kramer S, Gorich J, Gottfried HW, et al: Sensitivity of computed tomography in detecting local recurrence of prostatic carcinoma following radical prostatectomy. Br J Radiol 1997 Oct; 70(838): 995 -9.

258 Kahn D, Williams RD, Manyak MJ, et al: 111Indium -capromab pendetide in the evaluation of patients with residual or recurrent prostate cancer after radical prostatectomy. The ProstaScint Study Group. J Urol 1998 Jun; 159(6): 2041-7.

259 Koontz BF, Mouraviev V, Johnson JL, et al: Use of Local (111)In-Capromab Pendetide Scan Results to Predict Outcome After Salvage Radiotherapy for Prostate Cancer. Int J Radiat Oncol 2008 Jun; 71 (2): 358-361.

260 Texter JH Jr, Neal CE: The role of monoclonal antibody in the management of prostate adenocarcinoma. J Urol 1998 Dec; 160(6 Pt 2): 2393-5.

261 Wilkinson S, Chodak G: The role of 111indium-capromab pendetide imaging for assessing biochemical failure after radical prostatectomy. J

Urol 2004 Jul; 172(1): 133-6.

262 Schettino CJ, Kramer EL, Noz ME, et al: Impact of fusion of indium-111 capromab pendetide volume data sets with those from MRI or CT in patients with recurrent prostate cancer. AJR Am J Roentgenol 2004 Aug; 183(2): 519-24.

263 Beresford MJ, Gillatt D, Benson RJ., Ajithkumar, T. A systematic review of the role of imaging before salvage radiotherapy for post-prostatectomy biochemical recurrence. Clinical Oncology; 22; 46-55; 2010.

264 Martino P, Scattoni V, Galosi A, et al: Role of imaging and biopsy to assess local recurrence after definitive treatment for prostate carcinoma (surgery, radiotherapy, cryotherapy, HIFU). World J. Urol. 2011; 29: 595-605.

265 Rinnab L, Mottaghy FM, Simon J, et al: [11C] Choline PET/CT for targeted salvage lymph node dissection in patients with biochemical recurrence after primary curative therapy for prostate cancer. Preliminary results of a prospective study. Urol Int 2008; 81(2): 191-7.

266 Scattoni V, Picchio M, Suardi N, et al: Detection of lymph-node metastases with integrated [11C] choline PET/CT in patients with PSA failure after radical retropubic prostatectomy: results confirmed by open pelvic-retroperitoneal lymphadenectomy. Eur Urol 2007 Aug; 52(2): 423 -9.

267 Schilling D, Schlemmer HP, Wagner PH, et al: Histological verification of (11)C-choline-positron emission/computed tomography-positive lymph nodes in patients with biochemical failure after treatment for localized prostate cancer. BJU Int 2008 Aug; 102(4): 446-451.

268 Winter A, Uphoff J, Henke RP, et al: First results of [11C]choline PET/CT-guided secondary lymph node surgery in patients with PSA failure and single lymph node recurrence after radical retropubic prostatectomy. Urol Int 2010; 84(4): 418-23.

269 Chang CH, Wu HC, Tsai JJP, et al: Detecting metastatic pelvic lymph nodes by 18F-2-deoxyglucose positron emission tomography in patients with prostate-specific antigen relapse after treatment for localized prostate cancer. Urol Int 2003; 70(4): 311-315.

270 Harisinghani MG, Barentsz J, Hahn PF, et al: Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Engl J Med 2003 Jun; 348(25): 2491-9.

271 Ross RW, Zietman AL, Xie W, et al: Lymphotropic nanoparticle-enhanced magnetic resonance imaging (LNMRI) identifies occult lymph node metastases in prostate cancer patients prior to salvage radiation therapy. Clin Imaging 2009 Jul-Aug; 33(4): 301-5.

272 Meijer H, Debats O, Roach M, et al: Magnetic resonance lymphography findings in patients with biochemical recurrence after prostatectomy and the relation with the Stephenson nomogram. Int J Radiation Oncol Biol Phys 2012; 84: 1186-1191.

273 Fortuin A, Deserno W, Meijer H, et al: Value of PET/CT and MR lymphography in treatment of prostate cancer patients with lymph node metastases. In J Radiation Oncol Biol Phys 2012; 84: 712-718.

274 Even-Sapir E, Metser U, Mishani E, et al: The detection of bone metastases in patients with high -risk prostate cancer: 99mTc-MDP planar bone scintigraphy, singleand multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT. J Nucl Med 2006; 47(2): 287–297.

275 Kane CJ, Amling CL, Johnstone PA, et al: Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy. Urology 2003 Mar; 61(3): 607-11.

276 Fuccio C, Castellucci P, Schiavina R, et al: Role of 11C-choline PET/CT in the restaging of prostate cancer patients showing a single lesion on bone scintigraphy. Annals of Nuclear Medicine 2010 ; 24 (6): 485-492.

277 Fuccio C, Castellucci P, Schiavina R et al: Role of 11C-choline PET/CT in the re-staging of prostate cancer patients with biochemical relapse and negative results at bone scintigraphy. Eur J Radiology 2012; 81: e893-6.

278 Luboldt W, Küfer R, Blumstein N, et al: Prostate carcinoma: Diffusion-weighted imaging as

potential alternative to conventional MR and11C-choline PET/CT for detection of bone metastases. Radiology 2008; 249(3): 1017-1025.

279 Cher ML, Bianco FJ Jr, Lam JS, et al: Limited role of radionuclide bone scintigraphy in patients with prostate specific antigen elevations after radical prostatectomy. J Urol 1998 Oct; 160(4): 1387-91.

280 Choueiri TK, Dreicer R, Paciorek A, et al: A model that predicts the probability of positive imaging in prostate cancer cases with biochemical failure after initial definitive local therapy. J Urol 2008 Mar; 179(3): 906-10.

281 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 40988; 23(9): 1962-8.

282 Gomez P, Manoharan M, Kim SS, et al: Radionuclide bone scintigraphy in patients with biochemical recurrence after radical prostatectomy: when is it indicated? BJU Int 2004 Aug; 94(3): 299-302.

283 Okotie OT, Aronson WJ, Wieder JA, et al: Predictors of metastatic disease in men with biochemical failure following radical prostatectomy. J Urol 2004 Jun; 171(6 Pt 1): 2260-4.

284 Raj GV, Partin AW, Polascik TJ: Clinical utility of indium 111-capromab pendetide immunoscintigraphy in the detection of early, recurrent prostate carcinoma after radical prostatectomy. Cancer 2002 Feb 15; 94: 4.

285 Jadvar H, Desai B, Ji L et al: Prospective evaluation of 18F-NaF and 18F-FDG PET/CT in detection of occult metastatic disease in biochemical recurrence of prostate cancer. Clin Nucl Med 2012; 37:637-43.

286 Kotzerke J, Volkmer BG, Neumaier B, et al: Carbon -11 acetate positron emission tomography can detect local recurrence of prostate cancer. Eur J Nucl Med Mol Imaging 2002 Oct; 29(10): 1380-4.

287 Kwee S, Coel M, Lim H: Detection of recurrent prostate cancer with 18F-fluorocholine PET/CT in relation to PSA level at the time of imaging. Ann Nucl Med 2012; 26: 501-507.

288 Sandblom G, Sorensen J, Lundin N, et al: Positron emission tomography with C11-acetate for tumor detection and localization in patients with prostate-specific antigen relapse after radical prostatectomy. Urology 2006 May; 67(5): 996-1000.

289 de Jong IJ, Pruim J, Elsinga PH, et al: 11C-choline positron emission tomography for the evaluation after treatment of localized prostate cancer. Eur Urol 2003 Jul; 44(1): 32-9.

290 Picchio M, Messa C, Landoni C, et al: Value of [11C]choline-positron emission tomography for re-staging prostate cancer: a comparison with [18F] fluorodeoxyglucose-positron emission tomography. J Urol 2003; 169(4): 1337-1340.

291 Castellucci P, Fuccio C, Nanni C, et al: Influence of trigger PSA and PSA kinetics on 11C-Choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy. J Nucl Med 2009 Sep; 50(9): 1394-400.

292 García JR, Soler M, Blanch MA, et al: [PET/CT with (11)C-choline and (18)F-FDG in patients with elevated PSA after radical treatment of a prostate cancer]. Revista española de medicina nuclear 2009; 3: 95-100.

293 Giovacchini G, Picchio M, Coradeschi E, et al: Predictive factors of [(11)C]choline PET/CT in patients with biochemical failure after radical prostatectomy. Eur J Nucl Med Mol Imaging 2010 Feb; 37(2): 301-9.

294 Richter JA, Rodriguez M, Rioja J, et al: Dual tracer (11)C-choline and FDG-PET in the diagnosis of biochemical prostate cancer relapse after radical treatment. Mol Imaging Biol 2010 Apr; 12(2): 210 -217.

295 Rinnab L, Mottaghy FM, Blumstein NM, et al: Evaluation of [11C]-choline positron-emission/computed tomography in patients with increasing prostate-specific antigen levels after primary treatment for prostate cancer. BJU Int 2007 Oct; 100: 4.

296 Rinnab L, Simon J, Hautmann RE, et al: [(11)C] choline PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy. World J Urol 2009 Oct; 27(5): 619-

25.

297 Yoshida S, Nakagomi K, Goto S, et al: 11C-choline positron emission tomography in prostate cancer: primary staging and recurrent site staging. Urol Int 2005 ; 74(3): 214-20.

298 Seltzer MA, Barbaric Z, Belldegrun A, et al: Comparison of helical computerized tomography, positron emission tomography and monoclonal antibody scans for evaluation of lymph node metastases in patients with prostate specific antigen relapse after treatment for localized prostate cancer. J Urol 1999 Oct; 162(4): 1322-8.

299 Pelosi E, Arena V, Skanjeti A, et al: Role of whole-body 18F-choline PET/CT in disease detection in patients with biochemical relapse after radical treatment for prostate cancer. Radiol Med 2008 Sep; 113(6): 895-904.

300 Cimitan M, Bortolus R, Morassut S, et al: [18F] fluorocholine PET/CT imaging for the detection of recurrent prostate cancer at PSA relapse: experience in 100 consecutive patients. Eur J Nucl Med Mol Imaging 2006 Dec; 33(12): 1387-98.

301 Heinisch M, Dirisamer A, Loidl W, et al: Positron emission tomography/computed tomography with F-18-fluorocholine for restaging of prostate cancer patients: Meaningful at PSA < 5 ng/ml?. Mol Imaging Biol 2006 Jan; 8(1): 43-48.

302 Husarik DB, Miralbell R, Dubs M, et al: Evaluation of [(18)F]-choline PET/CT for staging and restaging of prostate cancer. Eur J Nucl Med Mol Imaging 2008 Feb; 35: 2.

303 Proano JM, Sodee DB, Resnick MI, et al: The impact of a negative (111)indium-capromab pendetide scan before salvage radiotherapy. J Urol 2006 May; 175(5): 1668-72.

304 Mitchell CR, Lower VJ, Rangel LJ, et al: Operational characteristics of 11 C-choline PET/CT for prostate cancer patients with biochemical recurrence following initial treatment. J. Urol. 2012; [epub ahead of print].

305 Krause BJ, Souvatzoglou M, Tuncel M, et al: The detection rate of [11C]choline-PET/CT depends on the serum PSA-value in patients with biochemical recurrence of prostate cancer. Eur J Nucl Med Mol Imaging 2008 Jan; 35(1): 18-23.

306 Giovacchini G, Picchio M, Scattoni V, et al: PSA doubling time for prediction of [(11)C]choline PET/CT findings in prostate cancer patients with biochemical failure after radical prostatectomy. Eur J Nucl Med Mol Imaging 2010 Jun; 37(6): 1106-16.

307 Breeuwsma A, Rybalov M, Leliveld A et al. Correlation of [11C]choline PET-CT with time to treatment and disease-specific survival in men with recurrent prostate cancer after radical prostatectomy. Q J Nucl Med Mol Imaging 2012; 56: 440-446.

308 King CR: The timing of salvage radiotherapy after radical prostatectomy: A systematic review. Int J Radiation Oncol Biol Phys 2012; 84: 104-111.

309 Dorff TB, Flaig TW, Tangen CM, et al: Adjuvant androgen deprivation for high-risk prostate cancer after radical prostatectomy: SWOG S9921 study. J. Clin. Oncol 2011; 29(15): 2040-2045.

310 Ayala AG, Ro JY, Babaian R et al: The prostatic capsule: does it exist? Its importance in the staging and treatment of prostatic carcinoma. Am J Surg Pathol 1989; 13: 21-27.

311 Sakr WA, Wheeler TM, Blute M et al: International Consultation on Prostatic Intraepithelial Neoplasia and Pathologic Staging of Prostate Carcinoma -- Workgroup 2: Staging and reporting of prostate cancer – sampling of the radical prostatectomy specimen. Cancer, 1996; 78: 366-368.

312 Van der Kwast TH, et al: Identification of patients with prostate cancer who benefit from immediate postoperative radiotherapy: EORTC 22911. J. Clin Oncol 2007; 25: 4178.

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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.

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