

Radiotherapy for Locally Recurrent Prostate Cancer

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Abstract: The optimal treatment of the patient at high risk for local recurrence of prostate cancer after radical prostatectomy is controversial. Similarly, there is much controversy over how to treat patients with a rising prostate-specific antigen (PSA), but without overt metastases, after radical prostatectomy. A recent randomized controlled trial of adjuvant radiotherapy versus observation following radical prostatectomy shows a significantly higher freedom from recurrence for patients receiving adjuvant radiotherapy, which may help to resolve the question of whether or not to wait for a rise in the PSA before offering treatment. For patients with biochemical recurrence after prostatectomy, part of the problem lies in the difficulty in determining whether a rise in the PSA is a sign of local recurrence or a harbinger of distant metastases. Making this distinction is critical, since patients with local disease may be cured with radiation therapy to the prostate bed, whereas those with metastatic disease will require a different treatment approach. In this article, we discuss the factors that must be taken into consideration when making treatment recommendations for these patients. In addition, approaches to the evaluation and management of patients with this difficult clinical problem are presented.

Adenocarcinoma of the prostate is the most commonly diagnosed malignancy in men in the United States. In 2005, an estimated 232,000 new cases will be diagnosed, and more than 30,000 deaths will occur from this disease.¹ Of these 232,000 new cases, about 70% (160,000) will have localized disease, and roughly 50% (80,000) of these patients will undergo radical prostatectomy.² Approximately 25% (20,000) of the patients undergoing radical prostatectomy will be found to have disease extending beyond the prostate gland.³ The majority of these men will develop biochemical failure.⁴ However, most of these patients are not offered additional therapy until relapse occurs.⁵

Following radical prostatectomy, the prostate-specific antigen (PSA) should become undetectable within a few weeks, and if the patient is cured the PSA should remain undetectable for the rest of his life. The first sign of relapse in the vast majority of men treated with radical prostatectomy is a rising PSA level without clinical or radiographic evidence of recurrence. In the United States, approxi-

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mately 30,000 men per year will experience biochemical recurrence following radical prostatectomy.⁶ Many of these men will be treated with radiation therapy (RT) in an attempt to salvage a cure.

In this article, we describe which patients appear to be at greatest risk for failure, discuss the natural history of a rising PSA level after radical prostatectomy, compare the results of treatment in the adjuvant versus the salvage setting, and conclude with future directions for research in the treatment of this patient population.

Adverse Prognostic Factors

The risk of recurrence after radical prostatectomy has been shown to depend most strongly upon several preoperative and postoperative clinicopathologic features.⁷⁻¹² Of the preoperative features, biopsy Gleason score, clinical tumor stage and PSA (both the absolute PSA value and the rate of change prior to surgery) have been shown to correlate with risk of biochemical recurrence. Other preoperative features that may be of importance include the percentage of biopsies involved with cancer and the amount of cancer in the biopsy specimens. Postoperative features most commonly associated with risk of relapse include Gleason score from the prostatectomy specimen; pathologic involvement of the surgical margins, seminal vesicles, and/or lymph nodes; extracapsular extension; and, to a lesser extent, perineural invasion. Similarly, shorter postoperative PSA doubling time, higher Gleason score, and decreased time from surgery to biochemical recurrence are associated with a greater risk of prostate cancer-specific mortality after radical prostatectomy.¹³

Recently, molecular markers such as DNA ploidy, p53, bcl-2, transforming growth factor β , CD44, and nuclear factor kappa β have also been evaluated as predictors of relapse after radical prostatectomy.¹⁴⁻¹⁷ Although this is a promising area of research, to date these markers have not been shown to consistently improve the predictive ability of the more readily available clinical and pathologic features mentioned previously.

Several authors have developed mathematical models or nomograms to predict biochemical recurrence after radical prostatectomy.¹⁸⁻²¹ The most widely utilized nomograms are those of Kattan and colleagues,^{20,21} both of which are available online, and have been validated retrospectively using large multi-institutional databases.^{22,23} The preoperative model considers PSA, clinical stage, and Gleason score, whereas the postoperative model incorporates preoperative PSA, Gleason score, capsular invasion, surgical margin status, seminal vesicle invasion, and lymph node involvement.

Table 1. Estimated Freedom From Distant Metastases at 7 Years After PSA Failure Without Any Treatment

| Risk Group | % Probability (95% CI) |
|---|------------------------|
| GS 5-7, IFS >2 yr, PSADT >10 mo | 82 (69-90) |
| GS 5-7, IFS >2 yr, PSADT \leq 10 mo | 60 (32-80) |
| GS 5-7, IFS \leq 2 yr, PSADT >10 mo | 59 (40-73) |
| GS 8-10, IFS >2 yr | 47 (33-60) |
| GS 8-10, IFS \leq 2 yr | 21 (9-35) |
| GS 5-7, IFS \leq 2 yr, PSADT \leq 10 mo | 15 (4-33) |

Data from Pound et al.²⁴

CI = confidence interval; GS = Gleason score; IFS = interval from surgery to rise in PSA; PSA = prostate-specific antigen; PSADT = PSA doubling time.

Natural History of a Rising PSA

In 1999, Pound and associates²⁴ reported on a series of 1,997 patients who underwent radical prostatectomy between 1982 and 1997. Of these patients, 315 had developed a rising PSA level after a median follow-up of 5.3 years. Eleven patients received early androgen deprivation therapy, leaving 304 patients who did not receive hormonal therapy until documentation of distant metastases. The median actuarial time from first rise in PSA to development of distant metastases was 8 years and to death was an additional 5 years. The authors subdivided patients into risk groups, depending on Gleason score (5-7 vs 8-10), interval from surgery to PSA recurrence (\leq 2 years vs >2 years), and PSA doubling time (\leq 10 months vs >10 months). These risk groups had probabilities of being free of metastatic disease at 7 years ranging from 15% to 82% depending on the combination of prognostic factors present (Table 1). No comment was made on the incidence of local recurrence, so the risk of isolated local failure in this patient population is not known.

More recent data suggest that the vast majority of patients who experience a rising PSA value after radical prostatectomy have at least a component of this rise attributable to local recurrence. Mosbacher and colleagues²⁵ evaluated a group of 62 patients treated with RT to the prostate bed for biochemical recurrence after radical prostatectomy. No patients received hormone therapy. Despite using relatively low doses of radiation (median dose=6,120 cGy), the overall response rate was

84% (50% complete, 34% partial). The highest complete response rates occurred in patients with a PSA less than or equal to 0.5 ng/mL (77%), Gleason score 7 or lower (-58%), and no seminal vesicle involvement (-52%).

Distinguishing Local from Distant Recurrence

While indicating the presence of residual or recurrent prostate cancer, an elevated PSA, per se, does not distinguish between a local recurrence and distant metastasis. In addition, the rise in PSA may predate a clinically detectable recurrence by several years.²⁶ Because RT is a local treatment, it is important to attempt to distinguish between patients with local versus systemic recurrences. Several approaches have been tried, but they have met with limited success.

Digital rectal examination has been utilized to try to detect early local recurrence in patients with a rising PSA after prostatectomy, but due to variations in the contour of the prostate bed after surgery, this method has not been very useful.²⁷ Similarly, needle biopsy of the prostate bed is positive only about half the time.²⁷ Biopsy may be guided by transrectal ultrasound, but an abnormal appearance of the prostate bed is not necessarily diagnostic of recurrence.²⁸ Although the addition of color Doppler imaging may improve the detection rate of residual or recurrent tumor,²⁹ in general ultrasound is neither sensitive nor specific enough to differentiate local recurrence from post-operative scar tissue.³⁰ Similarly, computed tomography (CT) scanning of the abdomen and pelvis is rarely useful in detecting an early local recurrence.³¹ Recent evidence suggests that endorectal magnetic resonance imaging (MRI) may be far superior to either CT or ultrasound in detecting small, potentially curable local recurrences, with sensitivity and specificity approaching 100%.³² Unfortunately, this technology is not widely available.

Despite the presence of risk factors for local recurrence,³³ and evidence to suggest that in most patients disease in the prostate bed is contributing at least in part to the rise in PSA,²⁵ many patients also have occult distant metastases.³⁴ It is critically important to attempt to detect distant disease before offering RT, since patients with disease outside the prostate bed will not benefit from local therapy. As stated previously, both CT scans and bone scans are of limited value, unless the PSA level is quite high (>20 ng/mL), or is rising quickly (>2 ng/mL/mo).^{31,35} Newer imaging modalities using either molecular or functional approaches may be helpful in distinguishing patients with true local recurrences from those with systemic disease.

To date, indium (¹¹¹In) capromab pendetide immunoscintigraphy has been the most extensively studied and widely utilized test for this purpose. This test utilizes a

monoclonal antibody reactive with prostate specific-membrane antigen. Despite the presence of a detectable PSA, the scan appears to be negative in about 30% of patients.³⁶ Of the patients with a positive scan, roughly one third will have uptake in the prostate bed only, one third will have a combination of uptake in the prostate bed and pelvic nodes, and one third will have evidence of distant metastases.³⁶ Of the patients with disease confined to the prostate bed, about 75% will achieve a durable complete response to salvage RT, although follow-up in these studies is too short to draw definitive conclusions.^{37,38} Other authors have challenged these findings, indicating that radioimmunoscintigraphy is inferior to CT or positron emission tomography (PET) in detecting lymph node recurrences,³⁹ or that the probability of remaining disease-free after RT to the prostate bed is no different whether or not immunoscintigraphy indicates no evidence of cancer beyond the prostate fossa.⁴⁰ This test, therefore, may be useful in selected patients, but more data are needed to better define its role.

Recent innovations in oncologic imaging may prove to be useful in better defining the source of a rising PSA value after radical prostatectomy. Although PET using the standard imaging agent 2-fluoro-2-deoxyglucose has proved insensitive in prostate cancer, newer agents, such as ¹⁸F-labeled choline or ¹¹C-labeled acetate appear more promising.^{41,42,43} In addition, high-resolution MRI using magnetic nanoparticles may permit visualization of otherwise undetectable lymph node metastases from prostate cancer.⁴⁴ More research is needed to better define the role of these studies in identifying optimal candidates for post-prostatectomy RT.

Currently, ¹¹¹In-labeled capromab pendetide immunoscintigraphy is the only imaging study that the authors regularly obtain in patients with a detectable PSA after radical prostatectomy. Bone scans, CT scans, or MRI of the pelvis and abdomen are reserved for patients with Gleason scores 8–10, rapid PSA doubling times (see below), or very high PSA levels (patients who would not be candidates for pelvic radiotherapy alone).

The pathologic findings at the time of surgery may also help to distinguish patients with local versus distant recurrence. In general, those with positive surgical margins and/or extracapsular extension are more likely to have local recurrence, whereas patients with negative surgical margins, high-grade tumors (Gleason 8–10), seminal vesicle invasion, and/or lymph node metastases are at greater risk of distant failure.^{11,45,46}

Finally, both the rate of rise of the PSA and the time from surgery to biochemical failure have been evaluated as possible means to distinguish occult local from distant failures. Trapasso and coworkers⁴⁷ found that patients who ultimately developed distant metastases had a shorter

PSA doubling time than did patients with local recurrence (4 vs 12 months). Similarly, Partin and coauthors⁴⁸ found that no patient who developed local recurrence experienced a rise in PSA within 6 months of surgery. Patel and colleagues⁴⁹ also found that shorter PSA doubling times (<6 months) predicted for distant metastases, whereas slower rates of biochemical progression were associated with local failure. Subsequent studies have confirmed these findings.^{25,45} Thus, while neither time to recurrence nor rate of change of the PSA level can absolutely differentiate between local and distant recurrence, distant metastases are, in general, associated with shorter PSA doubling times.

Patient Evaluation

In evaluating patients with biochemical recurrence after prostatectomy for salvage RT, the primary goal is to try to distinguish local from distant recurrence. In patients whose PSA level never became undetectable or who have developed a rising PSA level, a careful review of the pathology report should be undertaken to determine whether there are risk factors present that predict for local or distant failure (see above). If serial PSA measurements are available, it may be useful to calculate the PSA doubling time in order to estimate whether the disease is progressing rapidly or not. Finally, radiographic evaluation, including a bone scan, CT scan of the pelvis and abdomen, endorectal MRI and/or radioimmunosintigraphy scan may be considered, particularly if there is a high degree of suspicion that the recurrence may not be purely local. While a bone scan is likely to be negative, it may provide a useful baseline for future reference. Endorectal MRI and radioimmunosintigraphy are complimentary, and may be the most likely studies to yield information for treatment selection. These 2 studies are not uniformly available, and CT scanning may be a reasonable alternative.⁵⁰

Results of Treatment

Adjuvant Versus Salvage Therapy

The issue of whether to offer RT to the prostate bed as an adjuvant therapy to prostatectomy for patients with an undetectable PSA level but at high risk for local recurrence or to wait until there is evidence of biochemical failure before treating remains a subject of considerable controversy. This issue is particularly relevant to the patient with positive surgical margins. Arguments in favor of waiting include: 1) there are no data indicating a survival advantage for early rather than delayed RT⁵¹; 2) not every patient with adverse pathologic features will recur locally (rates of local recurrence at 10 years are 30–40%)⁵²⁻⁵³; 3) recurrences may be detected early via serial PSA monitor-

ing; and 4) there is a long natural history of progression in most patients even after prostate cancer recurs.²⁴ Arguments in favor of adjuvant therapy include: 1) randomized trials have shown a significant improvement in both clinical and biochemical progression-free survival with early versus delayed RT^{4,54}; 2) patients undergoing radical prostatectomy are the youngest healthiest patients with prostate cancer and, thus, are likely to live long enough to develop symptomatic metastases from untreated local disease⁵³; 3) commonly used PSA assays are unable to detect volumes of cancer less than 10^6 cells⁵⁶ so that an undetectable PSA does not ensure that a patient is free of disease; and 4) lower doses of RT may be used in the adjuvant setting which should reduce the chances of complications.⁵⁷

Table 2 summarizes the results of studies of RT in either the adjuvant or salvage setting following radical prostatectomy. Unfortunately, most of the studies were small and the follow-up relatively short. However, a recently published prospective randomized comparisons of immediate RT versus observation after prostatectomy directly addresses this question.^{4,58}

In the European Organization for Research and Treatment of Cancer (EORTC) trial 22911, a total of 1,005 patients were randomly assigned to either immediate adjuvant RT or to close observation following radical prostatectomy. All of the patients were node-negative, were without evidence of metastatic disease, and had 1 or more pathologic risk factors for recurrence (positive surgical margins, positive extracapsular extension, and/or seminal vesicle invasion). Five years after surgery, patients receiving adjuvant RT experienced significantly lower rates of biochemical progression (53% vs 74%, $P=.0001$). In addition, local control and clinical progression-free control were significantly higher in the adjuvant RT group. While mild (grade 1–2) toxicity was significantly higher in the group undergoing adjuvant RT, severe toxic side effects were rare and did not differ significantly between the 2 groups.

In SWOG 8794, 473 patients were randomized to either immediate radiotherapy or observation following radical prostatectomy. After a median follow-up of 9.7 years, there was a significant improvement in biochemical disease-free survival for the adjuvant radiotherapy arm (47% vs 23%) and a nonsignificant improvement in metastasis-free and overall survival in favor of immediate RT.⁴ These findings are supported by the collective results from retrospective studies (Table 2). Absolute improvement in FFR at 5 years ranges from 5% to 69%, depending on the study, with most showing improvement in FFR of 20–30%. To date, no survival advantage has been reported for adjuvant over salvage therapy. Longer follow-up of both the retrospective and prospective studies will be needed to determine whether this improvement in FFR

Table 2a. Studies Comparing Outcome for Adjuvant vs Salvage RT

| Reference | N | F/U (mo) | Freedom from Recurrence | Favorable Prognostic Factors |
|---------------------------|-------|----------|--|---|
| EORTC 22911 ⁵⁸ | 1,005 | 60 | 74% (adj) @ 5 yr 53% (salv) @ 5 yr | Post-op PSA ≤0.2 ng/ml, no SVI, positive surgical margins |
| Catton ⁸⁵ | 113 | 44 | 81% (adj) @ 5 yr ~12% (salv) @ 5 yr | Pre-RT PSA <7, Gleason Score <7 |
| Kalapurakal ⁸⁶ | 76 | 36 64 | 86% (adj) @ 5 yr 57% (salv) @ 5 yr | No SVI (adj), Gleason score <4 (salv) |
| Morris ⁷⁸ | 88 | 31 | 81% (adj) @ 3 yr 48% (salv) @ 3 yr | Adjuvant RT |
| Nudell ⁸⁷ | 105 | 36 | ~80% (adj) @ 3 yr ~44% (salv) @ 3 yr | Adjuvant RT, pre-op PSA <20 |
| Pacholke ⁸⁸ | 163 | 70 | 80% (adj) @ 5 yr 33% (salv) @ 5 yr | Adjuvant RT, no SVI, no neoadjuvant hormones |
| Peschel ⁸⁹ | 52 | 37 | 43% (adj) @ 5 yr 18% (salv) @ 5 yr | Pre-RT PSA <0.3 ng/ml, lower pre-op PSA, no seminal vesicle invasion |
| Taylor ⁹⁰ | 146 | 68 39 | 88% (adj) @ 5 yr 66% (salv) @ 5 yr | Adjuvant RT, SVI absent |
| Tsien ⁹¹ | 95 | 84 | 45% (adj) @ 8 yr 37% (salv) @ 8 yr | Gleason Score <7 (salv) |
| Valicenti ⁹² | 79 | 36 | 93% (adj) @ 3 yr 44% (salv) @ 3 yr | RT dose ≥64.8 Gy (salv) |
| Vicini ⁹³ | 57 | 46 | 67% (adj) @ 5 yr 44% (salv) @ 5 yr | Adjuvant RT |
| Mayer ⁹⁴ | 66 | 30–56 | 85% (adj) @ 5 yr 34% (salv) @ 5 yr | PT stage <T3b, well-moderate differentiation, lower pre-RT PSA |
| Hagan ⁹⁵ | 157 | 53–66 | ~82% (adj) @ 5 yr ~50% (salv) @ 5 yr | Pre-RT PSA <1 ng/ml |
| Kirkpatrick | 237 | 37 | 95% (adj) @ 3 yr 66% (salv) @ 3 yr 63% (adj) @ 5 yr 58% (salv) @ 5 yr | Lower pathologic T stage, adjuvant RT, lower Gleason score, no SVI or ECE |

adj = adjuvant; ECE = extracapsular extension; F/U = follow-up; PNI = perineural invasion; pts=patients; RT = radiotherapy; salv = salvage; SVI = seminal vesicle invasion.

translates into an improvement in survival or a reduction in deaths from prostate cancer. Nevertheless, the findings of the randomized studies led Swanson and colleagues to conclude that “pathologic T3 patients should be given the opportunity to receive postoperative radiation.”⁹⁴

From the data in Table 2 several clinical and pathologic features emerge that may aid in the selection of patients for radiotherapy. Favorable features include a longer post-operative PSA doubling time (>10–12 months), lower PSA prior to RT (<1–2 ng/mL), longer interval from surgery to the detection of biochemical failure (>2–3 years),

presence of positive surgical margins, and the absence of features which would predict for distant metastases (seminal vesicle involvement, Gleason score 8–10, lymph node metastases). While there does not appear to be an absolute PSA cut-off beyond which salvage therapy should not be considered, there is an indication that lower preradiotherapy PSA values are associated with a more favorable outcome.⁵⁹ Whether this finding indicates that a higher PSA reflects a greater local tumor burden, suggesting the need for higher doses of RT, or conversely, that patients with higher PSAs already have occult distant metastases

Table 2b. Studies of Outcome for Salvage RT or Salvage and Adjuvant RT Combined

| Reference | N | F/U (mo) | Freedom From Recurrence | Favorable Prognostic Factors |
|---------------------------|-----|----------|-------------------------|--|
| Anscher ⁷⁹ | 89 | 66 | 53% | RT dose >65 Gy |
| Cadeddu ⁷¹ | 57 | 40 | 20% | Gleason score ≤7, No SVI, PSA rise >1 year post-op |
| Cozzarini ⁹⁶ | 237 | 62 | 69% @ 8 yr | Early RT, no ECE, negative surgical margins, Gleason score <7, negative LN mets |
| Crane ⁶⁵ | 41 | 55 | 24% | No detectable post-op PSA, pre-RT PSA <2.7 |
| Do ⁸² | 60 | 36 | 55% | Pre-RT PSA <1.0, No PNI |
| Duchesne ⁸³ | 115 | 29 | 50% @ 5 yr | Gleason score <8, pre-RT PSA <1 ng/ml, PSA nadir after RT |
| Garg ⁹⁷ | 78 | 25 | 64% | Pre-RT PSA <2 |
| Hudson ⁹⁸ | 21 | 13 | 29% | No detectable post-op PSA |
| Kaplan ⁶⁴ | 39 | 27 | 44% | - |
| Katz ⁹⁹ | 115 | 48 | 46% @ 4 yr | Positive surgical margins, ECE, No SVI |
| Keisch ¹⁰⁰ | 10 | 5 | 50% | - |
| Lange ¹⁰¹ | 29 | 22 | 38% | - |
| Leventis ⁷² | 49 | 29 | 24% @ 5 yr | Pre-RT PSA <2.1 ng/ml, post-recurrence PSA doubling time >11.8 months |
| Liau ¹⁰² | 51 | 46 | 45% | No SVI, no LVI |
| Link ¹⁰³ | 25 | 18 | 32% | No detectable post-op PSA |
| MacDonald ¹⁰⁴ | 60 | 51 | 43% @ 5 yr | Pre-RT PSA <0.6, RT dose >64.8 Gy |
| McCarthy ¹⁰⁵ | 37 | 33 | 54% | No detectable post-op PSA |
| Medini ⁶² | 40 | >60 | 27% | - |
| Partin ²⁶ | 20 | 24 | 10% | Pre-op PSA <10 |
| Petrovich ¹⁰⁶ | 423 | 84 | 69% @ 5 yr | Gleason score ≤7, pT3b vs a |
| Peyromaure ¹⁰⁷ | 62 | 44 | 63% | Gleason score ≤7 |
| Pisansky ⁸⁰ | 166 | 52 | 46% @ 5 yr | pStage T3a, lower histologic grade, lower pre-RT PSA |
| Schild ⁶³ | 46 | 37 | 50% | No SVI |
| Stephenson ⁴⁵ | 501 | 45 | 45% @ 4 yr | Lower Gleason score, lower pre-RT PSA, positive surgical margins, long PSA doubling time, no SVI |
| Wu ⁷⁷ | 53 | 15 | 23% | Pre-RT PSA ≤2.5 |
| Zelefsky ⁶¹ | 28 | 24 | 53% | Pre-RT PSA <1.0, no detectable post-op PSA |

ECE = extracapsular extension; F/U = follow-up; LVI = lymphovascular invasion; PNI = perineural invasion; PSA = prostate-specific antigen; pts=patients; RT = radiotherapy; SVI = seminal vesicle invasion.

Table 2c. Studies of Outcome for Adjuvant RT Alone

| Reference | N | F/U (mo) | Freedom From Recurrence | Favorable Prognostic Factors |
|----------------------|-----|----------|-------------------------|----------------------------------|
| Kamat ¹⁰⁸ | 62 | 85 | 90% @ 5 yr | Gleason score <7, Pre-op PSA <11 |
| Choo ¹⁰⁹ | 73 | 59 | 88% @ 5 yr | Lower pre-RT PSA |
| Cheng ¹¹⁰ | 131 | 53 | ~95% @ 5 yr | - |

F/U = follow-up; PSA = prostate-specific antigen.

at the time of referral for RT is not definitely known. The pattern of relapse after postprostatectomy RT would suggest that the latter is true, since the incidence of local failure is less than or equal to 10% in most series, whereas distant metastases occur in 10–36%.^{26,60-65} Thus, these data suggest that early intervention with pelvic RT (ie, as soon as a detectable PSA is confirmed) is preferable to delaying until the PSA reaches an arbitrary threshold.

At Duke University Medical Center, we treated 237 patients with adjuvant or salvage RT after radical prostatectomy between 1990–2002. The median follow-up was 3.1 years. Most had advanced disease (80% pT3–4, 65% Gleason scores 7–10, 79% positive surgical margins, 32% seminal vesicle invasion). The adjuvant group was slightly younger (62 vs 66 years old), had a lower preoperative PSA level (8.7 vs 12.4 ng/mL), and was treated to a lower RT dose to the prostate bed as compared to the salvage group (60 vs 66 Gy). Otherwise, the groups were comparable. The FFR at 3 years was significantly better for the adjuvant group (95% vs 66%, *P*=.027), but there was no difference in overall survival.

Overt Local Recurrence

Although relatively uncommon in the PSA era, overt (palpable) local recurrences after radical prostatectomy represent a challenging problem. The available data would suggest that RT is able to achieve durable local control in most patients (70–100%), though few are cured.⁶⁶⁻⁷³ The predominant pattern of failure in this patient population after RT is distant metastases, which has been reported to occur in 20–100%.^{66,67,69,70}

Adjuvant Androgen Ablation

While androgen deprivation therapy in conjunction with RT for locally advanced and/or high-grade prostate cancers has been shown to be beneficial in randomized trials,^{73,74} its role in conjunction with RT after prostatectomy is less well defined. The available data are summarized in Table 3. Most studies report about a 20–30% absolute improvement in biochemical disease-free survival with RT plus androgen deprivation. Only the results from a subset of patients enrolled in Radiation Therapy Oncology Group (RTOG) trial 8531 represent randomized data.⁷⁵

This study reports a disease-free survival advantage for the addition of androgen ablation therapy, but as yet, no survival advantage has been noted. The results of 2 other randomized trials (RTOG 9601 and RTOG P-0011) are currently pending. Recently, Jani and associates⁷⁶ performed a complication-adjusted number-needed-to-treat analysis, and determined that the addition of androgen ablation to prostate bed irradiation was beneficial in both the adjuvant and salvage setting. Randomized trials will be needed to confirm this assertion.

Complications of Radiation Therapy

In general, pelvic RT after radical prostatectomy is well tolerated. Mild to moderate (grade 1–2) late gastrointestinal or genitourinary complications are reported in up to 40% of patients.^{58,77-83} More severe (grade 3–4) side effects occur in less than 5% of patients in most series. Authors reporting high incidences of severe late toxicity have generally attributed these findings to antiquated treatment techniques, which have been abandoned. Worsening incontinence may occur in up to 20% of prostate cancer patients undergoing radiotherapy, generally in the form

Table 3. Role of Androgen Ablation as an Adjuvant to Prostate Bed RT After Prostatectomy

| Ref | F/U, yr | AA Duration, mo | N (RT+AA/RT) | bNED, % (RT+AA/RT) | |
|-----------------------|---------|-----------------|--------------|--------------------|-------|
| | | | | Adj | Salv |
| Wiegel ¹¹¹ | 10 | Permanent | 27/29 | 80/50 | - |
| Corn ⁷⁵ | 5 | Permanent | 71/68 | 65/42 | - |
| Eulau ¹¹² | 5 | 6 | 29/74 | 56/27 | |
| King ¹¹³ | 5 | 4 | 50/79 | 57/31 | |
| Song ¹¹⁴ | 5 | 4 | 30/31 | - | 39/39 |
| Katz ⁹⁹ | 4 | 3 | 45/70 | - | 59/39 |
| Taylor ⁹⁰ | 5 | 24 | 35/36 | - | 81/54 |

AA = androgen ablation; Adj = adjuvant; bNED = biochemical disease-free survival; F/U = follow-up; RT = radiotherapy alone; RT+AA = combined radiotherapy plus androgen ablation; Salv = salvage.

of stress incontinence, which may resolve with time.⁶¹ Anastomotic strictures are seen in 5–10% of patients receiving post-prostatectomy RT. Prospective evaluations of the risk of urinary and intestinal side effects with the addition of RT after prostatectomy suggest that RT may slightly increase the risk of grade 1–2 complications, but not grade 3–4, over that seen with surgery alone.^{57,73} The SWOG study showed no difference in quality of life 2 years after treatment.⁴

Treatment Recommendations

The optimal therapy for patients who have undergone radical prostatectomy and are at high risk for local recurrence or have experienced biochemical failure remains to be determined.⁵⁰ Nevertheless, physicians and patients are faced with this decision every day. The following represents the approach utilized at our institution for patients not enrolled in clinical trials. For patients with an undetectable level of PSA and positive surgical margins only, it is recommended that they receive 60 Gy to the prostate bed using either 3-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT). For patients with an undetectable PSA level, but with risk factors for distant metastases (seminal vesicle involvement, Gleason score 8–10), the addition of androgen deprivation therapy to RT may be considered. Patients with biochemical failure and at low risk for distant metastases (PSA <2 ng/mL, PSA doubling time >1 year, Gleason score <8, positive surgical margins, negative seminal vesicles and lymph nodes) are offered RT to the prostate bed. In this situation, the recommended dose is approximately 66 Gy, again using either 3DCRT or IMRT. Patients with 1 or more adverse risk factors for distant metastases may be considered for adjuvant androgen deprivation therapy. Patients with overt local recurrence are considered at high risk for distant metastases. For these patients, 70 Gy to the prostate bed is recommended in addition to adjuvant deprivation therapy.

Future Directions

Randomized data are finally becoming available to address the role of adjuvant RT after radical prostatectomy in patients at high risk for local failure.^{58,84} Although the German study is available only in abstract form, both trials report a disease-free survival advantage for early RT. Much longer follow-up will be needed to determine whether or not this translates into an improvement in survival. The role of androgen deprivation therapy in this patient population remains to be determined. The RTOG 9601 study, in which patients with pathologic stage T3 prostate cancer were randomized to RT with or without

androgen ablation with high-dose bicalutamide, was designed to address this question. This study is closed to accrual, and results are anxiously awaited. Finally, with the recent demonstration of a benefit to chemotherapy in patients with hormone-refractory metastatic disease, the question of whether adjuvant chemotherapy may play a role in patients with adverse pathologic features after radical prostatectomy needs to be answered. Currently, several groups are studying this issue. As newer agents are shown to have activity in prostate cancer, their role as an adjuvant to radical prostatectomy will also be addressed.

References

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin*. 2005;55:10-30.
2. Cooperberg MR, Broering JM, Litwin MS, et al. The contemporary management of prostate cancer in the United States: lessons from the cancer of the prostate strategic urologic research endeavor (CapSURE), a national disease registry. *J Urol*. 2004;171:1393-1401.
3. Lu-Yao GL, McLerran D, Wasson J, Wennberg JE. An assessment of radical prostatectomy. Time trends, geographic variation, and outcomes. The Prostate Patient Outcomes Research Team. *JAMA*. 1993;269:2633-2636.
4. Swanson GP, Thompson IM, Tangen C, et al. Phase III randomized trial of adjuvant radiation therapy versus observation in patients with pathologic T3 prostate cancer (SWOG 8794). *Int J Radiat Oncol Biol Phys*. 2005;63(2 suppl 1):S1.
5. Ornstein DK, Colberg JW, Virgo KS, et al. Evaluation and management of men whose radical prostatectomies failed: results of an international survey. *Urology*. 1998;52:1047-1054.
6. Moul JW. Prostate specific antigen only progression of prostate cancer. *J Urol*. 2000;163:1632-1642.
7. Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. *J Urol*. 2003;169:517-523.
8. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Tomaszewski JE, Wein A. Prostate specific antigen outcome based on the extent of extracapsular extension and margin status in patients with seminal vesicle negative prostate carcinoma of Gleason score < or = 7. *Cancer*. 2000;88:2110-2115.
9. Endrizzi J, Seay T. The relationship between early biochemical failure and perineural invasion in pathological T2 prostate cancer. *BJU Int*. 2000;85:696-698.
10. Presti JC Jr, Shinohara K, Bacchetti P, Tigrani V, Bhargava V. Positive fraction of systematic biopsies predicts risk of relapse after radical prostatectomy. *Urology*. 1998;52:1079-1084.
11. Anscher MS, Prosnitz LR. Multivariate analysis of factors predicting local relapse after radical prostatectomy—possible indications for postoperative radiotherapy. *Int J Radiat Oncol Biol Phys*. 1991;21:941-947.
12. Freedland SJ, Aronson WJ, Csathy GS, et al. Comparison of percentage of total prostate needle biopsy tissue with cancer to percentage of cores with cancer for predicting PSA recurrence after radical prostatectomy: results from the SEARCH database. *Urology*. 2003;61:742-747.
13. Freedland S, Humphreys E, Mangold L, et al. Risk of prostate cancer specific mortality following biochemical recurrence after radical prostatectomy. *JAMA*. 2005;294:433-439.
14. Brewster SF, Oxley JD, Trivella M, Abbott CD, Gillatt DA. Preoperative p53, bc1-2, CD44 and E-cadherin immunohistochemistry as predictors of biochemical relapse after radical prostatectomy. *J Urol*. 1999;161:1238-1243.
15. Carmichael MJ, Veltri RW, Partin AW, Miller MC, Walsh PC, Epstein JI. Deoxyribonucleic acid ploidy analysis as a predictor of recurrence following radical prostatectomy for stage T2 disease. *J Urol*. 1995;153(3 pt 2):1015-1019.
16. Shariat SF, Shalev M, Menesses-Diaz A, et al. Preoperative plasma levels of transforming growth factor beta(1) (TGF-beta(1)) strongly predict progression in patients undergoing radical prostatectomy. *J Clin Oncol*. 2001;19:2856-2864.
17. Fradet V, Lessard L, Begin LR, Karakiewicz P, Masson AM, Saad F. Nuclear factor-kappa B nuclear localization is predictive of biochemical recurrence in patients with positive margin prostate cancer. *Clin Cancer Res*. 2004;10:8460-8464.
18. D'Amico AV, Whittington R, Malkowicz SB, et al. The combination of preop-

- erative prostate specific antigen and postoperative pathological findings to predict prostate specific antigen outcome in clinically localized prostate cancer. *J Urol*. 1998;160(6 pt 1):2096-2101.
19. Partin AW, Piantadosi S, Sanda MG, et al. Selection of men at high risk for disease recurrence for experimental adjuvant therapy following radical prostatectomy. *Urology*. 1995;45:831-838.
 20. Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. *J Clin Oncol*. 1999;17:1499-1507.
 21. Kattan MW, Eastham JA, Stapleton AM, Wheeler TM, Scardino PT. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. *J Natl Cancer Inst*. 1998;90:766-771.
 22. Graefen M, Karakiewicz PI, Cagiannos I, et al. International validation of a preoperative nomogram for prostate cancer recurrence after radical prostatectomy. *J Clin Oncol*. 2002;20:3206-3212.
 23. Graefen M, Karakiewicz PI, Cagiannos I, et al. Validation study of the accuracy of a postoperative nomogram for recurrence after radical prostatectomy for localized prostate cancer. *J Clin Oncol*. 2002;20:951-956.
 24. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA*. 1999;281:1591-1597.
 25. 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;8:242-246.
 26. Partin A, Pound C, Clemens J, Epstein J, Walsh P. Serum PSA after anatomic radical prostatectomy. The Johns Hopkins experience after 10 years. *Urol Clin N Am*. 1993;20:713-725.
 27. Lightner D, Lange P, Reddy P, More L. Prostate specific antigen and local recurrence after radical prostatectomy. *J Urol*. 1990;144:921-926.
 28. Foster L, Jajodia P, Fournier G, Jr., Shinohara K, Carroll P, Narayan P. The value of prostate specific antigen and transrectal ultrasound guided biopsy in detecting prostatic fossa recurrences following radical prostatectomy. *J Urol*. 1993;149:1024-1028.
 29. Sudakoff GS, Smith R, Vogelzang NJ, Steinberg G, Brendler CB. Color Doppler imaging and transrectal sonography of the prostatic fossa after radical prostatectomy: early experience. *AJR Am J Roentgenol*. 1996;167:883-888.
 30. Leventis AK, Shariat SF, Slawin KM. Local recurrence after radical prostatectomy: correlation of US features with prostatic fossa biopsy findings. *Radiology*. 2001;219:432-439.
 31. 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;61:607-611.
 32. Sella T, Schwartz LH, Swindle PW, et al. Suspected local recurrence after radical prostatectomy: endorectal coil MR imaging. *Radiology*. 2004;231:379-385.
 33. Anscher MS, Prosnitz LR. Multivariate analysis of factors predicting local relapse after radical prostatectomy—possible indications for postoperative radiotherapy. *Int J Radiat Oncol Biol Phys*. 1991;21:941-947.
 34. Pound CR, Partin AW, Epstein JI, Walsh PC. Prostate-specific antigen after anatomic radical retropubic prostatectomy. Patterns of recurrence and cancer control. *Urol Clin North Am*. 1997;24:395-406.
 35. 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;160:1387-1391.
 36. Raj GV, Partin AW, Polascik TJ. Clinical utility of indium 111-capromab pentetide immunoscintigraphy in the detection of early, recurrent prostate carcinoma after radical prostatectomy. *Cancer*. 2002;94:987-996.
 37. Levesque PE, Nieh PT, Zinman LN, Seldin DW, Libertino JA. Radiolabeled monoclonal antibody indium 111-labeled CYT-356 localizes extraprostatic recurrent carcinoma after prostatectomy. *Urology*. 1998;51:978-984.
 38. Kahn D, Williams RD, Haseman MK, Reed NL, Miller SJ, Gerstbrein J. Radioimmunoscintigraphy with In-111-labeled capromab pentetide predicts prostate cancer response to salvage radiotherapy after failed radical prostatectomy. *J Clin Oncol*. 1998;16:284-289.
 39. Seltzer MA, Barbaric Z, Belldegrin 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;162:1322-1328.
 40. Thomas CT, Bradshaw PT, Pollock BH, et al. Indium-111-capromab pentetide radioimmunoscintigraphy and prognosis for durable biochemical response to salvage radiation therapy in men after failed prostatectomy. *J Clin Oncol*. 2003;21:1715-1721.
 41. DeGrado TR, Coleman RE, Wang S, et al. Synthesis and evaluation of 18F-labeled choline as an oncologic tracer for positron emission tomography: initial findings in prostate cancer. *Cancer Res*. 2001;61:110-117.
 42. Hoh CK, Seltzer MA, Franklin J, deKernion JB, Phelps ME, Belldegrin A. Positron emission tomography in urological oncology. *J Urol*. 1998;159:347-356.
 43. Kotzerke J, Volkmer B, Neumaier B, Gschwend J, Hautmann R, Reske S. Carbon-11 acetate positron emission tomography can detect recurrence of prostate cancer. *Eur J Nucl Med*. 2002;29:1380-1384.
 44. Harisinghani MG, Barentsz J, Hahn PF, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. *N Engl J Med*. 2003;348:2491-2499.
 45. Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA*. 2004;291:1325-1332.
 46. Kupelian PA, Katcher J, Levin HS, Klein EA. 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;37:1043-1052.
 47. Trapasso J, deKernion J, Smith R, Dorey F. The incidence and significance of detectable levels of serum prostate specific antigen after radical prostatectomy. *J Urol*. 1994;152:1821-1825.
 48. Partin A, Pearson J, Landis P, et al. Evaluation of serum prostate-specific antigen velocity after radical prostatectomy to distinguish local recurrence from distant metastases. *Urology*. 1994;43:649-659.
 49. Patel A, Dorey F, Franklin J, DeKernion J. Recurrence patterns after radical retropubic prostatectomy: clinical usefulness of prostate specific antigen doubling times and log slope prostate specific antigen. *J Urol*. 1997;158:1441-1445.
 50. Scardino P, Anscher M, Babaian R, et al. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. *Prostate Cancer*. Jenkinstown, PA: National Comprehensive Cancer Network; 2004. Version 1.
 51. Schild SE. Radiation therapy (RT) after prostatectomy: The case for salvage therapy as opposed to adjuvant therapy. *Int J Cancer*. 2001;96:94-98.
 52. Anscher MS, Robertson CN, Prosnitz R. Adjuvant radiotherapy for pathologic stage T3/4 adenocarcinoma of the prostate: ten-year update. *Int J Radiat Oncol Biol Phys*. 1995;33:37-43.
 53. Elias S, Parker RG, Gallardo D, Law J. Adjuvant radiation therapy after radical prostatectomy for carcinoma of the prostate. *Am J Clin Oncol*. 1997;20:120-124.
 54. Bolla M, Van Poppel H, Van Cangh P, et al. Does post-operative radiotherapy (P-XRT) after radical prostatectomy (Px) improve progression-free survival (PFS) in pT3N0 prostate cancer (PC)? *Proc Am Soc Clin Oncol*. 2004;23:382.
 55. Halperin E, Schmidt-Ullrich R, Perez C, Brady L. Overview and basic science of radiation oncology. In: Perez C, Brady L, Halperin E, Schmidt-Ullrich R, eds. *Principles and Practice of Radiation Oncology*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2004:1-95.
 56. Anscher MS. Adjuvant therapy for pathologic stage C prostate cancer: a casualty of the PSA revolution? *Int J Radiat Oncol Biol Phys*. 1996;34:745-747.
 57. Van Cangh P, 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;159:164-166.
 58. Bolla M, van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet*. 2005;366:572-578.
 59. Anscher MS. Salvage radiotherapy for recurrent prostate cancer: the earlier the better. *JAMA*. 2004;291:1380-1382.
 60. Wu A, Whittemore A, Kolonel L, et al. Serum androgens and sex hormone-binding globulins in relation to lifestyle factors in older African-American, White, and Asian men in the United States and Canada. *Cancer Epidemiol Biomark Prev*. 1995;4:735-741.
 61. Zelefsky M, Aschkenasy E, Kelsen S, Leibel S. Tolerance and early outcome results of postprostatectomy three-dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys*. 1997;39:327-333.
 62. Medini E, Medini I, Reddy P, Levitt S. Delayed/salvage radiation therapy in patients with elevated prostate specific antigen levels after radical prostatectomy. A long term follow-up. *Cancer*. 1996;78:1254-1259.
 63. Schild S, Buskirk S, Wong W, et al. The use of radiotherapy for patients with isolated elevation of serum prostate specific antigen following radical prostatectomy. *J Urol*. 1996;156:1725-1729.
 64. Kaplan I, Bagshaw M. Serum prostate-specific antigen after post prostatectomy radiotherapy. *Urology*. 1992;39:401-406.
 65. Crane C, Rich T, Read P, Sanfilippo N, Gillenwater J, Kelly M. Preirradiation PSA predicts biochemical disease-free survival in patients treated with postprostatectomy external beam irradiation. *Int J Radiat Oncol Biol Phys*. 1997;39:681-686.
 66. Anscher MS, Prosnitz LR. Radiotherapy vs. hormonal therapy for the manage-

- ment of locally recurrent prostate cancer following radical prostatectomy. *Int J Radiat Oncol Biol Phys*. 1989;17(5):953-958.
67. Vander Kooy M, Pisansky T, Cha S, Blute M. Irradiation for locally recurrent carcinoma of the prostate following radical prostatectomy. *Urology*. 1997;49:65-70.
 68. Syndikus I, Pickles T, Kostashuk E, Sullivan L. Postoperative radiotherapy for stage pT3 carcinoma of the prostate: improved local control. *J Urol*. 1996;155:1983-1986.
 69. 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;64:760-764.
 70. Choo R, Morton G, Danjoux C, Hong E, Szumacher E, DeBoer G. Limited efficacy of salvage radiotherapy for biopsy confirmed or clinically palpable local recurrence of prostate carcinoma after surgery. *Radiother Oncol*. 2005;74:163-167.
 71. Cadeddu J, Partin A, DeWeese T, Walsh P. Long-term results of radiation therapy for prostate cancer recurrence following radical prostatectomy. *J Urol*. 1998;159:173-178.
 72. Leventis AK, Shariat SF, Kattan MW, Butler EB, Wheeler TM, Slawin KM. Prediction of response to salvage radiation therapy in patients with prostate cancer recurrence after radical prostatectomy. *J Clin Oncol*. 2001;19:1030-1039.
 73. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet*. 2002;360:103-106.
 74. Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma—long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys*. 2005;61:1285-1290.
 75. Corn BW, Winter K, Pilepich MV. Does androgen suppression enhance the efficacy of postoperative irradiation? A secondary analysis of RTOG 85-31. *Radiation Therapy Oncology Group*. *Urology*. 1999;54:495-502.
 76. Jani AB, Sokoloff M, Shalhav A, Stadler W. Androgen ablation adjuvant to postprostatectomy radiotherapy: complication-adjusted number needed to treat analysis. *Urology*. 2004;64:976-981.
 77. Wu J, King S, Montana G, McKinstry C, Anscher M. The efficacy of postprostatectomy radiotherapy in patients with an isolated elevation of serum prostate-specific antigen. *Int J Radiat Oncol Biol Phys*. 1995;32:317-323.
 78. Morris M, Dallow K, Zeitman A, et al. Adjuvant and salvage irradiation following radical prostatectomy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 1997;38:731-736.
 79. 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;48:369-375.
 80. Pisansky T, Kozelsky T, Myers R, et al. Radiotherapy for isolated serum prostate specific antigen elevation after prostatectomy for prostate cancer. *J Urol*. 2000;163:845-850.
 81. Valicenti R, Gomella L, Ismail M, Mulholland S, Petersen R, Corn B. Effect of higher radiation dose on biochemical control after radical prostatectomy for pT3N0 prostate cancer. *Int J Radiat Oncol Biol Phys*. 1998;42:501-506.
 82. Do T, Parker R, Do C, Tran L, Do L, Dolkar D. Salvage radiotherapy for biochemical and clinical failures following radical prostatectomy. *Cancer J Sci Am*. 1998;4:324-330.
 83. Duchesne GM, Dowling C, Frydenberg M, et al. Outcome, morbidity, and prognostic factors in post-prostatectomy radiotherapy: an Australian multicenter study. *Urology*. 2003;61:179-183.
 84. Wiegel T, Bortke D, Willich N, et al. Phase III results of adjuvant radiotherapy (RT) versus "wait and see" (WS) in patients with pT3 prostate cancer following radical prostatectomy (RP) (ARO96-02/AUO AP 09/95). *J Clin Oncol*. 2005;23(16S part I of II):381s.
 85. Catton C, Gospodarowicz M, Warde P, et al. Adjuvant and salvage radiation therapy after radical prostatectomy for adenocarcinoma of the prostate. *Radiother Oncol*. 2001;59:51-60.
 86. Kalapurakal JA, Huang CF, Neriampampill MM, et al. Biochemical disease-free survival following adjuvant and salvage irradiation after radical prostatectomy. *Int J Radiat Oncol Biol Phys*. 2002;54:1047-1054.
 87. Nudell D, Grossfeld G, Weinberg V, Roach III M, Carroll P. Radiotherapy after radical prostatectomy: treatment outcomes and failure patterns. *Urology*. 1999;54:1049-1057.
 88. Pacholke HD, Wajzman Z, Algood CB, Morris CG, Zlotecki RA. Postoperative adjuvant and salvage radiotherapy for prostate cancer: impact on freedom from biochemical relapse and survival. *Urology*. 2004;64:982-986.
 89. Peschel R, Robnett T, Hesse D, et al. PSA based review of adjuvant and salvage radiation therapy vs. observation in postoperative prostate cancer patients. *Int J Cancer (Radiat Oncol Invest)*. 2000;90:29-36.
 90. Taylor N, Kelly JF, Kuban DA, Babaian RJ, Pisters LL, Pollack A. Adjuvant and salvage radiotherapy after radical prostatectomy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2003;56:755-763.
 91. Tsien C, Griffith KA, Sandler HM, et al. Long-term results of three-dimensional conformal adjuvant and salvage radiotherapy after radical prostatectomy. *Urology*. 2003;62:93-98.
 92. Valicenti R, Gomella L, Ismail M, et al. Durable efficacy of early postoperative radiation therapy for high-risk pT3N0 prostate cancer: the importance of radiation dose. *Urology*. 1998;52:1034-1040.
 93. Vicini F, Ziaja E, Kestin L, et al. Treatment outcome with adjuvant and salvage irradiation after radical prostatectomy for prostate cancer. *Urology*. 1999;54:111-117.
 94. Mayer R, Pummer K, Quehenberger F, Mayer E, Fink L, Hackl A. Postprostatectomy radiotherapy for high-risk prostate cancer. *Urology*. 2002;59:732-739.
 95. Hagan M, Zlotecki R, Medina C, Tercilla O, Rivera I, Wajzman Z. Comparison of adjuvant versus salvage radiotherapy policies for postprostatectomy radiotherapy. *Int J Radiat Oncol Biol Phys*. 2004;59:329-340.
 96. 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;59:674-683.
 97. Garg M, Tekyi-Mensah S, Bolton S, et al. Impact of postprostatectomy prostate-specific antigen nadir on outcomes following salvage radiotherapy. *Urology*. 1998;51:998-1002.
 98. Hudson M, Catalona W. Effect of adjuvant radiation therapy on prostate specific antigen following radical prostatectomy. *J Urol*. 1990;143:1174-1177.
 99. Katz MS, Zelefsky MJ, Venkatraman ES, Fuks Z, Hummer A, Leibel SA. Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer. *J Clin Oncol*. 2003;21:483-489.
 100. Keisch M, Perez C, Grigsby P, Bauer W, Catalona W. Preliminary report on 10 patients treated with radiotherapy after radical prostatectomy for isolated elevation of serum PSA levels. *Int J Radiat Oncol Biol Phys*. 1990;19:1503-1506.
 101. Lange P, Lightner D, Medini E, Reddy P, Vessella R. The effect of radiation therapy after radical prostatectomy in patients with elevated prostate specific antigen levels. *J Urol*. 1990;144:927-932.
 102. Liauw SL, Webster WS, Pistenmaa DA, Roehrborn CG. Salvage radiotherapy for biochemical failure of radical prostatectomy: a single-institution experience. *Urology*. 2003;61:1204-1210.
 103. Link P, Freiha F, Stamey T. Adjuvant radiation therapy in patients with detectable prostate specific antigen following radical prostatectomy. *J Urol*. 1991;145:532-534.
 104. Macdonald OK, Schild SE, Vora SA, et al. Radiotherapy for men with isolated increase in serum prostate specific antigen after radical prostatectomy. *J Urol*. 2003;170:1833-1837.
 105. McCarthy J, Catalona W, Hudson M. Effects of radiation therapy on detectable serum prostate specific antigen levels following radical prostatectomy: early versus delayed treatment. *J Urol*. 1994;151:1575-1578.
 106. Petrovich Z, Lieskovsky G, Langholz B, Jozsef G, Streeter OE Jr, Skinner DG. Postoperative radiotherapy in 423 patients with pT3N0 prostate cancer. *Int J Radiat Oncol Biol Phys*. 2002;53:600-609.
 107. Peyromaure M, Allouch M, Eschwege F, Verpillat P, Debre B, Zerbib M. Salvage radiotherapy for biochemical recurrence after radical prostatectomy: a study of 62 patients. *Urology*. 2003;62:503-507.
 108. 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;170:1860-1863.
 109. 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 Biol Phys*. 2002;52:674-680.
 110. Cheng WS, Frydenberg M, Bergstrahl EJ, Larson-Keller JJ, Zincke H. Radical prostatectomy for pathologic stage C prostate cancer: influence of pathologic variables and adjuvant treatment on disease outcome. *Urology*. 1993;42:283-291.
 111. Wiegel T, Bressel M, Carl UM. Adjuvant radiotherapy following radical prostatectomy—results of 56 patients. *Eur J Cancer*. 1995;31A:5-11.
 112. Eulau SM, Tate DJ, Stamey TA, Bagshaw MA, Hancock SL. Effect of combined transient androgen deprivation and irradiation following radical prostatectomy for prostatic cancer. *Int J Radiat Oncol Biol Phys*. 1998;41:735-740.
 113. King CR, Presti JC Jr, Gill H, Brooks J, Hancock SL. Radiotherapy after radical prostatectomy: does transient androgen suppression improve outcomes? *Int J Radiat Oncol Biol Phys*. 2004;59:341-347.
 114. Song DY, Thompson TL, Ramakrishnan V, et al. Salvage radiotherapy for rising or persistent PSA after radical prostatectomy. *Urology*. 2002;60:281-287.