Therapeutic Radiation in Patients With a Rising Post-Prostatectomy PSA Level

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The optimal management of patients with an elevated post-prostatectomy prostate-specific antigen (PSA) level remains to be determined. In the pre-PSA era, many patients received immediate adjuvant radiation therapy on

Introduction

The optimal management of patients with suspected or proven residual disease following radical prostatectomy for prostate cancer remains uncertain.[1] Controversy still exists as to whether initial or primary treatment alters the natural history of patients when compared with watchful waiting.[2,3] There is no clearer evidence regarding the value of subsequent adjuvant or therapeutic local and/or systemic therapy.[4,5]

Adjuvant Therapy Post-Prostatectomy

Adjuvant systemic therapy in the form of hormones (eg, luteinizing hormone-releasing hormone [LHRH]) has improved the disease-free survival[6,7] and survival[7] of high-risk patients following radiation therapy. High-risk patients were defined as those with locally advanced (stage T3-4) disease, poorly differentiated (Gleason score more than 8) tumors, or regional lymphatic metastases. The optimal timing of hormonal intervention would appear to be at, or before, the discovery of overt distant disease but prior to symptom development. Unfortunately, there have been no similar trials following radical prostatectomy. Patients at risk for residual disease are advised to receive adjuvant local treatment with radiation following their surgery.[8-12] Risk factors, historically defined by reviewing the surgical pathology specimen, include positive margins, extracapsular extension, seminal vesicle and lymph node involvement, and grade (Table 1).[13-15] Other risk factors include tumor volume, DNA ploidy and the preoperative prostate specific antigen (PSA) level.[16] Combinations of multiple risk factors (eg, stage, Gleason score,[17] and margins) increase the predictive value for recurrence (Table 2).[18] Adjuvant radiation in patients at risk for recurrence appears to reduce that risk with minimal toxicity.[4,8-12] Several nonrandomized, single-institution studies have demonstrated that doses ranging from 45 to 64 Gy decrease the probability that the disease will recur. (Table 3). No survival advantage has been demonstrated thus far. However, a recent randomized trial coordinated by the Southwest Oncology Group (SWOG) that compared observation to postoperative radiation will eventually answer this question. Until this issue is resolved, however, the routine use of adjuvant irradiation is determined on a case-by-case basis.

The arguments against the use of adjuvant radiotherapy stem from its association with rectal injury or worsening incontinence. These risks are compounded by the fact that 50% to 70% of patients receiving treatment will not have local recurrences and thus are exposed to the risks of treatment without any benefit. Finally, the widespread use of neoadjuvant hormonal therapy, resulting in pathologic downstaging in up to 50% of patients, makes the assignment of a probability for recurrence based on patients' surgical pathologic specimen less accurate.[19,20]

Post-Prostatectomy PSA

Post-prostatectomy PSA levels have revolutionized the ability to detect treatment failures. An elevated post-operative PSA level (less than 0.4 ng/mL) is pathognomonic for residual/recurrent disease.[21] Unlike pathologic risk factors, a rising postoperative PSA level is specific for residual disease. However, a patient’s elevated PSA level may indicate local disease, systemic disease, or both. A number of procedures can discern where the residual disease is.

Most patients evaluated for an elevated postoperative PSA undergo radiographic studies, including
CT and/or bone scanning. However, for patients with a PSA ≤ 1.0 ng/mL, the yield of these studies is extremely low.[22] Scintigraphic scans using a radiolabeled monoclonal antibody to PSA-m (Prostascint) have demonstrated residual disease in 60% of those with an elevated PSA.[23] However, the sensitivity of this test is unknown and the specificity may be suspect due to the lack of pathologic confirmation of abnormalities in most reports.

Transrectal ultrasound (TRUS) may reveal abnormalities in the prostate bed. Pathologic correlation of these abnormalities denotes locally persistent disease in 40% to 75% of patients who are biopsied, depending on the number and location of the biopsies performed.[24,25] Hence, many patients with an elevated postoperative PSA level will not have demonstrable disease. Since serum PSA is specific for local recurrence and response to radiation is tumor-volume-dependent, treating patients early before they have overt evidence of disease should improve the probability of success.

To increase the specificity of an elevated postoperative PSA for predicting local disease, investigators have evaluated the pathologic stage, Gleason score, postoperative PSA nadir, timing and rate of PSA rise, absolute PSA level, and response to local treatment.[26-28] Patients with seminal vesicle or lymph node involvement at the time of surgery have a significantly higher rate of distant failure in conjunction with PSA elevation.[13] However, up to 30% of those who are pathologic stage T3c,N0 can be cured with therapeutic post-prostatectomy radiation.[29] A similar pattern of failure has been reported for patients with high Gleason scores (≥ 8).[30] Patients who achieve an undetectable postoperative PSA that subsequently rises are more likely to harbor residual local disease than those who never achieve an undetectable level.[31] Delayed and/or slowly rising PSA levels are also reported to favor local vs systemic recurrence. Finally, patients with a lower level of PSA at the time of therapeutic irradiation (≤ 2.0 ng/mL) are more likely to respond to treatment with a further decline in PSA, suggesting a higher probability of local-only disease.[29,32-33] Although, each of these factors predicts for a greater chance of local-only disease, nodal stage is the only relative contraindication to a course of curative therapeutic irradiation.

Therapeutic Radiation for an Elevated Postoperative PSA

A number of factors influence the efficacy and safety of postoperative radiotherapy. These include the volume, dose, field arrangement, and level of PSA. Elective nodal irradiation has not influenced the outcome of localized prostate cancer patients treated definitively with radiotherapy.[34] In the postoperative setting, especially in patients without pathologic nodal involvement, there is no evidence of clinical benefit from elective pelvic irradiation. However, it does significantly increase the volume of bladder and rectal irradiated.[35] The lack of benefit, coupled with the increased volume and possible risks of irradiation, suggest that elective nodal irradiation is not an important component of postoperative radiotherapy and should be eliminated.

Field arrangements have varied from unblocked rotational or four-field box techniques to three-dimensional (3D) conformally blocked multifield plans, including axial and nonaxial beam arrangements. Target volume is defined as the prostate and seminal vesicle bed and can be recreated using either preoperative imaging studies or postoperative radiographic findings, such as clips. It is recommended that patients be treated with a full bladder, and that simulation with intravesicle and urethral contrast be done to help identify the lower border of treatment, especially in those with positive apical margins.

Although it is often assumed that the volume of normal bladder and rectum receiving full-dose radiation would be greater in the postoperative setting than in patients with an intact prostate, this assumption was recently disputed. Sharma et al showed that the field size and volume of the rectum and bladder were identical in patients receiving conformal axial plus nonaxial fields either definitively or postoperatively.[36] As a consequence, the risk of chronic bladder or rectal complications were equal.

The probability of complications and control correlates, most likely, with the dose given; however, not enough data have been published to support this theory. Doses ranging from 50 to 74 Gy have been reported, but no clear dose response has been identified. If doses of 60 to 64 Gy are sufficient in the adjuvant setting, doses of 66 to 70 Gy are suggested as therapeutic radiation for an elevated postoperative PSA. These doses have proven to be effective and safe.[26,29]

Intratreatment Monitoring

During therapeutic postoperative radiotherapy, we have monitored the pattern of PSA decline on a weekly basis. Ninety percent of patients experienced a decline during treatment. Those who experienced a significant increase subsequently developed evidence of failure within 18 months.[26]
This is unlike the use of radiation therapy in patients with an intact prostate; in this situation, the PSA level may increase in 30% to 50% of patients, possibly as a result of radiation-induced prostatitis.[37,38] It is consistent with the observation that the risk of acute genitourinary toxicity is significantly lower in patients receiving postoperative vs definitive radiotherapy, however. Therefore, the symptoms often attributed to radiation cystitis may more often be due to radiation prostatitis, which does not occur in the post-prostatectomy setting.

**Results of Therapeutic Post-Prostatectomy Radiation**

The results and definitions of failure vary widely in the literature. A complete response is achieved if a patient's elevated postoperative PSA level becomes undetectable (eg, less than 0.1 ng/mL). There is no evidence of disease (NED) if an undetectable PSA level is maintained in the absence of hormonal therapy. From 30% to 83% of patients responded to radiation with median follow-ups ranging from 4 to 50 months (Table 4). Prognostic factors predictive of a higher probability of complete response (CR) and NED include pathologic stage (T2-3 vs T3c, N1), and preoperative or post-radiotherapy PSA levels.[29] Several investigators have seen a significantly higher CR and NED rate in patients with lower PSA values (≤ 2.0 ng/mL) at the time of irradiation.[29,32-33]

Between January 1992 and 1997, 67 patients with elevated PSA levels received therapeutic postoperative radiation at the Department of Radiation Oncology, Wayne State University. Patient characteristics are summarized in Table 5. The median dose was 66 Gy (range, 50 to 74 Gy). All 67 patients were given conformal/designed axial and nonaxial fields directed to the prostate and seminal vesicle bed. No patient received elective nodal irradiation or postoperative or preradiotherapy hormonal therapy. The median follow up was 30 months.

Thirty-eight patients (57%) had a complete response. At last follow-up, 44 (50%) were disease-free. Of those who achieved a CR, 36 (95%) remained disease-free. The 4-year actuarial probability of being disease-free was 74% for patients with a preradiation PSA ≤ 2.0 ng/mL vs 22% of those with a PSA more than 2.0 ng/mL (P = .001; Figure 1). In the 52 patients without seminal vesicle or lymph node involvement, these figures were 82% and 38%, respectively (P = .0002; Figure 2). Other investigators have also demonstrated the importance of PSA level in predicting outcome (Table 6). Treatment has generally been well tolerated with few severe complications reported following therapeutic postoperative irradiation. Lymphedema of the lower extremities or genitals is no longer seen. Rectal bleeding occurs in up to 10% of patients following postoperative radiation, and fewer than 10% report worsening levels of incontinence. Little data are available regarding erectile function following postoperative radiation therapy.

**Discussion**

Patients with an elevated post-prostatectomy PSA level have residual disease. Determining whether this disease is localized or disseminated is imprecise but can be partially predicted by the pathologic stage, Gleason score, PSA nadir, time to relapse, PSA level at relapse, and imaging studies, including TRUS and Prostascint scans.

Through careful case selection (low stage, low PSA level), careful treatment (3D planning), and adequate dose (66 to 70 Gy), excellent results can be achieved with low morbidity and significant response rates. The data suggest that patients with a PSA level ≤ 2 ng/mL have an 80% chance of being disease-free 4 years following postoperative radiotherapy.

The reasons for the wide variation in results reported in the literature include evaluation of patients with significant systemic risk, such as seminal vesicle or lymph node involvement, and the possible inclusion of patients with palpable local recurrences, who have a higher risk (~ 80%) of systemic relapse. Also, definitions of radiation fields and prescribed doses vary widely.

Whether or not definitive treatment of patients who relapse post-prostatectomy will improve their overall survival remains unanswered and awaits the performance of an adequate clinical trial. However, in practice, since most patients receiving postoperative radiotherapy do so within 2 years of surgery and often wish to maintain a potentially curative approach, they favor a second opportunity at curative treatment. How or when to integrate systemic therapy into the regimen of postoperative radiotherapy remains to be determined.

Our policy at the Barbara Ann Karmanos Cancer Institute has been to wait for patients who exhibit either a progressively rising PSA or radiographic evidence of asymptomatic disease. At present, we have moved away from the routine use of immediate adjuvant therapy so as to avoid irradiation in the 50% to 70% of patients who do not require it. We recommend early intervention instead (PSA ≤ 2.0 ng/mL) with adequate doses (66 to 70 Gy) of therapeutic irradiation to maximize the therapeutic
ratio in postoperative patients.

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