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Salvage External Beam Radiotherapy for Prostate Cancer After Radical Prostatectomy

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ABSTRACT

Prostate cancer is the second most common cause of cancer death in American men. What to do when prostate cancer recurs months or years after a patient undergoes radical prostatectomy is an area of active research. Patients who underwent radical prostatectomy without immediate adjuvant radiation therapy (ART) but subsequently have evidence of recurrent disease are candidates for Salvage Radiation Therapy (SRT). Though there are three prospective randomized trials illustrating the efficacy of post-operative ART for selected patients, similarly strong evidence is lacking for SRT. In this article, we define the biochemical recurrence of prostate cancer, distinguish SRT from ART, outline the evidence for SRT, and make recommendations with regard to radiotherapy volume and dose. We discuss the known side effects from SRT, weigh the cost and benefit of SRT, and discuss

possible tools that may improve the cost/benefit ratio for SRT by helping to select patients whom SRT may be more likely to benefit.

Prostate cancer is the second most common cause of cancer death in American men, with 192,289 new cases and 27,360 deaths expected in 2009.[1] While radical prostatectomy provides excellent control for clinically localized disease, approximately one-third of patients undergoing surgery will have positive surgical margins and another 9% will have seminal vesicle invasion.[2-5] Around one-third of patients will also have extracapsular extension.[5] These adverse pathological risk factors, in addition to the Gleason score and initial PSA level, are independent predictors of biochemical recurrence of cancer. Indeed, 40%-50% of high-risk patients have a biochemical recurrence after surgery, and many of those patients eventually develop metastases.[6-11] Currently, the majority of post-surgical patients without high-risk features are observed for signs of disease progression without active treatment. However, recently updated randomized trials have shown a very significant benefit to immediate "adjuvant" radiation therapy for prostate cancer at high risk of recurrence, such as pT3 disease.[12-14] Controversy surrounds the issue of what to do when prostate cancer recurs months or years after initial prostatectomy, and whether the risks and morbidity of radiation therapy in the "salvage" setting outweigh the intended benefits.

This review outlines the evidence for the use of salvage external beam radiotherapy for patients with biochemical relapse, and discusses current recommendations for a treatment target and dose prescription. In addition, we highlight why the treatment of prostate cancer recurrence is important as it relates to the cost and disability associated with metastatic disease. Though the relative cost, benefit, and risks are less defined than in the adjuvant setting, multiple studies have shown an excellent quality of life and low complication rates with salvage radiotherapy. Selected patients may have an improved likelihood of benefiting from salvage radiotherapy.

Definition of Biochemically Recurrent Prostate Cancer

Prostate cancer presents a unique situation in which physicians have the capability to oversee treatment response with a serologic marker that predicts treatment failure years before clinical progression.[15] Given the extended period between prostate cancer recurrence after radical prostatectomy and death, the use of PSA progression is commonplace in monitoring treatment success.[16,17] In principle, the PSA level should become undetectable within 6 weeks of radical prostatectomy (RP), as the prostate tissue

has been removed, and the half-life of PSA is around 3 days.[18] Therefore, a detectable serum PSA suggests either remaining prostate tissue or cancer, and is recognized as evidence of cancer recurrence.[19-21]

The American Urological Association (AUA) defines biochemical recurrence following radical prostatectomy as an initial serum PSA of ≥ 0.2 ng/mL, with a second confirmatory level of > 0.2 ng/mL.[22] The initial postoperative PSA is measured 6-12 weeks after surgery, and after confirmation the date of failure is the date of the first value above the 0.2 ng/mL. Although the AUA established this definition for the purpose of reporting information in a consistent manner and not as a standard for when to begin salvage therapy, this value also represents the threshold at which patients are at very high risk of developing additional PSA increases. In a retrospective evaluation of 358 men undergoing RP, they found that when PSA levels rose to levels
> 0.2 ng/mL after RP, the 1- and 3-year risks of additional PSA progression were 86% (95% CI 69%-97%) and 100% (95% CI 87%-100%), respectively.[23] Using this definition of PSA recurrence rather than a definition of failure that includes any detectable PSA decreases the likelihood of a falsely positive PSA due to retained benign prostate tissue.[22]

Though a major cooperative group advocated an optimal value to define PSA relapse of > 0.4, the two PSA levels have similar specificity.[24] As the lower PSA cutoff (> 0.2 and rising) is necessarily more sensitive, it could potentially lead to earlier initiation of salvage radiotherapy, at a lower disease burden and decreased likelihood for distant disease. This is especially true since the benefit of salvage radiation has been demonstrated to be inversely correlated to the serum PSA level at the time of radiation therapy (RT).[6,25]

Definition of Salvage Radiotherapy (SRT), and the Distinction Between SRT and Adjuvant RT (ART)

Generally, "salvage" radiotherapy (SRT) is defined as radiation treatment given for suspected recurrent malignant disease after a period of observation after prostatectomy. In contrast, "adjuvant" radiotherapy (ART) refers to treatment directly after prostatectomy in patients potentially without residual disease and with an undetectable PSA. There are several important distinctions between SRT and ART: 1) There is a higher likelihood of local residual disease without distant metastatic disease for patients in whom ART is indicated immediately post-prostatectomy versus a patient for whom SRT is being considered; 2) The burden of disease may be higher for SRT vs ART; and 3) Multiple prospective randomized trials have shown a benefit to ART, whereas similar evidence is

lacking for SRT [12-14] (although a randomized trial comparing SRT and ART is underway).[26]

ART is given for patients at high risk of localized recurrence, generally defined as: evidence for prostate cancer outside the capsule (extracapsular extension), positive surgical margins, or seminal vesicle invasion. In contrast, SRT patients can have recurrence years after RP, and it is often unclear whether the detected PSA represents recurrence locally within the prostate bed, seminal vesicle remnants, pelvis, or at a distant site. This is obviously important for RT planning, as delivering RT to the prostate bed is useless if no disease remains locally.

In general, the burden of disease may be different for ART patients versus SRT patients. Though ART patients can have gross residual disease remaining after radical prostatectomy, they also often have an undetectable PSA indicative of, at most, microscopic residual disease. In contrast, all patients who undergo SRT for a biochemical recurrence have either a large enough burden of disease to cause a detectable PSA, a palpable nodule on digital rectal exam, or gross disease detected on CT or MRI. Therefore, some authors suggest that in general, SRT patients have roughly ten times the disease burden of ART patients.[27]

Immediate "adjuvant" radiotherapy for patients at high risk of recurrence (pT3, etc.) has proven to be beneficial in three randomized trials. The European Organisation for Research and Treatment of Cancer (EORTC) 22911 clinical trial showed a biochemical progression-free survival (74.0% vs 52.6%; P <.0001), improved clinical progression-free survival (P = .0009), and a significantly lower rate of cumulative locoregional failure (P = .0005) with ART.[12] It is also worth noting that deferred postoperative radiation was given to almost half of relapsing patients in the observation group and there was still a demonstrated advantage to ART. The second randomized trial, the ARO96-02/AUO AP 09/95 study, compared ART after radical RP to RP alone in patients with pT3N0 tumors and an undetectable (< 0.1 ng/mL) postoperative PSA.[14] Biochemical progression-free survival in the ART arm was significantly improved over the observation group (72% vs 54%; HR = 0.53, P = .0015), even in this group of men with an undetectable PSA at the time of RT. Although the EORTC 22911 trial demonstrated a treatment effect for all subgroups, analysis in this study revealed only positive surgical margins; Gleason score 6 or less; PSA level > 10 ng/mL before surgery; and extracapsular extension without infiltration of the seminal vesicles to be predictors of improved recurrence-free survival. Longer follow-up is needed for both the EORTC and ARO96-02 studies to assess the impact of ART on metastasis-free and overall survival.

The third randomized trial that assessed the benefit of ART was the Southwest Oncology Group (SWOG) study, which randomized 425 men with one of three pathologic features: extracapsular extension, positive surgical margins, or seminal vesicle invasion to observation (n=211) or ART arms (n=214).[13] Like the first two studies, the SWOG group found a significant 60% reduction in the risk for biochemical recurrence (hazard ratio 0.43 (95% CI: 0.38–0.58, P < .001), which was similar in magnitude to the risk reduction for biochemical failure observed in both the EORTC (hazard ratio: 0.48, 98% CI 0·37–0·62, P < .001) and ARO96-02 studies (hazard ratio: 0.53; 95% CI, 0.37–0.79; P = .0015). In distinction from the other two randomized trials, with a much longer follow-up of median >12 years, the SWOG study also found a significant benefit to ART in metastasis-free survival (93 of 214 events in the ART arm vs 114 of 211 events in observation arm; HR 0.71, P = .016) and improved overall survival (88 deaths of 214 in the ART arm vs 110 deaths of 211 in observation arm; HR 0.72, P = .023). These findings are particularly noteworthy since of those men under observation—approximately one-third—ultimately received SRT. Furthermore, the use of hormonal therapy in the observation arm was almost twice that of the ART group. Subset analysis revealed that even though men with a detectable PSA after surgery benefit from ART, this group's metastasis rate is higher than that of men who had ART with an undetectable PSA (P = .03).

Whether an equivalent survival benefit can be attained with close surveillance and early initiation of SRT for patients with biochemical recurrence after RP is still an area of debate. However, a new study known as the Radiotherapy and Androgen Deprivation in Combination After Local Surgery (RADICALS) trial has been designed to clarify the timing of radiation therapy after prostate surgery.[26] In the trial, patients with adverse pathological features and an undetectable PSA after RP are randomized to RT within 2 months of surgery (ART) or treatment as soon as their PSA rises > 0.1 ng/mL (SRT). Patients will also be randomized to 0, 6, or 24 months of hormonal therapy to determine the role of androgen deprivation. The investigators aim to recruit more than 4,000 patients and the primary outcome is cause-specific survival.

Evidence for the Use of Salvage Radiotherapy

Recent evidence from these three randomized trials suggests that early intervention with ART can lengthen biochemical disease-free, metastasis-free and overall survival in patients with pathologically advanced prostate cancer.[12-14] However, a disadvantage of routine ART is treating those who would never develop biochemical recurrence after RP, and unnecessarily exposing an increased number of patients to the side effects of RT.

In addition, there is some evidence that the use of ART may be associated with an increased risk of toxicity as compared to SRT. A retrospective multi-institutional analysis of 959 men treated with either adjuvant (19%) or salvage (81%) RT found a low rate of toxicity with a 5-year rate of late grade 2 or higher genitourinary (GU) toxicity of 12% and a late grade 2 or higher gastrointestinal (GI) toxicity of 4%. More serious toxicity was rare, with grade 3 GU toxicities in only 1% of all patients and grade 3 GI toxicities in 0.2% of all patients. Given the small number of events, there were no predictors that correlated with late GI toxicity, and there was no difference in GI toxicity between ART and SRT. However, on multivariate analysis adjuvant RT as compared to both salvage RT (16% vs 11%) and the use of hormonal therapy (19% vs 11%) predicted for increased risks of grade 2 or greater urinary toxicities.[28] Therefore, the use of SRT might protect a significant portion of men who do not ever require radiotherapy, and in addition, even for those treated with RT may provide a modest reduction in GU toxicity. However, the cost of a strategy of using SRT in lieu of ART is that a certain portion of patients may have a lower chance of successful eradication of their disease with SRT. Whether an equivalent survival benefit can be attained with vigilant surveillance and early initiation of SRT upon PSA relapse is an unanswered question, and SRT cannot at present be considered to be equivalent to ART.

Given this uncertainty, two groups of investigators have attempted to define prognostic factors that predict the likelihood of obtaining a benefit from SRT. Trock et al. retrospectively analyzed 635 men, who either received no salvage treatment (n=397), SRT alone (n=160), or SRT combined with hormonal therapy (n=78).[29] The authors found that 70% of all deaths during follow-up were from prostate cancer with 10-year rates of prostate cancer–specific survival of 86% in those treated with salvage RT as compared to 62% without RT. This represented a 3-fold increase in prostate cancer–specific survival compared to those who received no salvage treatment (hazard ratio [HR], 0.32; $P < .001$). The addition of hormonal therapy to SRT did not improve prostate cancer–specific survival. Also noteworthy was that when SRT was restricted to the population of patients with pT3 disease who would have been candidates for ART, the use of salvage RT also provided an OS benefit with 10-year OS of 98% vs 89%. Interestingly, the prostate cancer–specific survival benefit of SRT was only seen in men with a PSA doubling time of < 6 months, independent of pathologic stage or Gleason score. This runs counter to the more commonly held principle that a short doubling time is indicative of distant disease and, therefore, a lack of benefit to SRT.[30] Moreover, patients who received SRT more than 2 years from the time of biochemical recurrence did not experience significant increases in prostate cancer–specific survival.

Further evidence for the use of SRT in prostate cancer comes from a retrospective study by Stephenson et al, in which they developed a model using a cohort of 1,540 patients.[25] The authors described several prognostic features that should be considered when predicting improved biochemical control after SRT: These included PSA level < 2.0 ng/mL at time of SRT, Gleason score of 7 or less, PSA doubling time > 10 months, positive surgical margins, androgen-deprivation therapy before or during SRT, and the absence of lymph node metastasis. It was again demonstrated that SRT may significantly alter the natural course of the disease, as 60% to 70% of patients with disease recurrence develop metastasis within 6 years if they do not receive salvage therapy.[15] In addition, SRT is recommended to patients with more favorable prognostic features, as they are thought to be at lower risk for widely disseminated disease.[31] However, the Stephenson study, like the one by Trock et al., suggests that patients with unfavorable prognostic features may also benefit from SRT if treatment is initiated early after biochemical recurrence. Indeed the Trock study would suggest that patients with the shortest doubling time are at the greatest risk for prostate cancer–specific death. Although these patients may be less likely to have PSA control, given their greater risk of death from prostate cancer if they do achieve disease control, this translates into a cause specific survival benefit. In contrast, those with a longer PSA doubling time may be more likely to achieve PSA control with SRT, but given the lower clinical risk this does not appear to change the risk of prostate cancer–specific death.

Current Treatment—Defining the Surgical Bed

Although some authors have reported on the use of low-dose rate[32] or high-dose rate [33] brachytherapy for the treatment of prostate cancer that has recurred after RP, by far the most commonly used treatment modality is external beam radiotherapy (EBRT). Therefore, our discussion will concern EBRT only. External beam salvage radiotherapy typically involves 3D conformal or Intensity Modulated Radiation Therapy (IMRT) to the prostate bed alone, with radiation fields designed to treat areas at the highest risk for local recurrence. Radiation therapy treatment volumes are in principle identical to those used for ART; therefore, lessons from ART randomized trials and ART consensus statements apply.

The randomized trials mentioned earlier were conducted in the era before the widespread adoption of 3D conformal or IMRT techniques, and therefore involved 9 × 9 cm or 10 × 10 cm fields centered around the prostatic fossa.[12-14] However, 3D conformal and IMRT techniques allow for the targeting of the prostatic fossa, urethrovesical anastamosis, and surrounding tissues at risk, with relative sparing of the rectum, bladder, and penile bulb.

Multiple consensus guidelines have been created for the definition of the clinical target volume (CTV), most significantly from the EORTC, RTOG, and RADICALS groups.[34-36]

All three consensus groups generally advocate for the treatment of the vesicourethral anastamosis (VUA) and surrounding periurethral tissue. However, they advocate therapy to different amounts of additional tissue such as the bladder and seminal vesicle beds. The RTOG and RADICALS groups recommend defining the VUA using the most inferior visualized urine in the bladder on sagittal reconstruction, while the EORTC defines the VUA as 15 mm cranial to the penile bulb. At the level of the pubic symphysis, anteriorly and posteriorly, all three consensus groups essentially cover the region from the pubic symphysis to the rectum, and laterally the medial border of the obdurator internus and levator ani muscles. The lateral borders were generally the pelvic fascia superior to the pubic symphysis. At the bladder wall, the EORTC has perhaps the most limited CTV definition, and in contrast to the RTOG and RADICALS groups, does not advocate for the inclusion of 1.5 cm of posterior bladder and bladder wall. In the rectovesical /seminal vesicle bed space, the EORTC and RTOG advocate for the coverage of the seminal vesicle beds if there is pathologic involvement of the seminal vesicles in the surgical specimen, but to otherwise largely spare the seminal vesicle beds (though they do say to cover where the base of the seminal vesicles used to reside). Any retained seminal vesicle remnants should be included if the seminal vesicles were involved pathologically. The superior border in the rectovesicular space is at or 5 mm above the level of the cut end of the vas deferens or at the level of the most superior surgical clips. Inferiorly, the RADICALS group recommends placing the border at 8-12 mm below the vesicourethral anastamosis, but not to include the penile bulb. There was some concern in the RTOG group that apical tumors could extend into the genitourinal (GU) diaphragm and inferior urethral sphincter, and this was the reason it was recommended that the inferior aspect of the CTV extend to a level just above the penile bulb.[35]

Separately, Miralbell et al. recommend a cylindrical CTV centered 0.5 cm posterior and 3 mm inferior to the VUA, measuring 4 cm in height and 3 cm in diameter.[37] This volume considerably spared the rectum, and may represent a way in which to limit radiation-associated toxicities and improve the quality of life of prostate cancer patients. This CTV recommendation was based on an MRI series of 60 men, and is consistent with another MRI study showing recurrences largely around the VUA.[38] However, this very VUA-centric volume stands in contrast to another MRI study which showed more local recurrences in the rectovesicular space outside of the proposed CTV.[39] Further studies regarding the optimal volume of treatment are necessary, and it is hoped that information from the RADICALS trial will shed more light.

Minimizing daily set-up error and ensuring reproducible localization of the prostate bed is a current area of study. Calypso beacon localization has been suggested as a useful tool for localization of the prostate bed,[40] as has daily portal imaging with implanted gold fiducial markers[41] or daily cone-beam imaging or kilovoltage imaging.[42] These techniques attempt to minimize daily setup error and take into account any variation in the location of the VUA depending on day-to-day differences in rectal volume and bladder distension. A general consensus on the differential benefit of these techniques has not been found, though most authors agree that daily localization is important for reducing treatment margins and thus further reducing radiation to normal tissue.

Dose

The proper radiation dose that delivers a balance of optimal disease control while limiting side effects is not clear; however, it is thought that the use of increased RT doses may provide higher chances of cure. Until recently, there were only three retrospective studies with small sample sizes that showed that doses above 64.8 Gy are beneficial.[43-45] While doses ≥78 Gy are used for RT in the definitive setting, doses for ART or SRT are generally lower because it is assumed that the tumor burden is microscopic,[46-48] and the presence of bladder and rectum within the prostate resection fossa increases the normal tissues radiated. As noted previously, randomized ART trials delivered radiation in the range of 60-64 Gy to relatively large fields.[12-14] The RADICALS trial is testing a dose of 66 Gy in 33 fractions, or 52.5 Gy in 20 fractions.[26] King et al. recommend at least 70 Gy based on a retrospective study showing a significant dose response between 60 and 70 Gy of radiation to the prostate bed.[49] Specifically, King et al. analyzed 122 patients with pathologically negative lymph nodes with a median follow-up > 5 years. Thirty-eight patients received a median dose of 60 Gy to the prostate bed and 84 patients received a median dose of 70 Gy. Sixty-eight patients received four months of androgen suppression therapy and 72 patients received whole-pelvic RT. The authors observed a significant dose response from 60 to 70 Gy (25% vs 58% biochemical disease-free survival at 5 years, respectively; P < .0001). On multivariate analysis the two clinical factors that predicted improved biochemical-free survival were a pre-RT PSA level ≤ 1 ng/mL (HR 0.28, P <.0001), and no seminal vesicle involvement (HR 0.44, P = .009). Thus, this study suggests that higher doses may help increase the likelihood of optimal disease-free survival.

The dose of 70 Gy correlated with an increased dose of 6 Gy required for SRT vs ART, which King et al. argued in a separate manuscript was due to the additional disease burden carried by SRT patients vs ART patients.[27] In the absence of evidence that this additional dose causes worse late toxicities in patients undergoing SRT, a radiation dose in

the region of 70 Gy is reasonable.[28] Currently, the American Society for Therapeutic Radiology and Oncology (ASTRO) advises the use of the highest dose of radiation that can be delivered with acceptable morbidity (at least 64 Gy at conventional fractionation) for SRT.[50]

Hypofractionated radiotherapy (daily radiation doses of greater than 2 Gy) has been considered for SRT in a retrospective analysis of 50 patients.[51] Hypofractionated therapy is potentially desirable due to its shorter overall treatment length and theoretically higher biologically equivalent dose. Though toxicity and 2-year biochemical control rate appeared equivalent to published data for standard fractionation, additional follow-up and greater numbers of patients are needed before widespread adoption of this technique.

Hormone Therapy

The use of hormone therapy in combination with SRT is an area of controversy that will hopefully be clarified by three randomized trials: 1) The RTOG 96-01 trial, 2) The RTOG 05-34 SSPORT trial, and 3) The RADICALS trial. The RTOG 96-01 trial is a prospective randomized trial comparing postoperative RT with and without 2 years of bicalutamide 150 mg/day which has completed and should be presented in 2010.[52] The RTOG 0534 is an ongoing phase III trial of short-term androgen deprivation with pelvic lymph node or prostate bed–only radiotherapy (SPPORT) in prostate cancer patients with a rising PSA after RP. This 3-arm randomized trial is assessing prostate bed RT vs prostate bed RT with short-term androgen ablation vs pelvic and prostate RT along with short-term androgen ablation.[52] As noted previously, the RADICALS trial is a prospective trial with two randomizations. The first randomization will investigate immediate ART versus delayed SRT at the time of biochemical recurrence. Patients receiving RT will then be further randomized to RT alone, RT + 6 months of hormones, or RT + 2 years of hormones.[26] Although hormone therapy has been shown to improve overall survival in combination with EBRT for men with prostate cancer of intermediate- or high-risk disease, the value of hormone therapy has not yet been proven for men undergoing either ART or SRT.[53-55]

Side Effects and Toxicities Associated With Radiotherapy After Prostatectomy

Radiation treatment is the only potentially curative treatment available for most patients with biochemical failure after RP. However, some would argue that quality of life (QOL) is as important as survival. Despite the evidence in support of using RT in this setting, the decision to use it must take into account the side effects associated with treatment. There have been multiple reports of acute and late toxicities after post-operative radiation

therapy in prostate cancer. Overall, RT appears to be well-tolerated in patients undergoing ART and SRT, and lessons drawn from patients undergoing ART are therefore broadly applicable to SRT.

In the SWOG 8794 study, no patients had to interrupt their RT secondary to side effects, although grade 2 or greater complications were more common in the ART group than in the observation arm (23.8% vs 11.9%, respectively; *P* = .002).[13] Urethral strictures (17.8% vs 9.5%; *P* = .11), and rectal complications (3.3% vs 0%; *P* = .02) were the most frequent toxicities. In a companion health-related QOL study, 217 of 425 SWOG 8794 patients completed a questionnaire at baseline, 6 weeks, 6 months, and annually for 5 years.[56] The 6-week assessment was included to record side-effects at their peak at the end or RT. Not surprisingly, patients being treated with RT had a greater likelihood of a decline in bowel QOL at the end of RT as compared to the observation arm, but after 2 years, there was no significant difference between the two groups in bowel QOL. With respect to genitourinary QOL, patients in the ART arm experienced significantly more urinary urgency than those in the observation arm. However, there was no statistically significant difference in erectile dysfunction (ED), but given that the SWOG trial was performed prior to adoption of nerve sparing RP, > 90% of patients in both the ART and observation arms had severe ED, limiting the ability to comment on the effect of RT on erectile function in this patient population. Most noteworthy was that although global health-related QOL was worse in the ART group initially, it became similar by year 2, and at 5 years, patients in the ART group reported an overall better QOL compared to those in the observation arm. This is not surprising when taking into account the increased risk for metastasis and death as well as the burden of salvage and hormonal therapies among the patients in the "wait-and-see" arm.

In EORTC trial 22911, radiation treatment was interrupted as a result of toxic effects in 3.1% of patients, consisting of diarrhea, urinary frequency, proctitis, cystitis and anal pain.[12] Grade 2 or 3 late effects were significantly more numerous in the ART arm (*P* = .0005), but grade 3 toxicities were uncommon, with a 5-year rate of 2.6% in the observation arm and 4.2% in the ART arm (*P* = .0726). No grade 4 or higher late toxic effects were reported. In comparison to the EORTC 22911 and SWOG 8794 trials, the patients in the ARO 96-02/AUO AP 09/95 study had a significantly lower rate of severe (grade 3 and higher) toxicities at only 0.3%.[14] This relatively low rate of complications is likely due to the use of three-dimensional treatment planning, which is known to reduce acute and late toxicities for RT for prostate cancer.

In addition to the toxicity data from these randomized ART trials, there have been several assessments of complications following SRT. In a phase II prospective study by Pearse et

al., 75 patients with biochemical relapse or local recurrence after RP were evaluated for acute and late complications after SRT and 2 years of ADT.[57] Twelve percent of patients had gastrointestinal (GI) dysfunction and 40% had genitourinal (GU) dysfunction prior to receiving RT. Median follow-up was 45.1 months. No patients interrupted treatment secondary to side effects. Overall, 94% of patients experienced acute complications, but grade 3 toxicities were rare and the cumulative incidences for severe GI and GU toxicities were 1.6% and 2.8% at 36 months, respectively. There were no late grade 4 complications. Patients with preexisting GU dysfunction and acute GU toxicity were more likely to have persisting late GU toxicity. In addition, the more severe the acute GU toxicity, the more likely it was to persist.

Peterson et al. reported on late toxicities (those occurring more than 90 days after completion of radiation treatment) in 308 postprostatecomy patients who had undergone salvage therapy.[58] In the study, radiation dose ranged from 54.0 to 72.4 Gy with a median dose of 64.8 Gy and was given in 1.8-2.0 Gy fractions. Median follow-up from the end of treatment was 60 months. Thirteen percent of patients reported late complications, but only an estimated 0.7% (95% CI, 0.0–1.6%) of patients would experience severe (grade 3 or higher) toxicities by 5 years. Among those reported in the study were grade 3 cystitis and grade 4 rectal complications. These results are consistent with those of other reports, including data from the three recently randomized trials on ART.

Finally, as mentioned previously, Feng et al. reported on 959 patients who received ART or SRT, with a median dose of 64 Gy.[28] At 5 years, grade 3 urinary complications were observed in 1% of patients and grade 3 bowel complications were only seen in 0.3%, indicating excellent tolerance to ART and SRT. Similar toxicity was seen in a series from UCSD[42] and Germany,[59] which showed resolution of acute urinary symptoms without grade 3 toxicity. Long-term toxicity was rare, and health related QOL changes were minor in comparison to baseline scores. Together, these studies support a low incidence of severe toxicities in patients receiving RT after RP.

The Effect of Post-operative Radiation Treatment on Sexual Functioning

Of particular concern for many men is the issue of erectile dysfunction after prostate cancer treatment. Indeed, there have been many studies showing that men feel discouraged and emasculated by this sexual dysfunction.[60-63] It can take erectile functioning 18 months to 2 years to recover after prostatectomy, and radiation may further damage vascular structures in the penis.[64,65] It is unknown whether receiving RT before healing completely from surgery exacerbates the problem. In addition to avoiding

overtreatment of patients, SRT has the benefit over ART of allowing patients more healing time. Of course, this advantage must be weighed against decreasing chances of efficacy if RT is postponed for too long.[66]

Research on the post-surgical effects of RT on erectile functioning is in the beginning stages and results are ambiguous. In the companion SWOG health-related quality-of-life study described previously, there was no statistical difference in erectile dysfunction between the ART and observation arms.[56] However, more than 90% of patients in both groups experienced sexual side effects, and the ART group's erectile functioning was consistently lower. Although not statistically significant, these results may suggest that RT exacerbates erectile dysfunction in post-operative patients. In a study by Hu et al, men who received SRT after surgery had worse sexual functioning than men who had surgery alone.[67] However, this study had several limitations in that it was not randomized, and patients who received radiation treatment had higher risk features and a lower use of nerve-sparing radical prostatectomy, as compared to the surgery-only group. Therefore, the lower erectile functioning of the SRT group could actually be related to confounding factors. Formenti et al. reported on a prospective study in which 94 (37%) of 255 patients received 45-54 Gy of ART after prostatectomy.[68] Three years after surgery, there was no difference between the ART and observation groups with respect to sexual functioning. However, the strength of these results is limited because higher radiation doses are delivered in current clinical practice.

Cost-Effectiveness of Salvage Radiotherapy After Radical Prostatectomy

As described above, recent studies have demonstrated not only that RT after RP can significantly lengthen overall survival but also that it improves long-term QOL. Nevertheless, given the rising cost of health care it is worth assessing the overall cost of this treatment. Metastatic prostate cancer is associated with a substantial increase in costs and pain along with a significantly decreased quality of life. In the United States, the cost of treating all cancer patients with metastatic bone disease is approximately $12.6 billion.[69] In fact, treatment of a patient with prostate cancer metastatic to bone costs almost three times that of treatment of a patient with localized disease ($56,281 per patient vs $19,781 per patient).[69] In addition to direct medical costs incurred with the treatment of metastatic disease there is also significant indirect costs through the loss of patient and caregiver productivity. The National Institutes of Health estimates that the indirect morbidity (lost productivity due to illness) and indirect mortality (lost productivity due to premature death) costs for all cancers are $18.8 billion and $116.1 billion, respectively.[70] The most cost-effective approach to treatment, therefore, may not necessarily be the one that is associated with least direct medical costs but instead the one that provides the best

clinical outcome. With respect to prostate cancer, one study estimated the cost of local radiation with intensity modulated radiation therapy (eg, IMRT) in post-prostatectomy patients to be $27,080 and associated with a health utility of 0.909.[71] The costs of hormone therapy (ADT) and end-of-life care (including chemotherapy) were $9,000 and $30,000, respectively. Hormone therapy and end-of-life care states were also associated with decreased health utilities of 0.74 and 0.6, respectively, with utilities measured with the EQ-5 EuroQol quality of life instrument.[72] In addition, there are several studies indicating that salvage radiotherapy does not significantly decrease health-related QOL.[28,42,59] Therefore, with a conservative estimate of a 4 year 40%–50% progression-free survival for selected patients who undergo salvage radiotherapy compared to a 0–20% progression free probability, it is easy to see that salvage radiotherapy would be acceptable under the generally accepted $50,000/QALY cost-effectiveness standard. To our knowledge, a formal study of the cost-effectiveness of salvage radiotherapy compared to hormone therapy or best supportive care has not been performed.

Risk-Prediction Tools Can Improve Cost-Effectiveness of Salvage Radiotherapy Post-Prostatectomy

In order to minimize costs and prevent overtreatment with SRT, it becomes necessary to identify which patients would benefit from radiation post-prostatectomy. Approximately two-thirds of men who do not receive treatment for PSA recurrence after radical prostatectomy will develop metastatic disease within 10 years.[15] As local disease could be successfully treated with SRT, one important question is whether biochemical failure represents regional or disseminated disease. Currently, there is no imaging technique that is able to reliably detect sites of local recurrence in patients with low PSA levels. However, endorectal coil magnetic resonance imaging has recently emerged as a promising new technology to assess post-surgical patients who may have local failure. There are two major studies that have evaluated this technology's accuracy in recognizing local tumor relapse sites. In Silverman et al., sagittal and axial fat-saturated T2-weighted fast spin-echo images and axial T1-weighted unenhanced and gadolinium-enhanced eMR images were obtained in a prospective study of 41 post-prostatectomy patients.[38] They achieved a sensitivity and specificity of 100%, with biopsy-proven disease as the standard. In a retrospective study by Sella et al., T1- and T2-weighted sequences (without gadolinium administration) from 48 patients were reviewed, and a sensitivity of 95% and specificity of 100% was achieved.[39] Taken together, these studies suggest that endorectal coil MRI may be a useful risk-prediction tool when evaluating post-surgical patients for local recurrence of malignancy. Although promising in initial studies, endorectal coil MRI has not been prospectively validated for pre-SRT risk stratification, or routinely adopted at this time.

A number of studies have looked at clinical features that may predict a favorable clinical outcome with SRT. The reports from single-institutional studies with respect to prognostic features have been inconsistent, however, in a retrospective multicenter review by Stephenson et al. of 501 patients, the features associated with progression after SRT were a Gleason score of 8 to 10, a pre-radiotherapy PSA level greater than 2.0 ng/mL, negative surgical margins, PSA doubling time (PSADT) of 10 months or less, and seminal vesicle invasion.[73] Favorable patients were defined as those without any of these poor prognostic factors, and 70% of favorable patients remained progression-free 4 years after SRT. However, Stephenson et al. also revealed that certain patients with adverse features such as high-grade disease or rapid PSADT may still benefit from SRT. For instance, when treatment was given with PSA still < 2.0, if a patient had a rapid PSADT (<10 months), positive surgical margins, and Gleason scores between 4–7, 4-year progression-free survival (PFP) was 64%. For patients with Gleason 8-10 disease, but with a PSA < 2.0, positive surgical margins, and PSADT > 10 mos, 4-year PFP was 81%. These results suggest that if a patient elected to not receive ART in the immediate post-operative setting, then the benefit of SRT is likely greater even in the setting of higher risk features if SRT is administered upon first sign of biochemical recurrence.

Nomograms have been designed to predict the outcome of SRT based on several patient characteristics. In a separate study by Stephenson et al., they developed such a model using multivariable Cox regression analysis and a multi-institutional cohort of 1,540 patients.[25] The nomogram had a concordance index of 0.69. They found several features that should be taken into account when predicting the 6-year-progression-free probability after SRT in post-prostatectomy patients. These included PSA level < 2.0 ng/mL, Gleason score of 7 or less, PSA doubling time greater than 10 months, positive surgical margins, androgen-deprivation therapy before or during SRT, and the absence of lymph node metastasis. This nomogram has been externally validated by Moriera et al.[74] The validation study involved 102 patients from the Shared Equal Access Regional Cancer Hospital (SEARCH) database who were treated with SRT for PSA failure after surgery. Even though the cohort was composed of lower-risk patients as compared to the original series, the overall concordance index of the Stephenson nomogram was reasonable, at 0.65. These authors also found that though the nomogram successfully predicted failure at the extremes of risk, it was less accurate in the intermediate groups. Negative surgical margins and high preradiotherapy PSA level were the only nomogram variables that were significantly linked to disease progression.[74] Although the Stephenson nomogram is the best available prediction tool currently available to predict who will obtain long-term benefit from SRT, there is still significant room for improvement in this risk-prediction model.

Conclusion

The treatment of prostate cancer that has recurred months or years after radical prostatectomy is an evolving field, and multiple consensus guidelines and prognostic features exist to help the clinician make a decision regarding treatment fields and likelihood of efficacy. Though there are multiple randomized trials supporting the use of ART in the immediate post-prostatectomy period for high-risk disease, similarly strong data are lacking in the salvage setting. However, the rate of serious complications has been low in patients undergoing SRT, and there are multiple retrospective studies showing a subset of patients who are likely to benefit. Although there have been no studies that address the specific question of whether SRT is cost-effective, extrapolating on available data, we believe that SRT is cost-effective in selected patients who are likely to benefit based on MRI findings of local disease or the Stephenson nomogram.

While the decision to use SRT should be based on the patient's personal wishes, clinical status, and ability to tolerate side effects, our general recommendation is that patients with long-life expectancies and PSA relapse of at least 0.2 ng/mL should have a discussion with a radiation oncologist regarding the utility of salvage radiation as soon as possible. Patients with a Gleason score of 7 or less, with a PSA as close to 0.2 ng/mL as possible, a history of a positive surgical margin without involvement of the seminal vesicles, and PSA doubling time greater than 10 months are likely have the best prognosis. Further questions regarding the comparison of delayed SRT to immediate ART, and the utility of hormone therapy will hopefully be answered in the currently accruing RADICALS trial,[26] while the North American SPPORT trial will help address the issues of field-size and the benefit of concurrent hormonal therapy in men undergoing SRT. Results from RTOG 96-01 should be reported in 2010, providing more information about the utility of hormone therapy in combination with SRT.

This article is reviewed in the following articles:
Who, When, Where, and How: Salvage Prostate Cancer With Radiotherapy
Deciding Which Patients to Treat With Salvage Radiotherapy After Prostatectomy

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