Salvage options for biochemical recurrence after primary therapy for prostate cancer

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Despite excellent success rates with radical prostatectomy and radiotherapy for the treatment of prostate cancer, a significant number of patients will experience a rise in their serum prostate specific antigen (PSA) level. A variety of salvage options in this scenario have been investigated and the choice to pursue surveillance, single therapy or combination therapy depends on clinical assessment of risk and location of tumor recurrence. After radical prostatectomy, for example, patients with low risk local disease may not require secondary therapy or may benefit from salvage radiotherapy. Those with higher risk disease, based on PSA kinetics and tumor pathology may require systemic androgen deprivation therapy (ADT) with or without radiotherapy. Local recurrence after radiotherapy has the options of cryotherapy, brachytherapy or salvage surgery. ADT can also be applied in these patients at high risk of disease progression and cancer-specific mortality. Risk assessment in these settings is paramount as all secondary therapy options for prostate cancer have potential side effects that may significantly affect quality of life. We review the literature and discuss the current methods of risk assessment and the treatment options in prostate cancer once primary therapy fails.

Key Words: prostate cancer, radical prostatectomy, radiotherapy, salvage therapy, PSA recurrence, biochemical recurrence, locally advanced

Introduction

Continued advancements in radical prostatectomy techniques, radiotherapy technology and patient selection for primary curative treatment have improved the management of prostate cancer. Despite these advances, a significant proportion of patients will experience biochemical recurrence (BCR) in serum prostate specific antigen (PSA). As treatment options for a rising PSA after primary therapy vary, the clinician must assess for local versus metastatic extension as well as risk of prostate cancer-specific death. Those with high risk disease may benefit from aggressive secondary combined therapies while those with low risk disease may be more likely to die from unrelated causes and can therefore avoid the potential morbidity of salvage therapies. These considerations combined with patient factors such as lifestyle, age and comorbidities at the time of recurrence present a challenging scenario for the clinician. This article reviews the current treatment options available for patients with prostate cancer who experience BCR after radical prostatectomy or radiotherapy.

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PSA relapse after radical prostatectomy

Observation

In modern series, BCR after radical prostatectomy for clinically localized prostate cancer occurs in 15%-20% of patients within 5 years.[1-4] After PSA relapse, 34% will develop metastatic progression at a median of 8 years (following BCR) and of these, 43% will die of prostate cancer after an additional 5 years.[2] On average, prostate cancer is one of the more indolent adenocarcinomas in terms of progression to metastases and death as 10-year overall survival in post-prostatectomy patients with BCR is only 5% less than those without PSA relapse (88% versus 93%, respectively).[5] Patients who are older, have significant comorbidities or have low risk disease at the time of recurrence may take advantage of this aspect and elect not to pursue salvage therapy. This option may benefit the patient long-term as all secondary therapies have potential quality of life-altering side effects, which may be avoided in those who are unlikely to die from their disease.

Assessing patient risk has recently been refined by Freedland et al using updated Johns Hopkins data initially reported by Pound.[6] In this retrospective series of 379 men with BCR who had PSA doubling time data after radical prostatectomy, the authors demonstrated that pathology Gleason score (≥ 8 versus < 8), time from surgery to BCR (≤ 3 years versus > 3 years) and PSA doubling time (PSADT) were statistically significant predictors of prostate cancer-specific mortality. PSADT was the strongest predictor and patients with a PSADT less than 9 months were very likely to die from prostate cancer. Conversely, a patient with a late recurrence, low Gleason score and a PSADT of ≥ 15 months carries only a 6% risk of dying from prostate cancer within 15 years and may avoid additional therapy. Using these predictors, Dr. Freedland produced tables listing 5-, 10- and 15-year risk estimates for prostate cancer death which can be used by the clinician and patient to determine risk and the need for subsequent therapy.[6]

Salvage external beam radiotherapy

Results from clinical trials looking at applications of radiotherapy indicate that the predominant pattern of biochemical failure after prostatectomy, even in those with high risk pathologic features, is local.[7-9] Therefore, a localized secondary therapy such as salvage external beam radiotherapy (RT) may be a viable option after prostatectomy. Stephenson et al showed that when salvage RT is administered when PSA relapse is ≤ 2 ng/ml, 4-year progression-free survival ranged from 18%-81% depending on Gleason score, margin status and PSADT.[10] Those with positive margins and PSADT > 10 months had the highest response rates. In a recent update, they demonstrated that even in patients with high risk features (PSADT ≤ 10 months, Gleason 8-10) typically considered harbingers of metastatic disease, 41% were disease free at 6 years when salvage RT was given before PSA level reached 0.5 ng/ml.[11] The number of patients in this subset was small, but the data illustrates the potential role of salvage radiotherapy in high risk patients when administered early.

Salvage hormone therapy

Few studies have been performed looking specifically at salvage hormonal therapy after radical prostatectomy. In a randomized prospective trial of post-prostatectomy patients with node-positive disease, Messing et al demonstrated a survival benefit to adjuvant androgen deprivation therapy (ADT) when compared to salvage ADT given at the time of boney metastases.[12,13] Wirth et al performed a similar randomized trial comparing adjuvant flutamide 750 mg to observation in node-negative patients after prostatectomy. Although there was a significant improvement in biochemical-free survival, there was no detectable difference in overall survival at a median of 6.1 years.[14] Salvage ADT for PSA-only recurrence was studied by Moul in a retrospective analysis of 1352 patients.[15] Despite starting ADT (LHRH, LHRH + anti-androgen, or orchiectomy) at a PSA level ≤ 5 ng/ml, there was no overall improvement in development of clinical metastases when compared to delayed administration of ADT. In patients with Gleason 8-10 disease or a PSADT < 12 months, however, early ADT significantly delayed the development of metastases by approximately 2 years when compared to late or no ADT. McLeod et al, on the other hand, reported on the combined Early Prostate Cancer trial program, which although showing a significant benefit in progression-free survival, failed to show an overall or cancer-specific survival benefit with the addition of adjuvant bicalutamide 150 mg to prostatectomy patients, including those with locally advanced disease (pT3-4 or node positive).[16] The prospective trials evaluating hormone therapy after radical prostatectomy are summarized in Table 1. Further studies are required to determine the role of ADT as a salvage monotherapy, which agent is most effective and when it is best administered.

Salvage radiotherapy combined with hormone therapy

To date, there are no published randomized controlled trials assessing the addition of hormone therapy to salvage radiation in post-prostatectomy patients. RTOG

TABLE 1. **Randomized prospective trials assessing benefit of adjuvant hormone therapy when combined with radical prostatectomy**

Trial	No. Pts	Treatment arms	Duration HT	Median F/U years	Overall survival benefit	p value
Radical Prostatectomy						
ECOG 7887[12,13]	98	Immediate goserelin or ochiectomy versus same deferred	Lifelong	7.1 11.9	20% 19%	0.02 0.04
Wirth et al[14]	309	Flutamide versus no adjuvant treatment	Lifelong	6.1	None	0.92
EPC 23,24,25[16]	4454	Bicalutamide (150 mg) versus no adjuvant treatment	Max 5 years	7.4	None	0.51

HT = hormone therapy; ECOG = Eastern Cooperative Oncology Group; EPC = Early Prostate Cancer

96-01 is investigating salvage RT versus RT plus bicalutamide in 800 patients with extracapsular extension or seminal vesicle involvement and PSA relapse after prostatectomy. This trial closed in 2003 and results are expected soon. A new international trial termed RADICALS (Radiotherapy and Androgen Deprivation in Combination after Local Surgery) is seeking to enroll over 4000 subjects to investigate adjuvant versus salvage RT in combination with nothing, 6 months or 2 years ADT.[17] Until these studies are completed, our understanding on the use of combined salvage therapy after prostatectomy is limited to retrospective data and the trends seen in adjuvant trials.

In a retrospective study by Katz involving 115 patients with post-prostatectomy PSA recurrence, ADT increased the PSA relapse-free survival 20% when combined with salvage RT compared to RT alone (59% versus 39%, respectively).[18] When these patients where stratified by predictors of PSA failure after salvage RT, those with one or more risk factors had a significant improvement in PSA control with the addition of neoadjuvant ADT ($p = 0.03$). The risk factors noted which may necessitate additional ADT were Gleason score 8-10, absence of extracapsular extension, seminal vesicle invasion, negative margins and a PSA > 0.6 at initiation of RT. Other retrospective reports have shown an increased survival benefit with adjuvant hormone therapy when applied to patients with high risk disease, including those with positive lymph nodes.[19-21]

Several prospective randomized trials have examined the benefit of adding hormone therapy to primary external beam radiotherapy and are listed in Table 2.[22-26] All trials showed significant improvements in either biochemical progression-free survival, local failure, metastatic development, overall survival and/or cancer-specific survival with the addition of adjuvant hormone therapy to RT. RTOG 86-01, however, failed to reach statistical significance despite a 9% survival benefit and TROG 96-01 reported no difference in overall survival in either group receiving adjuvant ADT.[24,26] Although these studies involve primary RT and overall survival benefits are meager (0%-16% at approximately 6 years), they clearly demonstrate improved disease control in high risk patients when ADT is added to radiotherapy. Hopefully, these benefits will apply to the salvage setting as well.

The duration of ADT required to achieve maximal benefit is unknown. The CUOG and TROG 96-01 studies compared different short-term regimens of neoadjuvant hormones combined with primary RT and failed to show a difference in overall survival, Table 2.[26,27] After 4 months of neoadjuvant hormones and radiotherapy, RTOG 92-02 examined an additional 2 years of goserelin versus no therapy.[28] This study reported a significant 10% improvement in overall survival at 6 years favoring longer therapy, but only in a subset of higher risk patients with Gleason score 8-10. In a pooled analysis of 311 high risk patients with advanced age (median 70) from three randomized prospective trials, the use of 3 years ADT was not associated with prolonged survival when compared to 6 months ADT.[29] Bolla, however, recently reported early results from EORTC 22961 at the 2007 ASCO Annual Meeting. In this study

TABLE 2. **Randomized prospective trials assessing benefit and duration of adjuvant hormone therapy when combined with external beam radiotherapy**

Trial	No. Pts	Treatment arms	Duration HT	Median F/U years	Overall survival benefit	p value
Radiotherapy						
RTOG 85-31[22]	977	Immediate versus deferred goserelin	Lifelong	7.6	10%	0.002
EORTC 22863[23]	385	Goserelin versus no adjuvant treatment	3 years	5.5	16%	0.0002
RTOG 86-10[24]	456	Goserelin plus flutamide versus no adjuvant treatment	4 months	6.7	9%	0.1
D'Amico et al[25]	206	LHRH plus flutamide versus no adjuvant treatment	6 months	4.5	10%	0.04
TROG 96-01[26]	802	Goserelin plus flutamide versus no adjuvant treatment	3 or 6 months	5.9	No difference (3% CSS in 6 months versus no treatment	n/a 0.4
Comparing HT duration						
CUOG[27]	361	Goserelin plus flutamide, 3 months versus 8 months neoadjuvant	3 versus 8 months	3.7	3%	0.13
TROG 96-01[26]	802	Goserelin plus flutamide, 3 months versus 6 months neoadjuvant	3 versus 6 months	5.9	No difference	n/a
RTOG 92-02[28]	1514	Neoadjuvant goserelin plus flutamide alone (4 months) versus additional goserelin (24 months)	4 versus 28 months	5.8	1.5% (10.3% in Gleason 8-10)	0.73 0.04

HT = hormone therapy; CCS = cancer-specific survival; LHRH = luteinizing hormone-releasing hormone; RTOG = Radiation Therapy Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; TROG = Trans-Tasman Radiation Oncology Group; CUOG = Canadian Urologic Oncology Group

comparing 6 months to 3 years ADT after primary radiotherapy, the short course of ADT was statistically inferior with respect to biochemical-free, progression-free and overall survival at a median 5.2 years.[30]

Pending results of RTOG 96-01 and similar trials, the benefit of adding hormone therapy to salvage radiotherapy for PSA relapse after prostatectomy is unclear. In the meantime, combination therapy with a minimum of 6 months ADT seems appropriate only for those with high risk pathologic features and/or PSADT less than 9 months. Additionally, as these patients are at increased risk for nodal involvement, whole-pelvic versus prostate bed-only radiotherapy should be considered.[31-33]

PSA relapse after radiotherapy

Assessing recurrence and risk

Depending on pretreatment clinical risk factors and radiation dose, approximately 10% to 60% of men treated with definitive radiotherapy for prostate cancer will experience biochemical recurrence.[34-37] Despite increased efficacy with dose escalations to 81 Gy using newer intensity-modulated radiotherapy techniques, approximately 25% of those with moderate- or high-risk disease suffer a PSA relapse. [38] A significant percentage of patients with BCR after radiotherapy are at risk for prostate cancer-specific death within 5 years.[39] Some of these recurrences will be organ confined and therefore

amenable to local salvage therapy. In patients who have received radiotherapy for prostate cancer, however, the task of assessing risk, locality and even defining PSA recurrence is more challenging than in post-prostatectomy patients.

PSA changes after radiotherapy can make diagnosis of local failure problematic, as 10% to 30% of patients exhibit PSA "bounces" within 3 years after radiotherapy and may take up to 18 months to normalize.[40,41] Distinguishing these benign PSA elevations from true recurrence has made defining BCR difficult. The definition of PSA recurrence after radiotherapy was recently updated from a Consensus Conference sponsored by the American Society for Therapeutic Radiology and Oncology (ASTRO) and the RTOG in 2005.[42] The panel recommended defining recurrence as a PSA rise of 2 ng/ml above the PSA nadir after external beam radiotherapy with or without hormonal therapy.

A large proportion of radiation failures will include local involvement as 60% to 70% of patients with BCR after radiotherapy and a negative metastatic work-up have a positive prostate biopsy.[43,44] Several imaging techniques have been applied in this setting to improve detection of metastatic disease, including PET and capromab pendetide (Prostascint) scanning. While initially favorable, especially in the case of capromab pendetide using fused CT imaging, results vary and the utility of these modalities is yet to be determined.[45-48]

As with prostatectomy patients, risk of prostate cancer mortality correlates highly with PSADT. Lee et al noted that a PSADT ≤ 8 months in patients treated with combined hormone and radiation therapy correlated with poor survival (29.7% overall at 6 years) compared to 79.1% in those with PSADT > 8 months (HR 5.6).[49] Similar results were obtained by D'Amico in patients with recurrence after radiotherapy alone, and PSADT was most predictive of cancer-specific mortality when < 3 months (HR 12.2).[50] The authors also demonstrated that a patient with a PSADT > 12 months has a 15.9%, 30.5% and 39.6% cancer-specific mortality risk at 5, 8 and 10 years, respectively. These values were double those reported for their prostatectomy cohort, indicating that observation for PSA relapse after radiotherapy may be a riskier option than when applied to post-prostatectomy patients.

Salvage radical prostatectomy

Salvage radical prostatectomy after radiotherapy is a technical challenge performed only by a subset of urologists. Normal tissue planes between the prostate and rectum are lost and most specimens exhibit significant anterior and lateral fibrosis.[51] As a result of these tissue changes, rectal injury and urethral stricture rates can be as high as 28% in experienced hands.[52]

Surgery can, however, achieve 44%-80% disease-free survival at 5 years depending on clinical risk factors.[53-55] In a series by Sanderson with 51 patients, favorable prognostic factors such as pT2N0 disease, pre-operative PSA ≤ 5 ng/ml, or Gleason score ≤ 7 yielded a 5-year progression-free survival of 100%, 80% and 67%, respectively.[56] Alternatively, those with positive lymph nodes, PSA > 10 ng/ml or Gleason score ≥ 8 fared poorly with progression-free survivals of 0%, 9% or 17%, respectively. None of the 51 patients experienced disease progression after 5 years. Bianco observed a similar relationship with pre-operative PSA citing an 86% 5-year disease-free survival if PSA was less then 4 ng/ml, compared to 28% for PSA > 10 ng/ml.[55] Studies with longer follow up cite a 65%-77% cancer-specific survival at 10 years.[53,55,57]

Salvage prostatectomy, therefore, provides excellent cancer control in properly selected patients and currently appears to offer the best chance for cure if patients have failed primary radiotherapy. It remains, however, the most technically challenging salvage option and is offered only by a fraction of urologists who perform primary radical prostatectomy. The rate of major complications has decreased in contemporary series from 33%-13%, but continues to have a significant impact on quality of life and must be factored into the decision process.[58]

Salvage brachytherapy

Reviewing retrospective data based upon small numbers of patients, disease specific survival in patients who undergo salvage brachytherapy is approximately 50% at 5 years.[59,60] As with radical prostatectomy, clinical risk factors at the time of brachytherapy are predictive of outcomes. Disease-free survival ranges from 30%-83% depending on Gleason score (≤ 6 favorable) and PSA (< 10 ng/ml favorable).[61] Major complications are observed less frequently in salvage brachytherapy compared to surgery and include urinary incontinence (6%-31%), pelvic pain (6%), urethral strictures (3%) and rectal injury (0%-15%).[59]

Salvage cryotherapy

Salvage cryotherapy for radiorecurrent prostate cancer has been explored as a less invasive, outpatient alternative to radical prostatectomy. Recent technical advances including urethral warmers, perineal mapping and smaller, gas-driven probes have reduced the complications of urethral sloughing and stricture,

rectourethral fistula and incontinence.[59,62,63] Whether these changes have an effect on established cancer control rates will need to be determined with further follow up. However, overall survival at 5 years following salvage cryotherapy ranges from 73% to 97%.[64,65] The only series to cite 8-year data had a 92% overall survival.[64] Similar to other salvage options mentioned above, patient selection and clinical variables strongly affect outcomes. In the series by Ng which included 187 patients, a pre-operative PSA < 4 ng/ml was associated with a 5-year biochemical recurrence-free survival of 56% compared to 14% in those with a PSA > 10 ng/ml.[64] Gleason score (6 or less versus 7 or greater) was the only other significant predictor of recurrence (HR 0.51).

Another study of 131 patients demonstrated that precryotherapy PSA, Gleason score, clinical stage and androgen-independent recurrence have an impact on biochemical failure.[65] Five year disease free survival rates were significantly increased in patients with a PSA less than 10 ng/ml (p = 0.0004), clinical stage T2 or better (p = 0.0041), Gleason score 8 or less (p = 0.012) or in those who had received hormone therapy with initial radiotherapy (p = 0.001).

In an older retrospective study comparing salvage cryotherapy to salvage prostatectomy in patients matched for PSA and Gleason score, 67% of the cryotherapy cohort experienced BCR compared to 29% of the prostatectomy patients (p = 0.0002).[66] This disparity is difficult to interpret as the cryotherapy cohort fared must poorer than those reported in other series.[63,64] More studies are required to determine if cancer control rates are truly dissimilar between the two salvage modalities and if this difference translates into a survival benefit favoring prostatectomy.

Hormone therapy

The benefit of hormonal therapy has been previously discussed, but the question of when to start hormone therapy in patients that have BCR after primary therapy has not been established. Messing demonstrated a survival benefit to early HT in prostatectomy patients with node-positive disease[13], but this has not been observed in node negative patients.[14,15] To address this issue in patients who have been administered radiotherapy, Shipley analyzed the subset of RTOG 86-10 patients who subsequently received salvage HT (54% of study, 247 patients).[67] For those patients with distant metastases at the start of salvage HT, overall survival was significantly reduced compared to those without metastases at the time of HT (31% versus 58% at 8 years). In the patients who received salvage HT without metastatic disease, however, overall survival was not significantly influenced by PSA at the initiation of HT (< 20 ng/ml versus > 20 ng/ml, p = 0.06). These data suggest that earlier treatment with salvage hormone therapy may improve survival, but when to start HT within biochemical failure only status is yet to be determined.

Summary

For patients with a rising PSA after radical prostatectomy or radiotherapy for prostate cancer, several salvage options exist. The choice for observation, local salvage therapy, systemic hormone therapy or a combination of the latter depends on clinical risk assessment. For both prostatectomy and radiotherapy failures, PSADT appears to be the most predictive clinical tool for prostate cancer mortality. Risk should be assessed early after PSA relapse as all salvage options appear to have improved cancer control with lower serum PSA values. In general, patients with biochemical recurrence experience relatively prolonged survival and the choice to pursue salvage therapy needs to be weighed against the potential side effects that can significantly affect quality of life.

Disclosure

Dr. Thomas Keane is a member of the Speakers' Bureau for AstraZeneca, Cytogen Corporation, Auxilium Pharmaceuticals and Sanofi-Aventis. He is on the advisory board for Sanofi-Aventis, and has done research for Cytogen Corporation. □

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