Treatment of radiation failure in prostate cancer

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Radiotherapy, both external beam and more recently, interstitial, have been therapeutic options for localized prostate cancer. Management of patients who have failed of local radiotherapy remains a challenge. Herein the current therapeutic options are reviewed.

Key Words: prostate cancer, radiotherapy, prostate-specific antigen

Radiotherapy, both external beam and more recently, interstitial, have been therapeutic options for localized prostate cancer. Management of patients who have failed of local radiotherapy remains a challenge. The nadir of serum prostate-specific antigen (PSA) levels is prognostic. PSA nadir above 1 or 1.5 ng/mL is associated with poor long-term disease control.[1,2] Various definitions of failure after radiation therapy have been used including the ASTRO definition (three consecutive rises in PSA, dating back to the midpoint between the nadir and the first rise in PSA following radiation) and modifications thereof.[3] Other definitions include the PSA reaching the nadir plus 2 or simply PSA exceeding 0.5.[4,5] Although the ASTRO definition had been widely used there had been some criticisms regarding its utility. The decision on management depends on numerous factors and range from early aggressive local extirpative surgery to 'delayed' endocrine therapy when metastases become evident.

A rising PSA after definitive radiation therapy precedes clinically detectable disease typically by 3 to 5 years. Without definitive local salvage therapy, at least 75% of patients will have clinical evidence of recurrent disease 5 years after the PSA elevation has been detected.[6,7] A wide range of prevalence of biochemical failure after radiation failure has been quoted but the range of 20%-30% is generally accepted 5 years after external beam,[8] and 10 years following brachytherapy.[9]

The management options include potentially curative therapy such as salvage prostatectomy, brachytherapy, and cryosurgery. As well there are some investigative modalities. Non-curative therapies include hormone therapy and chemotherapy. Considerations for the choice of therapy include the

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patient's age, co morbidities, current and projected quality of life, morbidity of the proposed therapy and patients' preference.

Salvage radical prostatectomy

The outcome of salvage radical prostatectomy depends on the likelihood of localized disease versus occult distant disease. Features suggestive of the former include a long PSA doubling time, and a long disease-free interval since radiation. Other favorable parameters include pre-radiotherapy PSA of less than 10 ng/mL,[10] pre-operative PSA less than 10 ng/mL[11] and low stage disease. Regardless of local salvage modality, meticulous patient evaluation is of paramount importance.

Thorough transrectal ultrasound guided biopsy targeting the seminal vesical and peri-prostatic tissue should be performed to document the local extent of disease. Detailed imaging should include computerized tomography of the abdomen and pelvis and possibly magnetic resonance imaging. A bone scan, regardless of PSA level, should be performed. The patient should also have a cystoscopy and urodynamic assessment to assess the extent of radiation damage, bladder capacity, status of the external sphincter, and whether salvage cystoprostatectomy should be considered. A recent report on the value of endo-rectal MRI for preoperative assessment appears promising for tumor localization and prediction of extracapsular extension and seminal vesical involvement.[12]

Several series in previous years have reported biochemical "no evidence of disease" (NED) rate of approximately 30%-60% at 5 years. Generally with PSA less than 10 ng/mL pre-operatively, the biochemical NED rate was 65% whereas with PSA greater than 10 ng/mL pre-operatively, only 15% had biochemical NED.[13] Of notable difference are the most recent series from Memorial Sloane Kettering Cancer Centre (MSKCC) and the Mayo Clinic with improved results. With the pre-operative PSA < 4 ng/mL, the progression-free probability was 86% with median progression free interval of 6.4 years in the MSKCC.[14-16] In the Mayo Clinic series of 199 patients, cancer specific survival was 65% at 10 years while progression-free survival was 7 years for salvage radical prostatectomy.[17] In spite of the detailed pre-operative assessment, there was significant under-staging with only 30% of the final pathology showing organ-confined disease. Complications of salvage prostatectomy were very significant in the earlier series with substantial blood loss averaging 1 liter, rectal injury at 6%-7%, bladder neck contracture approaching 20% and incontinence 40%-50%. The updated MSKCC series of 100 patients reported significant decrease in major complication rate, from 33% in 1984-1992, down to 13% in 1993 - 2004 (p value 0.02).[14-16] Rectal injury is now uncommon at 2%, compared to 15% for the previous decade. Close to 70% of patients have satisfactory continence, and in previously potent patients, 45% reported satisfactory post-operative sexual function. Similarly, the Mayo Clinic series report pad-free continence at 50% and an additional 20% of patients require only one pad per day.[17] In summary, salvage radical prostatectomy is now a technically safe procedure for the properly selected patients. Patients with low stage disease who are younger and have good performance status are the most suitable candidates. Understaging is still relatively common. Patients should be forewarned of the possibility of incontinence, rectal injury with possible temporary fecal diversion. The ideal candidate for salvage prostatectomy should have a life expectancy of at least 10 years with good aesthetic risk, and lower stage disease.

Salvage brachytherapy

Two small series (17 and 49 patients respectively)[18,19] reported the use of brachytherapy in a salvage situation after external beam radiation. The salvage rate was dependent on the PSA and grade of disease. Prognosis was best with PSA < 1 ng/dL, with 67% disease-free survival. Complications relate mostly to urinary function and rectal ulceration. Incontinence, hematuria and need for transurethral resection of the prostate were not infrequent.

Salvage cryosurgery

Salvage cryosurgery theoretically has advantages as a minimally-invasive procedure with negligible blood loss and should be better tolerated with older candidates with comorbidities. As well, limited extraprostatic disease can be targeted and treated. The outcome of a larger series included the MD Anderson cohort with 40% biochemical NED rate with a follow-up of 4.8 years[20] Chin et al also reported on 40% biochemical NED rate on 118 patients with a shorter follow-up of just under 2 years.[21] Other smaller series with a follow up of 2 years or less have higher rates of disease-free survival. Chin et al recently updated their series of 187 patients with follow-up of 8 years and the biochemical recurrent-free survival was 37% for

those with PSA less than 4 ng/mL at the time of cryosurgery. For those with PSA between 4 to 10 ng/mL, the 8 year biochemical recurrence-free survival was 24% (Unpublished data). The complication rates are listed in Table 1. The incidence of incontinence has improved to under 10% except for patients who have had prior transurethral resection of the prostate. Rectal urethral fistula, the most dreaded complication, should be under 5% for the properly-selected patient population. The use of a proper urethral warming device has decreased the incidence of urethral damage such as stricture disease and tissue sloughing.

The response rate of salvage cryoablation depends on the definition employed and the level of PSA cut-off. Our group has also performed serial biopsy after cryoablation at 6, 12, and 24 months.[22] The median follow up was 60 months. Approximately 20% had positive biopsies indicating local treatment failure. Repeat cryoablation is a possibility although potential complications such as incontinence and fistula formation are more likely. The biochemical failure rate, as noted earlier, is higher than the histologic failure rate, implying occult distant disease in these patients.

Bahn et al reported biochemical disease-free rate of 59% at about 60 months.[23] Donnelly et al reported 2-year biochemical disease-free rate of 44%.[24] As with salvage prostatectomy, the prevalence of complications has decreased significantly with more experience, improved technology and improved patient selection.

One concern of cryoablation is the finding noted both by Adel et al and Chin et al where serial biopsies revealed viable benign tissue persisting over several years after cryoablation.[20,22] Up to one third of biopsy cores had revealed viable, albeit benign tissue. The obvious concern was subsequent or co-existing undetected viable malignant tissue.

The finding by Chin et al on the percentage of biochemically disease-free patients as a function of PSA cut-off points, indicate that two thirds of patients still had a PSA under 4 in 5 years and over 50% had PSA's under 2 at 5 years.[21] The majority of these patients, even though they may be considered as biochemical failure, would not have started on hormone therapy until later (32% of patients started on hormone therapy, at a mean delay of 31 months), which would represent a meaningful deference in instituting hormone therapy and avoiding associated adverse effects.

The ideal candidates for salvage cryoablation, as with salvage radical prostatectomy, include patients with a life expectancy of at least 10 years. The pre-cryoablation PSA should be less than 5 ng/mL and Gleason score less than 8. In addition those patients who are considered less ideal for salvage prostatectomy based on medical considerations may still be candidates for salvage cryoablation.

TABLE 1. **Complications of salvage cryoablation (percentage)**

	1994-1999	**2000-2005**
Incontinence	75%	5%-30%
Erectile dysfunction	75%	70%-80%
Fistula	2%	2%-5%
Sloughing tissue	22%	5%-10%
Lower urinary tract symptoms (surgery required)	67% (17%)	30%-40% (10%)
Perineal pain	18%	3%-5%

Investigative modalities

Investigative salvage modalities include interstitial photodynamic therapy, high intensity focused ultrasound (HIFU), and ferromagnetic thermal ablation. Photodynamic therapy with a phyto-compound UST09 as a potent photo sensitizer has been reported.[25] Interstitial laser fibers are inserted via a brachytherapy template and intravenous UST09 is injected. Significant prostate tissue necrosis and PSA changes had been noted in some patients. Preliminary results from phase I study with 25 patients have led to a planned phase II trial.

High intensity focused ultrasound has been used, mostly as primary therapy, in several centers. A percentage of patients have had prior external beam radiotherapy.[26] Experience is still somewhat limited with incontinence and fistula formation being the main concern. Further efforts are underway to assess this modality.

Ferromagnetic thermal ablation using permanently implantable cobalt and palladium 'thermorods' produce therapeutic heat levels of 70 degrees centigrade with magnetic field oscillation by the Currie effect. The rods are implanted transperineally with a pre-plan as per brachytherapy. Short follow-up on a small number of patients appears promising.[27]

Summary

For definitive salvage therapy, meticulous patient selection is of paramount importance. Salvage

radical prostatectomy and salvage cryoablation are both accepted therapies and the selection of modality should be based on patient characteristics including age, comorbidities, and patient preference. Several new technologies on the horizon, are being evaluated. □

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