Review Article

Narrative review of principles of salvage radical prostatectomy

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Abstract: Prostate cancer remains a common diagnosis and cause of death for men in the US that will affect more than one in ten men at some point in their lives. At presentation, some men will have locally advanced or metastatic disease. Of those men with localized disease who elect treatment with curative intent including radical prostatectomy, radiation therapy (RT), or novel local therapies approximately one third of men will suffer recurrence of their disease which is most often diagnosed via biochemical recurrence (BCR) of prostate specific antigen (PSA). Salvage treatment can potentially lead to long-term cure in certain properly selected patients. Patients should be evaluated for possible salvage radical prostatectomy (SRP) with estimation of life expectancy and evaluation for distant disease via a variety of advanced imaging options including CT, bone scan, or MRI. Once patients are diagnosed with local disease recurrence confirmed via prostate biopsy, salvage therapies including SRP may be offered. Patients should be referred to surgeons with adequate experience performing salvage radical prostatectomies and counselling should include discussions about surgical approach and oncologic outcomes as well as functional outcomes. Salvage prostatectomy is associated with significant quality of life impact and adverse events including incontinence, erectile dysfunction, anastomotic strictures, fistulas, and rectal injury.

Keywords: Prostate cancer; biochemical recurrence (BCR); salvage prostatectomy

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Introduction

In 2019, there were an estimated 174,650 new cases of prostate cancer and 31,620 deaths from prostate cancer in the US. More than one in ten men will be diagnosed with prostate cancer at some point in their lives. Of these patients, 13% will present with spread to regional lymph nodes and 6% will have metastases at presentation (1). As aggressiveness of prostate cancer varies widely, treatments must be tailored to the patient, stage of cancer, and grade group or Gleason score. However, for men with localized prostate cancer, management can include active surveillance, radical prostatectomy, radiation therapy (RT) (in the form of brachytherapy, intensity modulated radiotherapy, proton therapy, or stereotactic body radiotherapy), or novel forms of focal therapy (cryotherapy and high intensity focused ultrasound). For men electing treatment with curative intent (surgery or radiation), up to one-third of men will suffer recurrence of their disease (2). For these men, additional local therapy has the potential to salvage this failure of biochemical control into long-term cure.

Among men who have completed surgery, the role of salvage radiation has been well described in multiple phase III clinical trials (3,4). Conversely, the management of RT failures is more challenging, as salvage radical prostatectomy (SRP) is a procedure described in low levels of evidence and associated with a high risk of morbidity (5). Indeed, 90% of men with biochemical failure after radiation receive androgen deprivation therapy (ADT) for control as opposed to cure (6). However, there is evidence of a benefit from SRP in select men, with durable survival in 70–80%

of men (5). With increasing utilization and description of focal therapy, the use of both salvage radiation and salvage surgery has been described.

In this review, the evaluation and selection of candidates for SRP after RT will be outlined along with the principles of surgery in these men. Where there are important differences in the management among men considering salvage after focal therapy, these differences will be reviewed. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/amj-20-60).

Biochemical recurrence (BCR) after primary RT or focal therapy

The first step in the identification of men for salvage prostatectomy is identification of recurrence. Currently, BCR represents the first signal of a potential local failure of therapy. For men who have undergone RT, BCR is defined as a rise by 2 ng/mL or more above the nadir prostate specific antigen (PSA) in the most utilized Phoenix criteria. The Phoenix definition has been shown to be a significant predictor of overall mortality, cause-specific mortality, and distant metastases thus accounting for its widespread use.

However, not all patients with BCR will have clinically meaningful progression or even mortality. In a study of 2,694 men treated with external beam radiation therapy (EBRT) for localized prostate cancer, 609 men suffered BCR (defined by PSA nadir +2 ng/mL), of whom only 47% were ultimately found to have distant metastatic disease and 18% died of disease. Predictors for clinical progression after BCR were shorter interval from end of RT to BCR (<3 years), shorter PSA doubling time (<3 months), higher initial clinical stage (cT3b/4), and higher pretreatment Gleason score (7-10). As such, these are the men with the greatest risk of distant failure from local treatment.

While it is important to understand who is at greatest risk for distant failure, it is equally vital to identify men with the greatest potential for local failure only, as these are the men where salvage local therapy may still provide a potential long-term cure. In one study of 184 patients evaluated with advanced imaging for BCR after RT, 54% of patients had a potentially salvageable recurrence, at a median PSA of 5.3 ng/mL. For these men, predictors of local only recurrence included the time from radiation to failure, the change in PSA from the nadir PSA, and the risk group of the patient at diagnosis (8). Together, these risk factors can be useful in selecting men where the work-up would likely point to a salvageable recurrence.

The definition of recurrence after focal therapy is not completely defined. Risk factors associated with histologic confirmation of recurrence have included baseline Gleason score and nadir PSA (9). More recently, Huber *et al.* reviewed various biochemical thresholds among 598 men treated with focal high-intensity focused ultrasound (HIFU). In this analysis, 35% of men had a documented failure, and the authors identified that a definition PSA nadir +1 ng/mL at 1 year post-treatment was associated with a high sensitivity and specificity for diagnosis of recurrence (10). While it is likely that the definition of BCR after focal therapy will further evolve, once a recurrence has been established, the evaluation for salvage surgery should proceed similar to the patient with a suspected radiation failure.

Evaluation for SRP

The evaluation of a patient for a SRP can be challenging. However, once the BCR has been established, there are three major factors to consider: life expectancy (where local therapy would provide a benefit), evaluation of distant disease, and confirmation of local disease.

Evaluation of life expectancy

Given the significant morbidity of a salvage local therapy, there exist a need for at least a balance between the predicted oncologic control and the patient's life expectancy. Various tools are available to assist with the evaluation of a patient's life expectancy. For example, social security life tables can be used to estimate life expectancy on the basis of a patient's age.

Similarly, an understanding of the predicted impact of conservative management needs to be considered. For men experiencing BCR in whom non-curative intent treatment is utilized, there are considerable toxicities from androgen deprivation alone including the risk of osteoporosis, cardiovascular disease, overall mortality, and development of castration resistance (6,11-13). Additionally, the increased risk of prostate cancer specific mortality is evident during the 8 years after experiencing a BCR, with a median time to prostate cancer specific mortality of 10 years from the onset of BCR (7,14). As such there is a potential survival advantage among men with BCR disease who are fit for additional curative intent therapy and in whom ADT would be poorly tolerated. Currently the National Comprehensive

Cancer Network (NCCN) recommends considering additional local therapy in men with a life expectancy >10 years (15).

Evaluation for distant disease

Once the decision has been reached that a patient has a BCR and could benefit from a curative intent therapy, the next step is evaluation for disseminated disease. Identification of disease outside of the pelvis represents a disease state beyond the scope of local salvage and identifies men in need of systemic treatment intensification given the increased understanding of the role of advanced hormonal manipulation in men with newly diagnosed metastatic disease (15).

Conventional imaging to identify the extent of disease frequently involves CT and bone scintigraphy. Bone scintigraphy is limited to the detection of bone metastases and provides no information regarding recurrence of lymph nodes, soft tissue, or local disease. Additionally, they are dependent on the bulk of disease as defined by the PSA (16). CT scans have similar limitations in detection on the basis of PSA values with low probability of detecting sites of recurrence (17). The EAAU-ESTRO-SIOG Guidelines advocate against the use of bone scan and CT scan in patients with BCR and a PSA <10 ng/mL or PSA doubling time >6 months (18). As such, the current recommendations by the NCCN for the evaluation for a site of recurrence typically involves advanced imaging with an multiparametric magnetic resonance imaging (mpMRI) and a positron emission tomography/computed tomography (PET/CT) (15).

Prostate mpMRI

The utilization of prostate mpMRI in several clinical scenarios for prostate cancer has become more and more widespread. The role of prostate MRI to assist in workup of prostate cancer recurrence has also been explored. A study of 9 patients assessed the findings on prostate MRI prior to and following RT for prostate cancer as well as biopsy proven recurrence and ultimately step-section pathology after SRP. Interestingly, the authors found similar appearances in the pre and post RT prostate MRI lesions as well as concordance with prostatectomy pathology suggesting that recurrences occur at the site of the primary tumor (19). In addition, a study of 129 patients with rising PSA after initial prostate cancer treatment found good concurrence for detection of prostate cancer recurrence in the pelvis between multiparametric MRI (mpMRI) and fluciclovine PET scan (20). Given the excellent diagnostic characteristics of mpMRI in the prostate and the finding that most recurrences after radiation are localized to the prostate and periprostatic soft tissues (8,21). mpMRI is invaluable in the evaluation of the local extent of the disease.

PET/CT

Functional imaging with a PET/CT represents an added measure for the identification of sites of recurrence. Multiple PET tracers have been studied with efficacy in the evaluation of the man with a suspected prostate cancer recurrence including ^{11}C-choline, ^{18}F-Fluciclovine, and ^{68}Ga-PSMA.

^{11}C-choline PET/CT

A large single-center series of patients with BCR following primary therapy for prostate cancer assessed outcomes in 4,426 ^{11}C-choline PET/CT scans performed in 3,203 patients. Of these scans, the authors found a 52.8% positive scan rate in 54.8% of the patients with distant findings observed in 29.4% of scans. The mean and median PSA values were 4.9 and 2.1 ng/mL respectively. Increased probability of positive scans correlated with increasing absolute PSA as well as utilization of ADT. The optimal PSA cutoff value was determined to be 1.16 ng/mL (22). In contrast, a review of 184 patients with rising PSA after RT for prostate cancer identified recurrence sites in 161/184 (87%) of patients. Histologic confirmation was obtained in 95 (59%) of these patients. Factors affecting recurrence detection included the difference between nadir PSA and PSA at time of the choline PET scan as well as NCCN high risk classification. The majority of these patients (54.3%) recurred in the pelvic soft tissue only while 33% had extra pelvic recurrence. The median PSA at the time of imaging was 5.7 ng/mL (8).

The major limiting aspect is the need for an onsite cyclotron to create the ^{11}C-labelled choline for the PET scan. Its half-life is 20 minutes which has limited more widespread utilization and adoption of this agent (23).

^{18}F-fluciclovine PET

^{18}F-fluciclovine PET scans are approved by the FDA and European Commission in patients with elevated PSA following prior definitive treatment for prostate cancer and their utilization has been added to the NCCN guidelines for prostate cancer recurrence or progression (24). The

FALCON trial assessed ^{18}F-fluciclovine PET scans in men with BCR following primary curative intent treatment for prostate cancer. Lesions were detected in 58/104 (56%) of patients with a median PSA of 0.79 ng/mL. As PSA increased, scans were more likely to be positive with 93% of scans positive when PSA greater than 2.0 (25). Similar results were found in another similar patient cohort of 213 men with median PSA of 1.00 ng/mL with ^{18}F-fluciclovine avid lesions detected in 122 men (57%). Amongst these men, 30% of lesions were detected in the prostate or prostate bed, 29% detected in lymph nodes, 2.3% identified in soft tissue, and the remaining 11% of lesions were bony lesions (24).

^{68}Ga-PSMA ligand PET

A study of 118 patients with recurrent prostate cancer after primary RT were studied with a PSMA PET CT yielding pathologic findings suggestive of prostate cancer in 107/118 (90.7%) of patients. Detection efficacy increases with PSA, with a rate of 81.8% (36/44) for men with PSA of 2 to <5 ng/mL and up to 96.8% (30/31) recurrence detection for men with PSA ≥10 ng/mL. Lesions were confirmed in 6 patients via histopathology, 29 via follow up imaging, and 3 patients via initiation of RT or chemotherapy followed by decrease in PSA or PSMA uptake of lesions on repeat scans (26). Further studies found similar findings with a lesion detection rate of 79.5% of a cohort of 1,007 men with recurrent prostate cancer and a median PSA of 2.2 ng/mL. Detection rates were also found to increase with rising PSA as well as utilization of ADT (27). Finally, 270 patients were studied with PSMA PET scans at PSA of less than 1 ng/mL. These patients had a median PSA of 0.48 ng/ML with 132/270 (49%) having a positive scan indicating utility in this patient population (28).

Regardless of the PET tracer employed, the key takeaway from these studies is that PET/CT is a superior imaging modality when compared to CT alone and can be invaluable in the selection of patients for further local therapy with curative intent.

Confirmation of local disease

Once disseminated disease has been ruled out, further work-up should be aimed at confirmation of local disease. Post-treatment biopsy should not routinely be performed but may provide useful information in patients with unfavorable post-treatment PSA levels who may be candidates for salvage treatments (29). Pathologic results of post RT prostate biopsies may be difficult to interpret. It is recommended to attempt to avoid biopsy until two to three years after radiation due to slow tumor growth as well as postmitotic cell death. A prospective study of 498 men with localized prostate cancer who underwent radiotherapy showed delayed tumor regression with eventual conversion to negative biopsies in 81 men (30%) at a mean time of 30 months. Indeterminate biopsies were as high as 33% for the first biopsy with a median time since RT of 13 months and decreasing with time to 7% indeterminate rates at the fourth biopsy at a median interval of 44 months since RT. Of the patients with indeterminate biopsies, some had subsequent normal biopsies while others progressed to local failure or distant failure. Among men with a negative postradiotherapy biopsy, 19% were later found to have residual local disease (30). While radiation treatment doses and utilization of ADT has changed since the publication of this report, it still serves an important role in elucidating timing of biopsy and the lack of clear pathologic answer in certain biopsy specimens. Cheng *et al.* also attempted to elucidate pathologic findings in post radiation prostate biopsy specimens. This study correlated prostate biopsy pathology with subsequent salvage prostatectomy specimens. Interestingly, needle biopsy was shown to underestimate Gleason pathology scores in 35% of men and overestimate in 14% when compared to prostatectomy specimen (31).

Another current study looked at the effect of post-treatment biopsy results with cause-specific survival (CSS), metastasis-free survival (MFS), and overall survival (OS) in a group of 232 patients with localized prostate cancer who were treated with high-dose radiotherapy. The patients were re-biopsied 24–36 months following the termination of RT with biopsy specimens categorized as negative or positive for residual malignancy. The patients received a median radiation dose of 77.0 GY with 62% of patients treated with long-term ADT, 17.7% receiving short-term ADT, and the remaining 20.3% receiving no ADT at time of RT. A total of 62 patients or 26.7% presented with a positive biopsy after treatment. Variables that correlated with a higher histological failure rate were PSA nadir (P=0.019) and use of hormone therapy (P<0.001). Patient age, clinical T stage, Gleason sum, pre-treatment PSA, number of positive cores at diagnosis, risk group, and radiation dose were not significantly correlated with subsequent post-treatment positive biopsy; 178/232 of the

patient population was alive at time of publication with 28 (12.1%) with distant metastases and 8 (3.4%) patients who passed from prostate cancer. Patients with confirmation of local recurrence were much more likely to suffer BCR, with 10-year biochemical disease-free survival (bDFS) of 20.6% in men with positive biopsies, compared to 69.9% (P<0.001) in those without confirmation. Interestingly, despite the differences in bDFS between negative and positive biopsy patients, there was not a statistically significant difference in OS or CSS however there was a difference in MFS. At 10 years, the MFS for patients with a negative biopsy was 95.4% versus 78.4% for patients with a positive biopsy (P<0.001) (32). While these authors did not find statistically significant differences in OS, other literature has shown MFS to be a strong surrogate for OS for localized prostate cancer that is associated with a significant risk of death from prostate cancer (33). Furthermore, Zelefsky *et al.* studied 382 patients with clinically localized prostate cancer who were treated with EBRT. Post treatment positive biopsies were associated with higher risks of distant metastases and prostate cancer related death. Lack of utilization of ADT and high risk disease prior to treatment were associated with higher rates of posttreatment positive biopsies (34).

SRP

Appropriate patient selection and counselling is key to successful salvage prostatectomy after failed local treatment. After appropriate workup and imaging as detailed above, men with localized prostate cancer recurrence, appropriate life expectancy, and no evidence of distant disease may be offered salvage prostatectomy. This should be offered by experienced surgeons, and patients should be counselled about long term outcomes. Adverse events are increased following radiation due to local fibrosis and impaired wound healing in radiated tissues. Additionally, the risk of incontinence and erectile dysfunction are much greater than in the setting of a primary prostatectomy. The choice of modality of surgical salvage is at the discretion and comfort of the performing surgeon and is beyond the scope of this review. However, both open and robotic approaches have been described. The only head to head assessment of these approaches is a retrospective report of 395 prostatectomies at 18 centers which found that complications were no different by approach, but that those patients managed robotically had low risks of incontinence, stricture formation, and lower blood loss (35).

Oncological efficacy

A meta-regression analysis assessed oncologic outcomes as well as functional outcomes of SRP, salvage high-intensity focused ultrasound (SHIFU), salvage brachytherapy (SBT), and salvage cryotherapy (SCT). In this study, no oncologic outcome differences (defined as BCR) were noted between any salvage therapy though no randomized trials have been performed in this space (36). In contrast, a retrospective review of SCT and SRP showed superior OS and biochemical disease free survival in patients undergoing SRP (37). An interesting retrospective study of 404 patients who underwent SRP for radiation-recurrent prostate cancer attempted to identify patients at risk for BCR, metastases, and death following SRP. All patients had biopsy proven prostate cancer prior to SRP with no radiographic evidence of systemic disease. Patients were followed post-operatively with DRE and PSA with BCR defined as PSA of 0.2 ng/mL and rising. The patient population had a median pre-SRP PSA of 4.5 ng/mL and approximately one-half had post-RT prostate biopsy Gleason score ≥7. Pathology from SRP specimens revealed 96 (24%) of patients had a Gleason score ≥8, 181 (45%) had extraprostatic extension (EPE), 120 (30%) had seminal vesical invasion (SVI), 65 (16%) had lymph node involvement (LNI), and 99 patients (25%) had positive surgical margins. 195/404 patients had subsequent BCR, 64 developed metastases, and 40 died from prostate cancer. At 5 years after SRP, the probabilities of BCR-free survival, MFS, and CSS were 48% [95% confidence interval (CI), 42–53%], 83% (95% CI, 78–87%), and 92% (95% CI, 88–95%), respectively; at 10 years, the probabilities were 37% (95% CI, 31–43%), 77% (95% CI, 71–82%), and 83% (95% CI, 76–88%), respectively. Predictors of both BCR and metastases included pre-SRP PSA and biopsy Gleason score. Pre-SRP PSA and SRP Gleason score predicted BCR and metastases and LNI was also a significant predictor of metastases. Finally, death from prostate cancer after SRP was predicted by higher pre-SRP PSA, clinical stage, presence of SVI, and biopsy and pathologic Gleason score (38).

Many authors have written about salvage robot assisted laparoscopic prostatectomy (sRALP) including a single-institution study of 34 men treated with sRALP after prior definitive therapy. Primary outcomes were biochemical failure with PSA persistence (PSA 0.1 ng/mL or greater following sRALP) and PSA recurrence (PSA 0.2 ng/mL or greater with confirmatory PSA). Median PSA prior to sRALP was 3.86 ng/mL with PSA doubling time of 10.1 months. Of these patients, the majority had Gleason

6 or 7 disease with 9 (16%) having Gleason 8–10 disease. Nine (26%) had positive surgical margins; 15% of patients had biochemical persistence and 3% had BCR at 16 months post-surgery (39). Overall, sRALP is a feasible treatment option for this patient population with similar expect oncologic control as an open SRP.

Given the equivalence of open and robotic procedures in oncologic control, it is reasonable to expect similar outcomes among these men and counseling of men with confirmed histologic local recurrence without disseminated disease, should proceed as described, with an expectation of biochemical control in one-third of men at 10 years, but with an excellent cancer-specific survival of >75%.

Complications and side effects

While the oncologic control of SRP has been well-described and supported the use of this approach, prior treatment to the prostate results in significant fibrosis of the prostate to the surrounding structures—namely the bladder neck, rectum, pelvic floor, and neurovascular bundles. As a result, performance of a salvage prostatectomy may be associated with difficulty with dissection of the bladder neck, posterior plane, and apex. Given this increased complexity, it is well understood that complications are greater for SRP than a primary prostatectomy.

A recent retrospective review evaluated the impact of SRP on quality of life and complications. They compared open versus robotic salvage prostatectomy in 395 patients following local recurrence after local nonsurgical treatment for prostate cancer. Of the 395 men, 186 patients underwent open surgery with 209 patients undergoing sRALP. Major risks of the procedure included anastomotic complications (strictures and leaks), rectal injuries, fistulas, incontinence, and impotence. For these men, robotic surgery was found to have lower blood loss and shorter hospital stay (P<0.001) with similar complication rates including rectal injury rates of 1.6% and fistula rates of 2.0%. Anastomotic strictures were more common in open salvage prostatectomy (16.6% versus 7.7%, P<0.01). Incontinence rates were approximately 25%, with robotic salvage prostatectomy as an independent predictor of recovery of continence on multivariable analysis (OR 0.411, P=0.022). Additionally, at 12 months 8.1% of men had preserved spontaneous and/or PDE-5 assisted erection and 15.56% who were potent before sRALP had preserved erectile function (35). In summary, a large systematic review article with 1,329 patients in 24 series found average rates of 50% urinary incontinence, 26% bladder neck stricture, 5% rectal injury, and 2.4% of patients experiencing a fistula after salvage prostatectomy (40).

Potency outcomes at the time of SRP are generally poor and are reflective of the salvage nature of this operation, where an increased focus is—and should be—on oncologic control of the disease. In this manner, the aim should be removal of all potential sites of resectable disease, inclusive of the neurovascular bundle. However, neurovascular bundle preservation has been described among men undergoing sRALP. In one study of 80 men treated over an 8 year period, 43 patients had at least 50% of their bundles preserved (41). For these men, potency was observed in 25% of the men without an increase in the risk of positive margins. Interestingly, most positive margins in these men were at the apex, likely reflective of the difficulty of the apical dissection from fibrosis to the pelvic floor. Selection of candidates for nerve sparing should be based on pre-operative potency, grade of the disease, and the local staging, similar to in men without prior local therapy. However, the patient should be appropriately counseled on the role of SRP as maximal oncologic control and that even with nerve sparing, the expected rates of potency are low.

Conversely, the continence outcomes are more optimistic. In the largest systematic review of men undergoing SRP, rates of continence ranged between 21–90% (6). More recently, rates of continence (0 pads) have been described in 50% of patients at 1 year, with almost 75% of patients requiring <2 pads per day after undergoing sRALP (41). To address continence, authors in this series performed a posterior reconstruction with an anterior urethral suspension stitch, which may add to the continence among these men.

In total, men considering SRP should be counseled on the goals of the operation (cancer control) and the potential for nerve sparing (with low expected potency), risk of incontinence at rates higher than in primary prostatectomy men, and the potential for significant anastomotic and rectal complications which occur at a low but non-zero rate.

Conclusions

Many men will be diagnosed with prostate cancer, and a significant portion of these men will suffer from BCR following local treatment. For men suffering recurrence after RT, salvage prostatectomy is an option for management, but is contingent upon appropriate patient selection and careful evaluation. Oncologic control can

be achieved in up to 50% of men but comes at the risk of significant quality of life impacts. Experienced surgeons should offer this as part of the treatment algorithm for the appropriately selected patient.

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Footnote

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