Management of Biochemical Failure of Prostate Cancer after Radical prostatectomy: Recent Advances and Future Opportunities

*William W. Wong, M.D.

Department of Radiation Oncology, Mayo Clinic Arizona, USA

Published 13/12/2017

For Correspondence

William W. Wong
Department of Radiation Oncology, Mayo Clinic Arizona,
13400 E. Shea Blvd.
Scottsdale, AZ 85259
U.S.A.

Email: wong.william@mayo.edu

Contact no: 480-301-8120

Fax no: 480-301-7687

Prostate cancer is the most common new cancer diagnosis and the third leading cause of cancer death in men in the United States. With the use of prostate-specific antigen (PSA) as a screening test, most new prostate cancers are diagnosed when the disease is localized. Standard definitive treatment options for localized prostate cancer include radical prostatectomy (RP) or radiation therapy (RT). The addition of androgen deprivation therapy to RT has been shown to improve treatment outcomes for intermediate and high risk prostate cancers. For patients who undergo RP, the PSA level should be undetectable after the surgery. However, more than a third of patients would develop recurrence of disease, which initially presents with an increase in the PSA to detectable level. The majority of these patients would have no suspicious findings in diagnostic work-up including clinical examination and imaging studies, and the condition is categorized as biochemical failure (BF). Without salvage treatment, the disease would progress to the development of local recurrence or distant metastasis that can be eventually detected clinically. However, the pace of disease progression is variable and may take many years before sites of recurrence can be identified. Management options for patients with BF include salvage radiation therapy, androgen deprivation therapy, and watchful waiting. Salvage radiation therapy is the only treatment that can potentially achieve a cure of the disease. Despite salvage RT, further relapse occurs in > 50% of these patients. Risk factors associated with further relapse include a short time interval from RP to biochemical relapse, PSA level at the time of salvage RT > 1 ng/ml, short PSA doubling time, and presence of seminal vesicle involvement.

To improve the treatment outcomes of salvage RT for patients with BF, the addition of antiandrogen therapy or androgen-deprivation therapy (ADT) have been evaluated. In a recently published Radiation Oncology Therapy Oncology Group (RTOG) 9601 study, patients with PSA levels of 0.2-4 ng/ml after surgery were randomized to salvage RT of 64.8Gy in 36 daily fractions plus bicalutamide 150mg daily for 2 years, or salvage RT plus placebo [1]. A total of 760 patients were enrolled from 1998 through 2003. The primary end point was overall survival. Patients were stratified according to the PSA level at entry, use of short-term ADT before surgery, PSA nadir after surgery, and presence of positive surgical margin. The median PSA level at entry was 0.6ng/ml, and the median interval between surgery and the first detectable PSA was 1.4 years. The 12-year overall survival was 76.3% in the bicalutamide group, as compared with 71.3% in the placebo group (hazard ratio for death, 0.77, P<0.04). The 12-year prostate cancer death rate was 5.8% in the bicalutamide group, as compared with 13.4% in the placebo group (hazard ratio, 0.49, P<0.001). The cumulative incidences of distant metastases and a second biochemical recurrence were also lower in the bicalutamide group, as compared with the placebo group (14.5% vs 23%, and 44% vs 67.9%, respectively). In multivariate analyses, negative prognostic factors of overall survival included assignment to the placebo group, a PSA level of >1.5 ng/ml at trial entry, a Gleason score of >8, a Karnofsky performance status score of <90, and age of >65. Gynecomastia developed in 69.7% of patients who received bicalutamide, as compared with 10.9% in the placebo group. There were no significant differences in other late toxicities.

RTOG 9601 is the first randomized study that shows a survival benefit by adding antiandrogen therapy to salvage RT for patients with BF after RP. It took a median follow-up time of 13 years to demonstrate this benefit. It was estimated that 20 patients would need to be treated with bicalutamide to avoid one death. The main late toxicity associated with bicalutamide is gynecomastia, which can be prevented with the use of low dose prophylactic irradiation to the breast tissue.

GETUG-AFU 16 is another randomized study that compares the use of short-term androgen deprivation therapy (ADT) plus salvage RT to salvage RT alone [2]. Patients with rising PSA of 0.2-2ng/ml after RP were randomly assigned to 66Gy in 33 fractions of salvage RT plus 6 months of goserelin, or salvage RT alone. Low risk disease was defined as Gleason score <8, positive surgical margins, PSA doubling time of relapse >6 months, and no seminal vesicle involvement. High risk disease was defined as Gleason score of >8, negative surgical margins, PSA doubling
time of <6 months, and seminal vesicle involvement. Between 2006 and 2010, 743 patients were randomized. The primary end point was progression-free survival (PFS). After a median follow-up was 63 months, the 5-year PFS was 80% in the goserelin group, as compared with 62% in the RT alone group (hazard ratio, 0.5, P<0.0001). There was no difference in overall survival (96% in RT plus goserelin, versus 95% in RT alone). In multivariate analysis, prognostic factors for disease progression were PSA level >0.5ng/ml, seminal vesicle involvement, negative surgical margins, and PSA doubling time <6 months. The 5-year PFS for low risk versus high risk group was 75% versus 58% in the RT alone group, and 87% versus 77% in the RT plus goserelin group.

Despite some differences in study design, RTOG 9601 and GETUG-AFU 16 have clearly demonstrated the benefits of adding antiandrogen or androgen deprivation therapy to salvage RT for patients with BF after RP. Previous studies in patients with non-metastatic prostate cancer suggested that high dose bicalutamide (150mg daily) provided similar efficacy as LHRH agonists. RTOG 9601 showed an overall survival benefit with the addition of 2 years of high dose bicalutamide to salvage RT, whereas GETUG-AFU showed an improvement in PFS but not overall survival with the use of 6 months of ADT concurrently with salvage RT. The primary endpoint for GETUG-AFU 16 was PFS, not overall survival. The shorter follow-up time of 5 years in GETUG-AFU 16 also might have contributed to the lack of overall survival benefit of adding short-term ADT. Prostate cancer progression is a slow process. It took RTOG 9601 13 years of follow-up time to demonstrate the survival improvement of bicalutamide.

The patient populations in the two studies might be different. Patients in RTOG 9601 appeared to have more locally advanced disease (2/3 with pT3 disease). In GETUG-AFU 16 study, about 45% had pT3 disease. The median time to detectable PSA after RP was about 1.4 years in RTOG 9601 and 2.5 years in GETUG-AFU 16. Shorter interval from the time of RP to the development of BF is a poor prognostic factor. Patients in RTOG 9601 also had higher median PSA level at the time of study entry (0.6 ng/ml), as compared with the GETUG-AFU 16 (0.3 ng/ml). In aggregate, patients in RTOG 9601 had more poor prognostic features compared to those in GETUG-AFU 16. These could potentially adversely impact the outcome of radiation therapy alone, and magnify the benefit of the addition of antiandrogen therapy in RTOG 9601.

The optimal radiation dose of salvage radiation therapy has not been clearly defined in the published literature. In RTOG 9601, patients received 64.8Gy in 38 fractions, while the dose in GETUG-AFU 16 was 66Gy/33 fractions. Advances in radiation treatment techniques have allowed radiation dose escalation with acceptable toxicities. Recent studies suggest that doses of >68Gy in conventional fractionation would achieve better disease control [3]. The use of image guidance technology such as cone beam CT at the time of treatment helps to ensure the intended target volume is encompassed in the treatment field and allows a tighter margin to minimize the side effects associated with radiation dose escalation.

Another important question raised by these two randomized studies is what the optimal duration of antiandrogen or ADT would be in the setting of salvage RT. Longer duration of antiandrogen therapy or ADT would have associated side effects and costs. Additional randomized studies would be needed to provide an answer on the optimal duration of antiandrogen therapy or ADT.

By definition, biochemical failure means that there is no demonstrable evidence of gross disease by clinical examination or imaging studies. CT scan and bone scan have limited sensitivity and specificity in detecting recurrent disease in the setting of BF when the PSA level after RP is low. Recent advances in MRI and PET scans have provided imaging options that are increasingly sensitive to detect local and distant relapses at a low PSA level (<2ng/ml). These studies include multi-parametric MRI scan, C-11 choline PET-CT scan, 18F-Fluciclovine PET/CT, Ga-68 PSMA PET-CT scan. In a study evaluating the use of C-11 choline PET-CT scan in patients with BF after RP with PSA <1.5ng/ml (median: 0.61ng/ml), 16 of 75 patients (21%) had abnormal findings [4]. In another study by
Gupta et al, PET avid lesions were detected in 46% of patients by Ga-68 PSMA PET-CT scan at a PSA level of <0.2ng/ml \[5\]. For patients with detectable recurrences on imaging studies, the treatment can be more tailored. If there is evidence of local relapse on these imaging studies, one option is radiation dose escalation (>75Gy) to the areas of abnormal finding by using a simultaneous integrated boost, while treating the entire prostate bed to the standard dose of 65-70Gy, as well as the concurrent use of ADT. If there is evidence of distant relapse without local failure, salvage radiation may not be indicated.

In summary, RTOG 9601 and GETUG-AFU 16 have provided level 1 evidence to support the use of combined antiandrogen or ADT with salvage RT for patients with BF after RP. Future randomized studies are needed to define the optimal duration of ADT as well as radiation dose for BF. Newer imaging modalities that can better detect local and distant relapses would also change the management of patients with BF as is defined today.

REFERENCES