**Case 9: Postoperative Radiation Therapy in Prostate Cancer: Timing, Duration of Hormonal Treatment and the Use of PSMA PET-CT**

A 58-year-old man with a history of arterial hypertension and hypercholesterolemia, for which he receives medical treatment, was referred to a urologist after an elevated prostate-specific antigen (PSA) level of 18 ng/mL was detected on PSA screening. Further workup with multiparametric magnetic resonance imaging, prostate biopsies, and a computed tomography (CT) scan and bone scintigraphy revealed a prostate adenocarcinoma with a Gleason score of 5 + 4 = 9 and clear extracapsular extension on multiparametric magnetic resonance imaging, but no clinically visible adenopathies nor distant metastases. Final staging was as follows: cT3a cN0 cM0. Primary treatment consisted of a radical prostatectomy with extended pelvic lymph node dissection. Definitive pathologic examination confirmed the Gleason score and revealed seminal vesicle invasion (pT3b) and positive section margins over a length of 2 mm. All removed lymph nodes (n = 14) were negative. The patient developed minor postoperative incontinence (National Cancer Institute Common Terminology Criteria for Adverse Events v4 grade 2), for which he was referred to the physiotherapist. The case was discussed at the multidisciplinary tumor board, and it was decided to follow up and perform early salvage radiation therapy if necessary.

Seven months later, the patient presents with a PSA rise of 0.21 ng/mL. The patient is referred to you, the radiation oncologist, for early salvage radiation therapy. After a discussion with your colleagues, you decide to perform a prostate-specific membrane antigen positron emission tomography/CT before radiation therapy. It shows no evidence of locoregional recurrence; however, a hypermetabolic lymph node is seen in the supraclavicular region of the neck on the left side (Fig. 1).

Fig. 1:18F-PSMA PET/CT imaging of the patient showing a hypermetabolic lymph node supraclavicular on the left side. Abbreviations: CT = computed tomography; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

**Expert 1: The Post-Prostatectomy Setting: What to Do and When to Do…**

1. In this clinical scenario, the ARTISTIC meta-analysis did not show a benefit for immediate adjuvant radiation therapy (RT), compared with an early salvage approach, while demonstrating significantly higher toxicity in the adjuvant arm. However, few patients had high-risk features in the meta-analysis compared with those shown in this case, and only longer follow-up may tell us if adjuvant irradiation may be beneficial in this subgroup. For the time being, an early salvage strategy is the ideal one for this patient.

2. We would not perform imaging before irradiation, but prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography for a rising prostate-specific antigen (PSA) level after radical prostatectomy would be justified in the frame of a well-designed phase 3 trial comparing the standard of care (early salvage RT) with a late, PSMA-directed, salvage RT. In this respect, the critical point would be to correctly choose the maximum allowed PSA before randomization because historical data clearly indicate that, in this setting, the efficacy of salvage RT is inversely related to PSA levels.

3. We would not add androgen deprivation therapy because the advantage of the association of androgen deprivation therapy is likely to be driven by PSA level at salvage RT with maximum benefit for PSA >0.5 ng/mL. Given the unusual location of PSMA findings, we would propose fine needle aspiration of the suspect supraclavicular node for pathology confirmation to guide the subsequent therapeutic approach. If fine needle aspiration were negative or not contributory, we would first treat the patient with hormonal therapy and repeat PSMA positron emission tomography/computed tomography to further inform whether active disease was present in the lymph node.

**Expert 2: The Time to Evaluate the Impact of PET PSMAs on Management of Prostate Cancer Is Now**

Q1 (The tumor board chose early salvage treatment. Would you have agreed on this strategy in this patient?). This is an acceptable tumor board recommendation based on recent data from RAVES, RADICALS-RT, GETUG-AFU 17, and the ARTISTIC meta-analysis.

Q2 (Do you perform a prostate-specific membrane antigen positron emission tomography/CT at this moment, or do you immediately proceed with early salvage radiation therapy? In the case of radiation, do you add hormonal treatment, and if so, what is the optimal duration that you advise?). Given the availability of prostate-specific membrane antigen positron emission tomography (PSMA PET) at our institution, we would recommend prostate-specific membrane antigen positron emission tomography for this patient before salvage radiation therapy. Regarding the addition ofandrogen deprivation therapy, we would order Decipher testing on the prostatectomy specimen based on a recent ancillary analysis of RTOG 9601, which showed a larger absolute benefit of bicalutamide in patients with high Decipher scores, even at presalvage radiation prostate-specific antigen <0.7. Thus, if his Decipher GC is low, we would consider omitting hormone therapy. If his Decipher GC is intermediate/high, we would recommend ADT for 6 months.

Q3 (What do you advise to your patient?). We would first recommend consideration of biopsy of the node to confirm prostate cancer metastasis. If positive, the case should be discussed in a multidisciplinary tumor board. Treatment options to be considered include hormone therapy only (androgen deprivation with or without second-generation antiandrogens), hormone therapy and pelvic radiation therapy with or without stereotactic body radiation therapy to the lymph node, or stereotactic body radiation therapy to the lymph node with or without hormone therapy. In the absence of level I evidence, enrollment on a clinical trial (eg, ECOG-ACRIN EA 8191) should be encouraged.

**Expert 3: PSMA PET: Enabling More Dose to Less Volume?**

Early salvage radiation treatment has replaced adjuvant radiation as the standard-of-care postprostatectomy, based on results from 3 randomized trials. This approach decreases the risk of radiation toxicity without compromising cancer control. This patient has multiple high-risk factors for recurrence both locally and distantly, but data do not support his outcome being improved with adjuvant radiation.

For patients with biochemical recurrence postprostatectomy, we recommend obtaining a prostate-specific membrane antigen positron emission tomography/computed tomography scan once the prostate-specific antigen is >0.2, if there is easy access to the scan. Benefits of this approach include better sensitivity for detecting metastatic disease to spare patients unnecessary local therapy and better disease delineation to allow focused high-dose radiation to metastatic deposits. However, for patients with limited access to the scan, it is reasonable to proceed with salvage radiation without it. Downsides of prostate-specific membrane antigen positron emission tomography/computed tomography include management uncertainty with ambiguous results, as the clinical application of these scans is still under investigation, which can lead to treatment changes with presumed but still-unproven benefit. If proceeding with salvage radiation, we recommend androgen-deprivation therapy with a luteinizing hormone-releasing hormone agonist for 6 months.

For this patient, we recommend ultrasound-guided biopsy of the supraclavicular node. If biopsy shows prostate cancer involvement, we recommend ablative radiation therapy to the node followed by close prostate-specific antigen monitoring. If biopsy is not possible due to small size of the node, we recommend surgical excision. This allows better quality of life without androgen deprivation therapy until further disease progression.

**Expert 4: Patience Is a Virtue**

Question 1 (The tumor board chose early salvage treatment. Would you have agreed on this strategy in this patient?): Early salvage radiation therapy (prostate-specific antigen >0.2 ng/mL) is best in this case.1 Despite low recurrence-free risk at 5 and 10 years (26% and 14%, respectively), his 15-year cause-specific survival is >90% ([www.mskcc.org/nomograms/](http://www.mskcc.org/nomograms/) prostate/post-op). Although young patients (<70 years old) with multiple risk factors (pT3, R1, Gleason 9) may be more likely to benefit from adjuvant therapy, his history of cardiac risk factors and persistent incontinence argue for deferred therapy. In ARTISTIC metanalysis, adjuvant therapy did not demonstrate an event-free survival advantage, regardless of Gleason score.2 As such, he may be spared unnecessary toxicity of early locoregional therapy and/or metabolic impact of androgen deprivation therapy (ADT) without a known detrimental effect on cause-specific survival. Deferred therapy allows continence and erectile recovery and facilitates tailored salvage therapy based on now available advanced imaging (ie, inclusion/boost of pelvic nodes, ADT with metastasis-directed therapy). Current trial data are limited by low inclusion of high-grade disease, biochemical eligibility/failure variability, and underpower for survival differences. Genomic classifiers are likely to enhance selection criteria for adjuvant therapy in this patient group.

Question 2 (Do you perform a prostate-specific membrane antigen positron emission tomography/CT at this moment, or do you immediately proceed with early salvage radiation therapy? In the case of radiation, do you add hormonal treatment, and if so, what is the optimal duration that you advise?): Prostate-specific membrane antigen positron emission tomography/computed tomography is the most sensitive restaging imaging with prostate specific antigen <1 ng/mL. For patients with imaging-negative biochemical failure, early salvage radiation therapy with 6 months ADT is most appropriate. Longer term ADT (12 months) and/or incorporation of novel antiandrogens may be appropriate in appropriately selected very high-risk patients or on trial.

Question 3 (What do you advise to your patient?): Image guided biopsy of the left supraclavicular node is recommended to confirm metastatic disease and exclude other diagnoses in this relatively uncommon location. Should biopsy confirm prostate cancer, ADT with or without stereotactic radiation therapy would be appropriate to consider for oligometastatic disease.

ChatGPT’s initial recommendation

**Expert 5: Salvage Radiation Therapy Combined with Systemic Therapy**

Based on the available information, my recommendation for this patient would be to proceed with salvage radiation therapy combined with systemic therapy, specifically androgen deprivation therapy (ADT).

1. The patient has a high-risk prostate cancer, as evidenced by the Gleason score of 9, extracapsular extension, seminal vesicle invasion, and positive surgical margins. These factors are associated with a higher likelihood of disease recurrence after radical prostatectomy.
2. The patient has experienced a rise in PSA levels (0.21 ng/mL) within seven months of the surgery, which suggests the presence of residual or recurrent disease.
3. The 18F-PSMA PET/CT shows no evidence of locoregional recurrence but identifies a hypermetabolic lymph node in the supraclavicular region on the left side. This finding could represent metastatic involvement, although it is unusual for prostate cancer to metastasize to this location without involving pelvic lymph nodes first. Nonetheless, we should consider this a potential metastatic site.
4. Salvage radiation therapy is an appropriate treatment option in this scenario since it can target the prostate bed and any potential microscopic disease within the pelvis. Additionally, it can be beneficial in patients with a rising PSA after prostatectomy, particularly when the PSA doubling time is less than 12 months, as in this case.
5. Combining salvage radiation therapy with androgen deprivation therapy (ADT) has been shown to improve outcomes in high-risk patients with biochemical recurrence after prostatectomy. ADT can target the systemic nature of the disease, potentially addressing the hypermetabolic supraclavicular lymph node and other undetected metastatic sites.

In summary, we would recommend proceeding with salvage radiation therapy to the prostate bed and regional lymph nodes, combined with androgen deprivation therapy for at least 18-24 months. This combined approach addresses both the local and systemic aspects of the disease and has the potential to improve disease control and overall survival for this high-risk patient. Close monitoring of the patient's PSA levels and potential side effects from the treatments is essential. Additionally, it is important to consider a biopsy of the suspicious supraclavicular lymph node to confirm its nature and to guide further management, which might include directed radiation therapy to the supraclavicular region if it is confirmed to be metastatic.

ChatGPT’s revised recommendation after seeing other human experts’ recommendations

**Expert 6: Personalized Approach with Multidisciplinary Decision-making**

Early salvage radiation therapy has become the standard of care post-prostatectomy, balancing the risk of radiation toxicity with cancer control. In this case, the patient has multiple high-risk factors for recurrence, both locally and distantly. To provide the most appropriate treatment, we recommend a personalized approach based on the patient's specific risk factors and the most up-to-date imaging and genomic information, while emphasizing the importance of multidisciplinary decision-making and evidence-based practice.

* Performing a PSMA PET/CT before initiating salvage radiation therapy, which has already been done in this case and showed a suspicious supraclavicular lymph node.
* Considering Decipher testing on the prostatectomy specimen to guide the use of ADT, tailoring the treatment based on the individual patient's risk profile.
* Recommending a biopsy of the supraclavicular node to confirm the nature of the lesion, which is crucial for guiding further management.
* Discussing the case in a multidisciplinary tumor board, considering the input of various specialists, and considering clinical trial enrollment if available.

This personalized approach ensures that the patient receives the most suitable treatment while minimizing unnecessary toxicity and maximizing the potential for cancer control.