



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

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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 (Q1).

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 (Q2). 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) (Q3).

Questions

1. The tumor board chose early salvage treatment. Would you have agreed on this strategy in this patient?
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?
3. What do you advise to your patient?

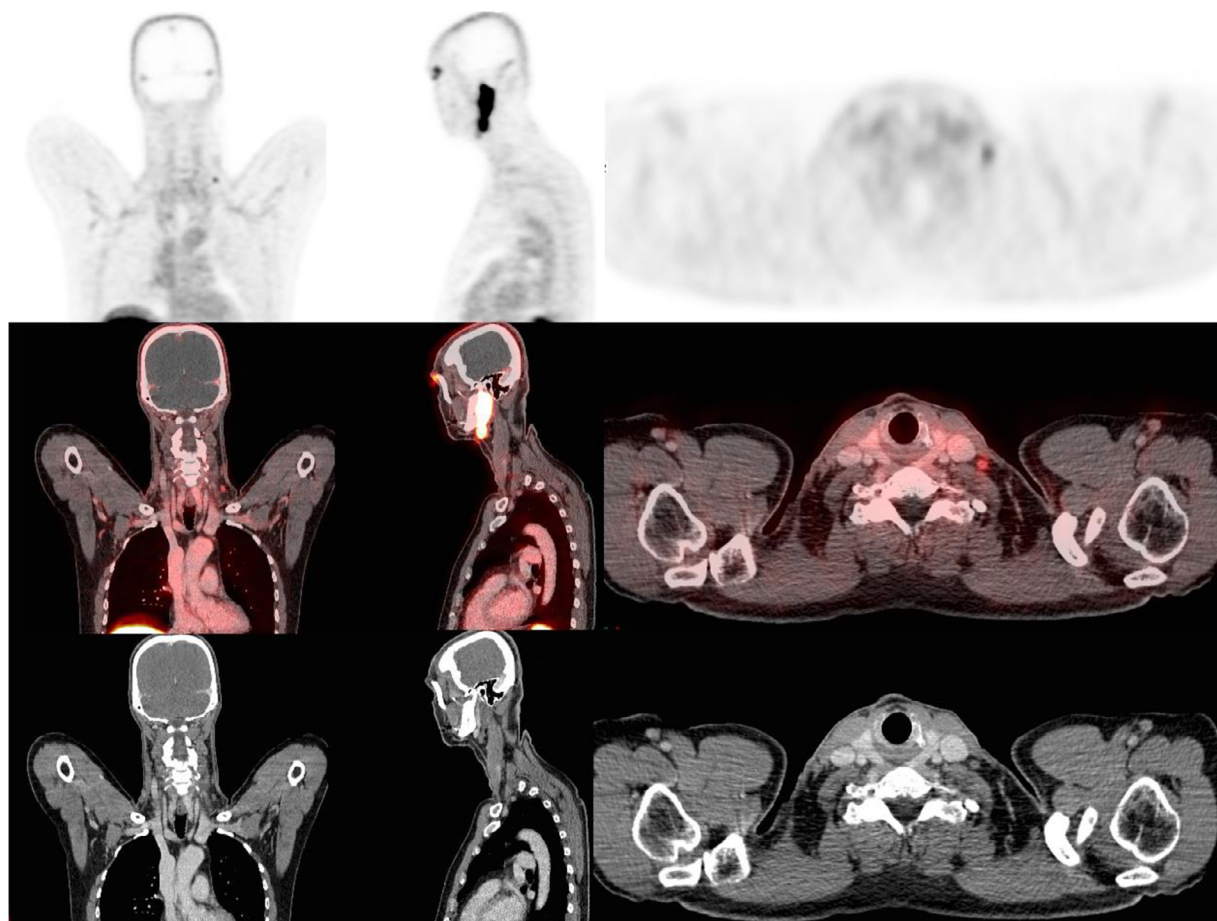


Fig. 1. 18F-PSMA PET/CT imaging of the patient showing a hypermetabolic lymph node supraclavicular on the left side. *Abbreviations:* CT = computed tomography; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

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GRAY ZONE EXPERT OPINION

**The Post-Prostatectomy Setting:
What to Do and When to Do...**

1. In this clinical scenario,¹ 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.² 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.³ 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.

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**The Time to Evaluate the Impact of
PET PSMA on Management of
Prostate Cancer Is Now**

Q1. This is an acceptable tumor board recommendation¹ based on recent data from RAVES, RADICALS-RT, GETUG-AFU 17, and the ARTISTIC meta-analysis.²

Q2. 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 of androgen 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 <0.7.³ 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. 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.

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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.¹ This approach decreases the risk of radiation toxicity without compromising cancer control. This patient² 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.³ 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.

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Patience Is a Virtue



Question 1: 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/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: 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: 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.

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ChatGPT-4: Salvage Radiation Therapy Combined with Systemic Therapy

User: You are an expert radiation oncologist from an academic center.

Please give your recommendation on the following case:

“ ... ”

Please give a specific recommendation of your most favored therapeutic approach in this patient case based on the available information and your reasoning for it.

ChatGPT-4: 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). Here is my reasoning:

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.

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.

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.

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.

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, I 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.

User: The tumor board chose early salvage treatment. Would you have agreed on this strategy in this patient?

ChatGPT-4: Yes, I would agree with the tumor board's decision to opt for early salvage treatment in this patient. Early salvage radiation therapy is a reasonable strategy for patients with high-risk features and biochemical recurrence after radical prostatectomy, as seen in this case.

The high-risk features in this patient, such as the Gleason score of 9, extracapsular extension, seminal vesicle invasion, and positive surgical margins, are associated with an increased likelihood of disease recurrence. Furthermore, the patient experienced a rise in PSA levels within seven months of the surgery, which is suggestive of residual or recurrent disease.

Early salvage radiation therapy has been shown to provide better outcomes in terms of biochemical control and overall survival compared to delayed radiation therapy. The rationale behind early intervention is to target microscopic disease before it becomes macroscopic and more difficult to control. Additionally, early salvage radiation therapy has the potential to reduce the risk of long-term side effects compared to adjuvant radiation therapy, which would be administered regardless of whether the patient has evidence of disease recurrence.

Considering the high-risk features and the rise in PSA levels, it is reasonable to initiate early salvage radiation therapy in this patient. Combining this treatment with androgen deprivation therapy, as previously recommended, can further improve disease control and overall survival. The decision to pursue early salvage treatment aligns with the goal of optimizing patient outcomes while minimizing the risk of long-term side effects.

User: 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?

ChatGPT-4: Given the patient's rising PSA level and high-risk features, it is reasonable to perform a prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT scan before initiating early salvage radiation therapy. This imaging modality can provide valuable information on the extent and location of the disease, helping to guide the radiation treatment planning and to rule out any distant metastasis. In this case, the PSMA PET/CT has already been performed and revealed a hypermetabolic lymph node in the supraclavicular region on the left side, which could represent metastatic involvement.

As for the treatment, I recommend proceeding with early salvage radiation therapy to the prostate bed and regional lymph nodes, combined with androgen deprivation therapy (ADT). Combining radiation therapy with ADT has been shown to improve outcomes in patients with high-risk prostate cancer and biochemical recurrence after prostatectomy.

The optimal duration of ADT in this setting is not universally established and may vary depending on the patient's risk factors and individual response to therapy. However, in general, a duration of

18-24 months is often recommended for high-risk patients like the one described in this case. This duration strikes a balance between the benefits of ADT in controlling disease progression and minimizing the side effects associated with long-term hormone therapy.

It is essential to closely monitor the patient's PSA levels and potential side effects from the treatments. Additionally, as mentioned before, a biopsy of the suspicious supraclavicular lymph node should be considered to confirm its nature and guide further management, which might include directed radiation therapy to the supraclavicular region if it is confirmed to be metastatic.

User: What do you advise to your patient?

ChatGPT-4: As a radiation oncologist, I would advise the following course of action for the patient:

- Proceed with early salvage radiation therapy to the prostate bed and regional lymph nodes. This treatment aims to target any residual or recurrent disease in the area and reduce the risk of further disease progression.
- Combine radiation therapy with androgen deprivation therapy (ADT) for systemic control of the disease. In this high-risk patient, ADT can help address the potential metastatic supraclavicular lymph node and any other undetected metastatic sites. I would recommend a duration of 18-24 months for ADT, but the specific duration should be tailored to the patient's risk factors and individual response to therapy.
- Consider a biopsy of the suspicious supraclavicular lymph node to confirm its nature. If the biopsy reveals metastatic involvement, directed radiation therapy to the supraclavicular region may be added to the treatment plan.
- Closely monitor the patient's PSA levels to evaluate the effectiveness of the treatment and detect any signs of disease recurrence early. Regular follow-up visits with the oncology team are crucial.
- Encourage the patient to maintain a healthy lifestyle, including a balanced diet and regular exercise, to support overall health and well-being during the course of the treatment.
- Inform the patient about potential side effects of the treatments, including radiation therapy and ADT, and work together with the multidisciplinary team to manage these side effects effectively.
- Provide emotional support and encourage the patient to discuss any concerns or questions regarding their diagnosis, treatment, and prognosis with the oncology team.

Overall, it is essential to maintain open communication with the patient and the multidisciplinary team to ensure optimal management of the disease and to address any concerns the patient may have throughout the treatment process.

User: Please summarize the other experts' recommendations in short sentences.

ChatGPT-4:

Expert 1: Recommends early salvage radiation therapy without immediate imaging. Advises against adding ADT for this patient and suggests considering fine needle aspiration of the suspicious supraclavicular node.

Expert 2: Suggests performing PSMA PET/CT before salvage radiation therapy and considering Decipher testing to guide ADT use. Recommends biopsy of the supraclavicular node and discussing treatment options in a multidisciplinary tumor board, with clinical trial enrollment encouraged.

Expert 3: Supports early salvage radiation therapy with ADT and recommends PSMA PET/CT if easily accessible. Advises ultrasound-guided biopsy of the supraclavicular node, followed by ablative radiation therapy to the node if positive.

Expert 4: Agrees with early salvage radiation therapy and performing PSMA PET/CT. Suggests image-guided biopsy of the supraclavicular node and considering ADT with or without stereotactic radiation therapy if the biopsy confirms metastatic prostate cancer.

User: As an expert radiation oncologist, which of the above experts' recommendation do you think the most proper?

ChatGPT-4: As an expert radiation oncologist, I find Expert 2's recommendation to be the most comprehensive and well-reasoned approach for the patient described above. This recommendation incorporates:

- Performing 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, taking into account the input of various specialists, and considering clinical trial enrollment if available.

This approach allows for a personalized treatment plan based on the patient's specific risk factors and the most up-to-date imaging and genomic information, while also emphasizing the importance of multidisciplinary decision-making and evidence-based practice.

User: At the beginning, you said that "I 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." In this case, which expert's recommendation is your initial suggestion closest to?

ChatGPT-4: My initial suggestion is closest to Expert 3's recommendation. Both recommendations involve:

- a. Early salvage radiation therapy to the prostate bed and regional lymph nodes.
- b. Combining radiation therapy with androgen deprivation therapy (ADT).
- c. Performing a PSMA PET/CT, which has already been done in this case.
- d. Recommending a biopsy of the suspicious supraclavicular lymph node to confirm the nature of the lesion.

The main difference between the two recommendations is the suggested duration of ADT. I initially recommended a duration of 18-24 months, while Expert 3 suggested 6 months of ADT. The specific duration should be tailored to the patient's risk factors and individual response to therapy.

User: After seeing the other experts' recommendations, are you going to update your own recommendation of your most favored therapeutic approach in this patient case? If so, what is your updated recommendation and which expert/experts is your update based on?

ChatGPT-4: After reviewing the other four experts' recommendations, I would like to update my recommendation to better align with the comprehensive approach proposed by Expert 2. My updated recommendation includes:

- 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, taking into account the input of various specialists, and considering clinical trial enrollment if available.

This updated approach allows for a personalized treatment plan based on the patient's specific risk factors and the most up-to-date imaging and genomic information, while also emphasizing the importance of multidisciplinary decision-making and evidence-based practice.