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Letter

Stereotactic ablative body radiotherapy for oligometastatic inguinal lymph node in castrate resistant prostate cancer

Dear Editor,

Introduction of prostate-specific membrane antigen positron-emission tomography/contrast-enhanced computed tomography (PSMA PET/CECT) for prostate cancer staging and follow-up have increased detection of metastases even in non-regional nodes, often in oligometastatic or oligorecurrent state [1]. Some of these merit metastases-directed therapy (MDT) such as surgery or radiotherapy (RT) with curative intent.

We discuss here a case of high-risk prostate cancer, who following initial prostatectomy and subsequent salvage therapies for biochemical failure, was detected to have isolated inguinal nodal metastases on PSMA PET/CECT 2 years from initial diagnosis and responded favorably to stereotactic ablative body radiotherapy (SABR) and systemic salvage therapy (SST). Informed consent was taken from the patient for treatment and publishing anonymized information.

A 53-year-old fit gentleman with unremarkable past or family history underwent radical prostatectomy with extended pelvic lymphadenectomy for a diagnosis of high-risk adenocarcinoma prostate (Gleason score 4+3, prostate-specific antigen [PSA] 62.4 ng/mL, stage T2cN0M0) (Fig. 1A); histopathology showed 60%–70% prostatic involvement including prostatic urethra, negative margins, and negative pelvic nodes (0/19); lymphovascular and perineural invasion were present. High postoperative PSA (0.377 ng/mL at 6 weeks, 1.24 ng/mL at 10 weeks) prompted early initiation of salvage image-guided RT (3 months postoperatively) to both prostate bed (70 Gy) and pelvic nodal regions (50 Gy) in conventional fractionation over 7 weeks. After initial PSA response (0.9 ng/mL 3 months post-RT), he experienced biochemical failure at 6 months post-RT (PSA 2.59 ng/mL) but with normal PSMA PET/CECT. Salvage androgen deprivation therapy (ADT) was started (leuprolide 22.5 mg every 3 months); after an initial response (PSA 0.036 ng/mL after 3 months ADT), there was a rapid PSA rise with doubling time under 2 months (0.553 ng/mL after 10 months ADT and 4.732 ng/mL after 14 months ADT). PSMA PET/CECT showed two PSMA avid nodes in left inguinal (maximum standardized uptake value 12.2, size 1.1 cm×1.5 cm) and adjacent external iliac (maximum standardized uptake value 10.3, sub-centimeter) region (Fig. 1B and C), metastatic on fine-needle aspiration cytology; immunocytochemistry showed granular cytoplasmic positivity for alpha-methylacyl-CoA racemase, confirming prostatic origin. A diagnosis of castrate-resistant prostate cancer (CRPC) with oligometastatic lymph node was made.

Considering his young age and good performance status, aggressive disease course, and limited recurrence volume, it was decided by the multidisciplinary tumor board to offer both focal RT and SST. SABR to recurrent nodes was planned after review of the previous RT plan (showing previous dose of 45 Gy–60 Gy in this region 19 months ago). Informed consent was taken for reirradiation morbidity in the form of inguinal subcutaneous thickening and lymphedema due to cumulative effects of prior pelvic surgery and two courses of RT, with a partial overlap of RT volumes expected in the lateral external iliac region. RT planning CT showed another new, suspicious, sub-centimeter node adjacent to PET-detected nodes. Planning target volume expansion of 1 cm was given to gross disease, constrained partially at skin and bones. Organs at risk included a skin strip (adjacent to planning target volume), left femur head, bladder, and rectum. A dose of 25 Gy in five fractions was prescribed to planning target volume with a simultaneous integrated boost to gross nodes (35 Gy) and treatment delivered on alternate days (Fig. 2). He tolerated the treatment well without any acute sequelae. SST with abiraterone acetate (1000 mg) and prednisone (5 mg) twice daily in addition to ADT was started 1 week after completion of SABR. PSMA

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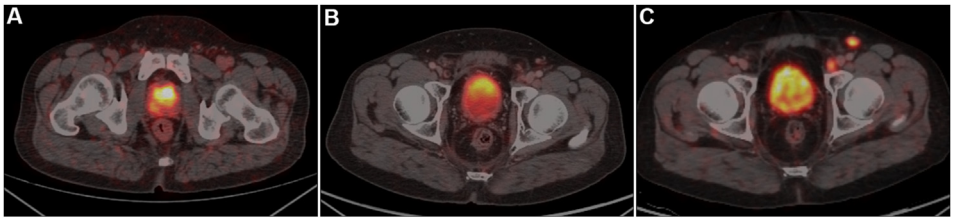
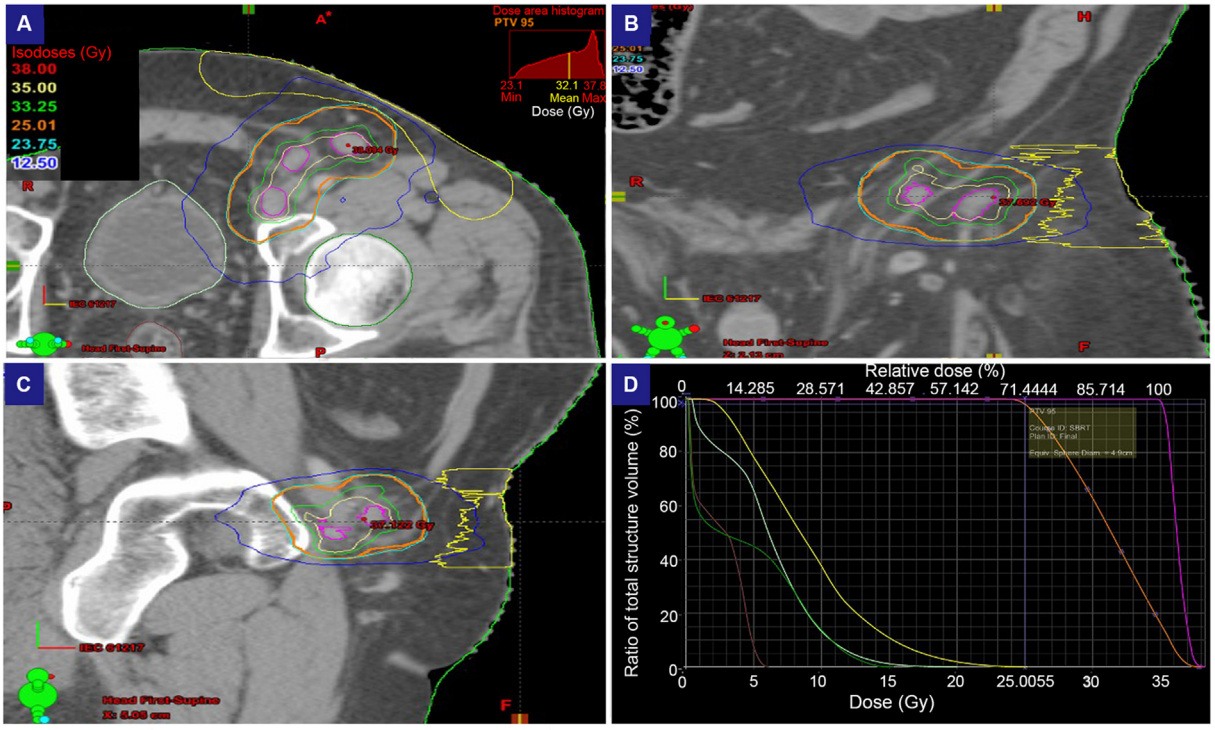


Figure 1 PSMA PET/CECT images. (A) Baseline PSMA PET/CECT of the patient showing enlarged prostate with heterogeneous attenuation (dimensions 3.8 cm×3.9 cm×4.0 cm) with multiple ill-defined intraprostatic PSMA-avid lesions in both lobes (SUV_{max} 10.3). There was no extracapsular extension, seminal vesicle involvement, pelvic nodal involvement, or distant metastases. (B) PSMA PET/CECT after 6 months of salvage radiotherapy showing no residual disease in prostate bed, pelvic nodes, or distant metastases. (C) PSMA PET/CECT at follow-up showing two small adjacent PSMA-avid nodes in left inguinal (SUV_{max} 12.2, size 1.1 cm×1.5 cm) and left lateral external iliac (SUV_{max} 10.3, sub-centimeter size) regions. PSMA, prostate-specific membrane antigen; PET/CECT, positron-emission tomography/contrast-enhanced computed tomography; SUV_{max}, maximum standardized uptake value.



DVH line	Structure	Volume, cm^3	Min dose, Gy	Max dose, Gy	Mean dose, Gy
	GTV	3.6	34.66	38.28	36.26
	PTV	62.6	22.73	38.28	31.24
	Skin strip	80.5	0.90	25.28	8.98
	Left femur head	118.6	0.12	15.32	4.49
	Rectum	28.5	0.20	6.15	2.54

Figure 2 Plan for stereotactic ablative body radiation therapy to left inguinal lymph nodes in a case of castrate resistant prostate cancer with oligometastatic disease. (A) Axial view; (B) Coronal view; (C) Sagittal view. Prostate-specific membrane antigen avid enlarged left inguinal nodes were delineated as GTV. PTV was generated around GTV with 1 cm margin, with modification at natural barriers. Organs at risk included a subcutaneous strip in left inguinal region, left femur head, bladder, and rectum. A dose of 25 Gy in five fractions was prescribed to 95% of PTV ($BED_{1.5}$=108.33 Gy, EQD2=46.4 Gy). Simultaneous integrated boost of 35 Gy was prescribed to 99% of GTV ($BED_{1.5}$=151.67 Gy, EQD2=65 Gy). (D) DVH of the plan showing the achieved target and organ at risk doses. DVH, dose volume histogram; GTV, gross tumor volume; Min, minimum; Max, maximum; PTV, planning target volume; $BED_{1.5}$, biologically equivalent dose assuming α/β ratio of 1.5 for prostate cancer; EQD2, 2-Gy equivalent dose; A*, anterior; P, posterior; R, right; F, foot-end.

PET/CECT at 6 months showed complete resolution of nodal metastases. At 14 months post-SABR, his PSA was 0.03 ng/mL and he continued to be on follow-up with good tolerance to therapy.

The use of PSMA PET/CECT has improved the sensitivity of detection of small metastatic foci and non-regional nodal metastases over bone scan and choline PET even at low PSA values (1—2 ng/mL), in addition to providing guidance for sampling and SABR targeting [2]. Unusual sites are more commonly seen in recurrent settings and do not fit into the Radiation Therapy Oncology Group nodal atlas definitions [3].

Standard managements for metastatic disease include systemic therapy (ADT, chemotherapy, second-generation antiandrogens, and radionuclides). However, the key studies defining the benefit of these strategies have an under-representation of oligometastases, especially in nodal sites. MDT in the form of lymphadenectomy, elective nodal RT, or SABR to oligometastases may either delay initiation of SST, or delay progression when given along with SST. MDT has shown superior ADT-free survival compared to surveillance alone in oligo-recurrent disease in the phase II STOMP trial [4]. A systematic review of SABR with biologically effective dose exceeding 100 Gy to oligo-recurrent nodes showed median progression-free survival and ADT-free survival of 22.5 months and 32.8 months, respectively, with only 5.5% patients experiencing Grade 2 or worse toxicity [5]. Several trials (namely, TRANSFORM, ORIOLE, and CORE) are exploring the utility of SABR-based MDT in oligometastatic prostate cancer. For oligo-recurrences in CRPC, SABR has helped yield "next line systemic therapy"-free survival of 16—21.8 months in retrospective series, which is encouraging [6,7]. Elective nodal RT for involved nodal region has higher toxicity than SABR to involved node only, but it is still unclear whether it is more effective than SABR [8,9]. A prospective randomized phase 2 trial, "PEACE V" (NCT03569241), is comparing a combination of MDT (using either lymphadenectomy or SABR) and short-term ADT with or without whole pelvic elective nodal RT in pelvic nodal oligo-recurrences, with metastases-free survival as a primary endpoint. In oligo-recurrent CRPC, randomized trials "PCS IX" (NCT02685397) and "ARTO" ((NCT03449719)) are exploring the benefit of adding SABR to luteinizing hormone-releasing hormone agonist or antagonist-enzalutamide or luteinizing hormone-releasing hormone agonist or antagonist-abiraterone combinations, respectively. Several other combinations with PARP inhibitors, durvalumab, pembrolizumab, and PSMA-directed therapies are also under evaluation. The Italian Association of Radiotherapy supports focal RT to metastatic sites in oligo-progressive prostate cancer, for both hormone-sensitive and CRPC states [10].

Our index case is a young patient with high baseline PSA and aggressive features of pan-prostatic involvement, urethral extension, lymphovascular, and perineural despite localized prostate cancer. Possible reasons for inguinal nodal recurrence in this case include: (a) aberrant lymphatic drainage due to disruption of normal lymphatic pathways during prior treatments; (b) inability to address the lateral external iliac nodes during surgery or adjuvant RT; and (c) escape from ADT-aided control of microscopic disease at CRPC conversion. Detection, sampling, and SABR targeting of recurrence aided by PSMA PET/CECT help timely delivery of salvage therapy and favorable response. Our findings suggest keeping a high index of suspicion for atypical metastatic sites in patients who have failed on routine salvage therapies, especially in younger patients with aggressive histology or short PSA doubling time.

Author contributions

Study concept and design: Shikha Goyal, Renu Madan.
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Data analysis: Shikha Goyal, Poorva Vias.
Drafting of manuscript: Shikha Goyal, Kannan Periasamy, Renu Madan, Poorva Vias
Critical revision of the manuscript: Shikha Goyal, Kannan Periasamy, Renu Madan, Poorva Vias, Vigneshwaran Chandran.

Conflicts of interest

The authors declare no conflict of interest.

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