Cureus
Part of SPRINGER NATURE

Open Access Case Report

Consolidative Prostate Radiotherapy in de Novo Oligometastatic Mixed Small Cell Neuroendocrine Prostate Cancer: A Case Report

Review began 10/13/2026
Review ended 10/27/2026
Published 10/30/2026

© **Copyright** 2026
Benhjar et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI: 10.7759/cureus.118848

Fatima Benhjar [1], Imane Bellahyane [1], Amal Bennani [2], Soumiya Samba [1], Ahmed Bensgheir [1], Soufiane Berhili [1], Mohamed Moukhlissi [1], Loubna Mezouar [1]

1. Radiation Oncology, Faculty of Medicine and Pharmacy, Mohammed First University, Oujda, MAR 2. Anatomopathology, Faculty of Medicine and Pharmacy, Mohammed First University, Oujda, MAR

Corresponding author: Fatima Benhjar, benhjarf@gmail.com

Abstract

Small cell neuroendocrine carcinoma of the prostate is a rare and aggressive variant, and its de novo coexistence with acinar adenocarcinoma is exceptional. We present the case of a 67-year-old man with a history of treated gastric adenocarcinoma who presented with dysuria and a prostate-specific antigen (PSA) level of 14.1 ng/mL. Multiparametric magnetic resonance imaging (MRI) revealed an 11-mm Prostate Imaging-Reporting and Data System (PI-RADS) 4 lesion of the left peripheral zone. Transrectal biopsy showed a mixed tumor combining acinar adenocarcinoma (Gleason score 5+5=10) and a focal small cell carcinoma component, diagnosed on morphology and positive for synaptophysin and chromogranin A (Ki-67 index 25%). Computed tomography showed no visceral or nodal disease, and bone scintigraphy revealed four bone metastases. The disease met the European Society for Radiotherapy and Oncology-American Society for Radiation Oncology (ESTRO-ASTRO) definition of oligometastatic disease, although two extra-axial lesions classified it as high-volume according to CHAARTED criteria. After multidisciplinary discussion, the patient received three cycles of cisplatin and etoposide with combined androgen blockade, followed by consolidative moderately hypofractionated intensity-modulated radiotherapy (IMRT) to the prostate and seminal vesicle base (68 Gy in 25 fractions), with only grade 1 genitourinary toxicity. Follow-up bone scintigraphy showed markedly decreased uptake at all known sites, without new lesions. Under continued androgen deprivation, the patient remained asymptomatic, without evidence of progression on conventional imaging, at 16 months, with a PSA level of 0.006 ng/mL. This single case shows that consolidative prostate radiotherapy combined with platinum-based chemotherapy and androgen deprivation is feasible and well-tolerated in a selected patient with de novo oligometastatic mixed adenocarcinoma-small cell carcinoma of the prostate. Its specific contribution to the outcome cannot be determined, and follow-up remains short. PSA mainly reflects the adenocarcinoma component and should not be used alone to monitor mixed tumors.

Categories: Urology, Radiation Oncology, Oncology
Keywords: hypofractionated radiotherapy, neuroendocrine, oligometastatic, prostate cancer, small cell carcinoma

Introduction

Small cell neuroendocrine carcinoma of the prostate, first described in 1977 [1], is a rare and aggressive variant, accounting for approximately 0.5-2% of prostate cancers [2,3]. It is characterized by early dissemination, prostate-specific antigen (PSA) levels that are often low relative to tumor burden, poor response to androgen deprivation therapy (ADT), and a median survival usually below two years [2,4]. It more frequently emerges after prolonged hormonal therapy, whereas de novo presentation, particularly as a mixed tumor combining acinar adenocarcinoma and small cell carcinoma (hereafter, mixed adenocarcinoma-small cell carcinoma), is uncommon [5-7].

Mixed tumors combine a hormone-sensitive acinar component and a hormone-independent neuroendocrine component that share a common clonal origin [8], and therefore require management addressing both components rather than a standard approach designed for either histology alone. Systemic treatment of the small cell component is extrapolated from small cell lung cancer and relies on platinum-etoposide chemotherapy, whereas ADT remains indicated for the adenocarcinoma component [9-11].

In newly diagnosed metastatic prostate adenocarcinoma, radiotherapy to the primary tumor improved overall survival in patients with a low metastatic burden in the STAMPEDE trial [12], and the STOPCAP meta-analysis showed that this benefit was confined to patients with fewer than five bone metastases [13]. The HORRAD trial did not show an overall survival benefit in unselected patients with bone metastases [14], whereas in the PEACE-1 trial prostate radiotherapy improved radiographic progression-free survival in patients with low-volume disease [15]. These trials enrolled patients with adenocarcinoma and did not report outcomes for small cell or neuroendocrine histology, so their results cannot be directly applied to mixed tumors. In neuroendocrine prostate carcinoma, the role of prostate radiotherapy has not been evaluated prospectively, and evidence is limited to registry data and small retrospective series [4,16].

Moderate hypofractionation has become a standard for localized prostate cancer, with non-inferior efficacy and comparable toxicity compared with conventional fractionation [17,18], and hypofractionated schedules were also used for prostate radiotherapy in the metastatic setting [12]. A shorter overall treatment time is of particular practical value in patients who also require chemotherapy and ADT.

Given the rarity of this entity and the absence of prospective data, the integration of chemotherapy, ADT, and local treatment should be decided within a multidisciplinary tumor board, as recommended by current guidelines [11]. We report a case of de novo oligometastatic mixed adenocarcinoma-small cell carcinoma of the prostate treated with platinum-etoposide chemotherapy, ADT, and consolidative moderately hypofractionated radiotherapy to the primary tumor, without evidence of progression on conventional imaging at 16 months.

Case Presentation

A 67-year-old man had a history of gastric adenocarcinoma diagnosed in 2021 and treated with neoadjuvant FLOT (docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil) chemotherapy followed by total gastrectomy. The recommended postoperative FLOT cycles were not administered because the patient was lost to follow-up after surgery; he subsequently resumed surveillance, with no evidence of gastric cancer recurrence. He was a former smoker (quit four years earlier) and a current user of chewing tobacco. His family history was notable for multiple cancers, including endometrial cancer (mother and one sister), breast cancer (two sisters), and gastric cancer (brother). Genetic counseling and germline testing were recommended but could not be performed because of financial constraints.

In December 2024, he was evaluated for dysuria, with a PSA level that had increased from 10 to 15 ng/mL over the previous three months. His Eastern Cooperative Oncology Group (ECOG) performance status was 0. Digital rectal examination revealed a hard nodule in the left lobe.

PSA was 14.1 ng/mL in January 2025. Multiparametric MRI (December 2024) showed a 20-g prostate with an 11-mm PI-RADS 4 lesion of the left peripheral zone (hypointense on T2-weighted imaging, hyperintense on diffusion-weighted imaging with restricted apparent diffusion coefficient, and moderately enhancing after gadolinium injection), without extracapsular extension, seminal vesicle invasion, or lymphadenopathy (Figure *1*). Transrectal targeted and systematic biopsies (March 2025) revealed acinar adenocarcinoma at all sampled sites: Gleason 5+5=10 (International Society of Urological Pathology (ISUP) grade group 5) in 4 of 5 targeted cores and Gleason 4+4=8 in 1; Gleason 4+4=8 and 5+5=10 in 3 cores each on the right side; and Gleason 5+5=10 on the left side. The tumor showed solid, cribriform, and trabecular architecture, with perineural invasion in the targeted cores and no lymphovascular invasion.

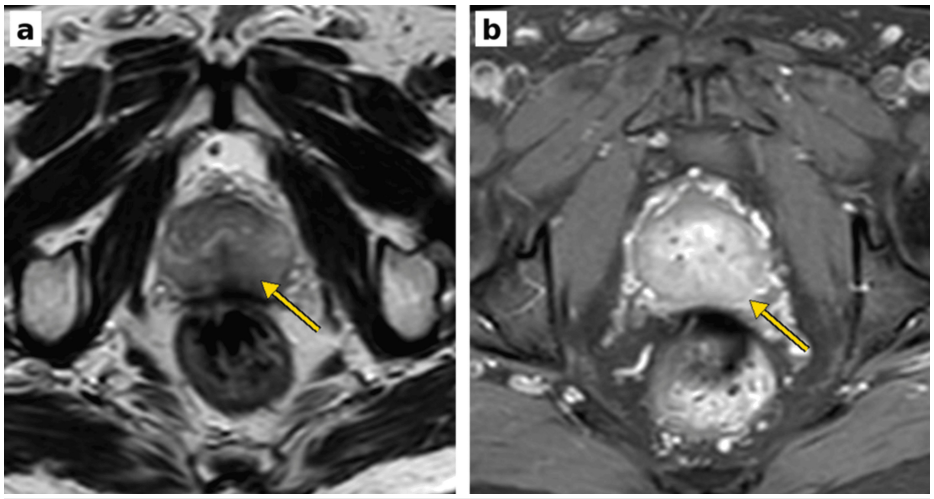


FIGURE 1: Multiparametric magnetic resonance imaging of the prostate at diagnosis

(a) Axial T2-weighted image at the mid-gland level showing an ill-defined hypointense lesion of the left posterior peripheral zone (arrow). (b) Axial post-contrast T1-weighted image at the same level showing moderate enhancement of the lesion (arrow). The lesion measured 11 mm and was classified as PI-RADS 4, without extracapsular extension or seminal vesicle invasion.

PI-RADS: Prostate Imaging-Reporting and Data System

In the targeted and left-sided cores, focal solid nests of small basophilic cells with scant cytoplasm and a

high nuclear-to-cytoplasmic ratio, morphologically distinct from the acinar component, were identified. Based on this morphology, these nests were diagnosed as a small cell neuroendocrine carcinoma component, and the diagnosis was confirmed by immunohistochemical positivity for synaptophysin and chromogranin A (Figure *2*). The proportion of each component was not quantified. The Ki-67 index, assessed on the two blocks containing the neuroendocrine component, was 25%. INSM1, CD56, androgen receptor, and NKX3.1 immunostaining could not be performed because these antibodies were not available in our laboratory.

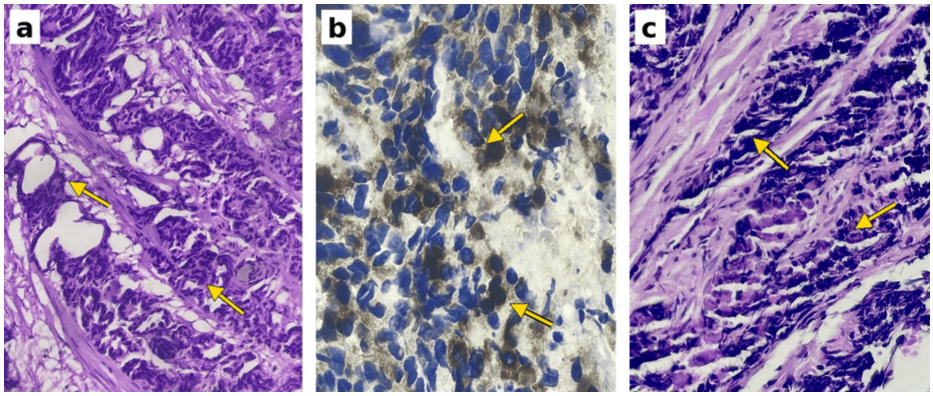


FIGURE 2: Histopathological features of the mixed prostatic tumor on biopsy

(a) Acinar adenocarcinoma, Gleason score 5+5=10, with solid and cribriform architecture (arrows) (hematoxylin and eosin staining). (b) Immunohistochemistry showing granular cytoplasmic synaptophysin expression in tumor cells of the neuroendocrine component (arrows). (c) Small cell neuroendocrine carcinoma component composed of nests of small basophilic cells with scant cytoplasm (arrows) (hematoxylin and eosin staining, ×20).

CT of the chest, abdomen and pelvis showed no visceral or nodal metastases, whereas bone scintigraphy revealed four bone metastases (T11, L4, right supraorbital region, right scapula); single-photon emission computed tomography (SPECT)/CT showed osteolytic lesions of T11 and L4 with peripheral tracer uptake (Figures *3A*, *3C*). Spinal MRI (April 2025) confirmed T11 and L4 involvement, without epidural extension or spinal cord compression. The disease was staged cT2a N0 M1b. With four bone metastases and no visceral or nodal disease, it met the ESTRO-ASTRO definition of oligometastatic disease, although the two lesions located outside the vertebral bodies and pelvis corresponded to high-volume disease according to CHAARTED criteria (see Discussion). Prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) was requested but could not be performed because of financial constraints, and staging therefore relied on CT and bone scintigraphy. The bone lesions were not biopsied.

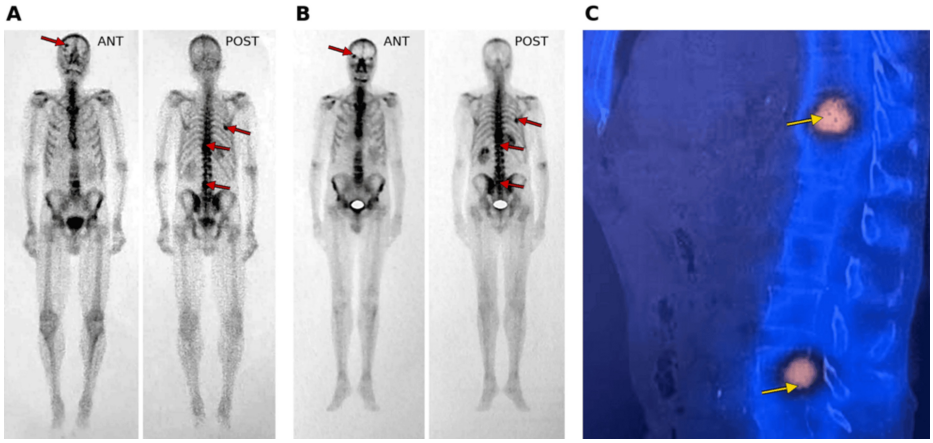


FIGURE 3: Whole-body bone scintigraphy and SPECT/CT before and after multimodal treatment

(A) Whole-body bone scintigraphy at diagnosis (April 2025), anterior (ANT) and posterior (POST) views, showing focal uptake in the right supraorbital region, the tip of the right scapula, T11 and L4 (red arrows). (B) Follow-up whole-body bone scintigraphy (November 2025) showing persistent foci with markedly decreased uptake at the same sites (red arrows) and no new lesion; the injected activity differed between examinations (530 MBq at baseline, 740 MBq at follow-up), which limits visual comparison of overall image intensity. (C) Sagittal SPECT/CT fusion at diagnosis showing osteolytic lesions of T11 and L4 with peripheral tracer uptake (yellow arrows).

SPECT: single-photon emission computed tomography

After multidisciplinary discussion, the patient received cisplatin-etoposide with concomitant combined androgen blockade (goserelin plus bicalutamide). Chemotherapy was stopped after three cycles by the decision of the multidisciplinary tumor board, based on tolerance after previous gastrectomy, the response obtained, and the aim of not delaying local treatment (see Discussion). It was well-tolerated, without grade 3 or higher toxicity, and PSA fell to 0.03 ng/mL. He was then referred for consolidative radiotherapy to the primary tumor: the prostate and base of the seminal vesicles received 68 Gy in 25 fractions of 2.72 Gy using intensity-modulated radiotherapy (IMRT), delivered as volumetric modulated arc therapy (VMAT) on an Elekta Versa HD linear accelerator (Elekta AB, Stockholm, Sweden), without elective nodal irradiation. Treatment was planned with the Monaco treatment planning system (Elekta AB); the clinical target volume included the prostate and the base of the seminal vesicles, the organs at risk included the rectum, bladder, anal canal, bowel, femoral heads and penile bulb, and the maximum dose was 72.6 Gy (106.8% of the prescribed dose) (Figure 4). No metastasis-directed radiotherapy was delivered. Treatment was well-tolerated, with only grade 1 genitourinary toxicity.

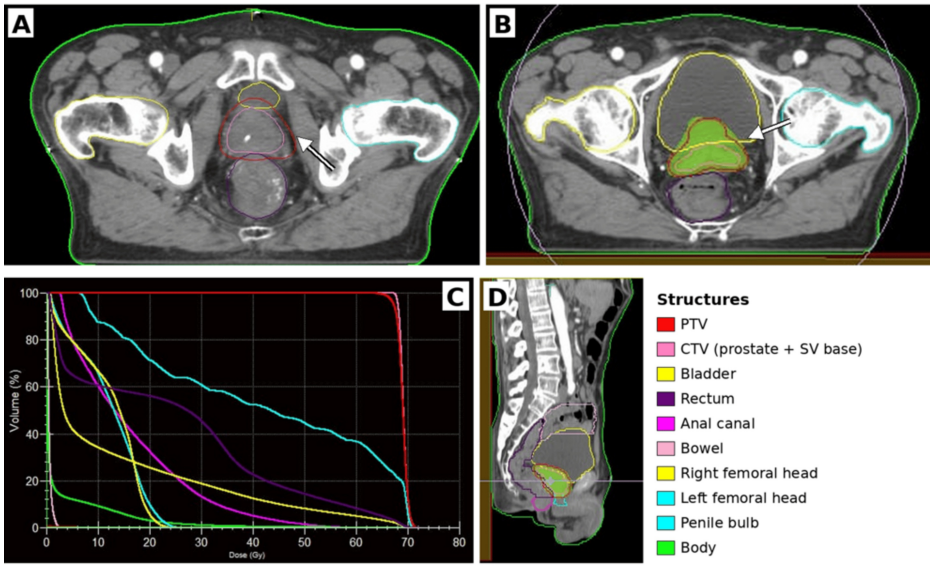


FIGURE 4: Moderately hypofractionated volumetric modulated arc therapy plan (68 Gy in 25 fractions)

(A) Axial planning CT through the prostate showing the planning target volume (PTV, red) surrounding the clinical target volume (CTV, pink) (arrow), with the bladder, rectum, and femoral heads contoured as organs at risk. (B) Axial CT at the level of the seminal vesicle base showing the dose distribution (green shading) conforming to the target (arrow). (C) Dose-volume histogram showing target coverage and organ-at-risk doses. (D) Sagittal view with the dose distribution. Structure colors are shown in the key.

SV: seminal vesicle

Bone scintigraphy performed at the end of radiotherapy (November 2025), seven months after the first goserelin injection, showed persistent but markedly decreased uptake at all known metastatic sites, without new lesions (Figure *3B*); control CT showed no visceral or nodal disease, and PSA was 0.015 ng/mL. ADT was continued, and stereotactic body radiotherapy (SBRT) was reserved for oligoprogression. Because PSA does not reflect the neuroendocrine component, follow-up is not guided by PSA: it includes clinical assessment and PSA every three months, and CT of the chest, abdomen, and pelvis with bone scintigraphy every six months, irrespective of PSA; CT also serves for surveillance of the gastric cancer. Any new or enlarging lesion, particularly lytic or visceral, with a low PSA would prompt fluorodeoxyglucose (FDG) PET/CT and, when feasible, biopsy to document neuroendocrine progression. CT in April 2026 showed no evidence of gastric cancer recurrence and no visceral or nodal disease. At last follow-up in July 2026, 16 months after diagnosis, the patient remained asymptomatic on ADT, without clinical or radiological evidence of progression on conventional imaging, with a PSA level of 0.006 ng/mL. The clinical course is summarized in Table *1*.

Timepoint	Event
December 2024	Dysuria; PSA increased from 10 to 15 ng/mL over three months; multiparametric MRI: 11-mm PI-RADS 4 lesion of the left peripheral zone, 20-g prostate
January 2025	PSA 14.1 ng/mL
March 2025	Targeted and systematic biopsies: acinar adenocarcinoma (Gleason 5+5=10, bilateral) with a focal small cell neuroendocrine carcinoma component (synaptophysin+, chromogranin A+, Ki-67 25%)
April 2025	CT chest-abdomen-pelvis: no visceral or nodal disease; bone scintigraphy with SPECT/CT: four bone metastases (T11, L4, right supraorbital region, right scapula); spinal MRI: no epidural extension (cT2a N0 M1b); first goserelin injection, with bicalutamide
June-August 2025	Cisplatin-etoposide, three cycles (last cycle in August 2025); second goserelin injection in July 2025
August 2025	PSA 0.03 ng/mL after chemotherapy
September-November 2025	CT simulation (September 2025); VMAT (Elekta Versa HD) to the prostate and seminal vesicle base, 68 Gy in 25 fractions, five fractions per week, completed in November 2025; grade 1 genitourinary toxicity
November-December 2025	Bone scintigraphy: persistent foci with markedly decreased uptake, no new lesion; CT: no visceral or nodal disease; PSA 0.015 ng/mL
April 2026	CT chest-abdomen-pelvis: no evidence of gastric cancer recurrence; no visceral or nodal disease
July 2026	Asymptomatic on ADT, no evidence of progression on conventional imaging; PSA 0.006 ng/mL

TABLE 1: Timeline of diagnosis, treatment, and follow-up

MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging-Reporting and Data System; PSA: prostate-specific antigen; SPECT: single-photon emission computed tomography; VMAT: volumetric modulated arc therapy; ADT: androgen deprivation therapy

Discussion

Small cell carcinoma of the prostate is rare, and about two-thirds of patients are metastatic at diagnosis, most often to the bone, liver, and lungs [2,4]. Treatment-emergent neuroendocrine disease, which arises through lineage plasticity under androgen receptor inhibition, is far more frequent than de novo disease [5]. Mixed tumors share a common clonal origin with the adenocarcinoma [8], which explains their dual behavior: a hormone-sensitive acinar component and a hormone-independent neuroendocrine component. Neuroendocrine transformation is associated with loss of androgen receptor signaling and of RB1 and TP53 [8,19], and combined tumor-suppressor alterations define an aggressive variant that is sensitive to platinum-based chemotherapy [10].

Small cell carcinoma is defined by morphology, and immunohistochemistry serves as confirmation; no Ki-67 threshold is required for diagnosis [6]. In mixed tumors, only the acinar component is graded [7]. In our patient, the diagnosis relied on solid nests of small basophilic cells with scant cytoplasm, distinct from the acinar component, confirmed by two neuroendocrine markers (synaptophysin and chromogranin A). The Ki-67 index (25%) is lower than usually reported for small cell carcinoma (often >50%) [20]. Because it was assessed on blocks containing both components, with a focal neuroendocrine component, it probably underestimates the proliferation of the small cell component, and limited biopsy sampling may also have contributed. The immunohistochemical panel was limited: INSM1 and CD56 would have strengthened the neuroendocrine diagnosis, and androgen receptor and NKX3.1 staining would have characterized the lineage and hormone sensitivity of each component. These markers could not be performed, and the proportion of each component was not quantified. The neuroendocrine component may also be underestimated by imaging: PSMA PET/CT is more accurate than conventional imaging for adenocarcinoma [21], but neuroendocrine differentiation suppresses PSMA expression [22].

Our patient had four bone lesions without visceral disease and therefore met the ESTRO-ASTRO definition of oligometastatic disease [23], whereas two extra-axial lesions corresponded to high-volume disease according to CHAARTED criteria [24]. These classifications are not equivalent, and the distinction matters because the benefit of prostate radiotherapy in metastatic adenocarcinoma is closely linked to metastatic burden. STAMPEDE showed improved overall survival only in patients with low-burden disease, defined

using CHAARTED criteria [12]; by this definition, our patient would have been classified as high burden. The STOPCAP meta-analysis restricted the benefit to patients with fewer than five bone metastases [13], HORRAD showed no survival benefit in unselected patients with bone metastases [14], and PEACE-1 showed improved radiographic progression-free survival in low-volume disease, together with fewer serious genitourinary events [15]. The indication for local treatment in our patient therefore relied on the low number of bone metastases, consistent with STOPCAP, and on the aim of local control of a high-grade tumor, not on CHAARTED volume.

Two levels of evidence must be kept separate. Randomized trials define which patients with metastatic adenocarcinoma benefit from prostate radiotherapy [12-15] or metastasis-directed therapy [25-28], but they enrolled patients with adenocarcinoma and cannot be directly applied to neuroendocrine tumors. Evidence specific to neuroendocrine prostate carcinoma is retrospective and hypothesis-generating only. In a National Cancer Database analysis of small cell carcinoma of the prostate, multimodal treatment was associated with improved survival [4]. In a retrospective series of 32 patients with neuroendocrine prostate carcinoma, 78% of whom had distant metastases, local therapy (radical prostatectomy or radiotherapy) was associated with longer median overall survival (36 vs 13 months), although selection bias cannot be excluded [16]. By analogy with extensive-stage small cell lung cancer, in which consolidative thoracic radiotherapy after response to chemotherapy reduced intrathoracic progression and improved two-year survival in the CREST trial [29], prostate radiotherapy after response to platinum-etoposide could improve local control of a highly proliferative primary tumor and prevent pelvic complications, but this remains hypothetical.

Published de novo mixed tumors treated with multimodal therapy are summarized in Table *2*. Platinum-etoposide with ADT was the usual backbone, given for six or seven cycles, and local treatment was rarely used [30-33]. Two patients with extensive or visceral disease remained controlled on systemic therapy alone at the time of reporting [30,32], cytoreductive prostatectomy after seven cycles provided only transient local benefit [31], and prolonged complete remission was reported after multimodal treatment including prostate radiotherapy [33]. Our case differs by its limited metastatic burden, a shorter chemotherapy course, and moderately hypofractionated prostate radiotherapy. These isolated favorable reports, including ours, are subject to publication bias, and follow-up is short in most of them.

Study	Stage and metastatic burden at diagnosis	Systemic treatment	Local treatment	Reported outcome
Brammer et al., 2011 [33]	T2c N1 M1c; extensive metastatic disease	Cisplatin-etoposide, 6 cycles; hormonal therapy	Prostate radiotherapy, 73 Gy	Complete remission lasting more than 36 months
Artamonova et al., 2024 [30]	T3c N1 M1; bone, retroperitoneal nodes, lung	Carboplatin-etoposide, 6 cycles; ADT, then apalutamide	None	Major response on PSMA and FDG PET/CT; alive on ADT plus apalutamide at report
Tang et al., 2026 [32]	T3b N1 M1; extensive bone metastases	Cisplatin-etoposide, 6 cycles; goserelin plus apalutamide	None	Disease controlled at about 8 months
Wang et al., 2026 [31]	T4 N1 M1c; pelvic and distant nodes, suspected lung metastases	Cisplatin-etoposide, 7 cycles	Cytoreductive radical prostatectomy	Local and nodal progression 5 months after surgery; death about 18 months after diagnosis
Present case	cT2a N0 M1b; 4 bone metastases (oligometastatic, CHAARTED high-volume)	Cisplatin-etoposide, 3 cycles; goserelin plus bicalutamide	Prostate and seminal vesicle base, 68 Gy in 25 fractions (VMAT)	No evidence of progression on conventional imaging at 16 months; PSA 0.006 ng/mL

TABLE 2: Published cases of de novo mixed adenocarcinoma-small cell carcinoma of the prostate treated with multimodal therapy

ADT: androgen deprivation therapy; PSMA: prostate-specific membrane antigen; FDG: fluorodeoxyglucose; PET: positron emission tomography; VMAT: volumetric modulated arc therapy; PSA: prostate-specific antigen

Chemotherapy was limited to three cycles, rather than the four to six usually given for small cell carcinoma [9,11], by the decision of the multidisciplinary tumor board. The decision took into account the patient's tolerance after total gastrectomy and FLOT chemotherapy, the marked biochemical response after three cycles (PSA 0.03 ng/mL) without new lesions, and the aim of not delaying local consolidation. The main risk of this strategy is that residual micrometastatic small cell disease was left untreated, and whether three cycles provide sufficient control of the small cell component is uncertain. This risk justified imaging-based

surveillance irrespective of PSA and the plan to reintroduce platinum-etoposide in case of neuroendocrine progression. Radiotherapy was delivered sequentially, as consolidation after response.

The schedule used (68 Gy in 25 fractions) corresponds to an equivalent dose in 2-Gy fractions (EQD2) of about 82 Gy for adenocarcinoma (α/β = 1.5 Gy) and about 72 Gy for the small cell component (α/β = 10 Gy), without correction for tumor repopulation, and allowed treatment to be completed in five weeks [17,18]. The EQD2 for the small cell component exceeds the doses used for limited-stage small cell lung cancer, such as 66 Gy in 33 fractions [34]. We chose a radical-dose schedule rather than the lower-dose schedules used in STAMPEDE (36 Gy in six weekly fractions or 55 Gy in 20 fractions) [12] because of the limited number of metastases, the good systemic response, and the aim of durable local control of a high-grade tumor harboring a small cell component; a radical prostate dose was also used in PEACE-1 [15]. Elective nodal irradiation was omitted because pelvic nodes were not involved, prostate-only fields were used in STAMPEDE and PEACE-1 [12,15], the biochemical benefit of nodal irradiation was demonstrated only in high-risk localized adenocarcinoma [35], and toxicity had to be limited after gastrectomy and platinum-based chemotherapy. Metastasis-directed SBRT was deferred because all lesions had responded, to limit cumulative toxicity and to keep it available for oligoprogression. Upfront SBRT to all four lesions would have been a reasonable alternative, supported by randomized phase 2 trials in oligometastatic adenocarcinoma [25-28] but not evaluated in neuroendocrine disease.

The limitations of this report include staging by conventional imaging, as PSMA PET/CT could not be performed for financial reasons; the limited immunohistochemical panel; the absence of histological confirmation of the bone lesions; and short follow-up. Because of the history of gastric adenocarcinoma, bone metastases from this primary could not be formally excluded. Several elements favor a prostatic origin: serial CT, also performed for gastric cancer surveillance, showed no anastomotic, nodal, hepatic, peritoneal, or other visceral recurrence, most recently in April 2026; isolated bone metastases from gastric cancer are rare; the lytic pattern is compatible with a neuroendocrine component; and all lesions showed decreased uptake in parallel with the PSA decline. However, endoscopy and gastric tumor markers were not performed, and cisplatin-etoposide is also active against gastric adenocarcinoma, so this response does not prove a prostatic origin. Only biopsy of an accessible lesion could have settled this question, and the attribution of all lesions to prostate cancer therefore remains presumptive.

Given the patient's two primary cancers and his family history of endometrial, breast and gastric cancers, a hereditary cancer syndrome such as Lynch syndrome or a BRCA2 pathogenic variant cannot be excluded. Germline testing is recommended for all patients with metastatic prostate cancer [11] and would have had direct therapeutic implications: BRCA2 alterations predict sensitivity to platinum agents and poly(ADP-ribose) polymerase (PARP) inhibitors, and mismatch repair deficiency is an indication for immune checkpoint inhibitors. It would also allow cascade testing and adapted screening of relatives. Neither germline testing nor tumor mismatch repair testing could be performed. Mismatch repair immunohistochemistry (MLH1, MSH2, MSH6, PMS2) on the archived prostate biopsy or gastrectomy specimen is a feasible, low-cost first step, and loss of expression would justify prioritizing germline testing. At progression, carboplatin-cabazitaxel [36] and delta-like ligand 3 (DLL3)-targeted therapies, such as tarlatamab [37,38], are emerging options.

Response assessment in this setting also deserves attention, because the neuroendocrine component may progress silently [9]. Each method used in our patient has limitations. PSA is produced by the acinar component, and low or discordant PSA levels are a recognized feature of aggressive variant prostate cancer [9]; the deep PSA decline therefore reflects the acinar component and does not exclude activity of the neuroendocrine component. Bone scintigraphy depends on osteoblastic reaction and may underestimate lytic lesions, which are frequent with neuroendocrine disease, and CT is of limited value for assessing bone response. PSMA PET/CT, although more accurate than conventional imaging for adenocarcinoma [21], may also underestimate this component because neuroendocrine differentiation suppresses PSMA expression [22], making FDG PET/CT a useful complement; neither could be performed. When PET is not affordable, bone scintigraphy combined with CT remains a practical alternative, provided that it is performed beyond the flare window described within the first 12 weeks of systemic therapy [39]. In our patient, bone scintigraphy was performed seven months after the first goserelin injection, so the decrease in uptake is unlikely to reflect a flare-related change. Progression of the neuroendocrine component would most likely appear as new or enlarging lytic or visceral lesions with a persistently low PSA, which would prompt FDG PET/CT and, when feasible, biopsy.

The particularity of this case lies in the dual nature of the tumor, which called for a strategy addressing each component: platinum-etoposide chemotherapy for the neuroendocrine component, ADT for the acinar component, and prostate radiotherapy for both. In a single case with 16 months of follow-up, the specific contribution of each modality cannot be determined, and the absence of progression cannot be attributed to radiotherapy.

Conclusions

Mixed adenocarcinoma-small cell carcinoma of the prostate is an aggressive variant that requires management addressing both of its components. In this single patient with de novo oligometastatic disease,

platinum-etoposide chemotherapy combined with ADT, followed by consolidative moderately hypofractionated radiotherapy to the primary tumor, was feasible and well-tolerated, and was followed by a favorable response without evidence of progression on conventional imaging at 16 months. Because the contribution of radiotherapy cannot be separated from that of systemic therapy, the origin of the bone lesions remains presumptive, and follow-up is short, this observation is hypothesis-generating and does not establish consolidative prostate radiotherapy as a standard treatment. In such rare tumors, treatment decisions should be made within a multidisciplinary tumor board, and follow-up should rely on periodic imaging rather than PSA alone. Larger cohorts and prospective studies are needed to define the role of local treatment in oligometastatic neuroendocrine prostate cancer.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Fatima Benhjar, Imane Bellahyane, Amal Bennani, Soufiane Berhili, Mohamed Moukhlissi, Ahmed Bensgheir, Soumiya Samba, Loubna Mezouar

Acquisition, analysis, or interpretation of data: Fatima Benhjar, Imane Bellahyane, Amal Bennani, Soufiane Berhili, Mohamed Moukhlissi, Ahmed Bensgheir, Soumiya Samba, Loubna Mezouar

Drafting of the manuscript: Fatima Benhjar, Imane Bellahyane, Amal Bennani, Soufiane Berhili, Mohamed Moukhlissi, Ahmed Bensgheir, Soumiya Samba, Loubna Mezouar

Critical review of the manuscript for important intellectual content: Fatima Benhjar, Imane Bellahyane, Amal Bennani, Soufiane Berhili, Mohamed Moukhlissi, Ahmed Bensgheir, Soumiya Samba, Loubna Mezouar

Supervision: Soufiane Berhili, Mohamed Moukhlissi, Loubna Mezouar

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Wenk RE, Bhagavan BS, Levy R, Miller D, Weisburger W: Ectopic ACTH, prostatic oat cell carcinoma, and marked hypernatremia. Cancer. 1977, 40:773-8. 10.1002/1097-0142(197708)40:2<773::aid-cncr2820400226>3.0.co;2-i
2. Deorah S, Rao MB, Raman R, Gaitonde K, Donovan JF: Survival of patients with small cell carcinoma of the prostate during 1973-2003: a population-based study. BJU Int. 2012, 109:824-30. 10.1111/j.1464-410X.2011.10523.x
3. Zaffuto E, Pompe R, Zanaty M, et al.: Contemporary incidence and cancer control outcomes of primary neuroendocrine prostate cancer: a SEER database analysis. Clin Genitourin Cancer. 2017, 15:e793-800. 10.1016/j.clgc.2017.04.006
4. Metzger AL, Abel S, Wegner RE, et al.: Patterns of care and outcomes in small cell carcinoma of the prostate: a national cancer database analysis. Prostate. 2019, 79:1457-61. 10.1002/pros.23864
5. Aggarwal R, Huang J, Alumkal JJ, et al.: Clinical and genomic characterization of treatment-emergent small-cell neuroendocrine prostate cancer: a multi-institutional prospective study. J Clin Oncol. 2018, 36:2492-503. 10.1200/JCO.2017.77.6880
6. Netto GJ, Amin MB, Berney DM, et al.: The 2022 World Health Organization classification of tumors of the urinary system and male genital organs-Part B: prostate and urinary tract tumors. Eur Urol. 2022, 82:469-82. 10.1016/j.eururo.2022.07.002
7. Epstein JI, Amin MB, Beltran H, et al.: Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. Am J Surg Pathol. 2014, 38:756-67. 10.1097/PAS.0000000000000208
8. Beltran H, Prandi D, Mosquera JM, et al.: Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer. Nat Med. 2016, 22:298-305. 10.1038/nm.4045
9. Aparicio AM, Harzstark AL, Corn PG, et al.: Platinum-based chemotherapy for variant castrate-resistant prostate cancer. Clin Cancer Res. 2013, 19:3621-30. 10.1158/1078-0432.CCR-12-3791
10. Aparicio AM, Shen L, Tapia EL, et al.: Combined tumor suppressor defects characterize clinically defined aggressive variant prostate cancers. Clin Cancer Res. 2016, 22:1520-30. 10.1158/1078-0432.CCR-15-1259
11. Spratt DE, Srinivas S, Adra N, et al.: Prostate cancer, version 3.2026, NCCN Clinical Practice Guidelines in

Oncology. J Natl Compr Canc Netw. 2025, 23:469-93. 10.6004/jnccn.2025.0052
12. Parker CC, James ND, Brawley CD, et al.: Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet. 2018, 392:2353-66. 10.1016/S0140-6736(18)32486-3
13. Burdett S, Boevé LM, Ingleby FC, et al.: Prostate radiotherapy for metastatic hormone-sensitive prostate cancer: a STOPCAP systematic review and meta-analysis. Eur Urol. 2019, 76:115-24. 10.1016/j.eururo.2019.02.003
14. Boevé LM, Hulshof MC, Vis AN, et al.: Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: data from the HORRAD trial. Eur Urol. 2019, 75:410-8. 10.1016/j.eururo.2018.09.008
15. Bossi A, Foulon S, Maldonado X, et al.: Efficacy and safety of prostate radiotherapy in de novo metastatic castration-sensitive prostate cancer (PEACE- 1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. Lancet. 2024, 404:2065-76. 10.1016/S0140-6736(24)01865-8
16. Kimura S, Terada N, Soumiya S, et al.: Local therapy can enhance the prognosis of certain patients with pathologically diagnosed neuroendocrine prostate carcinoma. Life (Basel). 2025, 15:797. 10.3390/life15050797
17. Dearnaley D, Syndikus I, Mossop H, et al.: Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol. 2016, 17:1047-60. 10.1016/S1470-2045(16)30102-4
18. Catton CN, Lukka H, Gu CS, et al.: Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. J Clin Oncol. 2017, 35:1884-90. 10.1200/JCO.2016.71.7397
19. Beltran H, Rickman DS, Park K, et al.: Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets. Cancer Discov. 2011, 1:487-95. 10.1158/2159-8290.CD-11-0130
20. Wang W, Epstein JI: Small cell carcinoma of the prostate. A morphologic and immunohistochemical study of 95 cases. Am J Surg Pathol. 2008, 32:65-71. 10.1097/PAS.0b013e318058a96b
21. Hofman MS, Lawrentschuk N, Francis RJ, et al.: Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet. 2020, 395:1208-16. 10.1016/S0140-6736(20)30314-7
22. Bakht MK, Derecichei I, Li Y, et al.: Neuroendocrine differentiation of prostate cancer leads to PSMA suppression. Endocr Relat Cancer. 2018, 26:131-46. 10.1530/ERC-18-0226
23. Lievens Y, Guckenberger M, Gomez D, et al.: Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. Radiother Oncol. 2020, 148:157-66. 10.1016/j.radonc.2020.04.003
24. Sweeney CJ, Chen YH, Carducci M, et al.: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med. 2015, 373:737-46. 10.1056/NEJMoa1503747
25. Ost P, Reynders D, Decaestecker K, et al.: Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. J Clin Oncol. 2018, 36:446-53. 10.1200/JCO.2017.75.4853
26. Phillips R, Shi WY, Deek M, et al.: Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. JAMA Oncol. 2020, 6:650-9. 10.1001/jamaoncol.2020.0147
27. Tang C, Sherry AD, Haymaker C, et al.: Addition of metastasis-directed therapy to intermittent hormone therapy for oligometastatic prostate cancer: the EXTEND phase 2 randomized clinical trial. JAMA Oncol. 2023, 9:825-34. 10.1001/jamaoncol.2023.0161
28. Palma DA, Olson R, Harrow S, et al.: Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet. 2019, 393:2051-58. 10.1016/S0140-6736(18)32487-5
29. Slotman BJ, van Tinteren H, Praag JO, et al.: Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet. 2015, 385:36-42. 10.1016/S0140-6736(14)61085-0
30. Artamonova N, Djanani A, Schmiederer A, et al.: Small cell neuroendocrine prostate cancer with adenocarcinoma components-case report and literature review. Transl Androl Urol. 2024, 13:868-78. 10.21037/tau-23-541
31. Wang Y, Wang Q, Yang H: Case report: cytoreductive prostatectomy after platinum-etoposide chemotherapy for de novo metastatic prostatic small cell neuroendocrine carcinoma. Front Urol. 2026, 6:1934905. 10.3389/fruro.2026.1934905
32. Tang Y, Cai Y, Jiang X, Qiao R, Gao Z: De novo small cell neuroendocrine carcinoma of the prostate with extremely elevated PSA and Gleason score 5 + 5: a case report. Front Oncol. 2025, 15:1741030. 10.3389/fonc.2025.1741030
33. Brammer JE, Lulla P, Lynch GR: Complete remission in a patient with metastatic mixed adenocarcinoma/extrapulmonary small cell carcinoma of the prostate. Int J Clin Oncol. 2011, 16:722-5. 10.1007/s10147-011-0198-2
34. Faivre-Finn C, Snee M, Ashcroft L, et al.: Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol. 2017, 18:1116-25. 10.1016/S1470-2045(17)30318-2
35. Murthy V, Maitre P, Kannan S, et al.: Prostate-only versus whole-pelvic radiation therapy in high-risk and very high-risk prostate cancer (POP-RT): outcomes from phase III randomized controlled trial. J Clin Oncol. 2021, 39:1234-42. 10.1200/JCO.20.03282
36. Corn PG, Heath EI, Zurita A, et al.: Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: a randomised, open-label, phase 1-2 trial. Lancet Oncol. 2019, 20:1432-43. 10.1016/S1470-2045(19)30408-5
37. Puca L, Gavyert K, Sailer V, et al.: Delta-like protein 3 expression and therapeutic targeting in neuroendocrine prostate cancer. Sci Transl Med. 2019, 11:10.1126/scitranslmed.aav0891
38. Aggarwal R, Rottey S, Bernard-Tessier A, et al.: Safety and efficacy of tarlatamab in patients with

neuroendocrine prostate cancer: results from the phase 1b DeLLpro-300 study. Clin Cancer Res. 2025, 31:3854-63. 10.1158/1078-0432.CCR-25-1211

39. Scher HI, Morris MJ, Stadler WM, et al.: Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016, 34:1402-18. 10.1200/JCO.2015.64.2702