

CASE REPORT

***De novo* mixed neuroendocrine prostate cancer: a case report and literature review**

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Abstract

Background: Neuroendocrine prostate cancer (NEPC) represents a rare and highly aggressive subtype of prostate cancer that is prone to early metastatic progression. Currently, no standardized treatment protocol has been established for this disease, posing substantial challenges for its diagnosis and management. **Case:** This report provides a detailed account of the diagnostic and therapeutic course of an 82-year-old patient with *de novo* NEPC. The patient presented with a prostate mass identified on routine physical examination and was diagnosed with NEPC after comprehensive clinical work-up. Multiple distant metastases developed six months after radical prostatectomy. Through multidisciplinary collaboration, a personalized therapeutic regimen was implemented, and the patient achieved a partial response. **Conclusions:** This case suggests that multimodal diagnostic approaches and comprehensive therapeutic strategies are clinically valuable in the management of NEPC and may provide a reference for future studies.

Keywords

Neuroendocrine prostate cancer; Prostate cancer; Diagnosis; Treatment; Case report

1. Introduction

Prostate cancer (PCa) is the most prevalent malignant tumor in the male genitourinary system, with its incidence rate ranking second only to that of lung cancer [1]. Neuroendocrine prostate cancer (NEPC) is a rare subtype of PCa, accounting for 0.5%–2% of initial diagnoses. It is characterized by high-grade malignancy and poor prognosis [2]. Currently, our understanding of NEPC remains limited. This article reports the clinical diagnosis and treatment course of an 82-year-old patient with NEPC. The patient was found to have a prostate nodule during a physical examination and was ultimately diagnosed with *de novo* mixed-type NEPC after comprehensive evaluation. Although the patient underwent radical surgery, multiple metastases still developed postoperatively; subsequent radiotherapy and chemotherapy resulted in a favorable therapeutic response. This case may serve as a valuable reference for the diagnosis, treatment decision-making, and prognostic evaluation of similar clinical cases.

2. Case report

In August 2022, an 82-year-old male patient presented to our hospital for evaluation of a prostate nodule detected during a routine physical examination. The patient denied any significant symptoms. The past medical history was unremarkable, and there was no surgical history. Digital rectal examination revealed a palpable nodule in the right lobe of the prostate, firm to the touch, non-tender, with no blood staining on the

examining finger upon withdrawal. Blood tests revealed a carcinoembryonic antigen (CEA) level of 14.96 ng/mL, a total prostate-specific antigen (tPSA) level of 1.38 ng/mL, and a free prostate-specific antigen (fPSA) level of 0.33 ng/mL. Multiparametric magnetic resonance imaging (mp-MRI) revealed space-occupying lesions in the central gland and right peripheral zone of the prostate, with extracapsular extension. It was assigned a prostate imaging reporting and data system (PI-RADS) v2.1 score of 5 (Fig. 1). Transrectal ultrasound (TRUS) revealed a hypoechoic mass located slightly to the right of the central gland of the prostate, with an ill-defined border between the mass and the adjacent seminal vesicle. Pressure-based elastography yielded an approximate score of 2 points. Contrast-enhanced ultrasound (CEUS) showed that the mass exhibited earlier enhancement and washout than the contralateral prostate tissue, with hyperenhancement, suggesting the presence of PCa (Fig. 2). On 09 August, ultrasound-guided transperineal prostate biopsy was performed, with a total of 12 cores obtained. In addition to a standard systematic biopsy (10 cores from the inner and outer glands and the apex of both lobes), two additional targeted cores were obtained from the abnormally enhancing lesions identified on CEUS. Pathological examination of the biopsy specimens revealed a neuroendocrine tumor. Immunohistochemical staining showed the following results: 34 β E12 (–), P504S (±), P63 (–), synaptophysin (Syn) (+), and chromogranin A (CgA) (+). Three days later, the patient underwent ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomogra-

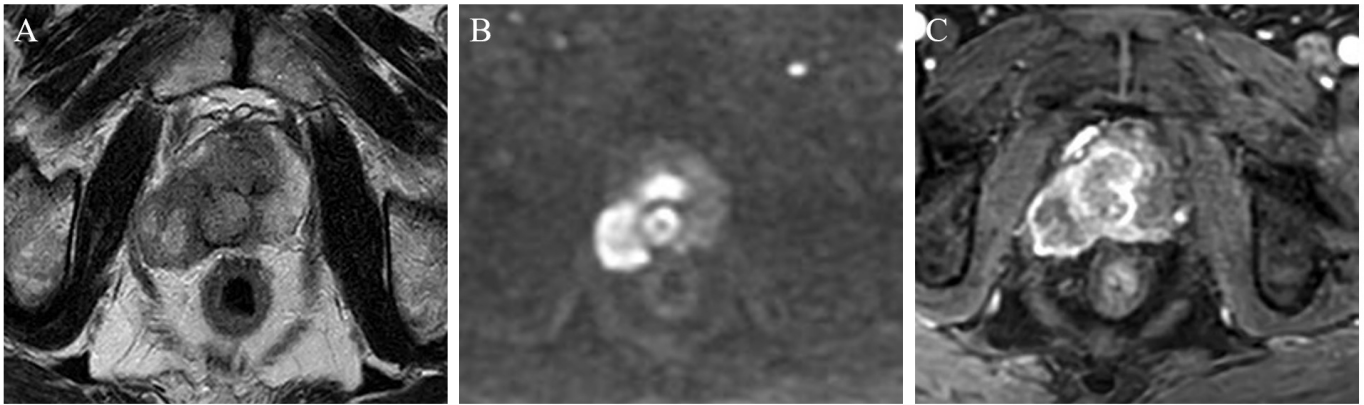


FIGURE 1. Imaging manifestations of NEPC on mp-MRI. (A) The lesion in the central gland and right peripheral zone of the prostate extends beyond the prostate capsule. (B) markedly restricted diffusion. (C) early heterogeneous enhancement following contrast administration.

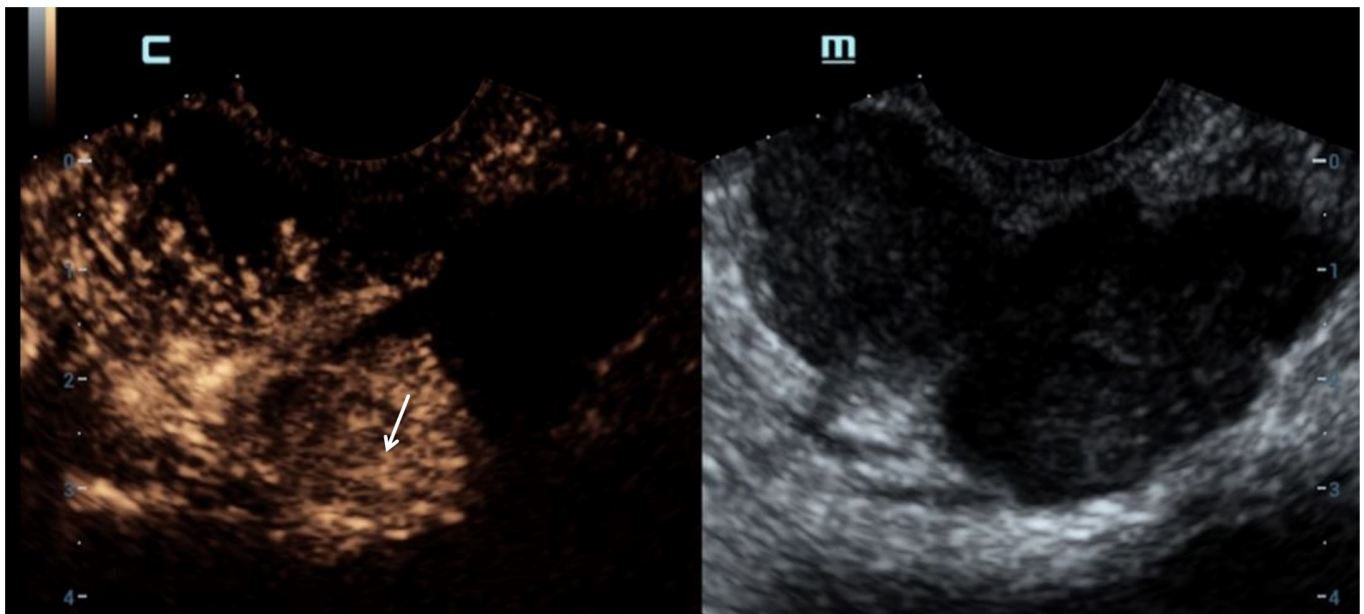


FIGURE 2. CEUS demonstrates the tumor-feeding vessel (white arrow).

phy/computed tomography (PET/CT) at another hospital, and no obvious evidence of metastases was detected.

On 10 September, the patient underwent laparoscopic radical prostatectomy (RP). Intraoperatively, a prominent nodule was observed in the right lobe of the prostate, which was adherent to the levator ani muscle. Given the aggressive nature of NEPC and the need to ensure complete tumor resection, preservation of the prostatic capsule was not attempted. Following resection of the prostate and seminal vesicles, bilateral pelvic lymph node dissection was performed, including the external iliac, internal iliac, and obturator lymph node groups. Ten lymph nodes (five from each side) were submitted for pathological examination. Postoperative histopathological examination revealed small cell carcinoma combined with acinar adenocarcinoma (Gleason score $3 + 4 = 7$, accounting for approximately 5% of the tumor), with the tumor involving approximately 70% of the total prostate volume; perineural invasion (+), lymphovascular invasion (+); surgical margins (–), extraprostatic extension (+), bilateral seminal vesicles

involvement (–), and bilateral vas deferens margins (–) were reported. The left obturator lymph nodes were negative (0/5), as were the right obturator lymph nodes (0/5) (Fig. 3). Immunohistochemistry findings were as follows: thyroid transcription factor-1 (TTF-1) (–), NapsinA (–), caudal type homeobox 2 (CDX-2) (–), proliferation marker protein Ki-67 (Ki-67) (+60%), CgA (+), Syn (+), cluster of differentiation 56 (CD56) (+), cytokeratin 5/6 (CK5/6) (–), PSA (–), P504S (+), androgen receptor (AR) (–). In view of the patient's lack of any relevant prior treatment history, the diagnosis of *de novo* NEPC (*dn*-NEPC) was favored. Due to the absence of AR expression in the tumor, even with a small proportion of the adenocarcinoma component (5%), the predominant neuroendocrine differentiation was considered likely to result in poor overall tumor response to androgen deprivation therapy (ADT). Consequently, ADT was not administered at that time. Given the patient's advanced age and the potential side effects of chemotherapy, the family declined the proposed chemotherapy regimen. Additionally, genetic testing was advised by the

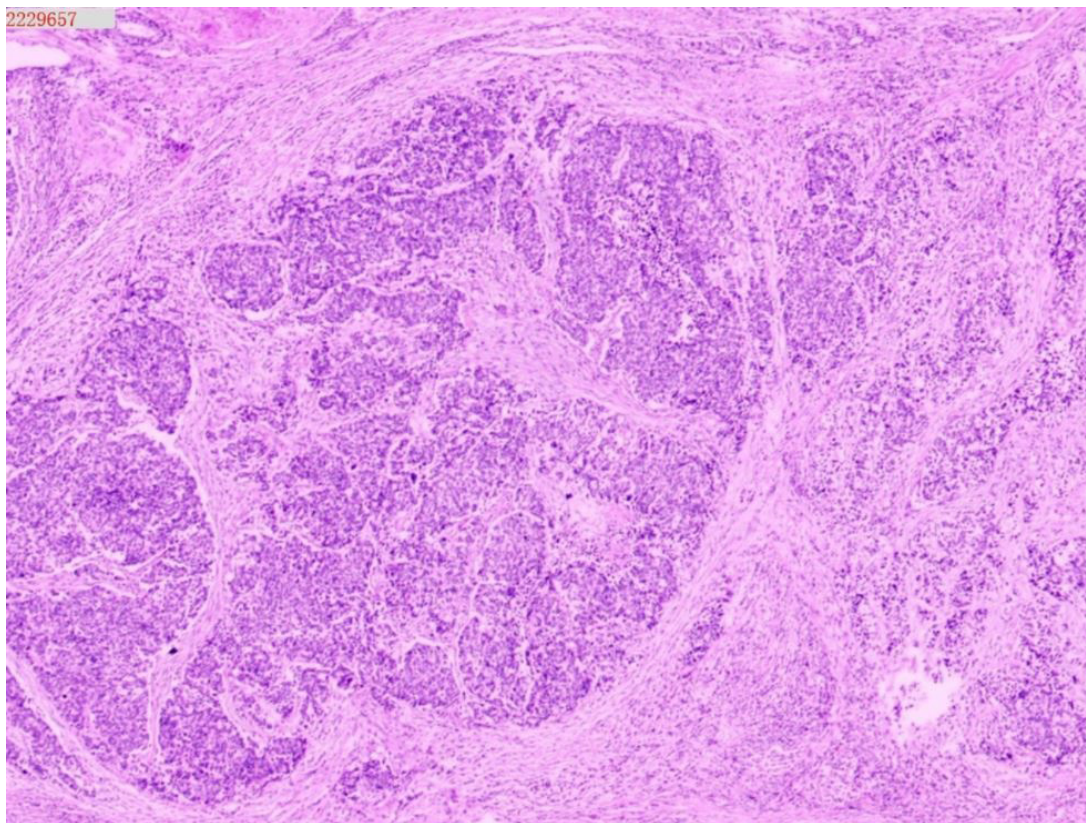


FIGURE 3. Pathological image of mixed neuroendocrine carcinoma (HE $\times 100$).

attending physician, but the family opted to defer testing.

Serum tumor markers were measured at 1, 2, and 3 months postoperatively. The results showed that PSA remained at very low levels (tPSA 0.04–0.05 ng/mL, fPSA 0.01–0.03 ng/mL), CEA ranged from 4.89 to 7.62 ng/mL, and neuron-specific enolase (NSE) levels were 6.9, 9.3, and 13.25 ng/mL, respectively, with all the values within the normal reference ranges. Non-contrast chest and abdominal CT performed 2 months postoperatively showed no significant abnormalities. At the 6-month routine follow-up, the patient complained of headache, and blood tests revealed that NSE had increased to 56.93 ng/mL, CEA to 64.68 ng/mL, and squamous cell carcinoma antigen (SCC) to 7.67 ng/mL, while fPSA and tPSA remained at low levels (0.06 and 0.04 ng/mL, respectively). ^{18}F -FDG PET/CT performed at another hospital revealed multiple metastatic tumors in the spleen and brain. On 21 March 2023, the patient received chemotherapy with a regimen of etoposide (120 mg) combined with cisplatin (50 mg) as fixed doses, and developed Grade IV myelosuppression after completing six cycles. Blood tests revealed the following results: white blood cell count of $0.8 \times 10^9/\text{L}$, absolute neutrophil count of $0.26 \times 10^9/\text{L}$, hemoglobin level of 123 g/L, and platelet count of $23 \times 10^9/\text{L}$. Subsequently, the patient received a transfusion of 10 units of single-donor platelets, along with subcutaneous injections of recombinant human thrombopoietin (15,000 IU) and recombinant human granulocyte colony-stimulating factor (0.15 mg) for six consecutive days. After recovery of bone marrow function, the patient underwent cranial radiotherapy at another hospital in September, with a total dose of 25 Gy delivered in 10 fractions. The most recent follow-up (as of

December 2024) revealed that the patient reported resolution of his headache. Radiographic imaging demonstrated a reduction in the volume of both splenic and intracranial metastatic lesions (Fig. 4). Blood tests revealed that NSE (9.2 ng/mL), CEA (2.43 ng/mL), and SCC (1.11 ng/mL) had all returned to normal ranges. The patient was subsequently lost to follow-up.

3. Discussion

Compared with prostatic adenocarcinoma, NEPC tends to metastasize earlier and is characterized by higher frequency of osteolytic lesions and visceral metastases (lung, liver, and central nervous system). At initial diagnosis, 45%–51% of patients already have distant metastases [3, 4]. Clinical presentation may be atypical, and some patients may develop Cushing syndrome secondary to ectopic adrenocorticotrophic hormone secretion [5]. NEPC is predominantly diagnosed at an advanced stage and is associated with an extremely poor prognosis. The median overall survival is approximately 15.5 months, while the 5-year cancer-specific mortality rate is significantly higher than those of other histological subtypes [6, 7].

Currently, histopathological examination remains the gold standard for diagnosing NEPC. According to the 2022 World Health Organization (WHO) classification, NEPC is categorized into three histological subtypes: small cell neuroendocrine carcinoma (SCNEC), large cell neuroendocrine carcinoma (LCNEC), and mixed NEPC. Approximately 50% of high-grade NEPC cases are classified as mixed neuroendocrine carcinoma, typically occurring following ADT [8]. Notably, the present case had no history of hormonal therapy, a scenario

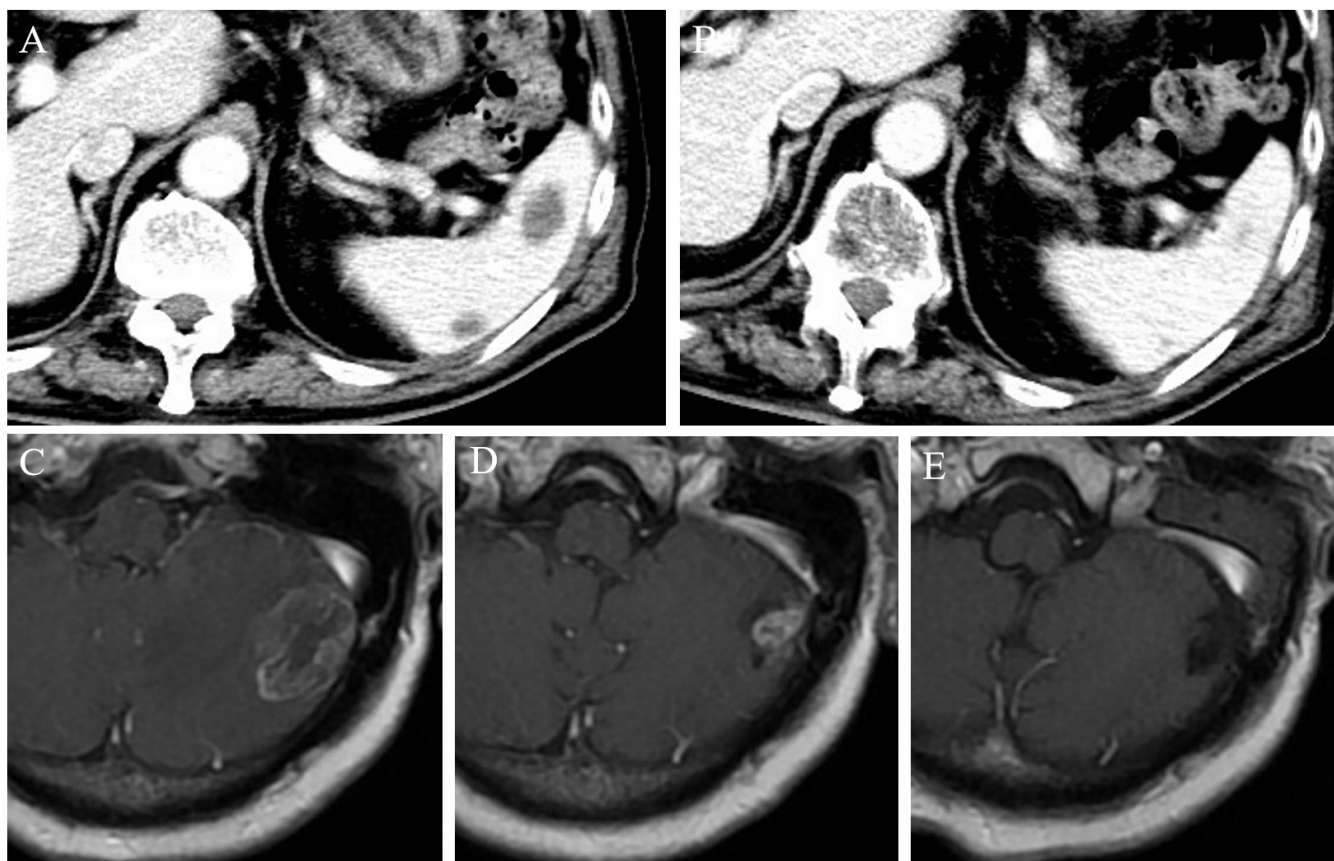


FIGURE 4. Follow-up imaging after chemotherapy for metastatic lesions. (A,B) Splenic lesions at 11 and 28 months postoperatively. (C–E) Intracranial lesions at 11, 18, and 28 months postoperatively.

that remains relatively rare in clinical practice. The transition between the small cell neuroendocrine and acinar adenocarcinoma components is typically abrupt in mixed NEPC. The Gleason score is determined solely on the basis of the adenocarcinoma components, and a score greater than 8 has been reported in 85% of such cases. Immunohistochemically, the Ki-67 labeling index is a classic marker for assessing tumor malignant potential. The Ki-67 index in NEPC typically exceeds 50%, which is significantly higher than that in conventional high-grade prostatic adenocarcinoma, and the Ki-67-based scoring system can be used for prognostic risk stratification [9, 10]. In addition, immunohistochemical markers including AR, NK3 homeobox 1 (*NKX3.1*), and insulinoma-associated protein 1 (*INSI*) are valuable for the detection and subclassification of NEPC [9].

When patients present with high-risk factors for NEPC but exhibit atypical clinical symptoms and imaging findings, reassessment should be considered. To achieve an early and accurate diagnosis of NEPC, the following clinical approaches can be employed to obtain critical diagnostic information.

1. ADT provides diagnostic clues for NEPC: NEPC can be classified into two subtypes: *dn*-NEPC and treatment-related NEPC (t-NEPC). Emerging evidence suggests that *dn*-NEPC is relatively rare and typically exhibits a more aggressive clinical course than t-NEPC. Studies have demonstrated that t-NEPC accounts for 15%–25% of castration-resistant prostate cancer (CRPC) that develop after ADT [11]. Currently, t-NEPC has been formally recognized as a distinct clinicopathological

entity. In patients with prior ADT exposure, the median time to the development of NEPC is 18 months [12]. Consequently, patients receiving ADT require regular disease monitoring to assess the risk of NEPC development.

2. The role of biomarkers in the diagnosis of NEPC: Unlike typical prostatic adenocarcinoma, NEPC is characterized by diminished androgen receptor signaling, upregulation of neuroendocrine markers, and frequent PSA negativity, highlighting the pressing need for novel screening biomarkers. Conventional neuroendocrine markers such as CgA, Syn, and NSE can serve as effective adjunctive tools for the detection of NEPC [13]. The sensitivity and specificity of circulating tumor cell (CTC)-based detection of NEPC are 51.35% and 91.14%, respectively [14]. In addition, Han *et al.* [15] detected elevated CEA expression in *dn*-NEPC. In the present case, CEA levels were elevated preoperatively, and both NSE and CEA increased upon detection of postoperative metastasis, returning to normal after treatment. These findings suggest that neuroendocrine markers and CEA may provide valuable clues for the screening and diagnosis of NEPC and for the assessment of treatment response.

3. The role of MRI in the diagnosis of NEPC: mp-MRI, which serves as an established imaging modality for staging and localizing PCa lesions, demonstrates an overall sensitivity of 0.74 and specificity of 0.88. This technique has enabled 27% of patients to avoid unnecessary prostate biopsies [16]. However, NEPC exhibits no characteristic imaging findings on MRI [17]. Hence, it is essential to incorporate additional

imaging and diagnostic modalities for disease staging, assessment of therapeutic response to ADT, and post-recurrence surveillance.

4. The role of ultrasound in the diagnosis of NEPC: CEUS clearly visualizes the morphology and trajectory of intratumoral neovascularization, providing more precise targets for needle biopsy. Ultrasound elastography (UE) quantitatively assesses the tissue stiffness of lesions, significantly improving the accuracy of detecting aggressive tumors [18]. However, ultrasonography is susceptible to operator-dependent variability and subjective interpretation, which may introduce bias in diagnostic results.

5. The role of PET/CT in the diagnosis of NEPC: To date, conventional imaging modalities have been unable to directly differentiate NEPC from other PCa subtypes, whereas PET/CT may improve diagnostic performance in NEPC through the use of distinct radiotracers. Currently, the most extensively studied radiotracers include ^{18}F -FDG, ^{68}Ga -DOTA-1-NaI(3)-octreotide (^{68}Ga -DOTANOC), and tracers targeting prostate-specific membrane antigen (PSMA) [19–21]. Additionally, PET/CT demonstrates high specificity for detecting pelvic lymph node and distant metastases. However, the heterogeneous histological composition of certain tumors may reduce their uptake of tracers targeting PSMA and somatostatin receptors, potentially leading to false-negative results [22]. Therefore, histological subtype variations should be taken into account during clinical diagnostic work-up.

6. The role of Artificial Intelligence (AI) in the diagnosis of NEPC: The ongoing advancements of AI in modern medicine underscores its potential to improve the differential diagnosis of PCa subtypes. Recent studies have focused on employing diverse machine learning algorithms to more accurate detection of histological variants of PCa [3, 23]. However, compared with conventional diagnostic modalities, the accuracy and interpretability of AI-based approaches require validation through large-scale clinical trials.

There is no consensus on the optimal treatment of NEPC. However, given its morphological and biological similarities to small cell lung cancer (SCLC), the management of NEPC largely follows the SCLC treatment paradigm. The 2022 National Comprehensive Cancer Network (NCCN) guidelines recommend a platinum-etoposide combination as first-line therapy for limited-stage disease [24]. Studies have demonstrated that cisplatin-based combination chemotherapy yields an overall response rate of approximately 50% in NEPC [25]. Given that a subset of patients may not have received ADT, Ikeda *et al.* [26] proposed a triple-combination regimen comprising darolutamide, ADT (degarelix), and docetaxel, the efficacy of which has been validated in patients with mixed NEPC. RP is the primary treatment modality for early-stage NEPC without distant metastasis [27]. Currently, there is no consensus on whether adjuvant chemotherapy should be administered after radical surgery in these patients, and its definitive value awaits validation through large-scale studies. Moreover, the clinical benefit of surgical intervention in patients with metastatic CRPC remains a subject of ongoing debate. In a study involving 718 patients with NEPC, the 1-year survival rate was 31.7% for combined therapy (surgery, radiotherapy, and chemotherapy), 24.0% for surgery alone

among patients with unknown chemotherapy status, 12.0% for surgery combined with chemotherapy, and 15.5% for chemotherapy alone [28]. While these studies indicate a possible association between RP and improved survival, the precise role of RP warrants further investigation.

In addition to conventional therapeutic approaches, emerging strategies offer renewed hope for patients with NEPC. Recent advances in immunotherapy suggest that programmed cell death protein 1 (PD-1) blockade combined with platinum-based chemotherapy may improve survival in patients with NEPC [29]. Furthermore, research into NEPC-specific targets has identified key biomarkers, including surface receptors (trophoblast cell surface antigen 2 (Trop2), delta-like ligand 3 (DLL3)); oncogenes (N-MYC proto-oncogene (*N-MYC*), aurora kinase A (*AURKA*)); tumor suppressors (retinoblastoma transcriptional corepressor 1 (*RBI*), tumor protein p53 (*TP53*)); and epigenetic regulators (RE1-silencing transcription factor (REST), forkhead box A1 (FOXA1), forkhead box A2 (FOXA2)). Among these, DLL3 is predominantly expressed on the surface of NEPC cells. Recent studies have demonstrated that ^{177}Lu -labeled radioimmunotherapy based on anti-DLL3 antibodies significantly prolonged overall survival in mouse models of NEPC [30]. Approximately 40% of NEPC cases exhibit co-expression of N-MYC and AURKA, which may synergistically promote tumorigenesis, and MLN8237 has been shown to partially delay NEPC progression by targeting the amplification and upregulation of both molecules [31]. Given that Ser/Arg repetitive matrix 4 (*SRRM4*) negatively regulates REST expression, targeting SRRM4 may represent a novel therapeutic strategy for NEPC.

This case report has several limitations. First, given its single-center nature, our conclusions require validation in larger cohort studies. Second, the absence of genetic testing in this case precludes a comprehensive assessment of potential targeted therapeutic strategies. Third, the lack of long-term follow-up makes it difficult to evaluate the long-term efficacy and safety of the treatment regimen used in this patient.

4. Conclusions

In summary, as a rare and highly aggressive malignancy, NEPC highlights the critical role of multidisciplinary collaboration and precision medicine in the management of rare tumors. The integration of various biomarkers with imaging modalities is essential for improving diagnostic sensitivity. Furthermore, treatment strategies for NEPC should be individualized based on tumor subtype, disease stage, and genetic mutation profiles to prolong progression-free survival. These conclusions warrant further validation in large-scale prospective studies.

ABBREVIATIONS

PCa, prostate cancer; NEPC, neuroendocrine prostate cancer; t-NEPC, treatment-related neuroendocrine prostate cancer; *dn*-NEPC, *de novo* neuroendocrine prostate cancer; ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; CEA, carcinoembryonic antigen; tPSA, total

prostate-specific antigen; fPSA, free prostate-specific antigen; mp-MRI, multiparametric magnetic resonance imaging; PI-RADS, prostate imaging reporting and data system; TRUS, transrectal ultrasound; CEUS, contrast-enhanced ultrasound; Syn, synaptophysin; CgA, chromogranin A; ^{18}F -FDG, ^{18}F -fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography; RP, radical prostatectomy; TTF-1, thyroid transcription factor-1; CDX-2, caudal type homeobox 2; Ki-67, proliferation marker protein Ki-67; CD, cluster of differentiation; CK, cytokeratin; AR, androgen receptor; NSE, neuron-specific enolase; SCC, squamous cell carcinoma antigen; WHO, World Health Organization; SCNEC, small cell neuroendocrine carcinoma; LCNEC, large cell neuroendocrine carcinoma; *NKX3.1*, NK3 homeobox 1; *INSML1*, insulinoma-associated protein 1; CTC, circulating tumor cell; ^{68}Ga -DOTANOC, ^{68}Ga -DOTA-1-NaI(3)-octreotide; PSMA, prostate-specific membrane antigen; AI, artificial intelligence; SCLC, small cell lung cancer; NCCN, National Comprehensive Cancer Network; PD-1, programmed cell death protein 1; Trop2, trophoblast cell surface antigen 2; DLL3, delta-like ligand 3; *N-MYC*, N-MYC proto-oncogene; *AURKA*, aurora kinase A; *RBI*, retinoblastoma transcriptional corepressor 1; *TP53*, tumor protein p53; REST, RE1-silencing transcription factor; FOXA, forkhead box; *SRRM4*, Ser/Arg repetitive matrix 4.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

AUTHOR CONTRIBUTIONS

YW—performed material preparation and data collection; wrote the first draft of the manuscript. LLZ—performed the analysis. Both authors contributed to the study conception and design. Both authors commented on previous versions of the manuscript. Both authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of Ningbo Hospital of Integrated Traditional Chinese and Western Medicine (Approval No. 2026-007). The patient information was de-identified, and written informed consent for the publication of this case report and accompanying images was obtained from the patient's next of kin, as the patient was deceased at the time of manuscript preparation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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