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CASE REPORT

Interstitial pneumonia after regression by olaparib for neuroendocrine prostate cancer with *BRCA1* mutation: a case report

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Abstract

A 67-year-old man with metastatic prostate cancer was treated with leuprorelin and enzalutamide, but presented radiographic progression after 1 year. Although docetaxel chemotherapy was initiated, liver metastasis appeared with elevation of nerve-specific enolase in serum. Pathological findings of needle biopsy of lymph node metastasis in the right inguinal region showed neuroendocrine carcinoma. FoundationOne CDx® using a biopsy sample of the prostate at initial diagnosis detected the *BRCA1* mutation (deletion of intron 3–7), but BRACAnalysis® test revealed no *BRCA* mutation in germline. Then, olaparib treatment was initiated, resulting in remarkable remission of tumors, but comorbidity with interstitial pneumonia. This case suggested that olaparib could be effective for neuroendocrine prostate cancer with *BRCA1* gene mutation, but may cause interstitial pneumonia.

Keywords *BRCA1* mutation · Neuroendocrine prostate cancer · Olaparib

Introduction

Neuroendocrine prostate cancer (NEPC) rarely emerges after hormonal therapy for prostate cancer [1]. NEPC is characterized by poor response to castration, and increased potential of progression, resulting in lethality [2]. There is no standard therapy for NEPC, although it is often treated with etoposide and cisplatin chemotherapy, based on the treatment for small cell lung cancer [3]. Olaparib is a poly ADP ribose polymerase (PARP) inhibitor, that is effective for *BRCA1*- or *BRCA2*-mutated prostate cancer [4]. We report a case of NEPC with *BRCA1* mutation treated with olaparib.

Case report

A 67-year-old man consulted a urologist, complaining of urinary hesitancy. The value of prostate-specific antigen (PSA) was 29.99 ng/mL, and the patient underwent a transperineal prostate biopsy that revealed adenocarcinoma of the prostate with the highest Gleason score of 5 + 5. Serum levels of nerve-specific enolase (NSE) and pro-gastrin-releasing peptide (proGRP) and immunostaining of biopsy specimen for neuroendocrine markers were not measured. A computed tomography (CT) scan and bone scintigraphy showed multiple bone and lymph node metastases. Then, the patient began a combination therapy using leuprorelin and enzalutamide (Fig. 1). After 1 year, although PSA levels declined to 2.88 ng/mL, a CT scan showed enlargement of multiple lymph nodes including inguinal region and bone metastases (Fig. 2A). At that time, the patient was referred to our department, and began subsequent treatment with docetaxel (70 mg/m^2) plus prednisolone (10 mg/day) (Fig. 1). Moreover, a spinal metastasis compressed the spinal cord and caused bilateral leg paresis, which was treated with palliative radiotherapy (RT, 29 Gy/13Fr) to Th3, Th 12 and pelvis. After four cycles of docetaxel chemotherapy, a CT scan showed multiple liver metastases and further enlargement of lymph node metastases (Fig. 2B). NSE in serum was

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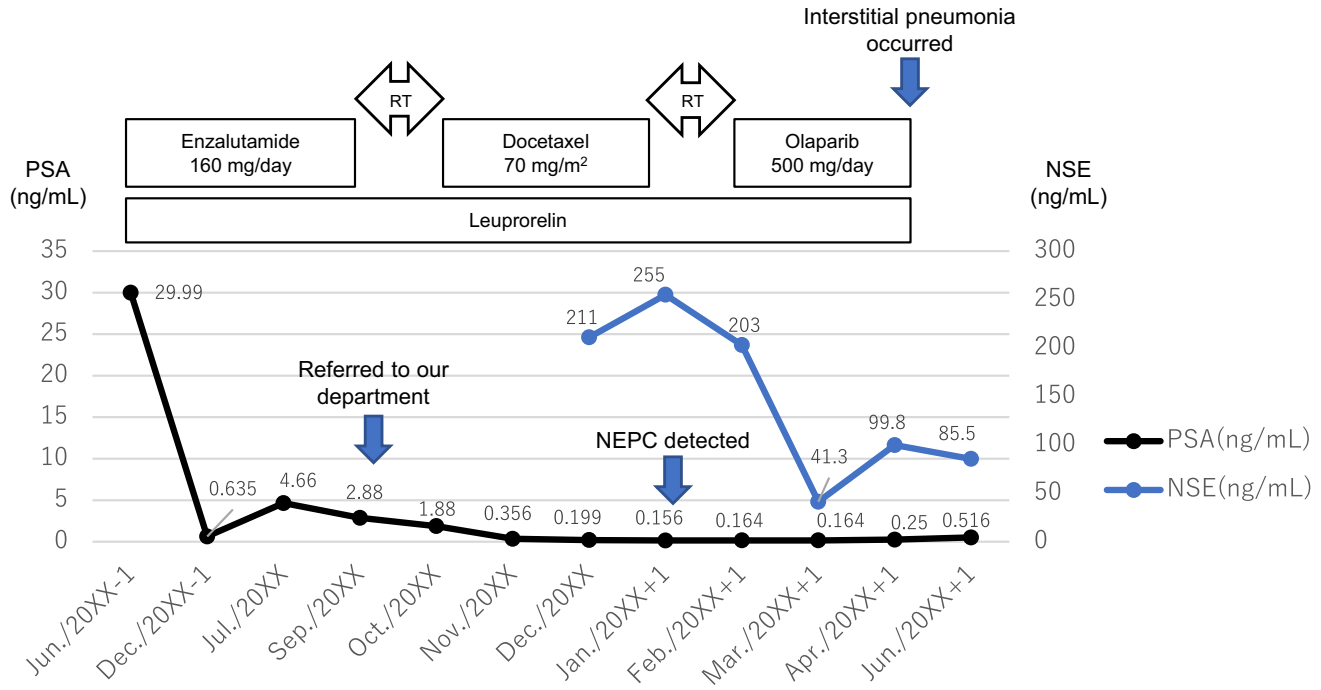

Fig. 1 Clinical course of this case. Prostate-specific antigen (PSA) and nerve-specific enolase (NSE) measurement levels correspond to the timeline showing therapy

elevated to 211 ng/mL, although the PSA level declined to 0.19 ng/mL and serum proGRP level was within the normal range (53.5 pg/mL). Consistently, pathological findings of needle biopsy of lymph node metastasis in the right inguinal region showed neuroendocrine carcinoma (Fig. 3). Also, because of pain, palliative RT (29 Gy/13Fr) to L3 and right inguinal region was performed. Furthermore, FoundationOne CDx® (Foundation Medicine, Inc., Cambridge, MA, USA) using a biopsy sample of the prostate at initial diagnosis detected the *BRCA1* mutation (deletion of intron 3–7) in addition to the *AKT1* mutation, *FUBP1-DFFA* fusion, *PTEN* loss, and *RB1* mutation. Subsequent BRACAnalysis® (Myriad Genetic Laboratories, Inc., Salt Lake City, UT, USA) test revealed no *BRCA* mutation in germline, indicating that his *BRCA1* mutation was of somatic origin. Accordingly, olaparib treatment was initiated at a reduced dose of 500 mg daily because there was severe anemia at treatment initiation. After 1 month, the serum NSE level declined to 41.3 ng/mL, and PSA and proGRP remained within normal levels. Consistently, the CT scan showed a partial response with shrinkage of multiple metastases in lymph nodes and liver (Fig. 2C). No adverse event was observed at 1 month. However, 2 months later the patient presented with high-grade fever and dyspnea. Although the serum KL-6 level was within the normal range (246 U/mL), the CT scan showed a ground glass shadow in bilateral lung fields (Fig. 4). Accordingly, interstitial pneumonia accompanied was diagnosed and treated with steroid pulse therapy, which led to the discontinuation olaparib. Although the pneumonia improved after intensive treatment, the patient's general condition worsened, and palliative and supportive care was administered. The patient died of prostate cancer 5 months after the initiation of olaparib treatment.

Discussion

Prostate cancer is the most frequent cancer in the Japanese male population. According to a survey by the National Cancer Center Japan, approximately 90,000 men are diagnosed with prostate cancer which causes over 12,000 deaths every year in Japan [5]. Since prostate cancer is initially an androgen driven disease [6], androgen deprivation therapy combined with androgen receptor (AR) axis targeted therapy is the standard treatment for metastatic prostate cancer [7]. However, continuation of this treatment possibly leads to resistance to castration [8]. Although most castration-resistant prostate cancers remain dependent on the AR signaling pathway, some acquire a histological transformation characterized by AR-negative, poorly differentiated small cells with neuroendocrine morphology [9]. It has been reported that 10–17% of cases with metastatic castration-resistant prostate cancer (mCRPC) acquire neuroendocrine features, while de novo NEPC is extremely rare (less than 2%) [1, 10]. Interestingly, recent researches on genomic alterations revealed that inactivation of *RB1*, *TP53* and *PTEN* were

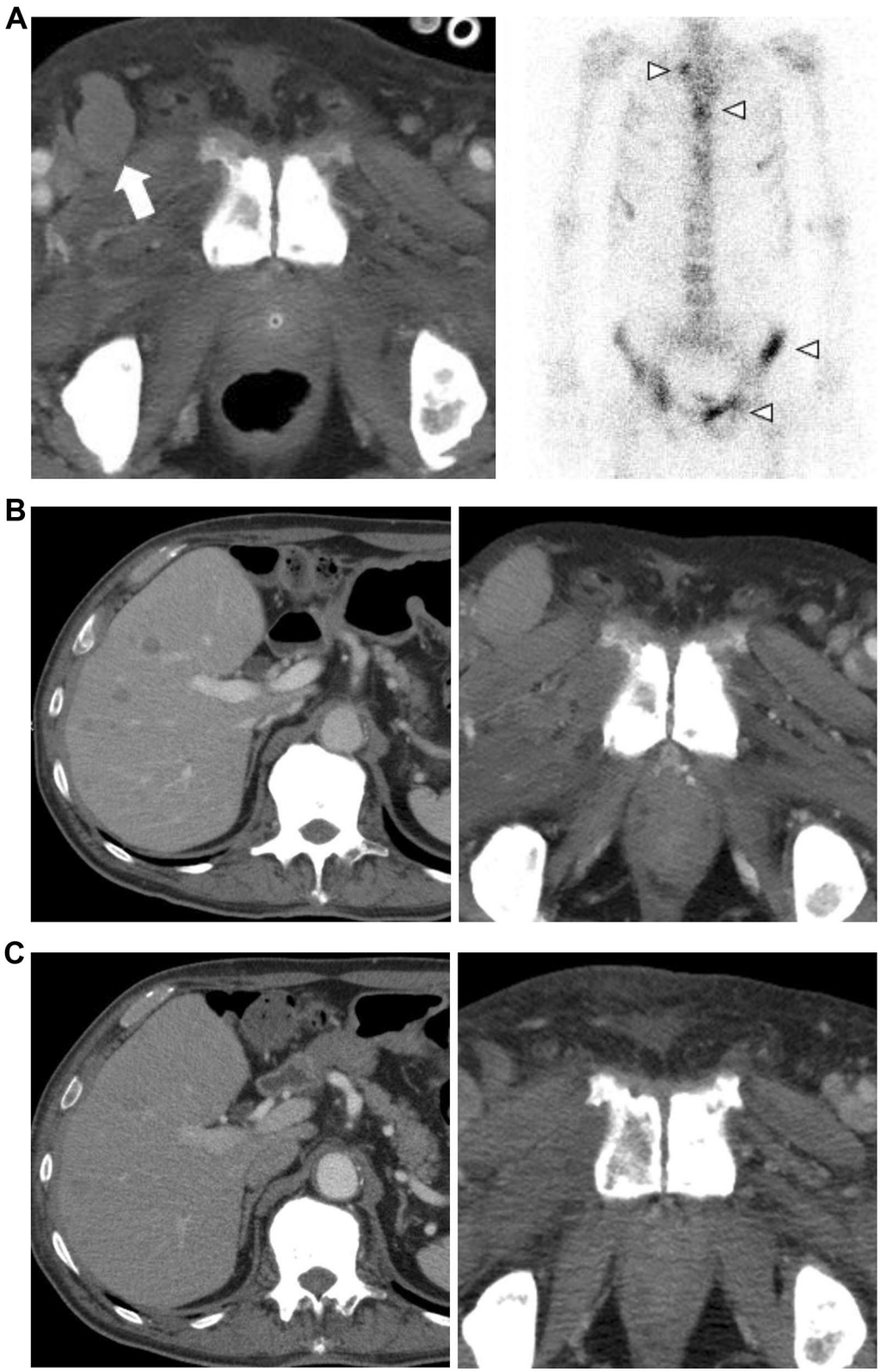

Fig. 2 **A** A CT scan when the patient was referred to our hospital shows inguinal lymph node metastases (white arrow), and bone scintigraphy also detected multiple bone metastases (arrowheads). **B** A CT scan after four cycles of docetaxel chemotherapy shows multiple liver metastases (left) and further enlargement of lymph node metastases (right). **C** A CT scan 1 month after olaparib initiation; downsize in the liver (left) and lymph node (right) metastases

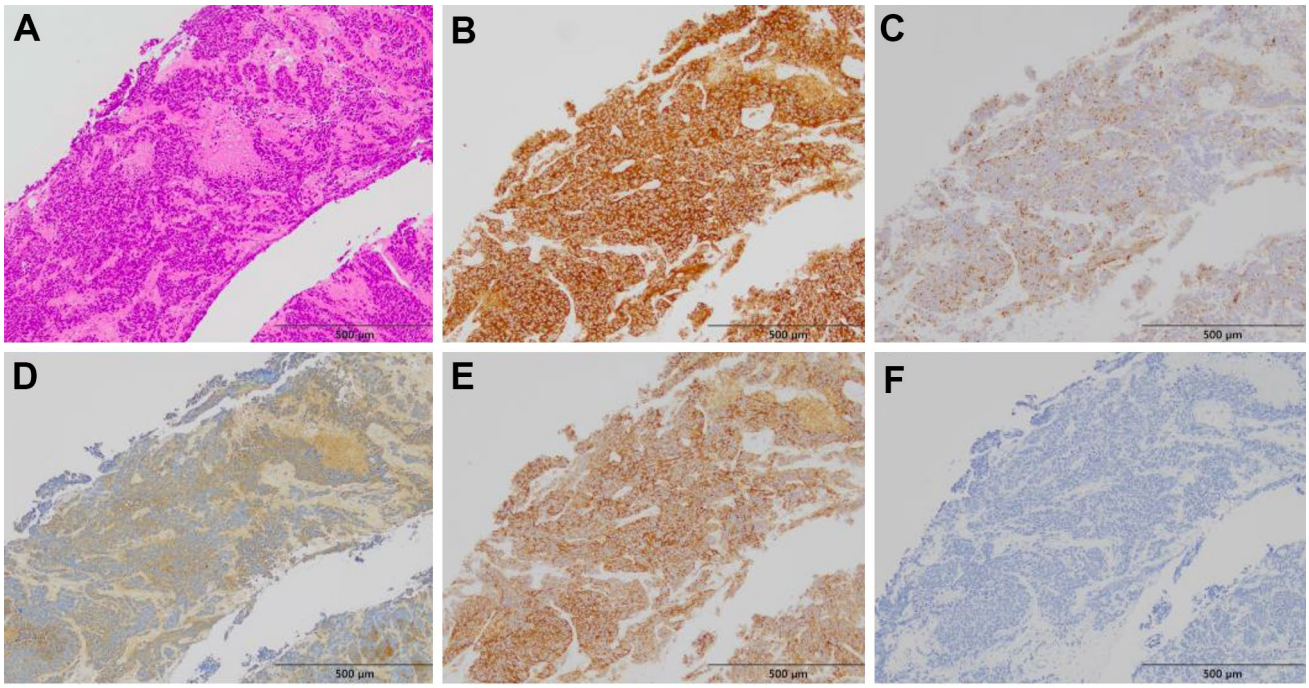

Fig. 3 Pathological findings of a lymph node metastasis in the right inguinal region. Microscopic finding shows atypical cells having hyperchromic and enlarged nuclei with tumor necrosis (**A**). Immunohistochemically, the tumor cells stained positive for synaptophysin (**B**), chromogranin A (**C**), NSE (**D**), and CD56 (**E**), and negative for PSA (**F**)

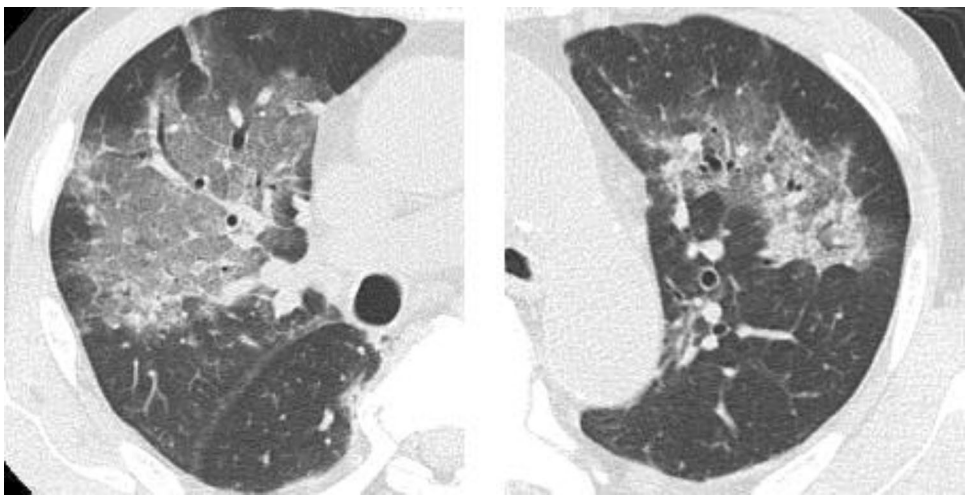

Fig. 4 A CT scan shows a ground glass shadow in the right superior lobe and left inferior lobe

commonly observed in NEPC [3]. Consistently, prostate tumor in this case carried *PTEN* loss and *RB1* mutation. Furthermore, coexisting of genomic alterations (*PTEN* loss and *AKT1* mutation) in PI-3-Kinase pathway were observed in the tumor, which is rare because this coexistence was not observed in The Cancer Genome Atlas Research [11]. Therefore, extremely augmented PI-3-Kinase pathway by double genomic alterations might be a driver of neuroendocrine differentiation in this case. NEPC is characterized by a poor prognosis; the median survival time from the diagnosis of NEPC is approximately 1.5 years [12]. Therapy for prostate cancer with neuroendocrine differentiation is controversial. Platinum-based chemotherapy is commonly administrated to patients with pure small cell carcinoma based on the treatment of small cell lung cancer, whose response is limited [3]. Although second-line treatment for NEPC is unestablished, few studies focused on NEPC have been reported [13].

Previous studies have revealed various types of genomic mutations related to prostate cancer [14–17]. Among them,

BRCA1, *BRCA2*, and *ATM* are the most well-characterized genes involved in homologous recombination repair (HRR), with 13% of patients with mCRPC harboring somatic or germline *BRCA2* alterations [18]. Regarding NEPC, Beltran et al. reported 29% of *BRCA2* mutations with 8% of identifiable biallelic alterations [19]. Consistently, Symonds et al. have reported a higher prevalence of *BRCA2* mutation in NEPC (26%), compared to those without NEPC histology (9%) [20]. HRR or non-homologous end joining repairs a DNA double-strand break. If there are loss-of-function alterations in HRR-related genes, only the non-homologous end joining repairs the double-strand breaks, with frequent repair errors that lead to cancer progression [21]. PARP enzymes repair DNA single-strand breaks, thus PARP inhibition leaves single-strand breaks unrepaired, causing the accumulation of double-strand breaks after DNA replication. As non-homologous end joining mainly repairs double-strand breaks in tumors with mutations of HRR-related genes, most of them cannot be efficiently repaired, eventually leading to cancer cell death [22–24]. The PROfound trial showed longer radiographic progression-free survival and overall survival with olaparib treatment than with androgen receptor (AR) axis targeted therapy (median radiographic progression-free survival, 7.4 months vs. 3.6 months; median overall survival, 19.1 months vs. 14.7 months) [4, 25]. The most common adverse events of any grade were anemia or nausea in the olaparib cohort, and fatigue or asthenia in the control cohort, while no interstitial pneumonia was reported [4]. However, the PROfound trial did not include NEPC patients, and then the efficacy of olaparib for NEPC with the *BRCA* mutation has not been well characterized.

To our knowledge, this is the first case report of NEPC with somatic *BRCA1* mutation treated with a PARP inhibitor as the first therapy after the detection of neuroendocrine differentiation. Pandya et al. reported a case of NEPC with germline *BRCA2* mutation with a complete response to platinum-based chemotherapy, but a limited disease control duration by maintenance treatment with olaparib [26]. Additionally, Turina et al. reported a case of somatic *BRCA2*-altered NEPC successfully treated by olaparib as a maintenance therapy [27]. Wu et al. reported a case of germline *BRCA1*-mutated NEPC, who showed partial tumor response over 2.5 months with olaparib and rapid tumor progression with subsequent combination chemotherapy with etoposide and cisplatin after treatment failure with olaparib [28]. Thus, it was suggested that NEPC with *BRCA1* or *BRCA2* mutation could be managed using olaparib, as supported by this case. However, more reports on the outcomes in patients with NEPC with HRR-related gene mutations are needed.

In addition, this case experienced interstitial pneumonia that emerged after olaparib treatment. A case of olaparib-related interstitial pneumonia after a 6-week treatment was reported in a patient with breast cancer with *BRCA1* deleterious mutation [29]. Furthermore, 107 cases (1.7%) of interstitial lung disease were reported among 6402 reports of olaparib in the public version of the U.S. Food and Drug Administration Adverse Event Reporting System [30]. Thus, although drug-induced interstitial pneumonia during olaparib treatment is rare, this disease should be recognized and carefully observed, especially during the early treatment phase. In this case, radiotherapy to thoracic vertebrae was performed before olaparib treatment, which might affect the occurrence of interstitial pneumonia although further report is required.

Conclusion

NEPC is an aggressive subtype of prostate cancer, and there is scarce evidence of adequate treatment. This case suggested that olaparib could be effective for NEPC with HRR-related gene mutations as in other advanced prostate cancers, but may cause interstitial pneumonia.

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Data availability The data in this report are available on request from the corresponding author.

Declarations

Conflict of interest Masaki Shiota received honoraria from Janssen Pharmaceutical, AstraZeneca, Astellas Pharma, and Sanofi. Masatoshi Eto received honoraria from Takeda Pharmaceutical, and Janssen Pharmaceutical, and research funding support from Sanofi, Bayer Yakuhin, Astellas Pharma, and Takeda Pharmaceutical.

Ethical approval This study was approved by the Institutional Ethics Committee (Approval No. 2021–123).

References

1. Nadal R, Schweizer M, Kryvenko ON et al (2014) Small cell carcinoma of the prostate. Nat Rev Urol 11(4):213–219. https://doi.org/10.1038/nrurol.2014.21
2. Wang HT, Yao YH, Li BG et al (2014) Neuroendocrine prostate cancer (NEPC) progressing from conventional prostatic adenocarcinoma: factors associated with time to development of NEPC and survival from NEPC diagnosis—a systematic review and pooled analysis. J Clin Oncol 32(30):3383–3390. https://doi.org/10.1200/JCO.2013.54.3553
3. Okasho K, Ogawa O, Akamatsu S (2021) Narrative review of challenges in the management of advanced neuroendocrine prostate cancer. Transl Androl Urol 10(10):3953–3962. https://doi.org/10.21037/tau-20-1131
4. de Bono J, Mateo J, Fizazi K et al (2020) Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 382(22):2091–2102. https://doi.org/10.1056/NEJMoa1911440

5. National cancer center Japan: Projected Cancer Statistics. https://ganjoho.jp/reg_stat/statistics/stat/short_pred_en.html [Accessed on 21 Sep. 2022]
6. Heinlein CA, Chang C (2004) Androgen receptor in prostate cancer. Endocr Rev 25(2):276–308. https://doi.org/10.1210/er.2002-0032
7. Ryan CJ, Tindall DJ (2011) Androgen receptor rediscovered: the new biology and targeting the androgen receptor therapeutically. J Clin Oncol 29(27):3651–3658. https://doi.org/10.1200/JCO.2011.35.2005
8. Galletti G, Leach BI, Lam L et al (2017) Mechanisms of resistance to systemic therapy in metastatic castration-resistant prostate cancer. Cancer Treat Rev 57:16–27. https://doi.org/10.1016/j.ctrv.2017.04.008
9. Vlachostergious PJ, Puca L, Beltran H (2017) Emerging variants of castration-resistant prostate cancer. Curr Oncol Rep 19(5):32. https://doi.org/10.1007/s11912-017-0593-6
10. Aggarwal R, Huang J, Alumkal JJ et al (2018) Clinical and genomic characterization of treatment-emergent small-cell neuroendocrine prostate cancer: a multi-institutional prospective study. J Clin Oncol 36(24):2492–2503. https://doi.org/10.1200/JCO.2017.77.6880
11. Cancer Genome Atlas Research Network (2015) The molecular taxonomy of primary prostate cancer. Cell 163(4):1011–1025. https://doi.org/10.1016/j.cell.2015.10.025
12. Tetu B, Ro JY, Ayala AG et al (1987) Small cell carcinoma of the prostate Part I A clinicopathologic study of 20 cases. Cancer 59(10):1803–1809. https://doi.org/10.1002/1097-0142(19870515)59:10%3c1803::aid-cncr2820591019%3e3.0.co;2-x
13. Yamada Y, Beltran H (2021) Clinical and biological features of neuroendocrine prostate cancer. Curr Oncol Rep 23(2):15. https://doi.org/10.1007/s11912-020-01003-9
14. Cooper CS, Eeles R, Wedge DC et al (2015) Analysis of the genetic phylogeny of multifocal prostate cancer identifies multiple independent clonal expansions in neoplastic and morphologically normal prostate tissue. Nat Genet 47(4):367–372. https://doi.org/10.1038/ng.3221
15. Boutros PC, Fraser M, Harding NJ et al (2015) Spatial genomic heterogeneity within localized, multifocal prostate cancer. Nat Genet 47(7):736–745. https://doi.org/10.1038/ng.3315
16. Fraser M, Sabelnykova VY, Yamaguchi TN et al (2017) Genomic hallmarks of localized, non-indolent prostate cancer. Nature 541(7637):359–364. https://doi.org/10.1038/nature20788
17. Ku SY, Gleave ME, Beltran H (2019) Towards precision oncology in advanced prostate cancer. Nat Rev Urol 16(11):645–654. https://doi.org/10.1038/s41585-019-0237-8
18. Robinson D, Van Allen EM, Wu YM et al (2015) Integrative clinical genomics of advanced prostate cancer. Cell 161(5):1215–1228. https://doi.org/10.1016/j.cell.2015.06.053
19. Beltran H, Oromendia C, Danila DC et al (2019) A phase II trial of the Aurora Kinase A inhibitor alisertib for patients with castration-resistant and neuroendocrine prostate cancer: efficacy and biomarkers. Clin Cancer Res 25(1):43–51. https://doi.org/10.1158/1078-0432.CCR-18-1912
20. Symonds L, Konnick E, Vakar-Lopez F et al (2022) BRCA2 alternations in neuroendocrine/small-cell carcinoma prostate cancer: a case series. JCO Precis Oncol 6:e2200091. https://doi.org/10.1200/PO.22.00091
21. Lozano R, Castro E, Aragón IM et al (2021) Genetic aberrations in DNA repair pathways: a cornerstone of precision oncology in prostate cancer. Br J Cancer 124(3):552–563. https://doi.org/10.1038/s41416-020-01114-x
22. Momozawa Y, Iwasaki Y, Parsons MT et al (2018) Germline pathogenic variants of 11 breast cancer genes in 7051 Japanese patients and 11,241 controls. Nat Commun 9(1):4083. https://doi.org/10.1038/s41467-018-06581-8
23. Enomoto T, Aoki D, Hattori K et al (2019) The first Japanese nationwide multicenter study of BRCA mutation testing in ovarian cancer: CHARacterizing the cross-sectionaL approach to Ovarian cancer geneTic TEsting of *BRCA* (CHARLOTTE). Int J Gynecol Cancer 29(6):1043–1049. https://doi.org/10.1136/ijgc-2019-000384
24. Momozawa Y, Iwasaki Y, Hirata M et al (2020) Germline pathogenic variants in 7636 Japanese patients with prostate cancer and 12 366 controls. J Natl Cancer Inst 112(4):369–376. https://doi.org/10.1093/jnci/djz124
25. Hussain M, Mateo J, Fizazi K et al (2020) Survival with olaparib in metastatic castration-resistant prostate cancer. N Engl J Med 383(24):2345–2357. https://doi.org/10.1056/NEJMoa2022485
26. Pandya D, Shah M, Kaplan F et al (2021) Treatment-emergent neuroendocrine prostate cancer with a germline BRCA2 mutation: identification of a candidate reversion mutation associated with platinum/PARP-inhibitor resistance. Cold Spring Harb Mol Case Stud 7(1):a005801. https://doi.org/10.1101/mcs.a005801
27. Turina CB, Coleman DJ, Thomas GV et al (2019) Molecular testing identifies determinants of exceptional response and guides precision therapy in a patient with lethal, treatment-emergent neuroendocrine prostate cancer. Cureus 11(7):e5197. https://doi.org/10.7759/cureus.5197
28. Wu Y, Gao Y, Dou X et al (2020) Metastatic castration-resistant prostate cancer with neuroendocrine transformation and BRCA 1 germ-line mutation: a case report and literature review. Onco Targets Ther 13:8049–8054. https://doi.org/10.2147/OTT.S264347
29. Suzuki H, Oshino T, Hagio K et al (2020) Interstitial pneumonia caused by olaparib during treatment of breast cancer-a case report. Gan To Kagaku Ryoho 47(9):1351–1353
30. Shu Y, He X, Liu Y et al (2022) A real-world disproportionality analysis of olaparib: data mining of the public version of FDA adverse event reporting system. Epidemiology 14:789–802. https://doi.org/10.2147/CLEP.S365513