Case Report

Salvage focal brachytherapy in castration-resistant prostate cancer with neuroendocrine differentiation after radiation therapy

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Abbreviations & Acronyms
ADC = apparent diffusion coefficient
ADT = androgen deprivation therapy
AR = androgen receptor
CgA = chromogranin A
CRPC = castration-resistant prostate cancer
CT = computed tomography
CVT = clinical target volume
DWI = diffusion-weighted imaging
EBRT = external beam radiotherapy
H&E = hematoxylin and eosin
IHC = immunohistochemical
IMRT = intensity-modulated radiation therapy
MRI = magnetic resonance imaging
NEPC = Neuroendocrine Prostate Cancer
NSCLC = non-small cell lung cancer
NSE = neuron-specific enolase
PCWG3 = Prostate Cancer Clinical Trials Working Group 3
PSA = prostate-specific antigen
PSMA = prostate-specific membrane antigen
SCLC = small cell lung cancer
SYP = synaptophysin
t-NEPC = treatment-related Neuroendocrine Prostate Cancer

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Introduction: Treatment strategy for castration-resistant prostate cancer with neuroendocrine differentiation after radiation therapy has not been established.
Case presentation: We described a case of castration-resistant prostate cancer with neuroendocrine differentiation after initial external beam radiotherapy followed by salvage androgen deprivation therapy. Magnetic resonance imaging detected recurrence of a suspicious lesion in the left lobe of the prostate, although the prostate-specific antigen level was <0.2 ng/mL. Transperineal prostate saturation needle biopsy detected adenocarcinoma with neuroendocrine differentiation. The patient underwent salvage focal brachytherapy and had a prostate-specific antigen progression-free survival of 20 months with no obvious adverse events. No recurrence has been detected on magnetic resonance imaging for 18 months.
Conclusion: Salvage focal brachytherapy for prostate cancer after external beam radiotherapy can be one of the treatment strategies for local recurrence of castration-resistant prostate cancer with neuroendocrine differentiation.

Key words: castration-resistant prostate cancer (CRPC) with neuroendocrine differentiation, prostate cancer, salvage focal brachytherapy.

Keynote message

Treatment strategy for castration-resistant prostate cancer (CRPC) with neuroendocrine differentiation after radiation therapy has not been established. We described a successful case of CRPC with neuroendocrine differentiation (CRPC-NE) after initial external beam radiotherapy. Salvage focal brachytherapy for CRPC-NE can be one of the treatment strategies for local recurrence of CRPC.

Introduction

The PCWG3 defines CRPC as a PSA level of >1 ng/mL after ADT.[1] In addition, according to the Phoenix definition, biochemical failure of prostate cancer after EBRT is defined as a PSA rise of ≥2 ng/mL above the lowest level.[2] Since there is no PSA criterion of prostate cancer recurrence after initial EBRT followed by salvage ADT for biochemical recurrence of prostate cancer, the CRPC definition is often used instead. In this report, we described one case of CRPC-NE that recurred with low serum PSA levels after initial EBRT followed by salvage ADT for biochemical recurrence of prostate cancer, followed by hemi-gland focal salvage iodine-125 prostate brachytherapy.

Case presentation

In 2013, a 66-year-old man presented with a serum PSA level of 24.6 ng/mL, and prostate cancer was suspected. A transrectal prostate needle biopsy was performed, which gave a Gleason score of 4 + 3. The patient was diagnosed with cT1cN0M0 prostate cancer, and he was administered EBRT of 70 Gy. Initially, he showed a good response to the treatment

(lowest serum PSA level = 3.68 ng/mL). However, his serum PSA level gradually increased to 5.9 ng/mL in May 2015, and he was diagnosed with biochemical recurrence of prostate cancer according to the Phoenix definition. Subsequently, he was referred to our hospital for subsequent therapy and administered salvage ADT. Leuprorelin acetate (11.25 mg/3 months or 22.5 mg/6 months) and bicalutamide (80 mg/day) were used. Initially, he showed a good response with decreased serum PSA levels of <0.01 ng/mL for ~3 years. However, in February 2020, his serum PSA level began to increase slightly and reached 0.10 ng/mL (Fig. 1). The serum testosterone level was 17 ng/dL when the serum PSA level increased to 0.06 ng/mL. Despite low serum PSA levels, local recurrence was suspected because of a continuous increase of serum PSA levels after salvage ADT. Therefore, the patient underwent pelvic MRI, which detected recurrence of a suspicious lesion in the left lobe of the prostate. DWI showed high intensity and ADC showed low intensity in the lesion. Transperitoneal prostate saturation needle biopsy detected adenocarcinoma accompanied by neuroendocrine differentiation in the lesion (Fig. 2a). The serum level of NSE was 11.8 ng/mL (within the reference level). IHC findings of the tumor-positive specimen showed negative PSA staining (Fig. 2b), positive AR staining (Fig. 2c), and positive SYP staining (Fig. 2d). No metastasis was detected in whole-body CT and 99m-Technetium-Hydroxymethylene Diphosphonate Bone Scintigraphy. In April 2020, left hemi-gland focal salvage iodine-125 prostate brachytherapy was performed. The prescribed dose of the left hemi-gland was 140 Gy. The delineation of CTV was based on the MRI image. To reduce the rectal dose, we utilized the hydrogel spacer. The postimplant dosimetry was performed a month after seed implantation (Fig. 3a), and it showed that the CTV D_{90} (the minimal dose received by 90% of the volume) was 186Gy, the rectum V_{100} (volume receiving 100% of the prescribed dose) was 0.01 cc, and the urethral V_{150} (volume receiving 150% of the prescribed dose) was 0 cc. The biologically effective dose of the CTV was 198 Gy (Fig. 3b).[3]

After the salvage brachytherapy, ADT was finished. Recurrence of a suspicious lesion in MRI has not been able to be detected for18 months. Serum PSA level slightly decreased and reached below the measurement sensitivity; <0.003 ng/mL. The patient had a PSA progression-free survival of 20 months with no obvious adverse events.

Discussion

CRPC-NE is one of the most aggressive prostate cancers.[4,5] CRPC-NE arises after salvage ADT as a result of (i) lineage plasticity, (ii) differentiation from adenocarcinoma to a neuroendocrine tumor, and (iii) escape from AR pathway inhibition.[6–9] NEPC detection is difficult because no useful marker has been found so far. SYP, CgA, and CD56 are often used as neuroendocrine markers, but their sensitivity is low.[10] In addition, serum PSA and PSMA do not help in NEPC detection. PSMA positron emission tomography/CT is useful for detecting small CRPC lesions but not NEPC.[11]

In this case, MRI detected a small NEPC. DWI MRI detects a SCLC, which is neuroendocrine cancer.[12] The ADC in SCLC is lower than that in benign lung tissue and NSCLC.[13] Despite the limited papers on the MRI findings of NEPC, a study reported the MRI findings of 13 patients with histologically confirmed NEPC.[14] Of these 13 patients, 3 were primarily diagnosed with small-cell prostate cancer, and after endocrine therapy, 10 cases were considered a neuroendocrine type from being an adenocarcinoma. They demonstrated the NEPC as moderate low-signal intensity in T2WI, high signal in DWI, and peak and wash-out pattern in dynamic contrast-enhanced imaging. The DWI finding is similar to this case. Similar to SCLC, compared with other types of imaging, MRI might be a better modality for NEPC detection.

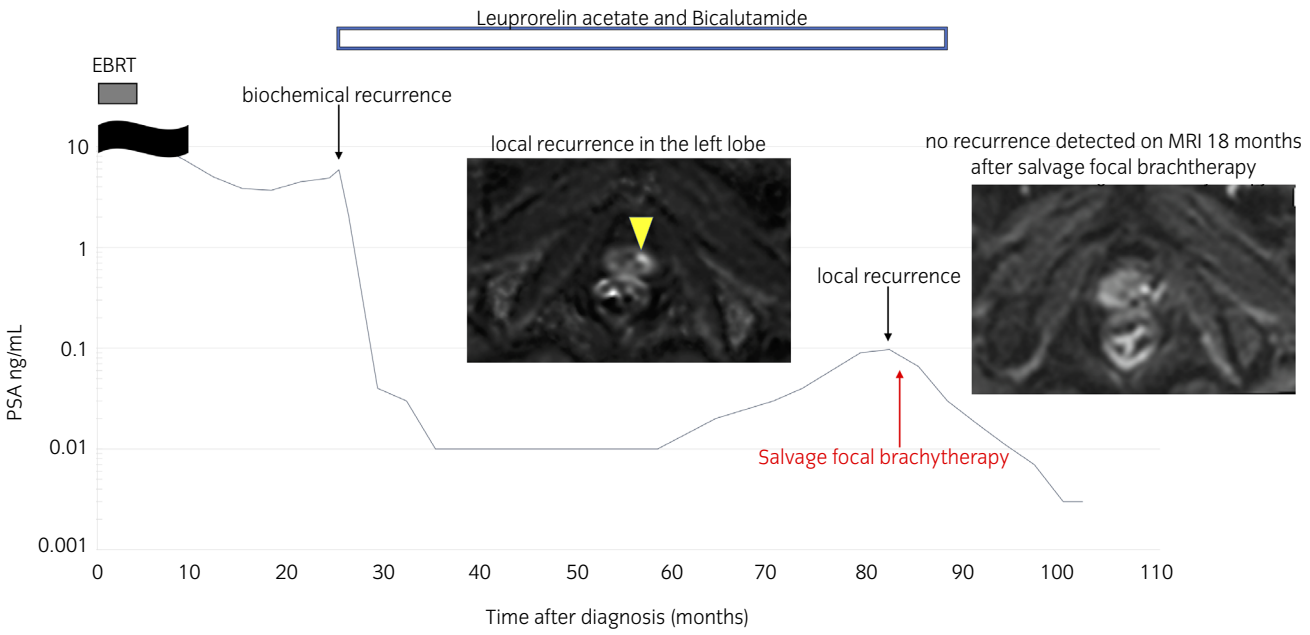

Fig. 1 Serum PSA levels and treatment course of this case.

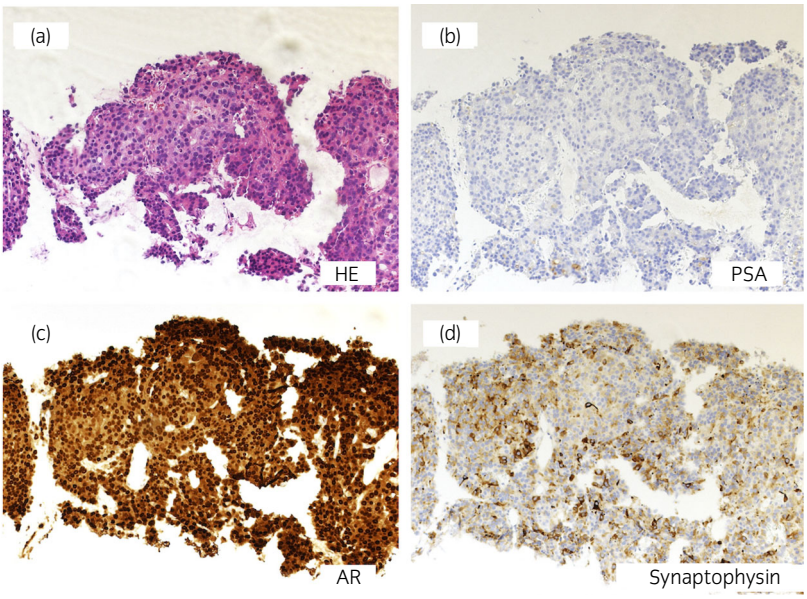

Fig. 2 Representative images of H&E staining (a), IHC staining (×100) of PSA (b), AR (c), and SYP (d) of prostate biopsy specimens when local recurrence was detected; a high-grade tumor defined by characteristic nuclear features, including lack of prominent nucleoli, nuclear molding, fragility, and high nuclear to cytoplasmic ratio accompanied by the signals of SYP in over 50% tumor cells.

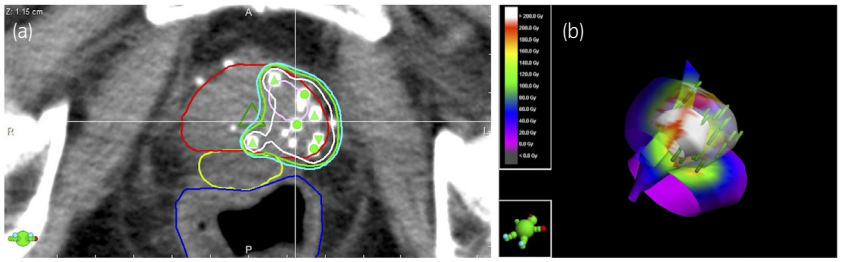

Fig. 3 The dose distribution in the post-planning (a, b). The cyan line, white line, pink line, yellow line, dark green line, and blue line indicate the 100% dose distribution, the 150% dose distribution, the CTV, rectal spacer, urethra, and rectum, respectively.

The serum PSA values at NEPC diagnosis and PSA rise per month were reviewed in a retrospective analysis of 87 patients with histologically confirmed de-novo NEPC or t-NEPC.[8] For patients with t-NEPC, the average PSA rise and percent PSA rise per month before t-NEPC biopsy diagnosis was 2 ng/mL and 16%, respectively. According to this analysis, the serum PSA level might have some importance in the follow-up of t-NEPC although other modalities such as MRI are needed. We measured NSE regularly during treatment, and it did not exceed the standard value.

NEPC is also resistant to both salvage ADT and AR-targeted therapy, so cisplatin-based chemotherapy is administered for metastatic cases instead of AR-targeted therapy. In this non-metastatic case, we performed focal therapy using salvage brachytherapy. Although the evidence for salvage focal brachytherapy in nonmetastatic CRPC recurrent after EBRT is limited, focal brachytherapy in this case did not result in either gastrointestinal or genitourinary adverse effect. In this case with nonmetastatic CRPC-NE recurrent after radiotherapy, focal brachytherapy showed a good therapeutic effect and no adverse effects were observed, although long-term follow-up is needed.

Author Contributions

Takahiro Komori: Conceptualization; writing – original draft. Takeo Kosaka: Conceptualization; methodology; writing – review and editing. Keitaro Watanabe: Methodology; project administration; visualization. Tomoki Tanaka: Methodology; visualization; writing – original draft. Yota Yasumizu: Investigation; resources. Hiroshi Hongo: Methodology. Shuji Mikami: Methodology. Toshio Ohashi: Methodology. Mototsugu Oya: Supervision.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

The study was approved by the Institutional Ethics Board of Keio University Hospital (No. 20160084, 20180015).

Informed consent

Consent to participate and for publication were acquired from the patient.

Registry and the Registration No. of the study/trial

Not applicable.

References

1 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.
2 Roach M 3rd, Hanks G, Thames H Jr *et al*. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix consensus conference. *Int. J. Radiat. Oncol. Biol. Phys.* 2006; **65**: 965–74.
3 Stock RG, Stone NN, Cesaretti JA, Rosenstein BS. Biologically effective dose values for prostate brachytherapy: effects on PSA failure and posttreatment biopsy results. *Int. J. Radiat. Oncol. Biol. Phys.* 2006; **64**: 527–33.
4 Wang HT, Yao YH, Li BG, Tang Y, Chang JW, Zhang J. 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.* 2014; **32**: 3383–90.
5 Kosaka T, Hongo H, Aimono E *et al*. A first Japanese case of neuroendocrine prostate cancer accompanied by lung and brain metastasis with somatic and germline BRCA2 mutation. *Pathol. Int.* 2019; **69**: 715–20.
6 Beltran H, Hruszkewycz A, Scher HI *et al*. The role of lineage plasticity in prostate cancer therapy resistance. *Clin. Cancer Res.* 2019; **25**: 6916–24.
7 Akamatsu S, Inoue T, Ogawa O, Gleave ME. Clinical and molecular features of treatment-related neuroendocrine prostate cancer. *Int. J. Urol.* 2018; **25**: 345–51.
8 Conteduca V, Oromendia C, Eng KW *et al*. Clinical features of neuroendocrine prostate cancer. *Eur. J. Cancer*. 2019; **121**: 7–18.
9 Yasumizu Y, Rajabi H, Jin C *et al*. MUC1-C regulates lineage plasticity driving progression to neuroendocrine prostate cancer. *Nat. Commun.* 2020; **11**: 338.
10 Park JW, Lee JK, Witte ON, Huang J. FOXA2 is a sensitive and specific marker for small cell neuroendocrine carcinoma of the prostate. *Mod. Pathol.* 2017; **30**: 1262–72.
11 Alipour R, Azad A, Hofman MS. Guiding management of therapy in prostate cancer: time to switch from conventional imaging to PSMA PET? *Ther. Adv. Med. Oncol.* 2019; **11**: 1758835919876828.
12 Hayashida Y, Hirai T, Morishita S *et al*. Diffusion-weighted imaging of metastatic brain tumors: comparison with histologic type and tumor cellularity. *Am. J. Neuroradiol.* 2006; **27**: 1419–25.
13 Usuda K, Iwai S, Yamagata A *et al*. Relationships and qualitative evaluation between diffusion-weighted imaging and pathologic findings of resected lung cancers. *Cancers*. 2020; **12**: 1194.
14 Zhang WH, Si TG, Yang XL *et al*. Clinical characteristics of 13 neuroendocrine prostate cancer patients. *Zhonghua Yi Xue Za Zhi*. 2017; **97**: 1316–9.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1. IHC staining (×100) of CgA; almost negative.