

depending on the risk category. Anti-androgen agents are frequently applied additionally to radiotherapy as neoadjuvant and adjuvant treatments, and in case of recurrence after surgery or radiotherapy.⁴ In our case, the biopsy specimen was initially diagnosed as pure adenocarcinoma. Our patient belonged to a high-risk group due to his high Gleason score.

In this case, recommended treatment options are radiotherapy, radiotherapy + androgen deprivation therapy, or radical prostatectomy. In contrast to pure adenocarcinoma of the prostate, NED is known for its resistance to hormone therapy and radiotherapy.³ Radiotherapy may have higher risk for treatment failure and surgery might have been the appropriate therapy in his case. Nowadays, the treatment options for prostate carcinoma are very complicated. Evaluating the character of the tumor precisely at the time of initial diagnosis may be helpful for deciding which treatment option to pursue.

At our institution, the biopsy specimen is usually stained with HE. In the presenting case, we additionally requested immunohistochemical examination which revealed the existence of focal NED changes. Retrospectively, atypical rosette formation can be seen even in the HE staining of the biopsy specimen. Screening all the biopsy specimens with neuroendocrine markers is neither reasonable nor recommended; however, in cases with unusual findings, such as low PSA and architectural/cytological anomalies in HE, immunohistochemistry may lead to a precise diagnosis. In 1994, Cohen *et al.* denied the correlation between the existence of NED in needle biopsy specimens and tumor progression. In their study, the object was limited to patients who had received radical prostatectomy.⁵ Whether NED in biopsy specimens may have an impact on prognosis if treated by other options has not been researched yet.

Editorial Comment

Editorial Comment to Prostate carcinoma with neuroendocrine differentiation successfully treated by early detection with imaging examination

Prostate carcinoma with neuroendocrine differentiation (NECAP) is thought to be a highly malignant subtype of castrate-resistant prostate cancer (CRPC) associated with resistance to androgen deprivation therapy (ADT), where cancer cell results in the transdifferentiation into NECAP phenotype as a sequel to prolonged ADT use. Usually, prostate-specific antigen (PSA) excretion from the NECAP tissue is scarce, making initial detection by PSA screening test complicated. In this case, Kobayashi *et al.* could diagnose potential prostate cancer with extremely low PSA value using conventional magnetic resonance imaging.¹ Apart from the usual imaging study, computed tomography with Ga-[DOTA-Tyr]-octreotate (Ga-DOTA-TATE), a somatostatin analog that binds somatostatin

Conclusion

Treatment options for prostate carcinoma have expanded drastically in recent years. Though, patients' physical status, PSA, PSA doubling time, and Gleason score remain the markers for prediction of clinical outcome.⁴ Immunohistochemical findings rarely influence the initial decision-making. Moreover, in many cases, the existence of NED is unknown at this timing. Further research of NED in biopsy specimens and its impact on clinical outcome in the current setting is interesting and will contribute to the precise assessment of the disease and more individualized decision-making.


Conflict of interest

The authors declare no conflict of interest.

References

- 1 Fine SW. Neuroendocrine tumors of the prostate. *Mod. Pathol.* 2018; **31**: 122–32.
- 2 Helpap B, Köllermann J, Oehler U. Neuroendocrine differentiation in prostatic carcinomas: histogenesis, biology, clinical relevance and future therapeutic perspective. *Urol. Int.* 1999; **62**: 133–8.
- 3 Hu C-D, Choo R, Huang J. Neuroendocrine differentiation in prostate cancer: a mechanism for radioresistance and treatment failure. *Front. Oncol.* 2015; **5**: 90.
- 4 Mottet N, van den Bergh RCN, Briers E *et al.* EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. 2018. [Cited 7 Jun 2019.] Available from URL: <https://uroweb.org/wp-content/uploads/EAU-ESUR-ESTRO-SIOG-Guidelines-on-Prostate-Cancer-large-text-V2.pdf>
- 5 Cohen MK, Arber DA, Coffield KS, Keegan GT, McClintock J, Speights VO Jr. Neuroendocrine differentiation in prostatic adenocarcinoma and its relationship to tumor progression. *Cancer* 1994; **74**: 1899–903.

receptor 2 with high affinity plays a role in evaluating the presence and/or extent of NECAP.² Hence, NECAP that presents in the heterogeneous tissue of the prostate gland should be differentiated from the usual adenocarcinoma. The complete genomic landscape of NECAP along with the impact on downstream transcriptional profile remains to be elucidated.³ Most recently, Aggarwal *et al.* exhibited that NECAP was significantly less likely to have amplification of androgen receptor (AR) or an intergenic AR enhancer locus, and demonstrated lower expression of AR and its downstream transcriptional targets using whole-genome sequencing method.³

Teruo Inamoto M.D., Ph.D.  and Haruhito Azuma M.D., Ph.D.
Department of Urology, Osaka Medical College, Takatsuki,
Osaka, Japan
tinamoto@osaka-med.ac.jp

DOI: 10.1002/iju5.12235

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Conflict of interest

The authors declare no conflict of interest.

References

- 1 Kobayashi M, Hagiwara M, Yamashina H, Ohbu M, Irie A. Prostate carcinoma with neuroendocrine differentiation successfully treated by early detection with imaging examination. *IJU Case Rep.* 2020; **3**: 282–5.
- 2 Gofrit ON, Frank S, Meirovitz A, Nechushtan H, Orevi M. PET/CT With ⁶⁸Ga-DOTA-TATE for diagnosis of neuroendocrine: differentiation in patients with castrate-resistant prostate cancer. *Clin. Nucl. Med.* 2017; **42**: 1–6.
- 3 Aggarwal RR, Quigley DA, Huang J *et al.* Whole-genome and transcriptional analysis of treatment-emergent small-cell neuroendocrine prostate cancer demonstrates intraclass heterogeneity. *Mol. Cancer Res.* 2019; **17**: 1235–40.