Title:

Neuroendocrine differentiation is a relevant prognostic factor in prostate cancer

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Neuroendocrine differentiation (NED) has been recognized in prostatic adenocarcinomas. It has been shown to increase in high-grade and high-stage prostate cancers and particularly in hormone-refractory tumors. However, the prognostic value of NED in prostate adenocarcinoma is not well understood due to conflicting results in reported studies. Genomic studies have suggested that there is intra-tumor heterogeneity of neuroendocrine differentiation in prostatic adenocarcinoma. In this study, 36 radical prostatectomy cases with a diagnosis of prostatic adenocarcinoma were selected, including 18 patients who developed recurrent cancer after curative surgery with PSA level >0.1 ng/mL, and 18 patients whose cancers did not recur during matched follow up times. NED was subjectively evaluated by performing immunohistochemistry (IHC) for Chromogranin A (CgA) and Synaptophysin, and the scores were evaluated independently by two GU-pathologists. Ten areas were randomly selected from cancer on each whole mount section, and the CgA IHC staining intensity in these areas was graded as 0-5. CgA staining intensity is positively associated with PSA serum level. Significant intra-tumoral heterogeneity of CgA staining intensity was observed. The cumulative CgA scores from 10 areas were higher in specimens from patients whose cancers relapsed, as compared with specimens from patients whose cancers did not recur. Mean cumulative CgA score is 18.72 ± 2.78 in the relapsed group and 8.28 ± 1.44 in the remission group. Synaptophysin is still undergoing evaluation. This study reveals that intra-tumor heterogeneity of NED exists in prostate adenocarcinoma, which may limit clinical evaluation. Though the data is not conclusive, we do observe a lower level of NED in patients in remission compared to patients with a clinical failure in treatment by thorough evaluation of NED in prostate sections. This study potentially provides guidance to clinical usage of NED markers for prognostication in prostate adenocarcinoma.