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Review article

Prognostic effect of neuroendocrine differentiation in prostate cancer: A critical review

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Abstract

Background: The multiple pathways that are involved in neuroendocrine differentiation (NED) in prostate cancer (PCa) are poorly elucidated. Evidence suggests that several environmental triggers induce NED leading to the adaptation of PCa to its close environment to maintain cell proliferation. Nevertheless, there is conflicting evidence regarding the prognostic role of NED in PCa.

Methods: In this review, we aimed to summarize all available data about NED and to assess the prognostic role of NED in disease progression and therapy resistance, and its role in routine clinical practice. This review was based on articles found through a PubMed literature search between 1993 and 2013. The study outcome measure was the effect of NED on oncologic outcomes at each PCa stage.

Results: In total, 59 articles reporting on the effect of NED on oncologic outcomes have been selected. In clinical practice, immunostaining for NED markers could have interesting predictive value for assessing the oncologic outcomes in patients receiving androgen-deprivation therapy. Thus, patients with high NED burden may be candidates for more aggressive treatment strategies targeting NED pathways. Conversely, strong evidence is lacking concerning its potential independent prognostic value in hormone-naïve PCa.

Conclusions: Current published data are not sufficient to recommend the use of NE markers in routine practice, particularly at early PCa stage.

Keywords: Prostate cancer; Neuroendocrine differentiation; Prognosis; Pathology; Immunostaining

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1. Introduction

Neuroendocrine differentiation (NED) is commonly present in the prostate gland, and its mechanisms have been studied extensively in the literature [1,2]. Nevertheless, multiple pathways are involved in the NED phenomenon and remain still unclear. Evidence suggests that several environmental triggers induce NED in prostate cancer (PCa), leading to the adaptation of PCa to its close environment to maintain cell proliferation. Thus, NED, an androgen-independent phenomenon, allows tumor cell growth under androgen-deprivation therapy (ADT) and may represent a viable option to escape hormone therapy and, thus, to contribute to cancer progression, mainly at castration-resistant stage. The functional network between adenocarcinoma cells and neuroendocrine (NE) cells may play an important role and may be the key mechanism in therapy and castration resistance, leading to disease progression.

In this review, we aimed to summarize all available data about NED and to assess the potential prognostic role of such differentiation in disease progression and therapy resistance and its role in routine clinical practice.

2. Methods

This review is based on articles found through a PubMed literature search between January 1, 1993 and December 31, 2013, using the following search terms: neuroendocrine differentiation, prostate cancer, ionizing radiation, androgen-deprivation therapy, chemotherapy, prognosis, immunohistochemistry, radical prostatectomy, and androgen therapy. The search terms were used one at a time and simultaneously in various combinations. Eventually, 1,270 articles were selected. Case reports, letters, or comments were excluded, as well as case series with fewer than 40 patients and articles regarding "pure small cell prostate cancer." Articles marked as nonrelevant (animal models and other NE tumors unrelated to PCa) were excluded (Fig.). Articles with limited availability (abstract only and conference papers) were also excluded. After excluding non–English-language abstracts, we selected 59 articles concerning focal NED in conventional prostate adenocarcinoma and its influence on oncologic outcomes. Also, the effect of NED on outcomes at each PCa stage was evaluated.

3. Results

3.1. NE cells in normal gland and PCa

3.1.1. Nonmalignant prostate gland

NE cells are present in normal prostate gland and were originally described by Pretl in 1944 [3,4]. They represent the third type of epithelial cell in the prostate gland after basal and exocrine secretory cells and account for $<1\%$ of all normal prostate cells. The role of NE cells is to regulate the cell growth and secretory activity via a paracrine mechanism [5]. However, the exact pathways underlying this regulation, as well the exact origin (neurogenic or stem cell origin) of these NE cells, remain debatable.

Evidence suggests that the NE cells promote prostate growth and thus may be causative for benign prostatic hypertrophy (BPH) via autocrine-paracrine regulatory loops [6]. Immunohistochemical (IHC) staining studies have confirmed the presence of NE cells in proliferating foci within BPH nodules. Conversely, Cockett et al. found that the overall serotonin immunoreactive NE cells decreased in BPH, suggesting that mature growth–arrested nodules were nearly devoid of NE cells, whereas areas of active growth contain numerous NE cells. These observations confirm the involvement of NE cells in the regulation of adjacent secretory cells. Nevertheless, authors have used serotonin-based immunostaining for NE cell identification. In a study including 43 samples of BPH tissue, Islam et al. [7] tested the relationship between NE cells and BPH evolution. Chromogranin A (CgA) has been used as a NE marker. These authors found that NE cells were distributed predominantly in the verumontanum and main prostatic ducts compared with their percentage in the terminal acini. Thus, the distribution of NE cells did not seem to be related to the development of BPH.

To date, no correlation has been demonstrated between NED and other prostate conditions such as chronic prostatitis or chronic pelvic pain syndrome.

3.1.2. Prostate cancer

NED in PCa is categorized into 3 groups according to the World Health Organization pathologic classification: (i) focal NED in conventional prostate adenocarcinoma, (ii) well-differentiated NE tumor classified as carcinoid tumor, and (iii) poorly differentiated NE carcinoma classified as small cell NE carcinoma [8]. As stated earlier, we only consider the first type, as the others are rare and the current literature is limited to case presentations or small case series making any attempt to define a consensus regarding the management of this disease almost impossible.

The origin of NE-like cells in PCa is still controversial. NE cells in PCa may be different than normal prostate NE cells in their protein expression [9]. These NE cells do not express androgen receptors (AR) or markers of proliferation such as Ki-67 antigen. NE cells are preferentially located close to Ki-67–labeled cells indicating the role of NE cells in controlling cell proliferation via a paracrine mechanism [10]. NE cells are more frequently reported in cases of high-grade or high-stage tumors or both and have been linked with a poor prognosis in univariate analysis [11,12].

There are a few studies regarding the correlation between NED and Gleason score, but a definite conclusion cannot be drawn because of the heterogeneity of the population studied and lack of statistical significance on multivariate analysis. McWilliam et al. [13], after evaluating 92 samples