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Original contribution

Prediction of bladder neck invasion and tumor extension to bladder neck margin by prostatic adenocarcinoma: a nomogram using biopsy data including transition zone tumor morphology ☆

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Summary Transition zone (TZ) prostatic adenocarcinoma can be identified on needle core biopsy based on tumor morphology, provided that the sample is preserved in a glutaraldehyde-based tissue fixative. TZ tumors have a propensity to grow larger than their peripheral counterparts without extraprostatic extension and finally to escape the gland by invading the bladder neck. We investigated the value of biopsy-determined parameters including TZ origin to predict the risk of isolated bladder neck invasion at radical prostatectomy. If reliable, this will enable urologists to expand their bladder neck dissection and avoid an isolated positive bladder neck margin. The study cohort consisted of 3942 patients with detailed pre operative biopsy information who underwent curative-intent radical prostatectomy between January 2010 and December 2015 in Western Australia. Multivariate logistic regression models were developed to predict isolated bladder neck invasion or isolated positive bladder neck margin. A predictive preoperative nomogram is presented. The predictive accuracy is shown in the calibration plot (the area under the curve: 0.777). The accuracy of the nomogram is dependent on the biopsy identification of transition zone cancer features, parameters only reliably interpretable after glutaraldehyde tissue fixation.

1. Introduction

Index prostatic adenocarcinoma originating in the transition zone represents approximately 20% of all prostate cancer. Usually these tumors are detected when significantly larger than their peripheral zone (PZ) counterparts, yet have a more favorable prognosis that is attributed to their lower histological grade (2005 Gleason grading system) [1-7].

Biological differences between TZ carcinoma and PZ tumors, remain largely unknown but, transition zone tumors rarely gain access to the seminal vesicles, or posterolateral penetrating peripheral nerves. Thus, their egress from the prostate gland is often via invasion of the bladder neck. Positive bladder neck margins in contrast to isolated positive

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bladder neck margin (IPBNM) are associated with significantly higher Gleason score (GS), tumor volume, tumor stage, preoperative prostate-specific antigen (PSA), seminal vesicle invasion and lymph node metastases [1,3,8], thereby indicating advanced disease, most commonly of peripheral origin. By contrast, IPBNM are usually not associated with these adverse findings and most likely represent large-volume TZ carcinoma encroaching on the bladder neck as one would expect from its anatomical proximity. This may simply reflect a large tumor volume rather than any inherent biological aggression or invasiveness. Of 8108 patients undergoing radical prostatectomy (RP) in Western Australia and evaluated in our laboratory, between September 1998 and December 2015, cases with IPBNM had an overall biochemical relapse rate of over 30%. Therefore, in larger TZ carcinoma, avoiding a positive margin at the bladder neck is critical in ensuring an enduring PSA-free survival, especially in what appears to be low-grade prostate cancer. The value of bladder neck preservation in pursuit of better urinary continence remains controversial [9-11] but it appears that although wider bladder neck resection is unlikely to impact subsequent urinary continence, it has the added potential risk of ureteral injury [12]. Therefore, identification of men at risk for isolated bladder neck invasion (IBNI) preoperatively may have significant value in targeting wide bladder neck resection and thus ensuring a negative surgical margin and subsequent PSA cure. At this time there has not been any reliable method proposed to recognize patients preoperatively who are likely to be diagnosed with isolated bladder neck margin positivity at radical prostatectomy. As many of these tumors represent low-grade anterior TZ cancers, preoperative multi-parametric magnetic resonance imaging (MRI) is of limited value [13]. This is further complicated by the similar radiologic appearance of bladder neck musculature to invasive carcinoma.

With the recent trend of increasing numbers of core biopsies taken in routine prostate needle biopsy, TZ cancers are more frequently sampled prior to radical intervention. However, in most centers such tumors cannot easily be recognized as transition zone in origin and separated from peripheral or central zone carcinoma based on needle core histology. Recent work in our laboratory has identified a reliable method, based on tissue fixation, to separate TZ from peripheral cancers on routine histology [14]. Using a glutaraldehyde-based tissue fixative modified for routine light microscopy, we identified large numbers of eosinophilic cytoplasmic granules in TZ cancers, which are usually lost in peripheral carcinogenesis. Our original work on prostate-secretory granules (PSG) [6] was based solely on transrectal core biopsies, and the impact of zonal origin on PSG content was not recognized. Most of the tumors in this early study, in particular, the high-grade lesions were of PZ origin, and we concluded that PSG content was inversely related to grade. Subsequently, the impact of tumor zonal origin on PSG content was recognized [14], which confirmed many previously untreated TZ cancers in contrast to PZ or central zone (CZ) tumors contain numerous PSG, irrespective of grade.

Using these data together with other histological features, we devised a reliable method to separate TZ from PZ carcinoma on preoperative core biopsy [14]. In this current study we investigate the use of this method to predict the risk of isolated bladder neck margin positivity preoperatively and thereby alert the operating urologists to expand his bladder neck dissection and potentially avoid an IPBNM.

2. Materials and methods

2.1. Case selection and patient details

A total of 4176 sequential patients who underwent curative-intent radical prostatectomy between January 2010 and December 2015 in Western Australia were identified from the West Australian radical prostatectomy database. Of the 4176 patients, 234 cases were excluded from analysis as the preoperative biopsies were performed by outside laboratories, which did not use glutaraldehyde-based fixation. The final study cohort was therefore 3942 cases with detailed preoperative biopsy information. The collection of patient details for research was approved by the Hollywood Private Hospital research ethics committee (HPH 128/132).

2.2. Biopsy data

A total of 13 different biopsy templates were used between 34 urological surgeons. These ranged from 8 to 20 targeted biopsy sites with a range of TZ targets from 2 to 4. All preoperative biopsy samples were assessed after routine fixation in a glutaraldehyde tissue fixative (Solufix) as has been previously described [14]. The presence or absence of TZ cancer on any biopsy core as defined by previous pathologic criteria [14] was noted, ie, 664 TZ tumor cases (with a mean number of 16.99 biopsy cores per case) containing PSG content >50% accompanying columnar cells >30% or pale cells or the presence of secretions *vs.* 3278 cases without TZ tumor characteristics with a mean of 16.20 biopsy cores per patient. The PZ and TZ tumor characteristics are demonstrated in Fig. 1A-B.

As many of the prostate glands contained multiple tumors of different zonal origin and these tumor types were frequently represented in the same biopsy core or set, no attempt was made to specifically separate or quantify the TZ-specific tumor characteristics as compared to co-existent PZ or CZ carcinoma.

2.3. Radical prostatectomy

All 3942 radical prostatectomies were collated according to the presence of IBNI with negative margins (37 cases – 0.94%) and IPBNM (129 cases – 3.27%). Bladder neck invasion was defined as the microscopic involvement of the muscular wall of the bladder neck by prostate cancer cells in the absence of benign prostatic glandular tissue on