

Review Article

Pitfalls of Diagnosis of Extraprostatic Extension in Prostate Adenocarcinoma

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Abstract

Extra prostatic extension (EPE) is of the important features to evaluate in pathological assessment of radical prostatectomy specimens. Despite the uncomplicated definition of presence of neoplastic glands outside the prostatic boundary, diagnosing EPE is not always straightforward, the main reason being absence of true capsule around prostate gland. Other confounding findings include intracapsular incision, desmoplastic reaction, intraprostatic fat, tumor displacement (pseudo invasion) and benign mimickers. This study reviews different situations obscuring the diagnosis of EPE and is the first study illustrating pseudo invasion in prostate.

Keywords

- Extra prostatic extension
- Prostate
- Adenocarcinoma
- Pseudo invasion
- Paraganglia

INTRODUCTION

Prostate adenocarcinoma (PCa) is the most common cancer in male. Radical prostatectomy (RP) is the treatment of choice for intermediate grade PCa (GS 7) as well as non - low volume, low grade (GS 6) PCa. Two most significant histological indicators of prognosis in PCa are grade and stage (assessed by Gleason Score (GS) and TNM systems respectively) that are vital for decision making in post RP management of PCa. Based on AJCC 7th edition (2003), the most significant features determining the stage are organ confinement, extra prostatic extension (EPE), seminal vesicle involvement and lymph node metastasis. Although clear guidelines have been proposed to diagnose EPE, a significant interobserver variability is present between pathologists [1]. Considering the importance of correct pathological staging, this study illustrates potential morphologic pitfalls in identification of EPE with a review of literature.

Definition of extra prostatic extension

Extra prostatic extension (EPE) is defined as presence of neoplastic glands beyond the normal boundaries of the prostate gland. Prostate gland has no true anatomical capsule [2]; a fact that confounds objective assessment of EPE. It is recommended to use an arbitrary line separating prostate gland from peri-prostatic connective tissue. Since most of the prostate is surrounded by loose connective tissue, an imaginary line separating the last thick muscle bundles of prostate tissue from the loose connective tissue and fat is considered to be the capsule, and identification of tumor infiltration through this line is considered EPE. There are exceptions to the rule in the apex and base of tumor.

I-Apex of prostate

The anterior aspect (apex) of the prostate gland has least

defined boundary and causes the most controversy; [3] therefore EPE in apex should be evaluated carefully. In this region of prostate gland, skeletal muscle bundles join together with normal prostate tissue, therefore benign glands are frequently intermixed with skeletal muscle [4]. The findings may be more alarming when malignant glands are present admixed with skeletal muscle bundles. Based on current recommendations, regardless of presence or absence of benign glands in such condition, the tumor is considered organ confined as long as there is no tumor present at the margin of prostatectomy [5]. Having both benign and malignant gland at the inked margin in apical sections should be considered intra - capsular incision (vide infra) [4]. When identifying malignant glands at the inked margin at apex, the finding is considered a positive margin in an area of EPE [3,6].

II-Base of prostate

Moreover, the boundaries of prostate are irregular at the base of the prostate and around seminal vesicles. In this region, presence of tumor next to fat is essential for diagnosing EPE.

Focal vs. non-focal EPE

Several studies have demonstrated that differentiating focal and non-focal EPE has significant impact on the outcome and management of the disease; [7-9] therefore one has to report the extend of EPE in the CAP criteria. Unfortunately, there are no unified criteria for distinction of focal and non-focal EPE. The initial recommendations considered limited neoplastic glands outside prostate gland boundaries as focal EPE, [7] which makes such evaluation very subjective. More objective methods consider focal EPE as less than one high magnification field in up to 2 sections, [8] or EPE limited to one slide only [9]. The author

uses the last method as it appears to be simpler, more practical and reproducible.

Intra-capsular incision

Intracapsular incision (ICI) is a rare finding that occurs when surgeon unintentionally fails to remove the entire prostate tissue, and some of the benign and malignant prostate tissue is left behind. It is most frequently identified around the neurovascular bundles, but can be seen anywhere in a RP specimen. The implications of ICI includes shortened or absence of PSA nadir and higher biochemical recurrence [10-12].

ISUP consensus recommended that any ICI is reported in the pathology report [4]. When ICI occurs in the tumor region, evaluation of EPE may not be possible. One common mistake is upstaging cases with ICI at tumor to pT3 in the absence of additional definite EPE. Studies have shown a worse prognosis for ICI compared to organ confined tumor (pT2), but better than extra prostatic excision (pT3a) [3,4,13,14]. Therefore, it is more appropriate to assign a stage pT2 (R1) in a situation where there is margin positivity in an area of ICI without additional evidence of EPE.

Margin positivity

According to AJCC 7th edition, margin status affects the outcome of RP and needs to be reported in the final stage; however there is controversy regarding what aspects of positive margin need to be reported. Some studies have shown correlation between GS at positive margin and biochemical recurrence; [15,16] but others failed to reveal any association [17]. Similarly, length of positive margin has been shown to have predictive value in biochemical recurrence in some studies [18] but not others [13].

Artifacts

There are several methods used in nerve sparing RP to avoid neural damage and yet achieve appropriate hemostasis. Occasionally, thermal and mechanical artifacts are formed because of operation and tissue processing methods that can be a source of frustration in evaluation of EPE [1]. It should be noted that prostate has very little loose connective tissue at the periphery that can be disrupted at any time during the operation or specimen handling [19]. Hong et al., identified periprostatic adipose tissue in only 48% of the RP cases in their series [20]. Simple measures like obtaining additional levels from suspicious block can usually be helpful in resolving the issue.

EPE usually forms irregular protrusion or breaching of cancer outside a neoplastic clone. In situations where artifacts compromise morphology, one should pay attention to the tumor nodule at scanning magnification. Numerous studies have shown that distance of tumor to the margin has no effect on stage or biochemical recurrence; [8,19,21,22] therefore in the absence of peripheral irregularity, a well - delineated tumor nodule can be safely considered organ confined as long as there are benign stromal cells between the tumor and periprostatic tissue.

Desmoplastic reaction

Fibrosis and desmoplastic reaction to EPE seldom happens. It blends in with the normal prostate stroma when there is extra prostatic extension in the posterior and posterolateral aspects of prostate [14]. In such events one may be able to identify dense

muscle bundles of prostatic stroma to show the boundary of prostate or residual adipose tissue in the desmoplastic reaction, [14] which is not always feasible.

Benign prostate stroma is composed predominantly of smooth muscle fibers with a variable population of fibroblasts, myofibroblasts and collagen fibers [23,24]. There is increased cellular density in the transition zone compared to the peripheral zone, mostly due to excess smooth muscle fibers [25]. Unlike the benign stromal cells that arrange in short streaming fascicles and have bland nuclear features, desmoplastic stroma in prostate cancer is enriched in fibroblasts and myofibroblasts and has less smooth muscle cells showing haphazard cellular arrangement with commonly plump nuclear features, clearing and clumping of chromatin, and more prominent nucleoli [24]. Similar features may be seen in infections and inflammations of the prostate; however inflammation associated stromal changes usually surrounds prostatic glands and is associated with conspicuous acute and chronic inflammatory cells. A combination of Mallory trichrome, vimentin, actin and desmin in differentiation can help in distinction [24].

Intraprostatic fat

The most helpful finding in establishing EPE is identifying tumor cells abutting adipocytes [26]. However, one has to bear in mind that adipose tissue can be found inside prostate gland [27-31]. The frequency may show a racial variation [27] and is reported to be focal rather than diffuse in prostate gland, therefore compromising EPE diagnosis in prostate biopsies. Luckily, this finding is very rare. This situation is not much of a concern in RP cases [31]. The author has confronted misplaced adipose tissue inside a circular tract of prostate core biopsy in RP.

Tumor misplacement (pseudo invasion)

Misplacement of tissue has been reported to occur infrequently after needle sampling of various organs, including thyroid [32-35]. The misplaced tissue may be non - neoplastic; however the findings cause confusion when translocation of neoplastic tissue occurs. The most significant implication of such finding includes misinterpretation of the pseudo invasion as true invasive disease, resulting in unnecessary intervention. So far, there has been no report of any adverse effect cause by misplaced malignant tissue; therefore it is of utmost significance to distinguish between true and pseudo invasion.

Displacement is defined as inadvertent placement of prostate tissue as an inclusion in a secondary location away from the origin that is usually due to invasive procedures like obtaining needle biopsy (Figure 1). This secondary location may be inside the prostate or in periprostatic soft tissue. Displacement of benign prostate tissue and corpora amylacea is a common finding in RP specimens, but rarely one can confront displacement of neoplastic tissue (high grade PIN or adenocarcinoma). When no sign of malignancy is present, presence of inclusion is of no concern. But when adenocarcinoma is displaced, differentiation with EPE is necessary. The features helpful in identification of benign displacement include identification of benign glands or corpora amylacea in the vicinity, lack of continuation between the displaced tissue and tumor nodule and association of inclusion with hemosiderin laden macrophages, chronic inflammation, fat necrosis or multinucleated giant cells (evidence of prior biopsy

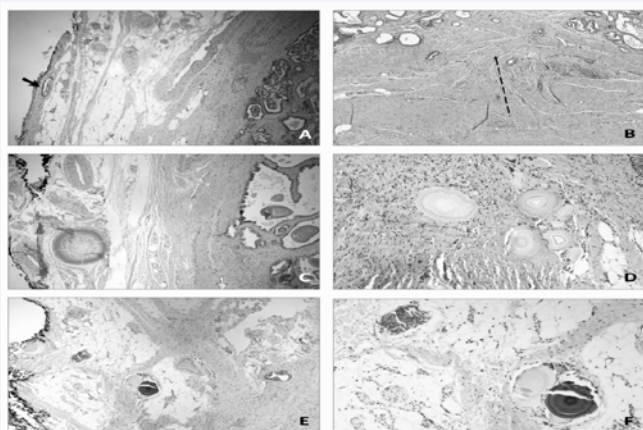


Figure 1 Displacement of prostate tissue (pseudoinvasion).

(A). Inclusion of a prostatic gland in periprostatic fat (arrow) in radical prostatectomy (H&E, 4X).

(B). Displacement of malignant glands outside prostate gland in a needle biopsy tract. The arrow highlights the direction of needle insertion. Note presence of inflammation and hemosiderin laden macrophages adjacent to the tract (H&E, 4X).

(C). Corpora amylacea seen as an inclusion outside prostate (H&E, 4X).

(D). Corpora amylacea seen as inclusion in an area of needle biopsy. Note foreign body reaction and hemosiderin laden macrophage aggregation (H&E, 10X).

(E & F). Displacement of malignant looking glands in the periprostatic fat. Note lack of tissue reaction and presence of corpora amylacea and foreign body giant cell reaction (H&E, 4X & 10X).

tract). In addition, EPE often causes a desmoplastic reaction and is usually found ipsilateral to the dominant tumor nodule. The author has confronted a case where the area of biopsy needle tract showed fat necrosis inside prostate, mimicking extraprostatic adipose tissue.

Similar argument holds when confronting displaced PCa in lymphovascular spaces, both inside and outside the prostate gland. EPE may be present in the form of lymphovascular invasion (LVI). Kryvenko et al., reviewed the differentiating features of true LVI with benign mimickers and found that benign prostate epithelium and corpora amylacea can be found inside a true vascular lumen in radical prostatectomy specimens, and should be considered benign [36]. In the presence of such findings, noticing malignant glands inside vascular lumen may represent a displacement process.

Paraganglia

Paraganglia can be identified in 8% of radical prostatectomies, [37,38] and with less frequency in TURP and prostate biopsies [39]. Because of morphologic appearance, paraganglia can be a mimicker of high Gleason grade prostate adenocarcinoma both inside and outside the prostate tissue, especially when there is thermal artifact or the cancer has foamy cell features [40]. It is usually identified in the posterior and lateral aspects of periprostatic connective tissue in association with nerve bundles and vascular channels (Figure 2). Most common morphologic patterns are individual or small clusters of neuroendocrine cells with abundant clear to finely granular cytoplasm without

nuclear atypia or conspicuous nucleoli. Ganglion cells can also be a mimicker of prostate carcinoma; they usually are identified inside nerve bundles and appear as large polygonal cells with abundant eosinophilic or amphophilic cytoplasm, rounded nuclei with a single prominent nucleolus.

Rarely, paraganglia can appear forming acinar structures (Figure 2D), which may be mistaken for EPE. When in doubt, positive immunostaining for S100 in paraganglia and chromogranin A and synaptophysin in ganglion cells as well as negative staining for prostate markers like PSA, AMACR, PSMA and Prostein can help rectify the issue.

Radial distance of EPE

Recent studies have looked into sub staging of prostate cancers with EPE (pT3a). Several studies have looked into features that affect outcome in prostate carcinoma, features like extent of EPE (Table 1) (41-47). In their study, Sung et al compared various protocols in reporting the EPE and found that only implementing

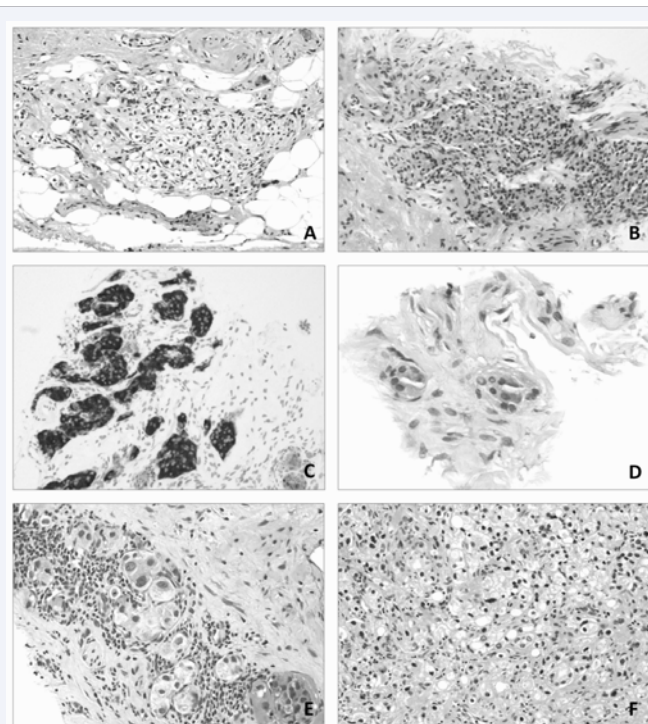


Figure 2 Paraganglia.

(A) Normal paraganglia with ganglion cells in periprostatic tissue (H&E, 20X).

(B) Normal paraganglia inside prostatic tissue in needle biopsy mimicking high grade prostate adenocarcinoma (H&E, 20X).

(C) Chromogranin-A corresponding to the cluster in (Figure 2B) (Chromogranin-A, 20X).

(D) Acinar forming paraganglia in a prostate needle biopsy, a mimicker of prostate adenocarcinoma. Deeper levels revealed typical paraganglial tissue (H&E, 40X).

(E) Extraprostatic extension of adenocarcinoma showing perineural invasion, resembling ganglion cell morphology. Note nuclear atypia and small focus of vascular invasion in right lower corner (H&E, 40X).

(F) Adenocarcinoma of prostate corresponding to Figure (2E) showing high grade cancer with cytoplasmic clearing. (H&E, 20X).

Table 1: Review of literature on extra prostatic extension in radical prostatectomy.

	Davis et al. (1999)	Sohayda et al. (2000)	Teh et al. (2003)	Chao et al. (2006)	Schwartz et al. (2007)	Sung et al. (2007)	vanVeggel et al. (2011)
Patient number	376	265	712	371	404	83	134
EPE (%)	105 (28)	92 (35)	299 (42)	121 (33)	121 (30)	83 (100)	134 (100)
Preop PSA in EPE + cases	Mean:17.9	Median:7.4	Mean:13.73	Mean:14.5	Median:8.5	n/a	n/a
EPE distance (mm)	Median (0.5); mean (0.8mm)	Median (1.1mm)	Median (2.0mm)	Median (2.4mm); mean (2.3mm)	Median (0.6mm); mean (0.9mm)	Median (0.75mm); mean (1.06mm)	Median (1.0mm)
EPE range (mm)	0.04-4.4	0.1-10.0	0.5-12.0	0.05-7.0	0.0-5.7	0.08-6.0	n/a

Abbreviations: EPE: Extra Prostatic Extension; Preop: Preoperative; mm: Millimeter; n/a: Not Available

radial distance of EPE from prostatic capsule using an ocular micrometer can help predict biochemical recurrence. [46] van Veggel et al., showed that the best discriminatory power belonged to dividing EPE into focal and non-focal subcategories, but in an effort to identify a more objective assessment of EPE, the authors found that maximal radial distance of 1 high power field (HPF) (equal to 0.6mm) can be used as a strong predictor of biochemical recurrence [47]. Additional studies are needed to attest the usefulness of radial distance measurement in the follow up of PCa.

Investigations have revealed potential serum markers for diagnosis of EPE preoperatively. Lee et al., showed that serum hormone binding globulin (SHBG) level is an independent predictive factor for extra prostatic extension of tumor in patients with clinically localized prostate cancer. [48] SHBG is a circulating glycoprotein that has great affinity for testosterone. Absence of diurnal variation like testosterone level in serum makes SHBG a better and more reliable surrogate marker for assessing systemic androgenicity. The findings however have not been validated. Immunohistochemical studies (i.e. P53) has been shown to correspond to malignant behavior but no use in EPE detection was identified [49].

CONCLUSION

Identification of EPE is of significant importance in the staging and management of PCa, and there are well-established criteria for diagnosis of EPE. Pathologists should be familiar with the morphological aspects as well as pitfalls of diagnosing EPE. Additional studies are needed to determine the extent of information in reporting EPE.

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