Journal of BUON **15:** 19-24, 2010

REVIEW ARTICLE

A clinical dilemma; single prostatic cancer focus in biopsy. Interpretation and management

I. Efthimiou[1], K. Skrepetis[2], E. Bournia[3]

[1]Department of Urology, General Hospital of Chios, Chios; [2]Department of Urology and [3]Departement of Pathology, General Hospital of Kalamata, Kalamata, Greece

Summary

Adoption of screening programmes for early diagnosis of prostate cancer has led to an increased number of sonographically guided prostate biopsies. Core needle biopsies are now among the most common specimens received from pathology laboratories. As a result, urologists and pathologists may encounter small volume prostate tumors with obvious clinical and diagnostic implications. These cases may be extremely challenging for two reasons. The diagnosis of small cancer foci is a challenge for pathologists as it carries the risk of false positive or negative diagnosis. Additionally, it represents a difficult clinical dilemma for urologists whether they should proceed or withhold treatment for local disease. This report highlights current concepts regarding pathologic diagnosis and clinical management of these cases.

Key words: biopsy, minimal cancer, prostate cancer

Introduction

Prostate cancer is one of the most important cancers in men with a worldwide incidence of 25.3 per 100,000. It also represents the third leading cause of male cancer deaths in Europe after lung and colorectal cancer [1]. The natural history of prostate cancer is not fully established but it is well known that the disease is often indolent with long latent phase. Although this is advantageous for screening, it is problematic for some tumors which are growing very slowly and may never become clinically important [2,3]. Given that many men who develop prostate cancer do not either develop clinically relevant disease or die as a result of their disease, overdetection may be an important issue. Associated with this issue is the detection and management of small cancer foci on prostate biopsy. A standardized terminology regarding a small focus of prostate adenocarcinoma detected on needle biopsy does not exist and authors use various terminologies and criteria to describe it such as focal, microfocal cancer, minute cancer, single prostatic cancer foci [4-8].

Initially it was defined as low grade adenocarcinoma covering <3 mm in a single prostate core biopsy [4]. Zackrisson et al. included also lesions involving two adjacent prostate biopsies ≤3 mm without Gleason score 4 or 5 [5]. Other authors included carcinomas ≤6 in Gleason score, <1 mm in size or occupying <1×40 field in a single needle specimen [6]. In a more recent paper by Boccon-Gibob et al. foci of moderately differentiated lesions, <5 mm in a single biopsy were reported as microfocal cancers [7].

Pathologic criteria for diagnosis of single foci of prostate cancer

The diagnosis of prostate cancer is mainly based on the architecture of the lesion on haematoxylin and eosin (H&E)-stained sections and ancillary studies with immunohistochemistry. The initial step in the pathologic evaluation of any individual needle biopsy is to discriminate with certainty the areas of the specimen where the glands are undoubtedly benign. It is impor-

Correspondence to: Konstantinos Skrepetis MD, PhD, FEBU. Ydras 103, 241 00 Kalamata, Greece. Tel: +30 27210 46399, Fax: +30 27210 33666, E-mail: Skrepetis@hotmail.com

Received 11-03-2009; Accepted 27-04-2009

tant to appreciate the normal architecture of the prostate gland before diagnosing minimal prostate carcinoma. Microscopically, the minimum number of glands required for the diagnosis of prostate adenocarcinoma is 3 malignant glands, and the mean number that is usually present is 10-20 [10-13]. A list of histological features for the diagnosis of minimal prostatic carcinoma is presented in Table 1 [11]. The major and minor criteria and diagnostic attributes of minimal carcinoma should be assessed specifically at low- and high-magnification. Pathologic work-up starts at lower power magnification in order to asses the morphology of the glands and epithelial structures. One pattern seen at low-magnification that should raise a suspicion of carcinoma is the presence of a focus of crowded glands. The most prominent diagnostic feature is nuclear enlargement. Nuclear hyperchromatism is a cytologic feature that may help to distinguish cancerous from benign glands. Previous studies have shown that this feature is present in more than 90% of the cases [9-10]. Infiltrative growth pattern is usually indicated by the presence of small malignant glands between the bigger and more complex benign glands. Benign glands are recognized by their larger size, papillary infolding and branching. The presence of small malignant acini situated in between benign glands is a manifestation of their infiltrative nature (Figure 1). Moreover, disordered glands with random dispersion in the stroma with absence of benign glands is another common pattern of infiltration [11]. Identification of infiltrative pattern is very important because it is a highly reliable marker of malignancy. However, this criterion is difficult to interpret when only a minimum number of malignant glands is present in the specimen and perineural invasion, which is another important finding in prostate cancer diagnosis, is very rarely present in minimal carcinomas [10]. Nucleolar enlargement is usually present but not a constant finding in prostate carcinoma. The presence of prominent nucleoli may be obscured by poor fixation, overstaining, section thickness or hyperchromatic nuclei. This last factor of lack of chromatin clearing might contribute to inability to detect nucleoli. The significance of prominent nucleoli must be taken in the context of the architectural pattern and other features present with the case. Complete lack of basal cells is an additional feature although it may be encountered in benign small glands as well, and can potentially create confusion with atypical small acinar proliferation (ASAP). Another common difficulty is that distorted, crushed, or poorly preserved carcinoma cells in minimal cancer foci can mimic basal cells. Some minor criteria, when present, may be very helpful, although these features are not specific for carcinoma [10]. These minor diagnostic criteria are intraluminal eosinophilic amorphous secretions, intraluminal crystalloids, amphophilic cytoplasm and hyperchromatic nuclei. With the exception of high grade PIN, none of the minor criteria should be used as a criterion for rebiopsy as they may be found in benign glands as well.

If there is uncertainty regarding the diagnosis of cancer the lesion may be reported as "ASAP suspicious of malignancy" and a repeat biopsy is highly recommended as the incidence of definite cancer in such cases may be as high as 40% (Figure 2). The term ASAP should be reserved for frankly suspicious lesions to prevent transforming this category into a hold-all for all uncertain lesions [14-16].

There are numerous benign conditions that may mimic prostatic carcinoma and may be recognised as malignant. The differential diagnosis of minimal prostatic adenocarcinoma includes a large number of benign diseases like adenosis, atrophy, prostatitis, Cowper glands and benign glands. Atypical adenomatous

Table 1. Criteria for the diagnosis of minimal prostate adenocarcinoma (adapted from [12])

Major criteria
Architectural: infiltrative small glands or cribriform glands too large or irregular to represent high-grade PIN
Single cell layer (absence of basal cells)
Nuclear atypia: nuclear and nucleolar enlargement
Minor criteria
Intraluminal wispy blue mucin (blue-tinged mucinous secretions)
Pink amorphous secretions
Mitotic figures
Intraluminal crystalloids
Adjacent high-grade PIN
Amphophilic cytoplasm
Nuclear hyperchromasia

PIN: prostatic intraepithelial neoplasia

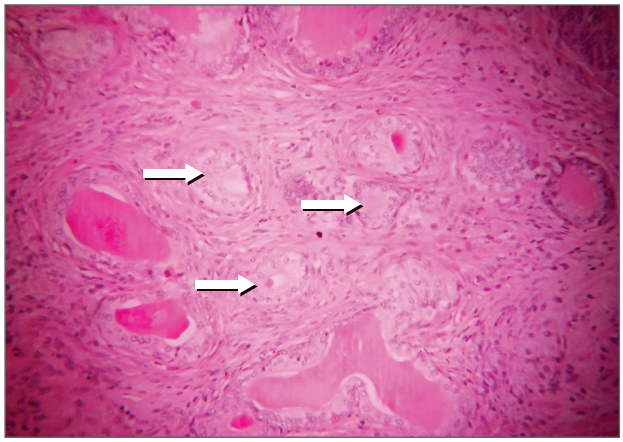

Figure 1. Minimal prostatic adenocarcinoma with small acini (arrows) (H&E ×300).

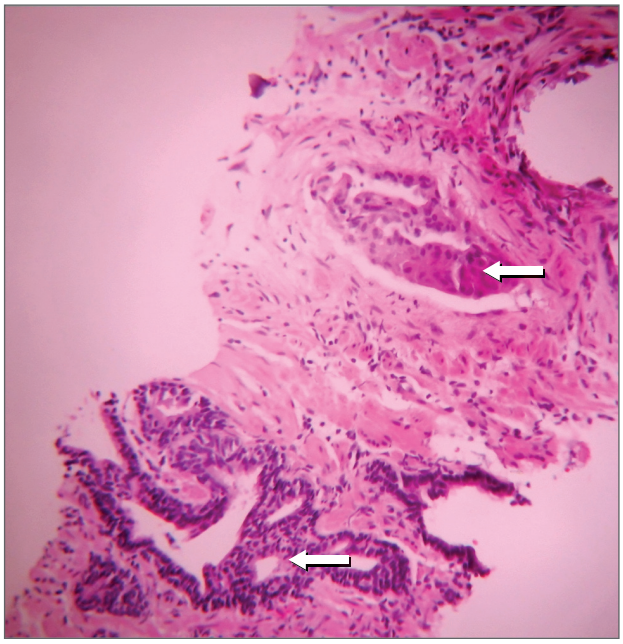

Figure 2. Low-grade prostatic intraepithelial neoplasia (LGPIN) at lower left (arrow) and a focus of atypical small acinar proliferation (ASAP) at upper right (arrow) (H&E ×300).

hyperplasia (adenosis) and atrophy are the most common benign conditions that may be misdiagnosed as prostate cancer (Figure 3). Adenosis can be confused with minimal well differentiated adenocarcinoma and atrophy can be confused with moderately differentiated adenocarcinoma. However, a minimal prostatic adenocarcinoma can have atrophic features. Atrophic prostate cancer can have significant cytoplasmatic volume loss and marked nuclear enlargement. In addition, high grade PIN and ASAP suspicious for malignancy can be false positive [16]. High grade PIN shares some common features with focal cancer and ASAP like nuclear atypia, prominent nucleoli, loss of basal cells layer and infiltrative pattern. High grade PIN can be often difficult to distinguish from invasive adenocarcinoma in needle biopsy tissue as it can closely resemble small acinar, minimal carcinoma in its architectural pattern (Figure 4). In such cases, provided there is sufficient specimen, immunohistochemistry is very useful in the differential diagnosis of atypia from minimal carcinoma.

Having the above pitfalls in mind and the fact that routine stain with H & E may lead to false positive results, immunohistochemistry with monoclonal antibodies which bind to basal cell cytokeratins and p63 nuclear staining has proven helpful in the diagnosis of focal prostate cancer [17-19]. Immunohistochemical stains for alpha-methylacyl coenzyme A racemase (AMACR), an enzyme involved in lipid metabolism, in combination with absence of p63 and high molecular weight cytokeratin (34betaE12) can overcome the limitations of stain with H&E. Immunohistochemical cocktails are particularly useful in evaluating small foci of atypical glands, and in substantiating a diagnosis of minimal adenocarcinoma [20]. This combination can significantly reduce false negative results by given cytoplasmatic, nuclear, or both types of reactivity in non-neoplasmatic acini (Figure 5) [18].

Clinical significance and management of single foci of prostate cancer

PSA screening test has led to increased frequency of focal carcinomas diagnosed in biopsy specimens. One study showed a frequency of 6-7.9% depending on the screening round [5]. The fundamental question is whether focal cancer can be managed as minimal cancer. Minimal cancer is an entity defined as a cancer that would not de life-threatening if left untreated. In prac-

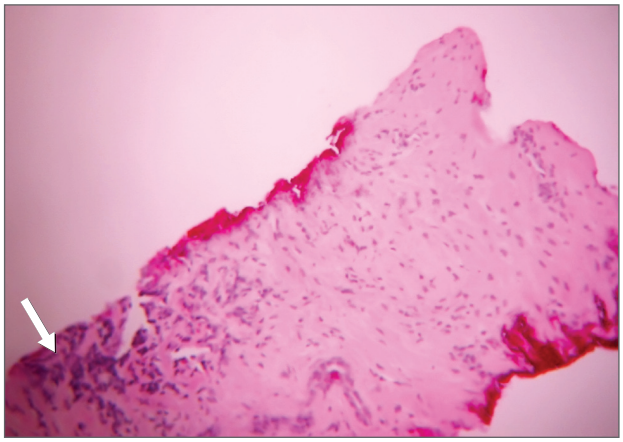

Figure 3. Atypical adenomatous hyperplasia (adenosis) and a focus of ASAP in the lower left corner (arrow) (H&E ×300).

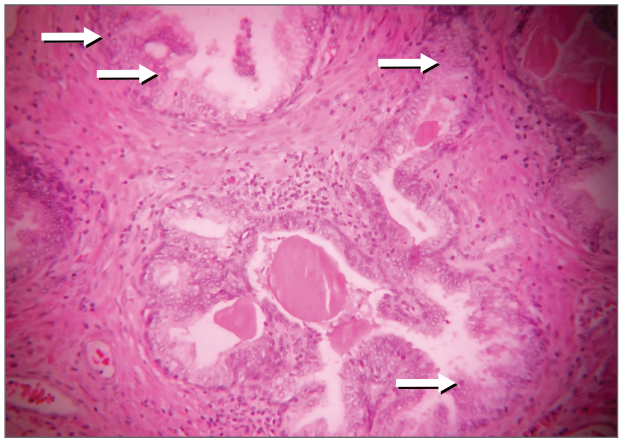

Figure 4. High-grade PIN. Nuclei have coarse chromatin and occasional prominent nucleoli (arrows) (H&E ×300).

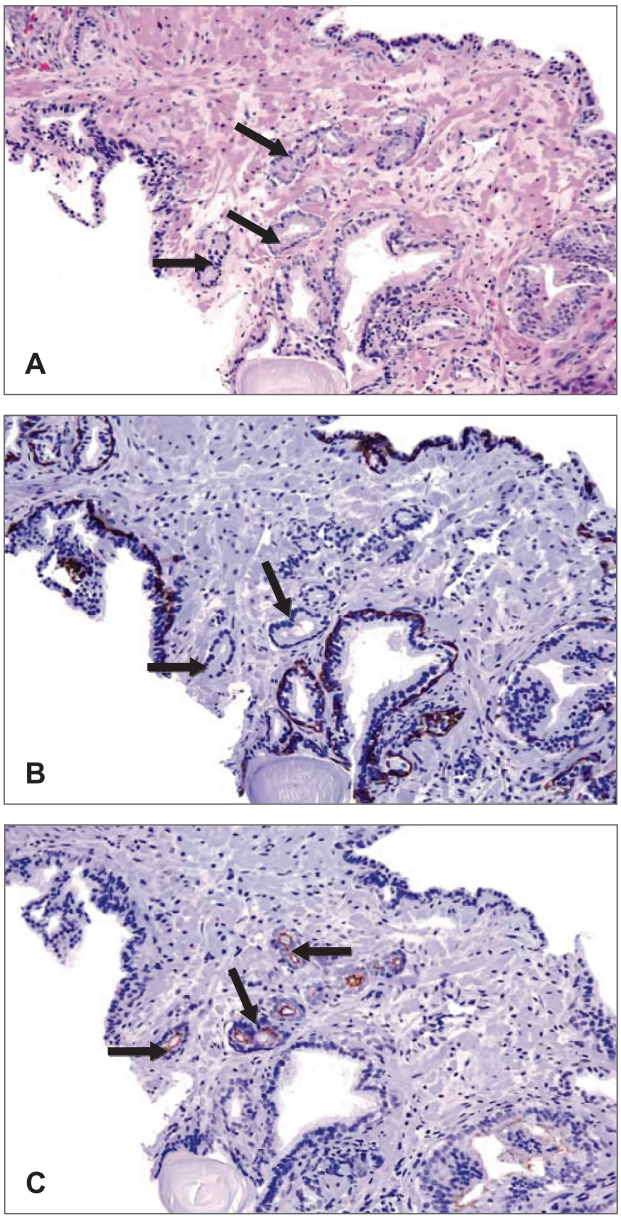

Figure 5. A: Small focus of atypical glands (arrows), highly suspicious for adenocarcinoma of the prostate. **B:** Stains for the high molecular weight cytokeratin (34βE12) are negative in atypical glands (arrows), consistent with adenocarcinoma. **C:** Stains for α-Methylacyl coA Racemase (AMACR) are intensely positive in the atypical glands, also consistent with adenocarcinoma. Note (lower right) a benign-appearing gland with some AMACR positivity (arrows). It is not uncommon to have benign-appearing glands adjacent to adenocarcinomas that are focally positive for AMACR (Reprinted with permission from [18]).

tice this definition includes cancer with volume <0.5 ml with no high Gleason grade. Studies conducted to answer the above question showed a variation in correspondence between the two entities. More specifically, a 30-70% of correspondence was shown, depending on definitions of focal disease, target population and variations in tumor volume measurements [5,7,21,22]. In a study from Egevad et al. the best predictor for a cancer volume <1 ml was a single focus <3 mm with Gleason score <7, provided an extended biopsy protocol was used [23]. Another study reported similar results but it also showed that increased prostate volume was inversely related to prostate cancer volume and was a prognostic factor for minimal cancer [24].

Histologic grade is commonly used to stratify patients into prognostic and therapeutic groups. The typical problem for Gleason grading in needle biopsy specimens for minimal and nonminimal carcinomas is undergrading the needle core tissue. A small amount of tumor in prostate needle biopsy specimens is not equivalent to low-grade tumor. In a study of ours, we also found that patients with 2-4 Gleason score on needle biopsy were undergraded in 76% [25]. On the other hand, minimal high-grade prostate cancer in needle biopsy tissue is predictive in most cases of high Gleason score in radical prostatectomy specimens [26]. In our series, preoperative Gleason score was a significant predictor of organ-confined disease, however, it was useful in <25% of individual patients. Additionally, we believe that the number of positive needle biopsies and the preoperative Gleason score are the two significant variables predicting extraprostatic disease. Our findings demonstrated that patients with ≥3 positive needle core biopsies and high Gleason score (7-9) have an increased probability (72%) of extraprostatic disease [25]. This preoperative information is potentially useful for selecting the most appropriate therapeutic approach for prostate cancer. However, speaking about the significance of the differences between pre- and posttreatment grading on an experimental basis, we agree that it is critical to be taken into consideration as a probability bias in outlining the results of studies and audits on prostate cancer.

Active surveillance comprises active monitoring, with tailored treatment only if there is evidence of disease progression. It is frequently practised in order to decrease overtreatment of early prostate cancer. Data from studies suggest that men with active surveillance alone may achieve similar survival rates with men treated with radical prostatectomy. However, a very important drawback of this strategy is the psychological burden for some men of living "with an untreated cancer inside them". Patients with single foci disease are suitable candidates for active surveillance provided they meet the criteria of Gleason score ≤6, PSA level ≤ 10 ng/ml and clinical stage T_{1C} or T_2 [27,28]. Clinical decisions should also take into account the patient's age and comorbidities. Patients with >10 years of life expectancy may not be good candidates for active surveillance. Digital rectal examination (DRE), PSA kinetics and repeat prostate biopsies are of value in the management of such

patients. A repeat prostate biopsy with an extended protocol should be used to decrease the chance of missing a clinically significant cancer. After repeat biopsy in such cases, absence of cancer is found in 30%, an upgrading to Gleason score 7 in 20% and in 50% multiple sites of cancer are discovered [29]. While further biopsies are at the discretion of the treating physician, until further data is available, it is recommended to perform a prostate biopsy at least once every 2 years in patients with life expectancy of >10 years in order to recognise early grade progression. The follow-up schedule should include DRE and PSA measurements every 6-12 months depending on life expectancy. PSA kinetics is also useful as studies have shown the speed of the rise in PSA prior to treatment of prostate cancer to be a strong predictor of outcome [30]. The National Comprehensive Cancer Network considers PSA velocity (PSA-V) >0.75 ng/ml or PSA doubling time (PSA-DT) <3 years as a sign of progression in its guidelines of expectant management in early prostate cancer [31]. At least 3 measurements over a period of at least 6 months should be used for these calculations. Numerous instruments are now available that automatically calculate PSA-V and PSA-DT during follow-up of patients on active surveillance. An example is illustrated in Figure 6.

Conclusions

Needle biopsy specimens from the prostate with minimal foci of cancer are increasingly sampled and pose diagnostic challenges for the histopathologist. Also, single prostate cancer focus is a real challenge for the urologist. Future developments in prostate cancer diagnosis, accurate volume assessment and molecular profiling will hopefully elucidate further this difficult clinical problem and identify which patients are suitable for active surveillance protocol.

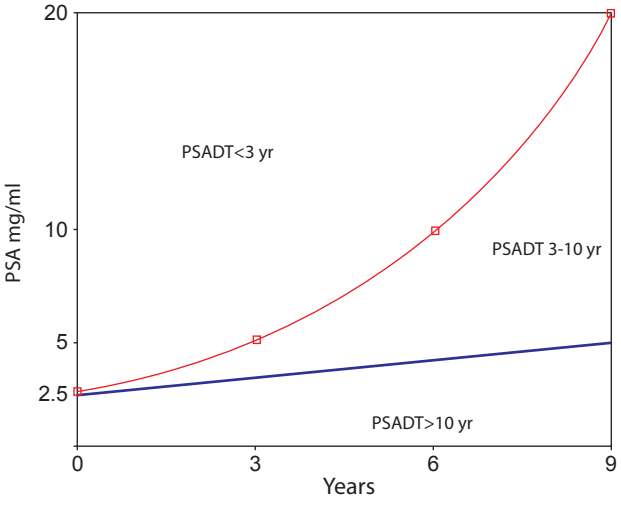

Figure 6. An example of a starting PSA 2.5 mg/ml with two different doubling times (DT). The red curve and the blue line show a doubling time of 3 and 10 years, respectively. The difference in PSA kinetics is obvious so the clinician can guide his management accordingly.

References

1. Jemal A, Siegel R, Ward E et al. Cancer Statistics, 2007. CA Cancer J Clin 2007; 57: 43-46.
2. Johansson JE. Expectant management of early stage prostatic cancer: Swedish experience. J Urol 1994; 152: 1753-1756.
3. Chodak GW, Thisted RA, Gerber GS et al. Results of clinically localized prostate cancer. N Engl J Med 1994; 330: 242-242.
4. Weldon VE, Tavel FR, Neuwirth H, Cohen R. Failure of focal prostate cancer on biopsy to predict focal prostate cancer: the importance of prevalence. J Urol 1995; 154: 1074-1077.
5. Zackisson B, Aus G, Bergdahl et al. The risk of finding focal cancer (less than 3 mm) remains high on re-biopsy of patients with persistently increased prostate specific antigen but the clinical significance is questionable. J Urol 2004; 1714: 1500-1503.
6. Allan RW, Sanderson H, Epstein JI. Correlation of minute (0.5 mm or less) focus of prostate adenocarcinoma on needle biopsy with radical prostatectomy specimen: role of prostate specific antigen density. J Urol 2003; 170: 370-372.
7. Boccon-Gibod LM, Toublanc O, Ravery V, Boccon-Gibod LA. Micro-focal prostate cancer: a comparison of biopsy and radical prostatectomy specimen features. Eur Urol 2005; 48: 895-899.
8. Van der Kwast T, Wolters T, Evans A, Roobol M. Single prostate cancer foci on prostate biopsy. Eur Urol Suppl 2008; 7: 549-556.
9. Thorson P, Arcangeli C, Keetch DW. Diagnostic features and follow-up of minimal carcinoma in prostate needle biopsies. Mod Pathol 1998; 11: 543-551.
10. Leroy X, Aubert S, Villers A et al. Minimal focus of adenocarcinoma on prostate biopsy: clinicopathological correlations. J Clin Pathol 2003; 56: 230-232.
11. Thorson P, Humphrey PA. Minimal adenocarcinoma in prostate cancer biopsy tissue. Ann Pathol 2000; 114: 896-909.
12. Algaba F, Epstein J, Aldape et al. Assessment of prostate carcinoma in core needle biopsy-definition of minimal criteria for diagnosis of cancer in biopsy material. Cancer 1996; 78: 376-381.
13. Thorson P, Vollmer RT, Arcangeli C et al. Minimal adenocarcinoma in prostate needle biopsy specimens: diagnostic features and radical prostatectomy follow-up. Mod Pathol 1998; 11: 543-551.
14. Cheville JC, Reznicek MJ, Bostwick DC. The focus of "atypal glands, suspicious for malignancy" in prostate needle biopsy. Am J Clin Pathol 1997; 108: 633-490.
15. Iczkowski KA, Bostwick DG. Criteria for biopsy diagnosis of minimal volume prostatic adenocarcinoma. Arch Pathol Lab Med 2000; 124: 98-107.
16. Iczkowski KA. Current prostate biopsy interpretation: Criteria for cancer, atypical small acinar proliferation, high grade prostatic intraepithelial neoplasia and use of immunostains. Arch Pathol Lab Med 2006; 130: 835-842.
17. Wojno KL, Epstein JI. The utility of basal cell specific anticy-

tokeratin antibody (34 beta E12) in the diagnosis of prostate carcinoma: a review of 228 cases. Am J Surg Pathol 1995; 19: 251-260.
18. Epstain JI. Diagnosis and reporting of limited adenocarcinoma of the prostate on needle biopsy. Mod Pathol 2004; 17: 307-315.
19. Garcia FU, Haber MM, Chen X. Prostatic basal cells in the peripheral and transitional zones: zonal variation in morphology and in immunophenotype. Prostate 2007; 67: 1686-1692.
20. Humphrey PA. Diagnosis of adenocarcinoma in prostate needle biopsy tissue. J Clin Pathol 2007; 60: 35-42.
21. Postma R, de Vries SH, Roobol MJ et al. Incidence and follow up of patients with focal prostate carcinoma in 2 screening rounds after an interval of 4 years. Cancer 2005; 103: 708-716.
22. Epstein JI, Sanderson H, Carter HB, Scharfstein DO. The utility of saturation biopsy to predict insignificant cancer at radical prostatectomy. Urology 2005; 66: 356-360.
23. Egevad L, Norberg M, Mattson S, Norlen BJ, Busch C. Estimation of prostate cancer volume by multiple core biopsies before radical prostatectomy. Urology 1998; 52: 653-658.
24. Ochiai A, Tripkov K, Yilmaz A et al. Validation of a prediction model for low volume/low grade cancer: application in selecting patients for active surveillance. J Urol 2007; 177: 907-910.
25. Skrepetis K, Doumas K, Lykourinas M. Discrepancy between Gleason score of biopsy and radical prostatectomy specimens. Eur Urol 2001; 40: 238.
26. Yang XJ, Lecksell K, Potter SR et al. Significance of small foci of Gleason score 7 or greater prostate cancer on needle biopsy. Urology 1999; 54: 528-532.
27. Choo R, Klotz L, Danjoux C et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. J Urol 2002; 167: 1664-1669.
28. Van de Berg RC, Reomeling S, Roobol MJ et al. Prospective validation of active surveillance in prostate cancer: the PRIAS study. Eur Urol 2007; 52: 1560-1563.
29. Boccon-Gobod LM, de Longchamps NB, Toublanc M et al. Prostate saturation biopsy in the re-evaluation of microfocal prostate cancer. J Urol 2006; 176: 961-964.
30. D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Eng J Med 2004; 351: 125-135.
31. Clinical practice guidelines in oncology. Prostate cancer v.2.2007. National Comprehensive Cancer Network Wed site. http: www.nccn.org.