SHORT REPORT

Minimal focus of adenocarcinoma on prostate biopsy: clinicopathological correlations

X Leroy, S Aubert, A Villers, C Ballereau, D Augusto, B Gosselin

J Clin Pathol 2003;56:230–232

Aims: To establish the clinicopathological features of minimal volume prostate adenocarcinoma on prostate biopsy.

Methods: Twenty four cases of minimal adenocarcinoma diagnosed on prostate biopsy and treated by radical prostatectomy were reviewed.

Results: The major microscopic criteria were nuclear enlargement (22 of 24), infiltrative pattern (19 of 24), prominent nucleoli (19 of 24), intraluminal eosinophilic secretions (15 of 24), and high grade intraepithelial neoplasia associated (11 of 24). Sixteen of 24 cases were assigned a Gleason score 6 on biopsy. When the whole gland was assessed, 22 of these tumours were localised to the prostate (stage pT2), and only two cases were stage pT3.

Conclusions: Minimal focus of adenocarcinoma on prostate biopsy is not an uncommon finding. It is usually an intermediate grade and localised stage neoplasm.

The development of prostate cancer screening with prostate specific antigen (PSA) has led to an increasing number of prostate biopsy specimens. A direct consequence of the earlier diagnosis is the detection of smaller volume prostate tumours. Thus, the pathologist is now more often confronted with limited amounts of carcinoma ("minute carcinoma") on fine needle biopsy, with an increased risk of confusion with benign conditions.¹ The aims of our present study were to present the recent experience of a single institution with a consecutive series of 24 cases and to correlate the pathological findings with the data on the whole gland.

MATERIALS AND METHODS

The criterion used for our study was one biopsy with carcinoma measuring less than 1 mm or forming less than 5% of the biopsy. In addition, only patients treated by radical prostatectomy were included. The cases were retrieved from the files of the department of pathology at Lille University Hospital from January 1997 to June 2002. In all cases, systematic sextant biopsies were performed with an 18 gauge needle (six to 14 biopsies/case according to the prostate volume). Biopsies were immediately fixed in 10% buffered formalin then embedded in paraffin wax. Sections of 3–4 µm thickness were prepared and stained with haematoxylin and eosin and saffron. All biopsies were studied on three levels of cutting. Surgical radical specimens were fixed in 10% buffered formalin and prepared according to the Stanford protocol.² All histological slides were available and were reviewed by two pathologists (XL, SA). Immunohistochemistry was performed on an automated immunostainer ES (Ventana Medical Systems, Strasbourg, France). The antibody used was directed against high weight cytokeratin (34βE12; Dako, Trappes, France).

Table 1 Summary of microscopic features in minimal focus of prostatic adenocarcinoma

Microscopic feature	Number of cases
Nuclear enlargement	22/24 (91%)
Infiltrative pattern	19/24 (79%)
Prominent nucleoli	19/24 (79%)
Intraglandular eosinophilic material	15/24 (62%)
High grade intraepithelial neoplasia	11/24 (45%)
Amphophilic cytoplasm	8/24 (33%)
Holmes crystalloids	6/24 (25%)
Collagenous micronodules	1/24 (4%)
Extraprostatic extension	0/24 (0%)
Perineural invasion	0/24 (0%)

RESULTS

Clinical findings

From January 1997 to June 2002, 557 adenocarcinomas were diagnosed on prostate biopsies. Forty one cases (7.3%) corresponded to the definition of minimal adenocarcinomatous focus. Only 24 of these patients were treated at our institution by radical prostatectomy. The mean age of this patient population was 64 years (range, 52–74). The mean PSA value before biopsy was 6.75 ng/ml (range, 1.13–25).

Pathological findings

Table 1 summarises the pathological findings.

The diagnosis of adenocarcinoma was confirmed in all cases on biopsy and on prostatectomy.

On biopsy, the mean number of neoplastic glands was 20 (range, 4–50). In a third of cases less than 10 glands were present (fig 1). An infiltrative pattern was found in 19 of 24 cases. The main constant cytological event was nuclear enlargement, which was present in 22 of 24 cases. Prominent nucleoli (nucleolus > 1.5 µm) were found in 19 of 24 cases (fig 2). The cytoplasm of tumour cells was amphophilic in eight of 24 cases. Intraluminal eosinophilic amorphous material was frequently seen (15 of 24 cases). In contrast, Holmes crystalloids were seen in only six of 24 cases. High grade prostate intraepithelial neoplasia (HGPIN) was present in 11 of 24 cases. Collagenous micronodules were identified in a single case (one of 24). No perineural or extraprostatic invasion was seen. Immunohistochemistry with high weight cytokeratin was performed in 11 of 24 cases and was always negative on the tumour focus (100%). Seventeen of 24 tumours were graded Gleason score 6, two were Gleason score 7 (3 + 4), and five were Gleason score 5.

The pathological examination of radical prostatectomies revealed that 17 of 24 tumours were confined to one lobe

Abbreviations: ASAP, atypical small acinar proliferation; HGPIN, high grade prostate intraepithelial neoplasia; PSA, prostate specific antigen

Figure 1 Minimal focus of neoplastic glands with infiltrative pattern.

Figure 2 Enlarged nuclei with prominent nucleoli.

Table 2 Comparison of Gleason score between biopsies and radical prostatectomies

Gleason score	Biopsies	Radical prostatectomies
3+2	5/24	3/24
3+3	17/24	16/24
3+4	2/24	3/24
4+3	0/24	1/24
4+4	0/24	1/24

(stage pT2a), five of 24 cases were multifocal and confined to the organ (stage pT2b), and two tumours were stage pT3a. The final Gleason score retained was score 6 in 16 of 24, score 7 in four of 24 (3 + 4 in three cases, 4 + 3 in one case), score 5 in three cases, and score 8 in one case (table 2).

DISCUSSION

Needle biopsy of the peripheral prostate is the gold standard to establish the diagnosis of prostate adenocarcinoma. The histological diagnosis is based on microscopic criteria. However, pathologists are mainly confronted with small foci of adenocarcinoma, which may cause confusion with benign processes.¹⁻⁴ The definition of limited adenocarcinoma is debatable but, according to the literature, we think that the best definition is a focus of adenocarcinoma occupying less

than 1 mm or 5% of the biopsy area.¹⁻⁶ To establish a diagnosis of prostate adenocarcinoma, the minimal number of tumour glands has also been discussed. Many authors recommend a threshold of three malignant glands.¹⁻⁶ In our present series, the minimal number was four tumour glands with a mean of 20 glands. These findings are consistent with other series.⁵⁻⁶ Similar to our results, Thorson *et al* found that 80% of minimal carcinomas contained many more than 10 tumour glands and the minimum number of glands seen was four.⁵⁻⁶

“When present on biopsy, an infiltrative pattern is a highly reliable marker of malignancy and is an important finding for the differential diagnosis with atrophy”

In addition to the lack of basal cells, we observed three major diagnostic criteria, namely: infiltrative pattern, nuclear enlargement, and prominent nucleoli. In previous studies, nuclear enlargement was the most constant criterion of malignancy (91%).⁵⁻⁸ Nuclear enlargement is easily detectable by comparison with normal adjacent glands. The presence of prominent nucleoli is another frequent finding in prostate carcinoma, although it is not constant. In our present series, large nucleoli were found in 19 of the 24 (79%) cases. Epstein, studying a large series of limited adenocarcinomas, observed prominent nucleoli in only 76% of cases.⁷ Not all prostate carcinomas have nucleoli and nucleoli may be obscured by hyperchromatic nuclei or overstained sections, and can sometimes be difficult to distinguish after formalin fixation.⁷⁻⁸ When present on biopsy, an infiltrative pattern is a highly reliable marker of malignancy and is an important finding for the differential diagnosis with atrophy. In the study by Thorson *et al* an infiltrative growth pattern was present in 82% of cases but only in cases with a Gleason score > 4.⁵ We agree with this finding, although an infiltrative pattern can be difficult to interpret when only three or four glands are present. In our experience, perineural invasion, which is usually an important criterion for prostate cancer diagnosis, is very rarely seen in minimal carcinomas. Some minor criteria are also useful. Intraluminal eosinophilic amorphous secretions were present in 15 of our 24 cases. In contrast, Holmes crystalloids and collagenous micronodules are more rarely encountered. According to Thorson *et al*, HGPIN was also regularly associated with minimal adenocarcinoma (45% of cases) in contrast to the series by Epstein (in which HGPIN was associated in 13% of cases).⁵⁻⁷ The lack of basal cells is of course a major criterion for malignancy. However, microscopic examination of routinely stained sections is sometimes insufficient, so that immunohistochemistry using antibody directed against high weight cytokeratin can be useful. In our present study, immunohistochemistry was performed in 11 of 24 cases when the number of glands was very small, and confirmed the lack of basal cells. The major risk with minimal foci is to overdiagnose prostate cancer. In our view, it is very important to be prudent and to use the term atypical small acinar proliferation (ASAP) when major criteria are not present in a small focus of suspicious glands and to recommend a repeat biopsy.⁹ The term ASAP should be reserved for frankly suspicious lesions to prevent transforming this category into a holdall for all uncertain lesions.

It is sometimes difficult to perform Gleason grade assessment on a minimal focus of adenocarcinoma. We assigned a Gleason score of 3 + 3 (6) in 17 of 24 (71%) cases. In a recent study, Rubin *et al* showed that 83.8% of their cases were assigned a Gleason score 6.¹⁰ They found that the correlation between the Gleason grade on biopsy and on radical prostatectomy was poor, with 31% of cases being upgraded and 5.7% being downgraded at prostatectomy.⁹ In our series, five cases were downgraded and two cases were upgraded at prostatectomy. Rubin *et al* concluded that the Gleason score on minimal carcinomatous foci did not predict the tumour stage

Take home messages

- Minimal focus of adenocarcinoma is frequently encountered in prostate needle biopsy
- Strict microscopic criteria must be used to avoid false diagnosis
- The most useful diagnostic criteria were: infiltrative pattern, nuclear enlargement, and prominent nucleoli
- Most minimal carcinomas are of intermediate grade and are localised to the prostate

on radical prostatectomy.¹⁰ However, we found that 17 of our 24 tumours were confined to the prostate (stage pT2). Only two cases were finally stage pT3a. Moreover, Thorson *et al* showed that the mean tumour volume on the whole prostate gland in cases of minimal tumour on biopsy was significantly smaller (1.1 ml) than in normal tumours (1.6 ml).^{5,6}

In conclusion, minimal focus of adenocarcinoma is a more and more frequent situation in prostate needle biopsy. Strict microscopic criteria must be used to avoid false diagnosis. Most of these minimal carcinomas correspond to intermediate grade and localised prostate tumours.

Authors' affiliations

X Leroy, S Aubert, D Augusto, B Gosselin, Department of Pathology, Huriez Hospital, 59045 Lille, France

A Villers, C Ballereau, Department of Urology, Huriez Hospital

Correspondence to: Dr X Leroy, Service d'Anatomie Pathologique, Faculté de Médecine, Pôle Recherche, CHR-U, 59045, Lille, France; x-leroy@chru-lille.fr

Accepted for publication 23 October 2002

REFERENCES

- 1 **Algaba F**, Epstein JI, Aldape HC, *et al*. Assessment of prostate carcinoma in core needle biopsy—definition of minimal criteria for the diagnosis of cancer in biopsy material. *Cancer* 1996;**78**:376–81.
- 2 **Stamey TA**, McNeal JE, Freiha FS, *et al*. Morphometric and clinical studies on 68 consecutive radical prostatectomies. *J Urol* 1988;**139**:1235–41.
- 3 **Bostwick DG**, Iczkowski KA. Minimal criteria for the diagnosis of prostate cancer on needle biopsy. *Ann Diagn Pathol* 1997;**1**:104–29.
- 4 **Varma M**, Lee MW, Tamboli P, *et al*. Morphologic criteria for the diagnosis of prostatic adenocarcinoma in needle biopsy specimens. A study of 250 consecutive cases in a routine surgical pathology practice. *Arch Pathol Lab Med* 2002;**126**:554–61.
- 5 **Thorson P**, Humphrey PA. Minimal adenocarcinoma in prostate needle biopsy tissue. *Am J Clin Pathol* 2000;**114**: 896–909.
- 6 **Thorson P**, Vollmer RT, Arcangeli C, *et al*. Minimal carcinoma in prostate needle biopsy specimens: diagnostic features and radical prostatectomy follow-up. *Mod Pathol* 1998;**11**:543–51.
- 7 **Epstein JI**. Diagnostic criteria of limited adenocarcinoma of the prostate on needle biopsy. *Hum Pathol* 1995;**26**:223–9.
- 8 **Murphy WM**, Ramsey J, Soloway MS. A better nuclear fixative for diagnostic bladder or prostate biopsies. *J Urol Pathol* 1993;**1**:79–87.
- 9 **Iczkowski KA**, Bostwick DG. Criteria for biopsy diagnosis of minimal volume prostatic adenocarcinoma. *Arch Pathol Lab Med* 2000;**124**:98–107.
- 10 **Rubin MA**, Dunn R, Kambhan N, *et al*. Should a Gleason score be assigned to a minute focus of carcinoma on prostate biopsy? *Am J Surg Pathol* 2000;**24**:1634–40.

Want to extend your search?

Cross journal searching

If you can't find what you are looking for in the *Journal of Clinical Pathology* you can extend your search across many of the more than 200 journals available for selection. You can restrict your search to specific subject areas (eg, clinical medicine, basic research), or select specific journals, or search all available titles.

www.jclinpath.com