Contemporary and past challenges of prostate cancer diagnostics

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Contemporary and past challenges of prostate cancer diagnostics

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Puncture biopsy of the prostate in the diagnosis of prostate cancer by Andersson et al. [1] is an eye opening article for urologists practicing 50 years later: Many challenges they describe are still with us. Progress has been made, but regardless, many issues in prostate cancer diagnosis remain under scrutiny today.

In the article, the authors describe a rather novel concept of prostate puncture biopsy. They primarily used Veenema’s punch and transperineal approach and considered this as a clear advantage compared to the most reliable method, transperineal open biopsy of the prostate! A novel concept, fine needle aspiration biopsy by using Franz’s needle, was also used.

413 biopsies were taken, ca. 50% of them containing cancer. The false negative rate was estimated to be 15%. It is noteworthy that only 10% of the biopsies were undiagnostic, not a bad performance under finger guidance. Puncture biopsy of the prostate was not a trivial undertaking: hospitalization was preferred and overall complication rate was 19.5%.

Since these days both the technique and instrumentation have evolved: Tru-cut needles in transrectal prostate biopsies came into widespread use in the late 1980s [2] and the development of transrectal ultrasound enabled prostate biopsies under direct vision [3]. During PSA era, the need for systematic random biopsies under visual guidance became obvious: the suspicion of prostate cancer was based rather on elevated PSA values than on clinical suspicion of cancer. Later the technique of prostate biopsies was defined further to optimize and balance cancer detection and number on biopsies [4]. Widespread use of PSA and subsequent prostate biopsies have resulted in a dramatic increase of newly diagnosed prostate cancers but not without a price: we have witnessed over detection of insignificant prostate cancers and increase of infectious complications after prostate biopsies.

Recent investigations have explored the utility of multiparametric MRI in cancer detection and it may well be that imaging can replace biopsies if there is no suspicion of high Gleason tumor [5].

The quest for optimal prostate cancer diagnostics is ongoing, but recent developments in the fields of imaging, biomarkers and genetics give us hope for a giant leap in this field in the 50 years to come.

References

Abstract. Experience from various clinical materials shows that diagnosis of prostatic carcinoma by rectal palpation is approximately 50% accurate. Since the treatment of this disease has serious sequelae, an exact diagnosis must be made whenever possible. Prostatic biopsy is the most reliable diagnostic method, preferably by perineal or transrectal puncture. Histo-pathological examination of tissue fragments and cytological analysis of aspirated cell material appear to be of equal value.

INTRODUCTION

It is sometimes difficult, or even impossible, on palpation to differentiate between carcinoma and benign inflammatory processes in the prostate. The fibrotic changes in chronic prostatitis may feel like an indurated, scirrhous carcinoma, the commonest kind of tumour in the prostate, and the less common medullary carcinoma may simulate an oedematous, acute inflammatory infiltrate.

In view of the serious sequel of treatment for prostatic cancer, whether an orchidectomy, continued hormone therapy, or radical prostatectomy, a firm diagnosis is imperative. Prostatic biopsy is an invaluable diagnostic help. The biopsy may be performed by either one of three methods:

1. transurethral resection
2. transrectal puncture
3. puncture or exposure of the prostate via the perineum.

Since carcinoma usually starts in the periphery of the gland, near the capsule in the posterior part of the lateral lobes (Geraghty & Boyd, 1912; Moore, 1935; Rich, 1935; Franks, 1954; Blennerhassett & Vickery, 1966), methods 2 and 3 are generally preferable in early cases.

Most published reports describe histo-pathological examination of tissue fragments removed (Barringer, 1922; Finkelstein, 1962/63; Sika & Lindquist, 1963; Madsen & Kaveggia, 1964; Melicow, 1964; and others). Other writers have performed cytological analysis of aspirated material (Ferguson, 1930; Franzén, Giertz & Zajicek, 1960; Zajicek, 1962; Ekman, Persson & Nakaarai, 1965; Esposito, 1966; Söderström, 1966).

In a relatively large number of cases we have used perineal puncture biopsy. In a smaller number of cases (1966) we used both the latter method and the transrectal aspiration biopsy according to Franzén, Giertz & Zajicek for comparison of the two methods. The aim of this paper is to report our experience of the reliability of the two methods, their complications and the initial difficulties encountered when introducing a new biopsy technique.

METHODS

Transperineal puncture with large-bore needle or punch

Biopsy was usually performed under caudal anaesthesia, occasionally under local or general anaesthesia. The patient was placed in a high lithotomy position. The skin was cleaned and sterile drapes applied to the perineum. A stab wound was made through the skin and superficial fascia about 1 cm anterior to the anus on the side of biopsy. With the aid of a finger in the rectum the instrument was introduced around the vascular urethral bulb to that part of the gland to be examined.

As a rule we used Veenema’s punch (Veenema, 1953) (Fig. 1). The cups were closed during introduction and opened in the prostatic parenchyma. By subsequent closure of the cups a piece of tissue was removed. Occasionally we used a modification of Silverman’s

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needle (Silverman, 1918; Riibl, 1939). After puncture the perineum was compressed for a few moments.

The biopsy specimens were fixed in 10% formalin, embedded in paraffin and then stained with eosin-haematoxylin and van Gieson in the usual way.

Transrectal aspiration biopsy with fine needle
Transrectal biopsy was usually performed after perineal puncture biopsy. In some cases only transrectal biopsy was done, and then without anaesthesia. In spite of this the patients tolerated the operation well.

We used Fransén’s instrument (Franzén, Gierz & Zajeck) with an adapter modified by Stormby and manufactured by KIFA Ltd, Sweden (Fig. 2). With a curved guide over the finger the examiner located the abnormal part of the gland per rectum. A long fine cannula (outer diameter 0.5 mm) was introduced into the prostate via the guide, after which material was aspirated several times by a syringe. It is important that the position of the tip of the needle in the prostate is changed somewhat with maintenance of the negative pressure in the syringe by keeping the piston withdrawn. With this procedure a sufficient amount of material is easily removed.

The material obtained was placed on a clean microscopic slide and spread out in the same way as in the preparation of blood smears. The slide was then immersed in 96% ethyl alcohol before the smear had time to dry. After the preparation had been fixed for at least one hour, it was stained with eosin-haematoxylin.

CLINICAL MATERIAL
379 patients were subjected to transperineal puncture biopsy following a suspicion of prostatic cancer. 64 other patients underwent both perineal puncture biopsy and transrectal aspiration biopsy.

RESULTS
Transperineal puncture biopsy was done on 413 occasions in 379 patients. Of the specimens obtained 42 (10.2%) were discarded, 39 of them containing no prostatic tissue, 2 containing insufficient material, and 1 because it had been inadvertently placed in the wrong fixative. Unsatisfactory specimens were mainly obtained when new operators were perfecting their technique.

In 190 patients the biopsy specimens revealed carcinomas of varying degrees of differentiation (Table I). In 187 the lesion appeared to be primary prostatic malignancy, in one it was sarcoma, and in the remaining 186 carcinoma. In 10 of these cases the first biopsy specimen had

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prostatic malignancy</td>
<td>187</td>
</tr>
<tr>
<td>Carcinoma of the bladder with infiltration of prostate</td>
<td>3</td>
</tr>
<tr>
<td>Assumed prostatic cancer</td>
<td>10</td>
</tr>
<tr>
<td>Inflammation or fibrosis</td>
<td>24</td>
</tr>
<tr>
<td>Normal prostatic tissue or benign hyperplasia</td>
<td>126</td>
</tr>
<tr>
<td>Biopsy specimen unsatisfactory</td>
<td>29</td>
</tr>
</tbody>
</table>

Table II. Age distribution of primary prostatic malignancy

<table>
<thead>
<tr>
<th>Age of patients</th>
<th>Number of patients</th>
<th>Number of patients with primary tumor of prostate</th>
<th>Frequency of cancer, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>4</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>40-49</td>
<td>15</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>50-59</td>
<td>54</td>
<td>20</td>
<td>37</td>
</tr>
<tr>
<td>60-69</td>
<td>131</td>
<td>56</td>
<td>43</td>
</tr>
<tr>
<td>70-79</td>
<td>127</td>
<td>79</td>
<td>62</td>
</tr>
<tr>
<td>80-</td>
<td>48</td>
<td>29</td>
<td>60</td>
</tr>
</tbody>
</table>
been negative. In one of them it was the third biopsy that revealed the cancer. The age distribution of the patients is given in Table II, which also gives the cases classified as primary prostatic tumour.

In 3 of the 190 patients the prostate was invaded by a tumour of the urinary bladder.

Ten specimens showed lesions suggesting cancer, but the pathologists were unable to decide with certainty whether the process was malignant or not. Follow-up, sometimes with a further biopsy, confirmed the suspicion in 8 of these 10. The ninth patient, treated with stilbestrol with consequent relief of symptoms and softening of the prostate, also probably had a malignant tumour, but the diagnosis was not confirmed. The subsequent course of the remaining patient indicated benign inflammatory process.

In 24 patients the biopsy specimen showed inflammatory changes or fibrosis. In one of these patients transcervical prostatectomy one week later, showed foci of carcinoma. In a further 2 patients

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the subsequent course disclosed prostatic malignancy. In another case, followed up for 3 years, there still remains a suspicion of localised carcinoma, which has remained unchanged under estrogen therapy.

In 126 patients the biopsy showed normal prostatic tissue or benign hyperplasia. Follow-up in these cases with further biopsy in some showed 30 additional cases of malignancy. In 3 cases it was a bladder carcinoma, one having invaded the prostate. The remaining 27 were primary prostatic carcinomas. A suspicion of malignancy remains in a further 4 patients, who have not yet been submitted to renewed biopsy. In the remaining 92 patients regular follow-up has so far revealed no signs of carcinoma. This group included a 46-year-old man with histologically confirmed renal amyloidosis and a 55-year-old man with widespread changes of sarcoidosis. In both cases the prostate was thought to be involved, but biopsy only showed normal prostatic tissue.

Complications

A man, aged 75, with prostatic cancer and widespread skeletal metastases, was operated on for inguinal hernia. At operation a perineal puncture biopsy of the prostate was performed. After operation the patient bled copiously from the operation field, presumably because of fibrinolysis. He was given blood transfusion, fibrinogen, vitamin K and calcium intravenously but the bleeding persisted—effective inhibitors of fibrinolysis were not available at that time. The patient died with a large accumulation of blood in the herniorrhaphy wound, in the abdomen and retroperitoneally. A haematoma was also seen in the perineum.

A man, aged 57, with prostatic cancer was subjected to prostatic puncture. The operation was followed by local bleeding with pain, tenderness and the development of a lump to the right of the prostate and a fall of the blood pressure to 100 mm Hg. After infusion of Macrodex and blood the patient improved but still complained of pain in the right lower quadrant of the abdomen which persisted for some weeks.

In 3 patients puncture biopsy of the prostate was followed by fairly heavy bleeding requiring repeated irrigation of the bladder for the first few days after the operation. Another patient returned to the department 8 days after the operation with bleeding into the bladder and urinary retention. A single catheterisation with aspiration of the clot gave prompt permanent relief and no further bleeding occurred. In a further 13 patients biopsy was followed by slight to moderate haematuria which disappeared after 2-5 days' treatment with Episkapron®. Many patients developed a small, insignificant haematoma in the perineum. One patient had a moderately large scrotal haematoma and fever for 6 days. Some patients reported haematospermia for some time after the biopsy.

Two patients with prostatic cancer, one aged 70 and the other 85 with coexisting renal carcinomas, developed signs of lower leg thrombosis after the biopsy. In both of them the signs of thrombosis disappeared during treatment with heparin.

On one occasion the tip of Veenema's punch became detached during the operation and remained in the prostatic parenchyma. The prostate was exposed transperineally but the metal tip could not be found. After the operation the patient had fever, but after 4 days' chemotherapy he was afebrile and symptom free.

On 38 occasions biopsy was followed by urinary obstruction requiring catheterisation. In one of these patients the obstruction lasted for 3 weeks; in one for 6 weeks; otherwise for less than one week. Fever (above 38°) occurred after a total of 22 biopsies, but was soon controlled by chemotherapy.

The frequency of the various complications is given in Table III.

### Combined perineal puncture biopsy and transrectal aspiration biopsy

In one year 64 patients were subjected to combined puncture and aspiration biopsy on a total of 77 occasions. Carcinoma was demonstrated in 36 patients; in 18 by both methods; in 11 only by the perineal method and in 7 only by transrectal biopsy. In some patients biopsy was repeated on various occasions to assess the effect of hormone therapy.

Nine of the specimens obtained by the perineal route and 26 collected by the transrectal route were discarded either because they contained barely any or no prostatic tissue or because the cytologic smears had developed artefacts owing to dehydration. During the first half of the year approximately 50% of the transrectal biopsies were unsatisfactory, but during the second 6 months the technical failures dropped to 25%. The operations were performed by seven urologists at the department. Most of the unsatisfactory specimens were among the first three biopsies performed by the respective urologists.
Six specimens obtained by the perineal route showed signs suggesting carcinoma. Transrectal specimens obtained at the same time showed malignant changes in 2 of the cases but the technique was unsatisfactory in the remaining 4. In 6 other cases the smears showed cells whose appearances suggested malignancy. Punch biopsy specimen showed clear-cut cancer in one of these cases but nothing remarkable in any of the remaining 5.

In at least one case the tissue obtained by the perineal route gave a false negative diagnosis— aspiration biopsy showed cancer and the acid phosphatase was increased. In none of the 12 patients in whom aspiration biopsy showed no signs of carcinoma could malignancy be confirmed by other methods.

Complications
Combined transperineal and transrectal biopsy were not followed by any serious complication. Mild haematuria occurred on 9 occasions, transient urinary obstruction on 2, and fever for 1–3 days on 5. These mild complications can presumably be ascribed to the perineal biopsy.

DISCUSSION
Transperineal punch biopsy specimens revealed cancer of the prostate in about 50% (190 of 379) of a series in which prostatic malignancy was suspected. In 3 of these cases the prostate had been involved by extension of a carcinoma of the urinary bladder. This finding of carcinoma in about half of the cases in which rectal palpation had suggested prostatic malignancy is in agreement with the figures given by Ferguson (1937) and by Sika & Lindquist for similar series, namely 51% of 136 patients and 43% of 300 patients, respectively.

In our material prostatic carcinoma was found in 20% of the patients in the 5th decade, 37% of those in the 6th decade, 43% of those in the 7th decade, and approximately 60% of those over 70 years of age. Thus, as expected, the frequency with which an induration or a nodule of the prostate was malignant increased with age.

Of the 9 patients in whom histological examination suggested, but could not demonstrate, cancer, all except one proved to have a malignant tumour.

The further course, sometimes with repeated biopsy, strongly suggested or showed the existence of a malignant tumour of the prostate in a further 36 patients. Previous biopsy of the latter cases had been of normal appearance or shown only benign changes. False negative specimens had thus been obtained in 15% of the patients. If only those cases be considered where biopsy gave a firm positive diagnosis, the accuracy of the method was 81%. The corresponding figures given by other investigators range from 69% (Hudson, Finkle, Jost, Trifilio & Stout, 1955) to 88% (Veeninga & Lattimer, 1963).

Some workers in this field (Geissler, Campbell, St. Martin & Pasquier, Jr, 1963; Finkelstein) prefer to perform the biopsy by the transrectal route on the grounds that it is more reliable than perineal puncture, easier to perform and does not require anaesthesia. However, it appears to carry a higher risk of infection, at least when it is performed with a large bore needle to secure tissue fragments (Finkelstein).

Analysis of our series showed that the chances of obtaining specimens from the actual tumour were better when the biopsy was performed by a surgeon versed in the method.

In experienced hands the chances of obtaining representative material by transperineal and by transrectal biopsy are probably equal, irrespective of the type of instrument used. We have found Veeninga’s punch convenient because the head of the instrument is easily palpated per rectum, and the removal of fairly large fragments of tissue is possible.

It is widely believed that open perineal biopsy of the prostate is the most reliable method (Fortunoff, 1962; Veeninga & Lattimer; Grabstald, 1965; and others) with an accuracy of 95–98% (Bergman & Hubmer, 1965). That part of the gland most often involved can then be inspected directly and small changes, if any, may be detected. However, it is by no means such a minor operation as puncture, and carries a risk of major complications, including impotence (Dahle & Goodwin, 1957) and incontinence (Grabstald). Open perineal biopsy is particularly valuable in the investigation of local tumours in patients in whom biopsy is to be followed immediately by radical perineal prostatectomy, if the specimen is positive.

Puncture biopsy is said to be the ideal method for confirming a provisional diagnosis of large tumours. In addition the method is useful for
examination of small tumours if conservative treatment is contemplated. An experienced surgeon can probably, as a rule, obtain an adequate biopsy specimen even from small tumours.

Puncture biopsy, irrespective of the method used, always carries a risk of implantation metastases. No such complication was seen in our series. This complication has occasionally been reported. Thus Veenema & Lattimer reported one case of such metastasis in a series of 1000 biopsies, and Clarke, Leadbetter & Campbell (1953) and Goldman & Samellas (1960) described one case each of perineal carcinoma after puncture of a malignant prostate. Fortunoff reported perineal metastases following puncture of a prostatic sarcoma. The information obtainable from biopsy thus more than outweighs the extremely small risk of metastasis.

Other serious complications are also rare. Our series included one case of fatal bleeding, probably due to fibrinolysis. The haemorrhage was due mainly to the herniorrhaphy and not to the actual puncture of the prostate performed during the operation.

The complication nevertheless exemplifies the risk of even minor operations on patients with fibrinolysis (Andersson, 1963) without adequate treatment with the new effective inhibitors of fibrinolysis now available for clinical use (Andersson & Nilsson, 1961).

Substantial bleeding, but not severe enough to require treatment other than catheterisation, pos-

Fig. 3. Highly differentiated prostatic adenocarcinoma. (a) Punch biopsy, HE x 80. (b) Aspirated material, HE x 320.

Fig. 4. Low-grade prostatic carcinoma. (a) Punch biopsy, HE x 80. (b) Aspirated material, HE x 320. Note much greater nuclear irregularities as compared to Fig. 3 b.
tumours are given in Figs. 3 and 4. The lower the degree of differentiation of the tumour the higher its degree of cellularity and the weaker the tendency of the cells to adhere. It is therefore easier to obtain adequate cell material from a poorly differentiated carcinoma than from a well differentiated one or the normal gland.

Since aspiration biopsy is practically without complications and leaves barely any scar in the prostate, it is a suitable method for studying the effect of treatment with oestrogens, cytotostatics or radiation. If the tumour responds favourably to treatment, cells in the specimen will often show degenerative changes, such as pyknosis or karyolysis. In patients treated with oestrogens, vacuolation of the cytoplasm owing to the deposition of glycogen occurs (Fig. 5). However, evaluation of the response to treatment requires a fairly large amount of cell material, preferably from different parts of the tumour, in order to avoid erroneous conclusions from aspirated specimens from a spontaneously necrotising part of the tumour.

Judging from our limited experience with fine needle puncture, the technique is more difficult to learn than puncture with a large bore needle or punch. It might therefore be wise to concentrate these investigations to a few surgeons to give continuous practice. In the hands of experienced operators the method has proved to be reliable (Espositi).

Since transrectal aspiration biopsy can be performed with but little preparation and even on ambulant patients, the range of indications for the method may be wide. If the results of aspiration biopsy are unsatisfactory or equivocal, the examination should be supplemented by large-bore needle biopsy.

Like all biopsy methods, a negative specimen does not exclude the possibility of cancer. If cancer is still suspected despite a negative specimen, biopsy should be repeated, and if the results are equivocal, it might occasionally be advisable to resort to perineal exposure of the prostate. As a screening test for malignant disease of the prostate no surgical procedure can replace rectal palpation, which should be included in all physical examinations of men over 40 years of age. However, if any abnormalities, suggestive of malignancy, are found, the examination should always be extended to include biopsy.
REFERENCES

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