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Ultrasound of prostate cancer

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Abstract Transrectal ultrasound now plays a central part in the diagnosis of prostate cancer. The role of ultrasound in prostate cancer diagnosis is to guide accurate biopsy, and current practice favours a systematic biopsy approach rather than targeted biopsy of focal abnormalities. The role of colour and power Doppler and sonographic contrast agents in prostate cancer diagnosis is still under evaluation, but these techniques may have a role in the assessment of the prognosis of an individual cancer.

Keywords Transrectal ultrasound · Prostate cancer · Colour Doppler · Contrast agents

Introduction

Prostate cancer is the most commonly diagnosed cancer in the U.S. and western Europe and is the second leading cause, after lung cancer, of cancer-related death in men. The incidence of prostate cancer in the U.S. has tripled since 1985 mainly because of the widespread use of serum measurements of prostate specific antigen (PSA) as a screening test. Screening is advocated because PSA-detected prostate cancers tend to be at an earlier stage. Routine screening of asymptomatic men for prostate cancer is, however, controversial because of uncertainties about whether treatment extends life, the variable natural course of prostate cancer, complications of treatment such as impotence and incontinence and false-positive results of screening. It has been shown that giving patients information about some of the aforementioned medical uncertainties can aid patient decision-making in deciding whether to have these screening tests for prostate cancer [1].

The easy availability of the PSA test has created a massive workload burden for departments of radiology.

Radiologists are involved in both the diagnosis and staging of prostate cancer, as much information is needed about a tumour in modern prostate cancer management: its location, its size and its aggressiveness. All have a bearing on treatment planning and prognosis. There was little interest from radiologists and urologists to the introduction of transrectal ultrasound (TRUS) in the early 1980s. This was understandable with a chair-mounted, low-frequency ultrasound probe, which had no biopsy facility. However, the subsequent introduction of hand-held higher-frequency transducers and spring-operated biopsy devices, together with extensive international contemporary experience, and an increased understanding of prostatic anatomy and pathology, has ensured that TRUS-guided transrectal needle biopsy of the prostate has now become a widespread and standard method of prostatic cancer diagnosis.

Most cancers are now detected by prostatic needle biopsy. Transrectal US is limited in identifying prostatic cancer because of the variability in the ultrasonic appearance of prostatic tumours, the poor specificity of

sonographic abnormalities, the frequent multi-focality of cancer within the prostate and the substantial percentage of isoechoic prostate cancers, which cannot be differentiated sonographically from adjacent benign tissues. There have been a series of technological developments in the equipment used for TRUS in the past decade, with the use of higher frequencies, broad bandwidth technologies, colour and power Doppler and most recently harmonic and contrast imaging. These refinements can all aid the demonstration of subtle focal alterations of echogenicity within the prostate. There is still, however, relatively little information available about the biological potential of prostate cancer in an individual patient, and no imaging test currently gives information in this field. Ultrasonic contrast agents are now available and theoretically can aid the visualisation of subtle alterations in prostatic echo texture by highlighting changes in the microvasculature. As tumour neovascularity is considered to have a relation to prognosis, it is possible that future Doppler techniques with colour Doppler might be able to give some prognostic information.

In recent years there has been enthusiasm for medical treatment of benign prostatic hyperplasia (BPH) with alpha blockers and five α -reductase inhibitors, and alternative minimally invasive treatments have been used such as cryo-surgery and laser therapy. These approaches have now become the first-line treatment for men with symptoms of outflow tract obstruction due to BPH. The consequence of these treatments, however, is that fewer men are having a transurethral resection of the prostate, and this together with the use of serum PSA, and TRUS-guided systematic needle biopsy of the prostate, has led to a marked reduction in the incidence of a stage T₁a and T₁b cancer [2], and an increase in T₁c cancer.

Prostate cancer presents a continuing dilemma for doctors, public health planners and health economists: only a small percentage of men with untreated prostate cancer die from the disease, yet the high prevalence of prostate cancer means that the annual mortality of prostate cancer is second to lung cancer in cancer-related deaths. Better methods of distinguishing patients with *significant* clinically progressive cancer from *clinically insignificant* prostate cancer are needed. There are problems with the definition of clinically insignificant cancer [3], but it has been claimed that 10% of tumours found by sextant biopsy may be clinically insignificant [4]. In a series of 379 radical prostatectomy specimens [5], cancer grade and cancer volume were highly predictive of disease progression, together with positive lymph node findings and intraprostatic vascular invasion. Poor cellular differentiation and histological grade are important predictors of prognosis and relatively straightforward to assess. Yet how are we to measure cancer volume pre-operatively, particularly in isoechoic

Table 1 Rare prostatic malignancies. (After [8])

Epithelial tumours: variants of adenocarcinoma
Adenocarcinoma with endometrioid features
Comedocarcinoma
Mucinous adenocarcinoma
Adenoid cystic carcinoma
Signet ring carcinoma
Adenosquamous carcinoma
Squamous cell carcinoma
Transitional cell carcinoma
Neuroendocrine neoplasms (carcinoid and small cell carcinoma)
Nonepithelial
Rhabdomyosarcoma
Leiomyosarcoma
Fibrosarcoma
Malignant fibrous histiocytoma
Osteosarcoma
Angiosarcoma
Chondrosarcoma
Malignant nerve sheath tumour
Carcinosarcoma
Malignant phyllodes tumour
Malignant lymphoma
Leukaemic infiltration of the prostate
Metastatic neoplasms

tumours? The area of cancer in each biopsy core, the number of positive cores, serum PSA, clinical and TRUS findings are some of the criteria of cancer volume that may be used in algorithms to preoperatively estimate cancer volume. There is the suggestion from recent work that an assessment of microvascular density may also be prognostically important. Most such studies have been based on pathological archive material [6, 7], but recent work is investigating whether colour Doppler could be used to make these prognostic assessments.

Ninety-five percent of all prostatic malignancies are prostatic acinar adenocarcinomas; the remaining 5% comprise numerous rare prostatic tumours. These latter tumours are uncommon but they commonly present in a similar manner to the typical prostatic adenocarcinoma. Despite this, they may differ considerably in their natural history and response to treatment. These rare tumours are listed in Table 1 and are considered herein, but many are considered to have no specific diagnostic imaging features [8]. Histological examination of biopsy material is required to differentiate them from other prostatic tumours.

The prostate is conventionally divided into a transition zone (TZ) and outer gland [peripheral zone (PZ) and central zone]. The TZ is the area where benign prostatic BPH develops and thus tends to comprise a larger proportion of the prostate in older men. The PZ is the site of approximately 70% of prostate cancers, and tumours developing in the PZ can be visualised by TRUS and MR imaging. It is usually particularly difficult to identify cancer in the transition zone by TRUS

and MR. The primary role of TRUS in the diagnosis of prostate cancer is in the performance of needle biopsy, as TRUS guidance of prostate biopsy improves the detection rate compared with digitally guided biopsy. Transrectal US is little used now in the staging of prostate cancer, following a multi-centre study that demonstrated a lower accuracy rate than MR [9].

There are numerous contemporary dilemmas in relation to the use of US for prostate cancer diagnosis, e.g. Should we undertake focal lesion directed biopsy or systematic biopsy? Biopsy of the prostate may be directed at focal abnormalities where focal sonographic abnormalities on grey-scale images of the prostate or focal alterations in vascularity on colour or power Doppler are sampled. Increasingly, however, this approach is supplemented or replaced by systematic biopsy of the gland, where numerous cores are taken mainly from the peripheral zone of both lobes in a systematic manner. What areas of the prostate should be sampled to give optimal results? Cancer occurs predominantly in the peripheral zone, but at least 20% of cancers occur in the transition zone. An analysis of the radical prostatectomy specimens from 148 consecutive patients with transition zone cancers was recently reported from Stanford University [10]. It was found that 80% of specimens had organ-confined disease, and 70% T1c impalpable disease. Of prostates, 63% had an initial positive prostatic biopsy, and 61% had a preoperative serum PSA of 10 ng/ml or greater. Only 15% of specimens showed capsular penetration, but 29 had positive anterior surgical margins, 3% seminal vesicle invasion and 3% node metastases. How many cores should be taken at systematic biopsy? This has been the subject of much recent research activity and is discussed below. When should repeat biopsies be undertaken? The original sextant systematic biopsy approach is not ideal and the six cores of the sextant approach probably undersample the prostate. There is evidence that the positive biopsy rate is 20–23% for a repeat second sextant biopsy after an initial negative sextant biopsy [11, 12].

Focal grey-scale abnormalities of the peripheral zone

Many cancers are isoechoic. The commonest focal abnormality of prostate cancer is that of a hypoechoic area in the peripheral zone (Fig. 1). Prostate cancer is frequently multifocal and thus multiple hypoechoic peripheral zone areas may be present in an individual patient. There is a wide differential diagnosis for hypoechoic areas in the peripheral zone of the prostate; as well as carcinoma, hypoechoic areas may be prostatic atrophy, inflammation, focal areas of acute prostatitis, granulomatous prostatitis, tuberculous prostatitis or prostatic intraepithelial neoplasia (PIN); primary lymphoma of the prostate occurs rarely but may be found

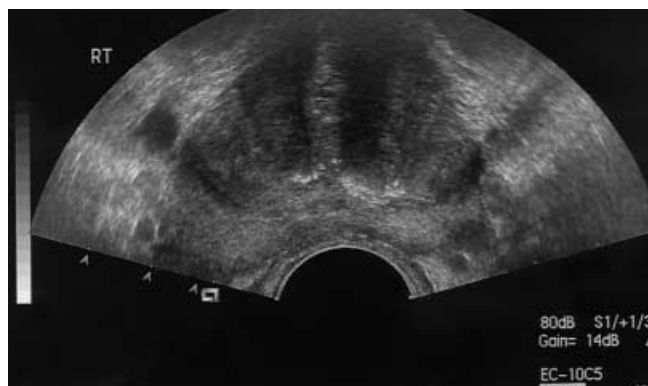


Fig. 1 Axial scan of the prostate: a hypoechoic cancer is present in the left peripheral zone

also as a hypoechoic area. Biopsy is needed to establish the diagnosis of a focal hypoechoic area in the peripheral zone. Lee et al. [13] assessed the significance of peripheral zone hypoechoic areas in the diagnosis of prostate cancer in a series of 256 patients and found that the positive predictive value of a peripheral zone hypoechoic area was 41%, but this increased to 52% if the PSA was elevated, and was 71% if the PSA was elevated and there was a palpable abnormality in the prostate. A significant percentage of small (< 0.2 cc) hypoechoic lesions in men with normal DRE, and PSA less than 10 ng/ml, are positive for malignancy [14]. From a study of 614 biopsies, the yield of separate hypoechoic area biopsies is low (4%), but approximately 15% of cancers would have been missed if directed hypoechoic area biopsies had not been undertaken at the time of systematic biopsy.

There have been relatively few reports of the sonographic features of the rarer prostatic tumours. Comedocarcinoma is the most malignant form of prostate cancer. Lile et al. [15] reported the TRUS appearances with this type of prostate cancer and noted that there were stippled multiple small hyperechoic foci within the hypoechoic area of the cancer. The appearances of two cases of adenoid cystic carcinoma of the prostate were described by Terris [16]. In both of these patients there were multiple small cysts of similar size in the prostate. Rhabdomyosarcomas represent a childhood malignant tumour and present as a soft tissue mass infiltrating the bladder and prostate. As such they have a completely different presentation and radiological features from prostatic adenocarcinoma [17]. Jackson and Clements [18] reported the radiological features (with 10-year follow-up) of a case of cystosarcoma phylloides of the prostate. This tumour had clinical and radiological features which were different from adenocarcinoma of the prostate, and presented as a large right-sided pelvic mass displacing the bladder. Lymphoma of the prostate tends to present in younger men and TRUS is reported

to show large hypoechoic masses in both the TZ and PZ [8].

Transition zone cancers

With advancing age, adenomas develop in the TZ and these have elements of both glandular and stromal hyperplasia. Unfortunately, the ultrasonic features of these pathologies have not been accurately correlated, and the relative frequency of specific sonographic features of cancer in the transition zone has not been reported. Transition zone cancer is thought to have different clinical features from cancer arising in the peripheral zone of the prostate [19]. Until recently, TZ cancers were incidental findings from transurethral resection of the prostate; presently, most TZ cancers are found by systematic biopsy cores taken specifically from the TZ. Little attention has been given to the assessment of hypoechoic areas in the transition zone due to the lower frequency of cancer in the TZ and the perceived lower potential for metastatic spread of primarily TZ cancer. There are no specific studies in the literature of the results of biopsy of focal TZ hypoechoic areas, nor of biopsy of specific focal alterations of TZ vascularity identified using colour or power Doppler.

Focal alterations in vascularity in the peripheral zone

With the availability of colour and power Doppler techniques, further information can be gained about intraprostatic vascularity from a US examination of the prostate. In the normal prostate, blood flow is typically periurethral (entering around the base of the prostate and seminal vesicles) and peri-capsular (supplied by the inferior neurovascular bundles; Fig. 2). Some vessels pass into the prostate in the surgical capsule between the transition and peripheral zones, but there is little flow within the remainder of the normal prostatic parenchyma. The role of colour Doppler and power Doppler in the diagnosis of prostate cancer has, however, been disappointing, and generally it has not helped significantly in the detection of cancers that are isoechoic on grey-scale examination. With Doppler techniques, an area of cancer may be demonstrated as a focal area of hypervascularity (Fig. 3). Such focal hypervascularity is, however, not specific for cancer, and some cancers which are clearly demonstrable on grey-scale imaging show no focal hypervascularity. This focal alteration in prostatic vasculature is found most commonly in areas that are hypoechoic in the peripheral zone on grey-scale imaging. There are several potential problems with the use of colour Doppler techniques in the prostate, the principal ones being the angle dependency of Doppler flow, the inability to detect low flow velocities and noise

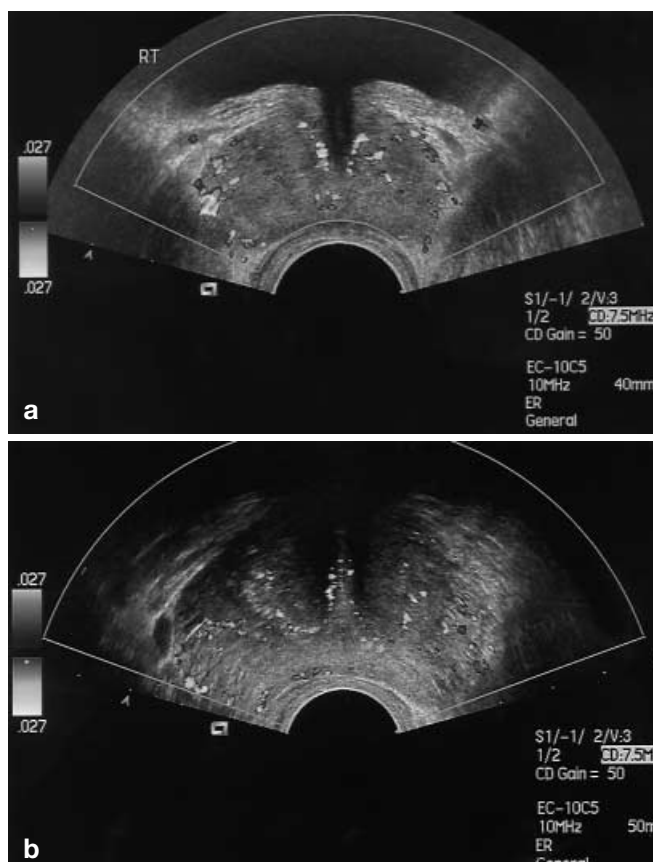


Fig. 2 Axial scans of prostate **a** at base of prostate, and **b** at mid-gland level. Normal prostatic vascularity

within the prostate mimicking increased flow. Transrectal power Doppler has theoretical advantages over transrectal colour Doppler, but in practice this has made little difference in prostate cancer diagnosis [20]. Neither technique reliably offers a great advantage over systematic biopsy [20] and/or focal biopsy of grey-scale abnormalities. Early papers on the use of colour Doppler to highlight prostate cancers showed a moderate increase in diagnosis [21], but there was a low specificity [22]. Lavoipierre [23] published a study of 100 consecutive patients with cancer diagnosed by biopsy of PZ hypoechoic areas, PZ hypervascular areas on colour Doppler and systematic sextant biopsies. Sixteen cancers were found purely by the use of colour Doppler in areas that were normal on grey-scale imaging, but 9 cancers were found in this study only by systematic biopsy; both colour Doppler and grey-scale US failed to reveal these cancers; thus, the use of colour Doppler did not obviate the need for systematic biopsy of the prostate in this study.

Two aspects of blood flow within prostatic tumours may be assessed by colour or power Doppler, firstly the distribution of the microvasculature within the area, and

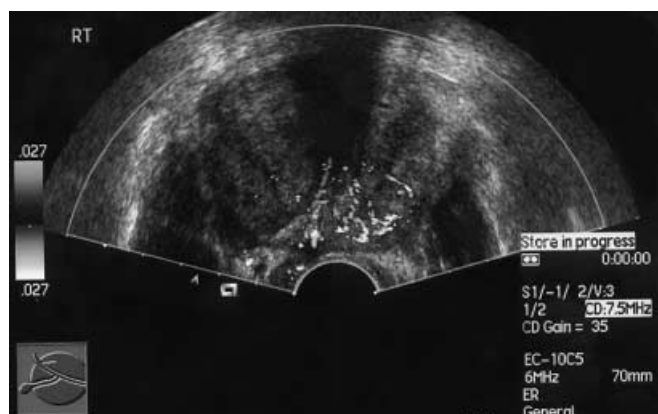


Fig. 3 Axial scan. There is a focal area of hypervascularity in the left peripheral zone, biopsy of which revealed prostate cancer

secondly the quantitative assessment of blood flow within the area. Both prostate cancer and prostatitis may show increased vascularity with power Doppler [24], and no specific flow pattern for cancer has been identified. Cancer is most commonly demonstrated as a focal area of hypervascularity, but not all tumours demonstrate increased vascularity. There has been recent interest in whether the assessment of prostatic microvasculature can be used as an index of prognosis of the tumour. This is important as there are suggestions that core biopsy underestimates histological grade and thus Gleason score [25]. There is increased microvascular density in prostatic cancer compared with benign prostatic tissue. Mean blood vessel count is higher in tumours with metastases than in those without metastases [26]. Recent papers have assessed whether the microvascular density can be used as a prognostic index both in the choice of treatment of the detected cancer and also in the follow-up of tumours that have been treated by radiotherapy. Intratumoral microvascular density was assessed in 98 cases of prostate cancer diagnosed at transurethral resection of the prostate between 1975 and 1983, and the mean cancer specific survival time was found to be significantly longer in patients with a vessel count below 135 than in those with a vessel count greater than 135 [6]. Similar results were reported by Borre et al. [7]. It is, however, currently not clear whether imaging by Doppler US techniques can reliably demonstrate neovascularity and objectively quantify microvessel density.

There has been considerable recent interest in the role of intravascular US contrast agents [27]. Research in this field has concentrated on their use in the liver, but it is natural to consider their potential role in other organs, e.g. in the prostate for detection of prostate cancer and as an aid to US-guided prostatic biopsy [28, 29, 30]. One of the problems with the use of contrast agents for highlighting areas for prostate biopsy has been the short

half-life of the agent. Infusion pumps are now available to enable a slow infusion of the solution rather than a bolus injection. Despite this advance, it remains unclear whether US contrast agents have a role in the diagnosis of prostate cancer. There are limited reports currently in the literature. Rickards et al. [31] reported a series of sextant biopsies of 22 patients and found that the use of sonographic contrast increased the sensitivity but decreased the specificity of prostate sextant biopsy. Broadly similar results, namely an increase in sensitivity with a decrease in specificity, were also been reported in 43 patients with prostate cancer in Austria [32]. Halpern et al. [33] have reported a further study of contrast use where contrast-enhanced TRUS demonstrated cancer in 24 sites in 15 subjects. This study confirmed increased sensitivity without loss of specificity. Use of US contrast agents increases the time and cost of US-guided prostate biopsy procedures, and because there has been no marked improvement in the accuracy of prostate cancer diagnosis with such agents, they have not been adopted into standard uro-radiological practice. If future research proves that these agents are able to help in the prognosis of prostate cancer in an individual patient, by enabling quantitative pre-operative assessments of microvascular density, then their impact on radiological practice could be considerable.

Systematic biopsy

The systematic biopsy technique was introduced by Hodge et al. [34] as a means of detecting isoechoic cancers in patients with an elevated PSA level but no palpable abnormality. The initial systematic biopsy technique involved taking six cores, three from each prostatic lobe in a para-sagittal line at the base, mid-gland and apex of the gland. Sextant biopsies are fairly sensitive for the detection of tumours greater than 2 cc and PZ tumours; however, this approach is not sensitive for small cancers or TZ tumours [35]. It was considered in the early 1990s that a four-quadrant systematic biopsy of the prostate might be sufficient for prostate cancer diagnosis, and that the six cores of the sextant biopsy were not necessary; however, increasing experience with the systematic biopsy approach during the past decade has confirmed the need for at least six cores of the prostate. In a contemporary systematic biopsy, a minimum of eight to ten cores would be taken now by most workers. There has been concern that cancers found by systematic biopsy may be clinically insignificant, but that does not appear to be the case. The sextant biopsy procedure appears to underestimate the presence of cancer [36, 37] and under-samples larger glands. A modification of the technique which increased the sensitivity of the sextant approach in the detection of prostate cancer was to take the mid-gland core further laterally. Some investigators

have proposed repeating the sextant biopsy after a negative initial biopsy [11] and supplementing the conventional para-sagittal sextant biopsy with additional cores, e.g. lateral cores [38, 39], mid-gland cores [40], lateral and mid-gland cores [41], and taking TZ cores [42, 43]. Numerous papers have been produced in recent years on this subject, all reflecting increasing cancer detection through the use of additional cores. Eskew et al. [41] took 13 cores per patient in a series of 119 patients and found that 35% of patients had tumours that would have been undetected had a sextant biopsy alone been used. The systematic biopsy approach was reviewed by Klein and Zippe [44]. Following that review, many radiologists and urologists are now adopting a minimum octant biopsy for the standard systematic approach. These techniques aim to reduce the need for repeat biopsy. In men with persistent elevation of serum PSA, repeat biopsy reveals cancer in 19, 20 and 23% of patients [11, 45, 46]. Extensive re-biopsy with an average of 22 cores has even been advocated [47]. Contrary to initial expectations, there does not appear to be significant additional patient discomfort from the taking of additional cores, but various workers are currently exploring the use of local anaesthesia during TRUS-guid-

ed biopsy [48]. The extra information obtained from the taking of additional cores of the prostate at systematic biopsy may be used in estimating the prognosis of the tumour, using the number of cores containing cancer to refine treatment decisions [49]. The role of TZ cores at systematic biopsy remains equivocal. Most workers do not take TZ as part of the initial systematic sampling, but would reserve TZ cores for a repeat biopsy in a patient with markedly elevated or rising PSA levels in whom the initial systematic biopsy was negative. Routine transition zone biopsy has a low yield of cancer, ranging from 0.6 to 1% [42, 50].

Conclusion

Prostate cancer diagnosis has developed considerably in the past 15 years, and TRUS plays a central role in the modern diagnostic process. Current evidence favours a systematic biopsy approach rather than techniques concentrating solely on focal sonographic or colour Doppler features. Doppler techniques will become more important if they are found to be valuable in quantifying neovascularity in the prostate.

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