Tuesday 24 June 16.00–17.00
Poster Session 5: Prostate Cancer: Investigation
Chairmen: R. Kirby and R. Persad

P041

Is a DRE essential in diagnosing early prostate cancer?

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INTRODUCTION

The diagnosis of early prostate cancer comprises PSA testing, a DRE and prostate biopsy. We assessed the role of the DRE in diagnosing and predicting pathological stage in early prostate cancer.

PATIENTS AND METHODS

The study included 195 consecutive patients (mean age 63.9 years, range 43–80) referred with a PSA of 2.6–10.0 ng/mL who underwent TRUS-guided prostate biopsy (12 cores) over an 18-month period. A DRE was undertaken by two experienced clinicians.

RESULTS

The DRE was recorded as suspicious in 96 patients, 39 (41%) of whom had cancer; 22 cancers were detected in patients with a normal DRE (T1c, 22%). In all, cancer was detected on biopsy in 61 patients. Men with cancer were older (65.3 vs 63.2 years) with higher median PSA level (6.8 vs 6.2 ng/mL). There was no significant correlation between DRE findings and a histological diagnosis of cancer. Furthermore, there was also no significant correlation between clinical staging (DRE) and final pathological staging in patients who underwent radical prostatectomy (39). The positive predictive value of a DRE was 41%, with a sensitivity of 64% and an overall accuracy of 60%.

CONCLUSION

There was no significant correlation between DRE, biopsy findings and pathological staging. The DRE did not contribute to the management algorithm. If patients are appropriately counselled before PSA testing, a DRE may not be essential in patients with a PSA of ≥10 ng/mL.

DRE	Clinical stage	Total	Cancer on biopsy	Benign on biopsy
Suspicious	T2a	64	26	38
	T2b	31	13	18
	T3	1	0	1
Not suspicious	–	99	22 (T1c)	77

P042

Periprostatic lignocaine infiltration for prostate biopsies: a double-blind placebo-controlled trial

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OBJECTIVE

To determine the efficacy of periprostatic lignocaine infiltration before transrectal biopsy of the prostate.

PATIENTS AND METHODS

Following ethical approval, 110 patients were randomly assigned to a periprostatic injection with 10 mL of 1% lignocaine or 10 mL of normal saline 5 min before their biopsy. The surgeon and patient were unaware of the solution given. The biopsy was taken with the patient in the left lateral position, using a 7.5 MHz biplanar TRUS system. After the biopsy, a nurse unaware of the procedure and biopsy interviewed the patient. Pain was assessed with a visual analogue scale (VAS) and a verbal description (VRS) of the pain for the biopsy itself, and for the entire procedure. On power analysis, 100 patients would give an 80% chance a detecting a difference of 1 on the VAS. The blinded data were statistically analysed.

RESULTS

In all, 106 patients were correctly randomized, 53 to each arm. Measured co-variates (age, number of previous biopsies, prostate volume, number of biopsies taken and number of benign or malignant biopsies) were similar in each arm. The mean pain score for the biopsy was 3.5 with saline and 2.1 with lignocaine ($P = 0.0012$); the mean pain score for the entire procedure was 3.5 and 2.6, respectively ($P = 0.044$). Using the VRS the results were similar; 32 patients who received saline rated the pain of the biopsy as moderate or severe, while only nine did so with local anaesthetic.

CONCLUSION

The use of 10 mL of 1% lignocaine administered as a periprostatic block significantly reduced the pain of a transrectal prostate biopsy, and the pain associated with the entire procedure.

Funding: Waikato Urology Research Trust

P043

Efficacy of entonox vs periprostatic infiltration of 1% lignocaine in providing analgesia during TRUS-guided biopsy of the prostate: a prospective randomized controlled trial

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OBJECTIVE

To compare the efficacy of entonox vs periprostatic infiltration of 1% lignocaine in providing analgesia during TRUS-guided biopsy of the prostate.

PATIENTS AND METHODS

The study included 180 consecutive men undergoing TRUS biopsy of the prostate for an elevated PSA or abnormal DRE. Patients were randomized to three groups: group A (66) was a control with patients receiving no analgesia before biopsy; in Group B (59) patients had a periprostatic infiltration of 1% lignocaine and the biopsies were taken 5 min after infiltration; group C (55) received entonox (nitrous oxide/oxygen 1 : 1) for 2 min through a breath-activated device before biopsy and afterward as and when the patient felt it necessary. All the patients were asked to indicate the level of pain experienced before and after biopsy on a horizontal visual analogue scale (VAS). The results were analysed using the Mann–Whitney *U*-test.

RESULTS

The mean age of patients were 69.1, 64.7 and 64.8 years and the mean VAS scores 2.9, 1.7 and 2.2, respectively, in groups A, B and C. Patients in group B had significantly less pain during biopsy than those in group A ($P = 0.001$). There was no statistical difference in pain scores between group A and C ($P = 0.092$) or between group B and C ($P = 0.066$).

CONCLUSION

Periprostatic infiltration with 1% lignocaine provides significant pain relief compared with entonox during TRUS-guided biopsy of the prostate.

P044

Role of peripheral basal biopsies in prostate cancer detection

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INTRODUCTION

TRUS-guided prostate biopsy is a standard diagnostic tool in prostate cancer diagnosis. In this study we aimed to assess the prostate cancer detection rate with a 12-core biopsy protocol.

PATIENTS AND METHODS

Over a 2.5-year period, 367 consecutive patients (mean age 64.8 years, range 43–84) with a PSA level of 2.6–10 ng/mL, and who had TRUS-guided prostate biopsies (12 core) taken, were assessed. The first six biopsies were obtained from the periphery of the gland directed more laterally at the base, mid-zone and apices. The remainder were standard para-sagittal sextant biopsies. Each core was analysed histopathologically.

RESULTS

Cancer was detected in 110 patients (30%); the men with cancer were older (mean 65.5 vs 64.1 years) and had a higher median PSA level (6.9 vs 6.3 ng/mL). Of the 110 cancers diagnosed, peripheral biopsies were positive in 98 and para-sagittal biopsies in 69 patients; 41 cancers (37%) were detected only from peripheral biopsies and would have been missed by standard sextant biopsies. Furthermore, 24 of these 41 cancers were positive in the peripheral basal biopsies. Interestingly, 12 cancers were diagnosed only in para-sagittal biopsies. Among the 12 cores, the maximum diagnostic yield was from the basal peripheral biopsies (37%).

CONCLUSIONS

Standard sextant biopsies missed 37% of the cancers; the cancer detection rate increased from 63% to 85% by adding peripheral basal biopsies (eight-biopsy protocol) to standard sextant biopsies and 96% of the cancers would have been detected with a cost-effective 10-biopsy strategy, omitting the peripheral mid-zone biopsies.

P045

The utility of the free/total PSA ratios in prostate cancer detection in younger men aged 50–65 years with a total PSA of 1.1–4 ng/mL: a prospective study of 773 men

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INTRODUCTION

The use of total PSA measurement as a tumour marker may allow the early detection of clinically organ-confined prostate cancer in men who may benefit from potentially curative interventions. However, it has been estimated that ≈20% of men with prostate cancer have a PSA within the currently accepted normal range (< 4 ng/mL). We screened an urban cohort of younger men to ascertain whether the use of free/total PSA ratios is useful in identifying those men with prostate cancer and a total PSA of 1.1–4 ng/mL.

SUBJECTS AND METHODS

A total of 773 young men aged 50–65 years (previously unscreened) accepted an invitation to undergo screening for prostate cancer via their local primary healthcare practice. The blood was centrifuged and the serum frozen at −70°C within 3 h of being drawn. Total and free PSA were calculated (Hybritech assay). All men with a total PSA of >4 ng/mL had a biopsy taken, as did men with a PSA of 1.1–4 ng/mL and a free/total PSA of <20%.

RESULTS

The overall cancer detection rate was 4.3% (33/773); of the 130 men with a low total PSA (1.1–4 ng/mL) and a free/total ratio of <20%, 112 agreed to have a biopsy. The cancer detection rate in this group was 11.6% (13/112). In this group all of the cancers were clinically localized and Gleason sum 5–6, except one of Gleason sum 7 which was associated with a particularly low free/total PSA ratio of <12%. Age-adjusted thresholds would have failed to detect all of these cancers, which were detected solely from a low free/total PSA. There were no insignificant cancers at pathological examination and all were organ-confined.

CONCLUSION

If a PSA threshold of 4 ng/mL had been used for biopsy the cancer detection rate would have been 2.58%; using our criteria the rate increased to 4.27%, representing a 40% increase in cancer detection. The cancers in this low PSA range were detected solely by their low free/total PSA. The application of age-adjusted thresholds would have failed to detect all of these cancers. The use of free/total PSA may provide a means of detecting organ-confined prostate cancer in young men who would benefit from curative treatment when the total PSA is 1.1–4 ng/mL.

P046

Does needle size matter? A single-blind study comparing goserelin and leuprorelin

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INTRODUCTION

Goserelin (Zoladex, AstraZeneca) and leuprorelin (Prostap, Wyeth) are commonly used LHRH analogues which are delivered using systems with significantly different needle sizes. An open crossover study suggested the patients preferred a smaller needle (Beese G, BAUN 2000, abstracts, 8–10). Patients' pain may have been influenced by seeing the size of the needle. We undertook a pilot study to investigate this.

PATIENTS AND METHODS

Thirty-one consecutive patients requiring hormonal manipulation for prostate cancer were included (15 on Zoladex and 16 on Prostap). Patients were excluded if they had received previous LHRH analogues or were unable to give consent. The choice of LHRH analogue was determined by the preference of the GP practice. Patients were blindfolded before the injection pack was opened. Pain was recorded on a visual analogue scale (VAS) for the first two injections, with the time taken and subsequent bruising.

RESULTS

The two groups were similar in age, PSA and stage. The median (range) VAS scores for the first injection were 5.0 (0–38) for Zoladex and 4.5 (0–30) for Prostap. These results were not significantly different for this or the second injection. Zoladex resulted in a higher rate of reported bruising (nine of 30 vs two of 32) and Prostap took significantly longer to administer, at a mean (SD) of 111.8 (21.4) s vs 42.0 (9.9) s for Zoladex.

CONCLUSIONS

There was no significant difference in reported pain when patients were blindfolded before administering Zoladex or Prostap. The patients' preconceptions of pain and needle size may have led to the previously observed differences.

Funding: AstraZeneca UK

P047

Changes in bone mineral density in patients with prostate cancer receiving hormonal manipulation, and testosterone recovery after ceasing long-term LHRH analogues

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INTRODUCTION

The long-term treatment of prostate cancer with LHRH analogues has been shown to decrease bone mineral density (BMD). However, even before hormone manipulation data show that 44% of patients with advanced cancer have osteoporosis. In this prospective study we monitored changes in BMD in patients receiving antiandrogens compared with LHRH analogues, and examined testosterone recovery in osteoporotic patients after conversion from LHRH analogues to antiandrogens.

PATIENTS AND METHODS

In all, 183 patients with locally advanced or metastatic prostate cancer had their BMD measured immediately before hormone manipulation. Osteoporotic (t score ≤ 2.5) patients (80) were commenced on long-term anti-androgens; the remainder received LHRH analogues. Eighty-nine patients were followed up with a repeat dual-energy X-ray absorptiometry (DEXA) scan at 1 year and 30 had a third DEXA scan at 2 years. Testosterone recovery was monitored in 16 patients after a mean of 26 months of LHRH therapy.

RESULTS

The osteoporotic patients showed no significant change in t score after 1 or 2 years. Those treated with LHRH analogues had a significant decrease in t score over 1 and 2 years (both $P < 0.001$). Thirteen (36%) of the osteopenic patients became osteoporotic after 1 year and 62% were osteoporotic at 2 years. Only four of the 16 men had testosterone recovery, with a mean (range) duration to recovery of 15 (12–18) months.

CONCLUSION

The choice of hormonal manipulation has an effect on BMD; antiandrogens maintain BMD in osteoporotic patients. Osteopenic patients commenced on LHRH analogues are at significant risk of developing osteoporosis. We recommend that patients should have their BMD assessed before receiving hormone manipulation, and annually thereafter. After discontinuing long-term LHRH analogues osteoporotic patients take at least a year to recover normal testosterone levels, and often much longer.

P048

Transdermal oestradiol for advanced prostate cancer: advantages over oral oestrogens and current hormone therapies

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INTRODUCTION

We previously reported that transdermal oestradiol therapy achieves an effective testosterone and PSA response. We now report the detailed effects of transdermal oestradiol on coagulation, vascular flow, bone density and quality of life (QoL) in patients with prostate cancer.

PATIENTS AND METHODS

Twenty men with advanced prostate cancer were followed a median (range) of 21 (18–24) months, using two or three patches per week of 7.8 mg oestradiol to maintain castrate levels of testosterone. Over 100 variables pertaining to all aspects of coagulation, vascular flow and bone density, as well as the EORTC QoL questionnaires, were completed at 6-month intervals.

RESULT

All patients remain with castrate levels; one patient had fluid retention and was withdrawn at 10 months, but no other cardiovascular toxicity occurred. Coagulation was not induced and elevated levels of prothrombin, fibrinogen and D-dimer were decreased ($P < 0.001$; <0.001 and 0.049). Arterial inflow was increased ($P = 0.004$), and arterial compliance improved ($P = 0.049$). Bone densities of the lumbar spine and hip increased ($P = 0.05$ and 0.031). There were clinically significant improvements in function and emotion, and in the overall QoL, and these benefits were maintained throughout the study period.

CONCLUSION

Transdermal oestradiol therapy reversed the hypercoagulable state often associated with prostate cancer and induced by oral oestrogens. Vascular flow improved, suggesting a long-term cardiovascular benefit. Bone density significantly increased, in contrast to conventional hormone therapy which accelerates osteoporosis. The QoL of the patients improved. Transdermal oestradiol therapy has significant benefits over current hormone therapies. Randomized trials are warranted to determine the place of transdermal oestradiol in the management of prostate cancer.

Funding: Internal NHS resource and unrestricted educational grants from Schering Health Care and the Hammersmith Trust.

P049

A biodistribution study of adenovirus-delivered nitroreductase in patients with operable prostate cancer

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INTRODUCTION

We are undertaking a clinical trial of 'suicide' gene therapy administered by direct intraprostatic injection of a replication-defective adenovirus CTL102 (in which nitroreductase is under the control of the cytomegalovirus 'immediate early' promoter) followed by intravenous injection of the prodrug CB1954. The study involves: (i) a biodistribution study in patients before radical prostatectomy (RRP); (ii) combination therapy with CTL102 and CB1954.

PATIENTS AND METHODS

For the biodistribution study cohorts of three to seven patients have undergone intraprostatic injection of CTL102 under TRUS control in escalating doses, from 10^{10} to 10^{12} particles, with RRP 48–72 h later. Nitroreductase expression was assessed by immunohistochemistry. The dose escalation is aimed at establishing the dose of CTL102 at which transgene expression likely to be effective in combination, with CB1954 detected as well as conventional phase I toxicity endpoints.

RESULTS

Ten patients have now been treated (10^{10} in three, 5×10^{10} in seven) with no serious adverse reactions. Dose escalation is underway and should be complete by May 2003. TRUS images after injection showed hyperechoic virus suspension disseminating through the prostate. Immunohistochemistry from the first four patients showed transgene expression confined to the glandular epithelium.

CONCLUSIONS

Direct intraprostatic injection of virus is feasible and safe, and virus disseminates via the prostatic ducts, although the virus previously has been shown to infect both stroma and epithelium in primary prostate tissue *in vitro*. Nitroreductase expression sufficient to initiate the second phase of the trial (combination with prodrug) has been achieved at the lowest dose level.

Funding: Medical Research Council UK, Cobra Therapeutics, Cancer Research UK

P050

Characterization of the putative prostate stem cell phenotype using Hoechst 33342 isolation

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INTRODUCTION

Prostate cancer is thought to originate from the prostate epithelial stem cell compartment. Identifying this compartment has not been possible to date because there were no specific cellular markers. We have successfully adapted the Hoechst 33342 fluorescent dye efflux assay, used in haematology to isolate an enriched stem cell 'side population' (SP), to isolate SP-containing putative stem cells from benign and malignant human prostate tissue.

MATERIALS AND METHODS

Prostate epithelial cells, isolated from benign and malignant TURP chips, were incubated with Hoechst 33342 with or without verapamil and the marker CD45. FACS-isolated CD45–ve SP and non-SP cells were then fixed to slides for dual fluorescence monoclonal antibody labelling with epithelial (BerEP4) and stem cell markers.

RESULTS

The isolated Hoechst 33342 prostate SP comprised 2% of the total epithelial population, with 80% verapamil sensitivity. Prostate SP cells expressed cytokeratin 5, 8, 14, 18 and the stem cell markers Notch 1, Cleaved Notch, β–catenin, p21CIP1 and p27KIP1. Their epithelial phenotype was confirmed by dual staining with BerEP4. The stem cell markers were absent in the non-SP population.

CONCLUSIONS

Hoechst 33342 efflux from stem cells is a widely accepted method of isolating stem cells from blood and bone marrow. This method is applicable to solid tumours such as the prostate, and the isolated SP is rich in small cells displaying markers consistent with a stem cell phenotype. This technique will enable future evaluation of differences between malignant and non-malignant SP/stem cells in benign and malignant prostatic diseases.

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