Prostate Cancer and Prostatic Diseases (2006) 9, 310–335

1365-7852/06 $30.00
www.nature.com/pcan

BAUS SECTION OF ONCOLOGY

THE BRITISH PROSTATE GROUP

PROSTATE CANCER – A MEETING OF MINDS

FINAL ABSTRACTS

Manchester International Convention Centre
24th – 26th November 2004

Does increasing the number of cores of prostate biopsy improve diagnostic accuracy? Indications and morbidity

Kapasi F, Chandrasekar P, Barber C, Samman R,
Potluri B and Virdi J.

Methods

A study was conducted on accurate data maintained on 400 patients who underwent transrectal ultrasound (TRUS) guided prostate biopsy. Patients were divided into three groups depending on the number of cores and each group was subdivided into two based on the PSA level (PSA<20 & PSA>20). TRUS biopsy procedure was carried out using B and K medical ultrasound scanner no. 2002 (Panther Unit) using Biplanor rectal probe (8551). An 18G, 20cm biopsy needle (Biopty gun) was used.

Intravenous Gentamicin 120mg, Metronidazole 500mg suppository given at the time of procedure, followed by oral Ofloxacin 400mg for three days were routinely used as antibiotic prophylaxis.The usual method of collection of the prostatic biopsy specimen is depositing it into a formalin pot directly from the biopsy needle; this leads to fragmentation of the specimen giving unsatisfactory results.

We have developed a new technique for the collection of biopsy specimen. In our method, the specimen from the needle is mounted onto a formalin soaked sponge (figure 1). The sponge is then secured in a small cartridge, which is locked and deposited into the formalin pot (figure 2). By this method all specimens are kept intact and delivered safely to the pathology department. This gives pathologists accurate numbers of cores, which are easy to process and adds to reduction in preparation time.

Introduction & Objectives

Transrectal ultrasound guided biopsy is the standard procedure for detecting prostate cancers. It is uncertain how many cores are needed to optimise the detection of these cancers. The aim of this study was to compare the diagnostic accuracy of Prostatic carcinoma relating to the number of cores of prostate biopsy and its associated morbidity.

The cancer detection rate for patients with a PSA of less than 20 is not significantly improved if the number of cores taken is increased from 6-7 to 8-9, 0.2>p<0.25 (1 tailed t-test); however, increasing cores from 8-9 to >10 and from 6-7 to >10 does significantly increase the detection rate, p valves of <0.025 and <0.005. There is no difference in the detection rate with the increase in number of core biopsies when the PSA is greater than 20. Mean detection rate 0.71, 95% CI = 0.57 to 0.85.

Complications

The complications were: clot retention in one (0.25%), rectal bleed in two (0.5%) and urethral bleed in two (0.5%). These were only observed in patients who underwent more than 10 core biopsies. None developed septicaemia requiring emergency admission.

Results and Conclusions

1. Diagnostic accuracy improved from 14% to 34% by increasing the number of cores from six to twelve when PSA is less than <20 particularly inT1c prostatic cancer, however, it did not improve when the PSA was >20 and >T1 disease.
2. In this study the complication relating to prostatic biopsy was 1.25%, which was recorded in patients who had more than 10 cores biopsy. In spite of this, to increase diagnostic accuracy in T1c disease we recommend more than 10 core biopsy.
3. Our antibiotic regime is effective in protecting episodes of septicaemia.
4. The method of collection of specimen has distinct advantages in preserving specimens and increasing speed of processing

Anorectal dysfunction after 3-D conformal radiotherapy for localised prostate cancer

Dickon Hayne, Nula Allen, Dan Ashdown, Amanda Mellon,
John Glaholm, Mike Foster
Good Hope Hospital, Birmingham,

Introduction:

Previous work (Ref 1, 2) has shown a very high incidence of anorectal side effects with associated changes on anorectal physiology following conventional radiotherapy for localised prostate cancer (CaP). We report early results on the first prospective study aiming to identify symptoms and quantify anorectal dysfunction after 3-D conformal radiotherapy (3D-CRT) for CaP.

Patients & methods:

Ethical approval was obtained from the North Birmingham Regional Ethics Committee. Twelve men (median age 66 years) with CaP were treated with 3D-CRT using a hypofractionated schedule of 55Gy in 20 fractions over 4 weeks. All patients completed incontinence/proctitis symptom scores, endo-anal ultrasonography and anorectal physiological studies before and 6 weeks after RT. Results were expressed as medians and ranges and compared using a Wilcoxon signed rank test.

Results:

Incontinence scores: 0 (0-5) v 0.5 (0-6) (p=NS) and proctitis scores: 0 (0-2) v 1.5 (0-5) (p<0.05), increased 6 weeks post-3D-CRT. There was no statistically significant change in anal canal manometry, rectal volumes, anal/rectal electrical sensitivity, pudendal terminal motor latencies or the sonographic appearance of the sphincter on endo-anal ultrasound.

Conclusions:

Proctitis was seen six weeks after 3D-CRT. Changes in incontinence scores and anorectal physiology were not demonstrated to a statistically significant degree. Though numbers are still small, comparison to previous work suggests that anorectal disturbance is less after 3D-CRT than conventional RT. Ongoing recruitment to this study should confirm this finding. However, future dose escalation is planned and may result in increased anorectal morbidity.

References:

1. Physiological changes of the anorectum following pelvic radiotherapy for the treatment of prostate and bladder cancer
RS Kushwaha, D. Hayne, E Wrightham, CJ Vaizey, HA Payne H, PB Boulos
Dis Colon Rectum. 2003 Sep;46(9):1182-8
2. Yeoh EE, Botten R, Russo A, McGowan R, Fraser R, Roos D, Penniment M, Borg M, Sun W (2000) Chronic effects of therapeutic irradiation for localized prostatic carcinoma on anorectal function. *Int J Radiat Oncol Biol Phys* 47: 915-924

PSA RESULTS FOR BRACHYTHERAPY IN THE UK WITH FOLLOW UP OVER FIVE YEARS

Sooriakumaran P, Henderson A, Langley SEM, Laing RW
St. Luke's Cancer Centre, Royal Surrey County Hospital,
Guildford, GU2 7XX

Introduction

We report early outcome data for patients who underwent prostate brachytherapy (BXT) using stranded I-125 implant (RapidStrand), with up to 5.5 years follow up.

Patients and Methods
We have prospectively collected data on PSA outcomes on all 482 patients we have treated to date. We report biochemical outcomes for the first 300 of these patients with a median follow up of 31m; range 16-66m. Patients were classified into low (49%), intermediate (37%), and high (14%) risk categories based on their Gleason sum, presenting PSA, and clinical stage. Patients received either BXT alone (32%), BXT with 3m neoadjuvant androgen deprivation (NAAD) (46%), or a combination of 3m NAAD, 45 Gy EBRT, and BXT (22%).
Results
Prostate cancer survival was 100%; no deaths occurred with rising PSA. 16 patients (5.3%) experienced biochemical evidence of treatment failure (ASTRO definitio). Actuarial PSA free survival for all patients was 95% at 66m. There was no significant difference in actuarial survival in hormone-naïve (95%) versus hormone-treated (94%) patients or between patients in different risk categories (low risk- 94%; intermediate risk- 95%; high risk- 98%). At 3yr median PSA was 0.2 for all patients (n=81); 0.3 for low risk (n=36), 0.2 for intermediate risk (n=29), and 0.1 for high risk (n=16) groups. There was no significant difference in median PSA at 3yr in hormone-naïve (0.4) (n=27) versus hormone-treated (0.2) (n=54) patients. 65/81 (80%) patients had a 3yr PSA $\leq$0.5.
Conclusion
These early results demonstrate the effectiveness of brachytherapy in the treatment of early prostate cancer and suggest that the excellent results achieved in the USA are reproducible in the UK.

Effects of prostate brachytherapy on erectile function- prospective UK data
Sooriakumaran P, Henderson A, Langley SEM, Laing RW.
St Luke's Cancer Centre, Royal Surrey County Hospital, Guildford, GU2 7XX

Introduction
We assess the effect of brachytherapy on potency in a prospective, patient administered questionnaire study.
Methods
Patients completed the International Index of Erectile Function (IIEF-5) prior to brachytherapy and at 6 weeks, 3,6,9,12,18 and 24 months post implant. Men with an IIEF-5 score of <12/25 were considered to have moderate or worse ED and were classed as impotent.
Results
180 patients completed baseline and >1 postimplant IIEF-5 questionnaire; 45% (n=81) were potent pre-implant. 80% of potent patients maintained potency at last follow up (mean FU 15m). For pre-implant potent patients, erectile function generally improved over time: 6wk-48%; 3m-64%; 6m-53%; 9m-63%; 12m-67%; 18m-61%; 24m-78%.
Conclusion
Erectile function generally improves with time post-brachytherapy with >75% pre-implant potent patients maintaining potency at 24 months. This compares favourably with surgery, radiotherapy, and cryotherapy for the treatment of early prostate cancer.

Thromboprophylaxis for Radical Prostatectomy: A Comparative Analysis of Present Practice between the USA, the UK and Ireland.
David J. Galvin, David Mulvin and David M. Quinlan
Department of Urology, St. Vincents' University Hospital, University College Dublin, Elm Park, Dublin 4, Ireland.

Introduction
A clinical dilemma exists in the management of patients undergoing radical prostatectomy whereby measures taken to reduce the risk of thrombotic events may adversely affect efforts to limit blood loss. No consensus exists in the literature on the ideal management of thromboprophylaxis in these patients. Our aim is to examine and compare current thromboprophylactic policy and practice in centres performing radical prostatectomy.
Methods
A questionnaire was forwarded to all urology residency programmes in Ireland, the United Kingdom and the United States, regarding their current practice with respect to thromboprophylaxis in radical prostatectomy. Completed questionnaires were returned by fax, and the data entered into a computer database.
Results
An overall response rate of 60% was achieved. The questionnaires demonstrated a significant difference in clinical practice between Urologists in the United States and the United Kingdom. Just 24% of American Urologists use pharmacological thromboprophylaxis in contrast to 100% of British Urologists, yet there is no difference in the incidence of reported thrombotic events. There was no difference in the use of non-pharmacological thromboprophylaxis. Units performing the largest number of radical prostatectomies do not use pharmacological thromboprophylaxis, whereas units doing fewer procedures do.
Conclusion
This study, which examines current clinical practice, demonstrates that the units performing the greatest number of radical prostatectomies do not use thromboprophylaxis, although the literature remains divided on this strategy.

Obesity, prior lower abdominal surgery and laparoscopic radical prostatectomy.
T. Gianduzzo, C. Chang and C. Eden
North Hampshire Hospital, Basingstoke.

Introduction:
Obesity and previous lower abdominal surgery are both relative contra-indications to laparoscopic pelvic surgery. However, patients exhibiting these features may gain more than most from a laparoscopic approach due to the additional difficulty encountered in operating on them by open surgery (Chang, 2004; Katz, 2002). Increased experience with laparoscopic radical prostatectomy (LRP) has allowed us to test this hypothesis.
Materials and Methods:
350 cases of LRP were performed from March 2000 to July 004, 111 using a transperitoneal and 239 using an extraperitoneal route. 20 patients were classified as obese (>100 kg). 97 had lower abdominal scars due to unilateral hernia repair (n=48), bilateral hernia repair (n=14), appendisectomy (n=31) or other procedures (n=4). Peri-operative and post-operative parameters were recorded for all patients and compared to investigate differences.

Results:
Patients' age, PSA, Gleason score, clinical stage and prostate volume were similar.
Non-obese & obese patients' mean values for operating time=195 & 183 min, blood loss=261 & 263 ml, complications=3.3% & 5.0%, hospital stay=3.1 & 3.9 nights, + margins=15% & 15% and biochemical recurrence=2.0 & 5.0%.
Mean values for patients without and with lower abdominal scars for operating time=175 & 185 min, blood loss=243 & 240 ml, complications=4.4% & 2.9%, hospital stay=2.7 & 3.1 nights, + margins=14% & 15% and biochemical recurrence=2.2 & 4.0%.
Conclusion:
Neither obesity nor a lower abdominal scar influenced any of the variables ($p>0.05$) listed above. Obesity and previous lower abdominal surgery do not appear to have the same negative impact on blood loss and operating time during LRP as has been reported during open radical prostatectomy (ORP). Obese patients and those with lower abdominal scars might be better served by LRP than by ORP.

Prostate Cancer Screening in Ireland: A feasibility study
Galvin DJ, Rea D, McDermott TED, Grainger R, Butler M, Thornhill JA.
Adelaide and Meath Hospital Incorporating the National Children's Hospital, Tallaght, Dublin 24, Ireland.

Introduction
The true prevalence of prostate cancer is unknown in Ireland. Its detection is currently low as no national screening programme exists. Randomised prostate cancer screening studies have demonstrated reductions in cancer-specific mortality. In order to assess the validity and feasibility of prostate cancer screening in Ireland, we developed two pilot prostate cancer screening programmes at our Institution.
Methods
The first study invited men aged 18 to 66 years from a nationwide financial institution to attend for Men's Health Screening. The second study invited men from the general population between 40 and 70 years to attend for prostate cancer screening. All men had a PSA taken and a DRE performed by a Consultant Urologist. Criteria for trans-rectal ultrasound (TRUS) guided prostate biopsy (six-core) were a PSA > 4 ng/ml or an abnormal DRE.
Results

Comparison of Both Prostate Cancer Screening Trials		
	STUDY 1	***STUDY 2***
Total Subjects	677	969
n	468	969
Mean Age	50.9 years	55.1 years
Mean PSA	1.2 ng/ml	1.35 ng/ml
Abnormal DRE	26 (5.5%)	39 (4%)
PSA >4ng/ml	12 (2.56%)	44 (4.5%)
TRUS Bx.	9 (1.9%)	34 (3.5%)
Cancer Detection	2 (0.42%)	13 (1.3%)
Radiotherapy	0	8
RRP	2	5

Conclusions
These two studies demonstrate the feasibility of prostate cancer screening in Ireland. If screening is to be introduced on a national basis, there are significant personnel and resource implications at both primary care and hospital settings.

Men's preferences for two different endocrine therapies in the treatment of prostate cancer
Jenkins, VA. , Edginton TL, Fallowfield, LJ
Brighton & Sussex Medical School, University of Sussex

Introduction
Anti-androgen therapy and Lutenising Hormone Releasing Hormone (LHRHa) have equivalent efficacy in the treatment of locally advanced prostate cancer (Iversen et al 2000, J Urol, 164: 1579 & See et al. 2002, J Urol, 168, 429-435), yet most clinicians prescribe LHRHa therapy. Both of these treatments have different side effect profiles impacting on men's quality of life. They are also administered differently either by injection or tablets. Our survey examined preferences of healthy men and reasons for these when presented with the profiles of both drugs.
Materials and Methods
Scenarios describing side effect profiles of Drug A (LHRHa treatment) and Drug B (anti-androgen therapy) were constructed and modified following expert feedback. A representative sample of 180 men without prostate cancer (68% over 65 years of age), read the scenarios and were asked to choose which drug treatment they would prefer, with a reason for their choice. Also participants stated the degree to which they wanted to avoid side effects specific to each drug.
Results
156/180 (86%) men choose anti-androgen therapy, the majority 115/156 wishing to avoid the side effects associated with LHRHa. 12 men chose LHRHa of whom 9/12 cited the method of administration as the main reason for their choice. 12 men could not decide. Examining which side effects men most wanted to avoid experiencing included, in descending order of importance, risk of fractures (85%), reduced physical strength (76%), hot flushes (56%), decreased sexual interest (56%), impotence (51%), breast enlargement (17%) and breast tenderness (13%). This did not differ significantly according to age, marital or socioeconomic status.
Conclusion
Although this study has the limitations associated with hypothetical research in a non-clinical group, it showed a compelling preference for anti-androgen therapy over LHRHa. Findings might encourage clinicians to present real patients with choices in treatment when efficacy is equivalent and discuss side effects that will impact on quality of life.

Who should perform trans-rectal ultrasound (TRUS) guided biopsy of the prostate: Urologists or Radiologists?
James A Forster, Jonathan Krell, Philip M.T. Weston, Tony J Browning, Kanwar Gill* and Subramanian Kanaga-Sundaram,
Departments of Urology and Radiology*, Pinderfields General Hospital, Mid Yorkshire Hospitals NHS Trust,
Aberford Road, Wakefield, West Yorkshire WF1 4DG.

Introduction:
Trans-rectal ultrasound guided biopsy of the prostate is a common procedure, and its use is increasing with the advent of PSA. Screening for prostate cancer in the US has lead to over one

million prostate biopsies being taken there every year. Traditionally in the UK radiology departments have provided this service. The pressures of cancer waiting times and increasing work-load have caused radiology departments difficulties in providing optimal service. The decision as to whether urologists or radiologists perform the procedure varies according to local policies and expertise. Although there is a good deal of data published on technique, results and complications of the procedure, to our knowledge there is no data comparing the results gained by urology and radiology departments. That is the purpose of this study.

Materials and methods:

Data of TRUS-guided prostate biopsy performed over a twelve month period commencing in January 2003 were retrospectively analysed. The indication for the procedure including PSA value, speciality of operator, number and position of cores and the histology results were analysed. The positive and negative predictive values of DRE, PSA and TRUS for each operator that resulted in a diagnosis of prostate cancer were calculated.

Results:

A total of 414 procedures were performed in the study period, 283 by consultant urologists and the rest by a radiologist. The cohort of patients in each group had similar PSA levels. Overall 175 biopsies were positive for prostate cancer (42%). The urologists had a positive biopsy rate of 41%; the radiologist had a positive biopsy rate of 44%. There was no statistical significance between the two groups (p=0.574). The positive predictive values of DRE performed by urologists were 59%, 75% and 37%. The negative predictive values of DRE performed by urologists were 67%, 60% and 81%. An elevated PSA (>4.0) gave a positive predictive value of 45%; a normal PSA (<4.1) gave a negative predictive value of 89%. Positive predictive value of TRUS was 77%, 67% and 50% for the urologists, and 52% for the radiologist.

Conclusion:

TRUS-guided prostate biopsy has a comparable yield of detecting cancer when performed by urologists and radiologists. With increasing pressure on waiting time and the introduction of office urology, in the future it is appropriate that this procedure is performed by adequately trained urologists. Our findings show that our department has similar predictive values in methods used to diagnose prostate cancer compared with national and internationally published data.

Cryotherapy for prostate cancer: Initial experience

J Cresswell, M Choudhary, S Asterling and D Greene
Dept of Urology, Sunderland Royal Hospital, Sunderland, UK

Introduction

The development of cryotherapy for localised prostate cancer provides a potentially curative option for patients with primary or recurrent disease, with reduced morbidity. We report the first 31 consecutive patients treated at our centre.

Patients and Methods

Data were collected prospectively for all patients. In 23 patients, cryotherapy was used as primary treatment, and as salvage therapy in 7 previously treated with radiotherapy (6 EBRT, 1 brachytherapy), and 1 following hormone treatment alone. All had biopsy proven prostate cancer and negative bone scans. Gleason grade was 7 or less in 25 patients and >7 in 5 patients (grade not recorded for 1 patient). Median PSA for primary treatment was 9.1μg/L (range 1.6 – 25.4μg/L) and 12.6μg/L (range 2.5 – 20.1μg/L) for salvage cases. A single urologist performed all treatments using an argon-based cryotherapy system with transrectal ultrasound. Median operative time was 146 mins (range 109 – 231 mins). A suprapubic catheter was placed intra-operatively and remained in place for 2 weeks post-operatively.

Results

All patients tolerated the procedures well and median hospital stay was 3 days. Median follow up time was 3 months (range 2 wks – 1 year). Of 23 patients with > 3 months follow-up, 17 reached a PSA nadir of <0.5μg/L at 3 months. Of the patients undergoing primary treatment 5 failed to reach this nadir. Three out of 4 salvage treatments reached a PSA nadir of <0.5μg/L at 3 months. Complications included 3 cases of urinary retention after removal of suprapubic catheter with 2 patients requiring subsequent TURP. Six patients developed urinary incontinence that persisted for a median of 3 months and all 11 patients with normal erections preoperatively, developed erectile dysfunction. No patient developed a fistula.

Conclusion

Preliminary results suggest that cryotherapy offers a safe and effective alternative for the primary and secondary treatment of prostate cancer. Advantages include shorter hospital stay and lower morbidity compared to radical surgery. Long-term follow-up is required to assess the durability of response and therefore probability of cure.

Prostate cancer in the over eighties - are we too aggressive?

A. Mampitiya, D. Wijewardena, D.N. Wood, S.S. Gujral
Harold Wood Hospital, Barking, Havering and Redbridge NHS Trust, Romford, Essex

Introduction:

Post-mortem studies in octogenarians reveal 60-80% prevalence of prostate adenocarcinoma(CaP) (Breslow N et al *Int J Cancer* 1977; 20(5):680-8). Diagnosis of CaP in this age group does not significantly reduce life expectancy (Welch HG et al *Ann Intern Med* 1996; 124(6):577-84). However, there is still pressure to diagnose and patients with CaP. Referral patterns and outcomes in these men were assessed.

Patients and Methods:

Case notes of octogenarians diagnosed with CaP at a single unit in 2001 were reviewed. Referral patterns, diagnostic criteria and outcomes were recorded.

Results:

143 octogenarians were referred for TRUS biopsies (35% of total biopsy referrals): 63% by GPs for raised PSA (9 to 53ng/ml), 30% from the "LUTS" clinic (abnormal DRE) and 6% for histological confirmation in clinically advanced disease. 77 had biopsy proven CaP. GPs did a DRE in 50% - their findings showed excellent correlation with those of urologists. GP PSA indications were screening (42%), simple LUTS (52%) and back pain (6%). 57% had T2 staging. 61% had bone scans - only 12% being positive (all with T3+ disease). 75% had low to moderate Gleason scores. Following counselling, 91% opted for immediate hormonal manipulation, 8% watchful waiting and 1 patient chose radical radiotherapy. At two years, there was a 30% recorded mortality, only 6% were CaP related.

Conclusion

Despite a known high prevalence of indolent CaP in octogenarians, many have PSA tests performed in the community which could sensibly be avoided if prior counseling were employed. Abnormal results lead to anxiety (often fuelled by the media) and subsequent urological referral for further assessment.

At this stage even with comprehensive counselling many of these men opt for active therapy on diagnosis rather than watchful waiting despite little evidence regarding survival or quality of life benefits. National guidelines for management of these men should be developed.

Patient satisfaction with Uro-oncology nurse specialists —A questionnaire survey

J. Masood, H. Forristal, R. Cornes, M. T. Vandal, S.S. Gujral
Department of Urology, Harold Wood Hospital, Romford, UK

Introduction

Specialist nurses have an established role in the management of Urological cancer in helping patients to understand their disease and treatment options, and in offering counselling and emotional support. There is evidence to suggest that patients who see the nurse specialist express more satisfaction and have less anxiety than those who see either a male or female junior doctor (Hammond C. Dissertation, University of Surrey, 1994). Other studies have found that the specialist nurses' clinical expertise compared favourably with that of other clinicians (Garvican et al., *BMJ*. 1998; **316** (7136): 976-7). The nurse specialists also provide unbiased counselling. This study describes patient satisfaction with Uro-oncology nurse specialists and their nurse led clinics.

Methods

One hundred, 15 point, patient satisfaction questionnaires were sent to new and existing patients with urological cancer who had been randomly identified by the Uro-oncology nurse specialist. The questions were mainly concerned with the provision of information to patients and with the satisfaction of the nurse specialist service.

Results

70 patients completed and returned the questionnaires. 73% of patients were over 70 years of age. 88% of patients were male. 94% of patients were Caucasian in background. 11% of patients saw the nurse specialist at diagnosis and 17% immediately after diagnosis. 76% found this consultation beneficial. 47% of patients felt it would be more beneficial to see the clinical nurse specialist before they saw the consultant. 79% of patients received information on their disease and treatment in verbal format, 15% received both verbal and written information and 1% received written information only. 55% of the patients received this information from the nurse specialist. 81% of these patients found the information very useful and 84% of patients found this information easy to understand. 90% of patients said they had adequate opportunity to ask questions and raise concerns with the nurse specialist and 93% were given a contact number for later use if required.

Difficult to contact	2	Unhelpful	0
Not enough contact	1	Considerate	42
Crucial to my recovery	10	Supportive	39
Promoted independence	2	Professional	46
Easy to contact	32	Condescending	0
Bossy	0	Rushed	0
Friendly	51	Invaluable	25
Wonderful	12	Poor	1
Adequate	1	Informative	39
Sensitive	24	Irrelevant	0

Table 1: Outlines words, which describe the care patients received from the Uro-oncology nurse specialist

Conclusion

Patients found contact with the Uro-oncology nurse specialist supportive, informative and beneficial to their treatment. Patients seem undecided whether they should see the nurse specialist before or after the consultant. We feel that raising the profile of the Uro-oncology nurse specialist would be beneficial to patient treatment and care.

www; the wild, wild web: Internet usage in patients with urological cancer in 2004

J. Masood, J. Shahzad, T.A. Ghazali, M. T. Vandal, S.S. Gujral
Department of Urology, Harold Wood Hospital, Romford, Essex, UK

Introduction

The Internet has an enormous number of health related web sites and can be a valuable source of medical information to the public and health professionals. Patients can independently search the Internet to learn about their illness and treatment options. There is evidence to suggest that there is a better outcome in patients who are well informed. However, of concern, is the quality of some information available on the "Net". Some Internet sites may contain erroneous information on cancer that can pose problems. We assess Internet usage and its benefit amongst our patients with urological cancer. We also assess if patients are advised to visit particular sites on the "Net" by health professionals

Methods

All patients attending our outpatient clinic in 2004 with any type of urological cancer were asked to complete a 10-point questionnaire. We assessed their use of the Internet to gain information about their cancer and if they were advised to look at any web sites by health professionals. Patients were asked if they could name any of the web sites they may have visited, if these sites were useful in improving their understanding of the disease and whether, the information they gathered helped them to make a more informed decision about the further management of their cancer.

Results

A total of 170 completed questionnaires were evaluated. These included 139 males (mean age 69years; range 52 - 86years) and 31 females (mean age 71 years; range 62 -81 years) in the cohort. 98% of patients said they had discussed their cancer with a health

professional. Only 42 patients (24%) had direct access to the Internet. Of the others, 36% had access via friends/family. Only 11 patients (6%) were advised to visit specific websites and all were advised to do so by the Uro-oncology nurse specialists. Only 20 patients (11%) in total had visited urology cancer web sites. Only 2 patients could recall the web sites they had visited. All patients who visited websites found them either "useful" or "very useful", and stated learning about staging, prognosis of their disease and complications of surgery and alternative treatment therapies. Not surprisingly, younger patients, males, patients of higher social class and those with direct access to a computer were more likely to use the Internet

Conclusion

We found that only 11% of patients with urological cancer in our cohort have used the Internet, and they found this resource very useful. Although Internet usage amongst the general urological patient population appears to be on the increase, (Hellawell et al., *BJU Int*. 2000; **86**(3): 191-4) patients with cancer tend to be older and may not have the facilities or the know-how to use the Internet. Health professionals are counselling too few patients about urological cancer websites. Urologists and nurse specialists should be made aware of the need to familiarize themselves with urological websites. Evidence that computer generated information systems are superior to written and verbal information exists (Bulmer et al., BJU Int. 2001; 88(6): 532-5). We advocate visual (using the internet during consultation) and verbal counselling of these patients. Patients can then be directed to high-quality sites so that they can educate themselves about their cancer and avoid misleading websites.

CYP1B1 expression is higher in the peripheral zone compared to the transition zone: a difference underlying zonal susceptibility to prostate adenocarcinoma?

Narasimhan Ragavan[1,2,4], Rebecca Hewitt[4], Andrew C. Hindley[2], Caroline M. Nicholson[3], Shyam S. Matanhelia[1], Francis L. Martin[4]

Departments of Urology[1], Oncology[2] and Pathology[3], Lancashire Teaching Hospitals NHS Trust. Department of Biological Sciences[4], Lancaster University, Lancaster. UK

Introduction

The prostate is a composite organ divided into zones. Prostate adenocarcinoma (CaP) mostly occurs in the peripheral zone. Cytochrome P-450 (CYP) isoenzymes are constitutively expressed and inducible enzymes, many of which (e.g. CYP1A1, CYP1A2 and CYP1B1 isoforms) are involved in hormone and carcinogen hydroxylation.

Aim

To assess variations in *CYP* expression in the prostate on an intra- (peripheral zone *Vs.* transition zone) and inter-individual basis.

Materials and Methods

Human prostates (n=24) were obtained, with ethical approval, from radical retropubic prostatectomies. Study participants exhibited low PSA (< 20 μg/l serum) and low volume of disease (< two/eight core biopsies positive for CaP). Following resection, tissue sets consisting of peripheral zone and transition zone were isolated from a lobe pre-operatively identified as negative for CaP. A histopathologist always examined adjacent tissue. Real-time RT-PCR was employed to quantitatively examine *CYP1A1*, *CYP1A2* and *CYP1B1*.

Results

CYP1A1 mRNA transcripts were detected in either or both zones of twenty tissue sets (in seven cases, in both zones) and were undetectable in four others. In eleven tissue sets, higher levels of *CYP1A1* expression were observed in the peripheral zone compared to the transition zone (maximum six-fold difference) whereas in nine other tissue sets this relationship (maximum 2.5-fold difference) was reversed. *CYP1A2*, although detectable in twelve tissue sets, was not quantifiably expressed. *CYP1B1* expression was detected in both zones of all tissue sets examined. Inter-individual variation in *CYP1B1* expression levels in peripheral zone (five-fold differences) and transition zone (ten-fold differences) were noted. In sixteen out of seventeen tissue sets found to be cancer free, *CYP1B1* expression was found to be two- to fifty-fold higher in the peripheral zone compared to the transition zone; in the remaining tissue set an equal level of gene expression was detected in both zones. In the tissue sets containing CaP, *CYP1B1* expression was higher in the cancerous zone (be it peripheral or transition) in five of six cases; in another tissue set containing PIN, an equal level of gene expression was again detected in both zones. Immunohistochemistry clearly demonstrated a nuclear staining pattern for CYP1B1 in epithelial and stromal cells of both zones; the staining density of this protein was markedly elevated in cancerous tissue.

Discussion

CYP1B1 preferentially catalyses the 4-hydroxylation of 17β-oestradiol, metabolically activates exogenous pro-carcinogens and inactivates anticancer agents. Future studies will investigate whether CYP1B1 may be employed as a target either for chemoprevention strategies or treatment of clinically invasive disease.

The Economic Consequences of Prostate Cancer in the UK.

N Ragavan, VK Sangar, SS Matanhelia, ME Watson, RA Blades
Department of Urology, Lancashire Teaching Hospitals NHS Trust, Preston, UK

Introduction

The incidence of prostate cancer is increasing due to heightened patient awareness and the availability of PSA testing. There is little data available on the impact of this disease on the UK health care economy. Availability of such data is necessary for the adequate direction of resources. The aim of this study was to assess the economic impact of prostate cancer

Method

All the new prostate cancers diagnosed in 2001-2002 were identified from BAUS section of oncology database. Corresponding patients were identified from the local hospital database to facilitate calculation of indirect costs.

The Total Cost (TC) of diagnosing, treating and following up patients for five years was estimated as the sum of Direct Costs (DC) (NHS) and Indirect Costs (IC) (loss of earnings).

Results

In the period studied there were 15099 newly diagnosed prostate cancers (mean age 72.3y) The treatments for these prostate cancer patients were radical prostatectomy (RRP) (n=1506), radical radiotherapy (RRT) (n=2735), hormone therapy (n=7127) and chemotherapy (n=18). There were 1320 patients for whom no treatment was available from the database so they were assumed to be on active monitoring. 1065 patients were entirely excluded from the calculation as the treatments they received were not clear.

The TC for the diagnosis, treatment and five-year follow up of prostate cancer patients diagnosed during 2001 – 2002 was estimated at £ 92.74 million

(Cost in £ Millions – Watchful waiting -1.8, Hormones 63.1, RRP-12.5, RRT-12.4

Chemo - 0.02, TURP1.9). The expenditure on hormonal therapy accounted for over two-thirds of the TC. The TC of radical radiotherapy and radical prostatectomy were similar, but almost one and half times more patients were treated with radical radiotherapy than with prostatectomy. The average cost of treatment of a prostate cancer patient was £ 7294.
The direct costs, which imply the burden directly borne by the National Health Service, form the greater proportion of the total cost (97.6%)

Conclusion
The management of prostate cancer has a significant impact on the health care budget. Cost effective treatment options without compromising the quality of care (e.g. orchidectomy) need to be revisited.

Expression and Differential Modulation of Adiponectin Receptors in Prostate Cancer Cell Lines

T Mistry[1,2], E Karteris[1], J Digby[1], J Chen[1], K Desai[2], H.S. Randeva[1]
[1]Biomedical Research Institute, Department of Biological Sciences, University of Warwick, Coventry, CV4 7AL, and [2]Department of Urology, University Hospitals Coventry and Warwickshire NHS Trust, Clifford Bridge Road, Coventry CV2 2DX

Introduction
Adiponectin is an adipocytokine that has been shown to have anti-atherogenic and anti-inflammatory actions, and has been implicated in the pathogenesis of insulin-resistant states such as obesity and Type 2 diabetes mellitus. Adiponectin orchestrates its actions by activating two membrane receptors (adipo-R1/R2) that despite possessing a classic seven transmembrane structure, have characteristics distinct from any known G-protein receptor. Recent studies have shown that adiponectin levels are significantly decreased in women with endometrial and breast cancer, other hormone-dependent cancers. To date, little is known about the role of adiponectin receptors in prostate cancer, the progression of which is positively correlated with obesity and hyperinsulinaemic states. Therefore, we hypothesised that there might be a direct link between insulin-resistant states and prostate cancer, via adiponectin receptors. In this study we aim to investigate in detail the expression of adiponectin receptors in prostate cancer cell lines, and the influence of various hormones and growth factors on their expression.

Materials and Methods
Expression of adiponectin receptors was determined using RT-PCR, sequencing analysis, Western blotting analysis and immunohistochemistry in two different cell prostate cancer cell lines, PC-3 (androgen independent) and LNCaP (androgen-dependent). RT-PCR and Western blotting were also used to investigate the regulation of adiponectin receptor expression by various hormones and growth factors.

Results
Adipo-R1 and adipo-R2 were detected in both PC-3 and LNCaP cell lines at mRNA and protein level using RT-PCR and Western blotting. Immunohistochemical analysis confirmed membrane localisation of both receptors. Down-regulation of adipo-R1 was found in response to TNF-α and dexamethasone in the cell lines studied, whereas testosterone caused down-regulation of both receptors. Growth hormone and β-estradiol had no effect on receptor subtype expression.

Conclusion
In this study we demonstrate for the first time the expression of adiponectin receptors in prostate cancer cell lines, suggesting that adiponectin can exert effects at the prostate level, acting in an endocrine/paracrine manner. Furthermore, we provide novel evidence about the differential regulation of these receptors by hormones, steroids and glucocorticoids. Further studies are required to investigate the potential role of adiponectin and its receptors in the aetiopathogenesis of prostate cancer and its relationship to the hyperinsulinaemic state.

Emergency bilateral orchidectomy –a life saving procedure in urological emergencies (apart from paraplegia) caused by carcinoma prostate

Makarand V Khochikar
Siddhi Vinayak Ganapati Cancer Hospital, Miraj (India)

Introduction
Acute paraplegia due to spinal cord compression in a case of metastatic prostate cancer is an oncological emergency. Usefulness of bilateral orchidectomy in this situation is very well proven. Disseminated Intravascular Coagulation (DIC), intractable hematuria, anuria due to ureteric obstruction, raised intracranial tension (ICT) with convulsions, acute breathlessness due to pulmonary metastasis are few other oncological emergencies in case of advanced /metastatic prostate cancer. Operative risk in these cases is very high. Effectiveness of bilateral orchidectomy in these situations is evaluated in this study.

Materials and Methods
During 1998-2004, 14 cases of advanced/metastatic prostate cancer with above-mentioned emergencies were dealt with. These were-disseminated intravascular coagulation (DIC)-7 cases, anuria due to ureteric obstruction-3 cases, raised ICT with convulsions –1case,acute breathlessness due extensive pulmonary metastsis-1 case and intractable hematuria –2 cases. Emergency bilateral orchidectomy was performed under local anaesthesia in all these cases.

Results
Bilateral orchidectomy was found to be extremely effective in all these cases. DIC and intractable hematuria could turn to normalcy within 72 hours, ureteric obstruction could open up within 48 hours, breathlessness could revert to stable respiratory status over 72hours and raised ICT could normalize within 4 days.

Conclusion
Advanced /metastatic prostatic cancer can manifest with oncological emergencies that need prompt /active treatment. Bilateral orchidectomy proves life saving in these situations, even in cases of DIC and acute respiratory failure where operative risk is higher.

An elevated PSA, which normalises does not exclude the presence of prostate cancer

Boddy JL[a], Pike DJ[b], Al-Hayek S[a], and Malone PR[a]
[a]The Harold Hopkins Department of Urology, Royal Berkshire Hospital, Reading, United Kingdom
[b]Department of Applied Statistics, The University of Reading, Reading, United Kingdom

Introduction:
Patients with an elevated prostate specific antigen (PSA) level are known to have an increased risk of harbouring prostate cancer (Stamey et al. N Engl J Med 1987; 317(15): 909-16). However, recent work has shown that a significant proportion of patients found to have an elevated PSA, will have a normal value if it is repeated (Eastham et al. JAMA 2003; 289(20): 2695-700). What is uncertain is how this relates to the presence of prostate cancer. The current study looks to address this issue by determining the incidence of cancer in patients who have an elevated referral PSA, which subsequently falls to within the normal range.
Materials and Methods:
A prospective study was conducted in men undergoing a prostate biopsy following the finding of an elevated PSA, according to their age-specific reference range (40-49 years 0-2.5ng/ml, 50-59 years 0-3.5ng/ml, 60-69 years 0-4ng/ml, 70-79 0-6.5ng/ml). Prior to the procedure a urological history, urine dipstick and repeat PSA test were performed and the results of a prostate examination recorded. The referral and repeat PSA value were then compared and related to the subsequent histology.
Results:
21 of the 160 (13%) study patients had a repeat PSA level which had fallen back to within the normal age-specific reference range. 5 of these 21 (24%) patients were diagnosed with prostate cancer, 3 of these patients had a suspicious digital rectal examination (DRE) before the procedure but 2 had a normal prostate examination.
Conclusion:
This study clearly demonstrates that just because the PSA normalises before the biopsy procedure does not mean that the presence of prostate cancer can be excluded, even if the prostate feels benign.

How are prostate biopsies performed in the United Kingdom and the Republic of Ireland?
Al-Hayek S, Malone PR, Boddy JL
Royal Berkshire Hospital, Reading, UK

Introduction:
Although prostate biopsy is the procedure of choice in diagnosing prostate cancer, it is not standardized. The aim of this study is to explore the current practice of obtaining prostate biopsies in the NHS units around UK and Republic of Ireland.
Materials and Methods:
Postal questionnaire was sent to 340 members of the British Association of Urological Surgeons (BAUS) working at 187 NHS hospitals. BAUS members' handbook 2002/2004 provided contact details. This covered the 21 regions specified in the urology book 1998 for United Kingdom and Republic of Ireland. The questionnaire detailed the following information; the grade and speciality of the operator, biopsy indications, pre biopsy preparations, counselling about complications, the number of biopsies taken, use of antibiotics, local anaesthetic, analgesia, how and when the pathology results are given to patients.
Results:
Overall response rate was 61%. Urologists performed 65% of the prostate biopsies whereas 22% were undertaken by radiologists and 24% were shared. The majority (76%) used age based PSA values at which prostate biopsy deemed to be indicated, however, the age related values varied. The number of biopsies taken ranged from 2 to 24 samples. Aspirin was stopped in 34% of patients prior to the procedure in comparison to Clopidogrel which was stopped in 49%. Interestingly, large minority (41%) did not use any sort of analgesia before taking the biopsy. Although the vast majority (96%) gave patients prophylaxis antibiotics, numerous (43) different combinations of antibiotics were prescribed.
Conclusion:
As a gold standard method of diagnosing a very common and important cancer, prostate biopsy does not follow the same guidelines in different NHS trusts. A national study comparing the pick up rate and patients' satisfaction is needed to clarify the requirements for a safe, comfortable and diagnosing biopsy.

Protocol for use of Zoledronic Acid in men with Hormone Refractory Prostate Cancer
Dr.David Dodds, Dr.Martin Russell
Beatson Oncology Centre, Western Infirmary, Glasgow

Skeletal related events are frequent and debilitating events in Hormone Refractory Prostate Cancer (HRPC). Treatment of these events can account for as much as 50% of the total treatment costs of an individual with prostate cancer (Groot, M.T, et al. Eur. Urol.2003;43:226-232) Zoledronic acid has been shown to reduce skeletal related events in men suffering from hormone independent prostate cancer (Saad et al. J. Natl Cancer Inst.2002;94:1458-1468, Lipton A et al. Cancer Invest.2002;20:45-55.). These include pathological fractures, episodes of hypercalcaemia and need for palliative radiotherapy. There is also an improvement in pain control and quality of life. No other bisphosponate has been shown to do this.
Questions remain regarding optimal timing of introduction of the drug and also how long treatment should be continued. The question of integration of Zoledronic acid with other existing supportive and palliative therapies is also unclear at present. The following document is an attempt to offer practical solutions to some of these issues utilising the available data as well as departmental experience gained with the drug over the last year.
Existing recommendations/treatment algorithm are based on the Third International Consultation on Prostate Cancer, June 21-23: 2002
The Scottish Medicines Consortium summary on the proposal for introduction of Zoledronic Acid in hormone refractory metastatic prostate cancer states that there is "a reduction in skeletal related events compared to placebo" It was the opinion of the SMC that this risk reduction of 36% for the first skeletal related event and 40% for the second event on multi-event analysis was insufficient to allow introduction of Zoledronic acid into standard practice.
In the light of the SMC decision and the evidence quoted, the BOC has drawn up the following protocol for Zoledronic acid use in HRPC in an attempt to standardise treatment within the department and to try to target therapy to those most likely to benefit.
References:
1. Groot, M.T, et al. Costs of Prostate Cancer Metastatic to the Bone in Netherlands.
Eur. Urol.2003;43:226-232
2. Saad et al. A Randomised, placebo controlled trial of Zoledronic acid in patients with
hormone refractory metastatic prostate carcinoma.
J. Natl Cancer Inst.2002;94:1458-1468
3. Lipton A et al. The new bisphosphonate , Zometa decreases skeletal complications in
both osteolytic and osteoblastic lesions: a comparison to Pamidronate. Cancer invest.
2002; 20: 45-55

Co-repressor complexes as targets for epigenetic therapy

Lyndon M. Gommersall, Henry S.O. Coulter, Asad Abedin, Donna M. Peehl, Alan P. Doherty, Nicholas D. James and Moray J. Campbell,

Introduction

Prostate epithelial cells express a broad complement of nuclear receptors including not only the androgen receptor but others which have an overt role is sensing nutrient and xenobiotic factors. For example, normal prostate epithelial cells are acutely sensitive to the antiproliferative action of several micro and macro nutrients such as the active forms of vitamins A and D. Often prostate cancer cell lines and primary cultures display suppressed sensitivity to these factors. We hypothesized that epigenetic mechanisms in prostate cancer cells suppress the ability of anti-mitotic nuclear receptors to transactivate key antiproliferative target genes thereby resulting in insensitivity to environmental signals. To dissect these relationships we have focussed on the vitamin D_3 receptor (VDR) and peroxisome proliferator activated receptors (PPAR).

Materials and Methods

In silico and *in vitro* protocols measured receptor levels, for example quantitative reverse transcription real time PCR (Q-RT-PCR) to measure PPAR and VDR mRNA levels and three known associated co-repressors (NCoR1, NCoR2/SMRT and Alien). Normal prostate epithelial cells (PrEC), cancer cell lines (LNCaP, PC-3 and DU-145) and primary cultures of prostate cancer (n = 12) and normal peripheral zone (n = 8) were examined. Receptor/co-repressor complexes were targeted with histone deacetylase (HDAC) inhibitors, either sodium butyrate (NaB), Trichostatin A (TSA) or Suberoylanilide hydroxamic acid (SAHA) in combination with nuclear receptor ligand. Parallel studies used siRNA approaches. The effects of these treatments were explored by proliferation and apoptosis studies, microarray approaches and target gene regulation by Q-RT-PCR.

Results

We found *in silico* that normal prostate epithelial cells express a rich compliment of at least 14 nuclear receptors, including FXR, LXR□ and ERR□ which provide a hitherto unsuspected local nutrient-sensing capacity. Cancer cell lines and primary cancer cultures frequently expressed significantly elevated NCoR2/SMRT levels, which correlated with reduced antiproliferative sensitivity for example to the VDR ligand $1,25(OH)_2D_3$. Thus 8/12 primary tumour samples had elevated NCoR2/SMRT mRNA levels (mean 4.2 fold increase); generally NCoR1 and Alien were infrequently elevated (3/12 and 2/12 respectively). Furthermore the antiproliferative action of a wide range of nuclear receptor ligands can be dramatically and significantly enhanced by co-treatments of ligand plus low doses of either NaB, TSA of SAHA. Interestingly cell fates differed. Thus treatments of $1,25(OH)_2D_3$ plus HDACi induced apoptosis, whereas PPARγ ligands plus HDACi resulted in type II (autophagic) non-apoptotic programmed cell death. cDNA microarray and gene expression studies confirmed the unique and significant up regulation of a number of antiproliferative target genes including MAPK-APK2 and GADD45 alpha. Supportively primary cancer cultures with elevated NCoR2/SMRT demonstrated suppressed GADD45 alpha induction compared to matched normal controls. Subsequently we knocked-down NCoR2/SMRT levels in PC-3 cells using siRNA resulting in a 95% reduction in the basal levels of SMRT mRNA after 72 hr, and found that GADD45 alpha induction by $1,25(OH)_2D_3$ alone became very significantly enhanced

Conclusions

These data demonstrate that the nuclear receptor co-repressor NCoR2/SMRT is commonly elevated in prostate cancer cells and drives transcriptional and therefore cellular insensitivity to a broad portfolio of nuclear receptor ligands. Individual molecular diagnostic profiling of early stage cancers will highlight individuals who would respond to targeting the co-repressor complex either through pharmacological or nutritional intervention.

Novel anticancer properties of pomegranate extracts; suppression of proliferation, invasion and xenograft growth of human prostate cancer cells

Lyndon M. Gommersall, Martin Albrecht, Ephraim P. Lansky EP, James Kumi-Diaka Moray J. Campbell,
Divisions of Medical Sciences *[LMG, MJC]*, University of Birmingham Medical School, Edgbaston, Birmingham. B15 2TH, Institute of Anatomy and Cell Biology, Philipps University, Marburg, GERMANY [*MA*], Division of Science, College of Liberal Arts, Florida Atlantic University, Davie, Florida, USA [*JKD*], Rimonest Ltd., Science Park Technion, Nesher, ISRAEL [*EP*]

Background

We have investigated the effects of several Pomegranate fruit (*Punica granatum)* extracts on the proliferation of normal, benign hypertrophic, and malignant prostate cells.

Methods

Cell proliferation and cell cycle analyses combined with staining of apoptotic cells were used to determine the effects of cold-pressed seed oil (*Oil*), fermented juice polyphenol fractions (*W*) and aqueous pericarp extract (*P*) on prostate cells. To evaluate changes in the gene expression profile following extract stimulation, we performed real-time RT-PCR studies. *In vitro* cell invasion assays and xenograft experiments were performed to test the influence of pomegranate extracts on cell invasion and metastasis.

Results

Oil, *W* and *P* all acutely inhibited *in vitro* proliferation of LNCaP, PC-3 and DU 145 cancer cell lines. The dose of *P* required to inhibit cell proliferation of the prostate cancer cell line LNCaP by 50% (ED_{50}) was 70 micro g/ml, whereas normal prostate epithelial cells (hPrEC) were significantly less affected (ED_{50} 250 □g/ml).

These effects were mediated by changes in both cell cycle distribution and induction of apoptosis. For example, the androgen independent cells DU 145 cells showed significant increase from 11% to 22% in G_2/M cells ($p<0.05$) by treatment with *Oil* (35 micro g/ml) with a modest induction of apoptosis. In other cell line and treatment combinations the apoptotic response predominated, for example PC-3 cells treated with *P*. These cellular effects coincided with rapid changes in mRNA levels of gene targets. Thus, 4 hr treatment of DU 145 cells with *Oil* (35 micro g/ml) resulted in significant 2.3 fold upregulation of the cyclin dependent kinase inhibitor $p21^{(waf1/cip1)}$ ($p<0.01$) and 0.6 fold downregulation of c-*myc* ($p<0.05$). In parallel, all agents potently suppressed PC-3 invasion through Matrigel, and furthermore *P* and supercritical CO_2 extracted pomegranate seed oil (*S*) demonstrated potent inhibition of PC-3 xenograft growth in athymic mice.

Conclusions

Overall this study demonstrates significant *in vitro* and *in vivo* antitumor activity of pomegranate-derived materials against human prostate cancer.

The potential use of Kerr gated Raman spectroscopy to diagnose prostate cancer.

Hart Prieto M. C, Crow P, Matousek P*, Parker A. W*, Wright M, Ritchie A. W, Stone N.
Gloucestershire Royal Hospital
*Central Laser Facility, Rutherford Appleton Laboratory

Introduction:
Raman spectroscopy is an optical technique that is able to interrogate biological tissues. In doing so it gives us an understanding of the changes in the molecular structure that is associated with disease development. The Kerr gating Technique uses a picosecond pulsed laser as well as fast temporal gating of inelastically (Raman) scattered light. The scattered light is collected at various time delays following the laser pulse. In utilising these techniques it was felt that Raman spectroscopy could be used to not only distinguish between pathologies within the prostate gland, but also to depth profile the prostate gland thereby increasing their potential use in vivo.

Materials and Methods:
The samples used for this study were taken following fully informed consent and ethical approval. Prostate samples were obtained by taking a chip at TURP. The samples were then snap frozen in liquid nitrogen and transferred to an -80°C freezer for storage. The samples were passively warmed and then scanned on an Optimised Raman System (Renishaw System 1000), to obtain in vitro Raman spectra. The prostate sample was placed onto a cell containing urea and then scanned. The Kerr gating system is based on the high throughput 4 picosecond optical Kerr shutter that was described in previous publications by Matousek et al (1, 2), and was used for depth profiling.

Results:
The spectra obtained as we go through the prostate gland tissue and on to the urea cell, clearly show the change in the spectra. The first 3 spectra are clearly tissue spectra with peaks at 1445cm-1 and 1650cm-1, which are consistent with protein peaks. The 4th spectrum has lost a lot of the signal and then in the following spectra the urea peak is clearly seen at 1003cm-1, and there is a loss of the protein peaks that are consistent with tissue.

Conclusion:
We have shown for the first time that we are able to obtain spectra from different depths through the prostate gland. This has major implications in the future of Raman spectroscopy as a tool for diagnosis. Up until now we have been able to distinguish between different pathologies within the prostate gland by sampling the tissue in vitro. This involves only looking at the surface of the sample. The prostate gland is usually biopsied via the rectum. This is a painful procedure and can give false negatives. With the help of Raman spectroscopy and Kerr gating we potentially would be able to pick up the spectral differences from a small focus of adenocarcinoma of the prostate gland in an otherwise benign gland.

References:
1. Matousek et al. Appl.Spectrosc 1999; 53: 1485.
2. Matousek et al. J. Raman Spectrosc 2001; 32: 983.

Prostate brachytherapy using the Bard Proseed technique: The Northampton experience.

RB Kunkler*, CRW Bell*, P Goldie, S Duggleby, T Hall*, C Elwell#.
Departments of Urology*, Oncology# and Medical Physics
Northampton General Hospital NHS Trust

Introduction
Prostate brachytherapy is an increasingly used option for the treatment of clinically localised prostate cancer. Advances in software design have led to the development of intraoperative dosimetry planning allowing radioactive seed implantation to be performed without the need for a separate volume study and preoperative planning. We report our initial clinical results and dosimetry data using the Bard Proseed technique for I125 seed implantation in a consecutive series of 55 patients.

Method
From May 2002 patients with clinically localised prostate cancer opting for brachytherapy were prospectively assessed preoperatively, with International Prostate Symptom Score (IPSS), sexual dysfunction score (SDS) and uroflowmetry. Patients were started on tamsulosin before implantation. Brachytherapy was performed under general anaesthesia according to the Bard Proseed technique. The urethral catheter was removed on completion of the procedure. The patient was discharged the following day when satisfactory voiding was achieved. Patients were followed up with PSA, IPSS, SDS and flow rate tests 3 monthly intervals for the first year, and subsequently at 6 monthly intervals thereafter. A CT scan of the prostate was performed 6 weeks after the implant in order to calculate post-implant dosimetry.

Results
55 patients (clinical stage T1c to T2c) with a mean age of 63 years (range 52 – 77) underwent treatment. The mean prostate volume was 38cc (range 14 – 88cc) The mean PSA fell from a pre-implant level of 7.8ug/L to 1.8, 1.3, 1.2, 0.9 and 0.8ug/L at 3, 6, 9, 12 and 18 months respectively. The mean pre-implant IPSS of 6.9 rose to 15 three months after implantation and subsequently subsided to 11.9, 10.6, 6 and 5.8 at 6, 9, 12 and 18 months respectively. The mean pre-implant SDS of 24 changed to 15.8, 22, 24.1, 24.8 and 24.6 at 3, 6, 9, 12 and 18 months respectively. Three patients required a catheter for longer than 2 weeks and 2 of these have subsequently resumed satisfactory voiding. No patient has yet required a TURP. Only one patient has developed significant (Grade 2) rectal toxicity.
All patients achieved the prescribed intraoperative (160Gy) and postoperative (140Gy) minimum dose to 90% of the prostate (D90). Mean doses achieved were 192 and 175Gy respectively. No patient exceeded the maximum intraoperative dose to 30% of the urethral volume (Urethral D30). The mean postoperative Urethral D30 was 229Gy, with 16 patients exceeding the proscribed limit. However has not been reflected in increased urinary symptoms in this group.

Conclusion
Prostate brachytherapy using the Bard Proseed technique has achieved excellent dosimetric results in all patients with a predictable fall in PSA to a nadir after 12 months. Urinary symptoms are universally increased following the implantation, but return to the pre-implant level by one year. Rectal toxicity is negligible.

Novel Prenylation Inhibition in Prostate Cancer *In Vitro*.

Richard Khafagy[1,3], Trevor Stephens[2], Claire Hart[1], Mick Brown[1], Noel Clarke[1,3]
[1]ProMPT Genito Urinary Cancer Research Group, Cancer Research UK, Paterson Institute, Christie Hospital NHS Trust, Manchester, UK.
[2]AstraZeneca, Alderley Park, Macclesfield, Cheshire, UK
[3]Department of Urology, Hope Hospital, Salford Royal Hospitals NHS Trust, Manchester,

Introduction:
There is a requirement for novel chemotherapeutic agents in the prevention or treatment of bone metastases in prostate cancer. AZD3409 is a novel oral *ras* protein prenyl transferase inhibiting both the Farnesyl Transferase pathway and the Geranylgeranyl escape pathway, with significant theoretical advantages over existing prenylation inhibitors.
Materials and Methods:
The anti-proliferative effect of escalating doses of AZD3409 on malignant PC-3 and LNCaP and non-malignant PNT2-C2 cell lines were tested in culture. Proliferation of isolated primary prostate epithelial cells from patients undergoing TURP was also quantified. PC-3 and PNT2-C2 cell colony formation was measured in co-culture using long-term human bone marrow stroma in the presence of escalating doses of AZD3409. The effect of AZD3049 on prostatic cellular invasion through matrigel (synthetic basement membrane) and through a cultured endothelial monolayer was also determined in invasion chambers using cytokeratin labeled quantitation of migrating cells. A mix assay system was employed to determine the effect of AZD3409 on haemopoietic progenitor colony formation.
Results:
AZD3409 displayed marked anti-proliferative properties on the PNT2-C2, PC-3 and LNCaP prostate epithelial cell lines. There was an IC_{50} of 9.81nM, 73.85nM and 22.06nM respectively after 3 days of exposure to AZD3409. There was also significant inhibition of primary BPH epithelial cells after 3 days of exposure, with an IC_{50} of 278.7nM. AZD3409 inhibited invasion through bone marrow endothelium towards bone marrow stroma, with an IC_{50} of 31.0nM, levels known to be attainable *in vivo*. AZD3409 also inhibited PC-3 colony formation in primary human bone marrow stroma. Co-cultures grown in the presence of escalating drug concentrations resulted in reduced numbers of colonies (IC_{50} of 160.2nM) and reduced epithelial colony size (IC_{50} of 59.9nM). AZD3409 had no significant effect on bone marrow progenitor colony formation and no statistical significance between counts of any of the drug doses or the controls was demonstrated (p=0.227).
Conclusions:
AZD3409 is a potent inhibitor of malignant and non-malignant prostate epithelial cell proliferation. AZD3409 is a potential anti metastatic agent inhibiting prostate epithelial cell invasion towards bone marrow stroma and inhibiting colony formation within bone marrow stroma.

The role of Serotonin (5HT) and 5HT antagonists in prostate cancer
E Siddiqui, M Shabbir, C Thompson, D P Mikhailidis, F Mumtaz
Department of Surgery/Chemical Pathology, Royal Free Hospital and University College Medical School, University College London, Pond Street, Hampstead, London. NW3 2QG.

Introduction
The ability of prostate cancer to survive androgen withdrawal therapy has led to a search for alternative pathways for control of tumour growth. Data indicates an increase in neuroendocrine cells in malignant prostate tissue. These cells release growth factors including neuropeptides and biogenic amines which are correlated to tumour progression, androgen independence and poor prognosis.
Serotonin (5HT) a monoamine neurotransmitter mediates a wide range of physiological activities by binding to receptor subtypes. We evaluated the effect of Serotonin (5HT) and 5HT receptor subtype antagonists on the growth of prostate cancer.
Materials and Methods
PC3 cells (androgen independent human prostate cancer) were obtained from the American Type Culture Collection. The cells were plated in serum supplemented growth medium at 5000 cells per well in 96 well plates. Drugs were added after 24 hours. The effect of Serotonin (5HT) and 5HT receptor antagonists on PC3 cell line was studied via colorimetric assay using crystal violet and was read using a spectrophotometric plate reader. Readings were done at 72 hours after addition of drugs.
Results
The 5HT receptor subtype antagonists used were 5HT1A, 5HT1B, 5HT1D, 5HT2, 5HT3, 5HT4. There was no 5HT1C receptor antagonist available. 5HT1B antagonist has a dose dependant growth inhibitory effect on PC3 cells inhibiting 78% (n=12, $P< 0.05$) cell growth at a concentration of 10^{-4}M at 72 hours. 5HT1A antagonist has a 20% (n=12, $P<0.05$) growth inhibitory effect on PC3 cells at the same concentration at 72 hours. The remaining 5HT receptor subtype antagonists had no effects on cell growth. Serotonin (5HT) caused a dose dependant cell proliferation leading to a 15% (n=12, $P<0.05$) increase in cells at a concentration of 10^{-8}M as compared to control at 72 hours.
Conclusion
Serotonin (5HT) leads to proliferation of prostate cancer cells whereas the 5HT1B receptor antagonist and to a lesser extent 5HT1A receptor antagonist have a growth inhibitory effect. Therefore, our results of growth inhibition of human prostate cancer cells by serotonin antagonists in vitro have suggested that 5HT antagonists, in particular 5HT1B receptor antagonist should be studied in detail as an anti-neoplastic agent.

Risk of cancer on follow-up biopsy following a diagnosis of prostatic intra-epithelial neoplasia on core biopsy.
Cane P, Kirby R, Corbishley C
St George's Hospital London

Introduction:
Prostatic intra-epithelial neoplasia (PIN) is associated with synchronous invasive carcinoma. The aim of our study was to quantify the rate of invasive carcinoma on follow-up core biopsy after an initial diagnosis of PIN. We also investigated factors that could predict the presence of invasive cancer i.e. Number and bilaterality of involved cores at initial diagnosis and PSA level.
Materials and Methods:
We identified a total of 57 patents who had PIN diagnosed by octant core biopsy between 2000 and 2003 in our department and had undergone follow-up biopsies.
Results:
28% (16 of 57) cases showed invasive cancer on follow-up biopsy. The rate rose to 40% (8 of 20) if more than one core was involved at initial biopsy and to 50% (8 of 16) if cores from both sides of the prostate were positive at initial biopsy. No significant predictive value was found for PSA and PSA Density values at time of initial biopsy. In 46% (26 of 57) of cases, the repeat biopsy showed PIN but no invasive cancer. Eleven of these cases went on to have a third set of biopsies, 2 of these showed invasive cancer and 4 contained further PIN.
Conclusion:
We confirm the presence of PIN in core biopsies carries a significant risk of there being concurrent invasive tumour, particularly if more than one core and cores from both sides of

the gland contain PIN. PSA values were not useful in predicting the presence of cancer.

The effect of ethnicity on PSA failure following radical retropubic prostatectomy.

C.J. Luscombe, J.G. Young, P.G. Ryan
City Hospital, Birmingham

Introduction:
There are no reported UK data concerning the effect of ethnicity on PSA failure following radical therapy for prostate cancer, and data from other countries are conflicting.
Materials and Methods:
The study group comprised 98 Caucasians and 28 Afro-Caribbeans who had a radical retropubic prostatectomy (RRP) performed by one surgeon between 1997 and 2003. Data were retrospectively collected. The statistical significance of variables on the time to PSA failure was calculated using Cox's regression. PSA failure was defined as a post procedure PSA>0.1ng/ml.
Results:
Pre-operative PSA was higher in the Afro-Caribbean group (p=0.013); median=15ng/ml, compared with 9ng/ml, however there were no differences in Gleason score>6, positive margin rates, seminal vesicle involvement (SVI), extra-capsular extension (ECE), perineural invasion or age. 20% of patients developed PSA failure during follow-up with an excess in the Afro-Caribbean group (Fisher's exact test, p=0.03). However, the mean follow up was longer for Afro-Caribbeans (834 days compared to 694). To control for this, time to PSA progression was studied. Only 3 of the variables listed above were significant independent predictors of time to PSA failure; Gleason score>6 (p=0.007, Hazards Ratio (HR)=3.2, 95% Confidence Interval (95%CI)=1.4-7.5), ethnicity (p=0.012, HR=2.9, 95%CI=1.3-6.6) and ECE (p=0.008, HR=3.1, 95%CI=1.3-7.1). In a multivariate analysis of all the variables, ethnicity was again a significant predictor (p=0.012, HR=4.5, 95%CI=1.4-14.5), as was positive margin rate (p=0.042, HR=2.6, 95%CI=1.0-6.4).
Conclusion:
These data confirm well-established predictors of PSA failure following RRP. Furthermore they demonstrate a significant association between ethnicity and time to PSA failure.

A comparison of the multidisciplinary team approach to men with clinically localised prostate cancer in two West London hospitals, and the difference in their choice of radical treatment

E Rowe *, O Karim+, A Pope*, M Laniado+, H Motiwala+,
J Maher*, V Mishra+, S Niewiorwski*
Wexham Park Hospital +, and Hillingdon Hospital *

Introduction
The aim of this study was to compare the Multidisciplinary Team approach (MDT), and treatment choices, of men with clinically localised prostate cancer in two West London Hospitals.
Materials and Methods
Men with clinically localised prostate cancer deemed suitable for radical treatment by the MDT panel where included in the study. A telephone interview was conducted in which men were asked the reasons for their treatment choice, and their attitudes towards the MDT approach. The results were compared between the two institutions.
Results
Thirty two men (mean age 63.3 years, mean PSA 8.2ng/ml) from hospital A were compared with 29 men form hospital B (mean age 62.9 years, mean PSA 7.4ng/ml). Seventy five percent of men underwent surgery at hospital A, compared to 52% at hospital B. All men from hospital A saw both an oncologist and a surgeon compared to 79% at hospital B. Twenty five percent of men at hospital A saw a cancer nurse specialist compared to 76% at hospital B. Ninety four percent of men at both institutions liked the MDT approach.
Conclusion
In this cohort of identical groups of men with localised prostate cancer the majority of men liked the MDT approach, but the process differs in different institutions, as does the outcome in terms of treatment.

The BAUS Cancer Registry – An inaccurate reflection of the proportion of histologically-confirmed prostate cancer in clinical practice?

B Patel[1], R Persad[2]
(Departments of Urology, Bristol Urological Institute[1], and Bristol Royal Infirmary[2])

Introduction
Histological confirmation of prostate cancer should be the "gold standard". However, in clinical practice, patients are sometimes diagnosed and treated in the absence of histological confirmation. Such a "clinical diagnosis" on the basis of an elevated PSA, high suspicion on DRE or other positive imaging may be a reasonable approach. The BAUS Cancer Registry Database (2002) states that 93.2% of the recorded cases of prostate cancer have histological confirmation. Individual hospitals record the diagnosis of prostate cancer on the Patient administration system (PAS) or Hospital Episode Statistics (HES).
This study investigates the rates of histological confirmation of prostate cancer in clinical practice, makes comparisons with the BAUS Cancer Registry and evaluates the reliability of a diagnosis of prostate cancer on the hospital PAS database.
Materials and methods
A retrospective study of 54 consecutive, newly diagnosed cases of prostate cancer recorded on the PAS database at a tertiary referral centre. The hospital histology database and PAS were searched in order to identify newly diagnosed and recorded cases of prostate cancer respectively. The results of both were then cross-referenced. The case notes of the identified patients were then examined to determine the basis for the diagnosis, and the relevant investigations.
Results
The PAS list identified 54 new cases of prostate cancer, 37 of which featured on the histology database. On case note review, 2 of the patients identified as having prostate cancer on PAS did not, in fact, have the disease and had been wrongly listed due to coding inaccuracies. The histology database identified 39 cases. 1 case had their histology omitted from the histology database. 2 patients with histological confirmation did not feature on the PAS list. 14 patients had a clinical or non-histological diagnosis of prostate cancer. Our rate for histological confirmation was 74.1%, with 25.9% of patients having no histological confirmation. The reason for the absence of confirmatory histology in these cases was usually high clinical suspicion in an elderly and frail patient, who, consequently, was not subjected to prostate biopsy. The PAS system had a sensitivity of 96.3%, with

a positive predictive value of the same. The sensitivity of the histology database was 72.2%.

Conclusion

Our rate for histological confirmation of prostate cancer (74.1%) is well below the figure quoted by the BAUS Registry, and reflects actual clinical practice where we are not registering many such cases. This may be partly explained by the fact that many consultants who submit to the BAUS Registry rely on their histology departments to prompt registration of new patients. Patients with a non-histological diagnosis may therefore be omitted from the registry as would patients primarily under the care of a non-urologist. We need to improve the registration of non-histologically confirmed prostate cancer cases by the BAUS Registry, and suggest that a combination of the hospital PAS or HES databases and the histology database be used in order to identify new cases and prompt registration.

Ultrasonic Shears in Open Radical Retropubic Prostatectomy

McCabe JE, Javle PM
Michael Heal Department of Urology, Leighton Hospital, Crewe

Introduction

Ultrasonic Shears (USS) are a cutting and coagulating surgical instrument. The device operates at a frequency of 55.5kHz through the conversion of electrical to acoustic energy. The advantages of the device are the reduction in lateral thermal tissue damage, combined cutting and coagulation in the same device and greater precision near vital structures. The instrument is used primarily in laparoscopy. We tested its use, by direct comparison with traditional methods of dissection and haemostasis, in open radical retropubic prostatectomy (RPP).

Materials and methods

Patients undergoing RPP were assigned to two groups and either underwent the procedure with the aid of the USS (*Autosonix, Tyco Healthcare*) or by traditional methods of haemostasis (control). The groups were analysed according to blood loss, operative time, post-operative complications and hospital stay. Blood loss was calculated by peri-operative drain loss and swab weight. Total transfusion was also recorded.

Results

Forty patients were analysed, of whom 22 underwent RRP in the control group (mean age 63, mean prostate weight 43.5g) and 18 in the USS group (mean age 59, mean prostate weight 76.8g).

There was a significant decrease in mean peri-operative blood loss with the USS group from 1392.5ml (control) to 587.5ml ($p<0.001$). This is reflected in a reduction of mean transfusion from 0.8 to 0.0 units. Operative time was improved with *Autosonix* from a mean of 195.3 to 175.6 minutes ($p=0.02$). Hospital stay also showed a reduction from 5.3 to 4 days ($p<0.001$).

Conclusion

This preliminary study strongly suggests that the use of the ultrasonic shears in RRP reduces blood loss, operative time and hospital stay.

Measuring tissue mechanical characteristics to assess malignant prostatic disease

S. Phipps[1], T.H.J. Yang[2], F.K. Habib[1], R.L. Reuben[2], S.A. McNeill[3]
[1]Prostate Research Group, University of Edinburgh, Western General Hospital, Edinburgh, UK.
[2]School of Engineering and Physical Sciences (Mechanical Engineering), Heriot–Watt University, Edinburgh, UK.
[3]Department of Urology, Western General Hospital, Edinburgh, UK.

Introduction

The mechanical behaviour of biological tissue shows a combination of viscous and elastic elements. Tissue mechanical properties can be derived by measuring the alterations to an energy wave passed through the sample. Using a novel test method, we sought to establish whether differences exist between benign and malignant prostatic tissue specimens assessed *in vitro*, and whether these were related to differences in tissue morphology.

Materials and Methods

Fresh tissue specimens were collected from patients undergoing TURP, 11 for benign (BPH) and 11 for malignant (PCa) prostatic enlargement. Using a specially designed test rig, individual TURP chippings underwent immediate mechanical testing, by applying a dynamic compressive strain to the samples. The amplitude ratio ($|E^*|$) and phase difference ($\tan \delta$) between the energy waves entering and arising from the tissue, measures of tissue elastic and viscous components respectively, were derived.

Individual sections from the processed specimens underwent immunohistochemical staining and computerised image analysis was used to measure the morphological characteristics of each TURP chipping. Mean values for each prostate were then calculated. Unpaired t-test assuming equal variances was used to compare the mechanical and morphological characteristics of BPH and PCa prostates and linear regression analysis was used to assess correlations between morphological and mechanical measurements.

Results

There were significant differences between the morphology of the BPH and PCa prostates. There was a significantly greater epithelial tissue (ET) content within the PCa prostates ($p=0.01$), which was composed of glandular acini whose mean area was significantly smaller than within the BPH prostates ($p=0.0008$). Tan δ was significantly smaller within the PCa prostates ($p=001$). There was no difference between the BPH and PCa prostates with respect to $|E^*|$. Within the PCa prostates, there was a strong negative correlation between the ET content and tan δ ($R^2=0.58$, $p=0.001$).

Conclusions

This study shows that measurable differences exist between the mechanical characteristics of benign and malignant prostates. These differences reflected the composition of the tissues, and there were significant correlations between prostatic tissue morphology and its mechanical characteristics. The ability to quantify prostatic tissue mechanical characteristics *in vivo* may allow the detection of malignancy, and by reflecting the volume and grade of the malignant tissue present, may aid in the staging of PCa. We therefore believe that this approach may be of clinical benefit in the future assessment malignant prostatic disease.

Laparoscopic vs. open radical retropubic prostatectomy — peri-operative cost comparison and experimental predictive model for costing at a tertiary U.K. referral centre

Sashi Kommu, Suril Patel, Mark P Wright, Raj A Persad
Bristol Urological Institute, Bristol, U.K.

Introduction

Laparoscopic radical prostatectomy (LRP) is becoming a gold standard treatment for localised prostate cancer in many units. Very few studies have looked at the economic impact of LRP despite the need for validation of this relatively new technique from a health economics point of view. The aim of our study was to perform a detailed comparison of the perioperative costs of patients undergoing laparoscopic radical prostatectomy and open radical retropubic prostatectomy (ORP) and to develop a predictive model for estimation of perioperative cost applicable in a U.K. setting.

Materials and Methods

A retrospective cost review was done of a cohort of randomly chosen cases from a database pool of radical prostatectomies performed during a 36-month period. 15 cases were selected from the LRP group and 15 from the ORP group. The hospital costs were evaluated for each patient using the categories of anaesthetic consumables, surgical consumables, post operative analgesia, antibiotics, blood units transfused and post operative days on ward. We omitted factors such as personnel fees and operating room time as these are not standardised and are subject to wide variability often only partially reflective of the actual procedure. We also developed a predictive model for estimation of cost and tested its applicability in predicting costs at two independent hospitals using their database of 2 LRP and 2 ORP cases.

Results

The median perioperative costs for surgical consumables were LRP=402.27 GBP vs. ORP=184.87 GBP.

The median perioperative anaesthetic consumables cost was LRP=225.15 GBP vs. ORP=168.84 GBP. Postoperative analgesia cost was LRP=10.13 GBP vs. ORP=14.43 GBP. There was no difference in antibiotic costs in the two groups (9 GBP). The cost of transfusing one unit of blood in the U.K. is 122.28 GBP. The transfusion rate for ORP was (2/15=13.3% i.e. average of 16.26 GBP per patient) vs. (1/15=6.7% i.e. average of 8.13 GBP) in the LRP group. The days of stay post op were LRP =2.7 vs. ORP 3.8. The median perioperative costs of patients undergoing LRP (662.81 GBP) were higher than ORP (393.40; P = 0.001). Our prediction model was able to estimate that on average a LRP will cost 1.7 times more than ORP using specific fixed variables. [GBP-Great Britain Pound]

Conclusion

Our study shows that the standard costs of LRP are greater than ORP by a factor of 1.7 if total hospital admission time is excluded. If hospital time spent is included the patient who undergoes ORP stays on average (3.8/2.7) 1.4 times longer than the LRP patient. The offset in costing as a result of the longer admission time in ORP depends on individual cost of a room per day. Our findings are reflective of some United States studies, which found that the cost of LRP is greater than ORP by a factor of approximately 1.5. The differences between open and laparoscopic radical prostatectomy remain to be fully defined in terms of long term oncological and qality of life outcomes but we feel that we have made a contribution in defining the procedure that places greater financial stress on NHS resources in the current health economic climate. Large-scale studies are needed to further validate our preliminary findings. Our cost prediction model may aid in defining some of the cost parameters and act as a template to build upon for further improvements in costing.

Periprostatic infiltration of local anaesthetic during transrectal ultrasound-guided biopsy of the prostate in an office based setting-the analgesic efficacy in a typical U.K. District General Hospital

Sashi Kommu, Amit Dhulkotia, Ravee S Surange, Vincent Gonzales and Neeraj K Sharma
The Royal Oldham Hospital, The Acute Pennine Hospitals NHS Trust. Oldham.

Introduction

Transrectal ultrasound (TRUS) guided needle biopsy of the prostate is the standard procedure to diagnose prostate cancer. With the current exponential increase in the number of men being biopsied to rule out prostate cancer, pain control and patient comfort are of major concern. Most published studies regarding use of local anaesthetic (LA) during TRUS biopsy were done in specialist centres in the past. The aim of this study was to test the analgesic efficacy of periprostatic infiltration of local anaesthetic during TRUS biopsy of the prostate and to look at complication rates in a typical U.K. district general hospital in an office based setting.

Materials and Methods

This was a prospective clinical trial in which a total of 308 patients were studied. Patients were sequentially allotted into two groups. In one group all men received a total of 15 mL of 1% lidocaine in the lateral and apical periprostatic regions, 5 mL in each point, approximately 10 minutes before the prostate biopsy. The other group received no analgesic. Pain after each biopsy (a total of 8-12 biopsies) was assessed using a 10-point linear visual analog pain scale to record visual analogue pain scores (VAS). We also looked at immediate and late complications associated with the procedure by establishing a nurse specialist lead follow up network.

Results

Patients who received LA had significantly lower pain scores compared to those not given analgesic. The relative risk of patients not given LA feeling pain was 2.9 (95 % confidence interval 2.3-3.6 ; P<0.00001) compared to those not receiving analgesic. There was no significant difference in complication rates between the two groups.

Conclusion

Periprostatic infiltration of LA significantly decreases pain in TRUS guided biopsy of the prostate with no additional risk of complications. We advocate the routine use of this procedure in all patients to improve patient comfort and tolerance. This study also shows that the procedure can be done safely and effectively in a district general hospital office based setting.

PSA test, how much non urologists know?

Mr Bashar Zelhof, Mr AJ Browning, Mr CS Biyani
Pinderfields General Hospital, Mid-Yorkshire NHS Trust
Wakefield

Introduction

The measurement of prostate specific antigen has contributed to the startling increase in the number of cases of prostate cancer diagnosed in the late 1980s. It was soon recognised that although PSA was sensitive, it lacked specificity. Concerns have being raised regarding the over-diagnosis of prostate cancer resulting

from widespread PSA testing. Therefore various guidelines [(1)] have been established regarding PSA test.
Between 1st of January 2003 and 30th of November 2003, 8350 PSA test were requested in the pathology department of Mid-Yorkshire NHS Trust. We noticed that 544 tests were requested on patients older than 85 years and 123 tests on patients less than 35 years of age.
We investigated the level of awareness hospital-doctors and GPs regarding the PSA guidelines.
Aim:
To improve the quality of PSA requests and reduce the overall costs.
Methods
PSA questionnaires were sent by post to most GPs in Wakefield region, and were handed personally to most hospital-doctors in the relevant specialities (General Medicine, Care of Elderly, General Surgery and Orthopaedics), by attending departmental meetings.
The questionnaire was designed to ask clinician on PSA indications, normal levels, false positive, digital rectal examination in conjunction with PSA, awareness of guidelines and discussion with patients.
We received **141** replies (52/70 GPs and 89/89 hospital doctors).
Results:
Most doctors know about the definition of PSA and its role in prostate cancer, however, factors that influence PSA and cause false positive results were not appreciated by majority of the respondents. 68% of the respondents were not aware of rise in PSA following instrumentation.
Only 48% of hospital doctor perform DRE with PSA request as compared to 69% of GPs.
60% of overall doctors discuss the test with their patients (92% GPs Vs 41% of hospital doctors).
Knowledge of PSA guidelines among hospital doctors was low (10%), in contrast 61% of GPs were aware of the guidelines.
Conclusion:
In the light of our results we feel that continuing medical education on PSA is very important to minimise patient's anxiety and to make it more cost effective.
References
1) British Association of Urological Surgeons and the Royal College of Radiologists' Clinical Oncology Information Network. Guidelines on the management of prostate cancer, section 1.2 and 1.3.

Molecular biopsy for Prostate Cancer using Carbonic Anhydrase *XII* Quantitative RT-PCR
C. P. Pipinikas[1], S. B. Nair[1, 2], R. S. Kirby[2], N. D. Carter[1] and C. D. Fenske[1]
[2]St George's Hospital and [1]Medical School, London SW17.

Introduction
The sensitive molecular technique, reverse transcriptase-polymerase chain reaction (RT-PCR), has been shown to detect prostate cells in peripheral circulation. Potential markers for CaP have been assessed for their accuracy in diagnosis. The hypoxia-inducible factor-1 (*HIF*-1) transcriptional complex is thought to be an important mediator of gene expression in tumours (Ivanov *et al.*, *PNAS* 1998; 95:12596-12601) The tumour–associated isozyme, carbonic anhydrase XII (CA*XII*), is known to be tightly regulated by this complex. The involvement of *CAXII* in the acidification of the extracellular milieu (Ivanov *et al.*, *PNAS* 1998; 95:12596-12601) may contribute to the formation of a microenvironment, conducive to tumour growth and spread. Using RT-PCR and quantitative RT-PCR (qRT-PCR), *CAXII* was analysed as a potentially accurate marker in the diagnosis and monitoring of prostate cancer development/progression.
Methods
Total RNA was extracted in quadruplet from blood taken from 112 patients. *CAXII* gene expression was analysed by RT-PCR and qRT-PCR using the LightCycler™ (Roche).
Results
RT-PCR results showed *CAXII* expression in patients diagnosed with benign prostatic hyperplasia (BPH, 5/7), localised CaP (LocCaP, 66/70) and metastatic CaP (MetCaP, 31/35). However, obvious differences in product band intensities were further investigated using qRT-PCR. Using relative qRT-PCR, mean *CAXII* expression was calculated to be 118.5 (BPH -10 patients), 703.9 (LocCaP-8 patients) and 40.1 (MetCaP-18 patients). *CAXII* expression in the LocCaP group was 6-fold higher than that of the BPH group and 18-fold higher than that of the MetCaP group. No correlation between *CAXII* expression and PSA/Gleason scores was found. No *CAXII* expression was demonstrated in female/male control patients.
Discussion
Our results demonstrate upregulation of *CAXII* expression in the LocCaP group and down regulation in the MetCaP patient group. The majority of MetCaP patients were hormone refractory. As *CAXII* is hypoxia-induced (via *HIF-1*), this would indicate that hypoxia is a mechanism involved in CaP development. However, down regulation of *CAXII* in MetCaP patients, indicates a possible alternative pathway that overrides the hypoxia-induced mechanism in hormone refractory end-stage CaP. *CAIX*, another hypoxia-induced carbonic anhydrase isozyme has been shown to demonstrate a similar expression pattern, being upregulated in well-differentiated gastric tumours, and down regulated in poorly differentiated tumours (Leppilampi *et al*. Abstract 6th Int. Conf. Carbonic Anhydrases June 2003 P14). qRT-PCR is an extremely sensitive, accurate technique for measuring expression of candidate CaP markers. *CAXII* is a potentially excellent molecular marker in routine clinical diagnosis and prognosis of CaP. Furthermore, *CAXII* is a potential target for therapy as it can be selectively and specifically inhibited by acetazolamide.

Summer Audit of TRUS Guided Prostate Biopsies
A MacLeod, J McKnight, C Hagan
Belfast City Hospital

We audited our prostate biopsy clinic for a period of 4 weeks starting from the 17 May 2004. The aims of this audit were to delineate the population demographics, referral patterns and waiting times for the clinic. The positive biopsy rate, complication rate and patient satisfaction were also worked out.
Method
All of the patients attending the clinic during the auditing period were asked to participate while consent was being obtained. All agreed to inclusion. The biopsies were taken as normal, using the same ultrasound probe for all biopsies, by 5 different operators After informed consent was obtained, the patient was given 120mg gentamycin. The patient then had a DRE, followed by an examination with ultrasound. Under ultrasound guidance 10mls of 1% lignocaine was infiltrated around the prostate. Biopsies were then taken. Following the procedure the patients were given 500mg metronidazole PR and 3 days of ciprofloxacin 500mg bd PO. The patients were asked to keep a record of any

complications, and this data was retrieved by a phone call several weeks later.

Results

Over the 4 week period 44 patients were given appointments to attend for biopsies. 38 biopsies were carried out. 3 were not able to be contacted for collation of results. Biopsies were taken on patients aged 46 to 88, the majority aged from 56 to 80. 15 were referred direct by the GP, 16 from clinic and 12 from other consultants who did not carry out biopsies as part of their practice. Most patients waited from 60 to 100 days. Positive biopsy rate was 55%. 22 of the patients had no pain to mild pain during the procedure. 8 had moderate and 5 severe pain. Most patients found pain was limited to the procedure, although 5 had pain for some hours and 7 for longer than 24hrs. 77% had haematuria (70% of which settled within a few days), 40% had blood PR (70% settled within one day) and 34% haematospermia which generally took several weeks to settle. A small number noticed flow problems (although a similar number noted improvements), dysuria, or signs of infection. One gentleman suffered a stroke after being off clopidogrel for 14 days and was the only patient to require admission due to the procedure. He still had dysphasia several weeks after the stroke.

Conclusions

The waiting time for prostate biopsies is far too long. All should be seen within 2 weeks. However, the waiting list is falling and will fall further with the addition of an extra list. In the 4 week period 4 procedures were cancelled because PSAs were not checked after being sent from clinic, 1 because he was still on clopidogrel, and one patient did not attend. Furthermore, 2 were biopsied who already had tissue diagnoses. Efficient utilisation of appointments is paramount, perhaps with utilisation of a database. Complications were expected and in most cases short duration with minimal impact on patients. The patient who had a stroke has prompted discussion about prophylaxis with other agents while off anti-platelet drugs and warfarin. Also most patients suffered little pain but those who did may benefit from more lignocaine. Also, a longer acting agent also may reduce the numbers of patients with pain post-procedure. Further audits are planned with regard to differing local anaesthetic agents and doses.

Effect of very low fat diet on progressive prostate cancer: experience from a dedicated clinic

J. Philip*‡, B. Rogers*, J.S. Grime§, N.J. Parr*
*Department of Urology, Wirral Hospital CH49 5PE and
§Department of Pathology, Royal Liverpool University Hospital, L7 8XP

Introduction

Total dietary fat has been associated with an increased incidence and mortality from prostate cancer (CaP). Animal models with implanted human CaP cell lines have reported arrest of growth in those changed to a very low fat diet (VLFD, <20% fat). We offered such a diet to patients with progressive CaP.

Patients and Methods

Over 4 years, 22 patients with good performance status undergoing either active surveillance (n= 8) or hormonal manipulation (n= 14), with biochemical evidence of disease progression (2 successive PSA interval rises) adopted VLFD. Fat-soluble vitamins were supplemented. Patients were reviewed 3-monthly in a dedicated nurse specialist clinic assessing body mass index (BMI), PSA, PSADT, PSA velocity, lipid profile and quality of life (QoL). PSA was log transformed as rapid cancer proliferation shows log linear growth.

Results

Mean age of the patients was 70.1yrs (range 59-80) with a PSA range of 3.5 –43.6 ng/ml on commencing VLFD. Mean follow-up was 54.8 wks (range 10-152). 16 patients were diagnosed with well/ moderately differentiated CaP (Gleason score $\leq$ 6) with six having poorly differentiated CaP (Gleason score <6). There was no significant difference in age between the groups. Patients with well/ moderately differentiated showed a significant increase in PSA doubling time (PSADT) [p= 0.037] and a reduced PSA velocity. Half of the patients with poorly differentiated CaP had a prolonged PSADT [Table 1]. BMI showed no significant change, but serum cholesterol fell significantly ($p<0.05$). Patients felt subjectively better on VLFD with only two reporting restricted QoL.

Conclusion

These early results are encouraging and suggest that in men with progressive prostate cancer, VLFD results in reduction in the rate of PSA progression with significant prolongation of PSADT in patients with well/ moderately differentiated CaP. A good QoL is also maintained. This merits further multi-centre studies involving larger populations.

Table 1: PSA doubling time Vs. Gleason Score

Tumour grade	No. of patients (improved PSADT)	PSADT before diet Mean (months)	PSADT after diet Mean (months)	p value ($p<0.05$)
Well/ Moderately differentiated (Gleason score $\leq$ 6)	16 (12)	13.14	49.87	0.037
Poorly differentiated (Gleason score >6)	6 (3)	11.22	10.34	0.976

PSA – what's that doc?

Priya Agrawal, Jonathan Olsburgh, Jeremy Elkabir
Northwick Park and St Mark's Hospitals

Introduction

There is an increasing incidence of PSA (prostate-specific antigen) screening in Primary Care.

Screening for prostate cancer with PSA is still controversial. Thus professional guidelines stress the importance of patients making informed decisions, based on an awareness of the potential risks and benefits related to testing. The aim of this study was to assess whether new patients attending Rapid Access Prostate Clinic had enough understanding to have given informed consent for the PSA test to be done. Did they understand?

- the role of the PSA test
- why it was checked in their individual case
- The implications of a positive PSA test.

Materials and Methods

All new patients referred to a special Rapid Access Prostate Clinic who had their PSA tested in Primary Care were asked to complete a questionnaire, under the supervision of a nurse, before their scheduled appointment. This was done over a period of five

months. The first 15 questionnaires were used as a pilot study resulting in a modified questionnaire. The patients were asked about their knowledge of the PSA test, where from and in what form this information had been given to them and their occupational background.

Results

Of 78 eligible patients, 76 completed the questionnaire. Only 22 patients (29%) felt they knew what PSA is. The other 54 patients (71%) were either not sure (12) or did not know (42) what PSA is. 72% of these 54 patients could not recall an explanation having ever been given, the other 28% was divided amongst those that had received a poor explanation (18%) or had forgotten the explanation (10%). Of the 22 patients that felt they knew what PSA is, only 58% knew that a high PSA indicated the possibility of prostate cancer and only 17% knew of the implications of a positive PSA test e.g. TRUS biopsy. In 46% of cases, the GP had offered the test. In the majority of cases (61%), the patient had presented with trouble with their waterworks. Only 12% remember having pre-test counselling and only 1 patient received any written information.

Conclusion

Men are being tested for prostate cancer in Primary Care without informed consent. The majority do not understand what PSA is, what its role is, or the implications of the test and thus cannot make an informed decision. This seems to be irrespective of age and occupational background.

Considering that prostate cancer is estimated to be the most common cancer in UK men by 2005, we recommend that there should be an increase in patient information made available **prior** to PSA testing. This information can be written and/or verbal. The latter can be from dedicated nurse practitioners, perhaps holding prostate awareness clinics in Primary Care. This has significant implications for Primary Care teams; however we believe that the benefit of empowering the patient will be reaped by both the patients and the health service.

Microstaging of carcinoma of the prostate: can biopsy findings predict if a tumour is clinically insignificant?

Alison Yates, Rhidian Hurle, D L Cochlin, H G Kynaston, D F R Griffiths
Departments of Urology, Radiology and Pathology, University Hospital of Wales, Cardiff.

Introduction

There is no consensus as to the correct treatment for a man with organ confined prostate cancer. A significant minority of tumours detected by PSA screening are clinically insignificant (less than 0.5ml tumour volume) and offer minimal risk to the patients . If these tumours could be identified then it would be appropriate to advise surveillance in these patients. In theory accurate sampling of the gland by a biopsy protocol should allow assessment of tumour volume but previous attempts at this have show poor predictive value, possibly because either variation in biopsy technique or suboptimal histological processing. The aim of this study was to determine if reasonable prediction of tumour size by biopsy findings was more likely in the context of consistent biopsy practise and meticulous histological processing.

Method

Analysis of prostates from 151 consecutive radical prostatectomy operations from patients who had previously had sextant or more biopsies that had been performed by one of two radiologists having a special interest in the biopsy technique. Biopsy specimens has been processed for histology in separate cassettes, embedded flat and three levels cut from each block. On average 15mm of core was examined from each sample. Radical prostatectomy specimens had been fully embedded and the volume of tumour estimated from the dimensions of the smoothed ellipsoid enclosing the tumour. Number of positive cores, maximum length of adenocarcinoma in a core (MLA), and RRP tumour volume had been recorded in each case.

Results

There was a strong correlation between both the number of cores positive and the MLA with the tumour volume and stage. 27 (18%) tumours had a volume of 0.5ml or less. 80 cases had a MLA on biopsy of ≤4mm and 71 cases had a MLA of >4mm. For the cases with a MLA of ≤4mm, 25 (32%) had a tumour with a volume of ≤0.5ml. For the cases with a MLA of >4mm, 2 (3%) had a tumour with a volume of ≤0.5ml. 29 cases had only a single core positive and an MLA of ≤4mm, of these 15 (52%) had clinically insignificant tumours.

Conclusion

With consistent biopsy technique and meticulous histological processing biopsy findings can predict tumour size. This microstaging could probably be improved if analysis was limited to octant biopsies or more and if PSA level, biopsy Gleason grade, and imaging findings are also taken into account. Future reports examining the predictive value of biopsies should give full details of biopsy technique and histological processing.

Inhibiting Prostate Cancer cell growth by the new technique of RNA interference on the emerging gene TSG101.

N C Borley, G Zhu, I R Hart, G H Muir
King's College and St Thomas' Hospitals, London.

Introduction

The gene TSG101 was originally defined as a tumour suppressor gene, raising the expectation that absence of the encoded protein should lead to increased tumour cell growth. There has been conflicting evidence as to the gene's function and the role it plays in cell growth. We have specifically inhibited the gene by RNA interference to study it's function.

Material and Methods

The technique of RNA interference (RNAi) was used to downregulate the gene TSG101 in PC3 (prostate cancer) cells. 2 controls were used, one with exactly the same cell handling, the other with "scrambled" RNA causing interference. Protein levels were detected by Western Blotting. The effect of this on the cells was examined with growth curves, colony formation assays, invasion and migration assys, and BUDR labeling to examine the cell cycle.

Results

An approximately 94% selective downregulation at the protein level was achieved. This treatment resulted in marked inhibition of tumour cell growth. The decreased level of TSG101 protein caused partial cell cycle arrest at the G1/S boundary. Additionally, RNAi-mediated downregulation of TSG101 reduced the colony forming capacity of the cells by approximately 89%. This treatment did not result in any effect on the migration or invasion behaviour of these cells.

Conclusion

These results firstly demonstrate the effects of the highly powerful technique of RNA interference. They also show that the TSG101 gene does not comply with the usual characteristics of a tumour suppressor gene that it had been thought to be. But rather that its expression may be necessary for activities associated with

aspects of tumour growth, having implications for both prostate and other cancers.

Silencing of the type 1 insulin-like growth factor receptor (*IGF1R*) gene enhances sensitivity of prostate cancer to DNA damaging agents through impaired homologous recombination

MA Rochester[1,2], BW Turney[1,2], SF Brewster[2], VM Macaulay[1]
[1]Molecular Oncology Laboratories, Weatherall Institute of Molecular Medicine, Oxford, UK; [2]Department of Urology, Churchill Hospital, Oxford, UK

Introduction

The IGF1R is overexpressed in prostate cancer, and IGF signalling enhances protection from apoptosis. Silencing the *IGF1R* gene by RNA interference leads to impaired survival of prostate cancer cells *in vitro*, and enhanced sensitivity to therapies which cause double-strand DNA breaks, but not to those which kill by other means, suggesting a link between IGF signalling and DNA repair. Previous work in our laboratory has shown decreased activation of ATM after IGF1R downregulation by antisense. ATM orchestrates the DNA damage response, and is the product of the gene mutated in Ataxia Telangiectasia. We wished to determine if the differential chemosensitisation in prostate cancer cells was a result of altered ATM function, and/or a direct effect on DNA repair.

Materials and Methods

We used oligofectamine to transfect IGF1R siRNAs or inverted sequence controls into two prostate cancer cell lines: DU145 (androgen-resistant, wild type *PTEN*), and PC3 (androgen-resistant, *PTEN* mutant). ATM function was measured by an ATM kinase assay, and response to double-strand DNA breaks induced by ionising radiation was assessed by pulsed-field gel electrophoresis (PFGE). DNA repair was evaluated directly using previously described *in vitro* assays of non-homologous end-joining (NHEJ) and homologous recombination (HR).

Results

Transfection with 200nM siRNA inhibited IGF1R expression to 15-20% of control levels. This treatment led to impaired ATM activation after 20 Gy irradiation, shown by a kinase assay. Pulsed field gel electrophoresis analysis revealed delayed DNA repair in siRNA-treated DU145 cells at time-points up to 6 hours after irradiation. *IGF1R* gene silencing had no effect on NHEJ, but in both PC3 ($p<0.001$) and DU145 ($p<0.05$) this led to approximately 50% reduction in ability to repair by HR.

Conclusion

IGF1R targeting by siRNA inhibited ATM kinase activity, in keeping with our previous report of impaired DNA damage responses following IGF1R downregulation. The delayed DNA repair up to 6 hours after *IGF1R* silencing shown by PFGE is not consistent with an ATM defect alone, since ATM null cells have normal kinetics of DNA repair at this time. We showed that siRNA treatment had no effect on NHEJ, but led to significant impairment of homologous recombination repair in both PC3 and DU145, suggesting a link between IGF signalling and the HR machinery. These results have implications for the choice of combination therapies when IGF1R targeting strategies reach the clinic.

A randomised controlled trial of topical glyceryl trinitrate for transrectal ultrasound-guided prostate biopsy

MA Rochester[1,2], K Le Monnier[2], SF Brewster[2]
Molecular Oncology Laboratories, Weatherall Institute of Molecular Medicine, Oxford, UK; [2]Department of Urology, Churchill Hospital, Oxford, UK

Introduction

Transrectal ultrasound-guided (TRUS) biopsy is the standard method of diagnosis of carcinoma of the prostate. Studies have shown decreased pain associated with this procedure following local anaesthesia. Many patients find anal distension to be the most painful part of their procedure, for which local anaesthetic infiltration has little benefit. Topical glyceryl trinitrate (GTN) paste is commonly used for the treatment of anal fissure. The mechanism of action is through reduced anal sphincter tone. We evaluated the efficacy and tolerance of topical 0.2% GTN paste versus placebo to reduce pain associated with TRUS biopsy.

Materials & Methods

Between October 2003 and April 2004, 134 consecutive patients referred for first prostate biopsy were randomised to receive either topical 0.2% GTN paste or placebo 30 minutes prior to biopsy. Participants completed a 10 point visual analogue pain score following the procedure. Pulse and blood pressure were recorded before and during the procedure.

Results

The mean age of the patients was 68.5 years for the GTN group and 68.8 for placebo. There was a significant decrease in mean pain score in the GTN group compared with placebo (3.7 versus 4.8, $p=0.0016$). There were no significant changes in pulse or blood pressure between the groups. 6 patients (10%) in the GTN group complained of headache.

Conclusions

Topical GTN paste is an effective and well tolerated method of reducing pain associated with transrectal ultrasound guided prostate biopsy. It is a safe and easy to use alternative to other methods and should be offered to patients undergoing this procedure.

Pathologists estimation of percentage carcinoma in radical prostatectomy specimens – A literature review and a grid method for calculation

Clare Verrill, Paul Strike, Clare Fuller.
Histopathology Department, Salisbury District Hospital, Salisbury.

Introduction

We reviewed the literature in an attempt to determine whether volume of prostatic adenocarcinoma is an independent prognostic variable for disease recurrence after radical prostatectomy. Percentage surface area of gland infiltrated by adenocarcinoma in radical prostatectomy specimens is routinely recorded within proforma standardised reports at Salisbury District Hospital. It is not a data item within the RCPath minimum dataset for prostate cancer. We wished to find an easy, reliable and time efficient method of measuring percentage surface area of tumour.

Materials and Methods

We compared 3 methods of measuring percentage surface area of gland infiltrated by adenocarcinoma in radical prostatectomy specimens; using a microscopic $1mm^2$ grid counting, macroscopic $10mm^2$ grid counting and visual estimation by pathologist without aid of a grid. We reviewed the literature using medline.

Results
The microscopic 1mm^2 grid, shown to be as accurate as computer assisted morphometry (Humphrey *et al, Mod Pathol* 1997;10:326-33) took 90 minutes per case. The macroscopic 10mm^2 grid took 10 minutes per case. The 2 methods gave similar results. Pathologists unaided by a grid were up to 25% out in their estimation.
Literature review showed that many of the published studies did not contain enough subjects to enable reliable interpretation of the results. Of the studies containing sufficient subjects, 2 showed that percentage carcinoma is an independent predictor of recurrence (Ramos *et al*, *J Urol* 2004; 172: 137-140 and Carvalhal *et al*, *Cancer* 2000; 89:1308-1314) and 2 showed that tumour size (as determined by alternative methods) is an independent prognostic factor (Renshaw *et al, Anat Pathol* 1999;111:641-644 and Stamey *et al, JAMA* 1999;281:1395-1400). 1 showed that tumour size was not an independent prognostic factor (Epstein *et al, J Urol* 1993; 149:1478-1481).
Conclusion
Literature review has found evidence that percentage surface area of carcinoma is an independent prognostic factor for disease recurrence after radical prostatectomy. We therefore recommend that this measurement is an essential data item for inclusion in histopathology reports. We have described a quick method which provides an accurate measurement and could be used in everyday practice.

Palliative pelvic exenteration for advanced prostate cancer.
S B Ganta, H Yamamoto, DA Ashdown, DMA Wallace.
University Hospital Birmingham, Birmingham, UK.

Introduction
Locally recurrent prostate cancer is debilitating with significant local symptoms. Pain associated with rectal involvement of the prostate disease is difficult to palliate using conventional techniques. We describe 6 patients who underwent a pelvic exenteration for palliation of advanced prostate cancer.
Materials and Methods
We retrospectively reviewed the data of six patients who underwent palliative exenteration and diversion for prostate cancer between 1986 and 2002. Patients were selected for total pelvic exenteration based on clinically advanced prostate cancer with intractable symptoms despite hormone treatment and radiotherapy. The median follow up was 25.7 months (range 12.1-47.2 months). Data were collected regarding cancer therapy, pain requirements prior to surgery, complications, symptom free survival and overall survival.
Results
The mean age prior to surgery was 68.4 years (range 62-78 years). The mean duration between diagnosis and operation was 5.1 years (range 4.3-6.9). The mean preoperative PSA was 31 (range 0.1-173). All patients had had radiation therapy to the pelvis and androgen deprivation treatment. One patient had prior radical retropubic prostatectomy. Surgery included total pelvic exenteration followed by an end colostomy and ileal conduit urinary diversion. The rectum was spared in one patient. There was no post operative mortality. The median symptom free survival was 12 months (range 4-36 months). The median overall survival was 25.7 months (range 12.1-47.2 months). Three patients died of disease progression and two died of other causes without disease progression and one is alive with disease progression.
Conclusion
Pelvic exenteration effectively palliated symptoms of advanced local recurrence for a median period of 12 months with acceptable post operative morbidity. It is an effective treatment in selected patients in experienced hands with multidisciplinary care.

'Laparoscopic' extraperitoneal retropubic prostatectomy; the Birmingham experience.
S B Ganta, D Ashdown, H Yamamoto A Doherty.
University Hospital Birmingham, Birmingham

Introduction:
Laparoscopic techniques for many urological procedures are now well established. Radical prostatectomy performed with minimal invasive surgery by an extraperitoneal route overcomes the limitations and complications entering the peritoneum and is similar to the most commonly performed open operation.
Patients and methods:
67 patients with clinically organ prostate cancer underwent a 'laparoscopic' extraperitoneal radical prostatectomy performed by one surgeon between June 2003 and November 2004. A modified 'Stolzenburg technique' [1] was utilized with nerve-sparing and a more reproducible bladder neck and urethral dissection. Prospective data collection of the grade, stage and volume of cancer, co-morbidity, intra and post operative complications.
Results:
The median (range) age was 65.2 (46-73) years, median PSA 7.0 (2.5-16) ng/mL, Gleason sum 7 (3+4), operative time was 240 (135-391) min, blood loss 375 (100-1800) mL and hospital stay after LRP 4.2 (2-26) nights. Nerve preservation was performed in 28% of patients. One patient required transfusion. Three patients were converted to an open procedure. There were six complications, rectal injury in two cases (one required a colostomy and the other had a successful intra-operative laparoscopic repair). Bladder neck stenosis, persistent urinary leak from drain, pulmonary embolus and paralytic ileus. The positive surgical margin rate reduced to 18% in the last 20 patients. Follow up was a mean 7.2 months (1-17.6). By 3 months 84 % of patients were pad-free. There have been two biochemical failures.
Conclusion:
Learning curve relates to perfecting a technique, training assistants and making best use of the equipment. Several technical modifications have been introduced. Prospective data collection allows for early identification and correction of problems and improvements in outcome. In addition to the standard benefits of minimally invasive surgery, the extraperitoneal approach mimics the open approach and offers improved visualization. We believe that this technique is safely performed by the oncologist who is familiar with the open technique.

The IGF1R/IRS1 axis and PI3K/PKB signalling in prostate cell lines
Jennifer C. Spalton, Norman J. Maitland & R. Michael Sharrard,
University of York

Introduction
Insulin-like growth factor 1 (IGF1) signals through the IGF1 receptor (IGF1R) to stimulate phosphatidylinositol 3-kinase

(PI3K) activity and subsequent phosphorylation and activation of protein kinase B (PKB). Insulin receptor substrate 1 (IRS1) is an important mediator of PKB activation as it acts as an adaptor between the activated IGF1R and PI3K. The PKB pathway is of particular interest with respect to prostate cancer as elevated plasma IGF1 levels are thought to have a positive correlation with the disease (Chan *et al*. *Science* 1998; 279: 563-566 ; Chokkalingam *et al. The Prostate* 2002; 52:98-105)**,** and deregulation of the PKB pathway, through the loss of the PTEN tumour suppressor gene, is one of the most common events in prostate cancer progression (Cairns *et al. Cancer Res.* 1997; 57:4997-5000; Li *et al. Science* 1997; 275:1943-1947).

Materials and methods

The expression and activation of key components of the PKB pathway were analysed in five prostate epithelial cell lines – non-malignant PNT2C2 and PNT1a, early tumour P4E6, and the LNCaP and PC3 metastatic cancer cell lines. Reverse transcription-PCR, Real-time (quantitative) PCR, immunoprecipitation and western blotting were used to assess the levels of expression of IGF1R and IRS1 in the prostate cell lines. The effects of IGF1 and the PI3K inhibitor LY294002 on IRS1 protein levels and PKB activation were determined by western blotting, using specific antibodies against IRS1, Phospho-PKB (Thr308 and Ser473), and total PKB. siRNA was used to determine the impact of IGF1R and IRS1 inhibition on PKB activation.

Results

Metastatic prostate cancer cell lines show reduced expression of IGF1R at both the mRNA and protein level when compared with the non-metastatic cell lines. The lack of full-length IRS1 protein in LNCaP was found to be caused by a single base deletion that results in the premature termination of the sequence. IRS1 protein levels are differentially regulated in the cell lines: IGF1 induced degradation of IRS1 protein in PNT2c2, PNT1a and P4E6, but this was not observed in PC3. PKB was still activated on IGF1 treatment even when the expression of IGF1R or IRS1 was inhibited by siRNA.

Conclusions

These results suggest that deregulation of IRS1 may contribute to the constitutive activation of PKB during prostate cancer progression through a positive feedback loop. Our results also highlight the potential for crosstalk between cell signalling pathways and signalling through alternative receptors or adaptor proteins.

Genotype and expression profiling of prostate cancer stem cells

Steven D. Bryce[1], Anne T. Collins[1], Mike J. Stower[2],
Norman J. Maitland[1]
[1]*YCR Cancer Research Unit, Department of Biology, University of York, York YO10 5DD*
[2]*Department of Urology, York District Hospital, York YO31 8HE*

The target cell for malignant conversion in prostate cancer remains to be definitively identified. The cancer stem cell model postulates that mutations occur only in stem cells.

We have previously shown that prostate stem cells express high levels of integrin $\alpha_2\beta_1$ and the haematopoetic stem cell marker CD133. These cell surface markers can be exploited to select cell populations highly enriched for stem cells.

We have recently identified that such $\alpha_2\beta_1^{High}$/CD133$^+$ cells comprise a small quantity of cells derived from prostate cancers (on average <0.01%). Furthermore these cells are maintained at a constant proportion in the primary cell cultures obtained from these tumours. As part of our ongoing studies to characterize these cancer stem cells we are using Affymetrix Mapping 10K 2.0 SNP arrays to derive comprehensive and detailed genotypes from the isolated tumour $\alpha_2\beta_1^{High}$/CD133$^+$ cells and matched lymphocyte controls. This in depth data is used to build up patterns of genomic loci loss in the cancer stem cells. In addition we are obtaining comprehensive gene expression profiles, using Affymetrix U133 plus 2.0 GeneChips, from the same cells.

This will enable us to map characteristic regions of gene loss and identify with fine precision (sub mega-base resolution) novel losses in clonal cell populations. The linking of comprehensive LOH profiles to the gene expression profiles will generate a unique depiction of the genetic changes underpinning this the development of this disease and provide solid evidence that these cancer stem cells are the targets for malignant transformation events.

Alterations in the expression and activation pathways of Protein Kinase B and its isoforms in the progression to metastasis of human prostate cancer

R. Michael Sharrard and Norman J. Maitland,
University of York

Introduction:

Progression to invasiveness and metastasis in epithelial tumours is characterised by cell growth and survival independent of growth factors (GFs) and cell-cell and cell-matrix contact. These functions are modulated by Protein Kinase B (PKB/Akt), activated by PIP3 generated by phosphatidylinositol 3-kinase (PI3K). Enhanced survival of metastatic prostate tumour cells has been linked to deregulation of PKB activation through loss of the tumour suppressor protein PTEN, which normally functions as an antagonist to PI3K by degrading PIP3. Protein Kinase B has multiple isoforms encoded by three separate genes (AKT1, AKT2 and AKT3), though until recently little has been established about the regulation and role of these isoforms. In this report we examine the expression of three major isoforms of PKB and their activation by growth factors during the progression to metastasis of prostatic cancer.

Materials and methods:

PNT2 and PNT1a (prostatic non-tumour epithelial), P4E6 (early prostatic tumour) and LNCaP and PC3 (metastatic prostate tumour) cell lines were grown in the medium containing serum, then transferred to serum-free medium overnight. 10μM LY294002 (PI3K inhibitor) or vehicle (DMSO) were added for 2 hours, followed by treatment with 5 ng/ml EGF or IGF1. Cells were then harvested and analysed by Western blotting for expression and phosphorylation of total PKB or its specific isoforms. Cells were also transfected with expression constructs encoding the three PKB isoforms and their capacity to activate the different isoforms in the presence or absence of GFs and LY294002 was analysed by Western blotting and immunocytochemistry.

Results:

Using these cell lines, we previously demonstrated that prostate tumour cells show reduced dependence of PKB/Akt activation on GFs or substrate adhesion, concomitant with enhanced sensitivity to the PI3K inhibitor LY294002. Our present investigations show that the different cell lines express different profiles of PKB isoforms, and the relative and absolute levels of these isoforms determines the phosphorylation status and total PKB activity present in these cells in response to GF stimulation.

Overexpression of exogenous PKBisoforms results in their hyperphosphorylation at serine 473 and also causes increased phosphorylation of endogenous PKB at this residue. Unexpectedly, this hyperphosphorylation was both independent of GF stimulation and resistant to inhibition by the PI3-kinase inhibitor LY294002. This indicates one mechanism by which overexpression of individual PKB isoforms may lead to increased activity in the other isoforms of this signalling kinase.

Conclusion:

Prostate cancer progression involves complex alterations to signalling pathways regulating proliferation and survival. The elucidation of the mechanisms by which alterations in the pattern of PKB isoform expression may lead to escape from normal dependence on growth factor- and cellular adhesion-dependent signalling provides a further step in understanding the basis of this progression. The possibility that altered expression of individual PKB isoforms may determine specific patterns of escape from normal growth constraints offers the exciting possibility that drugs designed against these isoforms may permit increased specificity of therapeutic targeting in the treatment of prostate cancers and their metastases.

High Intensity Focused Ultrasound (HIFU) for prostate cancer: The UK experience

I M Campbell, G N Collins, A A Adeyoju, R J Brough,
P H O'Reilly, S C W Brown.
Stepping Hill Hospital, Stockport, UK – On behalf of the North-West Uro-oncology Research Group

Introduction

High intensity focused ultrasound produces accurate tissue destruction of a target area without damaging the intervening tissues. It is emerging as an alternative treatment for several forms of cancer, including kidney, breast, bone and prostate. Stepping Hill Hospital is the first unit in the U.K. to introduce HIFU for the treatment of prostate cancer.

We describe the technique, practical aspects, efficacy and patient tolerability of HIFU treatment for prostate cancer in our own UK population.

Materials and Methods

A pilot study of 30 patients is in progress. The inclusion criteria are: biopsy proven prostate cancer, a PSA of <20ng/ml, a prostate volume of <40mls at baseline investigations, localized disease (T1/T2) and no contraindications to a 3-hour general or spinal anaesthetic. All are deemed to be unsuitable for radical surgery, through patient choice, anaesthetic or surgical factors. The patients receive either a general or a spinal anaesthetic. A preliminary channel TURP is performed. HIFU prostatectomy is then undertaken with the Ablatherm® device using a 3MHz transrectal probe. Serum samples are taken at baseline and at intervals post operatively to measure inflammatory markers, cardiac toxicity and PSA response. The flow rate and post-void residual are measured in all patients pre and post operatively. Quality of life issues are evaluated using IPSS and the UCLA prostate cancer questionnaire.

Results

Techniques, practical aspects, efficacy, governance and evaluation are described in detail.13 patients have been treated and their characteristics are as follows. Mean age 69 years, Gleason 3+3 (median) and a mean volume of 27cm^3. All patients had stage 1 or 2 disease with a mean PSA of 7.3ng/ml (range 3.4 – 17.3). 9 patients have reached 3 months follow up. There have been no intra-operative complications. The majority of patients were discharged on day 1 post operatively. All patients showed a PSA response with 5 out of 8 patients who received a complete treatment achieving a PSA less than 1.0 at 3 months. All patients had an elevated CRP post operatively, however this resolved in the majority by 1 week. 1 patient had an elevated Troponin T as a result of a pulmonary embolism. The QOL and IPSS scores had improved or remained static in 5 out of 6 responses so far.

Conclusion

This preliminary report of our very early experience suggests good tolerability and a promising initial PSA response.

Do type I receptor tyrosine kinases drive hormone refractory prostate cancer?

Dr J Edwards, Miss A F. Munro, Dr B Dunne, Miss C Pirrett,
Dr J. M.S. Bartlett.
Glasgow Royal Infirmary and University of Glasgow

Introduction

Relapse during androgen withdrawal therapy is a major cause of prostate cancer morbidity and mortality. Androgen receptor mutations (6-10%) and amplifications (20-30%) may explain relapse in some cases, however in approximately 70% of cases alternative mechanisms must be invoked. Our evidence suggests that type I receptor tyrosine kinases play a role in the development of hormone refractory prostate cancer.

Materials and Methods

Protein expression and activation of type I receptor tyrosine kinases was determined by immunohistochemistry in a cohort of matched tumour pairs (one taken before and one after hormone relapse) from 65 prostate cancer patients. Five antibodies were used, EGFR (Zymed), HER2 (DAKO HercepTestTM), phosphorylated EGFR (Cell Signalling), phosphorylated HER2 (Neomarkers) and EGFR VIII (Zymed). Detection and visualisation and was achieved using the LSAB$^+$ kit (DAKO Cytomation) and DAB (Vector Laboratories). Two independent observers using a weighted histoscore method scored each section.

Results

Tumour expression rates for EGFR and phosphorylated EGFR were low in both hormone sensitive (36% and 9%) and hormone refractory tumours (36% and 11% respectively), with no significant increase in expression or activation with the development of hormone refractory prostate cancer. Whilst expression rates were higher for HER2, phosphorylated HER2 and EGFR VIII no significant increase in median expression was observed with the development of hormone refractory prostate cancer (48% to 67.3 %, 43% to 42% and 100% to 100%).

Intriguingly, however, those patients whose tumours expressed low levels of phosphorylated HER2 in their primary tumour relapsed significantly earlier than those who expressed high levels of phosphorylated HER2 (0.039, Kaplan Meier).

By using matched tumour pairs we were able to identify patients, for each protein, whose tumours showed an increase in protein expression with the development of hormone escape, no change and or a decrease in protein expression. A change in protein expression was defined as an increase or decrease greater than the 95% confidence interval for inter-observer variation when comparing expression between pre and post hormone relapse cases.

Using this method time to death post hormone relapse, was markedly decreased for those patients with an increase in HER2 expression (15.4% of cases,0.004, Kaplan Meier), and an increase

in EGFR expression (7.7%, p=0.0004, Kaplan Meier), but not with phosphorylated HER2 (26.8%), phosphorylated EGFR (6.9%) or EGFR VII (10.3%)I. Almost 1/4 (23.1%) of cases showed increased HER2 or EGFR expression at hormone relapse, this was associated with a significant reduction in time to death from hormone relapse (3.00(1.75-4.25) versus 1.33(0.86-1.80), p = 0.0002, Kaplan Meier).

Conclusion

Increased expression of HER2 or EGFR appears to influence progression to hormone refractory prostate cancer in about a quarter of cases since a rise in HER2/EGFR expression at hormone relapse is associated with a significant reduction in time to death. These findings support the development of EGFR/HER2 targeted therapies in hormone refractory prostate cancer. We have demonstrated, using a carefully characterized patient cohort, that the EGFR/HER2 pathway may represent one of a number of independent routes to hormone escape in prostate cancer.

Transperitoneal or extraperitoneal laparoscopic radical prostatectomy: does the approach matter?

T. Gianduzzo, C. Chang and C. Eden.
North Hampshire Hospital, Basingstoke.

Introduction

Extraperitoneal laparoscopic upper tract surgery is associated with several advantages over its transperitoneal counterpart but is technically more difficult to perform. The situation with regard to laparoscopic lower tract surgery remains unclear.

Methods

The results of 100 cases of transperitoneal laparoscopic prostatectomy (TLRP) and 100 cases of extraperitoneal laparoscopic prostatectomy (ELRP) performed for ≤T3aN0M0 prostate cancer were compared.

Results

In-patient: mean values in TLRP & ELRP patients for operating time=239 & 191 (P <0.0001) minutes, blood loss=311 & 202 (P=0.02) ml, hospitalisation=3.8 & 2.6 (P <0.0001) nights.

Out-patient: mean values in TLRP & ELRP patients for follow-up=24.5 & 7.2 months, + margin=16% & 16%, pad-free rate at 1 year=90% & 96%, erection rate at 1 year=61% & 82%.

Conclusion

ELRP is superior to TLRP with respect to operating time, blood loss and hospitalization. Early oncological results are identical. Longer follow-up is needed to demonstrate differences in functional and results.

Multi-marker Quantitative RT-PCR Based Analysis of Blood and Bone Marrow in Prostate Cancer Patients

David Ross[1,3], Claire Hart[1], Iain McIntyre[4], Vijay Ramani[2], Mick Brown[1], Noel Clarke[1,2,3]
[1] ProMPT Genito Urinary Cancer Research Group, Cancer Research UK Paterson Institute, Manchester, UK
[2]Department of Urology, Christie Hospital NHS Trust, Manchester, UK
[3]Department of Urology, Salford Royal Hospitals NHS Trust, Salford, UK
[4]Department of Urology, Central Manchester Hospitals NHS Trust, Manchester, UK

Introduction

The natural history of prostate cancer (CaP) is difficult to predict. The key to appropriate treatment is detection of extra-prostatic disease. We have evaluated a quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) assay using a combination of established and novel molecular markers to detect small numbers of circulating prostatic cells in peripheral blood (PB) and bone marrow (BM).

Materials and Methods

Five nucleotide primers and probes were designed and optimised for PSA, prostate specific membrane antigen (PSMA), prostate stem cell antigen (PSCA), human kallikrein 2 (HK2) and DD3 using the LNCaP prostate cancer cell line. *In vitro* assay sensitivity was calibrated using dilutions of LNCaP cells in female PB. The PAXgene blood RNA system was optimised for PB and BM collection, storage and RNA isolation. Marker expression was quantified in serial dilutions and limits of detection determined using qRT-PCR. DD3 was also quantified using a plasmid construct. Paired PB and BM samples were then assayed from patients with well characterised CaP and compared with disease free controls.

Results

All five gene products were detected and quantified in LNCaP cells. Additionally, DD3 was detected in RNA derived from prostate biopsy samples. *In vitro* limits of detection were 1 LNCaP cell/10^5 nucleated cells for PSA and PSMA, 1:10^4 for PSCA and 1:10^3 for HK2. The DD3 assay could detect 100 copies of plasmid derived RNA/10^6 nucleated cells. Samples from 102 men with CaP and 38 healthy controls were evaluated. The qualitative results are presented below, detailing the percentage of samples reading positive for each marker in patients with different disease stages. Quantitation and threshold calibration of single markers levels and combinations of levels is currently awaited.

	PSA		PSMA		PSCA		HK2		DD3	
	PB	BM	PB	BM	PB	BM	PB	BM	PB	BM
Metastatic Escaped	100%	100%	57%	80%	29%	80%	86%	60%	29%	0
Clinically Localised	28%	33%	38%	81%	66%	79%	9%	12%	4%	2%
Controls	12%	14%	47%	86%	71%	93%	18%	0	0	0

Conclusions

We have developed a multi-marker qRT-PCR assay which can reliably detect the presence of spiked prostate epithelial cells in PB samples *in vitro*. Preliminary qualitative clinical data highlights the need for such a quantitative multi-marker technique the true clinical utility of which will be determined through further statistical modelling.

Prostatic biopsies in the over 80's: crucial or cruel?

Bott SRJ, Foley CL, Bull MD, Reddy CJ, Freeman A, Langley SEM
And contributing surgeons, nurse specialists and pathologists:
Davies JH, Emberton M, Kirby RS, Millroy EJG, Montgomery BS, Morgan RJ, Nigam AK, O'Donoghue EPN, Palfrey EL, Shridhar P, Pietrazic M, Higgins D, Denham P, Mannion E, Parkinson MC.
The Royal Surrey County Hospital, Frimley Park Hospital and The Institute of Urology, London

Introduction:
Prostate cancer is considered a tissue diagnosis commonly based on biopsy cores. Standard prostate biopsy has a reported minor complication rate of 60-79%, major complication rate of 0.4-4.4% and the need for hospitalisation in 0.4-3.4% of men (Norberg Eur.Radiol. 1996; 6: 457, Aus Br.J.Urol. 1996; 77: 851, Rietbergen Urology 1997; 49: 875, Rodriguez J Urol. 1998; 160: 2115-20) and infection risk increases with age (Lindert J Urol. 2000; 164: 76). This study examines whether prostatic biopsies are necessary in all men aged 80 or above.

Methods:
The pre-biopsy PSA, the DRE, the biopsy findings and staging bone-scan results of all men aged ≥80 years who underwent prostatic biopsies between 2000-2003 were reviewed. All biopsy samples had been examined in one of three histopathology units and thirty-three consultant urologists contributed.

Results:
211 men ≥ 80 years were identified, of whom 163(77%) had biopsy proven prostate cancer. 100% of 29 men with PSA ≥100, 98% of 47 with PSA ≥50, 97% of 77 with PSA ≥30 and 92% of 102 with PSA ≥20ng/ml had biopsy cores containing cancer. 63% of men with PSA <20ng/ml had cancer on biopsy. In men with cancer and a PSA ≥30ng/ml, 92% had Gleason grade ≥7and 93% were treated with antiandrogen therapy and /or pelvic radiotherapy. In all men with cancer the DRE was abnormal in 91%, the mean number of positive cores was 59% and the bone-scan was positive in 18%. The DRE was abnormal in 77% of men with benign biopsies.

Conclusions
In men ≥ 80 years with a PSA ≥30ng/ml, at least 97% had prostate cancer, over 90% of these men had high-grade disease and nearly all men with cancer received active treatment. The value of prostatic biopsy in this age group, with PSA ≥30ng/ml, is questionable.

Sensitive and non-invasive diagnosis of Prostate Cancer using *E2F3* quantitative RT-PCR

C. P. Pipinikas[1], S. B. Nair[1, 2], K. I. Konstantinou[3], R. S. Kirby[2], N. D. Carter[1] and C. D. Fenske[1]
[2]St George's Hospital and [1]Medical School, London SW17, [3]Department of Epidemiology and Public Health, Imperial College, Faculty of Medicine, London W2 1PG

Introduction
Reverse transcriptase-polymerase chain reaction (RT-PCR) is a sensitive molecular technique capable of detecting prostate cells in peripheral circulation. Quantitative RT-PCR (qRT-PCR) is an expansion of this technique, used to look at levels of gene expression. Potential markers for prostate cancer (CaP) have been assessed using qRT-PCR with the aim of more accurate diagnosis. *E2F3* gene, a member of the E2F family of cell cycle regulatory transcription factors (Oeggerli *et al. Oncogene* 2004; 23:5616-23) has been shown to be overexpressed in CaP, controlling proliferation rates and dictating CaP aggressiveness Furthermore *E2F3* directly modulates the expression of the *EZH2* gene, which also controls cellular proliferation and is up-regulated in CaP (Foster *et al. Oncogene* 2004; 23: 5871-9). Both genes, therefore, are potentially excellent candidate markers for CaP diagnosis. Using relative quantitative RT-PCR (qRT-PCR), *E2F3* and *EZH2* expression was analysed as potentially accurate markers for CaP.

Methods
Total RNA was extracted in quadruplet from blood taken from 110 patients. cDNA synthesis was carried out, followed by qRT-PCR using *E2F3* and *EZH2* gene specific primers and the LightCycler™ (Roche).

Results
Relative qRT-PCR for *E2F3* was carried out on four distinct patient groups, based on detailed clinicopathological information. *E2F3* expression showed highly significant differences between all patient groups (P<0.001): a 39-fold increase was found in the localised prostate cancer group (LocCaP: n=51;mean= 4.67) compared to benign prostatic hyperplasia group (BPH: n=8; mean=0.12). Levels in the metastatic prostate cancer group (MetCaP: n=23; mean =1.64) were lower than the LocCaP group, but still 14-fold higher than the BPH group levels. Of particular interest was the radical prostatectomy group (RP: n=18, mean = 4.08), which showed levels of *E2F3* expression similar to those of the LocCaP group. This would indicate the presence of tumour cells in peripheral circulation, suggesting undetected micrometastases. No *E2F3* expression was detected in male control samples (n=10). Preliminary results for *EZH2* showed a similar expression profile to that of *E2F3*, with significant up-regulation in CaP patients.

Discussion
The expression of *E2F3* has been shown to be highly up-regulated in prostate cancer. Results show that it can be used as a marker in accurate diagnosis of CaP using the non-invasive, sensitive technique of qRT-PCR.
E2F3 has been shown to directly modulate the expression of cellular proliferation genes, including *EZH2*, and is linked to *pRB*, a cell cycle protein (Huang *et al Nat Genet* 2003; 34:226-230). It is therefore possible that the *pRB-E2F3-EZH2* axis represents an underlying molecular mechanism involved in the development of CaP. This offers the potential of specific treatment based on patient's gene expression profile.

Prostate Cancer - The *MALE* Perspective

Michael G. Clarke, JRM Wilson, JD Graham, RP MacDonagh
Taunton & Somerset Hospital, Taunton

Introduction
It is essential when making judgements regarding the management of prostate cancer, that clinicians utilise both patient choice and life expectancy, in addition to the available clinical parameters. However estimations of life expectancy, based on co-morbidity, are often inaccurate and inconsistent. Whilst validated co-morbidity scores exist, these are often disease-specific and cumbersome to use. We therefore aimed to develop a computer software program that would enable clinicians (or other members of the multidisciplinary team) to accurately calculate an individual patient's life expectancy on the basis of their co-morbid factors, with the potential for use in the clinical and MDT setting.

Materials & methods
In collaboration with a professional actuary, actuarial tables were used in association with the 'numerical rating system' to derive mortality ratios. These evidence-based actuarial mortality ratios, which are used by the insurance industry and are continually updated in line with the available medical literature, are calculated on the basis of a patient's age, smoking habit and co-morbidity. They can therefore provide an accurate method of life expectancy assessment in patients with multiple co-morbid factors. 17 medical conditions were chosen, since they

significantly impacted on life expectancy and were relevant to >90% of patients seen in general urological outpatients clinics. A user-friendly computer program was then designed, in association with professional computer programmers, to enable easy access to this information via a PC and/or PDA. Using hypothetical patient scenarios, the program was tested to ensure ease of use and accuracy of results.

Results

A computer software model was developed: **Measure of Actuarial Life Expectancy (MALE)**. This was not only found to be user-friendly but also derived accurate results consistent with the actuarial tables integral to the program. The inputting of patient information, using the patient's case notes, enabled the calculation of 1) Predicted life expectancy (average number of years an individual of a given age is expected to live), 2) Percentage chance of survival to 5 years, 10 years and 15 years, 3) Graphical presentation of these results. The option to save these results and print reports was available. (NB *Screenshots and/or the computer program itself will be available if presented)*

Conclusion

This computer software provides an accurate and objective measure with potential for use in outpatient clinics and multidisciplinary team meetings. Research is ongoing to assess the impact of this life expectancy information on the management decisions of consultant urologists regarding patients with prostate cancer, as well as the patients' understanding of and their desire to know this information.

Functional analysis of domain specific zero function androgen receptor mutations in prostate epithelial cells

Richard Birnie and Norman J. Maitland
YCR Cancer Research Unit, Dept. of Biology, University of York

Introduction:

Androgen ablation is a powerful therapy for prostate cancer until the disease undergoes a transition to the hormone refractory form. In a subset of disease this may be achieved by mutation of the androgen receptor gene. Mutations are known to occur throughout the AR gene suggesting multiple mechanisms may exist to achieve androgen independence. We chose two previously characterised androgen receptor mutations found in prostate cancer to investigate the role of different protein domains in ligand sensitivity and AR trafficking. Specifically, a DNA binding deficient mutant (AR-C619Y) and ligand binding deficient mutant (AR-C784Y).

Materials and Methods:

Site directed mutagenesis PCR was used to introduce point mutations into the androgen receptor cDNA. Wild type or mutated androgen receptor cDNA in the episomal vector pCEP4 was transiently transfected into either PNT1A or PC3 prostate epithelial cell lines in which AR is under the control of a CMV promoter. Protein expression and localisation was assessed by western blot and fluorescent immunocytochemistry respectively 48h post transfection, during which period cells were exposed to hormones for the last 18h. The transactivation capacity of the different mutants was analysed using flow cytometry to measure activation of a promoter-EGFP reporter construct (PSA/Pb-EGFP).

Results:

Western Blot analysis showed that all three forms of AR are expressed at the predicted molecular weight in non-malignant PNT1A cells and in PC3 prostate cancer cells. The wild type protein is expressed at low levels in the absence of ligand in both cell lines and expression is increased by addition of DHT. The AR-C619Y and AR-C784Y mutants are expressed at high levels in PNT1A but show evidence of protein degradation whereas these proteins are constitutively low in PC3 cells. In the absence of ligand all three forms of AR show cytoplasmic localisation. When treated with DHT wild type AR translocates to the nucleus in both PNT1A and PC3 cells as does the AR-C619Y mutant. In the presence of the anti-androgen bicalutamide wild type AR and AR-C619Y undergo partial translocation to the nucleus while the AR-C784Y mutant remains cytoplasmic regardless of treatment. Wild type androgen receptor is able to induce EGFP expression in response to DHT treatment in a dose dependent manner in both PNT1A and PC3 cells, this activity is partially inhibited by bicalutamide. The AR-C619Y and AR-C784Y mutant androgen receptors are unable to transactivate the reporter construct.

Conclusion:

Transcriptional transactivation by the androgen receptor can viewed in terms of distinct functional modules directly related to the receptor structural domains. Disrupting the function of a single module can block the function of the entire receptor even if the other modules remain intact. We have shown that mutation of either the DNA binding or Ligand binding domain independently is sufficient to block downstream transactivation by the androgen receptor.

Isoliquiritigenin, a botanical COX inhibitor, suppresses prostate cancer cell proliferation, down regulates androgen-receptor and PSA protein expression

Sophie Chen[1,2], J. Gao[1,2], H. Dorota Halicka[1]
[1]Department of Medicine, New York Medical College, Valhalla, NY 10595,
[2]NovaSpes Research Lab, Hawthorne, NY 105322

Introduction

PC-SPES was a proprietary composition, comprised of refined extracts from 7 herbs used in traditional Chinese medicine plus Saw Palmetto extract. In several trials and experiments since 1997 its potent anti-prostate cancer activity was confirmed. In the continuing effort to isolate and investigate its biologically active components and mode of action we have identified further active compound Isoliquiritigenin (ISL). This report presents our findings of the in vitro mechanism of ISL. ISL is a chalcone belonging to the flavonoids family contained in the licorice root (one of the eight botanical components of PC SPES). It had been reported for estrogenic, anti-inflammatory and anti free radical activities. However its molecular action on prostate cancer was unknown.

Materials and Methods

MTT cell viability assay was used to evaluate the anti-proliferative activity of ISL towards both of the androgen receptor positive (LNCaP) and negative (DU-145) prostate cancer cell lines. Fluorescence microscopy (FM) was used to observe the cell morphology of the cells. To further understand the mechanism of action, flow cytometric and Western blot analysis were employed to investigate the effect on cell cycle, protein level of androgen receptor (AR) and prostate specific antigen (PSA). Enzyme immunoassay (EIA) was used to determine the inhibitory activity against cyclooxgenase (COX).

Results

ISL exhibited a potent activity in suppressing prostate cancer cell proliferation. The 50% inhibitory concentration (IC_{50}) determined by MTT was 23.3 ±3.4 and 15. 7 ±2.9 μM for LNCaP

and DU-145 respectively. FM examination revealed an increased frequency of apoptosis in both cell lines. At concentrations comparable to IC_{50} the flow cytometric data showed that ISL induced a G_1 phase arrest in LNCaP (AR positive), while it blocked the cell cycle at G_2M phase in DU-145 cells (AR negative). Western blot analysis further indicated ISL caused a down regulation of AR and PSA protein expression. The anti-inflammatory property of ISL was found to be directly associated with its strong inhibition on COX activity, with an IC_{50} of 10.6 μM for COX2.

Conclusion

Recent studies by various investigators confirmed the important role of AR and COX in controlling prostate cancer progression and metastasis. The fact that ISL is a COX inhibitor and an AR modulator makes it a potential candidate for prostate cancer chemo preventive agent. Further investigation on its molecular mechanism and possible clinical benefit are warranted.

Prostate cancer stem cells

Anne T Collins, Steven D Bryce, Katy Hyde, *Michael J Stower, Norman J Maitland
YCR Cancer Research Unit, Department of Biology, University of York, York YO10 5DD *Department of Urology, York District Hospital, York

It is important to recognize that solid tumours are more than just a clonal expansion of mutant cells, but are instead heterogeneous and structurally complex.

In this larger framework, tumour progression can be considered a developmental process in which a complex multicellular organ forms from rare tumour-initiating stem cells and evolving interactions with the microenvironment. In order to study these rare tumour-initiating cells we have identified markers present on normal stem cells that are also present on prostate cancer cells.

The $HEA^+/CD44^+,\alpha_2\beta_1^{hi}/CD133^+$ cells, selected from a series of primary and metastatic prostate cancers (n= 27; Gleason 5-6 (6), Gleason 7 (16), Gleason 8-10 (5) proliferate extensively *in vitro*, and comprise of 0.01% of the tumour population. The phenotype, $HEA^+/CD44^+,\alpha_2\beta_1^{hi}/CD133^+$ are clonogenic in soft agar, unlike their more differentiated progeny. The cancer cells display stem cell-like properties in that they are capable of generating new clones containing additional stem cells, as well as regenerating phenotypically mixed populations of non-clonogenic cells present in the original tumours

Therefore, if the initiating cell is indeed the stem cell, therapies that are more specifically directed at cancer stem cells should result in more durable responses for primary as well as metastatic disease.

Longitudinal changes in bone mineral density in advanced prostate cancer patients treated with androgen ablation or anti- androgen hormonal therapy and testosterone recovery following cessation of LH-RH analogues

Wadhwa VK, Weston R, Hussain A, Parr NJ.
Arrowe Park Hospital, Wirral, UK

Introduction

Androgen ablation with LH-RH analogues decrease serum testosterone levels and hence bone mineral density (BMD). They have been associated with accelerated bone loss and osteoporosis. An alternative is the anti-androgen bicalutamide which acts at the androgen receptor. Our aim was to study the effects of these 2 treatments on the BMD of selected groups of patients. In an attempt to reduce further demineralization, patients found to be osteoporotic while receiving LH-RH analogues were converted to anti-androgen monotherapy.

Materials and Methods

367 men (mean age 73years, range 53-93) with prostate cancer requiring hormone manipulation were prospectively followed from Oct 1999 to Aug 2004. BMD of the forearm was measured by dual energy X-ray absorptiometry (DEXA) prior to hormone therapy and annually thereafter. Osteoporotic patients (t-score≤-2.5) were commenced on bicalutamide. Osteopenic (t-score -1.0 to -2.4) and normal (t-score>-1.0) patients were treated with LH-RH analogues.15 osteoporotic patients receiving ≥12 months of LH-RH analogue were converted to anti- angrogen monotherapy. PSA and total testosterone were monitored at 3 monthly intervals.

Results

Osteoporosis was found in 42% of men with newly diagnosed prostate cancer prior to hormones. The osteoporotic group (n=155) did not show a significant change in BMD. (t-score at baseline -3.54;year1 -3.64; year2 -3.52; year3 -3.64; year4 -3.78). The osteopenic group (n=140) showed a statistically significant decrease in BMD, with 60% developing osteoporosis after 2 years on LH-RH analogues. (t-score at baseline -1.72; year1 -2.02; year2 -2.59; year3 -2.69; year4 -2.94). The normal BMD patients (n=72) also showed a significant decrease in BMD. (t-score at baseline -0.25; year1 -0.58; year2 -0.83 ;year3 -1.28; year4 -1.52).

All 15 patients converted to Bicalutamide demonstrated some testosterone recovery. Mean duration to initial detectable testosterone was 12.8 months(range6-22). Only 6 achieved a normal testosterone level after a mean of 17.5 months (range 14-30).

Conclusion

Our data showed that patients treated with androgen ablation showed a significant decrease in BMD whereas those on anti-androgen therapy maintained their BMD. We would advocate the routine assessment of BMD prior to hormone manipulation and surveillance thereafter to identify osteoporosis. This can be factored into the decision making process regarding the choice of androgen deprivation therapy.

As regards patients already on LH-RH analogues, following cessation of these, testosterone levels continue to be suppressed. Conversion to anti-androgen does not offer a significant benefit and we would suggest studies of alternative therapies such as bisphosphonates.