SpR Presentations East Anglian Meeting November 2015

10.40 – 11am:

K Patel: Detecting potentially aggressive Prostate Cancer early through ctDNA analysis

S Cashman: Correlating digital rectal examinations, MRI scans and TRUS biopsy results

11.30-1pm:

M Sut: Developing a disease specific Ureteric Stone Patient reported outcome measure: Stage 3 and 4

D Thurtle: Title: Can high quality mpMRI better identify which men will benefit from bone scintigraphy?

T Mitchell: Uncovering the genomic evolution of urological cancers

T J Johnson: An evaluation of a Selective Prostate Cancer Screening Program using family history as a supplementary screening tool to PSA

J Coode-Bate: Influence of Anaesthetic Type on Obtaining Detrusor Muscle during Transurethral Resection of Bladder Tumours at Ipswich Hospital Trust

B Pullar: Early multi centre experience of Ultra-Mini Percutaneous Nephrolithotomy in the UK

A Nelson: Development of a cell-line model for studies of estrogen receptor beta in prostate cancer.

14.00-15.20:

E Gordon: A Study of Male Urodynamic Studies: indications and outcomes at Ipswich Hospital

O Al Kadhi: A transcriptomic and metabolomic comparison between prostate zones

H M Alnajjar: Follow up after repeat biopsies for Atypical Small Acinar Proliferation (ASAP) and suspicious prostate lesions. Food for thought.

J Durrant: *Repetition of Theatre Checklists and Ability to Recall Important Information*

Karan Wadhwa: SIK2 is a novel secreted protein associated with a malignant phenotype in prostate cancer.

A Lamb: Integration of copy number and transcriptomics provides risk stratification in prostate cancer: a discovery and validation cohort study

S Banerjee: Follow up of superficial bladder cancer using the current NICE guidelines, what do we stand to gain and lose

Detecting potentially aggressive Prostate Cancer early through ctDNA analysis

Authors:

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Abstract:

Introduction: Prostate Cancer (PCa) is the most common cancer in UK men. Current methods of distinguishing between indolent and aggressive PCa are inaccurate, leading to over-treatment in many and under-treatment in the unlucky few. In PCa, the presence of genetic alterations may indicate aggressive disease (Beltran *et al.*, 2012). However, detecting these alterations during tumour biopsy is problematic due to PCa heterogeneity.

Circulating-Tumour DNA (ctDNA) represents an exciting opportunity to monitor cancer status non-invasively and may overcome issues of needle-biopsy in heterogeneous tumours. Furthermore, previous works in several early stage cancers have demonstrated detectable ctDNA (Bettegowda *et al.*, 2014; Beaver *et al.*, 2014).

Methods: DNA was extracted from tissue and plasma samples of men with PCa undergoing prostatectomy (n=19) and who later developed metastasis. TAm-Seq analysis of DNA was performed as previously described (Forshew *et al*., 2012).

Results: *TP53* mutant clones were detected in 10/19 men with metastatic disease. Of these, the malignant clone was identified from 6/6 of tissue and 2/3 plasma samples taken at the time of initial prostatectomy.

Conclusions: ctDNA analysis was able to detect potentially malignant clones at a treatable stage in this proof of principle study. In the future, ctDNA could play an integral role in PCa stratification, helping to distinguish between indolent and aggressive disease.

Correlating digital rectal examinations, MRI scans and TRUS biopsy results

Sophia Cashman

Peterborough City Hospital

The role of MRI scans in the diagnosis of prostate cancer continues to evolve, with a growing body of evidence evaluating the various roles that MRI can play. Prior to the introduction of MRI scans in the diagnostic pathway, initial evaluation of cases of suspected prostate cancer and raised PSA largely comprised of rectal examinations and transrectal ultrasound guided prostate biopsies alone.

In this study, the digital rectal examination, MRI scan and prostate biopsy results were evaluated in 50 patients who underwent all three investigations. All MRI scans were performed prior to prostate biopsy thus avoiding haemorrhage artefact.

Of the cases reviewed, correlation of all three parameters was only seen in 14 cases (28%). In two cases, both MRI and rectal examination were normal with cancer detected on biopsy, both of these cases being Gleason 6. However in almost half of cases (46%) abnormalities were detected on MRI scan with no cancer found on TRUS biopsy. Of the 16 cancers found on TRUS biopsy, just under half had a normal rectal examination. Just over half of patients (52%) had abnormal digital rectal examinations, of which 65% did not have cancer identified on TRUS biopsy.

This study has demonstrated relatively poor correlation of all three parameters. The main point of discussion now should be based around the follow up of those with abnormal MRI scans in the absence of cancer being found on initial biopsy. Whether or not all of these patients should go on to have further invasive diagnostic procedures remains controversial.

Developing a disease specific Ureteric Stone Patient reported outcome measure: Stage 3 and 4

Michal Sut, Maxine Tran, Xi Cheng, Jennifer Yip, Jane Collie, Sami Hayek, James Armitage and Oliver Wiseman

Introduction

Outcomes from surgery have traditionally been based on surgeon-reported outcomes. A paradigm shift in assessing healthcare productivity from output to qualitative outcome, has led to increased interest in patient-reported outcome measures (PROMS).

Method

We prospectively collected the data from our Cambridge Ureteric Specific PROM (CUSP) and EQ-5D-5L questionnaires completed by 21 patients with radiologically proven ureteric calculus at least an hour apart. Cronbach Alpha (Initial) test was first calculated to assess the overall reliability of the questions. Subsequently we performed interclass correlation coefficient (person's correlation) to investigate the agreement between the same questions in test and re-test analysis. Finally the Cronbach Alpha calculation was again performed to assess the consistency of the each question in relation to other questions within the same domain.

Results

We found overall good to very good reliability of the questions in most of questionnaire domains and a good to very good agreement between the answers provided by the patient in the test and re-test group.

Conclusions:

We performed test-retest validation and assessed reproducibility of our PROM questionnaire. We will now prospectively evaluate ureteric calculi therapy using our ureteric stone specific PROM together with the EQ-5D-5L both locally and nationally as part of the TISU (Therapeutic Interventions for Stones of the Ureter) study.

Title: Can high quality mpMRI better identify which men will benefit from bone scintigraphy?

D Thurtle[1], M Chedha[2], V Gnanapragasam[1], T Barrett[1]
1. Cambridge University Hospitals NHS Trust 2. Cambridge University Clinical School

Introduction

Bone scintigraphy (BS) remains a key staging investigation before radical curative therapy for prostate cancer (PCa), but is time-consuming and requires radiation exposure. NICE recommend lower thresholds for BS than either EAU or AUA. High-quality mpMRI is increasingly being used in PCa, but is not formally used in risk categorisation or to direct BS use. Here we audited BS use and investigated if mpMRI staging could be used as a triaging tool to refine the use of BS.

Patients and Methods

Radiology databases were interrogated for all patients receiving mpMRI from January 2010 through May 2015 in a large tertiary centre. PSA, Gleason scores and BS reports were retrieved for each case. Patients were categorised to low, intermediate and high risk according to NICE guidelines. BS outcome and subsequent imaging was assessed, over a median follow-up of 2.84 years.

Results

978 patients were included, of which, 438 had both BS and MRI within 6 months. 12, 147 and 279 of this cohort were low- , intermediate-, and high-risk respectively by Gleason and PSA alone. 97.3% of BS were performed in line with NICE guidelines. 9 of the 12 (75.0%) low-risk patients who received BS had an exceptional indication, such as bone pain.

Of this cohort who had both scans, 26 (5.94%) were positive for bone metastases, 65 (14.8%) were equivocal of which 11 (16.9%) proved to have metastases after further investigation. Of the final 37 metastases cases 14 (37.8%) had clear evidence of pelvic metastasis from the prostate MRI already.

Integrating mpMRI staging within risk categorisation, none (0%) of the 76 low- or intermediate-risk cases (stage T1-T2) undergoing BS had evidence of bone metastases. mpMRI staging did ‘up-risk’ 4 men from intermediate- to high-risk who had metastases on BS. Only 1/439 (0.2%) of the patients who were staged by mpMRI as organ-confined, and did not have initial BS, went on to develop bone metastases during our follow-up period.

Conclusion

Use of BS in our unit is compliant with NICE guidelines. mpMRI staging in the risk categorisation pathway provides a useful triaging tool to identify men who will benefit most from a bone scan. In particular, presence of mpMRI defined organ-confined disease and a normal pelvic scan should preclude the need for a BS.

Uncovering the genomic evolution of urological cancers

Authors: Tom Mitchell, Cancer Genome Project, PREDICT consortium, Academic Urology Group.

Institutions: Cancer Genome Project, Wellcome Trust Sanger Institute
Academic Urology Group, Department of Surgery, Addenbrooke's Hospital

Introduction and objectives:
The mutational landscape of all common cancers has now been determined with the help of large-scale collaborations. Significant questions remain, including determining which key mutational events have enabled cells to evolve from a normal phenotype, through pre-malignant lesions, to giving rise to localised, invasive and finally metastatic cancers. In this presentation, I shall outline three methods that I have been using to help uncover the mutational evolution in prostate, kidney, and bladder cancers.

Material and methods:
1. Detailed examination of sub-clonality within individual cancers from large scale collaborative databases can give insights into their phylogeny. I have developed methods to statistically integrate multi phylogenetic trees to reveal a consensus order of mutational events in prostate cancer. Methods have been validated across different datasets and are now being applied in a pan-cancer analysis.
2. Multi-region whole-genome sequencing of histologically normal tissue, primary lesions, and metastases can reveal intricate detail of the phylogeny of spatially separate tissue samples. I am applying computational techniques to infer the evolution of renal cancers from such a dataset. By examining the contribution to the mutational spectrum by a chronological signature, I aim to time cancer initiation and subsequent branching of metastasis according to key mutational drivers.
3. Mapping mutational clones within histologically normal tissue, pre-cancerous lesions, and invasive cancer is often limited by low tumour cell fractions and an uncertain admixture of normal and tumour DNA. By using recently developed tissue separating techniques and ultra-deep targeted sequencing, I plan to quantify the sizes and mutational constitution of cell populations from different parts of urothelium in cystectomy and nephro-ureterectomy specimens.

Results:
1. Clear evolutionary differences are seen in ETS positive and negative prostate cancers with different driving events. Widely differing results from other tumour types
2. Detailed phylogenetic trees and mutational signatures
3. Recruitment to study underway

Conclusions:
Determining the key steps and mutational processes involved in cancer formation, invasion and metastasis is possible by intelligent use of current technologies and will have important repercussions in screening, surveillance and treatment of cancer.

An evaluation of a Selective Prostate Cancer Screening Program using family history as a supplementary screening tool to PSA

Authors
TJ Johnston, AD Lamb, S Vowler, X Tengbin, V Gnanapragasam, AL Moore, P Holdings, P Herbert, M Davis, JA Lane, JL Donovan, FC Hamdy, DE Neal

Background/Aims

Prostate specific antigen (PSA) population-based screening is not recommended as too many men would be harmed from over-diagnosis and over-treatment. Research is now focused on identifying diagnostic strategies which can better detect clinically significant prostate cancer (PrCa). Selective screening of high risk groups has been put forward as a possible way of addressing this. We therefore evaluate the impact of family history as a supplementary screening tool to PSA in the Prostate testing for cancer and Treatment (ProtecT) trial.

Patients and Methods

Approximately 82,000 men were PSA tested during the recruitment phase of the ProtecT trial. Those with a PSA ≥ 3ng/ml were referred for a transrectal ultrasound-guided biopsy. Prior to PSA testing baseline data on any history of cancer amongst first degree relatives was obtained (80,240 men, complete data). A PSA value ≥ 3ng/ml and a first degree family history of prostate cancer were assessed as a selective screening tool within the ProtecT cohort.

Statistical analysis

The detection rate, risk ratio (RR), positive predictive value and specificity of PSA testing in men with and without a family history of prostate cancer were calculated. An estimation of the overall value of this population-based selective screening program was assessed in terms of sensitivity and specificity.

Results

A total of 4319 men (5.9%) had a positive first degree family history, of which 571 (13.2%) had a PSA ≥ 3ng/ml. 234 tumours were identified corresponding to a detection rate of 5.4%, a specificity of 91.8% and a positive predictive value (PPV) of 41%. Of the 69,234 men without a family history 7275 men (10.5%) were screen positive. The detection rate was 3.7%, specificity 92.9% and PPV 35%. Men with a positive family history had an increased risk of PrCA (RR1.47; 95%CI 1.28 – 1.68) with the greatest risk in affected relatives below 60 years (RR1.65; 95%CI 1.33 – 2.05) and men with an affected brother (RR 2.49; 95% CI 1.41 – 2.02). A positive family history had a higher risk of developing more aggressive cancer (Gleason score ≥ 8: RR 2.19; 95%CI 1.34 – 3.57). The estimated overall program sensitivity was 8.4%. This selective screening program would therefore have missed 91.6% of PSA detectable cancers.

Conclusion

Men in their 50's or 60's with a first degree family history are at an increased risk of developing prostate cancer with some displaying more aggressive disease. Such men should be adequately counselled regarding this risk when considering a biopsy. This study does not support selective screening at the population level as too many clinically significant cancers would have been missed. Future research will assess the impact family history has on survival.

Influence of Anaesthetic Type on Obtaining Detrusor Muscle during Transurethral Resection of Bladder Tumours at Ipswich Hospital Trust

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Background: Presence of detrusor muscle (DM), particularly during the initial resection of bladder tumours, is essential for accurate staging. It is therefore recognised as a surrogate marker for quality of resection. A known complication of electric loop resection of lateral wall tumours is the adductor reflex or jerk caused by stimulation of the obturator nerve, posing an increased risk of bladder perforation. One method of reducing the risk of adductor jerk is the use of muscle relaxants with general anaesthetic (GA).

Aims: This study aims to evaluate current outcomes from transurethral resection of bladder tumours (TURBTs) in obtaining DM, and investigate the potential influence of muscle relaxant during anaesthetic.

Methods: Electronic and paper notes for patients were reviewed from 136 consecutive procedures coded as TURBT at Ipswich Hospital. In each case data was collected on the patient's age, sex, current and previous histology, size and number of tumours, experience of surgeon, anaesthetic type and any recorded intra-operative complications.

Results: Patients ranged in age from 45-94 years (mean 74) with a male to female ratio of 3:1. From 136 cases, 60 (44%) contained no DM; 40 first resections, 8 re-resections and 12 recurrent tumours. No significant differences were identified in presence of DM according to grade of surgeon, patient sex or number of tumours. Size of tumour, considered greater or smaller than 3cm, did not reach significance (65% vs 49% respectively, $P=0.08$). However, DM was significantly more likely to be present with tumours invading lamina propria (82% compared to 43% non-invasive, $P<0.001$), and those of the higher grades G3 or high-grade G2 (77% compared to 41% low grade, $P<0.001$).

Assessing anaesthetic type revealed that only 39% of specimens from those receiving GA alone contained DM. This was significantly less than both spinal anaesthetic (65%, $P<0.05$) and GA with muscle relaxant (72%, $P<0.01$). No significant difference was seen between spinal and GA with muscle relaxant ($P=0.62$).

While five procedures had to be abandoned or altered due adductor jerk (one GA and four spinal), the four recorded bladder perforations showed no correlation to anaesthetic type (one GA, two GAs with muscle relaxant and one spinal).

Conclusions: TURBT specimens are most likely to contain DM with increasing grade and stage of tumour. GA with muscle relaxant is superior to GA alone for obtaining DM, but equivalent to spinal. Despite preventing adductor jerk, GA with muscle relaxant does not appear to protect against overall risk of bladder perforation.

Early multi centre experience of Ultra-Mini Percutaneous Nephrolithotomy in the UK

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Introduction

Ultra-mini percutaneous nephrolithotomy (UMP) is a novel technique recently introduced allowing percutaneous renal access to stones using a specially modified 11 or 13FR sheath, a 6Fr nephroscope, and permits laser fragmentation and stone evacuation. This study aimed to review the early practice of UMP in the UK.

Materials and methods

Data was submitted to a central database from 9 centres around the UK who performed UMP between July 2013 and December 2014. Data was collected on stone characteristics, patient demographics, intra-operative details, outcomes and complications.

Results

A total of 32 UMP cases were performed in the contributing centres.

Stone-free rates were excellent with 31/32 cases stone-free post procedure. 26/32 patients were left without a nephrostomy tube. 23/32 cases of UMP were 'totally tubeless' (without nephrostomy tube or ureteric stent). 28/32 patients were discharged the next day; the other 4 patients were discharged after 2 days.

Complications were uncommon; patient was readmitted with pain and 1 patient developed a perinephric haematoma which was managed conservatively.1 equipment failure led to conversion to the standard technique.

Conclusion

This multicentre series of initial experience shows that UMP is a safe and effective means of treating appropriately sized renal stones. It is associated with short hospital stay and few complications.

A major benefit of the UMP technique is the ability to leave the patient 'totally tubeless' post procedure (ie. without nephrostomy tube or ureteric stent). This reduces the morbidity associated with nephrostomy tube and stent placement (particularly stent symptoms) and also the need for a further hospital visit for stent removal. As experience grows, it is likely that confidence in leaving a patient 'totally tubeless' will increase in the future,

Its use is likely to be become more widespread for the treatment of some renal stones instead of standard PCNL, and as possible alternative for stones that may have previously been considered for ESWL or flexible ureteroscopy.

Development of a cell-line model for studies of estrogen receptor beta in prostate cancer.

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Introduction: Prostate cancer (PC) is the commonest, non-cutaneous cancer in men, with no cure for advanced, castration-resistant disease. Estrogen is important in PC with evidence from epidemiological, cancer cell-line, human tissue and animal studies. The prostate expresses estrogen receptor beta (ERβ), with most evidence suggesting that it has a tumour-suppressive role. However, some evidence suggests that ERβ may be oncogenic and its precise role remains unclear. It is recognised that conflicting data in the literature regarding ERβ function may be due to use of poorly characterized *in vitro* models of disease.

Materials and Methods: A panel of PC cell lines commonly used previously in the literature for studies of ERβ was assessed for expression of ERβ mRNA by real time polymerase chain reaction (qPCR), and ERβ protein by western blot, rapid immunoprecipitation-mass spectrometry (RIME) and selective reactive monitoring (SRM) mass spectrometry. A PC cell line (LNCaP) with stable, doxycycline-inducible ERβ expression was generated by transfection of a tetracycline-repressor construct, followed by clonal selection and further transfection with an ERβ-containing construct.

Results: Using previously validated ERβ antibodies; PC cell lines are shown not to express ERβ by either western blot or RIME techniques. Further confirmation of this finding is demonstrated by qPCR and SRM. The protocol for development of the LNCaP-ERβ cell line is presented, with validation of stable, inducible ERβ mRNA expression demonstrated by qPCR.

Conclusions: Further work will focus on studying the genomic mechanisms of ERβ, discovering its interacting partners and regulatory proteins to determine if ERβ-dependent pathways represent useful prognostic markers or therapeutic targets in PC.

A Study of Male Urodynamic Studies: indications and outcomes at Ipswich Hospital

Emma Gordon, ST4

Introduction:

This study looks at 99 men who underwent urodynamic studies (UDS) between May 2013 and June 2014 at Ipswich Hospital. The main reason for looking at our data was a difference of opinion between clinicians as to the usefulness of urodynamics in men. One opinion was that UDS is valuable in establishing the correct treatment for men with lower urinary tract symptoms (LUTS), the other opinion was broadly that all men with LUTS should undergo prostate surgery (TURP or HoLEP) regardless.

Methods:

A retrospective analysis of 99 consecutive male patients referred for urodynamic studies at Ipswich Hospital. All studies were performed by the same clinician. All patients had completed at least an initial treatment modality after their test. Referral indications were grouped into voiding, storage or mixed lower urinary tract symptoms. Management options were grouped into surgical, medical, lifestyle or catheter related. Outcomes of management were grouped into symptomatic relief, partial relief, on-going symptoms, no relief and a mixed group of other outcomes. Final outcomes were grouped into discharged, on-going review or lost to follow up.

Results:

Half of the men referred had mixed LUTS, a quarter voiding LUTS and a quarter storage LUTS. The main findings were bladder outflow obstruction with or without overactivity, overactive bladder or hypotonic bladder. A small number had nocturnal polyuria or sensory urgency. Half of patients were subsequently given medical management, 20% had lifestyle modification, 20% had bladder outlet surgery and the remainder had some form of catheter. 35% of patients had symptomatic relief from their treatment, 30% had partial relief, 17% ongoing symptoms but only 2% no relief. The final outcomes were half were discharged, 37% were having ongoing review, often for secondary symptoms or incidental prostate cancer, 8% were lost to follow up and one passed away from non-urological disease.

Conclusions:

This is complex group of patients who have intractable symptoms, mixed symptom presentations or who fail lifestyle or medical management of their symptoms. The decision to offer urodynamic studies was often made after FFR and PVR studies, upper tract imaging and flexible cystoscopy had already been performed. Only 10 patients had an IPSS score that was available on their electronic record. The results of the test had a bearing on the management offered to the patient, particularly where surgery had been discussed and in these cases was instrumental in the decision not to offer surgery.

A transcriptomic and metabolomic comparison between prostate zones

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Introduction

Prostate cancer is mostly identified in the peripheral zone. Several research studies have highlighted the molecular differences between cancerous and benign tissue of the prostate. Some of these studies have found specific gene sets and metabolites that correlate with tumour Gleason score and even risk of recurrence after treatment. However, there are limited data regarding the genetic and metabolomic variations within the prostate gland. In this study, we compared the gene expression and metabolite profiles between the peripheral and transition zones of the prostate in a group of men undergoing radical prostatectomy.

Methods

Adjacent benign prostate tissue samples were collected from consenting men (n=18) who underwent radical prostatectomy at the Norfolk and Norwich University Hospital NHS Trust. Metabolite profiles were obtained using a method that allowed histopathological assessment of each sample. Analysis of tissue extracts was performed using liquid and gas chromatography with tandem mass spectrometry (LC/GC-MS, Metabolon, USA). Next generation sequencing was performed at The Genome Analysis Centre (TGAC, Norwich). Functional annotation was carried out using (DAVID Bioinformatics Resources). All processed tissue was assessed by a single pathologist (RYB).

Results

Metabolite data showed abundance of lipid-based compounds in the peripheral zone belonging to fatty acid elongation and steroid hormone biosynthesis pathways. Next generation sequencing identified > 1400 significantly differentiated genes between the two zones. Functional annotation of gene expression data confirmed the metabolite findings with overrepresentation of sterol and fatty acid synthesis pathways.

Conclusion

The peripheral and transition zones of the prostate have unique metabolomic and transcriptomic properties. Lipid biosynthesis pathways that are upregulated in cancer are overrepresented in the benign peripheral zone which may explain the higher cancer rates in this part of the prostate gland.

Follow up after repeat biopsies for Atypical Small Acinar Proliferation (ASAP) and suspicious prostate lesions. Food for thought.

Hussain M Alnajjar, Johanna Selway, Georgina Wilson, Anup Sengupta, John McLoughlin

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Introduction and Aim

About 5% of needle biopsy pathology reports diagnosed as ASAP. It is known that for ASAP the risk of cancer on repeat biopsies is approximately 40% and for suspicious lesions is about 50%. Guidelines exist regarding repeat biopsies but not for management/follow up regime beyond their 2nd prostate biopsy.

We aimed to investigate the natural history of these conditions after an inconclusive 2nd biopsy.

Patients and Methods

Retrospective review of all prostate biopsy pathology reports coded as 'ASAP' or as 'suspicious for malignancy" on the first biopsy. Period covered July 2000 to Dec 2014. The pathology reports were manually reviewed and database was devised.

Exclusion criteria: cancer on first biopsy, HGPIN and PIN, atypical glands, hyperplasia and inflammation.

Those men with negative or inconclusive 2nd biopsy were further analysed.

Results

A total of 362 cases were coded as ASAP/suspicious. 148 cases were excluded. Total number of cases included in the study 214. The mean age was 68 years old .

On the second set of prostate biopsies: Twenty six percent (56/214) had prostate adenocarcinoma. Thirty percent (64/214) were benign and 31% (66/214) had no 2nd biopsy (see table).

	Discharged	OPA follow up	Lost to f/u	CaP diagnosed	Died
Benign/ inflammation (64)	45	8	4	5	2 (1x myeloma, 1x other)
HGPIN (10)	4	3	2	1	0
ASAP/suspicious (18)	7	4	1	2	4 (1x mets cap, 1x glioblastoma , 2x other)
No further bx (66)	30	23	6	2	5 (1xAAA, 4x other)
Total (158)	86 (55%)	38 (24%)	13 (8%)	10 (6%)	10 (6%) 1 (0.6%)

As expected there was a significant pick up of cancer on second biopsy.

However during follow up surprisingly few men went on to develop clinical evidence of prostate cancer. On 2 of 18 men with ASAP or suspicious change. The patients who received no repeat biopsy also seemed to do well with only 2 /66 going on to develop clinical evidence of prostate cancer.

Conclusion

Significant number of patients had prostate cancer on their second biopsy. Beyond that the low number of men who developed clinical evidence of cancer does raise a question as to whether these require prolonged follow up in an era of pressure to reduce follow ups. Validation of the pathology slides by a histopathologist would be required.

Repetition of Theatre Checklists and Ability to Recall Important Information

Jordan Durrant - Bedford Hospital NHS Trust

Introduction

The World Health Organisation launched the 5-step Surgical Safety Checklist in 2008 and this has now been widely adopted across the NHS. Studies have repeatedly shown that the checklist decreases complication rates, hospital stay and mortality[1]. One of the core tenets is that all persons in theatre should be engaged and aware of all of the key information for each operation, so that if a potential error is spotted by any team member, it can be averted. However, it has been noted from the outset that a specific challenge remains to engage staff and not have it be viewed as a 'tick-box exercise'[2]. Indeed, the opinion that the checklist is overly repetitious is not uncommon.

Conventional wisdom states that the more times risks are repeated to a person, the more aware and concerned the person will be about these - a 'monotonic increasing' relationship. However, there is also evidence that an 'Inverted U-shaped curve' relationship occurs[3], whereby repetition breeds ambivalence. Furthermore, studies of the effect of repetition on memory indicate that repetition of information in a short time-frame does not necessarily improve recall[4].

This audit aimed to test whether theatre staff can correctly recall key facts from the WHO checklist at various times throughout the operating list and then examine whether there was any evidence of improved recall with repetitions, or any evidence of inattention developing.

Methods

Theatre staff were questioned about various operation details in 3 different time slots - 5 minutes after theatre briefing, halfway through each operation and 5 minutes after 'sign out'. This was carried out on 4 all-day operating lists. Questions were posed in a non-leading manner. It was recorded in a log as to whether the question was answered correctly or incorrectly. Inability to recall was counted as an incorrect response. Results were recorded chronologically throughout the theatre list.

Results & Discussion

The percentage of correct answers were calculated by list, for each time slot. The mean percentage of correct answers after theatre briefings was 53%. The mean percentage of correct answers during the operation was 79%. The mean percentage of correct answers after the patient had left theatre was 75%. The highest rate of correct responses was for the 2nd operation in each list, where responses were 100% correct. The lowest rate of correct responses was for the last operation of the day, where the mean percentage was just 28% correct.

This data suggests that repetition of the checklist at the 'Time Out' significantly improves ability to recall key facts. The decrease in correct answers following the 3rd repetition at 'Sign Out' is not statistically significant. The only significant decline in correct responses is seen for the last operation of the list and may suggest either fatigue or that attention is divided between the operation and other tasks for finishing the theatre session. Therefore, repetition of the WHO theatre checklist does improve ability to recall key facts, but extra care should be taken to fully engage all team members with checklists for the last operation of the list.

[1] Effect of the World Health Organization Checklist on Patient Outcomes. Haugen et al. Ann Surg. May 2014.

[2] Implementation of the WHO Theatre Checklist - Survey. Patient Safety First. 2010.

[3] Inverted U-shaped model: How frequent repetition affects perceived risk. Lu et al. JDM. May 2015.

[4] Principles of Learning and Memory. Crowder RG. 2015.

SIK2 is a novel secreted protein associated with a malignant phenotype in prostate cancer.

Karan Wadhwa[1], Helene Bon, Kelly Holmes, Anne Warren, Hayley Whittaker, Jonathan D Kay, Lee Fryer, David Neal, Ian Mills, Vincent Gnanapragasam, Jason Carroll

1. Academic Urology Group, Addenbrookes & University of Cambridge

Introduction

Salt Inducible Kinase-2 (SIK2) autoantibody levels discriminate aggressive from indolent prostate cancer (Bon et al. 2015) but the function of secreted SIK2 is unknown. In this study, we explored the role of extracellular SIK2 and its relationship with aggressive prostate cancer.

Methods

Secretome analysis was performed by western blotting. Sandwich ELISA and subsequent clinical grade Meso Scale Discovery assays were created. All experiments were performed in triplicate at least. Plasma from 10 men with localised prostate cancer and 10 benign controls was obtained from the Cambridge Urology Biorepository.

Results

SIK2 is secreted only by androgen receptor (AR) positive cell lines (VCaP, LNCAP, C4-2, C4-2b) but not by benign (PNT1a) or malignant (DU145, PC3) AR negative cell lines. Knockdown of the AR by siRNA (siAR) increased SIK2 secretion (16.1 ng/mL) compared to scrambled siRNA (13.6 ng/mL, $p<0.05$). Androgen treatment reduced secretion of SIK2 (25.5ng/mL) compared to vehicle (47.8ng/mL, $p<0.05$). The use of a protein transport inhibitor reduced SIK2 secretion by 67% ($p<0.05$) and lysosomal inhibitor by 27% ($P<0.05$). The addition of media conditioned with SIK2 overexpressing cells induced cell proliferation in benign PNT1a cells and increased wound healing in malignant PC3 cells. In humans, SIK2 protein is present in the plasma of men with prostate cancer at higher levels than benign counterparts ($p<0.05$).

Conclusion

SIK2 is a novel secreted protein regulated by the AR, conventional protein transport machinery and lysosomes. Secreted SIK2 induces a more aggressive malignant phenotype in prostate cells in culture by increasing proliferation and migration.

Integration of copy number and transcriptomics provides risk stratification in prostate cancer: a discovery and validation cohort study

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Scientific Abstract

Background
Understanding the heterogeneous genotypes and phenotypes of prostate cancer is fundamental to improving the way we treat this disease. As yet, there are no validated descriptions of prostate cancer subgroups derived from integrated genomics linked with clinical outcome.

Methods
In a study of 482 tumour, benign and germline samples from 259 men with primary prostate cancer, we used integrative analysis of copy number alterations (CNA) and array transcriptomics to identify genomic loci that affect expression levels of mRNA in an expression quantitative trait loci (eQTL) approach, to stratify patients into subgroups that we then associated with future clinical behavior, and compared with either CNA or transcriptomics alone.

Findings
We identified five separate patient subgroups with distinct genomic alterations and expression profiles based on 100 discriminating genes in our separate discovery and validation sets of 125 and 99 men. These subgroups were able to consistently predict biochemical relapse (p=0.0017 and p=0.016 respectively) and were further validated in a third cohort with long-term follow-up (p=0.027). We show the relative contributions of gene expression and copy number data on phenotype, and demonstrate the improved power gained from integrative analyses. We confirm alterations in six genes previously associated with prostate cancer (*MAP3K7*, *MELK*, *RCBTB2*, *ELAC2*, *TPD52*, *ZBTB4*) in prostate cancer, and also identify 94 genes not previously linked to prostate cancer progression that would not have been detected using either transcript or copy number data alone. We confirm a number of previously published molecular changes associated with high risk disease, including *MYC* amplification, and *NKX3-1*, *RB1* and *PTEN* deletions, as well as over-expression of *PCA3* and *AMACR*, and loss of *MSMB* in tumour tissue. A subset of the 100 genes outperforms established clinical predictors of poor prognosis (PSA, Gleason score), as well as previously published gene signatures (p=0·0001). We further show how our molecular profiles can be used for the early detection of aggressive cases in a clinical setting, and inform treatment decisions.

Interpretation
For the first time in prostate cancer this study demonstrates the importance of integrated genomic analyses incorporating both benign and tumour tissue data in identifying molecular alterations leading to generation of robust gene sets that are predictive of clinical outcome in independent patient cohorts.

Follow up of superficial bladder cancer using the current NICE guidelines, what do we stand to gain and lose

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Introduction:

Follow up of non-muscle invasive bladder cancer is done largely with periodic cystoscopy and the frequency of this is often adjusted according to the perceived degree of risk of the cancer recurrences. Current EAU guidelines state that the risk of recurrence in low and intermediate risk NMIBC is 15%-24% at year 1 and increases to 31%-62% by 5 years. The risk of progression however are much lower in these groups varying between 0.2 -1% at year 1 to 0.8- 6% by year 5.

NICE has formulated the current guidelines for follow up of NMIBC which has suggested fewer cystoscopic follow ups compared to what is recommended by EAU. Although the current NICE guidelines appreciates that there is a trade off with cost saving versus a risk of recurrence and progression.

We present a snapshot of our current cystoscopic follow up (protocol based on EAU guidelines) and compare it with outcomes (recurrences detected and number of cystoscopies saved) had the current NICE guidelines been followed.

Method: Over a 3 month period the records of patients attending for flexible check cystoscopies were collected and outcome measures recorded. In particular the initial histology, risk category and recurrence grade and stage till date using the standard EAU guidelines were collated. These were then compared against the current NICE guidelines to determine how many possible extra cystoscopies were done and how many recurrences would have been missed.

Results: Over a 3 month period (August to October 2015) 175 patients had follow up check cystoscopies following bladder cancer. Of these, 99 patients (56.7%) had low or intermediate risk category superficial bladder cancer at presentation. Till date these patients had a total of 616 follow up check cystoscopies and 37 patients (37.3 %) had recurrences at some point during their follow up. However interestingly all the recurrences were superficial (24 patients had LASER ablation of tumour and 13 had TURBT). Had the new NICE guidelines been followed it would have resulted in 272 check cystoscopies (i.e. 344 fewer flexible check cystoscopies during this time period). Extrapolating these figures, over a period of one year this would mean 1376 less check cystoscopies.

Discussion: Based on observational studies, NICE has now recommended lesser number of cystoscopic follow ups and quicker discharge of patients to primary care in the UK. However as the current study demonstrates that there is a chance of missing up to 37% of cancer recurrences albeit they are all superficial recurrences. Given the fact that the current study is a retrospective observational study it is difficult to draw concrete conclusions and more evidence is needed to ascertain the true cost benefit ratio of following the new guidelines.