ISSN 1751-4975

Oncology news

Volume 9 Issue 4 • September/October 2014 • www.oncologynews.biz

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Volume 9 Number 4 • September/October 2014

Oncology News is published by McDonnell Mackie, 88 Camderry Road, Dromore, Co Tyrone, BT78 3AT, N Ireland.

Publisher: Patricia McDonnell

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Printed by: Warners Midlands PLC, T: +44 (0)1778 391057

The Road to Metastasis: A Brief Prospective

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The majority of deaths in cancer are not from the primary tumour, but from metastasis affecting vital organs. The dogma is that metastasis is a complex multistep linear process culminating in extravasation and colonisation of secondary sites. Current thinking, prompted by the identification of cancer stem cells (CSCs), challenges the dogma and suggests CSCs can self-renew, proliferate, differentiate and even revert back to a stem cell state; they can produce metastatic cells at unexpected stages of disease, ergo, they can arise from transformation of their normal counterparts.

Irrespective of the process of metastasis, epithelial-to-mesenchymal transition (EMT) has a pivotal role. EMT may best be described as a cellular process whereby polygonal appearing epithelial cells acquire a mesenchymal phenotype with a spindly-fibroblastic-like cell morphology with reduced adhesion, increased motility and greater invasivesness [1]. EMT is required for normal embryonic development, organ differentiation and functioning. However, in accord with Grant and Kyprianou [2] EMT is "hijacked" in cancer, by mechanisms that initiate tumour development and progression. This results from transcriptional reprogramming of abnormal survival signals by growth factor receptors affecting the regulation of apoptosis and cytoskeletal organisation [2]. Some of the major factors, beyond specific consideration in this brief commentary, include E-cadherin, β-catenin, TGF-β, Snail, Slug, Twist and Wnt.

While these and other factors have multifaceted and interactive roles, Wnt signaling, for example, is involved in the induction of normal physiological processes, but when it becomes aberrantly activated in carcinogenesis, it induces EMT in tumour cells; it thereby links CSCs and the initiation of EMT – 2 important components in tumour progression [3].

EMT may reflect the ultimate adaptation of cancer cells to survive cytotoxic drugs, thus being responsible for chemoresistance. Given the importance of EMT and its signals initiating tumours and their progression, they conceivably are an ideal target for therapeutic intervention. Hypothetically, such therapeutic approaches might prevent tumour invasion and inhibit metastasis if applied early in tumour growth. However, we are faced with at least 2 conundrums: (i) pathologists rarely see EMT in cancer tissues, wherein invading cells appear epithelial rather than mesenchymal, and usually do not express stem cell markers [4]; and (ii) as yet there is no therapeutic approach that specifically targets EMT, EMT-associated cancer cell migration or invasion [5]. However, Glackin [6] has suggested that targeting EMT by inhibiting Twist and Wnt signaling pathways that mediate EMT may sensitise select cells to further other treatments.

Given the foregoing, the question is whether CSCs arise from the transformation of their normal counterparts producing metastatic cells, rather than from fully differentiated cells through an adaptive trans-differentiation process *ergo*, EMT, then targeting signals promoting EMT and/or EMT-associated cancer cell migration or invasion, may reasonably be insufficient. A *caveat* here will be if cells with an EMT phenotype share molecular characteristics with CSCs; some consider they do, e.g., in epithelial ovarian cancer [7], whereas others opine, for the most part, that they do not [4]. ●

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Ancient Remedies and Modern Anticancer Therapies

Rediscovering Traditional Chinese Medicine

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One of the earliest records of description on tumours is the note of "nodules and lumps" by doctors in China during the Qin Dynasty (221-207 BC). Traditional Chinese Medicine (TCM) encompasses a range of early medical practices and remains widely used by healthcare professionals not only in China, but throughout Asia, Europe and America. As a part of the today's complementary and alternative medicine (CAM), TCM has been widely accepted, at least in China and the Far East, as a therapeutic approach in the management of malignancies, particularly in the supportive and palliative care of cancer patients. TCM still seems to be mystical in some ways, and is often seen as less convincing due perhaps to the poor scientific understanding of its pharmacodynamics, mechanisms of action, and unconvincing clinical evidence by today's standards and theory of medical science. However, in 2007 alone, $33.9 million was spent by adults in the USA on CAM [1], and *Nature* published in 2011 a series of correspondence about traditional Asian medicine. These have raised an interest in assessing the potential use of traditional Asian medicine in cancer management and in attempting to elucidate the mode(s) of actions of these traditional therapeutic approaches. Since the middle of the last century, clinicians and scientists have intensified their search for more effective anti-cancer therapies by looking into TCM, particularly the natural herbs used in this area. This has led to successes in the rediscovery of certain TCM therapies by providing supportive scientific and clinical evidence. For example, Icariside II, purified from the root of Epimediumkoreanum Nakai can induce apoptosis in human acute myeloid leukemia (AML) cells (U937) through the STAT3 pathway [2]. Another natural compound, Artemisinin, extracted from the Chinese medical herb Qinhao, has been widely used in the treatment of malaria and cancer [3-6]. Investigations of certain herbal medicines have reached clinical trials examining their efficacy and safety in cancer management that is based on sound evidence from well-designed clinical studies.

Adjuvant anti-cancer therapies

To date, surgery, chemo- and radio-therapies remain the cornerstones of the treatment for most solid tumours. Side effects and toxicity of chemotherapy and radiotherapy often restrict their application and effectiveness. Indeed, patients who undergo long term chemo- and radio- therapy may have to forego these treatments because of the accompanying toxicity and other side effects. A case can be made for TCM to enhance the responses to chemo- and radio-therapeutics and reduce the severity of these side effects due to conventional treatments. It can help improve quality of life and survival of cancer patients [7]. A number of herbal medicines seem to be beneficial to cancer patients, including single herb traditional herbal formulations and preparations of Chinese medicine. The following are some recent examples. The former includes Radix Astragali (Huang Qi), Ginseng (Ren Shen), Mylabris (Ban Mao), Toad venom (Chan Su), garlic (Da Suan) and Turmeric (Jiang Huang). Mylabris, in particular, can induce apoptosis of cancer cells and bolster the immune system. Its clinical application is nonetheless restricted due to renal toxicity and bone marrow suppression. On the other hand, Astragalus has a potential immunomodulatory role in combination with chemo- and radio-therapies by inceasing the activity of lymphocytes, natural killer cells and macrophages, thereby leading to the secretion of interferon (IFN), interleukin 6 (IL6) and tumour necrosis factor (TNF). It can also enhance the biological function of IL2, and simultaneously reduce its adverse effect [8,9]. A TCM formula, YangzhengXiaoji (YZXJ), which consists of 16 herbs including Radix Astragali, Ginseng, atractylodesmacrocephalakoidz, poriacocosetc (Table 1) has an anti-cancer action [10]. In a randomised double-blind trial in patients with lung cancers, conventional chemotherapy combined with YZXJ (n=304) showed significant disease remission (complete and partial remissions) compared with patients who received chemotherapy alone (n=103) (23.3% vs 14%, respectively, $p<0.01$) [10]. The patients who received YZXJ also had less bone marrow suppression. YZXJ has been used in treating liver,

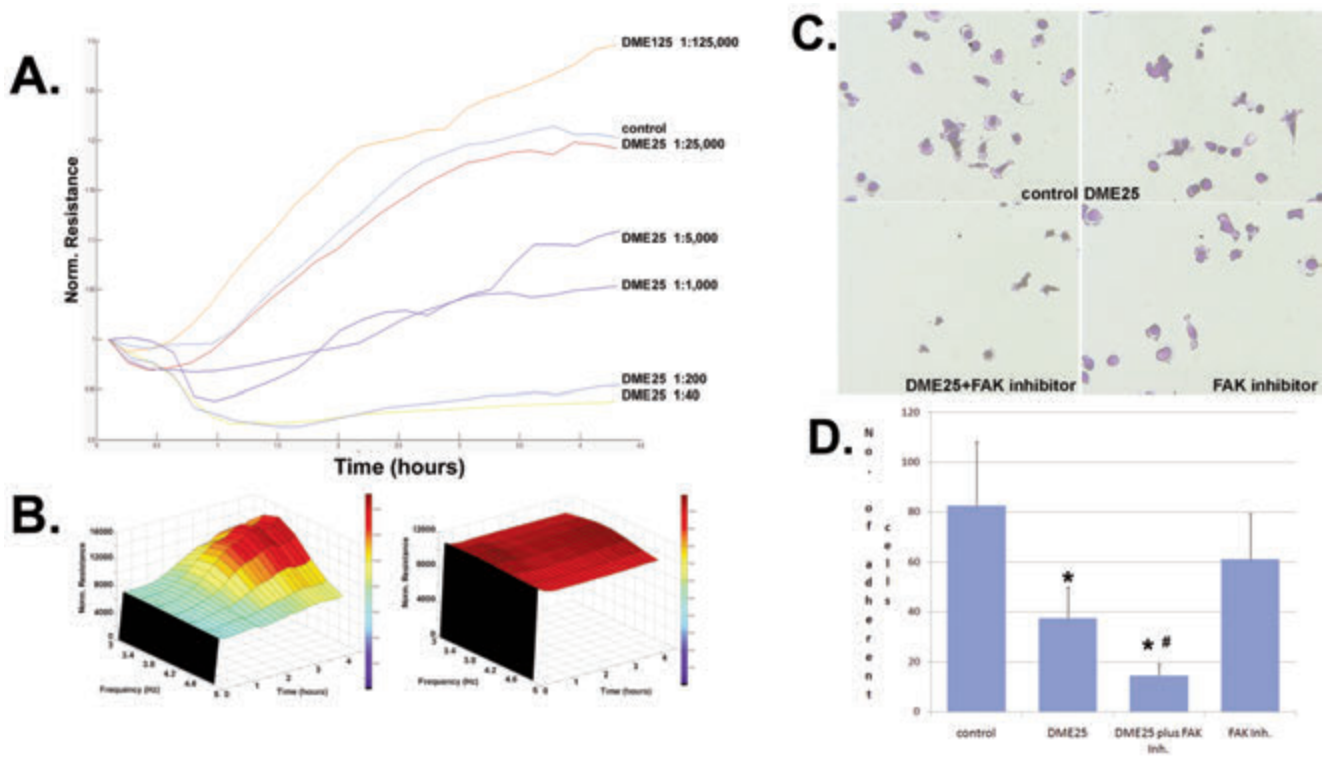

Figure 1. YZXJ (DME25) inhibition of the adhesion of vascular endothelial cell (HECV) to the extracellular matrix, enhanced by FAK inhibitor. A and B: Concentration dependent inhibition of the matrix adhesion of HECV cells by DME25, as demonstrated by ECIS (electric cell-substrate impedance sensing). YZXJ (DME25) was diluted from 1:40 to 1:125,000 (A). Dilutions below 1:25,000 showed inhibitory effect. B: 3D imaging of the adhesion determined by ECIS. Left: control HECV cells ; Right: HECV cells with DME25 at 1:1,000. X-axis: frequencies (Hz); Y-axis:Resistance; Z-axis: time in hours. C and D: cell-matrix adhesion investigated by conventional method. Namely, HECV cells were added to matrix coated culture surface. After 40 minutes, non-adherent cells were washed off. The remaining adherence cells were fixed and stained with Crystal violet. C: Images from crystal violet stained adherence cells; D: Number of adherent cell per high power field. * p<0.01 vs control; # p<0.01 vs DME alone and FAK inhibitor alone [21].

breast, lung, colorectal and gastric cancer. In a meta-analysis of clinical studies and trials, YZXJ significantly reduced the side effects of chemotherapy, which included bone marrow suppression, leukopenia, thrombocytopenia, adverse gastrointestinal reaction and hepatotoxicity [11].

Possible mechanism(s) underlying the anti-cancer effects by TCM

Effect of TCM on the immune system

During the development and progression of cancer, adoptive and adaptive immune response can be evaded by cancer cells. Radio- and chemo- therapy can also impair the immune system, especially through bone marrow suppression. Patients receiving radio- and/or chemo-therapy may benefit from herbal medicine because it has the capacity to improve immune system functioning in numerous ways. First, TCM therapies can enhance the immune response against tumours; second, they can suppress the immune inhibitory mechanisms and adjust the balance of the immune system; and third, they can restore an impaired immune system back to its normal state in treated patients. For example, Radix Astragali can increase INF and TNF secretion, and activate lymphocytes, natural killer (NK) cells and macrophages against tumours. It could also cooperate with IL2 to stimulate lymphokine-activated killer (LAK) cells directed against tumour cells [8, 9]. Mylabris might also restore anti-tumour T cell levels as well as TJ-41 formulation [12, 13].

TCM induces apoptosis and cell cycle arrest of cancer cells

TCM can induce cell cycle arrest and apoptosis of cancerous cells, thereby inhibiting tumour growth. Garlic extracts possess mainly sulphur compounds, especially allicin, diallylsulfide (DAS), diallyldisulfide (DADS), diallyltrisulfide (DATS) and ajoene, which have demonstrable anti-cancer activities. Their anti-proliferative effects have been related to the induction of apoptosis [14, 15]. Indeed, morphological changes and DNA fragmentation are seen in cells treated with DADs and DATs [16, 17]. Bu-Zhong-Yi-Qi-Tang (BZYQT), a formula comprised of astragaloside IV, ginsenoside Rb1 and Rg1, saikosaponina and c and glycyrrhizin, seems to inhibit liver cancer cell growth by arresting the cells in G0/G1 phase [18, 19].

TCM regulates adhesion and motility of cancer cells

Cell adhesion and invasion are important steps in the progression to metastasis. Our institute has focussed on metastasis and angiogenesis for decades, and recently found that YZXJ is effective in inhibiting cancer cell adhesion, migration and angiogenesis in vitro and in vivo[20-22]. Although a few pathways, such as focal adhesion kinase (FAK) and Akt, seem to be involved, more research is needed in understanding how these effects are manifested.

Anti-angiogenesis effect of TCM

Angiogenesis is vital for cancer progression and tumour development where, without an independent blood supply, tumour size

Table 1. Sources table for YangzhengXiaoji capsule

Description	Scientific name	Part of plant
Panax ginseng	Panax ginseng C.A. Mey.	Root and rhizome
Membranaceus	Astragalusmemebranaceus (Fisch.) Bge.var. mongholicus (Bge.) Hsiao	Root
Fructusligustrilucic	Ligustrumlucidum Ait.	Fruitage
Radices curcumaezedoariae	Curcuma phaeocaulis Val.	Rhizome
Ganodemalucidum	Ganodemalucidum	Cystocarp
Gynostemmapentaphylla	Gynostemmapentaphylla (Thunb) Mak	Overground
Atractylodesmacrocephala	AtractylodesmacrocephalaKoidz	Rhizome
ScutellariabarbataD.Don	ScutellariabarbataD.Don	Whole plant
Oldenlandiadiffusa	Oldenlandiadiffusa (willd.) Roxb.	Whole plant
Poriacocos	Poriacocos	Sderotium
DuchesneaindicaFocke	DuchesneaindicaFocke	Whole plant
SolanumlyratumThunb.	SolanumlyratumThunb.	Whole plant
Herbaartemisia	Artemisia scoparia (Bge.) Ki	Overground
CynanchumpaniculatumKitag	CynanchumpaniculatumKitag	Root and rhizome
Eupolyphagasinensis Walker	Eupolyphagasinensis Walker	Dried bodies of females
Endothelium corneumgigeriaegalli	Gallus domesticusBrisson	The wall of sand bag

would be limited due to its reliance on simple diffusion in its immediate micro-environment. The importance of this has long been realised, leading to the development and implementation of anti-angiogenic strategies in the treatment of cancer [23, 24]. The mechanisms through which these various herbal medicines exert their anti-cancerous role are now being elucidated. Together with their direct role on cancer cells, a few herbal medicines affect tumour progression through their anti-angiogenic properties. For example, Koltermann et al. [25] identified an anti-angiogenic role for the standardised extract of G. biloba, EGb® 761[25]. This extract enhances tyrosine phosphatases, such as SHP-1, which in turn prevents signal transduction through the Raf/MEK/ERK pathway in response to growth factor stimulation (FGF or VEGF). YZXJ can suppress angiogenesis in which FAK is involved (Figure 1) [21].

Targeting precancerous disorders

Precancerous conditions or premalignant conditions, such as actinic keratosis, Barrett's oesophagus, atrophic gastritis and oral submucous, are generally considered to increase significantly cancer risk. Two decades ago, researchers began examining the preventive effects of herbal formulas on different precancerous conditions. For example, Anticancer 2 tablet, composed of 6 TCM herbs, was tested on epithelial dysplasia in the cheek pouches of hamsters exposed to a carcinogen [26]. Herbal supplements (quercetin, curcumin, silymarin, ginseng and rutin) added into the diet can be beneficial to patients with precancerous lesions in the large intestine [27]. These supplements can also suppress aberrant crypt foci in an azoxymethane-induced rat colon cancer model and induce apoptosis by regulating Bax (pro-apoptotic) and Bcl-2 (anti-apoptotic), leading to capase-9 activation. Clinical trials using Zengshengping (ZSP) to treat oesophageal epithelial dysplasia have been carried out in 2 districts in China where there is a high risk of oesophageal carcinoma [28, 29]. YZXJ has also been reported to improve atypical dysplasia of the stomach [30]. These are a few examples of clinical studies indicating the potential therapeutic effects of TCM on precancerous conditions or lesions.

There is more evidence now showing that herbal remedies from TCM can be developed as therapeutic approaches for management of some malignancies. The possible benefits of these remedies include: their ability to act as effective therapies for certain malignancies, reducing side effects when combined with chemotherapy/radiotherapy, and having a chemopreventive effect for certain precancerous conditions/lesions, thereby improving quality of life and prolonging survival. On the other hand, side effects and toxicity of herbal medications need to be considered and included in any evaluation made in clinical trials. Although progress in seeking clinical efficacy of TCM in cancer treatment is moving forward, well controlled and blinded clinical trials remain scarce. Investigations into the mode (s) of actions and possible clues in the active ingredient(s) in the TCM continue to be difficult tasks. However, these ancient and traditional medicines do appear to have positive effects on patients with cancer; rediscovering their values in cancer, both clinically and scientifically, will bring further value to the rising challenges of cancer treatment. ●

"Herbal remedies from TCM can be developed as therapeutic approaches for management of some malignancies. They may well bring further value to the rising challenges of cancer treatment"

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In situ breast cancer profiling

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Invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) are the two most common types of invasive breast carcinoma. IDC is derived from the ducts and accounts for 80% of all invasive breast cancers, whereas ILC arises from cells in the lobules of the breast and accounts for 10-15% of invasive breast cancer. The incidence of ILC is increasing in post-menopausal women, and epidemiological evidence suggests that this is due to the increased use of hormone replacement therapy [1]. Both types of carcinoma can be associated with a pre-invasive lesion, ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) (Figure 1). Since the introduction of screening mammography the diagnosis of DCIS and LCIS has become more common. Approximately 20% of screen-detected tumours are DCIS, and in the UK are generally treated in a similar manner to invasive breast cancer with wide local excision and radiotherapy. By contrast, patients with LCIS alone do not receive any further treatment and, even if incompletely excised, no further surgery is performed. It is therefore extremely important for patients and doctors to know which cases of in situ disease might give rise to invasive disease, so that appropriate screening and treatment can be offered and those at low risk of invasive disease can be confidently spared unnecessary treatment.

The disparity in treatment between the two types of in situ disease arises from evidence that DCIS is a non-obligate precursor of IDC, with similarities in genetic and molecular markers between DCIS and subsequent invasive disease. In contrast the link between LCIS and progression to invasive disease is not so clear and there is still debate as to whether LCIS is a true precursor or merely a risk factor for subsequent disease.

Patients with DCIS previously misdiagnosed with benign breast disease who received no surgical intervention were retrospectively followed up to investigate the natural progression of untreated DCIS. The odds ratio for developing subsequent carcinoma was 20.1 [2]. In studies where DCIS has been treated with breast-conserving surgery alone with no radiotherapy, long-term follow-up shows that up to 30% of women develop a recurrence (half of which will be DCIS and half invasive cancer) by 10 years.

Women with LCIS have 2-11 times higher risk of developing invasive breast cancer compared to women of comparable age who do not harbour LCIS [3]. Interestingly not all invasive disease post LCIS is ILC, although there is an excess of ILC, women also develop ductal and mixed lobular-ductal invasive cancers. These cancers occur in both the ipsilateral and contralateral breast and for this reason LCIS is often considered a risk factor for breast cancer rather than a true precursor lesion. However there is evidence that LCIS has similar genetic changes to ILC, indicating that it should also be considered as a precursor (Figure 2). The timescale for the development of invasive carcinoma after an initial diagnosis of LCIS in either breast varies greatly between individuals. One study demonstrated that two thirds of patients developed invasive disease within 15 years of the in situ lesion, however another study found that 50% of patients developed ILC as long as 15-30 years later [4].

Considering that the cumulative risk of developing invasive disease in the ipsilateral or contralateral breast following LCIS is 18% and 14% respectively, the current recommended treatment is frequent breast examination and mammography [5]. However ILC is often not detected on a mammogram so other options for patients at high risk of developing invasive disease post LCIS include screening with magnetic resonance imaging (MRI) or chemoprevention with drugs such as tamoxifen or the aromatase inhibitor, anastrozole, which have been shown to be effective at reducing invasive disease post LCIS [6]. In order to identify patients who would benefit most from such interventions it is firstly essential to understand the molecular basis of LCIS in order to identify biomarkers of progression to invasive disease.

Historically, molecular profiling of LCIS has been challenging for a number of reasons. As LCIS is not commonly associated with clinical abnormalities, and rarely presents clinically with a palpable mass nor does it occur with micro-calcifications, a diagnosis is frequently incidental on a core biopsy. Furthermore as it is not common practice for treatment to be surgical if LCIS is not associated with ILC there are limited amounts of tissue available for profiling studies.

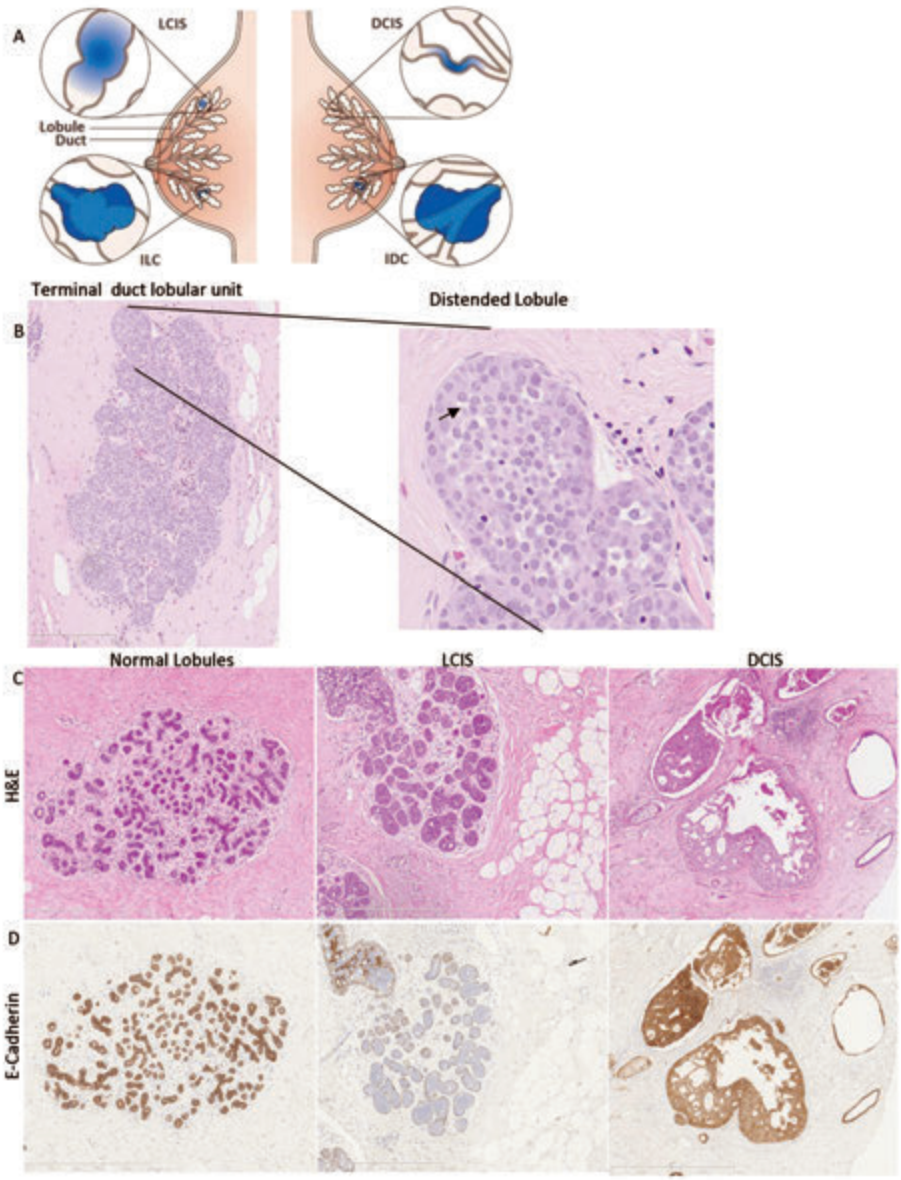

Figure 1. A) Diagrammatic representation of structures contained in the breast indicating the origin of both ductal and lobular variants of *in situ* and invasive carcinoma. Source: Cancer Help UK B) Criteria for the diagnosis of LCIS states that a minimum of half the lobules within a lobular unit must show distension while maintaining the overall structure of the lobule. The arrows indicate discohesion between the cells, a key feature of LCIS. C) Haematoxylin and Eosin stained breast tissue shows distended ducts and lobules. D) Diagnostically, LCIS can be differentiated from DCIS and other non-invasive lesions of the breast by the use of the well characterised marker, E-cadherin. E-cadherin is a transmembrane protein with an important role in intracellular adhesion coded by *CDH1*, a gene located on 16q22.1 Staining of E-cadherin shows loss of expression in LCIS compared to normal lobules and DCIS.

This issue has been addressed by the GLACIER (Genetics of lobular carcinoma in situ in Europe) study, which has recruited over 2000 patients with either LCIS or ILC with an aim of understanding genetic predisposition and progression of LCIS to ILC. Peripheral blood and formalin fixed and paraffin embedded (FFPE) tissue were collected from all patients. This has provided a vast tissue resource from which DNA/RNA can be extracted for profiling. Another significant obstacle is the quality of material obtained from FFPE samples. The key issue is the method of fixation and length of time before fixation of the tissue. Variations in both will cause differing levels of degradation to both the extractable RNA and DNA [7]. DNA and RNA of higher quality can be obtained from fresh frozen tissue, however as tissue banking of fresh frozen tissue from in situ disease has not been routinely performed by established breast tissue banks, this is a scarce resource.

In recent years, there have been vast technical developments, which allow DNA or RNA molecular interrogations to be performed in samples where tissue is scarce or quality of material is relatively poor. For example, molecular inversion probes (MIPs) overcome specific issues arising from genotyping and the assessment of copy number variations in degraded DNA. MIPs are small sequences of DNA, the ends comprise two small sequences which are complementary to two adjacent sequences on the genome, which results in successful probe binding requiring only a 40 bp target binding site. Such assays have been carried out with as little as 40 ng of DNA [8].

In addition when conducting profiling studies the different histopathological subtypes of the lesion under investigation need to be considered. To date LCIS can be classified into three groups, classical (cLCIS), pleomorphic (pLCIS) and florid (fLCIS), all of which have been shown to have differing molecular profiles which have differentially clustered on unsupervised hierarchical clustering of genome copy number profiles. An interrogation of fLCIS by array comparative hybridisation has revealed this lesion to be genetically more aberrant compared to the classical variant. Together with the fact that fLCIS is more frequently found with invasive disease has highlighted a need for differential clinical treatment of variants of the same lesion. A region of amplification, 11q13.3 containing the CCDN1, cyclin D1 gene was also identified and validated immunohistochemically (IHC). In this analysis 80% of cases with amplification also had higher protein expression. This

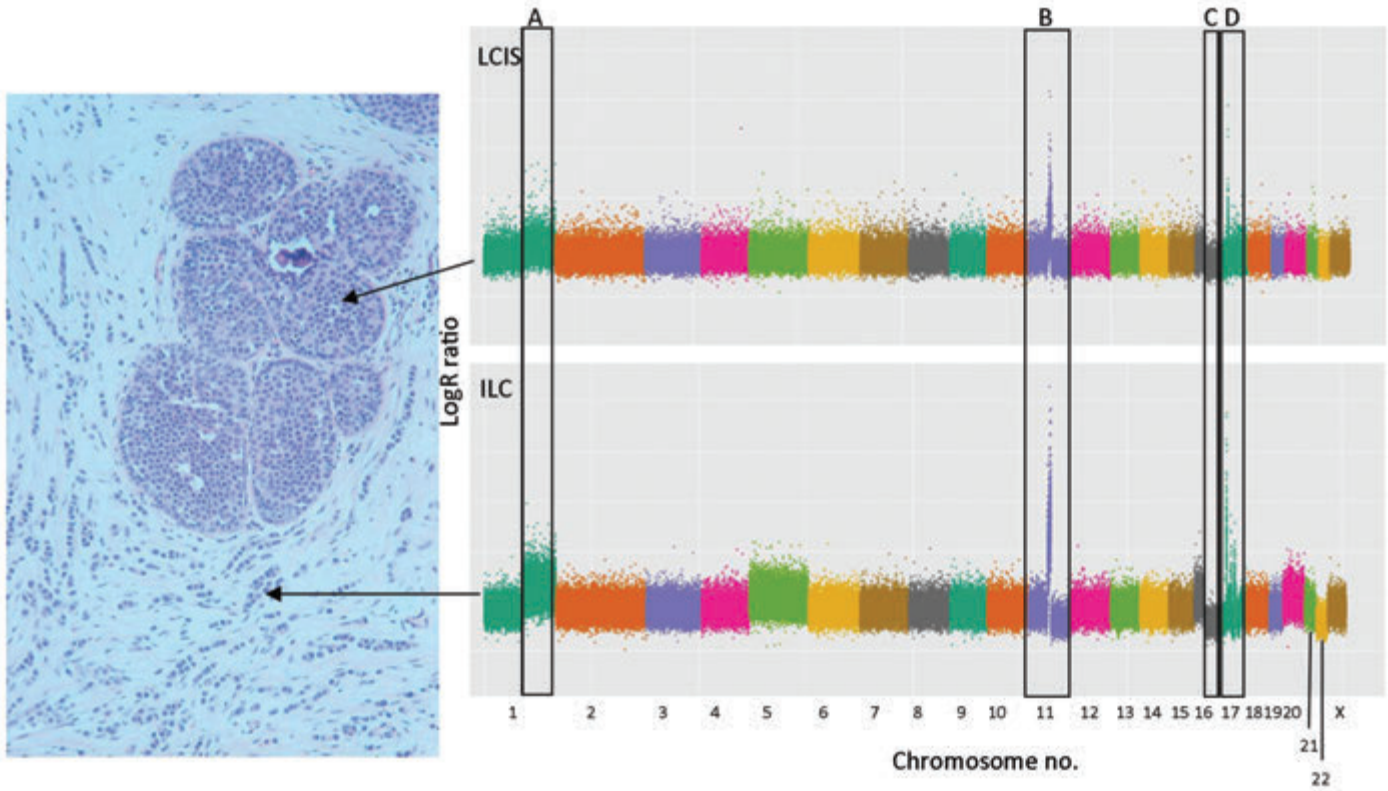

Figure 2.
A) 1q gain, characteristic of lobular lesions
B)Amplification in region containig *CCND1*, codes for cyclinD1
C) 16q loss, characteristic of lobular lesions
D) *HER2* amplification
Copy number profile (OncoScan™ array, Affymetrix) obtained from microdissected LCIS and adjacent ILC shows similar genetic changes: gain 1q, amplification of cyclin D1 and her 2 gene, 16q loss.

is an interesting cell cycle regulatory gene which has been identified in several studies which suggests it may have a role in disease progression [9].

Due to the limitations surrounding the molecular profiling of LCIS, obtaining a complete gene expression profile has been difficult. In 2008 the first global gene expression profile of LCIS was created. Analysis was carried out to identify genes which were differentially expressed between LCIS and normal breast epithelial cells in order to uncover dysregulated pathways. As only one complete RNA profile was obtained, subsequent validation of findings was carried out at the protein level using IHC on a larger number of LCIS cases. Proof of validity was achieved by the observed characteristic down regulation of E-cadherin. The two main findings of this work showed down regulation of claudin 4, a tight junction protein, which according to the functional biology of this molecule would correlate with E-cadherin dysregulation and interestingly, over expression of matrix metalloproteinase 9 (MMP9). MMP9 is thought to be essential for the process of cancer cell invasion and could therefore play a role in the development of invasive disease [10].

The advent of next generation sequencing means that whole exome, genome and transcriptome analysis of tumours is now feasible. As well as identifying genes or pathways which may be important in progression of DCIS/LCIS, these techniques also allow more global analyses, looking at genetic diversity and clonal structure. These may also prove to be biomarkers of progression as they measure the carcinogenic process as a whole. These techniques require good quality DNA/RNA and have not yet been widely applied with success to FFPE material. Next generation sequencing has the added complication for in situ disease of requiring relatively large amounts of DNA/RNA that are often not easy to obtain from the limited tissue available. However the field is rapidly evolving and massively parallel targeted sequencing is now an option for small quantities of FFPE material although paired germline DNA is essential in order to differentiate between germline and somatic mutations. A recent comparison of library preparation methods, from both low quality and quantity RNA for sequencing has shown that from 100 ng of fragmented RNA, it was possible to achieve over 60% 5' and 3' end coverage with a low duplication rate and percentage of ribosomal RNA, factors which indicate good library performance [11].

As LCIS is more commonly bilateral than DCIS and is more common in women who have a first degree relative

diagnosed with breast cancer it has been suggested there may be an inherited component to LCIS development. A recent study has shown that 8% of the cases with bilateral LCIS harbour rare truncating germline CDH1 mutations [12].

In addition a genome wide association study has focused specifically on finding common low risk genetic variants associated with ILC and /or LCIS. The results showed many of the genetic variations predisposing to ILC also predispose to LCIS, with some having a stronger effect on LCIS than ILC, given further support to the hypothesis that LCIS is a precursor of ILC. Once genetic predisposition to ILC and LCIS is fully understood it may be possible to identify those patients most at risk of developing invasive disease by genotyping germline variants using DNA extracted from a blood sample [13].

Similar issues exist with DCIS with one of the main barriers to identifying biomarkers being the lack of large patient cohorts. 90% of published DCIS biomarker studies have used less than 50 cases. More recently, the Genomic Health DCIS score, based on the expression of a commercially-protected unknown set of genes, has been shown to predict recurrence of pure DCIS, but this awaits validation [14] Two large DCIS resources exist in the UK (Sloane Project and ICICLE study) but again only FFPE material. As with LCIS, DCIS can also be divided into different subtypes based on grade and architecture.

Although profiling has provided no firm changes in the treatment of LCIS / DCIS to benefit patient outcome to date, this is a rapidly changing field particularly with the development of RNA seq and genome/exome sequencing. Identification of biomarkers that identify those women most likely to develop invasive disease following DCIS/LCIS would dramatically impact on the clinical care of these women. This area has been highlighted as a critical gap in breast cancer research internationally. There is concern regarding over-treatment of DCIS and this is reflected in new clinical trials of DCIS offering observation alone following biopsy for low and intermediate grade DCIS (LORIS trial, UK and LORD trial, the Netherlands). However, for some women omitting radiotherapy is associated with a high risk of development of invasive disease. For observation-only to be a viable treatment option, it is imperative that biomarkers are identified in order to avoid under treatment of those most at risk following a diagnosis of DCIS or LCIS. ●

"Identification of biomarkers that identify those women most likely to develop invasive disease following DCIS/LCIS has been highlighted as a critical gap in breast cancer research internationally and would dramatically impact on the clinical care of women with DCIS/LCIS"

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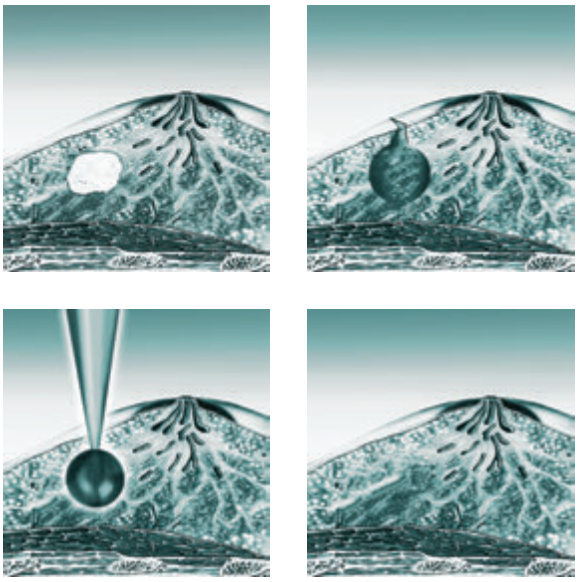

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A reconstructive approach to the perineal defect

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Abstract

Perineal reconstruction after resection of rectal and anal malignancy can be challenging. The nature of the defect, available donor sites and the impact of neo-adjuvant radiotherapy are amongst the most important factors that govern the reconstructive course taken.

Introduction

Surgical resection of rectal and anal malignancy can result in perineal defects that require soft tissue reconstruction. It is important that the reconstructive approach is flexible, adaptable and optimises wound healing in an anatomical area where wound problems can cause significant morbidity.

The many options of reconstruction aim to avoid visceral herniation and result in primary healing, particularly when neo-adjuvant radio-chemotherapy has been used.

This review article aims to provide the reader with an overview of the reconstructive options used in perineal reconstruction.

Choosing a reconstructive approach

Factors which play a significant role in the choice of reconstruction include the size and position of the defect (sacral resections vs perineal) and whether a double sided reconstruction is needed in order to include the posterior wall of the vagina. Previous surgeries, for example, those involving the abdomen or intra-operative ligation of vessels, may preclude some reconstructive options or at least make them more challenging to undertake.

The size and the underlying bony support of the defect needs to be assessed, so that the flap meets the reconstructive need with respect to size, sturdiness and application. It may even be necessary to employ a combination flap technique when dealing with bigger wounds, which span a larger area or two outside surfaces. The size of a gracilis flap is finite and cannot cover a vast defect, however it is independent of the internal iliacs and can provide double-sided reconstructions. Buttock rotation flaps can be advanced repeatedly should the initial rotation be inadequate.

Multiple previous operations can be common in this cohort of patients and make operative planning challenging. It can impact significantly on the availability and quality of donor tissue. For example, lower extremity flaps may be preferred if abdominal donor sites are unavailable or there is potential donor site morbidity. A previously operated abdomen makes the raising of the VRAM flap (discussed below) more complicated as the posterior sheath of the rectus is often adherent to the rectus muscle and with that the pedicle, therefore, raising that flap can leave an abdominal wall defect which may not be amenable to direct closure.

Intra-operative ligation of the internal iliac vessels, carried out to reduce pelvic bleeding also, theoretically, precludes the buttock-based flaps for reconstruction. One should be aware of the potential risk of necrosis of this territory in such cases. In addition, it is good practice to plan a secondary reconstructive approach that can be followed if difficulties are encountered at the time of flap harvest or inset to the recipient site.

Irradiated tissue heals poorly due to the fibrosis of the small vessels and is reflected in the high rate of complications related to radiotherapy use [1,2]. In this setting, there is a greater need for the provision of well vascularised muscle coverage to the affected site. Bringing well-vascularised tissue into the defect ensures primary healing. The role of radiotherapy in the treatment of low rectal cancer is increasing and so has resulted in a greater overall need for myocutaneous perineal reconstruction [3]. However, certain flap vascular pedicles may be compromised through scarring and be included in the area of irradiation. Ideally, proposed donor sites should not coincide with radiation sites to avoid problems that can increase the risk of flap failure.

Other factors for consideration include the time on-the-table for the patient, complexity of reconstruction and patient positioning. Turning the patient repeatedly intra-operatively is cumbersome. Reconstruction with the posterior thigh and gluteal-based flaps can be performed entirely in the prone position. However, if the patient is presented prone, this should not entirely preclude an abdominally based flap if it is the best reconstructive option. This then necessitates either the VRAM flap to be raised first, then banked, after which it is inset last, or

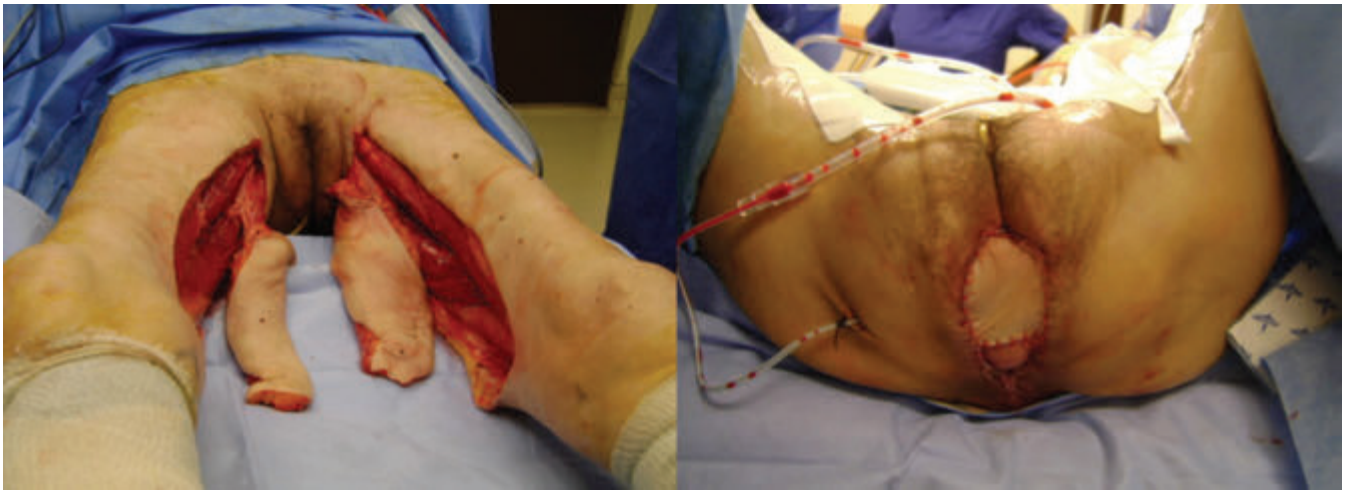

Figure 1: Bilateral gracilis flaps.

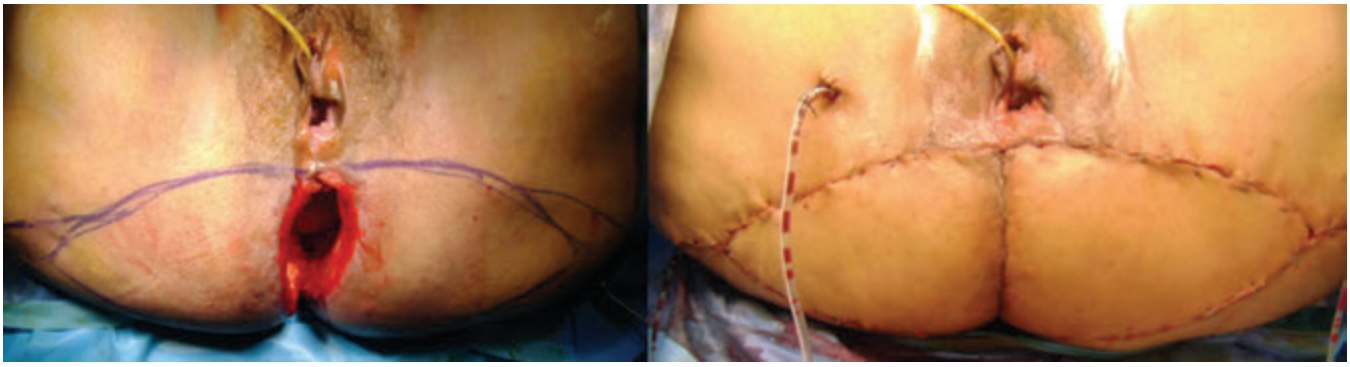

Figure 2: V-Y gluteal advancement flaps

the patient turned repeatedly and the abdominal wound re-opened. If the rectus is raised first, kinking of the pedicle must be avoided during the delay.

It is always necessary to have a 'plan B', which ideally has been discussed with the patient pre-operatively. This is because as the operation proceeds, the initial plan may have to be changed. It is never a good idea to offer only one solution, especially when faced with complex 3-D reconstructions.

Specific post-operative requirements include nursing in the lateral or prone position to avoid pressure at the wound site and patients to be mobilised gently. Drains may need to be placed for prolonged time periods and the nutritional state of the patient must be optimised.

The short guide to flaps

VRAM flap

The vertical rectus abdominis (VRAM) flap is based on the deep inferior epigastric vascular pedicle. It can be used with or without an extended skin paddle and has a wide arc of rotation. This flap has been shown to provide reliable wound healing in perineal reconstruction and in particular in patients who have undergone extensive abdominoperineal reconstruction with or without radiotherapy [4, 5]. This may be owed to its' relatively robust vascular pedicle. However, the presence of stomas exiting via the anterior abdominal wall can preclude the use of this flap. The flap must always be taken from the opposite site of the stoma, as otherwise it will result in umbilical loss.

Gracilis flap

The gracilis flap (figure 1) can be used as a myocutaneous or muscle only flap (based on the medial femoral circumflex artery). It has a relatively small muscle bulk so is more useful when dealing with small narrow perineal defects. However, bilateral flaps can be harvested for use in larger or double sided defects. Unlike abdominally based flaps, it has the advantage of not interfering with the creation of a colostomy site in the setting of abdominoperineal resections. This flap has shown to reduce the incidence of major infection associated with perineal closure in cases of immediate reconstruction [6].

In addition, dynamic graciloplasty can be performed, whereby the gracilis muscle is transposed to the anus with the implantation of stimulating

"It is important that the reconstructive approach is flexible, adaptable and optimises wound healing in an anatomical area where wound problems can cause significant morbidity"

electrodes to produce functional neosphincters and therefore restore normal defecatory function [7].

V-Y advancement flap

V to Y gluteal advancement flaps (figure 2) rely on a subdermal blood supply and preserves the gluteus maximus muscle beneath. Medial advancement is permitted by subcutaneous tissue laxity. Once coverage of the defect is achieved, the secondary lateral defect created by advancement is closed primarily [8].

iGAP flap

The inferior gluteal artery perforator (iGAP) flap is based on perforators of the superior or inferior gluteal artery. These types of flaps have the advantage of sparing muscle and so reducing donor site morbidity but still provide adequate tissue coverage in extensive cases of perineal defect [9].

Buttock rotation flap

The gluteus maximus musculocutaneous rotation flap is based on the inferior blood supply and medially on the superior gluteal artery. It is elevated in the plane overlying the gluteus medius muscle, but can include this. This flap is particularly useful in the coverage of sacral defects but has been employed successfully in perineal reconstruction [10]. The beauty of this flap is that it can be re-rotated to fit into the defect and double-breasted for strength and sturdiness.

Posterior thigh flap

The posterior thigh flap is based on the descending branch of the inferior gluteal artery perpendicular to the gluteal crease and is comprised of fascia overlying the hamstring musculature along with the inferior portion of gluteus maximus. The flap may remain sensate as it is elevated along with the posterior cutaneous nerve of the thigh. It can provide excellent wound coverage and versatility in the perineal region [11] for the prone patient.

Conclusion

Perineal wounds present an interesting problem for both the colorectal and plastic surgeon. Muscular and myocutaneous flaps have shown to be efficacious in promoting wound healing. The nature of the defect, available donor sites and the presence of irradiated tissue are major factors that determine the reconstructive course. Careful pre-operative planning and involving the plastic surgeon at an early stage is required to optimise wound healing and improve patient quality of life. ●

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Imaging to Detect Cervical Cancer in Low-Resource Settings

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Cervical cancer prevention remains a top medical priority for much of the developing world [1]. Research in the developed world has shown that combining a screening method (cytology – the Pap Smear), with an appropriate follow-up program can reduce cervical cancer deaths by up to 80% [2]. Cervical screening is most effective when combined with colposcopy and cervical biopsy as follow-up. Although cytology has been an effective screening method in developed countries, it requires a laboratory infrastructure seldom found in developing countries; moreover, in the developing world it is not uncommon for a patient to travel several miles by foot to get to a clinic, making follow-up appointments difficult. A highly preventable disease, cervical cancer has been fought in developed countries, yet it is a leading cause of cancer death for women in developing countries [3], with nearly 85% of the prevalence rate occurring in the latter [4].

In order to minimise the gap in screening, availability between the developed and the, developing worlds, visual inspection with acetic acid (or VIA) was proposed as a cheap, relatively efficient and easy to implement screening method for low-income settings. VIA requires little infrastructure and training of health care practitioners and allows for immediate treatment following a positive diagnosis [5]. As a result, in many developing countries, VIA is the primary step, and the standard, for cervical cancer screening; however, it is rarely corroborated by colposcopy and biopsy.

Recently it was shown that VIA has successfully reduced cervical cancer mortality by 31% when coupled with cryotherapy [6], in which compressed CO_2 or N_2O refrigerant are used to ablate pre-cancerous or cancerous tissue. Cryotherapy is minimally invasive, fast and effective at mitigating the risks from the cancer returning in 89-91% of cases [7]. Though rare, some serious side effects may occur following cryotherapy, these include infection, bleeding, and excessive treatments which can lead to infertility [8]. Given its cost effectiveness, easy and quick application, minimally invasive status, cryotherapy has become the treatment of choice for clinics operating in low-resource settings. Together, VIA and cryotherapy form the "screen-and-treat" approach, which combines screening and treatment into one visit – a design critical in low-resource settings, which has been adopted as the standard for cervical cancer interventions in low-resource settings.

Figure 1: The Mobile Colposcope, disassembled into each of its component parts. From left to right: illumination unit, optical lens assembly, cell phone case, and Motorola Moto G Smartphone.

Despite its success, VIA presents a major challenge: with a positive predictive value (PPV) of 17% [9], five out of six patients receive cryotherapy unnecessarily, as a result of a false positive VIA result. In order to reduce the number of false positives, MobileOCT has developed a mobile colposcope that serves as an adjunct to VIA, while also providing a technological platform that enables high-end multi-modal imaging. At its core, the device consists of a cell phone, an illumination system, and an optical attachment (Figure 1). With a 3D printed phone case and handle, containing the batteries and light system, all the core elements come together into one compact device. Additionally the phone contains an application designed to view, record, document and share images of the cervix. The device will enable clinicians to observe, diagnose, and document cervical abnormalities on-site in a single visit.

Figure 2: The assembled Mobile Colposcope.

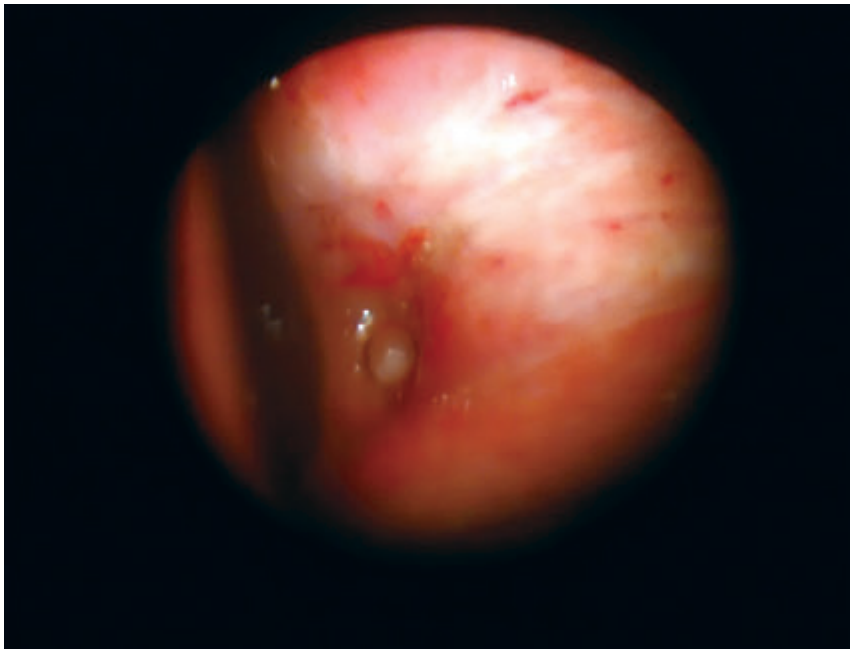

Figure 3: Image of a cervix taken during cervical exam of patient at a clinic in Haiti with the Mobile Colposcope (courtesy of Dr Jonas Eddy).

Low-cost cervical imaging with the Mobile Colposcope

The mobile colposcope is an adjunct to existing detection procedures. The device is designed to improve the detection of cervical cancer precursor lesions in 3 ways:

1. It provides a magnified image of the cervix that is similar to that of many developed world colposcopes.
2. It allows for documentation of clinical images and diagnoses, as well as the possibility of sharing that documentation with colleagues for remote quality and offline quality control.
3. It provides a platform for integrating biophotonics technologies that are currently being developed.

While the biophotonics technologies require developing additional hardware, providing image sharing and analysis capabilities can be done with software alone. Proprietary software that enable for image sharing and analysis has already been integrated into the prototypes being tested in the field. With these features, the device application allows a doctor to access an image taken by the device instantly from anywhere in the world with an internet connection.

The current Mobile Colposcope prototype (Figure 2) allows for high-resolution bright-field imaging of the cervix – the visualisation method that clinicians are used to working with on conventional colposcopes. The device has been positively received by clinical workers using it in the field in: Kenya, Haiti, Botswana, Mexico, and the US. One Image from the Haiti clinic is shown in Figure 3.

Future iterations of the Mobile Colposcope will integrate high-resolution bright-field imaging with two biophotonics modalities, polarisation difference imaging (PDI) and multi-spectral imaging. In polarisation difference imaging, the two polarisation components of light are imaged separately; this modality can provide information on micro-structural patterns within the superficial tissue layer. Multi-spectral imaging collects information on the composition of the tissue, the size and distribution of scattering particles, and other related information.

Multi-Modal Imaging on the Mobile Colposcope

While the addition of colposcopic imaging and telemedicine capabilities will likely improve detection of cervical cancer precursor lesions in low-resource settings, higher accuracy is required for screening devices [10]. Advanced analytical methods, such as those offered by biophotonics, are therefore necessary. Here, the different components of the light used to image the cervix (i.e., wavelength, polarisation) are detected independently. Together, these data cumulate into a dataset from which tissue parameters can be measured.

Multi spectral imaging

The transport of light through the tissue is a function of the (wavelength-sensitive) optical properties. The transport varies greatly by tissue type and optical setup, and it is critical to use the right expression if one wants to make accurate measurements. In tissues, scattering, as described by the reduced scattering coefficient μ_s', is the dominant event. Its wavelength dependence is given by [11]

$$\mu_s'(\lambda) \approx a\,(\lambda/\lambda_0)^{-b} + c\,(\lambda/\lambda_0)^{-4}$$

The first term represents anisotropic scattering from larger structures (nuclei, mitochondria), while the second term represents isotropic scattering from smaller structures (collagen fibrils and cross links). Scalars a and c represent the relative concentrations of larger and smaller structures, respectively. The decay coefficient b (≈1) depends on the size distribution of the structures. Practically, isotropic scattering dominates at lower

wavelengths (<500 nm), while the anisotropic scattering dominates at higher visible and near infrared wavelengths.

The wavelength dependence of the absorption coefficient depends on the absorption spectra of the tissue. Total absorption can be approximated as a simple sum of its individual chromophores. For most tissues there are 3 dominant chromophores: water, and oxy- and deoxy- hemoglobin.

$$\mu_a(\lambda) = C_{water}\mu_{a\ water}(\lambda) + C_{blood}(SO_2 \bullet \mu_{a\ oxy}(\lambda) + (1 - SO_2) \bullet \mu_{a\ deoxy}(\lambda)).$$

Here, the 3 chromophore concentrations are re-represented in terms of parameters of interest to clinicians, namely as the water content C_{water}, blood content C_{blood}, and oxygen saturation SO_2.

Collectively, it is possible analyse images and solve for these 6 parameters (a, b, c, C_{water}, C_{blood}, and SO_2) by illuminating the tissue with 6 (or more) wavelengths. This can be done by illuminating with inexpensive sources such as LEDs.

Polarisation difference imaging

Just as the optical properties of tissues depend on wavelength, they also depend on polarisation. The polarisation of the light changes with each scattering event, and thus most of the light that escapes the tissue is depolarised [12]. However, there is one region in which light transport between the two orthogonal polarisation states differ – the superficial region of the tissue less than one scattering event [13]. The depth of this region is a few hundred microns, depending on the optical properties of the tissue. For many tissues (including the cervix), this single scattering layer roughly corresponds to the epithelial layer where dysplasia (cervical intraepithelial neoplasia, or CIN) forms. However, most of the light that returns comes from the underlying stroma. Consequently, it is difficult to analyse epithelial structures as this small signals sits atop a strong background from the stroma.

One way to isolate this superficial epithelial layer is to implement polarisation difference imaging [13]. With linearly polarised illumination, the difference between the parallel and orthogonal components cancels out the strong background caused by the stroma, revealing structures within the epithelium. Differences in epithelial structures can inform of structural abnormalities associated with low-grade or high-grade CIN.

The hardware changes required to implement both PDI with multi-spectral imaging are minimal – all that is required are some LEDs and polarising filters. Together, these biophotonics methods can be adapted to a mobile device such as the mobile colposcope, offer a powerful way to augment standard bright-field imaging techniques like colposcopy in order to extract additional information about the tissue. Currently, several prototype units have been developed, and these devices have started undergoing extensive clinical testing at four sites in three countries.

Concluding Remarks

Across much of the developing world, the standard of care for cervical cancer screening is VIA, in which the cervix is examined with a naked eye. A smartphone-based mobile colposcope can augment this procedure by adding imaging and magnification capabilities, as well as remote image analysis, while providing a platform for biophotonics methods such as PDI and multi-spectral imaging. With the right implementation and engineering design, these methods have the potential to integrate into the standard of care for cervical cancer screening in low-resource settings. ●

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"At its core, the device consists of a cell phone, an illumination system, and an optical attachment. With a 3D printed phone case and handle, containing the batteries and light system, all the core elements come together into one compact device"

Localised biomaterial-based adjuvant chemotherapy for neuro-oncology

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Glioblastoma (GBM) is the most prevalent and aggressive malignant brain tumour with a median survival from diagnosis of 12 to 15 months. Standard-of-care treatment consists of radical surgery followed by radiotherapy with concomitant systemic temozolomide. Nevertheless, due to the infiltrative nature of GBM, this treatment strategy almost universally fails to eradicate minimal volume residual disease, which typically recurs within 2cm from the original lesion [1]. A homogeneous treatment regime and re-growth of the tumour locally, presents a firm clinical and scientific rationale in which to develop innovative therapies delivered interstitially. There is a critical need to develop more effective and targeted chemotherapy regimes that can eradicate residual GBM cells following neurosurgical resection, thereby improving local control within the brain parenchyma beyond the surgical cavity wall and reducing the risk of tumour recurrence [2]. The opportunity to deliver therapeutic cancer drug concentrations locally creates the possibility of improving both the safety (low toxic dose systemically) and efficacy (high effective dose locally) of cancer chemotherapy, thereby enhancing the benefit of surgery, as well as continuing anti-neoplastic treatment during the interval between surgery and commencement of systemic adjuvant therapy.

Although a myriad of drug-polymer devices have been developed to date, the Food and Drug Administration (FDA) and National Institute for Health and Clinical Excellence (NICE) has solely approved the use of chemotherapy impregnated polymeric wafers (Gliadel®) for local chemotherapy delivered via a biomaterial, for the treatment of primary and recurrent malignant glioma. These wafers which are neurosurgically implanted at the time of tumour resection, gradually release the chemotherapeutic agent carmustine, which then diffuses into the surrounding brain and targets the residual cancer cells that have infiltrated the brain tissue. These studies and trials offer hope to this mode of intra-cavity drug delivery, with results showing a moderate but significant survival benefit of 2.3 months and 1.8 months median survival for newly diagnosed and recurrent high grade gliomas respectively [3,4]. The treatment has nevertheless shown limited efficacy mainly due to: (i) poor drug diffusion, restricted to 2-3mm bordering the implant; (ii) implants not maintaining close contact with the resection cavity rim and falling to the bottom of the cavity; (iii) only one drug being delivered [5]. OncoGel™, a controlled-release formulation of paclitaxel in ReGel™, comprising a thermosensitive triblock copolymer (PLGA-PEG-PLGA), has shown much pre-clinical promise. This system is water soluble at 2-15°C and turns into a viscous gel at body temperature [6]. Pre-clinical and early clinical investigations demonstrated OncoGel™'s ability to physically target paclitaxel to brain tumour tissue via intralesional injection into the tumour cavity following resection, with an acceptable safety profile and moderate increase in survival in a rat gliosarcoma model [7].

Our partners at the School of Pharmacy, University of Nottingham, have developed a novel formulation of Poly(lactic-co-glycolic acid) (PLGA)/poly(ethylene glycol) (PEG) copolymer microparticles which creates a mouldable paste when mixed with liquid. At body temperature only, the paste hardens into a solid matrix, potentially releasing multiple drugs simultaneously over several weeks (Figures 1 and 2). We have previously described this PLGA/PEG formulation as the only drug delivery formulation to our knowledge that can be pasted onto the tumour resection cavity wall, thereby potentially offering closer proximity of drug depot to residual tumour cells than existing methods (Figure 3). The material has clear clinical utility as we have demonstrated the relative ease of application ex vivo, distinguished the biomaterial on MRI/CT clinical scans and shown that the material can withstand a 6-week clinically-relevant radiotherapy dosing schedule [8,9].

The rationale of these polymer-based approaches is to improve upon drug efficacy, increase exposure time of tumour cells to drug, protect drugs from degradation and clearance by the immune system until its release from the

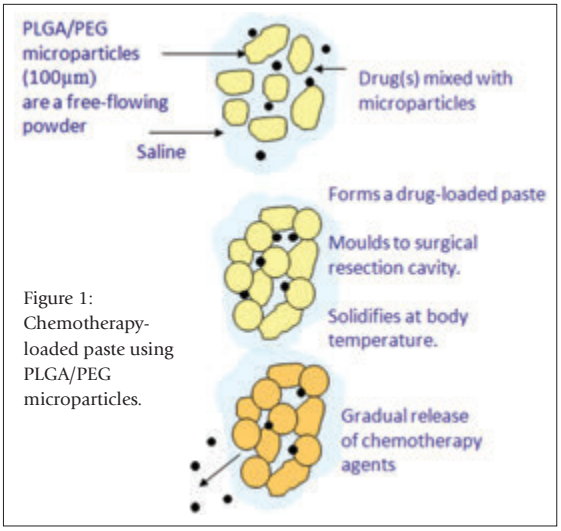

Figure 1: Chemotherapy-loaded paste using PLGA/PEG microparticles.

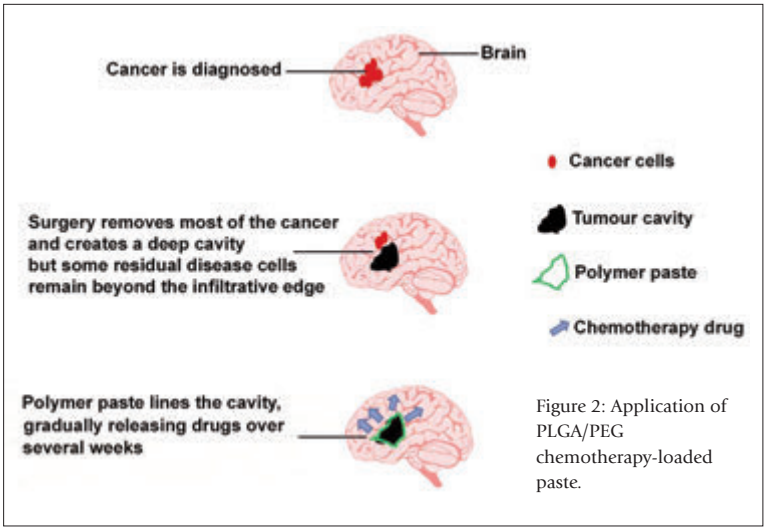

Figure 2: Application of PLGA/PEG chemotherapy-loaded paste.

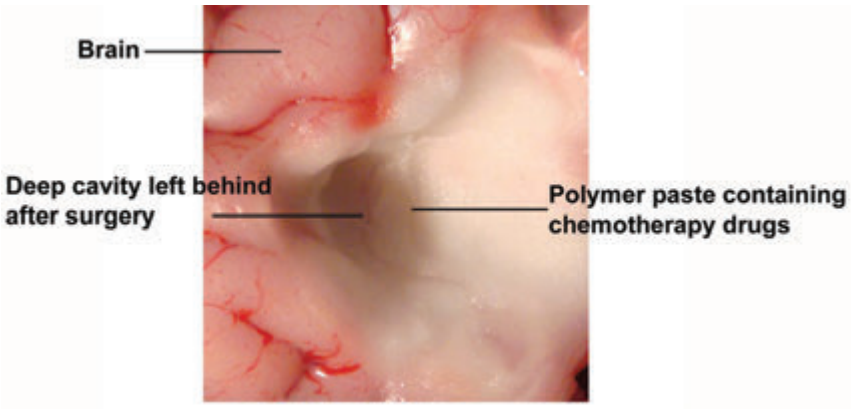

Figure 3: PLGA/PEG paste can be moulded to the surgical resection cavity lining (ex vivo ovine brain shown).

polymer, and reduce the debilitating sequelae of current systemic chemotherapeutics, allowing oncological treatment to be maintained in the interval between surgery and radiotherapy.

However it is not clear whether the failure of chemotherapy drugs to achieve durable responses in GBM is due to the intrinsic resistance of residual disease or the lack of drug penetration at therapeutic doses. The former can realistically only be overcome using next-generation molecularly-targeted chemotherapeutics, whereas the latter is a considerable obstacle for more efficacious drug delivery in the future. However, given the difficulty associated with measuring chemotherapeutic drug distribution in the CNS, tissue-based pharmacokinetic measurements are typically not achievable in human clinical settings. Therefore drug distribution has been measured in the brains of rodents and non-human primates as surrogate models to advance drug selection for the treatment of brain tumours. Such approaches rely on high numbers of animals and cannot address how non-labelled native drugs released from a local delivery system behave when diffusing throughout brain tissues. Technologies that utilise mass spectrometry (MS) as a detector for diverse analytes could potentially overcome some of these limitations, by directly measuring individual molecular species in complex samples. One such method is liquid extraction surface analysis MS (LESA-MS), a novel ambient surface profiling technique that combines liquid extraction of analytes from a solid surface (e.g. organ-specific tissue) with nano-electrospray MS [10,11]. The distribution of drugs could thus be characterised rapidly by analysing anatomical contexts ex vivo, such as brain slice cultures, where the delivery system can be incorporated. LESA-MS presents added benefits including the ability to discriminate multiple drugs simultaneously, lower costs, little-to-no sample preparation, rapid analysis and analysis in an ambient environment - features important for effective spatially-resolved drug localisation.

Drug delivery using a single local administration requires careful consideration of potential damage to healthy neural cells. Understanding drug distribution from the polymer is crucial to predict the effect on tumour cells and normal brain. One difficulty is that therapeutic doses and maximum tolerated doses (MTD) typically relate to systemic delivery. To overcome this we anticipate loading drug amounts in our polymer system based on drug release data from in vitro and in vivo studies, ensuring that the early burst release is less than the MTD. Selection of locally-delivered chemotherapeutic agents that display widespread brain tissue distribution will benefit brain tumour patients by potentially offering more efficacious treatment directly at the site of the tumour.

As we progress towards an era of individualised medicine, equipped to target specific molecules and pathways in GBM and other brain tumours, we need to continue to develop local drug delivery systems as a crucial corollary. Drug delivery innovations will enable us to expand the selection of chemotherapeutics that will become amenable for use in the clinic, ultimately to the benefit of the patients and their families. ●

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Commentary on Dr Richard Ablin and Ronald Piana's book "The Great Prostate Hoax" [1]

Denys N Wheatley (Editor)

Prostate cancer awareness and detection – a burgeoning medical problem

Prostate cancer has now assumed a significance in men almost akin to that of breast cancer in women, with campaigns and organisations using celebrities and the media to drive home throughout the media the need for surveillance and early diagnosis. It is the most common form of cancer in men, which in the near future might have such prominence as to be a major burden to any healthcare system. This is because its incidence increases with age, and as medical advancement over the last two decades has led to significantly increased longevity, this ironically exacerbates the problem. Unless an even wider policy of "wait and see" (active surveillance) is pursued, every man who lives to a hundred will have or have had some prostatic dysplasia, precancerous or cancerous in most cases. Many may outlive prostate cancer, but there will also be many who will not. Early diagnosis is therefore central issue, especially as progression in prostate cancer is unpredictable and can be very rapid. Like breast cancer, prostate cancers can suddenly metastasise, and "active surveillance" may involve review intervals that are too far apart to catch cases of rapid dissemination. Our dilemma is that we know virtually nothing about how this change in invasiveness comes about [2], also discussed by Dr Ablin in the editorial to this issue.

Campaigns

Have the campaigns to build public awareness in men about prostate cancer and the possibility that they might be vulnerable been effective? If we consider another tumour, lung cancer, we have seen campaigns in the UK (e.g. one of them featuring Sir Alec Ferguson) that try to get the message across. Some people may take notice; but the perennial question is whether those most vulnerable heed these warnings. Putting danger of death on cigarette packets might help, but it seems that hardened smokers are still prepared to run the risk. It is different with the prostate because there is no clearly associated habit or life-style that precipitates cancer, other than a genetic defect in the GST gene, which can in some cases indicate a hereditary basis. Do campaigns like those featuring Bob Monkhouse or Bill Bailey (his "Men United" promotion) in the UK get the message across - do they alarm rather than alert men, or do they largely go unnoticed because they have become too widespread? Even the franking of letters can include words about prostate campaigns.

Many websites in the UK have charities doing their best to get men to understand the importance of knowing more about prostate problems and how might develop cancer, but has there been a significant increase in the number of hits on these sites? Are men in general better informed today, and will the more vulnerable men, often reluctant to visit their medical centres with problems that relate to urination and sexual dysfunction, take better notice?

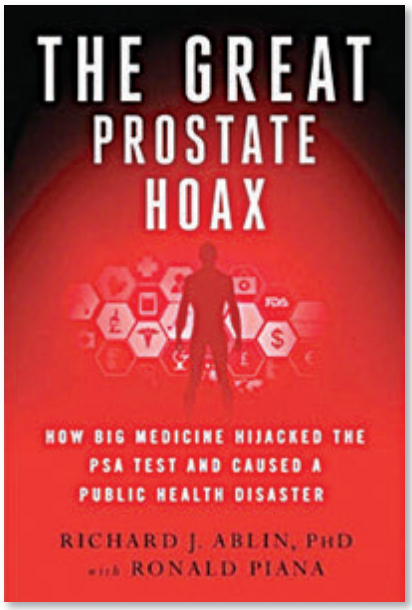
PSA and prostate cancer

There is no doubt that the UK took a more sensible approach than the US in its attitude towards Prostate Specific Antigen, PSA [3], for which an assay was devised at the Rothwell Park Cancer Institute in Buffalo, NY State, USA, those responsible referring to it thereafter as a prostate cancer specific antigen. Thus a biomarker that ought to be a predictive test of the disease continued under the acronym PSA! PSA is a weak guide, one of the factors

that might be affected by prostate cancer, but it is by no means a directly correlated parameter when present at >4 ng/ml blood. Its presence in the blood simply means that some tissues, usually the prostate (but it possible others, especially inflamed tissues) release this enzyme, kallikrein 3 (KK3, a serine protease). In the early years of PSA testing, over 75% gave false-positives, which speaks for itself.

Dr Richard Ablin, the discoverer of PSA, in "The Great Prostate Cancer Hoax" [1] takes to task in a comprehensive manner the people and organisations that misled men for over 40 years, with the situation only being corrected in the last few yearsapparently without apology or recompense, especially to men who unnecessarily had radical prostatectomy. This surgery often led to complications, which in some cases caused persistent problems, with considerable discomfort and loss of quality of life. The whole saga is spelled out in this book, especially the misleading aspect mentioned above, which refers to the whole business as a "hoax". This implies that, although it should have not involved in malice, there was intent.

Screening all men regularly to check their PSA level in some countries, including the US, is not cheap, and sending men with elevated PSAs for prostatectomy has lined the pockets of some medical practioners. The difficulty is to determine whether it was intentional rather than unintentional on their side, otherwise suggesting some ignorance or unwittingness for them to look deeper into the significance of PSA, with unfortunate consequences. The medical (licensing) authorities in the US allowed this misunderstanding to continue until very recently; they did not listen to the experts and therefore remain blameworthy – which amounts in the long-term more to a scandal than a hoax. Dr Ablin goes into detail about the scientific and medical aspects of prostate tumours following his discovery of PSA, but it is not an academic book. The research needed for it that has gone into it focuses on this inappropriate, if not irresponsible, behaviour of individuals and authorities. Ablin and co-author Ronald Piana have comprehensively compiled the evidence, which provides be the very documentation a lawyer would use in litigation (the hundreds of notes in the book's appendix would be invaluable to any prosecuting counsel). But will the



book reach the right readership and will any action follow? Only time will tell. Come what may, the truth is finally out, and the recent "sea-change" in the attitude and recommendations of the US authorities proves this point.

The future

Having drawn a line under the PSA debacle, PSA will still be used as one small indicator if levels change significantly when there is suspicion of disease. The first signs of this otherwise asymptomatic cancer are that urination becomes slower and there is an increase in nocturnal of visits to the toilet. There can be undesirable changes in sexual function, but otherwise there is not much else to go on; this is why educating all men about these problems must continue, but how this is done in future needs careful thought. A visit to the doctor is warranted when these first signs are noted, and a digital rectal examination (DRE) carried out that takes usually no more than a minute, not just a PSA test on a blood sample. The prospect might seem daunting to many men, but it is necessary. It tells the doctor whether the prostate is enlarged, and is smooth or rough. Referral will be made if there is any suspicion, and sequential PSA readings over a short period of time might also be considered useful at this stage, should it rise quickly. At the urology clinic further examination will also measuring the rate of urine flow and perhaps a scan. This is followed by biopsies, at least 3 on each side of the prostate, which is nothing more than mildly discomforting, but again many men would be reluctant to undergo the procedure.

Histopathology gives a relatively conclusive answer to the question of the stage of the disease, based on Gleason score, which determines in relation to age whether further intervention is needed rather than active surveillance. To reduce the burden of prostate cancer as far as medical intervention in the future is concerned, men do need to know about these procedures and not be alarmed by the measures that need to be taken, which can make the difference between a life and an early death.

There are other tests now being put forward that add some weight to the use of biomarkers as predictive of developing disease. Another antigen PCA3, known since 1999 [4], is only expressed in human prostate tissue, but once again we are back to DRE being used in which the prostate is massaged, following which a short time later a urine sample is examined for PCA3. Although the gene is overexpressed in many prostate cancer cells, its restricted expression profile means that it is its RNA that can be useful as a biomarker. But today it is advisable to use four criteria as indicative of the possibility of prostate cancer: (i) Free PSA, (ii) Total PSA, (iii) Intact PSA (a subfraction of Free PSA), and (iv) PCA3 (aka DD3, KLK2). To what extent these will now be used to improve diagnosis remains to be seen.

The indicators of prostate cancer relate mostly to the functional disturbance that cancer can cause, and therefore greater attention to these changes remains the best guide to taking as early as possible the right course of action, the rapid spread in some cases being the most disturbing issue where action is delayed.

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Are you organising an annual meeting or conference which you would like to tell our readers about?
Or would you like to write a report on a meeting or conference of particular interest?
If so, contact Patricia McDonnell at Oncology News on T/F: +44 (0)288 289 7023, E: patricia@oncologynews.biz

British Neuro Oncology Society Annual Conference

Date: 9-11 July 2014. Venue: Liverpool, UK. Report by: Maryanne Roach

"Contemporary Approaches to Paediatric and Adult Brain Tumours", held in Liverpool recently was, with its best ever attendance of 350, a very professionally organised and interesting conference. The opening Education Day provided parallel sessions for scientists and clinicians. One track focussed on novel experimental approaches, modelling strategies and genome-wide screening platforms to advance the molecular characterisation of brain tumours whilst the other comprised presentations of interesting and challenging cases complete with history and radiology, following which literature and clinical trial evidence were succinctly reviewed. Parallel sessions continued throughout the main meeting, also ensuring that there was plenty of interest for the nursing and allied healthcare professionals wanting to cover topics such as rehabilitation, epilepsy and Quality of Life.

The mission of the SIOG conference is to bring together international experts in geriatric oncology to present the latest evidence based research in the care of older adults with cancer.

The National Cancer Intelligence Network has now published data from 2007-2011 which includes 10,743 new cases of GBM, at 4.1/100,000/year higher than in the USA and level with the highest European countries. Over 90% of cases have histological confirmation. Incidence increases with age and is slowly increasing. Median survival is six months, 28% survive for one year and 11% for two years. Median survival for those over 50 is < 1 year and for those over 60 is < 6 months. 61% of the youngest age groups survive one year. Maximal treatment increases survival in all ages but only 34% had maximal therapy and this reduces with age. It was pointed out that enrolment into clinical trials could be increased.

Presenters repeatedly commented that there is no new robust trial data to prove whether any particular treatment is or is not superior to standard treatment, and described problems associated even with agreeing appropriate endpoints. Comparison of trial results, even those purporting to use the same regimes, is complicated by dosage variation and differences in radiotherapy regimes between centres, particularly between countries. For example: the American 'CODEL' study (for grade 3 glioma) was so long in development that it has most probably been overtaken by 10 year follow up by the EORTC and RTOG, but, due to lower toxicity and ease of administration, patients in the USA with grade 3 disease are now treated with the Stupp regime, even though there is no clinical trial evidence of efficacy. The Ependymoma II study took 8 years to develop – is the complexity of trying to answer too many questions in one study slowing down design? Or, with patient numbers so low, is it essential that investigators make the most of every cohort? Despite European collaboration via SIOP, paediatric trials are an even greater challenge (450 cases per annum in the UK, comprising numerous tumour subtypes, especially when divided by stage and age).

Whereas in 2011 there were only 13 glioma and 8 non glioma trials in the NCRI portfolio, in 2014 there are 17 and 18 respectively. If a patient has a Performance Status of 0/1, there is now a trial for every type of brain tumour and the number of studies available is now comparable to other tumour types. However, the majority of these trials are academic, very few are sponsored by Industry, and none developed in partnership. Recruitment to interventional trials remains poor. A nationwide study has shown that barriers are resources, patient pathway and availability of trials. When questioned, patients don't remember being asked if they wish to participate in a trial – or believe that no suitable trials are available. It was possibly felt that the existence of too many sites in the UK may itself hinder recruitment due to the high administration cost per site, although further centralisation was considered unlikely.

Another recurring theme was molecular characterisation, speakers emphasising differing prognoses and response to treatment in genomic sub groups and the fact that molecular stratification is now vital. However, biomarker assay is currently time consuming and molecular tests to be carried out are not standardised. An economically and technically feasible method of applying array- and next-generation sequencing-based technologies is being trialled in Germany to replace individual tests. Sequencing can be done even from very small samples and is accomplished in two weeks. By this means, the Phase II INFORM study, covering all paediatric tumour types at relapse, identifies drug targets from tissue samples and then compares the effect of giving random chemotherapy versus individualised therapy. 55 centres are taking part with 30 patients recruited to date and 20 fully sequenced (in >50% a drug target has been identified).

Proton beam therapy is probably no more effective than traditional radiotherapy but minimises adjacent tissue damage and should reduce the frequency of second malignancies. Subsequently, if one includes the cost of treating the adverse secondary effects of traditional therapy, the total cost is no greater. Since 2008, in the absence of proton beam installations in the UK, 470 cases (224 adults and 383 children) have been approved for foreign treatment (two US and one Swiss centre) at a budget of £10m. NHS England want to enhance this programme by widening the paediatric list, ensuring better equity across the country, extending it to include the TYA group and developing outcomes tracking. Once the Christie and UCH sites are up and running in 2018 the UK plan is to treat 1500 cases per annum.

Another topic of focus was metastases. With approximately 25% of all cancer patients developing CNS metastases there are about 30,000 patients per annum in the UK, of whom 2000 are considered suitable for treatment. Incidence varies even within one primary tumour type and prognostic factors vary by type of primary. Disease control in the brain has not translated to improved survival – possibly because metastatic brain disease is not the principal determinant of life expectancy in patients with disseminated disease – though there has been modest survival gain after local treatment to metastases where active disease is confined to the brain. Further, randomised trials are required in cancer patients where systemic disease is controlled, which should compare primary chemotherapy (not as an add-on to current therapy) with radiotherapy alone, and must study biomarker-enriched populations which are sub group specific. Optimal timing of treatment of CNS disease in cancer remains unknown as it is no longer certain that spread to the brain occurs late in the course of the disease; small molecule chemotherapy may be needed to prevent brain metastases from forming later in the patient's cancer pathway.

BNOS 2015 will be on 1-3 July in Nottingham.

BTOG 2015

13th Annual BTOG Conference 2015

Wednesday 28th - Friday 30th January 2015 – Dublin

IMPORTANT DATES

Poster submission opens	1st August 2014
Poster submission deadline	1st October 2014
(please note this date will not be extended)	
Registration and hotel booking opens	1st September 2014

The conference updates all attendees on state of the art management of lung cancer and mesothelioma, increases understanding on the nature of clinical practice and research and seeks to develop new national and international clinical research studies.

BTOG is a multi-disciplinary group for professionals involved with thoracic malignancies.

BTOG aims to improve the care of patients with thoracic malignancies through multidisciplinary education, developing and advising on guidelines for patient care and facilitating and nurturing clinical trial ideas into full protocols. Chair: Dr Sanjay Popat

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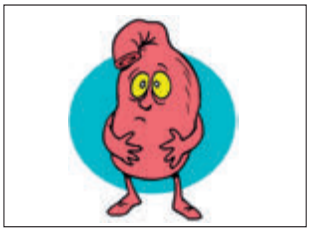
BTOG 2015 Information is available on the website:

www.BTOG.org

The Christie
School of Oncology

Study Days at The Christie: Sep/Oct 2014

Education Centre, Wilmslow Road, Manchester, M20 4BX



Upper GI Cancer (15 Sep)

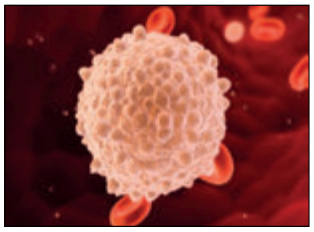
One day course discussing epidemiology, aetiology, pathophysiology, investigations, surgery and exploring the patient's journey

Fees: £75/£65/£50

Acute Oncology (15 Oct)

Patient scenario based learning event which will identify acute problems caused directly by malignant disease

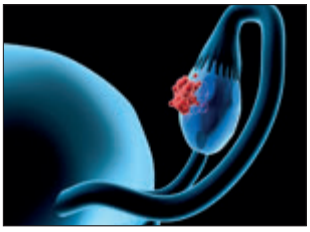
Fees: £75/£65/£50



Myeloma for Nurses (20 Oct)

Expanding basic/intermediate level of nurses knowledge caring for haematology patients to be applied in the clinical environment

Fees: £50/£30



Gynaecology: Ovarian Cancer (24 Nov)

Exploring and examining a patients journey from diagnosis to follow up care, and updating the MDT team on treatments available

Fees: £75/£65/£50

FURTHER INFORMATION: www.christie.nhs.uk/school-of-oncology or education.events@christie.nhs.uk

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Corina van den Hurk PhD, Research Chemotherapy

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European Society For Medical Oncology Congress
Madrid, Stand 118

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2014 2–5 November 2014

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- Primary care
- Prevention
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- Targeted therapies

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The Royal Marsden Study Day Programme 2014 - 2015

Please visit: www.royalmarsden.nhs.uk/studydays

22 Sep	**Targeted Treatments of the Digestive System**	ID 398
25 Sep	**Gastro-Intestinal Cancers Study Day**	ID 460
09-10 Oct	**Foundation Oncology Skills For Nurses Working in Paediatric and Adolescent Cancer Care**	ID 421
11 Oct	**The Royal Brompton Chest Radiography Study Day**	ID 251
15 Oct	**The Royal Marsden Palliative Care Update**	ID 436
05 Nov	**The Royal Marsden Gynaecological Cancers Study Day**	ID 439
06 Nov	**Psychotherapeutic Issues in Cancer Care**	ID 438
11 Nov	**Introduction to Paediatric Cytotoxic Medication**	ID 425
24 Nov	**The Royal Marsden Haematology Study Day**	ID 443
01 Dec	**Medicine Management Study Day**	ID 465
02 Dec	**Molecular Mechanisms of Targeted Cancer Treatments**	ID 397
09 Dec	**Advances in the Nutritional Care of Cancer Patients**	ID 444
19 Jan 2015	**National Head and Neck Study Day**	ID 455
26 - 27 Jan 2015	**Essential Oils in Cancer Care (2-Day Course)**	ID 450
28 Jan 2015	**Essential Oils for Skin Management**	ID 451
29 Jan 2015	**Essential Oils for Respiratory Conditions**	ID 452
30 Jan 2015	**Aroma-Psychology in Cancer Care**	ID 453
27 Feb 2015	**Leaving with Sexuality and Cancer Master class**	ID 432
10 Mar 2015	**The Royal Marsden Paediatric Palliative Care Study Day**	ID 431
14 Mar 2015	**The Royal Marsden Imaging Day on Urological Cancers**	ID 495
25 Mar 2015	**National Pain Management Study Day**	ID 413
26-27 Mar 2015	**Supporting Workers with Cancer (2-day Course)**	ID 457

The Royal Marsden Conference Programme 2014 – 2015

Please visit: www.royalmarsden.nhs.uk/conferences

12 Sep	**The Royal Marsden Endometrial Cancer Conference** www.royalmarsden.nhs.uk/endometrial	ID 430
02 Oct	**The Royal Marsden Neuro-Oncology Conference** www.royalmarsden.nhs.uk/neuroconference	ID 433
03 Oct	**The Seventh Annual Royal Marsden Breast Cancer Meeting: Hot Topics in Breast Cancer** www.royalmarsden.nhs.uk/breastmeeting	ID 434
10 Oct	**The Royal Marsden Bladder and Testicular Cancer Conference** www.royalmarsden.nhs.uk/bladdertesticular	ID 435
16-17 Oct	**Anaesthesia for Major Surgery: What's New** www.royalmarsden.nhs.uk/anaesthesia	ID 437
07 Nov	**The Seventh Royal Marsden Pain and Opioid Conference** www.royalmarsden.nhs.uk/painconference	ID 440
14 Nov	**The Sixth Annual Royal Marsden Head and Neck Conference** www.royalmarsden.nhs.uk/headneckconference	ID 441
21 Nov	**The Second Royal Marsden Skin Cancer Conference: a GP Focus** www.royalmarsden.nhs.uk/skin	ID 442

For further information please email: conferencecentre@rmh.nhs.uk
Tel: 020 7808 2921

To have your event listed in the Oncology News diary, E: patricia@oncologynews.biz by October 5th 2014.

2014

September

2nd International Medical Student Cancer Conference
6-7 September 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events,
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

RCR Annual Scientific Meeting 2014
8-10 September 2014; London, UK
W: www.rcr.ac.uk

New Entry
Principles of reconstructive plastic surgery and burn injury care
8 –10 September 2014; Glasgow, UK
E: burns@glasgow.ac.uk
W: www.gla.ac.uk/schools/medicine/nursing/

New Entry
Managing Complex Lymphoedema
8-12 September, 11-14 November 2014; Glasgow, UK
Evelyn Selfridge
E: Evelyn.Selfridge@glasgow.ac.uk
W: www.gla.ac.uk/schools/medicine/nursing/

New Entry
Targeted Cancer Treatments: De-mystifying the Science
9 September 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44 (0)161 446 3773 or
E: education.events@christie.nhs.uk

New Entry
Haematology: Anatomy & Physiology of Blood Cancers
11 September 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

1st National Cancer Pain Update
12 September 2014; London, UK
W: www.mahealthcareevents.co.uk

Endometrial Cancer Conference
12 September 2014; London, UK
W: www.royalmarsden,nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

ASTRO's 56th Annual Meeting
14-17 September 2014;
San Francisco, USA
W: www.astro.org

New Entry
Upper GI Cancer: The Patient Pathway
15 September 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

3rd Annual Cancer Vaccines Conference
15-16 September 2014; London, UK
E: events@smi-online.co.uk

Advanced Clinical Practice Cardiovascular Masterclass
16 September 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

VIII Congress of Oncologists and Radiologist from the ex-USSR countries
16-18 September 2014; Kazan, Republic of Tatarstan, Russia
W: www.kazan2014.com

New Entry
Precision Medicines Androgens 2014
17-19 September 2014; London, UK
E: PrecisionMedicines@imperial.ac.uk

New Entry
Christie Robotic Pelvic Oncology Symposium
17 September 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

Still Confused about Feeding Tubes?
18 September 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

Targeted Treatments of the Digestive System
22 September 2014; London, UK
W: www.royalmarsden.nhs.uk

TYA/Paediatric Study Day
23 September 2014; London, UK
W: www.royalmarsden.nhs.uk

Upper GI Study Day
25 September 2014; London, UK
W: www.royalmarsden,nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

New Entry
Providing Spiritual and Religious Care in Health Care
25 September, 30 October 2014; Glasgow, UK
Evelyn Selfridge
E: Evelyn.Selfridge@glasgow.ac.uk
W: www.gla.ac.uk/schools/medicine/nursing/

ISSC - Sexual Consequences of Cancer Treatment
26-27 September 2014; London, UK
W: www.royalmarsden.nhs.uk

14th National Conference of FHNO (Foundation for Head and Neck Oncology)
26-28 Sep 2014; Chandigarh, India
W: www.fhno2014.com

39th ESMO Congress
26-30 September 2014, Madrid, Spain
W: www.esmo.org/events/madrid-2014-esmo-congress.html
E: congress@esmo.org
T: +41 (0)91 973 19 26

Teenagers and Young Adults with Cancer 10th Anniversary Conference: Working Together
30 September 2014; Leicester, UK
W: www.tyac.org.uk
E: info@tyac.org.uk

New Entry
Lymphoedema Core Skills & Knowledge
30 September-3 October 2014; Glasgow, UK
E: lymph@glasgow.ac.uk
W: www.gla.ac.uk/schools/medicine/nursing/

October

New Entry
Research Methods and Statistics
1 October, 7, 14, 21 November, 3 (SDL), 10 December 2014; Glasgow, UK
Evelyn Selfridge
E: Evelyn.Selfridge@glasgow.ac.uk
W: www.gla.ac.uk/schools/medicine/nursing/

7th Annual EUROHNC
1-3 October 2014; Poznan, Poland
T: +48 61 88 50 929
E: ehnc@wco.pl

New Entry
Advanced Health Care Practice
2 October 2014, 23 April 2015; Glasgow, UK
Evelyn Selfridge
E: Evelyn.Selfridge@glasgow.ac.uk
W: www.gla.ac.uk/schools/medicine/nursing/

New Entry
Advanced Targeted Treatments: Haematological Cancers
2 October 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

Neuro-Oncology Conference
2 October 2014; London, UK
W: www.royalmarsden.nhs.uk/neuroconference

Journal of Clinical Oncology

Pathological and Molecular Features Correlated With Long-Term Outcome After Adjuvant Therapy of Resected Primary GI Stromal Tumour

Corless CL, Ballman KV, Antonescu CR, et al. Journal of Clinical Oncology 2014; May 20: 32(15):1563-70.

Purpose: The ACOSOG (American College of Surgeons Oncology Group) Z9001 (Alliance) study, a randomised, placebo-controlled trial, demonstrated that 1 year of adjuvant imatinib treatment prolonged recurrence-free survival (RFS) after resection of the primary GI stromal tumour (GIST). We sought to determine the pathological and molecular factors associated with this patient outcome. **Patients and Methods:** There were 328 patients assigned to the placebo arm and 317 to the imatinib arm. Median patient follow-up was 74 months. There were 645 tumour specimens available for mitotic index or mutation analysis. **Results:** RFS was better in the imatinib arm (hazard ratio, 0.6; 95% CI, 0.43 to 0.75; Cox model-adjusted P<0.001). On multivariable analysis of patients in the placebo arm, large tumour size, small bowel location and high mitotic index were associated with lower RFS, whereas tumour genotype was not significantly associated with RFS. Multivariable analysis of patients in the imatinib arm yielded similar findings. Comparing the 2 arms, imatinib treatment was associated with higher RFS in patients with a KIT exon 11 deletion of any type, but not a KIT exon 11 insertion or point mutation, KIT exon 9 mutation, PDGFRA mutation, or wild-type tumour, although some of these patient groups were small. Adjuvant imatinib did not seem to alter overall survival. **Conclusions:** Tumour size, location and mitotic activity, but not tumour genotype, are associated with the natural history of GIST. Patients with KIT exon 11 deletions given 1 year of adjuvant imatinib had longer RFSs.

Reviewer's opinion: Gastrointestinal stromal tumours (GISTs) are uncommon mesenchymal tumours of the gut, and the prognosis of advanced GISTs has been revolutionised by the efficacy of imatinib, targeting aberrant cKIT signalling, with an expected overall survival of in excess of 5 years. Imatinib has been studied in the adjuvant setting after primary GIST resection and Phase III trial evidence suggests that 3 years of adjuvant treatment for GISTs with adverse features improves overall long-term survival. This study reports on a translational sub-study from the ACOSOG Z9001 trial aimed at correlating prognosis without treatment and benefit of adjuvant therapy with imatinib and the molecular and histopathological features of the tumours. The Z9001 study showed a significant reduction in risk of tumour recurrence (without any effect on overall survival) with one year of adjuvant therapy, which led to regulatory approval for imatinib for 1 year in resected primary GI stromal tumours. The results confirmed that the 'conventional' risk factors for recurrence were tumour size, non-gastric (i.e. small bowel, rectum) tumour location and mitotic index. By studying the placebo group, the authors were able to show that, in univariate analysis, the presence of a KIT exon 11 deletion was associated with a higher risk of recurrence. Patients with a mutation in KIT exon 11 seemed to benefit more from adjuvant imatinib therapy than patients with KIT and PDGFRA wild-type tumours but this was restricted to patients with exon 11 deletions rather than point mutations or insertions. However, the dose of imatinib was 400 mg daily; there is certainly evidence in advanced disease that a higher dose of 800 mg daily is required for patients harbouring this mutation. Overall, this study shows the importance of the molecular pathology of early GISTs in response to adjuvant therapy in parallel with the situation for advanced disease. Indeed, the nature as well as the location of the genetic lesions may influence benefit from imatinib.. – AR

Randomised, Controlled, Double-Blind, Cross-Over Trial Assessing Treatment Preference for Pazopanib Versus Sunitinib in Patients with Metastatic Renal Cell Carcinoma: PISCES Study

Journal of Clinical Oncology. 2014; May 10; 32:1412-8.

Purpose: Patient-reported outcomes may help inform treatment choice in advanced/metastatic renal cell carcinoma (RCC), particularly between approved targeted therapies with similar efficacy. This double-blind cross-over study evaluated patient preference for pazopanib or sunitinib, and the influence of health-related quality of life (HRQoL) and safety factors on their stated preference. **Patients and Methods:** Patients with metastatic RCC were randomly assigned to pazopanib 800 mg per day for 10 weeks, a 2-week washout, and then sunitinib 50 mg per day (4 weeks on, 2 weeks off, 4 weeks on) for 10 weeks, or the reverse sequence. The primary end-point, patient preference for a specific treatment, was assessed by questionnaire at the end of the 2 treatment periods. Other end-points and analyses included reasons for preference, physician preference, safety, and HRQoL. **Results:** Of 169 randomly assigned patients, 114 met the following prespecified modified intent-to-treat criteria for the primary analysis: exposure to both treatments, no disease progression before cross over, and completion of the preference questionnaire. Significantly more patients preferred pazopanib (70%) than sunitinib (22%); 8% expressed no preference (P<0.001). All preplanned sensitivity analyses, including the intent-to-treat population, statistically favoured pazopanib. Less fatigue and better overall QoL were the main reasons for preferring pazopanib, with less diarrhea being the most cited reason for preferring sunitinib. Physicians also preferred pazopanib (61%) than sunitinib (22%); 17% expressed no preference. Adverse events were consistent with each drug's known profile. Pazopanib was better than sunitinib in HRQoL measures measuring fatigue, hand/foot and mouth/throat soreness. **Conclusions:** This innovative cross-over trial showed a significant patient preference for pazopanib ccompared to sunitinib, with HRQoL and safety as key influencing factors.

Reviewer's opinion: The management of metastatic clear cell renal cell carcinoma underwent a paradigm shift in 2007 from immunotherapy with α-interferon to targeted therapies inhibiting signalling in the VEGF pathway (amongst others) with a better objective response rate and median progression free survival with sunitinib compared to α-interferon in a randomised Phase III trial. Both sunitinib and pazopanib are anti-angiogenic tyrosine kinase inhibitors and have robust Phase III efficacy in this disease. In this context, as many patients are under treatment for almost a year, tolerance and adverse effects on QoL become particularly important. By studying patient preference, QoL and adverse events over a 10 week period for each drug (sequential, with a 2 week wash-out period), almost three quarters of the patients preferred pazopanib, which reduced fatigue, stomatitis and hand-foot syndrome, as well as taste disturbance. This is an important study that has examined patient-centered outcome in terms of patient preference. However, only about three-quarters of the study population completed the preference questionnaire and the 10 week trial for each drug was relatively short. The single-point of preference assessment may also have favoured pazopanib as sunitinib is administered in a 4 weeks-on-2 weeks off schedule. – AR

NEW ENGLAND JOURNAL OF MEDICINE

Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer

Olivia Pagani, Meredith M. Regan, Barbara A. Walley, et al. for the TEXT and SOFT Investigators and the International Breast Cancer Study Group. N Engl J Med, 2014; 371:107-118 (July 10, 2014).

Background: Adjuvant therapy with an aromatase inhibitor improves outcomes compared with tamoxifen in postmenopausal women with hormone-receptor–positive breast cancer. **Methods:** In two phase 3 trials, we randomly assigned premenopausal women with hormone-receptor–positive early breast cancer to the aromatase inhibitor, exemestane, plus ovarian suppression or tamoxifen plus ovarian suppression for 5 years. Suppression of ovarian estrogen production was achieved with the gonadotropin-releasing hormone agonist, triptorelin, oophorectomy, or ovarian irradiation. The primary analysis combined data from 4690 patients in the two trials. **Results:** After a median follow-up of 68 months, disease-free survival at 5 years was 91.1% in the exemestane–ovarian suppression group and 87.3% in the tamoxifen–ovarian suppression group (hazard ratio for disease recurrence, second invasive cancer, or death, 0.72; 95% confidence interval [CI], 0.60 to 0.85; P<0.001). Freedom from breast cancer at 5 years was 92.8% in the exemestane–ovarian suppression group compared with 88.8% in the tamoxifen–ovarian suppression group (hazard ratio for recurrence, 0.66; 95% CI, 0.55 to 0.80; P<0.001). With 194 deaths (4.1% of the patients), overall survival did not differ significantly between the two groups (hazard ratio for death in the exemestane–ovarian suppression group, 1.14; 95% CI, 0.86 to 1.51; P=0.37). Selected adverse events of grade 3 or 4 were reported for 30.6% of the patients in the exemestane–ovarian suppression group and 29.4% of those in the tamoxifen–ovarian suppression group, with profiles similar to those for postmenopausal women.**Conclusions:** In premenopausal women with hormone-receptor–positive early breast cancer, adjuvant treatment with exemestane plus ovarian suppression compared with tamoxifen plus ovarian suppression significantly reduced recurrence.

Reviewer's opinion: Use of aromatase inhibitors (AI) as an adjuvant treatment in the oestrogen receptor-positive, post-menopausal age group of breast cancer patients has been the current accepted gold standard worldwide. Though the majority of the patients recruited in the trials comparing adjuvant AI versus tamoxifen had natural menopause, a subset of patients were selected following artificial menopause. Ovarian suppression with or without hormonal therapy in younger pre-menopausal women proved similar to adjuvant CMF. The results confirm that an AI exemestane is better than tamoxifen following ovarian suppression in pre-menopausal oestrogen receptor-positive breast cancer patients, particularly those also given with adjuvant chemotherapy. However, whether PFS gain will eventually translate into significant long-term survival imporvement remains to be seen. Similarly, superiority of adjuvant tamoxifen plus ovarian suppression compared to tamoxifen alone is still unproven in the pre-menopausal age group. Unfortunately, sexual dysfunction, musculo-skeletal discomfort, fractures and osteoporosis were more common with exemestane, which may be of greater significance and relevance than hot flushes with tamoxifen in younger females. These results offer another management option to the pre-menopausal age group with high risk breast cancer patients requiring chemotherapy which might further reduce the risk of relapse. – SU

Latest developments on products and services from the industry. To have your news included contact Patricia McDonnell at Oncology News on T/F: +44 (0)288 289 7023, E: patricia@oncologynews.biz

Varian Medical Systems Selected to Equip First Satellite Radiotherapy Centre in Scotland

Cancer patients in the west of Scotland will gain access to state-of-the-art cancer treatment closer to home when a new radiotherapy center opens near Glasgow next year. Varian Medical Systems has been selected to equip the new department and an order was placed in June for four TrueBeam™ medical linear accelerators.

Two of the new TrueBeam systems, which offer fast and efficient radiotherapy and radiosurgery treatments, will replace older treatment machines at the Beatson West of Scotland Cancer Centre in Glasgow. The hospital treats more than 7,000 patients each year on 11 Varian medical linear accelerators. With a catchment area covering half the population of Scotland, the centre has a history of pioneering advanced radiotherapy treatments.

The other two Varian TrueBeam systems will equip the Beatson's new satellite department at Monklands Hospital in Airdrie, situated about 15 miles east of Glasgow. Around 80 patients a day are expected to undergo radiotherapy at the new satellite service.

These new machines represent the latest in linear accelerator technology so we can extend the range of treatments to more patients," says Garry Currie, head of radiotherapy physics. "The planned opening of the new facility in Monklands as a satellite of the Beatson will be the next step forward for our patients in the west of Scotland in delivering high quality and effective radiotherapy treatments."

For further information contact:
Neil Madle, Varian Medical Systems,
T: +44 7786 526068,
E: neil.madle@varian.com
W: www.varian.com

OSL secures distribution agreement for INTRABEAM System

Oncology Systems Limited, the largest independent provider of radiotherapy equipment and software in the UK, is delighted to have successfully secured the distribution agreement for the INTRABEAM System within the UK and Ireland. The INTRABEAM System, produced by Carl Zeiss, uses intraoperative radiotherapy (IORT) to treat the tumour bed from within, ensuring radiation treatment accuracy.

Neil Roberts, Head of Medical Division, Carl Zeiss Ltd, adds "OSL have established themselves as a well respected provider of oncology products, so were the natural choice for Carl Zeiss Meditec to represent our Intrabeam Intraoperative Radiotherapy system in the UK. We are delighted to be working with OSL at such an exciting time, as we prepare ourselves for the full adoption of this technology in the UK based on the NICE evaluation and initial recommendation".

This pioneering breast cancer treatment has been in the public eye since draft guidance from the National Institute for Health and Care Excellence (NICE) approved the use of this type of radiotherapy for those in the early stages of the disease.

Oncology Systems Limited, T: +44 (0)1743 462 694 E: enquiry@osl.uk.com instead W: www.osl.uk.com

Provectus Biopharmaceuticals' PV-10 clinical data on the treatment of melanoma to be presented at the ESMO 2014 Congress

Provectus Biopharmaceuticals, Inc, a development-stage oncology and dermatology biopharmaceutical company (the "Company" or "Provectus"), will have clinical data on PV-10 presented at the European Society for Medical Oncology's (ESMO) 2014 Congress in Madrid, Spain. The presentation, titled "Subgroup efficacy in patients receiving intralesional rose bengal to all existing melanoma in phase II study PV-10-MM-02," will be held on Sunday, September 28, 2014, beginning at 12:45pm local time. Dr Craig Dees, PhD, CEO of Provectus, said, "Provectus is happy to see our PV-10 data on melanoma shared with those attending the ESMO Congress this year."

PV-10, a 10% solution of Rose Bengal that is currently being examined as a novel cancer therapeutic, is designed for injection into solid tumours (intralesional administration), thereby reducing potential for systemic side effects.

For further information visit: www.pvct.com

Negotiations on Licensing PV-10 in China Opened

Provectus Biopharmaceuticals, Inc, ("Provectus"), announced today that it entered into a Memorandum of Understanding ("MOU") with Sinopharm-China State Institute of Pharmaceutical Industry ("Sinopharm-CSIPI"), the leader among all pharmaceutical research institutes in China, and Sinopharm A-THINK Pharmaceutical Co., Ltd. ("Sinopharm A-THINK"), the only injectable anti-tumour drug research and development, manufacture and distribution integrated platform within Sinopharm Group.

The key component of the MOU provides that "Sinopharm-CSIPI and Sinopharm A-THINK desire to obtain an exclusive license to commercialise PV-10 within [the People's Republic of] China territory, and PVCT is willing to grant such license to Sinopharm."

During the next three months, the parties will seek to enter into a definitive licensing contract, subject to additional negotiation, due diligence, and any required regulatory and corporate approvals. The parties will further address the details of the license; the use of the technology from Provectus to Sinopharm A-THINK in China; the process for commercialisation; and payments to Provectus (upfront, milestone and royalties). Provectus intends to manufacture PV-10 in the USA and Sinopharm A-THINK will distribute PV-10 in China.

The MOU, which is governed by Chinese law, stems from negotiations led by Network 1 Financial Securities, a financial advisor to Provectus. The parties met at the headquarters of Sinopharm-CSIPI in Shanghai, China. In attendance were the senior management members of Sinopharm Group, as well as senior Provectus personnel. Provectus presented clinical and nonclinical data of its drug, PV-10. The experts and scientists from Sinopharm-CSIPI and Sinopharm A-THINK had an extensive and substantial discussion with the Provectus team.

For more information, visit: http://www.pvct.com

Dr Ruman Rahman receives British Neuro-oncology Society Young Investigator Award

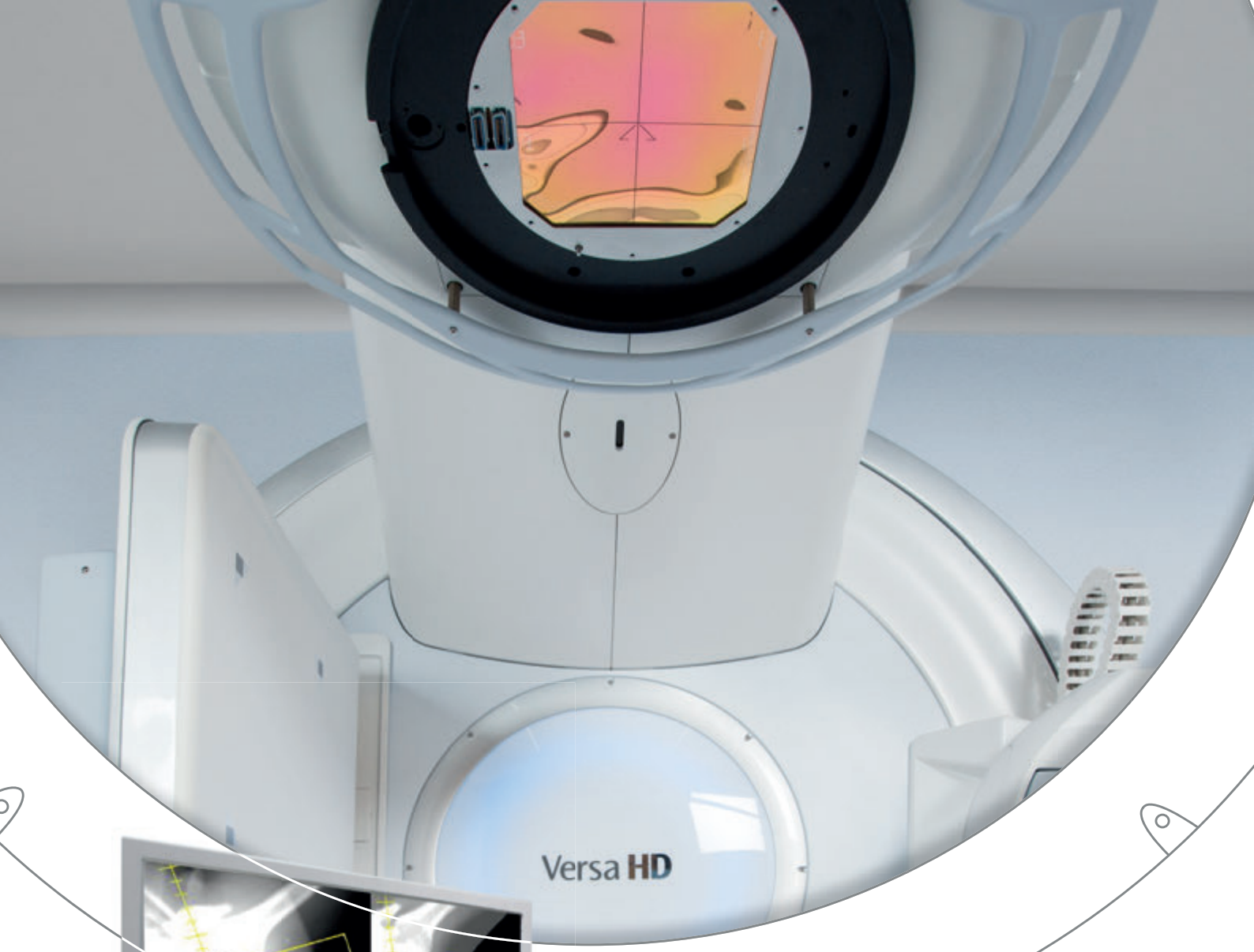
Dr Rahman, Assistant Professor in Molecular Neuro-Oncology received the Brain Tumour Research "Young Investigator Award" at the British Neuro-oncology Society (BNOS) Conference. Unanimously selected by BNOS Council judges for his outstanding contribution to Neuro-oncology in the UK Dr Rahman, 35, is credited with leading studies that developed a polymer which could be successful in delivering chemotherapy drugs directly to the brains of brain tumour patients. It is expected to go into clinical trial within three years.

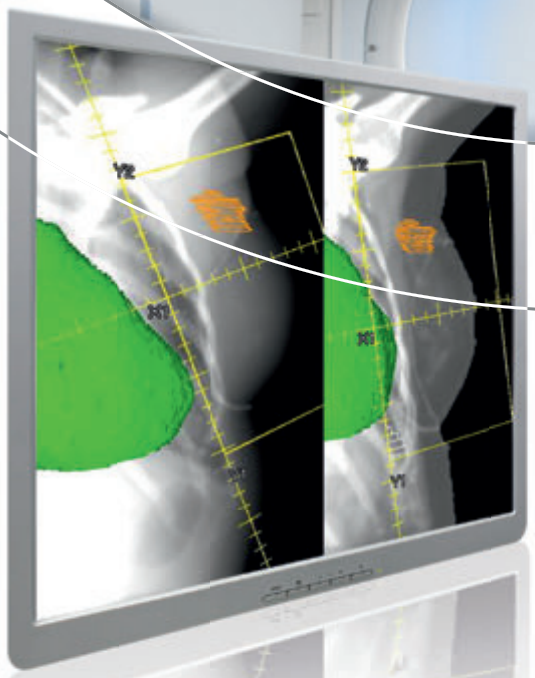
Dr Rahman said: "I am proud to receive this prestigious award from my peers in the British neuro-oncology community. This is a welcome and timely boost for our investigations."

Brain Tumour Research's Chief Executive Sue Farrington Smith said "Brain tumours receive just 1% of the national spend on cancer research and a deeply worrying consequence of this poor research funding is that talented young researchers, otherwise inclined to work in the field, are deterred and end up leaving for alternatives where research spending is more plentiful and better coordinated."

http://www.braintumourresearch.org/uploads/document/BNOSpressrelease19Jun.pdf

For further information contact Katie Abbotts
T: 07810 504380
E: katie@braintumourresearch.org





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Wang, W., et al., Rapid automated treatment planning process to select breast cancer patients for active breathing control to achieve cardiac dose reduction. Int J Radiat Oncol Biol Phys, 2012. 82(1): p. 386-93.
Versa HD is not available for sale or distribution in all markets. Please contact your Elekta representative for details.