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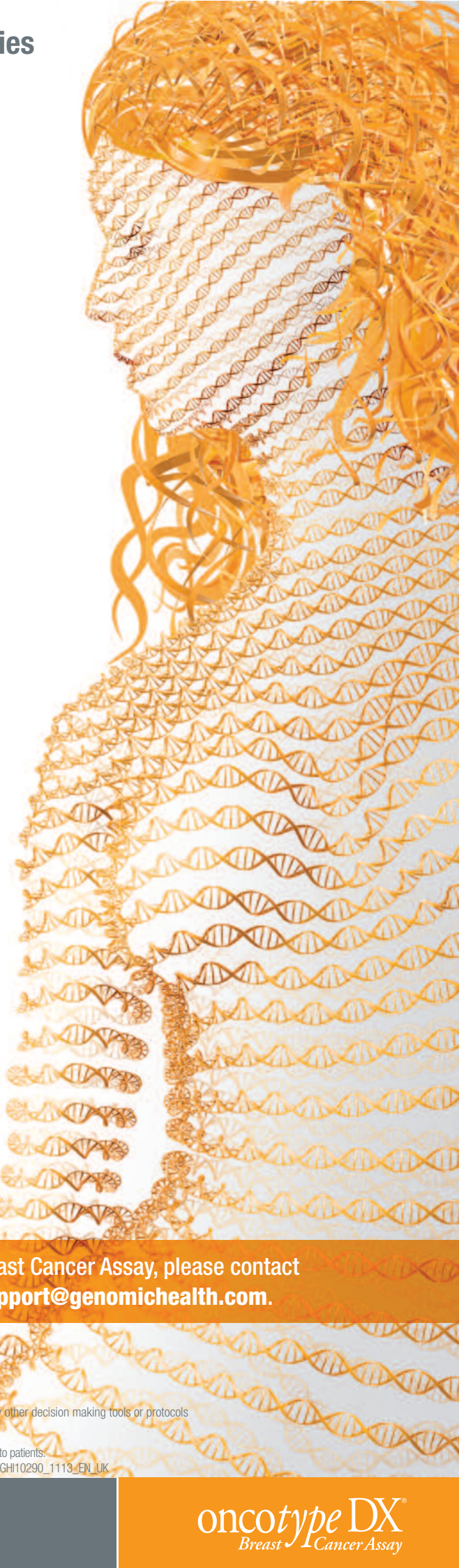

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1. NICE: Diagnostics guidance, DG10. Sept 2013

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The fundamental basis of cancer – is there a general theorem on which to build?

Denys Wheatley
Editor

As a young graduate 53 years ago, I spent my postgraduate days working for a PhD on the invasiveness of malignant cells, with the (naïve?) hypothesis in mind that, if one can stop spread and dissemination of tumour cells, a cancer will remain contained and can probably be cured (resected) in many cases. It still seems a practical approach, but we would have to know a lot more about the invasiveness, which is not exclusive to cancer cells. This is not simply about cell motility. The seeding of specific organs by certain types of tumour leads to metastases, which are often the killers, but their growth can be suppressed by the presence of the primary. Thus the interactions between the cells of a tumour and other tissues are complex, and we need to know much more about them. Unfortunately, funding of research into these aspects of cancer research is small relative to the continued quest for the development of highly targeted drugs that try specifically to kill tumour cells, primary and secondaries.

My first 4-5 years of post-doctoral work were, however, spent with Sir Alistair Currie in Aberdeen, investigating the carcinogenic mechanism(s) of DMBA causing breast tumours in rats (Huggin's tumour). We found DMBA had to be metabolically converted to 7-OH-DMBA as the proximate carcinogen (with Huggins actually being with us at the time this was discovered – a few months later he learned he had won the Nobel Prize, but not for breast cancer work). It was supposed to work by intercalating into cellular DNA and causing mistakes in replication. This could be all part and parcel of the Somatic Mutation Theory. If disruption in the DNA of cells were to be specifically blamed for its carcinogenic action, we would still need to explain why breast epithelial cells were almost invariably affected by this powerful proximate carcinogen, sometimes producing 3 or 4 breast cancer in the same animal. It is clear that much more is involved in the process of tumour formation, with both internal and environmental influences being at work. But does this metabolite, like benzpyrene followed by croton oil, provide a necessary initiation step, but not much happens without a promoter or promoters. Papillomas appear over the entire area where the promoter has been applied, a "field" effect, where not just one mutant cell is starting a tumour; stochastically it is highly improbable that so many cells in the same field make the same mistake at the same time. So what is initiation; and can we therefore translate this into the axiom that all cancers need to be initiated, but perhaps through a common mechanism? If tumours arise spontaneously, they would also have to be by some mistake in either the regulation of division or as a result of an inappropriate response to local signals (see below). But if multiple causes and factors are responsible, as seems much more likely, the crucial issue is whether a fundamental theorem of cancer is plausible? More to the point, is there an axiom, i.e. a self-evident truth, on which cancer research can now be seriously based, other than all tumours have somehow to be initiated?

One senior figure in molecular biology, taking the reductionist approach, has thrown in the towel in his pursuit of a fundamental change in the regulatory molecules controlling cell division through mutation as being responsible [1]. Can it be that the cancer research community (especially those working at the bench and who are relatively new to the field) have not been told that cancer is not a single disorder (disease), that all tumours are different, and within each one there is great heterogeneity, a heterogeneity that is in flux with cells constantly changing their feature (e.g. often becoming resistant to treatments)? A blinkered approach is not the best policy, and therefore future research must be more concerned with the diversity and complexity of cancer rather than trying to establish a fundamental theorem, which is impossible, however much we wish it to be our ideal.

Another hypothesis considers that there is nothing "wrong" with cancer cells – they act like miscreants in society in starting to behaving badly and putting the rest of the body at risk [2]. Local disagreement between neighbouring tissues has encouraged us to look at the relationship of potentially proliferative ("precancerous") tissue with its stroma. On a similar tack, the stem cell idea harps back to the Connheim-Ribbert notion of embryonic rests, stem-like cells possibly misplaced; some pundits believe that cancer is a disorder in differentiation of cells within particular (inappropriate?) tissue environments. However credible, one cannot escape asking yet again what induces/initiates this misguided differentiation in the first place.

In conclusion, we have a number of hazy ideas about how cancers begin and progress, with considerable polarisation among their proponents. None of them may be right or, more probably, they are all partly right, but there has been little attempt at a general synthesis. The elusive event remains initiation, which needs to be researched more carefully, with the reductionist approach being seen as only one facet, since initiation must happen one way or another in every case where a tumour arises, highly implausibly by one common mechanism. ●

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Review of Re-irradiation in Recurrent Head and Neck Cancer

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Head and neck cancers account for approximately 560,000 new cases of cancer diagnosed and 300,000 deaths each year. The epidemiology of this cancer is changing with increasing incidence in younger population and Human Papilloma virus (HPV) association. A multidisciplinary approach including a combination of surgery, radiotherapy and chemotherapy is considered due to the potential morbidity due to treatment. Despite this more than half of these patients have loco-regional recurrences along a high incidence (3-7% per year) of second metachronous malignancies.

Surgery has always been preferred over radiotherapy for recurrent cancers. The long term survival after salvage surgery varies between 25-45%. Despite the negative margins, there is a local failure risk of about 59%. Salvage surgery may not be feasible due to the proximity to the critical structures or technical challenge of operating in previously operated or irradiated areas. During these situations, platinum based palliative chemotherapy is considered. Vermorken et al. reported an improvement in the overall survival from 7.4 months to 10.1 months with the addition of Cetuximab to Cisplatin/Carboplatin and 5-FU [1].

Radiotherapy was historically avoided due to high risk of toxicities; grade 3-4 mucositis reported in 10-40%. Other chronic side effects including temporal lobe necrosis, trismus, fistulas, osteoradionecrosis, blindness, spinal cord myelopathy have been reported. Langer et al has reported an 80% incidence of serious toxicities at six months, treatment related mortality of 8% which included 2-5% of patients with Carotid blowout [2].

Despite the above reports, there is more evidence for the use of re-irradiation in head and neck cancer recurrence which have reported acceptable toxicity profile with availability of newer radiotherapy techniques. Various options available include re-irradiation using external beam radiotherapy (EBRT), concurrent chemoradiotherapy, postoperative radiotherapy, IMRT (Intensity modulated radiotherapy) and IGRT (Image guided radiotherapy), brachytherapy and stereotactic body radiotherapy. Evolution of advanced radiotherapy techniques have ensured improved conformality and reduction of toxicity due to effective sparing of the critical structures. There is sufficient evidence from pre-clinical animal models which have noted atleast 50% recovery from RT damage after one to two years. Ang et al. (2001) reported about 60% recovery in resus monkey spinal cord at one year and additional recovery in two to three years [3].

Evidence for EBRT and chemoradiotherapy

External beam radiotherapy has been used for re-irradiation previously. Stevens et al. reported a local control of 60% for second primary tumour (SPT) and 27% for a recurrent tumour, and five year survival of 17% for recurrent and 27% for SPT's in group of patients receiving ›50Gy EBRT (82% of patients) and/or brachy boost (14%) [4].

Addition of concurrent chemotherapy as a radiosensitiser, like hydroxyurea, cisplatin, 5-fluorouracil and paclitaxel have been used during several phase I/II trials in University of Chicago. A pooled analysis of four studies was reported by Haraf et al. using hydroxyurea, 5-FU, cisplatin and concurrent radiotherapy with a locoregional control, progression-free and overall survival rate at five years as 20%, 13.5% and 14.6% [5]. There was no difference in the conventional daily RT, split course conventional fractionation with concurrent chemotherapy and split course hyperfractionation with concurrent chemotherapy. Henceforth, the role of concurrent chemoradiotherapy is still uncertain.

Impact of IMRT, IGRT and Adaptive radiotherapy

The IMRT technique will allow higher dose delivery with acceptable toxicity due to organ sparing. Salama et al. reported a 3-year overall survival and locoregional control rate of 30% and 56%, respectively, for patients who received doses of › 58 Gy compared with only 6% and 33%, respectively, for those who received ‹58 Gy [6]. Duprez et al. (RadiotherOncol 2009) have reported five year local control and overall survival of 40% and 20% respectively with a mean RT dose of 69Gy. Lee et al. (IJROBP 2007) have reported improved two year locoregional progression free

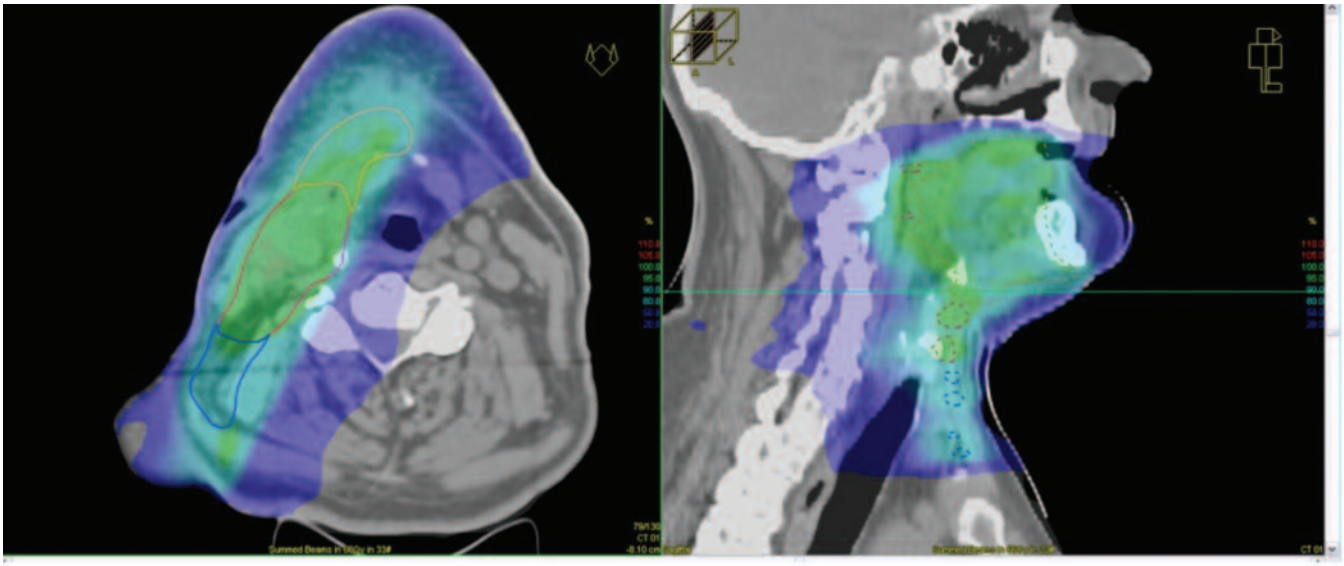


Figure 1 SCC tongue IMRT plan.

survival with IMRT when compared to EBRT (52% vs 20%) and the median dose was 59.4Gy. The acute and late grade ≥3 toxicity was of 23% and 15%, lesser than the previously reported toxicities.Hua et al. (EJC 2012) reported 5-year local control rates (LCR) andoverall survival rates (OS) for nasopharyngeal carcinomas with re-stage I, II, III, IV were 80.0%, 85.0%, 80.0%, 78.7% and 71.4%, 62.9%, 35.5%, 30.2%, respectively. The median dose to GTV (gross tumour volume) was 70.4 Gy (range 62.1–77.6 Gy).

The margins from CTV (Clinical target volume) to PTV (planning target volume) used in several studies vary from 0.3cm to 2cm, and the treatment dose ranged from 59.4Gy to 68Gy. The decision on the dose is influenced by the proximity to the critical structures and interval from the primary treatment.

IGRT has further reduced set up uncertainties by three-dimensional image guidance and ensured accurate treatment when using small planned treated volume (PTV) margins. Further to this, the concept of Adaptive Radiotherapy which involves modification of the treatment plan to anatomical changes (e.g. movement of critical structures due to tumour shrinkage or dose changes due to patient weight loss) during the treatment schedule will ensure accuracy of the treatment. The contemporary planning systems have the capability to produce a cumulative plan where cumulative doses to various organs can be calculated.

Brachytherapy and SBRT

Brachytherapy as a low dose rate (LDR) and high dose rate (HDR) is a viable option for re-irradiation as high dose delivery can be achieved with rapid dose fall off sparing surrounding tissues. Mazeron et al. and others have reported a five-year local control rate of 57–69% and a five-year overall survival rate of 14–40% [7].

SBRT involves delivering a very high dose using a single or few fractions of RT with high conformality. Rogh et al. (2009) reported an 80% global response rate after 30 Gy (range 18-40 Gy) in 3-5 fractions administered. A two-year survival rate of 30.9% and a treatment related mortality of 2.9% were reported [8]. Unger et al. (IJROBP 2010) treated patients with a median re-irradiation dose of 30 Gy (21-35 Gy) in 2-5 fractions and reported a two-year overall survival and locoregional control rates of 41% and 30%.

In view of the high precision involved in both modalities, accurate staging improves the outcomes further.

Post-operative re-irradiation

A phase 3 trial conducted by GORTEC (Janot et al. 2005), comparing observation and post-operative RT (60Gy over 11 wks, 2Gy/day) with concurrent hydroxyurea and 5-FU reported significant improvement in disease free survival but no statistically significant overall survival benefit. An increase in acute and late toxicity was noted in the RT arm (39% v 10% at 2 years) [9].

Factors influencing outcomes and choice of patients

1. Premorbid functional status – better outcomes in patients with good baseline function and performance status.
2. Size of the tumour – a large single centre experience reported by De Crevoisier et al. (JCO 1998) the only two factors with significant correlation with mortality were the surface area and volume of the second RT course, and a surface area of ‹125cm^3 or a volume of ‹650cm^3 had significantly greater overall survival.
3. Treatment free interval – a treatment free interval of at least six months is suggested in most of the trials and some even prefer 12 month since the initial RT. This period allows the tissues to recover from late toxicity.
4. Tumour location – the laryngeal cancer recurrences, amenable for resection has 80% chance of long term control (Goodwin WJ Jr, Laryngoscope 2000). Nasopharyngeal recurrences are mainly managed using EBRT, IMRT, brachytherapy or SBRT. The advances in skull base surgery have increased the possibility of salvage nasopharygectomy.
5. The outcomes from metachronous tumours are better when compared with recurrent disease, due to likely presence of treatment resistant malignant clonogens.

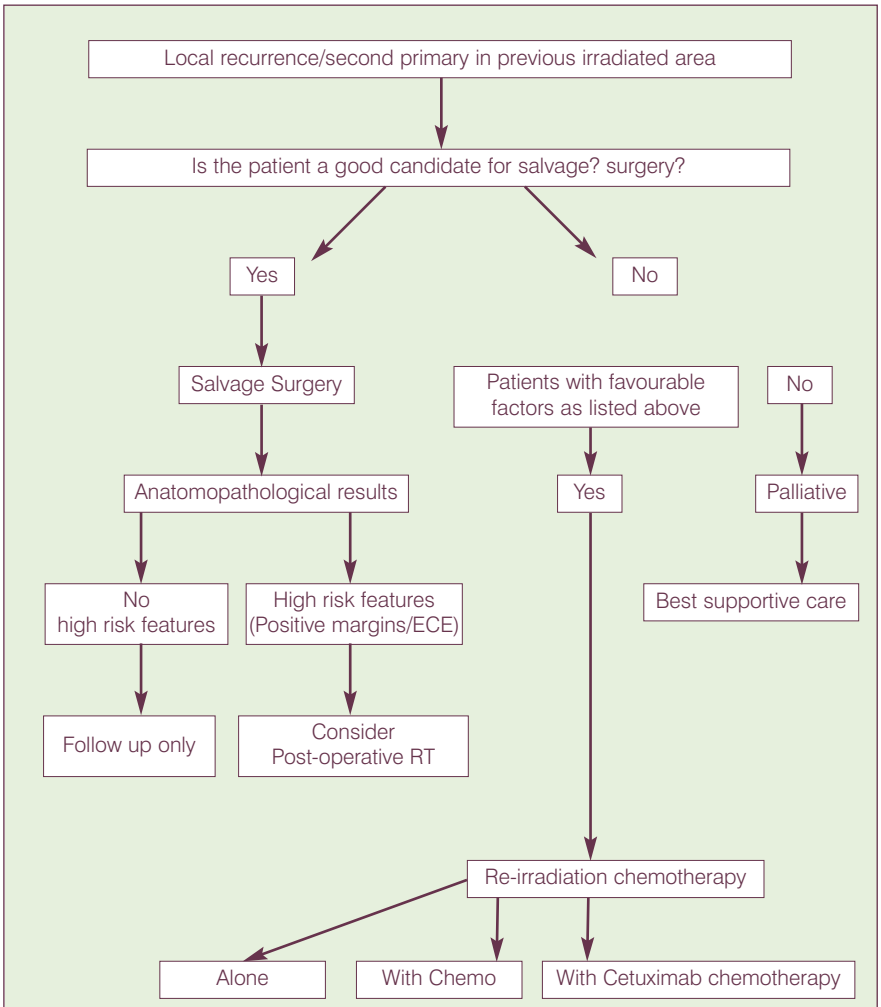
6. Previous surgery is an independent factor of the favourable outcomes during re-irradiation.
7. HPV associated malignancies respond better to therapies and have better outcomes.

Management of the patient with recurrence

A good clinical history and clinical examination will help us also to gauge the functional impact on the patient and also access the performance status. A full endoscopic examination is required to look for the extent of the recurrence and also to detect metachronous tumours. A detailed assessment of all previously irradiated areas to ensure there are no chronic radiotherapy side effects (e.g. laryngeal necrosis). A PET-CT scan is indicated to assess the extent of the disease recurrence and also to determine nodal or metastatic disease. A Doppler ultrasound might be beneficial if there is a suspicion of Carotid involvement. A multidisciplinary approach is recommended in view of the expected increase in toxicity. Nutritional support may be required and a PEG tube is inserted.

Conclusion

The patient has to be optimally staged and assessed for fitness at presentation. If the disease is potentially operable, salvage surgery is offered. The post-operative RT is only offered for patients with high risk of recurrence i.e. involved margins and extracapsular spread. The choice of treatment modality is based on the location and the extent of the recurrence and should be customised to each patient. Larger recurrences are usually considered for EBRT or IMRT with IMRT being the preferable technique. Adaptive radiotherapy will be extremely helpful when treating recurrences in close proximity to the critical structures. There is no clear cut evidence for concurrent chemotherapy as there is no survival benefit, more research is required with newer chemotherapies and targeted agents like Cetuximab. Brachytherapy and SBRT are also available for re-irradiation. With the emergence of new evidence and technological advances multimodality treatments may be considered. There is currently no clear guidance on the choice of Radiotherapy. Any management decisions about re-irradiation should include careful consideration about the factors affecting the outcomes. ●



Optimal pathway for management of H&N cancer recurrence. Reirradiation modality based on extent and location. (Cacicedo et al. 2014)

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Value of Prognostic and Diagnostic Histological and Molecular Glioma Markers

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This review will highlight how molecular tests help improving the diagnosis of gliomas and inform about prognosis and therapeutic options. Relevant molecular markers in glioma diagnostics are chromosomal losses 1p and 19q, and mutations of the IDH and ATRX genes in oligodendroglial and astrocytic tumours of WHO grades II (low grade gliomas) and III (anaplastic or high grade gliomas). In glioblastoma, the most malignant glial brain tumour, the value of testing the methylation of the promoter of the DNA repair enzyme MGMT will be discussed. The following questions, focussing on diagnostic and predictive/prognostic values of the tests, will be addressed:

1) What is the benefit of 1p/19q and IDH molecular testing for the patient?
2) Is there a benefit to use the marker ATRX in glioma diagnostics?
3) What is the predictive and prognostic value of the MGMT promoter methylation?

Epidemiology of gliomas

Astrocytic and oligodendroglial tumours have an annual incidence of 10.1 new tumours per million population in Western countries, and glioblastomas have an incidence of 35.5 per million and that of all intrinsic brain tumours is 52.7 per million [1-3]. Extrapolated for the UK (population 63.7 million), this equates to approximately 640 new oligodendroglial and astrocytic tumours, and more than 2000 GBM annually.

IDH gene mutations

Mutations in the isocitrate dehydrogenase (IDH) 1 or 2 genes occur in approximately 75% of astrocytomas and oligodendrogliomas [4], Figure 1. The majority of the mutations occur in the IDH1 gene, mostly being the R132H mutation. Less commonly, the IDH2 gene is mutated, mostly resulting in the amino acid change R172K. IDH mutations in gliomas are thought to be early pathogenic events, and are associated with several clinically relevant parameters including patient age, histopathological diagnosis, combined 1p/19q deletion, TP53 mutation, ATRX mutation, MGMT promoter hypermethylation and patient survival [5-9]. As a consequence, these mutations are also present in so-called secondary glioblastomas, which developed in situ from pre-existing diffuse or anaplastic astrocytomas.

Testing of the IDH status is relevant for diagnostic and prognostic considerations in primary brain tumours. An antibody, specific for the IDH1 (R132H) mutation was developed in 2009 and is commercially available for diagnostic testing on paraffin sections (10). This antibody detects 90% of IDH mutations, present in 74% of astrocytic and oligodendroglial gliomas (Figure 2 [Figure 3 – IHC image]). However, all other IDH1 and all IDH2 mutations would be missed and it is recommended to test all IDH immunonegative cases (i.e. 8.2% false negatives and 26% true negatives) by sequencing [7,11]. IDH immunostaining is a simple and cost effective test, which can be implemented in all routine pathology laboratories and thus it is debated if IDH sequencing needs to be considered an essential routine test. It is suggested that selected low grade gliomas in a patient group where IDH mutation status would impact on treatment decisions, should be additionally tested. Performing these tests on DNA extracted from paraffin sections is relatively straightforward and can be done in selected referral centres.

High-grade gliomas with IDH mutations show a better prognosis [9,12], whilst the prognostic role of IDH mutations in low grade gliomas is less well established and conflicting results have been reported [13,14].

LOH 1p/19q

The combined loss of the chromosomal arms (LOH, loss of heterozygosity) 1p and 19q is a significant predictor of outcome for patients with tumours of oligodendroglial and oligoastrocytic histology. LOH 1p/19q is associated longer progression free survival and for chemotherapy response. This was reported and validated in multiple studies [15-22].

There is a transition of morphological features between oligodendrogliomas and astrocytomas, resulting in considerable interobserver variability to diagnose astrocytomas, oligoastrocytomas and

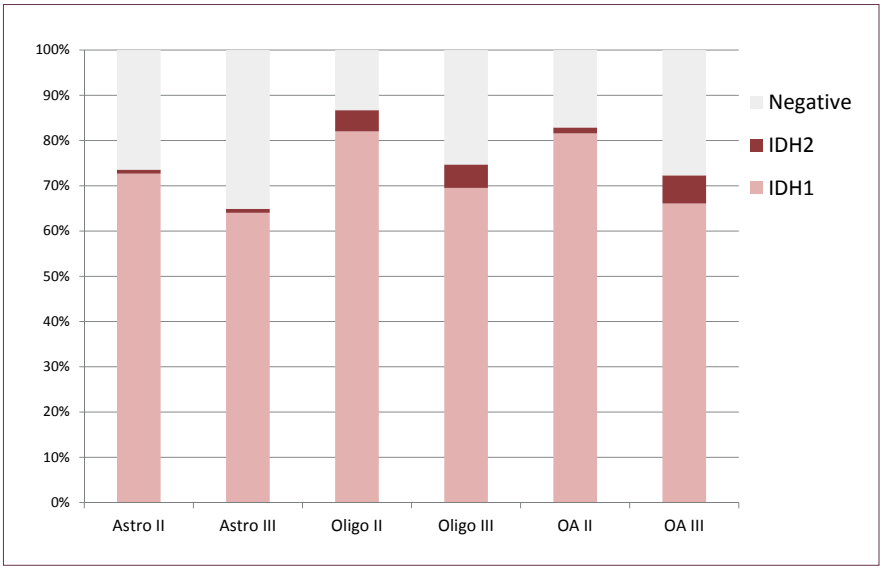

Figure 1: Frequency of IDH1 and IDH2 mutations in astrocytomas, oligoastrocytomas and oligodendrogliomas (WHO Grade II) and their anaplastic forms (WHO Grade III). The majority of IDH mutations are in the IDH1 gene, and a much smaller number in the IDH2 gene. IDH1 and 2 mutations are mutually exclusive. As a general rule the IDH mutation frequency is higher in oligodendroglial tumours than in astrocytic tumours, is higher in low grade than the respective high grade forms, and IDH 2 mutations occur more often in oligodendroglial tumours than in astrocytomas. The data are based on frequencies published in a large scale study on 1010 tumours (4). Other studies showed similar frequencies.

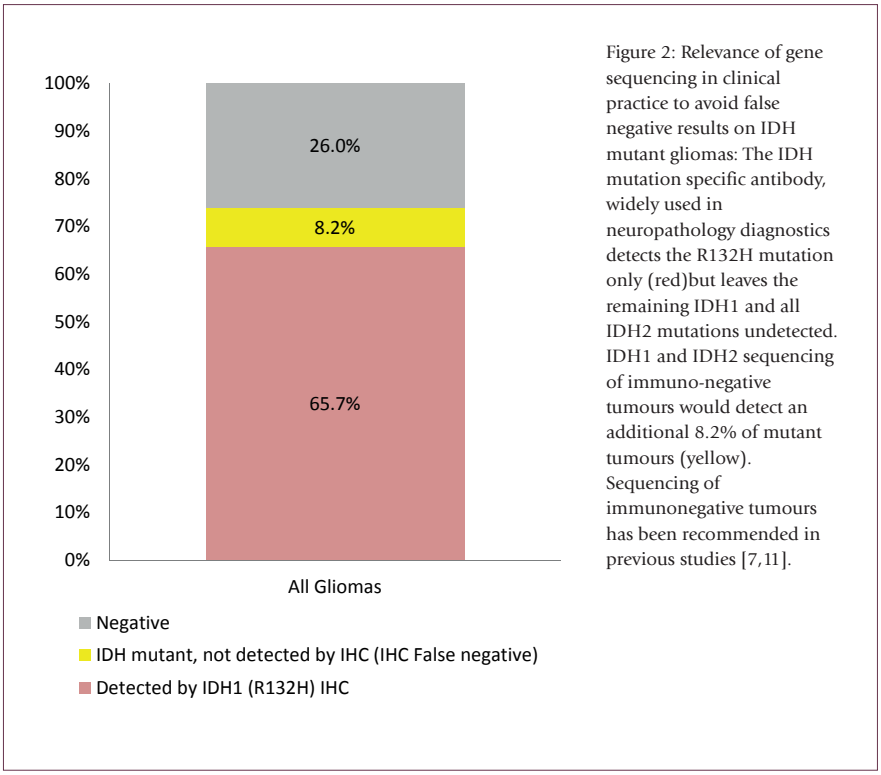

Figure 2: Relevance of gene sequencing in clinical practice to avoid false negative results on IDH mutant gliomas: The IDH mutation specific antibody, widely used in neuropathology diagnostics detects the R132H mutation only (red)but leaves the remaining IDH1 and all IDH2 mutations undetected. IDH1 and IDH2 sequencing of immuno-negative tumours would detect an additional 8.2% of mutant tumours (yellow). Sequencing of immunonegative tumours has been recommended in previous studies [7,11].

oligodendrogliomas [23,24].

In current clinical practice patients with gliomas (WHO grade II/III) carrying 1p19q co-deletions will now usually be treated with first line chemotherapy with a good clinical response. Therefore, the need for radiotherapy with its adverse side-effect can be delayed particularly in this group of patients with predicted long-term survival. In contrast, patients without 1p19q deletions will be usually offered first line radiotherapy due to the limited chance of response to chemotherapy. There is no other way of reliably determining best treatment for these patients.

Role of ATRX

The ATRX (alpha-thalassemia/mental retardation syndrome X-linked) protein [25] is an essential member of a multiprotein complex with a role in regulating chromatin remodelling, nucleosome assembly, telomere maintenance and deposition of histone H3.3 at transcriptionally silent regions of the genome. ATRX loss has been described in pancreatic neuroendocrine tumours, [26], neuroblastoma [27], and in paediatric glioblastoma [28]. More recently, a strong diagnostic and prognostic value of ATRX loss in IDH mutant gliomas has been described, in that ATRX loss occurs almost exclusively in IDH mutant tumours, and that ATRX loss and 1p/19q co-deletion are almost mutually exclusive (Figure 3). ATRX loss is a favourable prognostic marker [29] in the "biomarker cohort" of the NOA-04 clinical trial. The NOA-04 trial compared the efficacy and safety of radiotherapy versus chemotherapy with either PCV or temozolomide (TMZ) as initial therapy in patients with newly diagnosed, supratentorial anaplastic gliomas (WHO grade III) and examined the clinical relevance of 1p/19q LOH, O6-methylguanine DNA-methyltransferase (MGMT) promoter methylation, and IDH1 mutations in these tumours [30].
Based on the molecular profiles and the clinical outcome, the authors [29] suggested a stratified diagnostic algorithm to distinguish "molecular" astrocytomas, oligodendrogliomas and glioblastomas. Importantly, the positive effect of ATRX loss on survival applies to anaplastic gliomas where patient underwent chemo-radiation. Instead the histological value of the ATRX test goes beyond this limitation, as is helps eliminating the ambiguity of the rather vaguely defined group of oligoastrocytomas.

MGMT promoter methylation

MGMT (The O(6)-Methylguanine-DNA Methyl Transferase) is a DNA repair protein that reverts the naturally occurring mutagenic O6-methylguanine back to guanine. This prevents errors during DNA replication. In the context of chemotherapy with alkylating agents (e.g. temozolamide, TMZ) it removes a cytotoxic lesion, thus counteracting the chemotherapeutic effects of the drug.

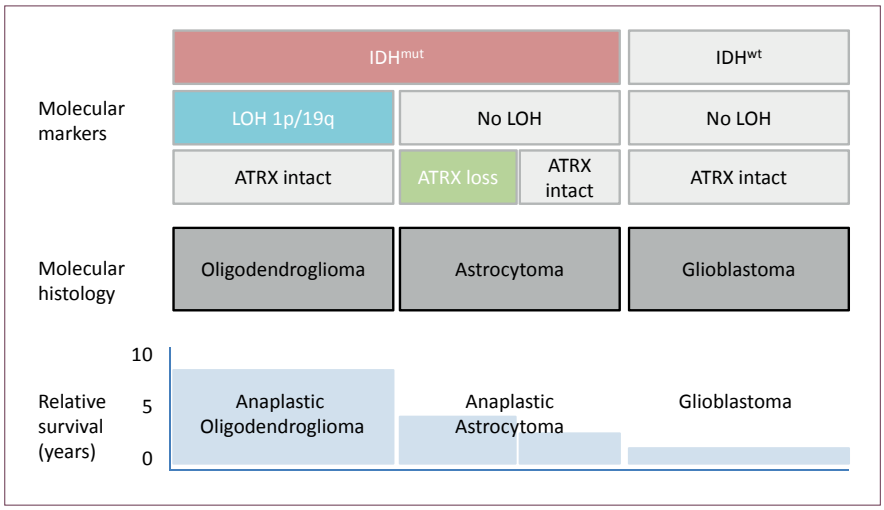

Figure 3: Simplified diagnostic algorithm for oligodendroglial and astrocytic tumours. This study is based on results of the biomarker cohort of the NOA-04 trial (29), which analysed ATRX and IDH mutations and 1p/19q status in relation to treatment response. The trial was carried out in patients with WHO Grade III tumours and the survival data in the graph refer to this cohort. These data suggest that 1p/19q LOH and ATRX mutations are almost completely mutually exclusive and in practical terms the combination of LOH1p/19q, IDH and ATRX tests allow a more accurate and reproducible histological diagnosis, eventually minimising the diagnosis of oligoastrocytomas.

Aberrant, cancer-related methylation of the MGMT promoter region leads to its silencing, a reduction of the MGMT enzyme expression and subsequently to less repair activity of DNA damage, including that induced by TMZ.

A landmark clinical trial of the effect of TMZ on newly diagnosed glioblastoma [31,32] showed that MGMT promoter methylation was an independent favourable prognostic factor. Patients with tumours with a methylated MGMT promoter had a survival benefit when treated with temozolomide and radiotherapy, compared to those who received radiotherapy only, whilst absence of MGMT promoter methylation resulted in a smaller and statistically insignificant difference in survival between the treatment groups. Further studies showed that patients with MGMT promoter-unmethylated tumours had no survival benefit from chemotherapy, regardless of whether given at diagnosis together with RT or as a salvage treatment [33,34]. Two prospective randomised trials, (NOA-08 [30] and the Nordic trial [35] concluded that MGMT promoter methylation is a useful predictive biomarker to stratify elderly glioblastoma patients for RT versus alkylating agent chemotherapy. Accordingly, these consistent trial results suggest that elderly glioblastoma patients eligible for either RT or TMZ should undergo MGMT testing prior to clinical decision making.

The MGMT status can be reliably tested by a standardised methylation-specific PCR [36]. Previous attempts to simplify the tests by detecting MGMT protein by imunohistochemistry had failed, in that it showed a poor inter-observer agreement and thus no correlation to molecular test results [37]. The use of imunohistochemistry to inform about MGMT promoter methylation status is therefore not advised.

In contrast to the promising predictive and prognostic values of the MGMT promoter methylation; there is no diagnostic value in testing for the MGMT methylation status.

Conclusion

The landscape of glioma diagnostics is rapidly changing. Large scale comparative whole genome expression [38] or methylation studies [39,40] helped identifying and biomarkers with diagnostic, predictive and prognostic value. These markers, further validated against survival and treatment responses are now gradually complementing morphological diagnosis. The greatest advantage for the clinical teams, and ultimately the patients will be an increasing accuracy and consistency of histological diagnoses. This will facilitate the clinical decision making process of adjuvant treatments, and stratification of patients to clinical trials. ●

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Meet the Editorial Team

Professor Denys Wheatley is Editor, and is Director of BioMedES. He has strong research ties in Albany, Davis, Auckland, Valencia, Detroit, Budapest, St Petersburg, Heidelberg, Zürich and Hong Kong. He is eager to establish strong interaction with cancer and cell biology teams worldwide, and initiate programmes in the areas in which his expertise lies. His work in cancer research, other scientific fields, with IFCB, and in publishing and scientific communication has led to his receiving awards in recent years.

Dr Richard J Ablin (Associate Editor), is Professor, Pathology, University of Arizona College of Medicine and a Member of the Arizona Cancer Center, Tucson, Arizona. He received the First Award for scientific excellence from The Haakon Ragde Foundation for Advanced Cancer Studies. Dr Ablin discovered prostate-specific antigen (PSA) in 1970. A pioneer of cryosurgery and cryoimmunotherapy, he has extensive experience in cancer research.

Alan Cooper is Assistant Editor – Urology, and is Lead Scientist with the urology research group in Southampton University Hospitals and senior lecturer (albeit with virtually no lecturing burden) in the Department of Biomedical Sciences at Portsmouth University.

Dr Tom Lynch is Assistant Editor – Imaging, and is a Radiologist and Lead Nuclear Medicine Physician in the Northern Ireland Cancer Centre based at the Belfast City Hospital. Tom specialises in PET/CT scanning and nuclear medicine with a special interest in paediatric nuclear medicine.

Dr Miriam Dwek is Assistant Co-Editor - Breast Cancer, she is a Senior Lecturer in Biochemistry at the Department of Molecular and Applied Biosciences, School of Life Sciences, University of Westminster in London.

Prof. Mohammed RS Keshtgar BSc, FRCSI, FRCS (Gen), PhD is Assistant Co-Editor – Breast Cancer, and is a Professor of Cancer Surgery and Surgical Oncology, Royal Free London Foundation Trust. His main area of interest is minimally invasive approaches in diagnosis and treatment of breast cancer. His research interest is in sentinel node biopsy, intra-operative radiotherapy, quantum dot nanotechnology in breast cancer.

Professor Geoffrey J Pilkington is Assistant Editor Neuro-Oncology, is a Professor of Cellular and Molecular Neuro-oncology at the Institute of Biomedical and Biomolecular Sciences, Portsmouth. His research focuses on the development of models for the study of intrinsic brain tumours, elucidation of their metabolism and mechanisms underlying diffuse local invasive behaviour.

Farrokh Pakzad is Assistant Editor – Skin Cancer, and is currently Consultant Oncoplastic Breast and Melanoma Surgeon at Royal Surrey County Hospital. His main areas of specialist interest are in the management of breast disease, oncoplastic and reconstructive breast surgery and the management of skin cancers, in particular, melanoma. Farrokh completed his higher surgical training in London, during which he was selected onto the highly competitive National Oncoplastic Fellowship program.

Dr Constantino Carlos Reyes-Aldasoro is Assistant Editor - Image Analysis. He is a Lecturer in Biomedical Image Analysis at the School of Engineering and Mathematical Sciences, City University London. He has developed a unique portfolio of interdisciplinary skills that span from the acquisition of microscopical images to the analysis of biomedical datasets such as magnetic resonance, computed tomography and microscopy to advanced computer programming and website development.

Mriganka De is Assistant Editor - Head & Neck Oncology. Mr De is a Consultant ENT/Head and Neck surgeon at Royal Derby Hospital, Derby. His interest is head and neck cancer with particular focus on management of early laryngeal cancers.

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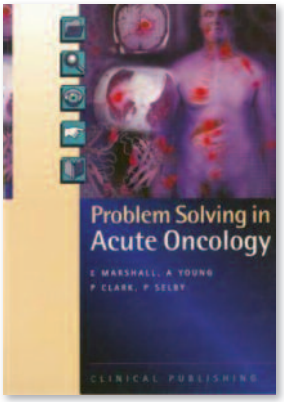
Problem Solving in Acute Oncology

Editors: Ernie Marshall, Alison Young, Peter Clark and Peter Selby. Published by: Clinical Publishing 2014. ISBN: 978-1-84692-1087.



The editors of this book, Dr. Marshall, Prof. Clark are consultant in Medical Oncology at Clatterbridge Cancer Centre, Merseyside, UK. The other two editors, Dr. Young and Prof. Selby work at the St. James's Institute of Oncology University Hospital, Leeds, UK.

The book has in total has 256 pages including the index and references pages, divided into six sections. In total 47 relevant topics are discussed and covered in the book divided in six sections. The chapters in the book range from a minimum of two topics per section to a maximum of 14 topics per section and each chapter is written by a different author. Overall the book covers a range important topics pertaining to cancer management, including complications of systemic therapy and radiotherapy.

The first section of the book titled "Perspectives in the Development of Acute Oncology"

open the book and sets the scene perfectly for the readers, sketching in details the most recent and advance developments in the area of acute oncology. The section includes chapters that provide UK readers a perspective on the management of acute oncological conditions outside the country from the United States, Canada and Australasia. This section also includes chapters detailing on how to stratify acute oncological emergencies and their management in a HDU setting. In total this section includes 11 chapters. The 2nd chapter of the book is titled "Complications of Systemic Therapy" and is by far the longest section of the book and includes 14 chapters. This section of the book is very comprehensively written and covers a range of relevant and important topics related to chemotherapy toxicities. I thoroughly enjoyed reading this section as it succinctly covers all the commonly encountered emergencies in the wards in cancer patients undergoing chemotherapy. I am sure the other readers of the book will equally enjoy reading this section as much as I did including the readers preparing for competitive medical exams. This section very well covers in detail most of the topics that are required to be known from an exam perspective, negating the need to look elsewhere. The third section is titled "Complications of Radiotherapy". This section covers a range of radiation induced toxicities of skin, lung and CNS and includes 5 chapters in total. The fourth section of the book is titled "Complications of Cancer" and is the second longest section of the book including 12 interesting chapters. This section covers the commonly encountered complications from cancer disease including complications of cancer metastasis, local and systemic complications, metabolic disorders, and common surgical, cardiovascular and peripheral nervous system emergencies. I liked reading the included topics in this section as it lends a good overall generic perspective to the complications of various cancers. The fifth section of the book is titled "Acute Palliative Care and Pain Control" and includes two chapters on pain management and neuropathic cancer pain management. This section provides readers an insight into the patho-physiology of the origin of pain in cancer and the current available management options. The last section of the book is titled "Patients in Clinical Trials" and includes three chapters. This section has topics that cover management of acute toxicities in clinical trials, recording and reporting of adverse events in the context of clinical trials and issues around informed consent in clinical trials. The issues covered in this section are important for clinicians to know, and therefore, I feel the book winds up on a very good note covering a range of topics of academic and clinical relevance.

Overall, I have found this to be a very well written, easy to read and very informative. I would definitely recommend this book as a good starting point to all the clinicians, allied health care professionals involved in dealing with cancer management and junior doctors involved in the management of cancer patients in the Oncology wards.

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POSNOC

POsitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy. A randomised controlled trial of axillary treatment in women with early stage breast cancer who have metastases in one or two sentinel nodes

Women with early breast cancer that has spread to the first one or two lymph glands (sentinel nodes) will receive chemotherapy or endocrine therapy (hormone therapy), or both. Radiotherapy is given to the breast in all women who undergo breast conserving surgery, and to the chest wall in some who undergo mastectomy. These treatments are called adjuvant therapy.

Currently, these women also have treatment to their axilla. This treatment is either a second operation to remove all the lymph glands in the axilla (axillary node clearance), or radiotherapy to the axilla.

Axillary treatment and arm morbidity

Axillary treatment is recommended for these women on the assumption that it reduces the risk of axillary recurrence, and might improve survival. Axillary node clearance is usually a second operation, but some hospitals use intra-operative sentinel node assessment and so perform axillary node clearance at the same time as breast conserving surgery or mastectomy. A drain is left in the wound for a few days afterwards. The operation lasts one to two hours and requires a stay in hospital of one to two days.

Axillary radiotherapy is given five days a week for three to five weeks based on the local protocols. Axillary radiotherapy is offered only in some specialist centres, and some women may need to travel a considerable distance.

Axillary treatment damages the drainage channels of the lymphatic system. Fluid called lymph begins to collect in the arm and doesn't drain in the normal way. So the arm and hand may swell. This swelling is called lymphoedema. One in five women may have lymphoedema in the arm after axillary treatment. Lymphoedema can be painful and make it difficult to move the arm. It cannot be completely cured, and without treatment it may get worse. Lymphoedema can start at any time after the armpit treatment. Also, one in three women may have numbness or pain; and one in five may experience shoulder stiffness [1-7]. These problems can be upsetting, impair quality of life and are costly to the NHS in terms of rehabilitative treatments (such as physiotherapy and lymphoedema clinics).

Adjuvant therapy

The systemic adjuvant therapy is now so effective for early breast cancer that axillary treatment may offer no additional protection against axillary recurrence, and so may be overtreatment. This hypothesis is supported by several small studies [8].

In the past, information from axillary node clearance with regard to the number of nodes with cancer was used to guide systemic therapy. However, decisions about these adjuvant therapies are now more commonly based on biological tumour markers and molecular determinants of prognosis and predictors of treatment benefit. Early data from the EORTC AMAROS trial [9] suggests that the 'extent' of nodal involvement does not affect the decision to administer systemic therapy.

There is variability in practice in relation to the use of post-mastectomy radiotherapy and radiotherapy to the supraclavicular fossa region. The degree of axillary nodal involvement is a significant driver and women with cancer spread to four or more nodes are candidates for chest wall and supraclavicular fossa radiotherapy [10]. This information will be absent if axillary node clearance is omitted. The proportion of patients having four or more positive lymph nodes in the AMAROS trial was low (8%) [11]. This figure is estimated to be lower than 5% in the POSNOC trial as ultrasound node negative patients have a lower axillary tumour burden [12].

Evidence from systematic reviews and randomised trials

Axillary treatment may now be over treatment for early breast cancer; as diagnosis tends to be earlier so patients present with smaller tumours and a low axillary tumour burden; adjuvant therapy has improved and is better at preventing breast and axillary recurrence [13]; and sentinel node biopsy has

already removed the lymph nodes most likely to have metastasis [14]. Moreover, if adjuvant therapy includes radiotherapy to the breast or chest wall, the lower axilla will be treated inadvertently as it is included in the tangential irradiation field, and some lower level axillary nodes may be removed at mastectomy [15].

There are three randomised trials assessing axillary treatment. The first [16] was a three arm study that recruited 1079 clinically node-negative women. They were randomised to receive either radical mastectomy (mastectomy with axillary node clearance), or total mastectomy with axillary irradiation, or total mastectomy alone without axillary treatment. Women had larger tumours, higher axillary tumour burden compared with today's patients and they did not routinely receive adjuvant systemic therapy. All three arms had similar 25 year overall survival, suggesting that axillary treatment did not improve survival.

The second study [17] randomised 435 clinically node-negative women to breast conservation without axillary treatment or breast conservation plus axillary radiotherapy. Axillary recurrence was low in both groups (no axillary treatment 1.5% vs. 0.5% axillary radiotherapy). Both arms had similar disease free survival.

In the third more recent trial [18] patients with tumours less than 5cm in size, treated by breast conserving surgery and whole breast radiotherapy, with sentinel node metastases, were randomised to axillary node clearance (n=445) or not (n=446). Axillary recurrence was low, and there were no clear differences between the two groups (axillary clearance 0.5% vs. no axillary clearance 0.9%) at 6.3 years. The trial was terminated before its targeted accrual. There was a potential for bias in this study as the radiation oncologists were aware of the treatment allocation, and it is not reported whether this influenced their decision about how much of the axilla to treat with tangential radiotherapy. Generalisability of the results is limited as some centres recruited fewer than five patients, axillary recurrence was not a pre-specified endpoint, mastectomy patients were excluded, and the trial protocol did not mirror NHS practice.

A recent meta-analysis [8] of randomised trials and observational studies which included patients who had sentinel node biopsy concluded that more evidence is needed to guide management of the axilla in patients with early breast cancer and sentinel nodes metastasis.

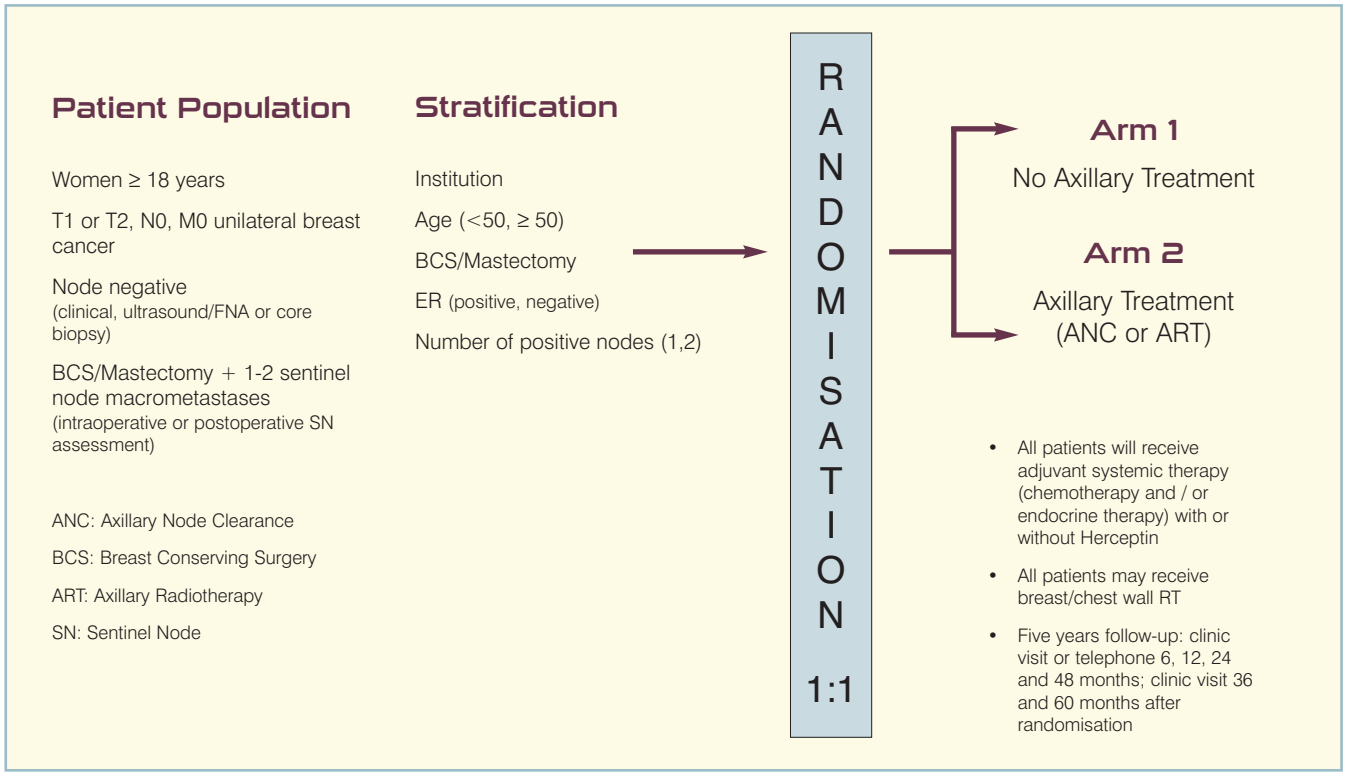
Why we need a trial now

Biological factors may be more important for recurrence than surgical removal or radiation eradication of axillary nodes. If axillary surgery is merely a staging or diagnostic procedure, then adverse effects are likely to be minimal if it is omitted and sentinel node biopsy alone is used to guide subsequent treatment in women with early stage breast cancer who have one or two sentinel node metastases. Also, axillary treatment (axillary node clearance or axillary radiotherapy) was introduced several decades ago without formal evaluation and is associated with significant short- and long-term morbidity. Since axillary treatment was introduced, chemotherapy and endocrine therapy have dramatically improved outcome. Therefore, it is timely to assess whether adjuvant therapy alone is an acceptable alternative to adjuvant therapy plus axillary treatment.

POSNOC trial

POSNOC is a pragmatic, randomised, multicentre, non-inferiority trial. Recruitment starts July 2014.

Aim: For women with early stage breast cancer and one or two sentinel node macrometastases, to assess whether adjuvant therapy alone is no worse than



adjuvant therapy plus axillary treatment, in terms of axillary recurrence within five years.

Patient Population: Women with unifocal or multifocal invasive breast cancer, largest primary lesion ≤5cm, clinically and ultrasound node negative, who undergo sentinel node biopsy (SNB) and have 1 or 2 sentinel node macrometastases (›2mm), with no extranodal extension.

Interventions: The study will compare adjuvant therapy alone with adjuvant therapy plus axillary treatment (axillary node clearance or axillary radiotherapy).

Primary Outcome: Axillary recurrence at five years.

Secondary Outcomes: Arm morbidity, quality of life, anxiety, local (breast or chest wall) recurrence, regional (nodal) recurrence, distant metastasis, time to axillary recurrence, axillary recurrence free survival, disease free survival, overall survival, contralateral breast cancer, non-breast malignancy, economic evaluation.

Sample Size and Follow-up: 1900 participants. Participants will be followed up for five years.

Adjuvant Therapy: All participants will receive adjuvant systemic therapy (chemotherapy and/or endocrine therapy). All participants may receive breast/chest wall radiotherapy. Axillary and supraclavicular fossa radiotherapy is not allowed when randomised to adjuvant therapy alone.

Conclusion

POSNOC Trial aims to address an important clinical question of axillary management in a randomised setting. For further information regarding participation in this important multicentre trial please contact the POSNOC trial team on 0115 884 4924 or email: posnoc@nottingham.ac.uk. ●

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Hedgehog Pathway in Basal Cell Carcinoma

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Basal cell carcinoma (BCC) is the most common malignant neoplasm of the skin worldwide, and its incidence is increasing. Although generally slow-growing, locally invasive tumours may cause tissue destruction, disfigurement and severe morbidity. Surgical resection is the mainstay of treatment. Other treatments may include photodynamic therapy, topical cytotoxics such 5-fluoruracil, immune modulators such as Imiquimos, cryotherapy and radiotherapy. Where such treatments are ineffective (eg: those with recurrent disease, refractory to radiotherapy, or with metastatic spread), treatment options maybe limited and highly destructive surgery becomes the only hope. More recently, inhibiting the Hedgehog pathway has opened avenues in targeted systemic treatment for BCC and potentially other cancers.

Hedgehog pathway – overview

The Hedgehog (Hh) pathway comprises a group of proteins involved in the regulation of cell growth, differentiation and promoting stem cell proliferation. It was discovered for its role in organogenesis in Drosophila, where the lack of the hedgehog gene resulted in failure of organ development and migration [1]. The resultant 'spiky' appearance of defective embryos lead to the pathway being named Hedghog. In humans, as well as facilitating embryonic growth, the Hh pathway is an important regulator of adult stem cell function involved in maintenance and regeneration of adult tissue.

Hedgehog (Hh) proteins are secreted paracrine molecules that are ligands for the trans-membrane receptor known as Patched (PTCH). In the resting cell, PTCH has a tonic inhibitory effect on a G-protein coupled membrane receptor called Smoothened (SMO). Binding of Hh to PTCH releases this inhibition, allowing SMO to initiate a cascade of events resulting in the transcription of genes that promote cellular proliferation. Of the three hedgehog proteins identified, Sonic hedgehog (SHH) has been the most well characterised, the others being Desert Hedgehog and Indian Hedgehog homologues.

In a healthy adult cell, the hedgehog pathway will be activated in the presence of SHH (see fig1). GLI activation downstream from SMO has been shown to have a number of effects. It increases expression of cyclins D1 & B1, promoting progression through cell cycle and suppressing apoptosis. E-cadherin expression is decreased, reducing cell adhesion and the integrity of tight junctions and encouraging cell separation and the development of metastases. It also increases angiopoietin-1 and angiopoeitin-2 expression, promoting angiogenesis [2].

Mutations in PTCH or SMO result in SHH-independent or constitutively activated pathways, leading to uncontrolled proliferation of basal cells in BCC. Congenital mutations in PTCH have been linked to Basal Cell Naevus Syndrome (also known as Gorlin syndrome), which predisposes to the development of BCC. Defects in the Hh-signaling pathway have also been implicated in over 90% of sporadic BCC [3]. The development of medulloblastoma, rhabdomyosarcoma and pancreatic cancer have all been linked to overactive hedgehog signaling, thus targeting this pathway may potentially lead to treatment for a variety of cancers [3].

Inhibiting hedgehog pathway signals

Cyclopamine, the first identified inhibitor of the Hh pathway is a naturally occurring alkaloid derived from the extract of the corn lilly plant. Its teratogenic effects were discovered in sheep grazing on corn lilly leaves, where amongst a number of congenital malformations, cyclopia was frequently seen (hence the name Cylopamine) [4]. Subsequent attempts at developing drugs that inhibit the hedgehog pathway have been modeled on its structure. Saridegib and Vismodegib are small molecule, synthetic analogues of Cyclopamine that inhibit SMO. Saridegib initially showed promise in phase I trials involving a range of advanced or metastatic solid tumours. However, phase II trials in chondrosarcoma and metastatic pancreatic cancer were terminated early, due to unfavorable results as compared to the placebo arms [5]. The potential use of Saridegib in treating BCC is yet to be explored. Vismodegib (trade name Erivedge) is the first and currently the only, hedgehog pathway inhibitor that has been licensed for use in BCC's that are not amenable to surgery or radiotherapy. A 2-pyridyl amide molecule with oral bioavailability as once daily 150mg dose, it blocks hedgehog signaling by selectively inhibiting SMO, consequently preventing the induction of the target genes, which underlie BCC growth.

The Erivance BCC trial found tumour shrinkage in 30% and 43% of patients with metastatic and locally advanced BCC respectively. Of the patients with

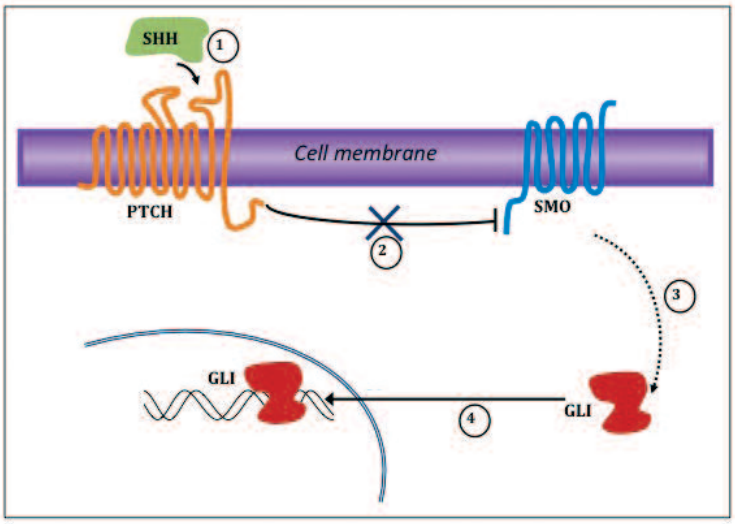

Figure 1:
1. SHH binds to the extracellular portion of PTCH1.
2. PTCH1 inhibition of SMO is relieved.
3. SMO initiates a signaling cascade, which activates the GLI (Glioma Associated Oncogene) family of transcription factors.
4. GLI enters the nucleus to regulate the expression of genes, which promote cell survival.

Figure 2: Corn lily (veratrum spp.) from which cyclopamine is derived.

locally advanced BCC, 54% had no residual disease in biopsy specimens obtained during treatment with Vismodegib, indicating a complete response [6].

Although no control group was utilised in this study, given the lack of alternative effective therapies available and the improbability of spontaneous resolution, the therapeutic potential is evident. Another phase II randomised, placebo-controlled study recruited patients with Gorling's syndrome. Vismodegib was shown to significantly reduce the size of existing BCCs compared with the placebo (reduction of 65% in treatment group versus 11% in placebo arm), as well as decreasing the incidence of new BCC lesions (2 cases / group / year vs 29 in the placebo group) [7].

Adverse drug reactions to Visemodegib appear to be common. In the Erivance trial, all enrolled patients reporting at least one adverse effect. While majority of these were minor side effects (most commonly gastrointestinal disturbances, anorexia, alopecia), 25% were grade 3 / 4 reactions that included muscle spasms, weight loss and fatigue. For 13 patients (12%), Visemodegib was discontinued due to adverse effects, with this figure being much higher (54%) in patients in the BCNS study. In patients with BCNS, rebound recurrence after cessation of Vismodegib has also been reported [8]. This has fueled concerns over the use of Visomodegib in this population, where the rate of drug intolerance appears to be high. Vismodegib is hightly teratogenic as well as ebryogenic. Therefore highly effective forms of birth control measures are advised for both male and female patients on treatment (and up to 7 months for women and 2 months for men after the last dose given).

Resistance to Vismodegib therapy due to mutated SMO has been encountered in trials for medulloblastoma [9]. The antifungal agent Itraconazole has been explored for its potential in blocking the hedgehog pathway via an as yet unclear mechanism that is independent of SMO inhibition. Pre-clinical studies have suggested that this may offer an option in resistant disease [10].

Summary

Vismodegib is an oral inhibitor of the hedgehog pathway and the first systemic treatment for patients with locally advanced or metastatic basal cell carcinoma that is not amenable to surgery and radiotherapy. Data on overall survival with Vismodegib is currently limited, however, response demonstrated in early clinical trials has been promising.

To date, inappropriate activation of the hedgehog signaling cascade has been implicated in many other types of cancer. There is also emerging evidence to support crosstalk between the Hh pathway and other cancer pathways. As such, the synergistic role of targeted Hh-inhibition with EGFR, MEK, mTOR or PI3K inhibitors is currently being investigated in a range of solid and hematological malignancies [11]. ●

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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

ESMO Congress 2014

Date: 26-30 September 2014. Venue: Madrid, Spain. **Preview**

The European Society for Medical Oncology is the leading European professional organisation committed to advancing the specialty of medical oncology and promoting a multidisciplinary approach to cancer treatment. ESMO represents a community of over 7,300 oncology professionals from over 120 countries.

ESMO Congress

The ESMO Congress is the largest and most important meeting in the world for medical oncologists.

A record-breaking 16,394 delegates attended ESMO 2012 in Vienna, making it ESMO's biggest and best congress yet! Over the five days, 140 scientific and educational sessions were staged. And following an impressive increase in the number of abstract submissions – up 30% on 2010 – 1,238 were selected for presentation, including 31 late-breaking abstracts. Over 3,000 delegates attended the Presidential Session where Dr Alice Shaw from Massachusetts General Hospital Cancer Center, Boston, USA, presented her practice changing study on the use of crizotinib in ALK positive NSCLC patients. Resources from ESMO 2012 can be found here.

2014 is another ESMO Congress year and a unique opportunity for the oncology community to come together, disseminate state-of-the-art scientific information, and improve oncology practice. ESMO members who register for the Congress save nearly 50% on the early registration fee compared to non-members. All members who cannot join us in at ESMO 2014 in Madrid have access to the Congress webcast at no additional charge—ESMO's webcast library is included in the membership fee.


JY Douillard


R Stahel


J DeBono

ESMO 2014 will take place 26-30 September in Madrid. ESMO will provide a programme that builds on the highly successful models of ESMO 2010 in Milan and ESMO 2012 in Vienna, while extending breadth and depth. You can expect to learn about the latest results in basic, translational, and clinical research, expressing the broader concepts of precision or personalised medicine in specific treatment options.

The theme for ESMO 2014 is 'Precision Medicine in Cancer Care.' Providing optimal treatment for patients according to individual circumstances and the molecular characteristics of their disease is a key theme for ESMO. Whether you are a medical or surgical oncologist, radiotherapist, immunologist or pathologist, practicing precision medicine means we are all working towards a common goal—improved patient outcomes. This is the ultimate goal of ESMO 2014.

ESMO 2014 Important Deadlines:

Abstract submission	**7 May 2014**
Early registration	**18 June**
Late registration	**20 August**

www.esmo.org www.esmocongress.org

Cancer innovation tops bill at Teenage Cancer Trust's International Conference on Teenage and Young Adult Cancer Medicine

Date: 7-8 July 2014. Venue: London, UK. **Preview**

Oncology health professionals from around the world are invited to London this summer for the biennial Teenage Cancer Trust International Conference on Teenage and Young Adult Cancer Medicine – and the 2014 programme is as dynamic as ever.

Keynote speaker, Lord Saatchi, will call for more innovation in the development of cancer treatments and identify the major challenges, actions and commitments needed to address innovation in cancer. The conference will also focus on international perspectives, clinical trials, new approaches to service delivery and transition, specific diseases, survivorship, as well as education and communication with young people.

Conference highlights include:

- An International Perspectives Panel: Models of care and cultural differences – with panellists from Paris, Milan, Edinburgh, Marrakech and Beijing.
- Biology rather than age in acute lymphoblastic leukaemia.
- Precision medicine in Hodgkin lymphoma, medulloblastoma, and melanoma
- T Cell products and advances.
- Proton beam therapy and other innovations in radiation treatment.
- Pharma Perspectives: responding to the challenges of the TYA population.

Breast Cancer Care's Healthcare Professional Annual Conference 2013

Date: 15 November 2013. Venue: London, UK.

Breast Cancer Care's Annual Conference for healthcare professionals, took place recently in London. Two hundred and ten delegates were in attendence, listening to presentations from speakers addressing topics that are frequently talked about in practice.

Sir Richard Peto, for the Early Breast Cancer Trialists' Collaborative Group, discussed 10 v 5 years of adjuvant endocrine therapy. He presented recently published evidence showing that 10 years of tamoxifen provides extra benefit to patients compared to the current standard of 5 years. However, extending treatment has implications for those struggling with adherence and for younger women wanting to start a family.

Katy Hogben, Consultant Breast and Reconstructive Surgeon, Imperial College Healthcare Trust, spoke about the complexities of lobular carcinoma in situ (LCIS), now included in the umbrella term lobular neoplasia along with atypical lobular hyperplasia. The discovery of LCIS in women under 40 is a suggested marker of increased breast cancer risk. This means difficult discussions with patients when deciding on management, which can include surveillance, surgical excision, or tamoxifen or raloxifene for risk reduction.

Fiona MacNeill, Consultant Breast Surgeon, Royal Marsden Hospital, addressed a question that an increasing number of patients with unilateral breast cancer ask: Should I have a bilateral mastectomy? High-risk patients clearly benefit, but others may mistakenly assume contralateral mastectomy to the healthy side will reduce their risk of dying from the disease. While bilateral mastectomy reduces the risk of new primary disease, there's no evidence it reduces mortality, and contralateral mastectomy won't alter the prognosis from the ipsilateral cancer.

Karen Scanlon, Head of Research and Evaluation at Breast Cancer Care, outlined the research that informed Breast Cancer Care's Moving Forward work, now an integral part of its information and support services. She described the transition of the patient to 'survivor', through a period of relief, reflection, recuperation, recovery and rehabilitation, identifying the points at which support is often required to help patients move through and beyond their experience.

Richard Howell, Consultant Obstetrician and Gynaecologist at Royal Sussex County Hospital, described fertility issues before and after breast cancer treatment and the complex decisions women face. He reinforced that all women of reproductive age should have a fertility consultation before treatment and a test of ovarian reserve three months after stopping tamoxifen to assess the realistic chances of a natural conception.

Even with today's adjuvant treatment planning tools, many women with breast cancer are over-treated. Professor David Miles, Consultant Medical Oncologist at Mount Vernon Cancer Centre, spoke about multiparameter gene assays such as MammaPrint and Oncotype DX and how they are beginning to change treatment recommendations.

Finally, Emma Pennery, Clinical Director at Breast Cancer Care, gave the Jane Haynes memorial lecture and contemplated specialist breast care nursing roles. She reminded us that despite increased demands on our time and skills, the CNS is a crucial part of successful care, making a substantial difference to patient experience.

Before closing the conference, Emma Pennery, Jane Hinnrichs, Chair of the Board of Trustees for Breast Cancer Care, and Amanda Mealing, Breast Cancer Care Ambassador, announced the 2013 Nursing Network Awards winners. These awards champion best practice in specialist breast care nursing and recognise individuals or teams who have demonstrated innovative and pioneering ideas that make a difference to patient care.

Amanda also described her experience of breast cancer and the breast care nurses who supported her through treatment and beyond. She said: 'If pay equalled worth, I'd be in a room full of millionaires.'

Catherine Priestley, CNS Primary Breast Cancer at Nottingham Breast Institute.

- Research findings in 'Chemo Brain'.
- Traversing a cultural divide: The challenges of communicating with young people.

As the world's most significant conference focusing on teenage and young adult cancers, the event is aimed at a wide range of disciplines including oncologists, haematologists, epidemiologists and research scientists. The two day conference will include a diverse range of world-class speakers showcasing the latest developments, research and challenges in the field of cancer in teenagers and young adults, as well as sharing thoughts, best practice and experience

Rachel Hough, Consultant Haematologist at University College Hospital London said: "This conference is a must for anyone involved in caring for teenagers and young adults with cancer. You will hear first-hand from experts at the very cutting edge of teenage and young adult cancer care"

Prior to the Conference an optional day on Sunday 6 July, offers a nursing and allied healthcare symposium discussing the 'Psychosocial Aspects of Teenage and Young Adult Cancer.'

Teenage Cancer Trust is the only UK charity dedicated to improving the quality of life and chances of survival for young people with cancer aged between 13 and 24. We build specialist units within NHS hospitals, bringing young people together to be treated by teenage cancer experts in a place designed just for them. We want every young person with cancer to have access to this specialist support, no matter where they live.

Visit: www.teenagecancertrust.org/what-we-do/international-conference/ for further information.

Paediatric Adolescent Wild-type & Syndromic GIST Clinic

Europe's first specialist clinic for rare cancers at CUH Addenbrooke's Hospital has been hailed a success. Ten patients and their families travelled from across the UK to the centre in Cambridge to meet specialist clinicians who'd also gathered from across the country. They spent the day sharing experiences and running tests in quest to investigate very rare Paediatric and wild-type GIST cancers for which there is currently no successful treatment.

Dr Ramesh Bulusu, Consultant Oncologist at Cambridge University Hospitals, is the national lead consultant for PAWS-GIST. He said "The feedback so far from patients and their families has been brilliant. We're really looking forward to extending the work by running two more similar clinics before the end of this year."
Here is a summary of some of the patient feedback:

Name: Sarah Nash
Age: 29
From: Middlesbrough
First diagnosed: aged 16

The first tumour was found when she was 16 years old. Doctors thought it was just an infection at first. She had the tumour removed and nothing was said on her follow up. In November, 2012 she was diagnosed with anaemia. In May 2013 she was throwing up blood and was rushed into hospital where she underwent an emergency tumour removal – her tummy tumours had spread. She has been put on a course of medication which has made her tumours shrink.

"This is brilliant! It's about time that a clinic like this was created. It's given me and other people hope for the future. Meeting other people and hearing their stories gives me hope and support to get through everything."

Jemma Mitchell

Michelle Paisley

Name: Jemma Mitchell
From: Sussex
Was was first diagnosed with anaemia in 2008 when she had her first daughter. In 2009 whilst pregnant with her second daughter her anaemia got worse and at 35 weeks in her pregnancy she was rushed into hospital and was close to dying with a severe internal bleed. She underwent 10 blood transfusions over three days. She underwent an endoscopy which found a tumour. She gave birth to her daughter and the tumour was removed six weeks later.

In November 2013 she was undergoing a routine ultrasound when doctors found liver lichens. She then discovered that she had four tumours in her liver – they have not grown or shrunk.

"I feel less alone now that I have met people going through the same experience as me. There needed to be a clinic like this and I'm so glad there finally is."

Name: Michelle Paisley
Age: 28
From: Sheffield
First diagnosed: aged 22
She had already been diagnosed with anaemia when she developed stomach pains and shortness of breath. She was rushed into hospital after throwing up blood. A tumour was found in her stomach so she underwent an operation to remove the tumour along with two thirds of her stomach. She was given medication but the first dose didn't work – it gave her a severe rash all over her body. She started having shortness of breath again but ignored the symptoms. She ended up getting rushed into hospital with heart failure. They found more tumours and she is now on medication that is keeping her stable.

"I think this clinic is a really good idea and it's a good thing to be part of. It's really nice having people to talk to who know exactly how you feel."

TYAC 10th Anniversary Conference: Working Together

Date: 30 September 2014. Venue: Leicester, UK.

Preview

Founded in 2004, Teenagers and Young Adults with Cancer (TYAC) is a multi-disciplinary membership organisation which brings together professionals who work with teenagers and young adults with cancer. The fundamental aim of TYAC is to help TYA professionals to work together through sharing good practice, learning and networking. TYAC has previously held education days focussing on the TYA aspect of a range of topics which have included: research, bone tumours, brain tumours, ethics, law, sexuality, fertility, survivorship, loss, cancer services and communication.

To celebrate our 10th anniversary, TYAC will be hosting a celebratory conference on the theme of 'Working Together'.

At the conference, survivors will share their experiences of being diagnosed with cancer as a young person and highlight why dedicated TYA services are needed. A GP will share his good practice and discuss the issues that doctors in primary care face in recognising and diagnosing cancer in teenagers and young adults. A question time session will provide an opportunity for lively debate on regional, national and international strategy for TYA cancer care. In the afternoon, an inspirational author and trainer will share some of the 'secrets' of positive psychology, and look at the key ingredients that breathe life into great team work.

TYAC's 10th Anniversary Conference will continue the organisation's reputation as an important forum for sharing knowledge and uniting professionals from across the UK and overseas. Please join us on 30 September for a varied, informative and inspirational day.

For more information visit www.tyac.org.uk

6th International Workshop on Advances in the Molecular Pharmacology and Therapeutics of Bone and other Musculoskeletal Diseases

Date: 28 June - 2 July 2014. Venue: Oxford, UK.

Preview

It is our pleasure to invite you to attend the 6th International Workshop on Advances in the Molecular Pharmacology and Therapeutics of Bone and other Musculoskeletal Diseases in Oxford, 28 June to 2 July this year.

For those who've attended before, you'll know this means an exceptional meeting which combines cutting edge exciting science with a friendly and supportive atmosphere, and which encourages discussion and collaboration both in and out of the lecture theatre.

Topics include:

- Current therapies: benefits and controversies (clinical)
- Paget's disease and related issues
- Therapeutic directions in rare genetic diseases
- New approaches to therapies in bone diseases and osteoporosis
- Epigenetics and RNA-based therapeutics
- Mechanical systems biology
- Advances in cell biology and therapeutic implications
- Arthritis/fracture repair/pain
- Ageing
- New advances in cancer and bone
- Therapies for muscle diseases
- Bisphosphonates and related topics

Some comments from previous attendees:
"A unique scientific conference in a unique setting."
"The entire conference was superb."
"I really learned a lot from the variety of talks and have to reconsider my work on the basis of some of the newer mechanisms presented."
"It's an excellent meeting and a great opportunity for interaction with the top people in the field."

Residential and non-residential registration packages are available. We encourage delegates to take advantage of the residential registration options to make the most of the opportunity to network with others in a uniquely relaxed and informal environment. Please pass to any colleagues who could have an interest.

We hope to see you in Oxford!
Professor Graham Russell, Organising Committee Chairman.

Visit: www.oxfordbonepharm.org

BTOG presents an annual lifetime achievement award

The British Thoracic Oncology Group (BTOG) presents an annual lifetime achievement award to a health care professional involved in thoracic oncology who is considered to have made a major impact in the thoracic oncology field. BTOG is proud to announce that Professor Julian Peto was presented with the BTOG Lifetime Achievement Award 2014 at the 12th Annual BTOG Conference 2014 held in Dublin in January 2014. The award was presented by Mr John Edwards, Consultant Thoracic Surgeon at Northern General Hospital, Sheffield.

Professor Julian Peto holds the Cancer Research UK Chair of Epidemiology at the London School of Hygiene & Tropical Medicine. After five years as a statistician at Edinburgh University, the Institute of Psychiatry and the Medical Research Council's T.B. Unit he moved to Oxford in 1974 to join the ICRF Cancer Epidemiology and Clinical Trials Unit headed by Sir Richard Doll. In 1983 he was appointed to the Cancer Research UK (formerly CRC) Chair of Epidemiology at the Institute of Cancer Research. He moved to the London School of Hygiene and Tropical Medicine in 2004. His work on asbestos, which began almost 40 years ago, included the dose-response models for lung cancer and mesothelioma that were used internationally to regulate working conditions when asbestos was still being used, the first projection of future mesothelioma rates, and the MARS (Mesothelioma and Radical Surgery) Trial. He is now conducting case-control studies on asbestos lung burden and lifetime occupational history in relation to lung cancer and mesothelioma to predict future mesothelioma rates and assess the extent of current occupational and environmental asbestos exposure from the asbestos still present in many buildings.

Dr Sanjay Popat, Professor Julian Peto and Mr John Edwards.

For further information visit: www.btog.org

Professor Andrew Tutt appointed as Director of the Breakthrough Toby Robins Breast Cancer Research Centre

Professor Andrew Tutt, one of the UK's leading specialists at running clinical trials of targeted therapies for breast cancer, has been appointed as Director of the Breakthrough Breast Cancer Research Centre at The Institute of Cancer Research, London.

Professor Tutt will be working as Centre Director while maintaining his roles as Director of the Breakthrough Breast Cancer Research Unit at King's College London and Consultant Oncologist at Guy's and St Thomas' NHS Foundation Trust - linking Breakthrough and The Institute of Cancer Research (ICR) with these prestigious institutions.

Professor Andrew Tutt, Director of the Breakthrough Toby Robins Breast Cancer Research Centre and Consultant Oncologist at Guy's and St Thomas' NHS Foundation Trust, said: "I'm enormously proud to have been offered this role. My vision is to enable Breakthrough to harness the potential of the resources we are fortunate enough to receive from donors and use them to recruit and partner with talented scientists from around the world to generate fresh ideas and in turn stimulate a new era of life-saving research."

AACR awards honouring Ludwig Cancer Research scientists

- Jedd Wolchok, MD, PhD, Director of Ludwig's Collaborative Laboratory at the Memorial Sloan Kettering Cancer Center (MSK) received the 38th Annual AACR-Richard and Hinda Rosenthal Memorial Award for his significant and continuing contributions to the development of immunotherapy for melanoma and his application of the strategy to other malignancies.
- Web Cavenee, PhD, who has since 1991 been the Ludwig Institute for Cancer Research San Diego founding director is best known for having provided the first indisputable evidence of tumour suppressor genes. He has received the 8th Annual Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research for his sustained contributions to the prevention and cure of cancer.
- A team of Ludwig scientists at Johns Hopkins University, including Bert Vogelstein, MD, and Kenneth Kinzler, PhD, co-directors of the Ludwig Center for Cancer Genetics and Therapeutics at Johns Hopkins, are co-recipients with researchers from the US National Cancer Institute and Duke University of the Eighth Annual Team Science Award. They are honoured for their contributions to the scientific understanding of brain tumours and the development of novel therapies for such tumours.

Blue Faery Rewards Liver Cancer Research

Blue Faery: The Adrienne Wilson Liver Cancer Association is proud to announce the fifth annual Blue Faery Award (BFA) for Excellence in Liver Cancer Research. Primary liver cancer, also known as hepatocellular carcinoma (HCC), is the third leading cause of cancer deaths worldwide. Blue Faery created the award to recognise medical professionals who develop innovative research in the fight against HCC, which has no cure.

This year's recipient of the Blue Faery Award is Dr Xin Wei Wang, Liver Carcinogenesis Section Chief and Senior Investigator at the Center for Cancer Research at the National Cancer Institute (NCI). Dr Wang's work seeks to identify better biomarkers for early detection, molecular signatures that can help predict prognosis and molecular mechanisms of liver cancer that may allow for personalised therapy for the treatment of HCC and other liver diseases.

Andrea Wilson started Blue Faery in honour of her sister Adrienne, who died of HCC only 145 days after her diagnosis at the age of 15. Blue Faery announces the recipient of the BFA on April 8 – Adrienne's birthday. She would have been 28 years old this year. Dr Wang will receive $3,000 to commemorate his achievement; he is donating his cash reward to NCI.

For more information on how to apply for the BFA, visit www.bluefaery.org. To learn more about liver cancer, sign up for the Blue Faery quarterly e-newsletter. You can also call Andrea Wilson at 818.636.5624 or email her at andrea@bluefaery.org

Queen's University Vice-Chancellor receives top European award

Queen's University Belfast's Vice-Chancellor, Professor Patrick Johnston, whose work has transformed cancer care in Northern Ireland, has been elected as a Fellow of the European Academy of Cancer Sciences.

Professor Johnston, whose leadership has seen cancer survival rates in Northern Ireland move from the bottom of the UK league table to near the top, has been honoured for his outstanding contribution to cancer research.

Professor Johnston has worked alongside some of the world's leading cancer experts and patient groups to launch a European Cancer Patient's Bill of Rights. The result of two years of work by the European Cancer Concord and Co-Chaired by Professor Johnston, it aims to address the disparities that exist in cancer care from one European country to the next.

12th Annual British Thoracic Oncology Group (BTOG) Conference 2014

29th to 31st January 2014 – Dublin
Published in *Lung Cancer* - Lung Cancer 83 Suppl. 1 (2014) S1–S83
Link to supplement http://www.lungcancerjournal.info/issues?issue_key=S0169-5002(14)X0003-6#

Poster Number	1st Author	From	Category	Poster Title
84	R Punwani	The Royal Marsden NHS Foundation Trust	Networks & Pathways	Community pharmacy referrals project to increase awareness and early diagnosis of respiratory disease via a direct pathway to secondary care
102	NB Ngwenya	Centre for Family Research, University of Cambridge	Nursing & Supportive Care	Sharing bad news understanding the communication processes of a lung cancer diagnosis
147	AG Bradshaw	Sheffield Teaching Hospitals NHS Trust, Weston Park Hospital	Radiotherapy	Sequential chemotherapy and continuous hyperfractionated accelerated radiotherapy CHART for non small cell lung cancer NSCLC experience from nine UK centres

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

May

IMPAKT Breast Cancer Conference "Anticipating the future of personalised medicine in Breast Cancer"
8-10 May, 2014; Brussels, Belgium
Juan Pablo Fernandez
E: juanpablo.fernandez@esmo.org
W: http://www.esmo.org/Conferences/IMPAKT-2014-Breast-Cancer

RCN Women's health conference and exhibition: Women's health and gynaecology – What's new?
9 May 2014; London, UK
Laura Benfield
E: laura.benfield@rcn.org.uk
T: +44 (0)20 7647 3591
W:www.rcn.org.uk/WH14

Biological Basis of Cancer Therapy: Medical Physics
12-16 May 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events,
T: +44(0)161 446 3773
E: education.events@christie.nhs.uk

Advances in the Nutritional Care of Cancer Patients
13 May 2014; London, UK
W: www.royalmarsden.nhs.uk

Association of Breast Surgery Conference & AGM
19-20 May 2014; Liverpool, UK
www.associationofbreastsurgery.org.uk

Upper GI
20 May 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

Practical Image Guided Gynaecological Brachytherapy
22 May 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

2nd National Oncology Update for Palliative Care Physicians
22-23 May 2014; Preston, UK
W: http://www.stcatherines.co.uk/education-and-training/study-sessions/the-second-national-oncology-update-for-palliative-care-physicia/
E: education@stcatherines.co.uk

2014 ASCO Annual Meeting
30 May- 3 June 2014; Chicago, Illinois, USA
W: http://am.asco.org

June

Targeted Treatments for Urological Cancers
5 June 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

Improving clinical outcomes through quality improvement activity: a focus on lung, bladder and oesophageal cancers Clinical Oncology Audit Conference
6 June 2014; London, UK
W: www.rcr.ac.uk/oncologyevents
E: conf@rcr.ac.uk

Everything you ever wanted to know about Lung Cancer Imaging
7 June 2014; London, UK
W: www.royalmarsden.nhs.uk

International Symposium on Pediatric Neuro-oncology
8 June – 2 July 2014; Singapore
W: ispo2014.com

NEW
Thyroid Cancer Conference
9 June 2014; London, UK
W: www.royalmarsden,nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

Late Effects in Cancer Survivors - 5th biennial Sheffield meeting
12-13 June 2014; Sheffield, UK
E: lateeffects@sheffield.ac.uk

Targeted Treatments for Haematological Cancers
16 June 2014; London, UK
W: www.royalmarsden.nhs.uk

Camstrand Research Conference
17-18 June 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

ABS Trainees Meeting
19-20 June 2014; Glasgow, UK
www.associationofbreastsurgery.org.uk

Haematology Nurse Study Day (Stem Cell Transplantation)
23 June 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

Pain in the Cancer Patient
23-24 June 2014; London, UK
W: www.royalmarsden,nhs.uk/paincancerpatient

WIN 2014 Symposium
23-24, 2014; Paris, June
W: www.winsymposium.org

NEW
BLA Annual Conference 2014
26 June 2014; London, UK
W: www.britishlaryngological.org/annual conference

Bone Research Society Annual Meeting
25-26 June 2014; Sheffield, UK
W: www.brsoc.org.uk
E: events@brsoc.org.uk

NEW
Paediatric Brain Tumour Study Day
26 June 2014; London, UK
W: www.royalmarsden,nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

Brachytherapy
26-27 June 2014; Leeds, UK
W: www.rcr.ac.uk/oncologyevents
E: conf@rcr.ac.uk

NEW
Cancer Treatments: An introduction
26 June 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

6th International Workshop on Advances in the Molecular Biology and Therapeutics of Bone Disease
28 June – 2 July 2014; Oxford, UK
W: www.oxfordbonepharm.org
E: events@janet-crompton.co.uk

NEW
Tripartie Colorectal Meeting 2014
30 June-3 July 2014; Birmingham, UK
W: www.tripartite2014.org
T: +44 (0)131 624 6040

July

NEW
Tracheostomy Care Study Day
1 July 2014; London, UK
W: www.royalmarsden,nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

NEW
Mesothelioma in the West Midlands
3 July 2014: Birmingham, UK
E: events@irwinmitchell.com

NEW
Medicine Management Study Day
3 July 2014; London, UK
W: www.royalmarsden,nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

Molecular Mechanisms of Targeted Cancer Treatments
3 July 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
Nursing and Allied Health Professionals Symposium: Psychological Aspects of TYA Cancer
6 July 2014; London, UK
Sarah Wallace T; +44 (0)20 7612 0709 or
E: sarah.wallace@teenagecancertrust.org

Beatson International Cancer Conference "Powering the cancer machine"
6-9 July 2014; Glasgow, UK
www.beatson.gla.ac.uk/Conference.html

TRIPARTITE COLORECTAL MEETING 2014

INTERNATIONAL CONVENTION CENTRE BIRMINGHAM

30th JUNE – 3rd JULY 2014

Exhibitors as confirmed on 28 April 2014

Applied Medical
Aquilant Surgical
Ardmore Healthcare Ltd
Bard Ltd
B. Braun Medical Ltd
Bowel Disease Research Foundation
BK Medical
CJ Medical
Coloplast Ltd
Cook Medical
Covidien
Dendrite Clinical Systems Ltd
Elemental Healthcare
Ethicon
Ferring Pharmaceuticals Ltd
Fisher & Paykel Healthcare Ltd
Frankenman International Ltd
Gastrointestinal Nursing
Henleys Medical Supplies
Hodgson Solutions Ltd
IA (The Ileostomy and Internal Pouch Support Group)
International Ostomy Association
Karl Storz Endoscopy (UK) Ltd
Kimberley Clark
KLS Martin UK Ltd
MacGregor Healthcare Ltd
Medtronic Ltd
Norgine Pharmaceuticals Ltd
Oceana Therapeutics
Olympus Medical
Oncology News
Pierson Surgical Ltd
ProStrakan
Richard Wolf UK Ltd
Rocket Medical PLC
Shire Pharmaceuticals
Sigmacon UK Ltd
Smith and Nephew
SRA Developments Ltd
Stericom Ltd
St Mark's Academic Institute
Sucampo Pharma Europe Ltd
Synmed Ltd
Teleflex
THD Lab
Touchstone
Ultroid Uk Ltd
University of East Anglia
Uroplasty Ltd
Wisepress
W.L Gore & Associates

The Christie
School of Oncology

The Christie School of Oncology Events

Education Centre, Wilmslow Road, Manchester, M20 4BX

Targeted Treatments for Urological Cancers - Dr Elaine Vickers (5 Jun 2014)
Provides a description of the faulty genes and proteins that drive prostate, kidney, bladder and testicular cancer and an overview of targeted treatment approaches for these diseases. **Fee:** £75

Haematology Nursing: Acute Lymphoblastic Leukaemia (23 Jun 2014)
Part of The Christie's Haematology Nurses Education series, this day will provide a good understanding of ALL treatments, side effects & associated issues. **Fees:** £30

Cancer Treatments: An Introduction - David O'Halloran (26 Jun 2014)
Understanding the role of radiotherapy, chemotherapy and targeted therapies in the treatment of cancer and the side effects associated. **Fees:** £75

Molecular Mechanisms of Targeted Cancer Treatments (3 Jul 2014)
Covering a wide range of licensed and experimental cancer treatments, explaining the biological mechanism of action at a molecular and cellular level. Presented by Dr Elaine Vickers. **Fees:** £75

The Christie International Student Cancer Conference (6-7 Sep 2014)
Aimed at students & trainees from all disciplines (including medicine, nursing, pharmacy, primary care, surgery, allied health professionals) with a keen interest in cancer care. **Fees:** £50

Targeted Treatments: De-Mystifying the Science for Cancer Nurses - Dr Elaine Vickers (9 Sep 2014)
Intermediate-level course gives research nurses and trials staff the knowledge and confidence to discuss the latest and most advanced targeted cancer treatments with their patients and colleagues. **Fees:** £75

Upper GI Cancer Study Day (15 Sep 2014)
Aims to discuss epidemiology, aetiology, pathophysiology, investigations and surgery for this patient group. It will explore the patient's journey when referred to The Christie. **Fees:** £65

Advanced Clinical Practice Cardiovascular Masterclass (16 Sep 2014)
This masterclass will be taught by expert clinicians and will include revision of cardiovascular anatomy and physiology and management of acute & chronic cardiac conditions. **Fees:** £75/£125

Targeted Treatments for Haematological Cancers (2 Oct 2014)
Explaining unique cellular and genetic features of haematological cancers and covers a diverse range of treatments in development for leukaemia, lymphoma and multiple myeloma. **Fees:** £75

Lymphoma Study Day (7 Oct 2014)
To educate health professionals about lymphoma, including histopathology, current management of different subtypes, immunochemotherapy, radiotherapy and stem cell transplantation. **Fees:** £65

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

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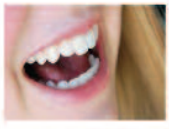

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The Royal Marsden Study Day Programme 2014 - 2015

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

13 May	**Advances in the Nutritional Care of Cancer Patients**	ID 426
07 Jun	**Everything you ever wanted to know about Lung Cancer Imaging**	ID 427
16 Jun	**Targeted Treatments for Haematological Cancers**	ID 396
26 Jun	**Paediatric Brain Tumour Study Day**	ID 454
01 Jul	**Tracheostomy Care Study Day**	ID 418
03 Jul	**Medicine Management Study Day**	ID 445
22 Sep	**Targeted Treatments of the Digestive System**	ID 398
25 Sep	**Upper GI Study Day**	ID 460
11 Oct	**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
24 Nov	**The Royal Marsden Haematology Study Day**	ID 443
27-28 Nov	**Supporting Workers with Cancer Study Day**	ID 457
02 Dec	**Molecular Mechanisms of Targeted Cancer Treatments**	ID 397
09 Dec	**Advances in the Nutritional Care of Cancer Patients (Repeat)**	ID 444
19 Jan 2015	**National Head and Neck Study Day**	ID 455
27-28 Feb 2015	**ISSC – Sexual Consequences of Cancer Treatment**	ID 432
10 Mar 2015	**The Royal Marsden Paediatric Palliative Care Study Day**	ID 431
25 Mar 2015	**National Pain Management Study Day**	ID 413

The Royal Marsden Conference Programme 2014 – 2015

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

09 Jun	**The Royal Marsden Thyroid Cancer Conference** www.royalmarsden,nhs.uk/thyroid	ID 417
23 – 24 Jun	**The Second Annual Pain in the Cancer Patient Meeting** www.royalmarsden,nhs.uk/paincancerpatient	ID 428
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

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IMPORTANT DEADLINES

7 May 2014	Abstract submission
18 June 2014	Early registration
20 August 2014	Late-breaking abstract
20 August 2014	Late registration

The Lancet

Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial

Cuzick J , Sestak I, Forbes JF, Dowsett M, Knox J, Cawthorn S, Saunders C, Roche N, Mansel RE, von Minckwitz G, Bonanni B, Palva T, Howell A: on behalf of the IBIS-II investigators. The Lancet; Dec 12, 2013.

Background: Aromatase inhibitors effectively prevent breast cancer recurrence and development of new contra-lateral tumours in postmenopausal women. We assessed the efficacy and safety of the aromatase inhibitor anastrozole for prevention of breast cancer in postmenopausal women who are at high risk of the disease. **Methods:** Between Feb 2, 2003, and Jan 31, 2012, we recruited postmenopausal women (40-70 years) from 18 countries into a double-blind randomised placebo-controlled trial. To be eligible, women had to have at increased risk of breast cancer (based on specific criteria). Eligible women were randomly assigned (1:1) by central computer allocation to receive 1mg oral anastrozole or matching placebo daily for 5 years. Randomisation was stratified by country and done with blocks of 6, 8 or 10. All trial personnel, participants, and clinicians were blinded to treatment allocation, and only the trial statistician was unmasked. The primary endpoint was histologically confirmed breast cancer (invasive cancers or non-invasive ductal carcinoma in situ). Analyses were done on by intention to treat. **Findings:** 1920 women were randomly assigned to receive anastrozole and 1944 to placebo. After a median follow-up of 5 years (IQR 3·0-7·1), 40 women in the anastrozole group (2%) and 85 in the placebo group (4%) had developed breast cancer (hazard ratio 0·47, 95% CI 0·3-0·68, p<0·0001). The predicted cumulative incidence of all breast cancers after 7 years was 5·6% in the placebo group and 2·8% in the anastrozole group. 18 deaths were reported in the anastrozole group and 17 in the placebo group, and no specific causes were more common in one group than the other (p=0·836). **Interpretation:** Anastrozole can effectively reduce incidence of breast cancer in high-risk postmenopausal women. This finding, along with the fact that most of the side-effects associated with oestrogen deprivation could not be attributed to treatment, provides support for the use of anastrozole in postmenopausal women at high risk of breast cancer.

Reviewer's opinion: Breast cancer in women particularly with presence of high risk factors is common. The result of this trial, which was simultaneously presented at San Antonio Breast Cancer Symposium 2013 by Jack Cuzick from London, is encouraging and predictable considering similar data already available on chemo-prevention of breast cancer in these women. However, the challenge remains how to define 'women at increased risk' and target most appropriate individuals for true prevention. Moreover, it is doubtful that there will be any meaningful mortality gains with chemo-prevention using current agents like anatrazole (IBIS-II), exemestane (MAP.3 trial), tamoxifen or raloxifene. Though the incidence of side effects was small in IBIS-II, they cannot be ignored because 20% of the women had to discontinue the active treatment due to adverse events, and the nature of late side effects need to be explored. Compliance and optimum method of screening to detect the sub-clinical lesions as well as duration of therapy remain an issue. Aromatase inhibitors can be offered to only post-menopausal women and have no impact on the development of more aggressive hormone receptor negative tumours. – SU

Neuro-Oncology

Comparative study of IDH1 mutations in gliomas by immunohistochemistry and DNA sequencing

Agarwal S, Sharma MC, Jha P, Pathak P, Suri V, Sarkar C, Chosdol K, Suri A, Kale SS, Mahapatra AK, Jha P. Neuro-Oncology 2013; 15(6):718-26.

The IDH1 gene on chromosome 2q33.3 encodes the enzyme isocitrate dehydrogenase 1 (IDH1) that catalyses NADPH production via oxidative decarboxylation of isocitrate to alpha-ketoglutarate in the Krebs citric acid cycle. IDH1 mutation is an early step in gliomagenesis and has been identified in grades II and III astrocytomas, oligodendrogliomas (OG), oligoastrocytomas (OA), and secondary GBM, with implications on diagnosis and prognosis. About 90% of reported IDH1 mutations involve exon 4 at codon 132, histidine replacing arginine (R132H). Rarer ones include R132C, R132S, R132G, R132L, R132V, and R132P. Although these mutations are rare in the pediatric age group (patients aged ≥ 18 years), they seem to be associated with younger age at presentation and a better prognosis (progression-free survival) associated with grade II-IV gliomas. Most tests of IDH mutations are based on DNA sequencing is not available at every diagnostic centre. In addition, false-negative results arise due to limited sensitivity caused by inadequate tumour DNA. The results of immunohistochemistry (IHC), using mAb H09 for IDH1-R132 mutations as an alternative method, have been compared with those of DNA sequencing in 50 diffuse gliomas. Agreement between IHC and DNA sequencing was seen in 88% (44/50) cases. The other 6 cases were immunopositive with the DIA-H09 antibody. In 3 of these 6 cases, DNA sequencing showed no mutations, and an R132L mutation was found in the other 3 cases. Notably, 47% (14/30) of the immunopositive cases had only a fraction of tumour cells stained. This indicates that IHC is a quick and easy method of detecting IDH1-R132H mutations, but there may be some discrepancies between IHC and DNA sequencing.

Reviewer's opinion: IDH1 mutation testing is being used as a diagnostic tool in many neuropathology centres in the prognosis for brain tumour patients. A reliable and efficient method is needed for testing and ensuring the accuracy of the result. IHC testing for IDH1 mutation with an antibody for IDH1-R132H is used in clinical centres worldwide. The IHC method also compared with immunostaining results using H09 with direct DNA sequencing in 50 cases of diffuse glioma. IHC was more sensitive than DNA sequencing in detecting IDH1-R132H mutations, but awareness of the possibility of heterogenous staining pattern and cross-reactivity with variant mutant proteins was essential for correct interpretation of the results. A new finding was the cross-reactivity of IDH1-R132H monoclonal antibody with R132L protein in formalin-fixed paraffin-embedded sections. In view of the rarity of mutations other than R132H in gliomas, IHC testing of IDH1 mutation with a larger number of glioma cases is needed to assess the sensitivity and specificity of this immunostaining method. – QA

Neuro-Oncology

Enhancing drug delivery for boron neutron capture therapy of brain tumours with focused ultrasound

Alkins RD, Brodersen PM, Sodhi RN, Hynynen K. Neuro-Oncology 2013; 15(9):1225-35.

The dismal prognosis associated with glioblastoma is attributable not only to its aggressive and infiltrative behaviour, but to its location typically deep in the parenchyma of the brain. Surgical corridors and extent of resection are limited by the potential of further neurological injury. Photon-based radiation therapy is a mainstay of treatment, but causes significant collateral injury to the brain that worsens with time. In addition, the blood-brain barrier (BBB) limits the accumulation of many therapeutic agents, particularly in infiltrating cells advancing beyond the tumour margin. The blood-tumour barrier (BTB) is variably more permeable, but remains a significant obstacle to therapy. With regard in particular to the brain, therapies need to spare healthy tissue as much as possible, but many of those that have selective activity against malignant cells are hindered by the cerebrovasculature. Boron neutron capture therapy (BNCT) is a treatment whereby a 10B-containing drug preferentially accumulates in malignant cells and causes highly localised damage when exposed to epithermal neutron irradiation. 10B-enriched L-4-boronophenylalanine-fructose (BPA-f) complex uptake can be improved by enhancing the permeability of the cerebrovasculature with osmotic agents. This study used MRI-guided focused ultrasound in combination with injectable microbubbles to non-invasively and focally augment BPA-f uptake. In a 9L gliosarcoma model in Fisher 344 rats, the BBBs and BTBs were disrupted with pulsed ultrasound using a 558 kHz transducer and Definity microbubbles; BPA-f (250 mg/kg) was given intravenously for 2 h. 10B concentrations were estimated with imaging mass spectrometry and inductively coupled plasma atomic emission spectroscopy. The tumour to brain ratio of 10B was 6.7 $\pm$ 0.5 with focused ultrasound compared with 4.1 $\pm$ 0.4 in the control group ($P < 0.01$), corresponding to a mean tumour [10B] of 123 $\pm$ 25 ppm and 85 $\pm$ 29 ppm, respectively. 10B uptake in infiltrating clusters treated with ultrasound was 0.86 $\pm$ 0.10 times the main tumour concentration, compared with only 0.29 $\pm$ 0.08 in controls. This suggests that ultrasound increases the accumulation of 10B in the main tumour and infiltrating cells. These findings, in combination with the expanding clinical use of focused ultrasound, may offer improvements in BNCT and the treatment of glioblastoma.

Reviewer's opinion: Due to the unique features of brain tumours, e.g. location, cellular heterogeneity, infiltrative invasion and existence of BBB, prognosis of patients remains poor despite current advances in therapeutics. One of the greatest challenges currently being faced in the successful treatment of brain tumour patients is the development of tumour-specific therapy that minimises damage to healthy surrounding brain tissue. The authors investigated enhanced drug delivery in boron neutron capture therapy with focused ultrasound. The findings are interesting and have clinical implication of this emerging therapeutic strategy. However, evidence of improved survival is lacking and the findings need confirmation by using a larger numbers of animals. Its clinical application in human patients requires optimisation to have any benefit over existing conventional therapy. – QA

New England Journal of Medicine

A Randomised Trial of Bevacizumab for Newly Diagnosed Glioblastoma

Gilbert MR, Dignam JJ, et al. New England Journal of Medicine; 2014;370; 699-708.

Background: Concurrent treatment with temozolomide and radiotherapy followed by maintenance temozolomide is the standard of care for patients with newly diagnosed glioblastoma. Bevacizumab, a humanised monoclonal antibody against vascular endothelial growth factor A, is currently approved for recurrent glioblastoma. Whether the addition of bevacizumab would improve survival among patients with newly diagnosed glioblastoma is not known. **Methods:** In this randomised, double-blind, placebo-controlled trial, we treated adults who had centrally confirmed glioblastoma with radiotherapy (60 Gy) and daily temozolomide. Treatment with bevacizumab or placebo began during week 4 of radiotherapy and continued for up to 12 cycles of maintenance chemotherapy. At disease progression, the assigned treatment was disclosed, and bevacizumab therapy could be initiated or continued. The trial was designed to detect a 25% reduction in the risk of death and a 30% reduction in the risk of progression or death, the 2 co-primary end-points with the addition of bevacizumab. **Results:** A total of 978 patients were registered and 637 underwent randomisation. There was no significant difference in the duration of overall survival between the bevacizumab group and the placebo group (median, 15.7 and 16.1 months, respectively; hazard ratio, 1.13). Progression-free survival (PFS) was longer in the bevacizumab group (10.7 vs. 7.3 months; hazard ratio 0.79). There were modest increases in rates of hypertension, thromboembolic events, intestinal perforation, and neutropenia in the bevacizumab group. Over time, an increased symptom burden, a worse quality of life and a decline in neuro-cognitive function were more frequent in the bevacizumab group. **Conclusions:** First-line use of bevacizumab did not improve overall survival in patients with newly diagnosed glioblastoma. PFS was prolonged but did not reach the pre-specified improvement target. – 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

ZedScan™ I zilico real-time medical diagnostics a new standard in colposcopy

ZedScan uses Electrical Impedance Spectroscopy (EIS), to analyse tissue structure and identify pre-cancerous and cancerous cells in women suspected of having cervical neoplasia following an abnormal cervical smear test.

ZedScan is a non-optical device used as an adjunct during colposcopy and consists of a portable hand-held device, docking station, software for installation onto a PC and a single-use EIS Sensor. The results of ZedScan are immediately displayed on the handset. The clinician can make decisions about the clinical management of the patient at first visit. Dependent on the decision, they would treat the patient immediately, take a directed biopsy, or return to routine surveillance.

ZedScan clinical benefits are identifying the optimum biopsy site, reducing the number of cervical biopsies required while facilitating a wider use of 'See & Treat'.

Five clinical trials in the UK and EU have supported the clinical efficacy of ZedScan, including a pivotal multi-centre trial of 429 women across three hospitals in the UK and Ireland. An independent health economics further demonstrates the benefits for a healthcare system.

For information please contact Rob Atkinson
E: robatkinson@dpmedicalsys.com or T: +44 (0)7917 694040.

Milan Cancer Centre introduces wider range of treatments using Varian's Edge™ Radiosurgery System

Humanitas Cancer Center in Milan has become one of the first hospitals in the world to commence cancer treatments using the new Edge™ radiosurgery system from Varian Medical Systems. This precise, non-invasive alternative to conventional surgery has been used to treat several patients with lung, prostate, brain, and liver lesions.

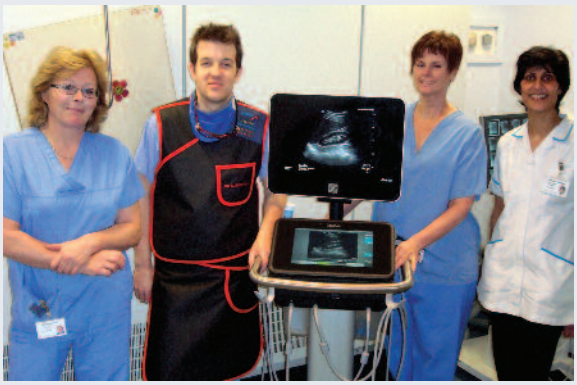
"Edge radiosurgery gives us the opportunity to further minimise damage to healthy tissues and increase the dose per treatment session, making it a valid alternative to surgery, especially for inoperable patients," says Dr Marta Scorsetti, director of the hospital's radiotherapy and radiosurgery department. "In particular, Edge allows us to start new protocols for treating prostate cancer patients in just four daily sessions rather than the six to eight weeks typically required with conventional radiotherapy."

The Edge radiosurgery system enables clinicians to attack tumours from outside the body using carefully shaped high-energy X-rays. There are no incisions and patients contend with few of the healing, pain, and recovery issues typically associated with conventional surgery.

"In addition to enabling us to introduce new treatment protocols for prostate cancer patients, Edge Radiosurgery in combination with the Calypso system allows us to treat lung lesions more precisely by tracking the tumour in real time during treatment delivery." adds Stefano Tomatis, head of radiotherapy physics at Humanitas Cancer Center.

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

FUJIFILM SonoSite X-Porte™ offers real benefits for interventional radiology



The Radiology Department at the Royal Surrey County Hospital NHS Foundation Trust has recently taken delivery of its first FUJIFILM SonoSite X-Porte™ point-of-care ultrasound system for use in the interventional radiology suite. Dr Alex Horton, Consultant Radiologist, commented: "I was lucky enough to see the new X-Porte at a pre-launch event, and knew straightaway that it was particularly well suited to interventional radiology. The image quality is probably the best of any point-of-care ultrasound machine I've seen; it has a large, full-screen display and the resolution is comparable to many much larger instruments, but at a third of the cost. The very rapid boot-up time and good battery life are also perfect for interventional procedures, particularly as the system is so portable and robust, meaning it is always available where and when we need it."

"The X-Porte is very easy to use – it has one of the most intuitive interfaces of any point-of-care system – and the built-in electronic manuals and online help mean that virtually no training is required. It has few controls, allowing you to quickly set the gain, brightness, depth and colour Doppler very quickly, which, again, is perfect for interventional radiology use."

For more information please contact:
FUJIFILM SonoSite Ltd, T: +44 (0)1462 341151,
E: ukresponse@sonosite.com or W: www.sonosite.co.uk

SonoSite's X-Porte™ ideal for critical care

The Neurosurgical Critical Care Unit at the Royal Hallamshire Hospital in Sheffield has recently taken delivery of its first FUJIFILM SonoSite X-Porte™ point-of-care ultrasound system, giving staff the ability to perform transthoracic echocardiograms (TTEs) on demand. Dr David Turnbull, a consultant anaesthetist specialising in neurosurgical care, explained: "Bedside TTE is becoming increasingly commonplace in a critical care setting, providing valuable information about a patient's pre- or post-operative condition that can help to direct their care. Previously, we have relied on borrowing a portable instrument from the radiology or cardiology departments, but the systems are in high demand, making availability an issue."

"When we looked at purchasing our own instrument, we asked the radiology department for a recommendation, and they performed a side-by-side comparison between the X¬Porte and two portable instruments from another manufacturer. Despite the sonographer having no previous experience with SonoSite equipment, the X¬Porte was the clear winner in terms of image quality and ease of use. The large screen makes it easy to see the structures of interest – it is really well thought through and easily tips and tilts to the right angle – and the probes are very robust."

For more information contact: FUJIFILM SonoSite Ltd, T: +44 (0)1462 341151, E: ukresponse@sonosite.com Web: www.sonosite.co.uk

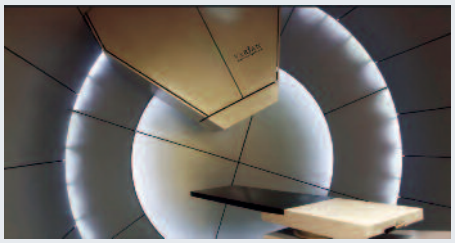
PSI extends R&D collaboration with Varian and expands capacity for clinical research

Varian Medical Systems and the Paul Scherrer Institute (PSI) are announcing an extension of their existing collaboration in the field of proton therapy to offer patients more precise cancer treatments using intensity modulated proton therapy (IMPT). Under the agreement, Varian will also supply PSI with a state-of-the-art proton therapy delivery gantry to help meet a growing demand for clinical research and treatments at PSI.

Proton therapy targets tumours with concentrated doses of radiation while offering superior protection of surrounding healthy tissue. IMPT, which was pioneered using pencil-beam scanning at the Paul Scherrer Institute and made commercially available by Varian Medical Systems, is a radiation delivery technique that enables clinicians to optimise precision when treating tumours.

"This multi-year R&D collaboration will enable Varian and PSI to continue their productive research activities in the areas of advanced pencil beam scanning delivery systems, on-board imaging, clinical workflow optimisation, and accelerator technology to further develop high proton treatment technology over the coming years," says Moataz Karmalawy, head of Varian's Particle Therapy group. "Our original collaboration led to the commercialisation of IMPT and we are delighted to expand our partnership to develop more revolutionary technologies."

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



Provectus Biopharmaceuticals' PV-10 data to feature in Poster Presentation by Moffitt Cancer Center at ASCO

Provectus Biopharmaceuticals, Inc, development-stage oncology and dermatology biopharmaceutical company, announced today that data on its investigational drug PV-10 will be featured in a presentation by investigators from Moffitt Cancer Center in a Poster Highlights Session of the American Society of Clinical Oncology (ASCO) Annual Meeting at McCormick Place, Chicago, IL, May 30-June 3, 2014. The time and date of the presentation are available on the ASCO website, http://am.asco.org

The poster, based upon abstract #9028, is entitled "Assessment of immune and clinical efficacy after intralesional PV-10 in injected and uninjected metastatic melanoma lesions," and is authored by Amod Sarnaik, MD and colleagues of Moffitt.

Craig Dees, PhD, CEO of Provectus said, "We value our relationship with Moffitt greatly, and we are excited by the assessment Dr Sarnaik has made on clinical and immunologic activity of intralesional PV-10."

Provectus has recently submitted an application to the FDA for breakthrough therapy designation for PV-10 based on the results from its Phase 2 clinical study of melanoma and is researching its efficacy for other indications.

For further information visit www.pvct.com

One first in Europe to treat patients using Varian's TrueBeam 2.0 System with six degrees of freedom couch

Kaiser-Franz-Josef Hospital in Vienna has become one of the first oncology departments in Europe to introduce clinical treatments using the PerfectPitch™ six-degrees-of-freedom robotic couch from Varian Medical Systems. The hospital has introduced this enhanced patient positioning device, which enables more flexibility during radiotherapy treatments, as an integrated element of its latest TrueBeam™ 2.0 treatment system.

The PerfectPitch system enables the patient to be positioned more flexibly during treatments, taking advantage of 'pitch and roll' positioning to optimise the treatment. "If the couch can pitch and roll as well as moving up, down and sideways, it gives us more precision and flexibility while imaging and treating, and it helps to reduce the time it takes to set-up the patient," says Dr Anne-Marie Schratter-Sehn, head of radiation oncology at KFJ Hospital. "These additional positioning capabilities in combination with TrueBeam's advanced image guidance and motion management tools introduced with the TrueBeam 2.0 upgrade will enable us to extend our stereotactic radiosurgery capabilities and offer more patients a wider range of high precision radiotherapy and radiosurgery treatments."

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

Provectus Appoints Dr Joseph Chalil to Strategic Advisory Board

Provectus Biopharmaceuticals, Inc, a development-stage oncology and dermatology biopharmaceutical company, announced that it has appointed Dr Joseph M Chalil, MD, MBA, FACHE, to its Strategic Advisory Board.

Dr Chalil is Associate Director, Health Science Executives of Boehringer Ingelheim, the world's largest privately held pharmaceutical company. In addition to his responsibilities at Boehringer Ingelheim, Dr Chalil is the Co-Chair for the Industry Physician Committee of the American Association of Physicians of Indian Origin (AAPI) and has served as Scientific Advisor to AAPI for the past three years.

A veteran of the United States Navy Medical Corps, Dr Chalil is also board certified in healthcare management, and has been awarded Fellowship by the American College of Healthcare Executives.

Craig Dees, PhD, CEO of Provectus Pharmaceuticals said, "Adding Dr Chalil to our Strategic Advisory Board will strengthen our collective expertise in healthcare marketing, sales and business development. His depth and breadth of experience in these fields will enable Provectus to take greater advantage of the opportunities that lie ahead."

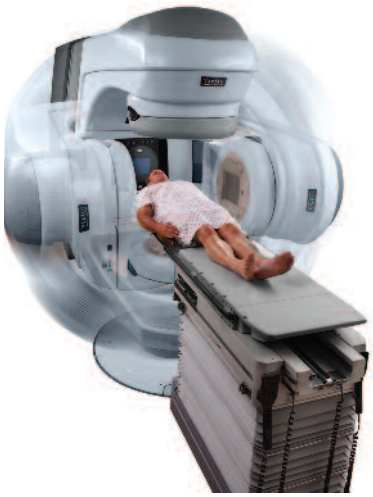
Dr Chalil said, "I am honoured to join the Provectus Strategic Advisory Board at this critical juncture of the company's development as it brings PV-10 and other treatments through the developmental regulatory approval processes."

For further information visit www.pvct.com

Fast and precise RapidArc® radiotherapy treatments introduced for benefit of cancer patients in Greece

A 37-year-old patient with advanced tongue cancer has become the first person in Greece to be treated using fast and precise RapidArc® radiotherapy technology from Varian Medical Systems. The pioneering treatment took place at Metropolitan Hospital in the south of Athens.

The RapidArc capabilities, which were installed on one of the hospital's two Varian Clinac® radiotherapy treatment machines, deliver precise image-guided IMRT (intensity modulated radiotherapy) up to four times faster than was possible with earlier generations of technology. With RapidArc, the machine quickly delivers the treatment while continuously rotating around the patient, and the beam is constantly shaped and reshaped during the rotation to match the shape and size of the tumour. RapidArc makes it possible to deliver these sophisticated treatments in as little as two minutes. Studies show that faster treatments allow for greater precision, since there is less chance of patient or tumour movement during treatment delivery.



According to radiation oncologist Dr Johannes Athanasios Dimopoulos, conventional IMRT for head and neck cancer patients is usually performed with static beams delivered from nine different angles over a 15-20 minute time period. "RapidArc significantly reduces the treatment time without compromising on the quality of the treatment," said Dr Dimopoulos.

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PV-10 Selected for Poster Highlights Session

Provectus Biopharmaceuticals, Inc, a development-stage oncology and dermatology biopharmaceutical company, recently announced that data on treatment of cutaneous melanoma using its investigational drug PV-10 have been selected to be part of the Poster Highlights Session of the American Society of Clinical Oncology (ASCO) Annual Meeting this year at McCormick Place, Chicago, IL, May 30-June 3, 2014. The time and date of the session are available on the ASCO website, http://am.asco.org

Sanjiv S Agarwala, MD, is lead author of abstract #9027, entitled "Efficacy of intralesional Rose Bengal in patients receiving injection of all existing melanoma in phase II study PV-10-MM-02."

Craig Dees, PhD, CEO of Provectus said, "Being selected for the Poster Highlights Session is an honour, and we look forward to sharing the results of our Phase 2 study with attendees."

Provectus has recently submitted an application to the FDA for breakthrough therapy designation for PV-10 based on the results from its Phase 2 clinical study related to cutaneous melanoma and is researching its efficacy for other indications.

For further information visit www.pvct.com

Provectus Biopharmaceuticals signs agreement with China's Tririver Capital

Provectus Biopharmaceuticals, Inc recently announced that it has entered into an advisory agreement with China's Tririver Capital to help identify distribution and joint venture partners for the Company's novel oncology drug PV-10 in China, as well as other therapeutics that Provectus is developing.

The Tririver agreement is intended to provide further reach into China for PVCT as it seeks partnering opportunities with pharmaceutical companies. The new agreement will further bolster the current initiatives by Provectus in conjunction with existing advisory groups to develop partnering opportunities in various countries in Asia including China, India and Japan, where the Company has held numerous detailed discussions with pharmaceutical companies over the last year.

Provectus believes significant opportunities exist for PV-10 and PH-10 in Asia including those for its lead melanoma indication, as well as for liver cancer treatment and other oncology and dermatology treatments. As an example, nearly 55% of world-wide cases of liver cancer occur in China each year and there is a tremendous unmet medical need.

For further information visit www.pvct.com

PV-10 treatment decreases melanoma cells in tumours and boosts T-cells within 7-14 Days

Provectus Biopharmaceuticals, Inc has announced that a poster presentation detailing significant decrease in melanoma cells in patients' injected tumours 7-14 days after intralesional PV-10 treatment that was accompanied by similar decrease in uninjected bystander tumours was presented by researchers from the Moffitt Cancer Center at the American Association for Cancer Research Annual Meeting in San Diego, CA. These clinical and pathologic changes were accompanied by increases in important immune cell populations detected in the patients' peripheral blood.

The poster presentation, based upon abstract #630, entitled "Induction of anti-melanoma immunity after intralesional ablative therapy," was authored by Hao Liu, Krithika Kodumudi, Amy Weber, Amod A Sarnaik and Shari Pilon-Thomas of the Moffitt Cancer Center.

Provectus' investigational drug PV-10, a 10% solution of Rose Bengal, is currently being studied as a novel cancer therapeutic, and Provectus has applied to the FDA for breakthrough therapy designation of PV-10 for the treatment of melanoma based on a 7 center international single-arm trial. PV-10 is designed to selectively target and destroy cancer cells without harming surrounding healthy tissue, significantly reducing potential for systemic side effects. In melanoma patients, intralesional (IL) injection of PV-10 has led to regression of injected lesions as well as uninjected metastases. The mechanism of regression of uninjected lesions is under investigation at Moffitt Cancer Center (NCT01760499).

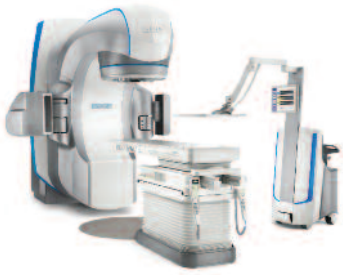
For further information visit www.pvct.com

Varian demonstrated Motion Management and Radiosurgery Technologies at ESTRO 33 in Vienna

Varian Medical Systems, a world leader in radiotherapy equipment and software, demonstrated its full range of radiotherapy delivery systems and software at the 33rd ESTRO (European Society for Radiotherapy and Oncology) meeting recently in Vienna. The Varian booth featured the company's technology and products for radiotherapy, radiosurgery, brachytherapy, and proton therapy.

Varian's TrueBeam™ 2.0 platform for radiotherapy and radiosurgery were displayed along with the RapidArc® image-guided intensity-modulated radiotherapy system, the PerfectPitch™ six-degrees-of-freedom couch, and the Calypso® 'GPS for the Body' system, all of which are aimed at helping clinicians to deliver treatments with both precision and speed. Varian also exhibited its powerful new RapidPlan™ software for improving the quality and speed of treatment planning.

Visitors to the Varian booth learnt more about the company's new Edge Radiosurgery™ system, Varian's first dedicated, fully integrated end-to-end solution for planning and delivering advanced radiosurgery treatments using



new real-time tumour tracking technology and motion management capabilities. Clinicians from the first three hospitals to commence treatments with Edge Radiosurgery -- Champalimaud Center for the Unknown in Lisbon, Humanitas Cancer Center in Milan, and the Henry Ford Health System in Detroit, U.S. -- presented results from early treatments for lung, brain, spine and liver tumours at the Varian 'Cutting Edge' symposium on April 6th.

For further information contact:
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ONCOassist deployed in The Clatterbridge Cancer Centre as Enterprise system

The Clatterbridge Cancer Centre NHS Foundation Trust have today announced an enterprise agreement which will see ONCOassist, a revolutionary new CE approved software system, being deployed as the main oncology decision support system used within Clatterbridge.

ONCOassist was launched in January of last year following extensive development involving oncologists, system developers and compliance personnel in Europe and the United States. Since launch ONCOassist has garnered growing acceptance amongst oncology professionals throughout the UK and Ireland. In August of this year, the platform was offered as an enterprise system. This enables individual trusts and institutions to integrate their guidelines and protocols and make them available throughout the trust in an easy to access and intuitive format.

Thomas Poulter, Head of IM&T at The Clatterbridge Cancer Centre, said: "Having ONCOassist available in clinics and on the wards will save our clinicians time. The oncology nurses and clinicians will have access to all of the key oncology decision support information and tools they need. For example, our nurses often need to reference protocols or treatment algorithms when delivering chemotherapy treatment. ONCOassist makes it easy to do this."

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CyberKnife Centre officially opens at Hermitage Medical Clinic

Hermitage Medical Clinic officially opened its CyberKnife Centre on Saturday 1st March. The centre was opened by Prof Berndt Wowra, Professor of Neurosurgery, European Cyberknife Centre in Munich.

The official opening took place after the CyberKnife Symposium where speakers included Dr Alan Katz, Consultant Radiation Oncologist who presented on CyberKnife Radiosurgery for Early Prostate Cancer, Dr Ronald Beaney from the Cyberknife Unit, Harley St Clinic, London and Dr Geoff Heyes, Principal CyberKnife Physicist, OE Birmingham.

At the official opening Left to Right: Mr. Danny Rawluk and Prof Berndt Wowra.

Dr Clare Faul, Radiation Oncologist also spoke of her experience to date of CyberKnife at Hermitage and the patient referral pathway. The event was chaired by Mr Danny Rawluk, Consultant Neurosurgeon and attended by Consultants from different specialties including Radiation & Medical Oncology, Neurosurgery, Neurology, Urology and Respiratory Medicine.

The Hermitage Medical Clinic's CEO, Mr Eamonn Fitzgerald, acknowledged the continued commitment and support of the investors in developing the hospital as a centre of excellence for patient care through the dedication of skilled and compassionate staff as well as cutting edge medical technologies.

For further information contact: Hermitage CyberKnife Centre, T: +353 (0)1 645 9045, F: +353 (0)1 645 9128, E: radiotherapy@hermitageclinic.ie

Meet the scientists and take a guided tour of the UK's first dedicated brain tumour research laboratory

Find out more about the ground-breaking science being carried out at the Brain Tumour Research Centre of Excellence in the University of Portsmouth.

The charity Brain Tumour Research helps fund long-term and sustainable research, supporting the UK's largest team of Neuro-oncologists. The Brain Tumour Research lab tour is a fantastic chance to see the extremely interesting and valuable research taking place every day. You will be able to ask questions about the research and how the work is helping get closer to a cure. One of the charity's Regional Fundraisers is also on hand to talk about the role of the charity.

Lab Tours often coincide with a formal placement of plaques on our Wall of Hope, a permanent recognition of the funds raised through the efforts of our amazing supporters.

Dates for the Lab Tours can be found on the Brain Tumour Research website here www.braintumourresearch.org/portsmouth-centre-lab-tours

To register for your visit, contact Brain Tumour Research via email sarah@braintumourresearch.org or call +44 (0)1296 733011.

Faecal M2-PK – highly sensitive adenoma detection for improved bowel cancer screening

Faecal M2-PK detects colonic adenoma (polyps) in more than 2 1/2 times as many subjects as the faecal immunochemical test (FIT – OC Sensor), according to a major study from Dublin*. Invitations went to 1800 asymptomatic 50 to 74 year old residents, and both M2-PK and FIT (only a single sample was required for M2-PK, but two samples for FIT) were tested in nearly 1000 subjects to screen for colorectal cancer.

Only 23 subjects were "double positive", reflecting the different principles behind the tests. Raised faecal M2-PK concentrations result from a switch in glucose metabolism, whereas FIT detects blood in the stool.

Importantly, in 186 patients who proceeded to colonoscopy, adenoma were detected in 40 (of 157) patients with raised faecal M2-PK (M2-PK > 4 U/ml), but in only 15 (of 51) FIT-positive patients (one or both FIT sample > 100ng/Hb/ml). Fifty patients had adenoma if either faecal M2-PK or FIT was elevated.

This far greater sensitivity of faecal M2-PK for detecting polyps (using only a single sample) is of great importance considering that polyp detection and removal is a primary goal in bowel cancer screening and prevention.

*Leen R et al. Eur J Gastroenterol Hepatol 2014; 26: 514 – 518.

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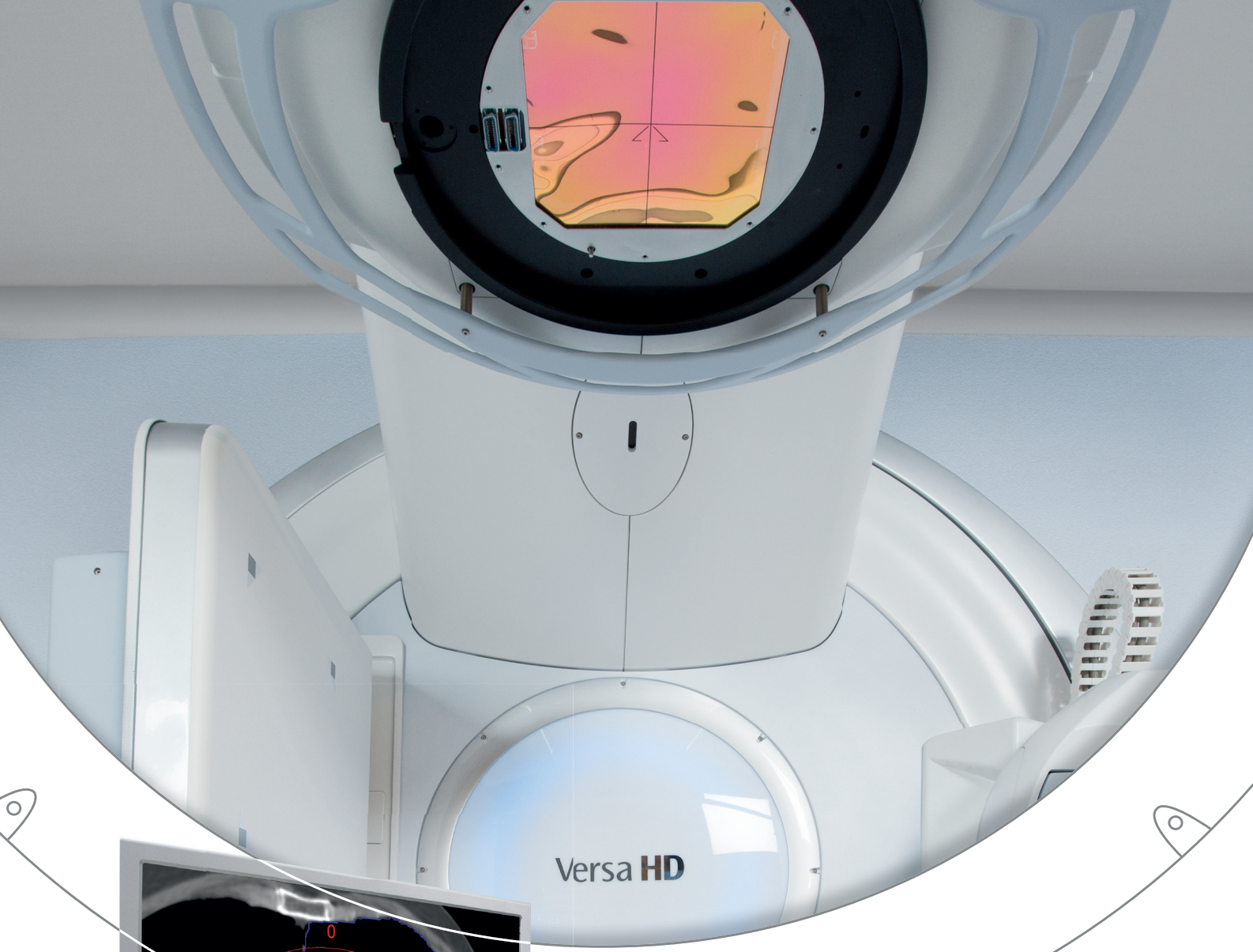
FDA expected to make determination within 60 days upon receipt

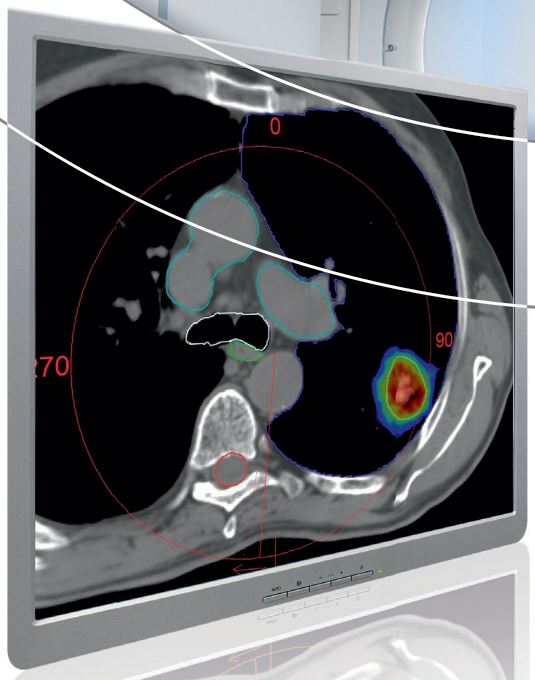
Provectus Biopharmaceuticals, Inc, a development-stage oncology and dermatology biopharmaceutical company, announced today that it has applied to the FDA for Breakthrough Therapy Designation (BTD) for PV-10 for the treatment of melanoma. FDA guidelines state that the Agency will make a decision on the application within 60 days of receipt. The Agency's records for FY 2013 show that the Agency's Center for Drug Evaluation and Research (CDER) met that guideline 97% of the time.

Craig Dees, PhD, CEO of Provectus said, "The decision to apply for BTD stems from our Type C meeting held with the FDA's Division of Oncology Products 2 in December 2013. At the meeting FDA expressed willingness to work with Provectus toward initial approval for the novel investigational oncology drug PV-10 in locally advanced cutaneous melanoma. This included a statement in the minutes that data in a cohort of patients that received PV-10 to all existing lesions should be submitted in a formal BTD application."

Dees concluded, "We are confident that the studies done thus far illustrate the effectiveness and safety of PV-10: if you inject PV-10 into melanoma tumours, the tumours go away. For recurrent, aggressive skin cancers this unique mechanism confers tangible benefit to patients."

For further information visit www.pvct.com





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As compared to previous generation Elekta digital linear accelerators. Stieler F, Steil V, Wenz F, Lohr F, Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Germany.
Versa HD is not available for sale or distribution in all markets. Please contact your Elekta representative for details.

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