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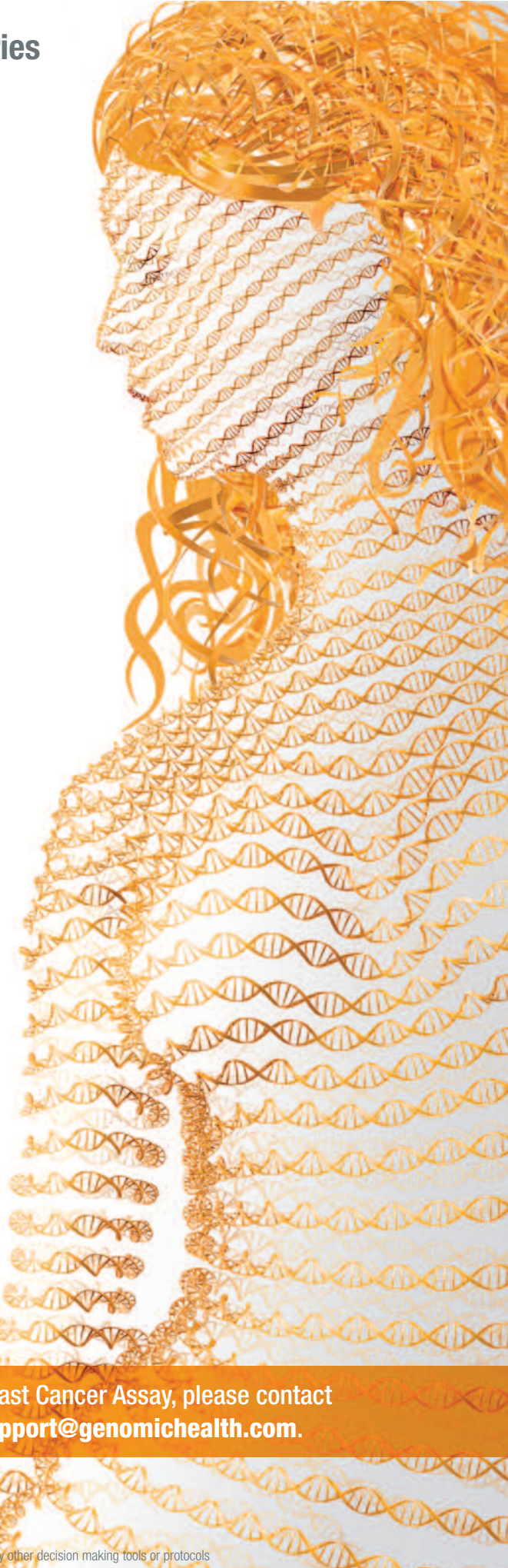

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1. NICE: Diagnostics guidance, DG10. Sept 2013

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An Enemy of the People – "War" on Cancer

Denys Wheatley
Editor

Enemies and Wars

Cancer has been with us (mankind and other living things) throughout evolution. It is an insidious and unwarranted manifestation in which cells behave in an uncontrolled manner, putting an organism at risk of an earlier death than by "natural causes". We see it as an aberration – an enemy of the people – to be attacked, and ultimately and ideally prevented or cured. Richard Nixon's declaration of war on cancer in the '70s was based on encouraging advances regarding RNA viruses and cancer, leading to the notion that if enough money is thrown at the problem, it could be conquered in a decade or two – truly wishful thinking.

Forty years on, we hear the rallying call again for attack in the guise of battle-zones and war-zones [1]. A consensus reached among its thought-leaders was that "for most forms of cancer, enduring disease-free responses are rare, and cures even rarer." Curiously, however, this sort of war capitulation comes attached to the equally categorical non-sequitur – "despite extraordinary progress in our understanding of disease pathogenesis..." In the context in which cancer research and therapeutics operate, these two statements dominating the narrative may be characterised as a "lack of fit" or paradoxical. Generals (some of the thought-leaders"?) are needed to take charge of the "war", cooperating internationally and using all possible tactics from every possible angle. Progress in the last four decades saw many leaps forward, but some commentators suggest the advances overall have not been significant [2-4]. Assuming our semi-demoralised community of cancer researchers can regroup, redeploy their forces more effectively and adopt better strategies [1,2], would a reassessment 40 years on be any better? Waging outright war would undoubtedly advance us a few more steps, but complete prevention and cure are untenable goals. Cancer is a perennial problem, not one that can be defeated within a given time-frame. For this reason, Hanahan's analogy [1] seems farfetched and overstated (e.g. his penultimate sentence refers to a "multidimensional cancer battlespace vision" – but read on!). The problems with a holistic war are how it can be implemented, co-ordinated and financed. Wars are extraordinarily expensive; the announcement (page 9) that the Ludwig Foundation will spend half a billion US dollars over five years may bring dividends, but will probably be seen in due course as a drop in the ocean.

External versus internal factors

A top priority must be prevention, for which intimate knowledge of external risk factors related to carcinogenesis is required; thanks to the contributions of epidemiologists, there is a quite sophisticated list of those risks. It is more difficult to increase the chances of prevention where genetic and internal factors predisposing people to cancer are concerned, especially in asymptomatic cancers. Cancer might also be due to a misplaced cell in the society of cells – the original (stem?) cell idea called an embryonic rest by Cohnheim-Ribbert [5] – or as stressed in Smithers "attack on cytologism" (6).

Control and Quality of Life (QOL)

Curing cancer remains a pipe-dream; the disorder will arise as long as our species exists, with increased longevity now exacerbating the problem. We must think in terms of *control* being a more practical goal, which requires rational intervention coupled with excellent management "on all fronts." Management has to be customised since all tumours are unique and constantly changing, and the teams involved nowadays include professions from surgeons to chaplains. The cost, especially with ageing populations, might soon run away with all health budgets. The focus should also remain firmly on QOL, however short life-expectancy might be, since this often brings the greatest benefit to the patient.

Guerrilla tactics – metastasis

We have to understand how tumour cells invade other tissues near and far; without dissemination, cancer becomes a much more manageable problem. "Guerrilla tactics" are extremely difficult to combat, especially when the enemy keeps changing its characteristics and tactics. This changing behaviour leads to resistance, an issue that should also have high priority. To take our analogies further, my impression is that cancers are more like terrorist activities that have many different origins, and that need to be prevented in the first place, otherwise contained and eliminated as best possible in each case, which has little semblance to outright war.

Our struggle against cancer is an enduring activity, not a battle or war with a victory in sight. The notion that this is achievable by all-out war is poorly founded and insensitive in that it continues to give false hope to many cancer sufferers. ●

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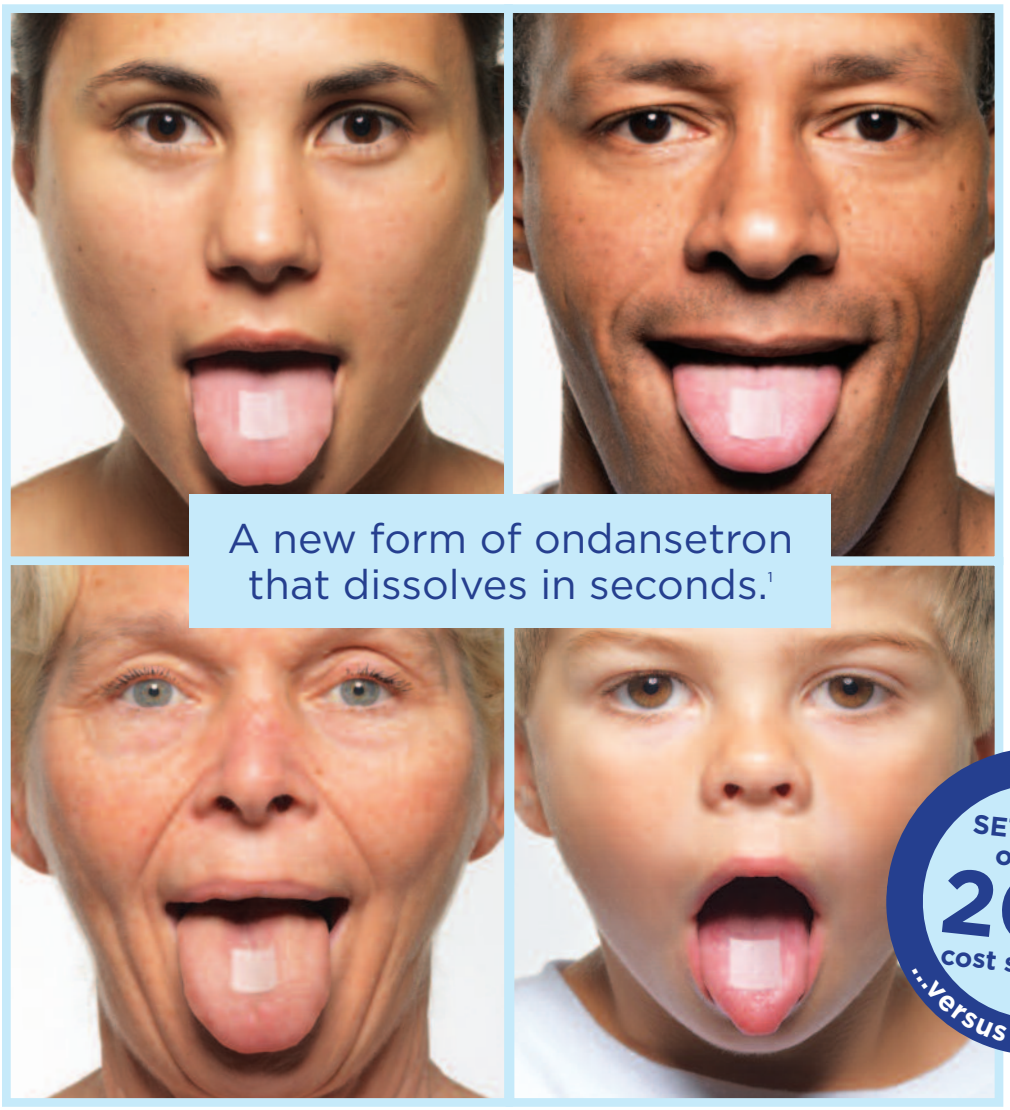

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Table 1: BSA and Weight based dosing for Chemotherapy

BSA	**Day 1[a,b]**	**Day 2-6[b]**
<0.6m²	5mg/m² i.v*plus 2mg**orally after 12 hrs	2mg** orally every 12hrs
≥0.6m²	5mg/m² i.v*plus 4mg**orally after 12 hrs	4mg orally every 12 hrs
Weight	**Day 1[a,b]**	**Day 2-6[b]**
≤10kg	Up to 3 i.v*doses of 0.15mg/kg every 4 hrs	2mg** orally every 12hrs
>10kg	Up to 3 i.v*doses of 0.15mg/kg every 4 hrs	4mg orally every 12 hrs

a The intravenous dose must not exceed 8mg.
b The total daily dose must not exceed adult dose of 32mg.
*SETOFILM is an oral preparation only, and is not available in an intravenous formulation. **SETOFILM is only available in films of 4mg and 8mg. It is not possible to divide the film to obtain a 2mg dosage. The dose for children weighing ≥40kg is 4mg Setofilm, one hour prior to anaesthesia, followed by one further dose of 4mg after 12 hours. **Contra-indications:** Hypersensitivity to ondansetron or to other selective 5-HT3-receptor antagonists or to any of the excipients. Concomitant use with apomorphine. **Warnings and precautions for use:** Use with caution to patients who have or may develop QT prolongation, patients taking other medicinal products that lead to QT prolongation, cardiac rhythm or conduction disturbances, significant electrolyte disturbances and patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents. Patients with sub-acute intestinal obstruction and with adeno-tonsillar surgery should be carefully monitored following ondansetron administration. Paediatric patients with hepatotoxic chemo-therapeutic agents should be monitored closely for impaired hepatic function. It should be noted that when administering three doses at 4 hourly intervals, the total daily dose will be higher than if one single dose of 5mg/m² followed by an oral dose is given. The comparative efficacy of these two different dosing regimens has not been investigated in clinical trials. **Interactions:** Phenytoin, carbamazepine and rifampicin are potent inducers of CYP3A4 and therefore decrease ondansetron blood concentration levels. Ondansetron may reduce the analgesic effect of tramadol. Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Use with cardiotoxic drugs may increase risk of arrhythmias. **Pregnancy and lactation:** Use in pregnancy or breastfeeding is not recommended. **Side effects:** A very common side effect reported is headache. Common side effects are sensation of warmth or flushing and constipation. Other effects that have been reported are hypersensitivity reactions, including anaphylaxis, transient visual disturbances, QT prolongation, arrhythmias . For full list and frequency of adverse events, consult with the SmPC. **Licensing and Legal Category:** Legal Category: POM. Cost: Basic NHS price: £28.50 for 10 by 4mg orodispersible films. NHS price: £57.00 for 10 by 8mg orodispersible films. MA number: PL: 20142/0011 (4mg) and PL 20142/0012 (8mg). **For further information contact:** Norgine Pharmaceuticals Limited, Moorhall Road, Harefield, Middlesex, UB9 6NS. Tel: 01895 826606. E-mail: medinfo@norgine.com. SETOFILM® is a registered trademark. **Date of preparation/revision:** SE3472-MAY-2013.

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2. MIMS, May 2013.

Date of preparation: July 2013. **SE/3650/JUL/13.**

NORGINE

Use of Transoral Laser Microsurgery for Treatment of Hypopharyngeal Cancer

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Squamous cell carcinoma of the hypopharynx is relatively rare compared to other major sites of the head and neck, and accounts for approximately 3% to 5% of all head and neck squamous cell carcinomas. Despite this low incidence, hypopharyngeal carcinomas show the worst survival rates within the head and neck region. Advanced stage of disease at the time of diagnosis seems to be mainly responsible for the poor prognosis. Interestingly, oncologic results for hypopharyngeal carcinomas have not significantly improved during recent decades regardless of the chosen management scheme [1].

Traditionally, total laryngopharyngectomy followed by postoperative radiation has been the preferred treatment in many centres. In the last decade, with the emergence of organ preservation protocols, a tendency towards chemo-radiotherapy has reduced the percentage of primary surgery in head and neck carcinomas. However, the success of organ preservation protocols relies not only on favourable survival and preservation rates, but also on adequate function of the remaining organ, together with the feasibility of adequate salvage surgery for cases with local and regional failure. Long-term toxicity in patients treated with concurrent chemo-radiotherapy, with the subsequent loss of function of many preserved organs and inability to benefit from radiation in the future has made chemo-radiotherapy a suboptimal choice of treatment [2].

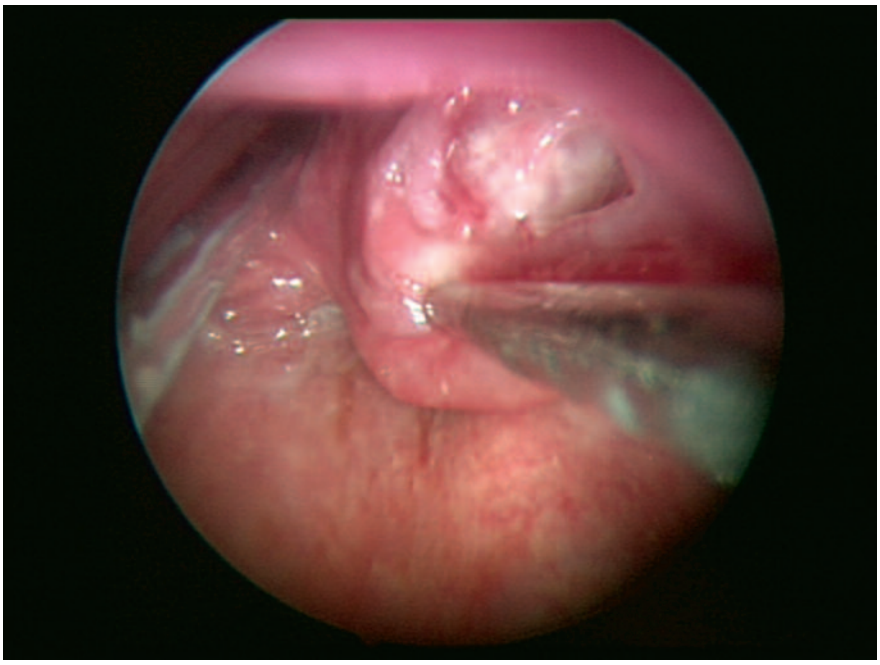
This is especially relevant in piriform fossa because the dose administered to the pharyngeal constrictor muscles cannot be reduced due to these structures being the primary target and the feasibility of salvage surgery is low in comparison to laryngeal carcinoma .Takes et al analyses the current trends in the initial management of hypopharyngeal carcinoma and concludes that, in early stages, both surgery and radiotherapy are considered good organ-preserving treatment options. For advanced disease, most patients are treated with total laryngopharyngectomy followed by chemo-radiotherapy or up-front chemo-radiotherapy. However, the authors propose that the TNM classification may be a better tool to guide physicians in treatment decisions involving organ preservation strategies than overall stage classification [3].

In a further review, Gourin and Johnson reveal that despite the increasing popularity of organ preservation protocols, primary surgical therapies continue to play an important role. The authors suggest that primary surgery is indicated in selected hypopharyngeal carcinomas when the surgical approach offers an alternative to radiation or the possibility to reduce the intensity of adjuvant therapy or when the extent of the primary tumour mandates a surgical approach to optimise survival and function [4].

Transoral Laser Microsurgery (TLM) for hypopharyngeal carcinoma

Use of CO2 laser for oncological purposes in the upper aerodigestive tract was first introduced by Steiner in the late 1980s; His initial results were given no credit by many head and neck surgeons, but encouraged by others [5]. In the early 1990s, Zeitels et al reported a case series of supraglottic and hypopharyngeal carcinomas treated with laser only or with laser plus radiotherapy, The lesions were highly selected for small volume and endoscopic accessibility. The authors concluded that endoscopic resections were less morbid and more cost-effective than open surgery or radiotherapy [6]. While use of TLM in early laryngeal carcinoma has become increasingly used, its use in treatment of hypopharyngeal carcinomas remains to be the less established (Figure 1).

In 2010, Karatzanis et al evaluated 119 patients with T1 and T2 hypopharyngeal carcinomas primarily managed with laser surgery. Local control and 5-year disease-specific survival were 90 and 77.8% for T1, and 83.1 and 70% for T2. 2.5% of Patients received permanent trachesotomies due to chronic post operative aspirations and 2.5 % were reported to require permanent gastrostomy tubes due to impaired swallowing. More recently, A retrospective comparison at the same institution, comparing the outcomes of TLM



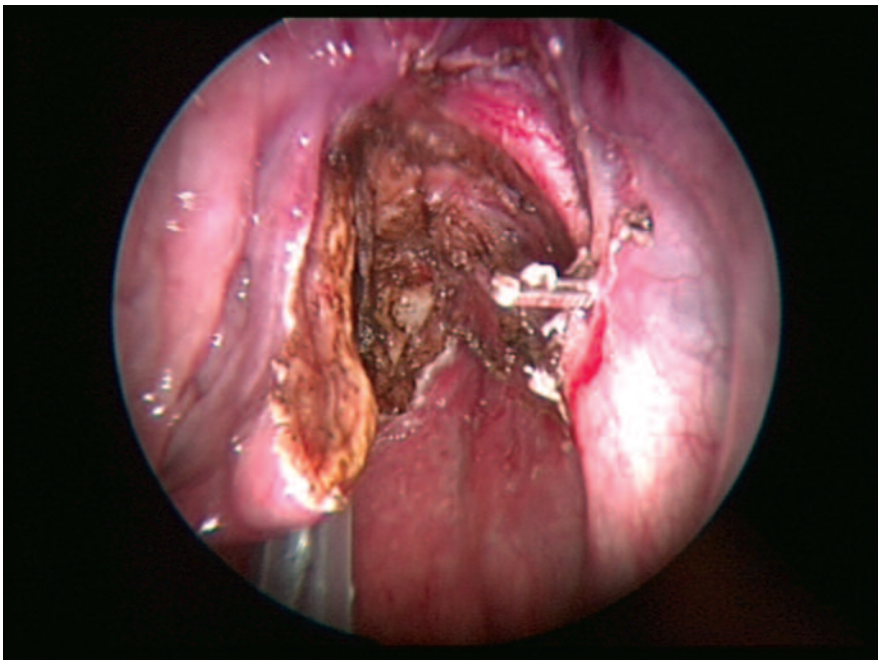


Figure 1 showing a TLM on a hypopharyngeal tumour arising from the right piriform fossa a) before b) after surgery.

with other treatment modalities for similarly staged tumours, showed that the local control and disease specific survival were totally comparable with open surgical techniques (P>0.05) and better than those of radiation-based protocols (P<0.001) [7].

Previous to that in 2001, Eckel et al reported a 92% organ preservation rate in a sample of 46 patients with T1 and T2 hypopharyngeal tumours treated by organ-sparing surgery with or without postoperative radiotherapy. Twenty-three of those patients were treated with TLM. The 5-year overall and disease-specific survival rates for the 46 patients were 61.1 and 75.9%, respectively [8]. Rudert and Hoft confirmed these initial results with their series of 29 T1–T2 hypopharyngeal tumours treated with TLM, with a 5-year overall and disease-specific survival of 58 and 48%, respectively, and 100% larynx preservation. Almost all patients underwent neck dissection and adjuvant radiotherapy [9].

Later, Kutter et al reported the outcomes of 55 patients, mostly T1–T2, with a local control of 90% after a median follow-up of 2 years and a local and regional control and overall survival rate of 72% and 78%, respectively. The authors highlighted the early recovery of swallowing compared with open approaches, with only 67% of the patients needing a gastrostomy tube and a significant reduction in the period of time [10].

For more advanced tumours, experience with TLM is still limited. The first series of patients with early and locally advanced hypopharyngeal carcinomas treated with TLM was published by Steiner et al , with a 5-year overall survival rate of 71% in early stages and 47% for stage III and IV disease [11]. In 2004, Vilaseca et al published their preliminary results in a group of 28 consecutive early and advanced tumours (stages II–IV) with a 4-year overall survival of 43% and 79% larynx preservation. Only 14% of the patients received adjuvant radiotherapy to the tumour site, whereas 57% underwent adjuvant radiation to the neck because of positive nodes. The local control was 100% for T1, 91.6% for T2, 56.2% for T3, and 100% for T4 [12].

Technical requirements and patient selection

Careful selection of the cases suitable for laser surgery is paramount in order to obtain satisfactory results. For TLM to work, optimal access to the complete tumour is essential making the tumours arising from the lateral pharyngeal wall, which are, in general, easily accessed more suitable.In post cricoid tumours, laser surgery is only suitable for superficial lesions without cartilage involvement and without involvement of the arytenoid joints. At least one mobile arytenoid should be preserved to avoid aspiration. In tumours of the medial wall and the fornix of the piriform fossa, the absence of anatomical barriers to the supraglottic larynx and the paraglottic space allows rapid invasion of these areas. Therefore, the ipsilateral supraglottis and the paraglottic space lateral to the vestibular fold are usually included in the resection specimen. The invasion of the paraglottic

space lateral to the true vocal cord usually precludes the indication of TLM. These limitations reduce the percentage of patients with hypopharyngeal carcinoma that are suitable for TLM at presentation [2].

Advantages of transoral laser microsurgery

In contrast to radical surgical procedures, TLM allows minimisation of the loss of healthy tissue and thus avoiding extensive reconstruction procedures. In most cases, tracheotomies are not required and the need for postoperative gastrostomy tubes is lower when compared to other conservation regimen or to open surgery. The preservation of pharyngeal sensory nerve function results in better postoperative swallowing and further reduces postoperative morbidity such as aspiration pneumonia. TLM can be seamlessly integrated into any therapeutic regimen while maintaining all salvage treatment options.

Furthermore, the minimally invasive nature of TLM increases indications in the elderly whenever the general performance status is adequate to allow surgery. Compared with organ preservation protocols, one of the advantages of TLM is the possibility to obtain prognostic information from the surgical specimen. Precise data on tumour characteristics, nodal status, or the presence of perineural or vascular invasion will allow rational administration of adjuvant treatment preventing overtreatment.

Disadvantages of transoral laser microsurgery

One of the limitations of TLM is the reduced percentage of patients suitable for this technique at presentation. Although few authors have published good results in moderately advanced cases, the best functional and oncologic results are obtained in T1–T2 which make only 20% of hypopharyngeal carcinomas.

An advanced learning curve in the field of TLM is required to approach and treat moderately advanced hypopharyngeal carcinomas with a favourable success rate. According to the low percentage of early cases at initial presentation, it could be difficult for most of the surgeons to achieve such a learning curve, but, with the increasing use of the laser and the emerging field of transoral robotic surgery, an increase in experience is to be expected in the future.

Conclusion

In experienced hands, TLM is a real alternative to any other surgical or nonsurgical therapeutic regimen in the treatment of early hypopharyngeal carcinoma. High rates of organ and function preservation can be achieved without compromising the oncologic outcome and with relatively low morbidity. A careful selection of suitable patients is mandatory for this kind of surgery. Randomised studies comparing primary surgical approaches and organ-preservation protocols are necessary to clarify the role of primary surgery in the treatment of hypopharyngeal carcinomas. The inclusion of outcomes such as survival rates, organ and function preservation rates, cost of the procedures and quality of life should be mandatory. ●

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Ludwig Cancer Research Bestows Half a Billion in New Funding to Six Eminent US Research Institutions

In January 2014 Cancer research in the US got a critical boost today as the six Ludwig Centers at Johns Hopkins University, Harvard University, the Massachusetts Institute of Technology, Memorial Sloan-Kettering Cancer Center, Stanford University and the University of Chicago received a total of $540 million as part of a gift from Ludwig Cancer Research, on behalf of its founder, Daniel K Ludwig. This new funding ranks among the largest private philanthropic gifts to cancer research.

This gift adds to the endowments established in 2006 to create the Ludwig Centers at each institution, bringing the Ludwig total funding at these institutions to $900 million. Ludwig's global contribution to advancing cancer research is now $2.5 billion.

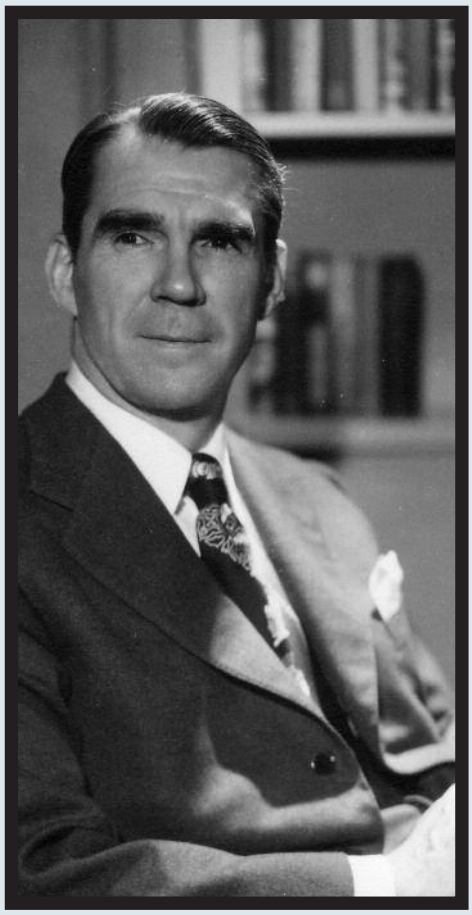
"Never before has the cancer community had the knowledge and tools to probe so deeply into understanding cancer and discovering new ways to defeat it," said Ed McDermott, Ludwig trustee and president and CEO of the Ludwig Institute for Cancer Research. "More must be done in terms of funding to ensure continued progress in an era of shrinking global resources for research. Providing reliable, long-term support to scientists fosters high impact, innovative research and must remain a priority for the cancer community."

Initial funding to the six US-based Ludwig Centers has already yielded groundbreaking discoveries. It has paved the way for the first comprehensive maps of the genomic landscapes of cancers, transformative "smart drugs" and immunotherapy treatments, and fast-tracked research to bring new treatments for various types of metastatic and rare cancers.

"The additional funding received today will allow the Ludwig Centers to expand and amplify their efforts in perpetuity. Sustained support enables the Centers to continue training the best and the brightest of the next generation of scientists," said Bert Vogelstein, MD, co-director, Ludwig Center at Johns Hopkins. "Ludwig puts great faith in its scientists by providing ongoing investment that allows them to expedite research and take risks – the only way to make truly breakthrough discoveries."

This gift complements the late American businessman Daniel K Ludwig's global plan for financing cancer research. The new funding was realised by the sale of New York real estate investments held by Mr Ludwig. Ludwig's first contribution to cancer research was made in 1971 when he established the Ludwig Institute for Cancer Research – a not-for-profit that supports more than 600 cancer researchers at dedicated labs around the world. Ludwig Cancer Research comprises the Ludwig Institute, the six US-based Ludwig Centers and select affiliated scientists across the globe.

"With independent, flexible, and long-range funding we can now take an idea based on the best scientific and medical insights, and pursue it further regardless of how long it may take or the size of the eventual patient population it may benefit," said George D Demetri, MD, co-director, Ludwig Center at Harvard. "We also have the freedom to collaborate with leading scientists around the globe, which can lead to new innovations to help cancer patients."



Visit: www.ludwigcancerresearch.org

Axl as a Therapeutic Target in Merlin-Deficient Tumours

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Deficiency of a tumour suppressor Merlin leads to the development of tumours of the nervous system such as schwannomas, ependymomas and meningiomas occurring spontaneously or as a part of a hereditary disease neurofibromatosis type 2 (NF2) [1,2]. Current therapies surgery and radiosurgery are only partly effective and new treatments are urgently needed for this group of tumours. Merlin loss is also found in a proportion of other cancers e.g. mesothelioma, melanoma, breast cancer and glioblastoma. Our group successfully studies pathobiology of tumours caused by Merlin mutations [3-10] and aims to find molecules involved in tumour development which could be targeted by specific pharmacological inhibitors. Using our human in vitro model for Merlin-deficient tumours, comprising human primary schwannoma cells, we found that Merlin deficiency results in strong overexpression and activation of platelet-derived growth factor receptors (PDGFR) [3], insulin-like growth factor I receptor (IGF-IR) [6], Integrins [11] and ErbB2/3 [4, 12] leading to strong activation of the downstream signalling pathways such as ERK1/2, AKT1/2, JNK, FAK/Src, Wnt and increased proliferation, cell-matrix adhesion and survival in schwannoma [3-5, 10]. Importantly drugs, such as Sorafenib, Nilotinib, Imatinib, Lapatinib, BEZ-NVP235, R1507 were then tested in our human in vitro model and some of the most promising taken further in to clinical trials [3, 13]. Despite successful studies and detection of good therapeutic targets to treat schwannoma and other Merlin-deficient tumours a comprehensive dissection of signalling matrix involved in tumour development is needed. Inhibition of a single pathway may create a feedback loop towards activation of alternative pathways contributing to tumour development. We have therefore investigated additional mechanisms contributing to schwannoma development. Tyro3 (Sky), Axl and Mer are members of the TAM family of receptor tyrosine kinases shown to be overexpressed in cancers, being markers for poor prognosis and correlating with multi drug resistance (MDR).They also contribute to tumourigenesis by regulating migration and invasion, angiogenesis, cell survival and tumour growth. TAM family receptors are significantly overexpressed in schwannoma tissues [4]. The relevance of Axl in merlin-deficient tumours is underlined by findings showing that Axl

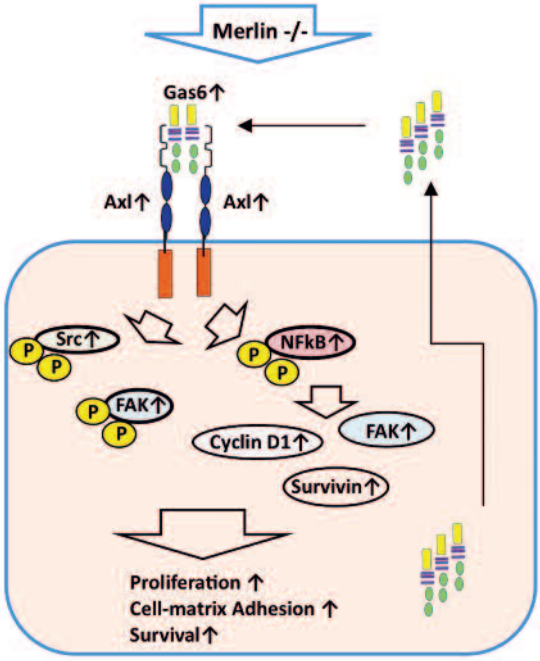

Figure. Merlin deficiency (Merlin -/-) causes increased expression and activation of Axl followed by strong phosphorylation/activation of Src, FAK and NFkB, increased expression of cyclinD1 and survivin and potentiated proliferation, cell-matrix adhesion and survival of schwannoma tumour cells. Gas6 is released and acts in auto/paracrine manner.

is negatively regulated by Merlin and positively regulated by E3 ubiquitin ligase CRL4DCAF1. Merlin seems to inhibit E3 ubiquitin ligase CRL4DCAF1, which is responsible for tyrosine kinase receptors expression changes in Merlin-deficient tumours [14]. The ability of Axl to positively regulate oncogene Yes-associated protein, a downstream member of Hippo pathway known to be under Merlin regulation in schwannoma and involved in increased proliferation of meningioma and mesothelioma, further support for a potential role of Axl in Merlin-deficient tumours [15]. Moreover, TAM family receptors' agonist Gas6 stimulates human Schwann cell proliferation in vitro via Axl and Tyro3 [16]. Using our human schwannoma in vitro model, we demonstrate strong overexpression of all three members of Axl, and the ligand Gas6 in human schwannoma. We show that Gas6 is mitogenic and increases schwannoma cell-matrix adhesion and survival acting via Axl in schwannoma cells. Furthermore, Gas6 signalling via specifically Axl involves focal adhesion kinase (FAK) and Src, but not the ERK1/2, JNK1/2 and AKT signalling

pathways. We also demonstrate the role of NFkB, which regulates Gas6/Axl mediated overexpression of survivin, cyclin D1 and FAK leading to enhanced survival, cell-matrix adhesion and proliferation of schwannoma. NFkB expression was found to be Merlin dependent and its activity depended on Axl. We thus suggest Axl as a promising therapeutic target for schwannoma and other merlin-deficient tumours. ●

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Medics & IT specialists combine for unique training App

Medical consultants in Belfast have teamed up with IT specialists to develop a mobile training app that can identify a doctor's specific weakness in interpreting X-rays. The app then helps medics develop their skills where required, leading to more accurate diagnosis and better patient care. The app provides immediate feedback to the user, and the more it is used by a doctor the more targeted and personalised the feedback and professional development becomes.

Primarily the application, known as Experior Medical, will be used in accident and emergency and cancer departments, but could eventually be rolled out across all health specialities and even into education, industry and financial services. It is expected that medical trials will start in Northern Ireland A&E units late this year.

The driving force behind the new device is Dr Tom Lynch (pictured), head of nuclear medicine at the Northern Ireland Cancer Centre in Belfast and Kevin Donaghy of Belfast based IT firm Experior Medical. Tom Lynch says, "This is the medical and IT worlds coming together in Northern Ireland and producing something which is really unique. The App contains thousands of typical x-ray images. While some are obvious, some aren't, but they are typical X-rays that doctors would see in an emergency department. This is a state-of-the-art testing and training tool which will be used to improve the decisions made by junior doctors, and lets them know where they have gone wrong, immediately and over the longer term. Because it is a mobile application, remotely monitored, medics right across the globe can use it."

Dr Lynch added: "We already have doctors as far away as Australia and New Zealand using our app. Wherever a doctor is in the world, X-rays are the same. Thousands of doctors are already using Experior Medical. Wherever we have demonstrated the product we have received a very positive response, from clinicians, administrators and from medical students. The Northern Ireland health service is making a positive effort to position the region as a driver of e-health solutions and we believe the Experior product can demonstrate that in a very tangible way."

Dr Kevin Donaghy provides the IT expertise. He said: "When Tom first approached me with the idea of improving the skills of doctors with X-rays, I thought 'how do we build a solution that can be utilised by doctors and training organisations around the globe? How can we harness the best medical brains in the world to the benefit of all doctors and ultimately, all of their patients?' So we put our IT expertise together with Tom's medical experience and knowledge and Experior was the outcome. We are very excited at the potential of this application. Our bottom line is that we wanted to develop a solution that improves diagnosis and health care for everyone.

"With that in mind we used the 'lean start-up model' to prove that we can do this, and lead the way with the best medical and IT expertise in Northern Ireland to deliver a world-class solution. We really believe that Northern Ireland can lead the way in the development of innovative health solutions."

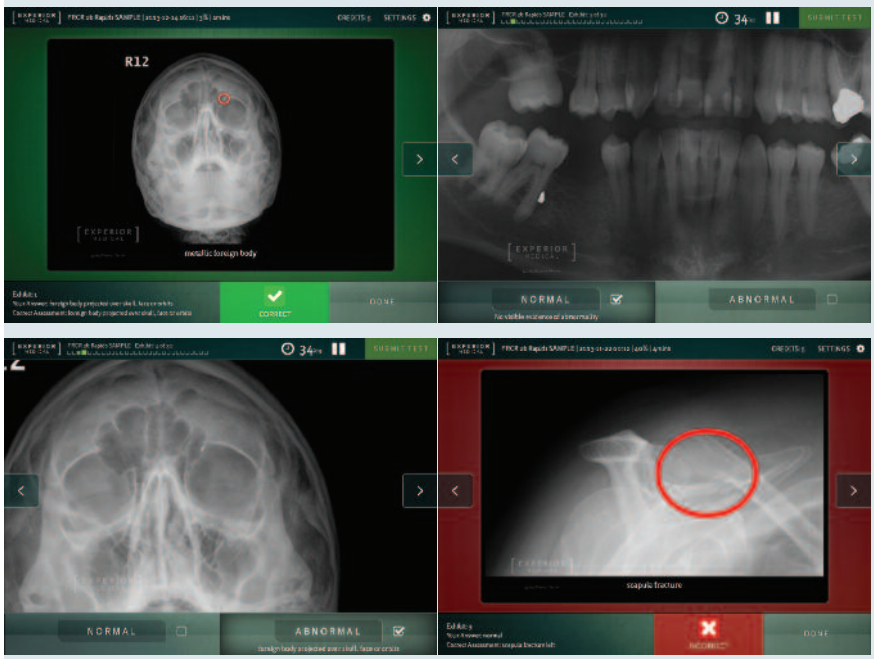

Image Based Tissue Segmentation:

Towards the Automation of Mammographic Risk Assessment

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Historically, mammographic risk assessment, i.e. estimating the probability of the development of breast cancer, has been based on an individual's personal and family background. It has been shown that the amount of fibroglandular tissue as well as its distribution of anatomical tissue in mammographic images is strongly correlated with the probability to develop breast cancer. However, manual assessment shows inter- and intra-observer variability and automation of this process has therefore been considered desirable. Such automated methods cover fatty versus dense tissue segmentation, more advanced segmentation approaches and feature space classification. We provide an overview of various approaches to mammographic risk assessment and how this might be used in future computer aided diagnosis (CAD) systems.

Mammographic risk assessment

Over the past decades, a number of links have been investigated between mammographic risk assessment and patient-specific and environmental aspects, covering family history, diet and genetic markers. Such aspects are currently captured in a number of associated models, e.g. the Gail model [1] and the Tyrer-Cuzick model [2].

However, it should be noted that the above-mentioned mammographic risk models are based on non-image based information and how to integrate image-based information into such risk models is an area of current research [3]. In the late 1960's and mid 1970's, Wolfe [4-6] started to investigate the links between mammographic image information and mammographic risk assessment and found that based on his four risk classes there was a significant difference in risk between the lowest and the highest classes (by a factor of up to twenty in specific studies [5]). Wolfe's classes include aspects of both parenchymal patterns and intensity variations in the mammographic images. This work was followed up by Boyd [7], who established a model based on the percentage dense tissue. Further to this, Tabár and Dean [8] extended the work of both Wolfe and Boyd by describing normal mammographic tissue by four specific building blocks: radiolucent (fatty), homogeneous, nodular and linear tissue, and linked the distribution of these to mammographic risk assessment.

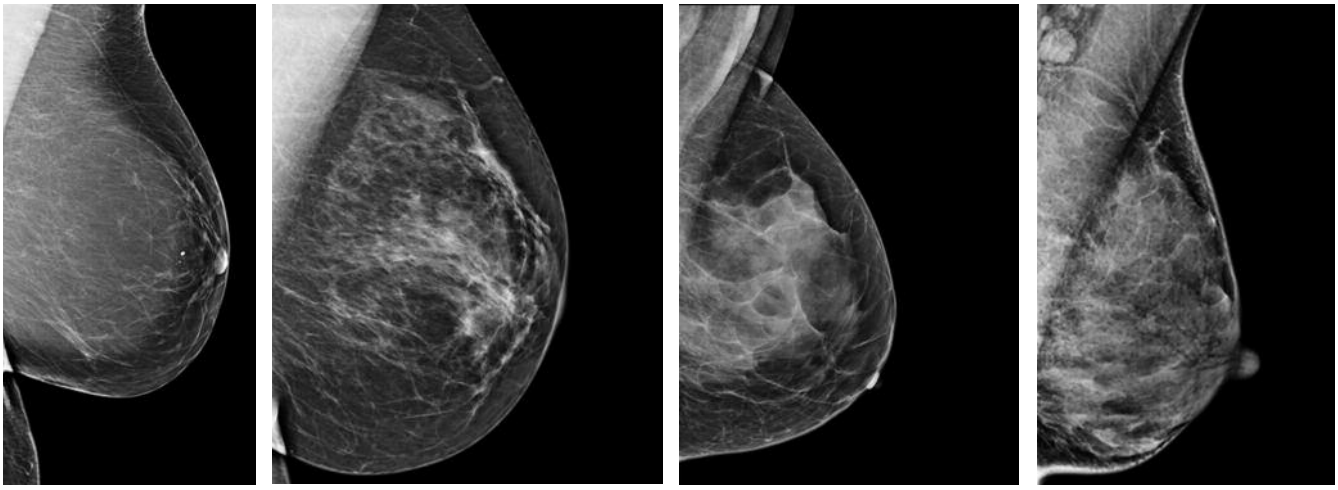
Closely related to Boyd's work, the four Breast Imaging-Reporting and Data System (BIRADS) classes as defined by American College of Radiology BIRADS lexicon are: BIRADS I) the breast is almost entirely fatty, BIRADS II) there are scattered areas of fibroglandular density, BIRADS III) the breasts are heterogeneously dense, which may obscure small masses, and BIRADS IV) the breasts are extremely dense, which lowers the sensitivity of mammography. A set of example mammographic images can be found in Figure 1, which shows BIRADS I to IV cases. Work by Muhimmah et al. [11] has shown that there is clear correlation between the various image based mammographic risk assessment models. Various breast screening and breast cancer detection programmes have adapted mammographic risk assessment [9,10], but it should be noted that none of these currently incorporate the automatic analysis of mammographic image information.

Dense/fatty tissue

For early research involving automated analysis the methods were closely related to the work of Boyd et al. [7], with a strong emphasis on segmentation and estimation of dense tissue within the breast (the fatty tissue is simply the remaining breast tissue). This work was further developed into "*Cumulus*", which is an interactive software that has been used as a standard within the field [12].

Since the development of Cumulus, there have been a number of approaches that proposed a fully automated method for estimation of dense mammographic tissue. A typical example of this is the recent work by Nickson et al. [13] which provides breast density segmentation based on histogram statistics and boundary gradients information. In contrast, Chen and Zwiggelaar [14] developed an automated density segmentation approach based on fuzzy c-means [15], which incorporates local spatial and intensity information. In both cases, the robustness of the developed approaches was evaluated on large

Figure 1: From left to right mammographic images representing BIRADS I to IV.



datasets. Figure 2 shows how the images shown in Figure 1 are segmented using Chen and Zwiggelaar [14].

Closely related to the described automated work is the development of approaches which incorporated a density-normalised step-wedge into the mammogram capture process [16]. The resulting step-wedge information can be used to estimate the segmentation of differently dense tissue areas, which can in turn be linked with mammographic risk assessment. A slight disadvantage of this approach is that it cannot be used on historical datasets that do not include the step-wedge information.

There have been a number of approaches developed based on the fatty versus dense tissue segmentation work. One of the most successful has been the work by Oliver et al. [17], who provided an initial segmentation of dense and fatty tissue after which they extracted texture and density features from the two regions. The feature space was exploited for the classification of mammographic images into the four BIRADS classes, with correct classification results for the MIAS [18] and DDSM [19] databases of 86% and 77%, respectively. Advanced machine learning techniques were investigated by MacParthalain et al. [20], which improved the classification results to 91% and 89%, respectively.

There has been some work focussing on the links between mammographic risk assessment and volumetric estimation of dense tissue. This takes into account the mammographic projective imaging process. Some of the original work was covered by Highnam and Brady [21]. Additional work was completed by Karssemeijer's research group, which also covered correlation with MRI mammographic data [22].

Recent approaches

The approaches described in the previous section are based on the distinction between fatty and dense tissue, which only represents part of the clinical descriptions: e.g. both Wolfe and Tabár included parenchymal patterns as part of their classification.

He et al. [23] have used Tabár's work as a foundation to develop mammographic segmentation incorporating anatomical tissue types. Some of this initial work looked at moments as image descriptors, but alternative approaches have also been investigated. The moments-based description provided individual segmentation models for the four (i.e. radiolucent, homogeneous, nodular and linear) tissue types. Such work provides enriched segmentation results as shown in Figure 3. Tabár's original tissue percentages can be directly linked to mammographic

Figure 2: Dense tissue segmentation of the mammograms shown in Figure 1 based on the fuzzy c-means methodology developed by Chen and Zwiggelaar [14].

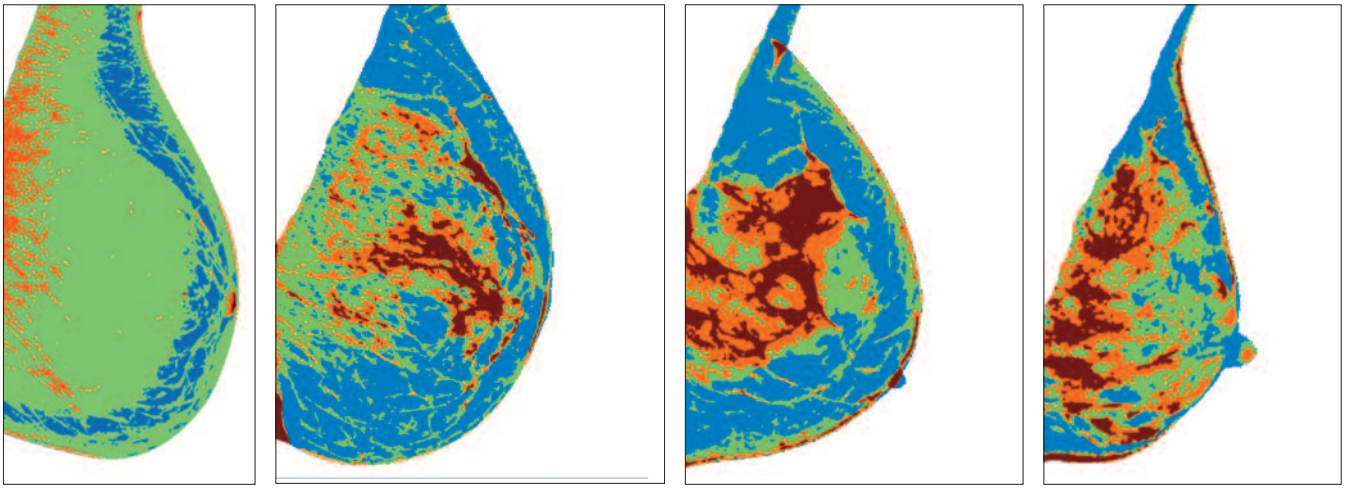
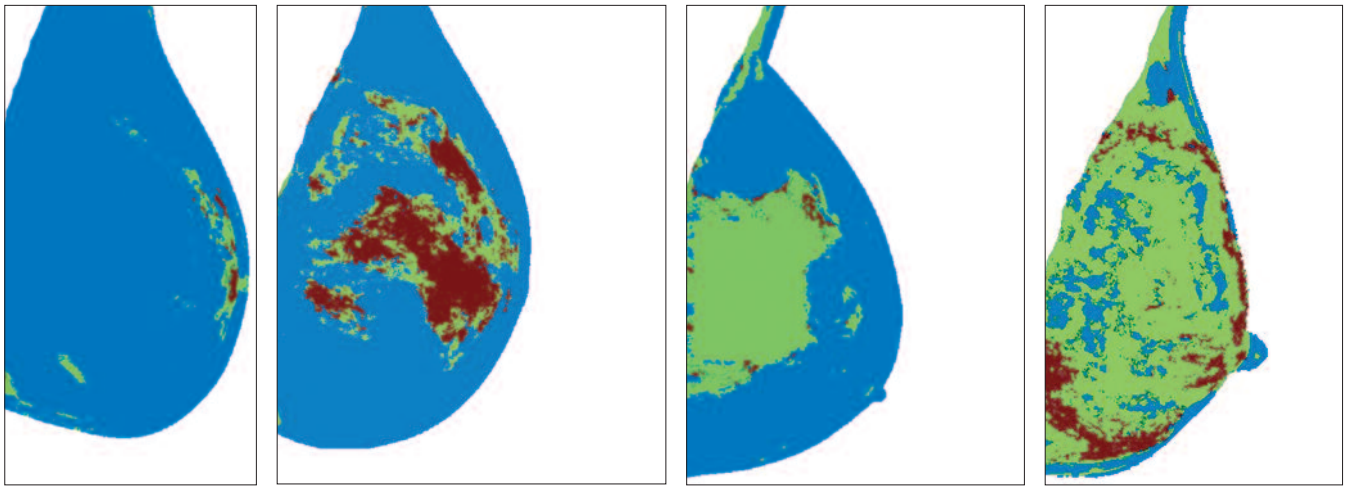


Figure 3: Segmentation of the images shown in Figure 1 using the methodology developed by He et al. [23] which shows radiolucent (blue), nodular (brown) and homogeneous (green) tissue regions.



risk assessment and the most recent results on digital mammographic data show correct classification rates of about 79%. This approach has been evaluated on both digitised and digital mammographic images and has shown robustness with regard to this.

Closely linked to the Tabár tissue type based segmentation developments, Chen et al. [24] have developed a mammographic blob distribution model, which we believe models the homogenous and nodular tissue types. A standard approach to blob detection in images has been adapted to estimate the distribution of blobs at multiple scales and the prior expectation of the two tissue types has been taken into account. In Figure 4 a blob representation of a set of example mammograms is shown, which indicates how the multi-scale blob distribution changes with the BIRADS density classification. This resulted in a number of metrics, which were linked to mammographic risk assessment and achieved classification accuracies close to 80% for the MIAS database.

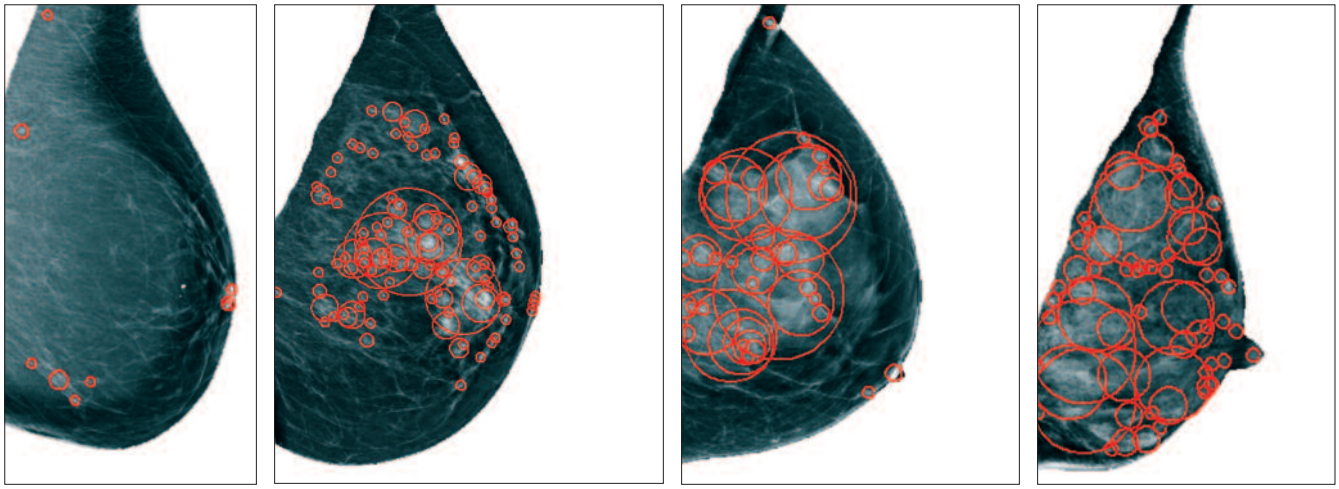
Over recent years we have also started to incorporate both topology and manifold learning techniques into our computer vision approaches. Such techniques provide low dimensional models of data in high dimensional feature space and can be used for dimensionality reduction and noise suppression. We have used this to obtain improved segmentation of the dense regions in mammograms [25] with initial results on a limited dataset showing significant improvements. An alternative segmentation technique was developed by Chen et al. [24], which was based on a topographic map of the whole breast, representing both topographic and geometrical structures. Their initial results indicate the potential for advanced techniques to make a contribution to mammographic risk assessment.

Future directions

The main aim of the development of mammographic risk assessment techniques is to identify women at high risk of getting breast cancer in future and then triage them into optimal paths of screening, diagnosis and treatment paradigms. It is hoped that novel risk assessment techniques will eventually integrate into commercial CAD systems. There are two potential aspects for which the risk assessment based on density or tissue segmentation approaches can be used: 1) the identification of high-risk cases, which could receive additional attention, different subsequent imaging such as ultrasound or breast MR and/or could be invited more often for screening, and 2) as input information for fully automated computer detection algorithms. Both these avenues could increase the probability of detecting breast cancer at an early stage.

It should be noted that there are a

Figure 4. Blob representation of the images shown in Figure 1 using the methodology developed by Chen et al. [24].



number of commercial systems available, which are currently aimed at estimating volumetric breast density and/or area breast density for Full-Field Digital Mammography (FFDM) images. Such systems are used to assist radiologists in the assessment of breast tissue composition and provides a density score, which can be linked to BIRADS breast composition categories. These systems include *Quantra* (Hologic Inc.), *Volpara* (Volpara Solutions), and *MicroDose SI* (Philips Healthcare).

The systems described above are aimed at helping mammography practices achieve a reader independent objective breast density assessment. After the adoption of tomosynthesis images, it is expected that conventional FFDM images will phase out and, there will be a need to translate the currently developed approaches of breast density estimation using FFDM to the new modality of tomosynthesis. This would possibly provide a close to volumetric density/tissue segmentation, which may lead to a more reliable mammographic risk assessment.

It should also be noted that another aspect for further development of the Tabár-based work is the temporal analysis of not just changes in density, but also in parenchymal patterns. ●

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Lung Cancer – Raising Awareness Without Stigmatising

Each year over 2,000 new cases of lung cancer are diagnosed in Ireland [1]) and 900 in Northern Ireland [2]. In 2011, over 38,000 cases were recorded in the United Kingdom [3]. At a global level, lung cancer has been the most common cancer in the world for several decades, and by 2008 (the latest available data), there were an estimated 1.61 million new cases, representing 12.7% of all new cancers [4]. It is the most common cause of death from cancer across the world, with 1.38 million deaths in 2008 (18.2% of the total) [4]. Once a disease of older men, lung cancer cases among women are rising. A recent report from the National Cancer Registry of Ireland (NCRI) shows lung cancer mortality in Irish women is the fourth highest in Europe, which is over 50% above the European average and is still increasing [1]. Yet according to the Global Lung Cancer Coalition (GLCC) more than one in five people seem to be unaware of the symptoms, making the need for education about lung cancer even greater.

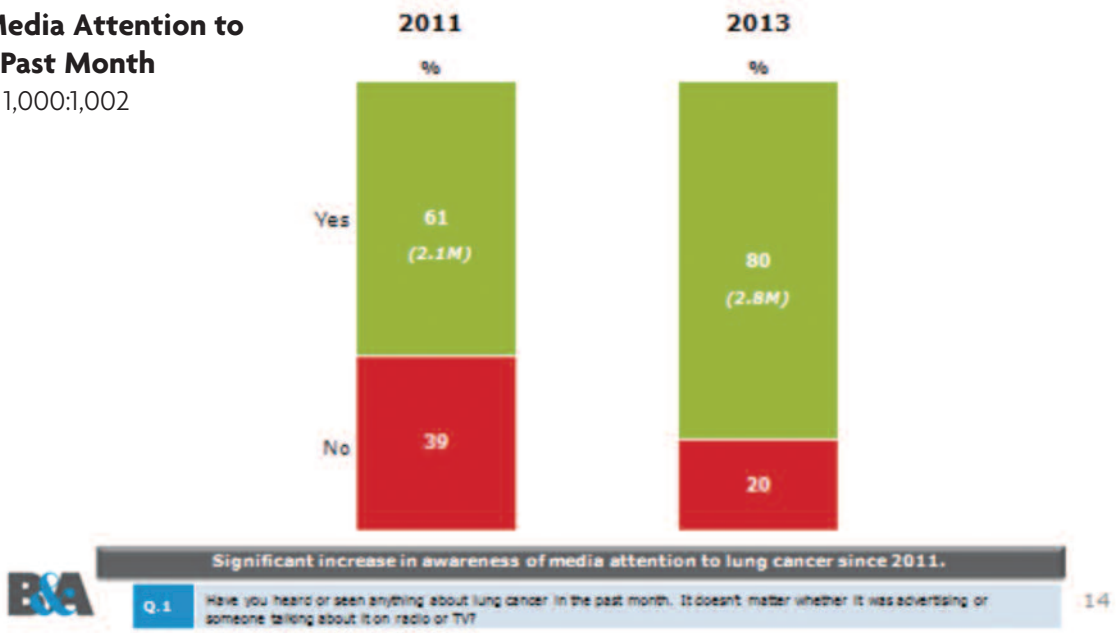
The GLCC survey, carried out by Ipsos MORI was launched at the World Conference on Lung Cancer in October 2013, which investigated awareness of the symptoms of lung cancer and smoking prevalence in 21 countries. They found that 22% of people admitted that they could not name any symptoms of the disease. Of the 17,000 people surveyed, former smokers were slightly more likely to be aware of symptoms than current smokers or people who have never smoked. Respondents from Ireland were more likely to say that breathlessness and unspecified or general coughing are symptoms of lung cancer than in the other countries surveyed (56% of all Irish respondents). The second highest proportion of respondents who could name at least one symptom was found in Ireland, with only 9% saying they did not know any. To what can we attribute this level of knowledge?

Raising awareness without stigmatising

In 2011, the Irish Cancer Society launched a three-year advertising and PR campaign to raise awareness of lung cancer in a novel and engaging way. The Society wished to move away from the

Part of the Irish Cancer Society's Lung Cancer Awareness Campaign.

Awareness of Media Attention to Lung Cancer in Past Month
Base: All adults – 1,000:1,002



Increase in awareness of the campaign over 3 years.

grim, grey, tobacco-led and often frightening messages and imagery that tend to be associated with lung cancer. The campaign's aim was to avoid adding to the stigmatisation of lung cancer, but instead encouraged people concerned about lung cancer and those already affected by it to contact the Society's National Cancer Helpline. The campaign comprised of National outdoor poster and radio advertising, distribution of 'Look after your Lungs' – a publication highlighting the importance of lung health, issuing a press release and holding radio interviews over a two-week period in January.

Behaviour & Attitudes (an independent marketing company) undertook market research that had been commissioned by the Irish Cancer Society in 2011 and 2013 to gauge the efficacy of the campaign; just nearly three million adults recalled some media attention on the issue of lung cancer in February 2013. This was considerably up on 2011 levels (2.1 million Vs. 2.8 million). Whilst just over 6 in 10 were aware of some media attention in January 2013, this figure rose to 7 in 10 among smokers.

The strongest campaign message coming out of the research related to quitting smoking and informing people that smoking was bad for them. This element was significantly stronger than in 2011 (58 vs. 35%). The second most frequently mentioned message was to visit your GP and get checked; once again this message came out stronger in 2013. In keeping with the GLCC survey, the two key symptoms of lung cancer mentioned spontaneously were a cough that did not go away and being short of breath.

By removing the link between lung cancer and grim tobacco messaging by communicating a message of empowerment, more people engaged with the campaign, which was deemed a success. During the campaign, the National Cancer Helpline received more preventative and undiagnosed enquiries about lung cancer than any other cancer. The majority of contacts were female aged 50-59 years of age, i.e. our target audience. A sharp rise in webpage viewings was noted and social media interaction exceeded expectations. Interestingly the market research also confirmed that the general public were fully aware of the link between lung cancer and smoking, highlighting this link was not essential when promoting lung cancer awareness.

'Do you smoke?'

Public health campaigns around the world have traditionally stressed the undeniable link between tobacco smoking and lung cancer. However, some argue that this public health approach led to the stigmatisation of lung cancer patients. Stigma is not normally associated with many other cancers, yet on hearing a lung cancer diagnosis many people would ask of the sufferer 'Do you smoke?' The strong association between tobacco smoking and lung cancer has led many to believe it is a self-inflicted disease [5]. This is probably due to the combined effect of public health campaigns and the billions the tobacco industry spends convincing smokers that they can choose to smoke.

At the 2013 annual meeting of the American Society of Clinical Oncology (ASCO), Schiller et al. [6] presented a study on explicit and implicit attitudes toward lung cancer relative to breast cancer. This was an online study that involved over 1700 respondents from different sectors, including healthcare providers, public care-givers and patients. Explicit attitudes were recognised by answers to specific questions, and implicit attitudes were by responses to a rapid series of photographs and words. For implicit attitudes, about 74% had negative attitudes toward lung cancer vs 20% against breast cancer. The authors noted that lung cancer is perceived as self-induced due to its strong association with cigarette smoking, but that addiction to tobacco is powerful and very difficult to break.

The effect this stigma is having on lung cancer patients is unclear. In 2012,

Chambers et al. [8] reviewed reports on lung cancer stigma and suggested that it is reasonable to assume it has a negative effect on the psychosocial well-being of people affected by lung cancer, both patients and their loved ones. At the same time Cataldo et al. [7] published a study of almost 200 lung cancer patients in which strong associations were found between lung cancer stigma and depression and quality of life. No significant difference was found between never and ever smokers [9]. These authors recently developed an instrument to measure the stigma perceived by lung cancer patients – the Cataldo Lung Cancer Stigma Scale (CLCSS). The CLCSS can be used to identify not only the presence of stigma, but the effect it has on the lung cancer patient. It is hoped that the introduction of this tool will eventually lead to effective interventions that can be used to combat the negative effects of stigma [7].

'An emotional rollercoaster'

Research clearly suggests that stigma is a very real issue for lung cancer patients. This burden is in addition to knowing that they have been diagnosed with the biggest cancer killer worldwide. The majority of patients are diagnosed at a late stage with a poor prognosis; they often experience debilitating symptoms, making it unsurprising that lung cancer patients can become distressed. The impact of a cancer diagnosis can evoke a range of emotions, anything from fear, anxiety, and anger to denial. There is no right or wrong way to feel, no right time to experience any one particular emotion. Patients often describe this as being like 'an emotional rollercoaster.' This may be a normal reaction to a cancer diagnosis; however 25-30% of all newly diagnosed cancer patients experience elevated levels of emotional distress [1] and struggle to cope with the impact of their disease. The National Comprehensive Cancer Network (NCCN) defines distress as:

> *'A multifactorial unpleasant emotional experience of a psychological (cognitive, behavioural, emotional), social, and / or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment.' [11]*

A well-recognised study by Zabora et al. [10] in 2001 examined the prevalence of psychological distress by cancer site and found considerable variation. Of the patients surveyed, 43% of lung cancer patients experienced increased levels of distress in comparison to 32% of breast cancer patients, 31% of bowel cancer patients and 30% of prostate cancer patients. Similarly Joyce et al. [11] found lung cancer patients scored high on distress levels due to poor prognosis and self-attribution due to smoking. The authors noted that low survival rates associated with lung cancer allows the patient little time to adjust to their diagnosis and prognosis, contributing further to their distress levels (12).

'No one in the world deserves lung cancer' – Global Lung Cancer Coalition

No one in the world deserves lung cancer. It is the role of organisations like the Irish Cancer Society, Cancer Focus Northern Ireland and the Roy Castle Lung Foundation to increase awareness of the disease and provide support to those already affected by lung cancer. Raising awareness is vital, but we must be mindful to do so without stigmatising and adding to the burden of lung cancer. ●

USEFUL WEBSITES:

Irish Cancer Society: http://www.cancer.ie

Global Lung Cancer Coalition: http://www.lungcancercoalition.org

National Comprehensive Cancer Network: http://www.nccn.org

Cancer Focus Northern Ireland: http://cancerfocusni.org

Roy Castle Lung Foundation: http://www.roycastle.org

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IF MOST OF THE PEOPLE WE HELP TODAY DON'T NEED PALLIATIVE CARE, WHAT DO THEY NEED?

'They often need someone to listen calmly and with empathy to their feelings and fears. And I can help with that.'

Margaret
Macmillan Support Line Officer

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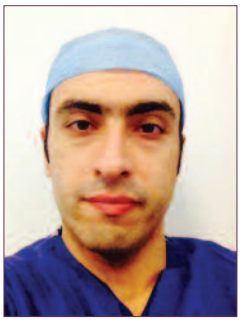
TOGETHER WE CAN HELP MORE PEOPLE AFFECTED BY CANCER

Borderline Resectable Pancreatic Head Cancer:

Neoadjuvant Chemotherapy and Portal Vein/Superior Mesenteric Vein Reconstruction as The Current Standard of Care



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The cornerstone of pancreatic cancer treatment is surgical resection, which can be performed with low morbidity and mortality in experienced centers. Since longterm survival can only be achieved with R0 resections (tumour resected with negative margins) [1], the goal of the surgical procedure is complete tumour resection.

Increasing use of neoadjuvant chemotherapy and/or chemoradiation combined with vascular resection and reconstruction have allowed potentially curative resection of tumours previously considered unresectable.

Such "borderline resectable" pancreatic cancers are those that have portomesenteric venous with hepatic and/or hepatic artery/coeliac trunk involvement in such extent that resection might still be technically feasible under skilled hands; yet, they still carry a high risk of margin-positive resection (R1/2) unless surgery is preceeded by neoadjuvant therapy [2,3]. Aim of this review is to present the current standard of care in the management of such tumours in accordance to the latest peer-reviewed guidelines, based on data published by the current leading institutions in the cure of this highly aggressive malignancy.

Definitions

One of the earliest descriptions of "marginally resectable" pancreatic cancer as defined by radiographic criteria was by Mehta et al. in 2001. Since then, two definitions have become established in the literature: that of the MD Anderson (MDACC) Group [4] and that of the APHBA/SSO/SSAT in their Consensus Guidelines [5], which have been incorporated into the NCCN Guidelines for pancreatic cancer treatment [6]. A comprehensive definition has recently been proposed that is used in the Intergroup pilot study of borderline resectable pancreatic cancer now accruing (Alliance Trial A021101) [3].

This definition, while conceptually similar to the one used by the MD Anderson group [4], is more precise. It states that "borderline resectable tumours meet any one or more of the following radiographic criteria":

1. "An interface exists between tumour and the SMV/portal vein measuring 180 degrees or greater of the vessel wall circumference, and/or reconstructable venous occlusion;
2. an interface exists between tumour and the SMA measuring less than 180 degrees of the vessel wall circumference;
3. a reconstructable, short-segment interface of any degree exists between tumour and the common hepatic artery;
4. and/or an interface exists between tumour and the celiac trunk measuring less than 180 degrees of the vessel wall circumference"[2].

Treatment

The necessity of neoadjuvant therapy: A strong rationale exists for the administration of neoadjuvant chemotherapy and/or chemoradiation [3]:

1. 20-30% of patients with potentially resectable pancreatic cancers have radiographically occult metastatic disease [7].
2. Chemotherapy and radiation may be more effective on well-oxygenated tumour cells than on those that have been devascularised by resection.
3. The risk of tumour cells shedding during surgical manipulation also may be decreased if the tumour has been pretreated.
4. Perhaps the most compelling reason for treating patients with neoadjuvant therapy is that the treatment period offers a window for occult metastatic disease to become detectable [8].
5. De novo resection of cancers that infiltrate to the left-lateral aspect of the SMV/portal vein have a high risk for margin-positive resection and a particularly poor prognosis with or without concomitant venous resection in the absence of preoperative therapy.
6. 23-79% of patients enrolling in neoadjuvant trials ultimately undergo surgical resection with median overall survival rates as high as 34 months for resected patients.

The current neo-adjuvant protocols include 5-FU or Gemcitabine monotherapies or their combinations or FOLFIRINOX with or without external beam

radiation. Objective radiographic responses are rare and downstaging to resectable tumours is exceedingly rare [3]. Nonetheless, a single retrospective study showed that, up to 66% of patients may undergo tumoour resection with a 95% rate of R0 resection [9].

Staging Laparoscopy

It should always precede pancreatectomy if CA 19–9 level is ≥150 U/ml and tumour size ≥3 cm, since it may reveal occult metastatic disease in 31% of patients.

Surgical resection

Unfortunately, only 15%–20% of patients are suitable candidates for surgery [15], either due to locally advanced disease or because of synchronous distant metastases. Pancreatic tumour frequently extends directly into the retroperitoneal spaces and involves the superior mesenteric vein–portal vein (SMV-PV) [15]. In an effort to improve life expectancy, in many centres a more aggressive approach has been employed, involving SMV-PV resection (VR) in view to increase the curability of pancreatic cancer [15].

Venous resection and reconstruction should be performed for borderline resectable tumours involving the SMV/portal vein as long as "reasonable venous inflow and outflow is present and the surgeon feels that an R0 or R1 resection likely can be accomplished" [10,15]. When such operations are performed at high-volume institutions, survival rates become similar to those for patients undergoing pancreaticoduodenectomy without venous resection [11]. Despite apparent intraoperative tumour adherence to the vein, only 60- 70% of specimens will show histopathologic evidence of venous invasion11. Those that do, however, have poorer prognosis [12].

Hepatic arterial resection and reconstruction during pancreaticoduodenectomy for borderline resectable pancreatic cancer may be reasonable in highly selected patients treated at specialty centers experienced in vascular reconstruction [6,15]. Resection of the SMA as part of a pancreaticoduodenectomy, however, is associated with high morbidity rates and is thus not recommended [13,15].

Adequate regional lymphadenectomy means at least 15 nodes harvested [6,15]. Lymphadenectomy should routinely include periduodenal and peripancreatic nodes as well as those to the right of the hepatoduodenal ligament and the superior mesenteric artery (SMA) and the anterior and posterior pancreaticoduodenal lymph nodes. Prospective, randomised trials have shown that extended lymphadenectomy offers no survival benefit and may result in lower quality of life than standard lymphadenectomy [14].

The surgical margin most likely to be positive is the SMA margin (the retroperitoneal margin) [10]. NCCN guidelines recommend "skeletonisation of the SMA down to its adventitia anteriorly, laterally, and posteriorly to minimise the risk of a positive margin in this location"[6].

Pancreatoduodenectomy with portal vein/superior mesenteric vein reconstruction (PD-VR):

The first case of pancreatectomy with VR was reported by Moore et al. in 1951. In recent years, VR can be safely performed [15]. However, arterial resection in pancreatectomy remains a challenging procedure with significantly high morbidity and mortality rates [13,15].

Although duration of Whipple's procedure along with vascular reconstruction is longer and operative blood loss is greater in such cases, mortality and morbidity rates are comparable between the two groups (3.3% and 41.9% respectively) [15]. It is reasonable to assume that as a surgeon's experience increases, operative time and blood loss will likely decrease [6]. Results from two prospective randomised studies showed that the surgery group had significantly better survival than the palliative gastrobiliary bypass group or radiochemotherapy group [15,16]. Furthermore, the overall survival did not differ between operation with VR and without [15]. As quoted by Tempero et al. "this is consistent with the hypothesis that tumour with portal vein adherence or invasion may represent a function of tumour location, and possibly tumour size, rather than an indicator of aggressive tumour biology" [6]. Moreover, as Lygidakis et al. have marked, "tumour extension to the SMV-PV does not necessarily indicate tumour invasion" [16]. Perhaps remarkably, on the most recent meta-analysis on SMV-PV reconstruction for borderline pancreatic cancer [14], histopathology evaluations revealed that "a considerable percentage of patients (43.1%) who underwent VR for pancreatic cancer were found to have inflammatory adhesions without cancer invasion".

The depth of SMV-PV wall invasion is an indicator of poor outcome after PD-VR, since mesenteric vessels resected en bloc with the lesion on macroscopic grounds carry documented worse prognosis if the vessel walls prov to be infiltrated by malignancy rather than having been thickened by the the pericancerous fibrosis. However, it is difficult to differentiate malignant from inflammatory adherence of the SMV-PV pre-operatively since detecting the precise site of tumour infiltration is only possible by histopathological analysis [16].

Principles of surgical technique

A thorough description of the current surgical approach advocated by the American College of Surgeons is the one eloquently described by Weitz et.al, who comment [18]: "In an effort to achieve complete resection of a pancreatic head cancer, resection of the portal vein, the superior mesenteric vein, or both, needs to be performed if there is suspected invasion of the venous wall. To adhere to the principles of oncologic surgery, this resection should be performed without violating the integrity of the tumour. The key components of the technique are early identification of the superior mesenteric artery, which serves as a guide throughout the resection, complete mobilisation of the right hemicolon and mesenteric root if necessary, and control of all vascular structures, with resection of the portal vein, pancreatic head, and tumour as the last part of the resection phase" [18]. A trial dissection along the portal vein or shaving the tumour off the portal vein during resection, with separate resection and reconstruction of

the involved part of the portal vein, should be avoided at all costs; transecting across tumour may result in a higher rate of tumour recurrence" [18], Weitz et al warned.

Management in high-volume centres

As Evans et. Al [10] quoted: "the tide of literature is moving in a direction supporting better outcomes in higher-volume centers for patients with pancreatic cancer" [10]. That being said, specifically addressing the issue of vascular resection and reconstruction, it remains to be proved if management in such centres will ensure optimised results: "venous involvement remains difficult to ascertain in many patients, thus, if the surgeon is unprepared for venous involvement or is unfamiliar with the techniques necessary to adequately treat these patients, then substandard care will result". "In this situation, one of two outcomes may occur: either the resectable patient fails to get a potentially therapeutic procedure altogether or a technically inadequate operation occurs, resulting in a grossly positive margin or marked morbidity".

Conclusions

Pancreatic tumour resection remains the mainstay of therapy for physiologically and surgically eligible patients [10]. "Coupled with improvements in imaging, more consistent classification schemes and the use of nonsurgical adjuvant therapies", the major achievements of our era in the battle against pancreatic cancer have been "extension of potentially curative resection to those previously considered ineligible" [10]. Evolution in therapy may have improved survival by allowing treatment of previously untreatable patients or by downstaging patients with more advanced disease such that their outcomes are similar to disease at an earlier stage.

Several reports demonstrate equivalent morbidity and mortality for patients undergoing PD with or without vascular resection [10]. It is important to note that reports of vascular resection generally come from larger or high-volume centers. "Unlike extended lymphadenectomy where no survival benefit exists, vascular resection allows complete tumour clearance (R0 resection) when this would otherwise be precluded" [10].

In terms of surgical technique, "the key to portal vein resection for advanced pancreatic cancer is the superior mesenteric artery" [18]. "Dissection on the right and posterior aspect of this artery guides the surgeon through the critical part of the procedure and helps to achieve a complete tumour resection without violating the integrity of the tumour" [18].

Based on all data available, PV/SMV resection and reconstruction is the current standard of care during a pancreatoduodenectomy when there is a reasonable expectation for an R0 resection. PD with portal venous reconstruction is justified since it may result in R0 resection and long-term survival comparable to that obtained with standard resection.

All these remarkable achievements in surgical approach and chemoradiation put aside, overall improvements in survival have remained elusive, unfortunately only strengthening the notion that tumour biology continues to be the most significant factor influencing these patients' outcomes. ●

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Understanding Breast Cancer Survival with Epidemiology

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There is convincing evidence to suggest that lifestyle factors are important in both the development and progression of breast cancer, and a significant number of cases may be prevented if diet, activity and weight modifications were adopted by appropriate groups of individuals [1]. The American Institute for Cancer Research [2] estimates that approximately 38% of breast cancers may be preventable, yet concurrently 49,564 and 397 cases of female and male breast cancers respectively were reported in 2010 and almost 11,600 patients succumbed to the disease in the UK that same year [3]. Considerable efforts to understand these statistics and to develop Public Health measures targeting decreasing incidence and mortality rates are on-going, yet recent evidence suggests that there is still much work to be done [4].

The role of epidemiology in understanding how diet and lifestyle affect breast cancer outcomes

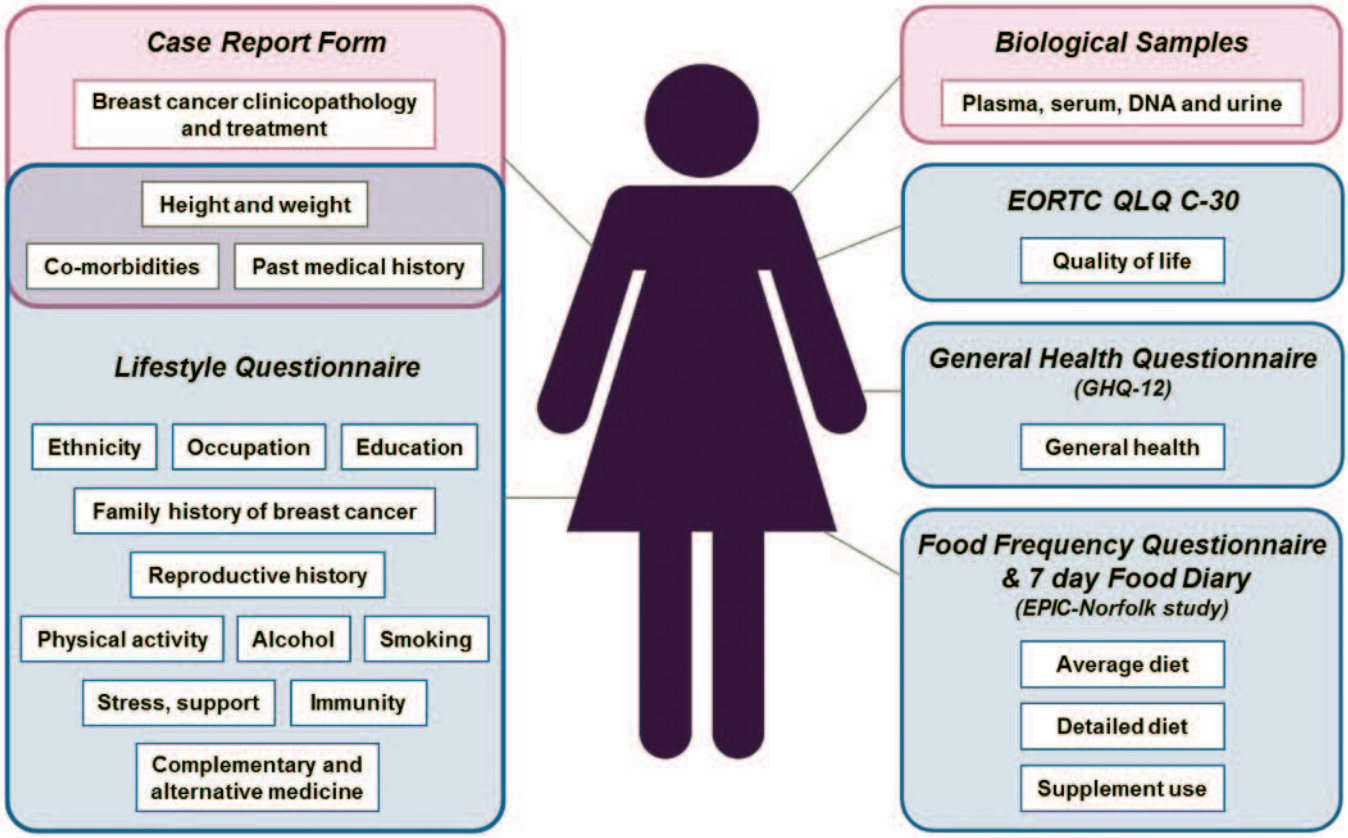
In vitro and *in vivo* studies have been key to our understanding of cancer pathology and prognosis. Controlled laboratory investigations clarify how cancer-causing substances (for example: tar, benzene, arsenic and nitrosamines) cause DNA damage and subsequently affect cellular behaviour. Molecular approaches such as those concerned with genome wide analysis, epigenetic, transcriptomic and proteomic changes have started to explain some of these discrepancies, but the role of environment remains a particularly complex area of research. Prospective observational studies of heterogeneous populations in free-living settings have shown that biological adaptations observed in lab-based studies explain only a fraction of cases (for example up to 30% of lung cancer; [5]). Where effects are convincing (and large), the importance of human risk assessment is clear; but the path to discovery of cause and effect where effect sizes are smaller, and perhaps less consistent, is challenging.

Utopia for risk factor epidemiology in breast cancer research would be formulation of prevention and management strategies integrating the best available evidence and linked to measureable health outcome improvements. Patients are however variably exposed (and reactive) to many diverse factors prior to and following a diagnosis of breast cancer. Determining their individual and collective influences on disease-related risk constitutes "a much duller scalpel" [6] than consideration of results obtained from randomised controlled trials. We must acknowledge however that biomedical research is unlikely to address the challenges of either genetic or biological susceptibility to cancer, unless careful consideration of socio-demographic and behavioural factors (among others) is made [7].

Estimates of the population risk of developing cancer must be considered in the context of diverse biological and environmental information. It is clear that exposure to environmental factors must precede the disease outcome. Therefore, the challenge for research teams aiming to elucidate the effects of exposures – both singly or combined (in the so-called 'eposome') – is how best to control for errors including (but not limited to) incomparable diagnostic methods, mis-reporting errors (a particularly relevant issue when quantifying dietary intake estimates and reports of lifestyle habits), biological plausibility, specificity, and consistency. Epidemiology is thought to hold the key to formulation of dietary and lifestyle recommendations, yet interpretation of our work – by all that use it – requires rigour.

It is acknowledged that exposure to risk factors does not remain static: most, if not all, vary within the general population. Action on Smoking and

Figure 1: A complex picture of breast cancer patient diet and lifestyle is collected in the DietCompLyf study. Pink boxes show the information and samples collected by the Study Centres, the blue boxes show information reported by the patients to the coordinating centre.



Health [8], for example, estimates that within the UK population, 22% of adult men, 19% of adult women and 32% of those aged 25-35 years smoke. Those in lower social classes smoke more, and regional differences in smoking prevalence are also apparent and relevant. Whether an individual who drinks/smokes infrequently would classify themselves as a drinker/ smoker is subjective and highly variable within and between populations, and from one day to the next. These statistics serve merely to highlight the complexity of factors which scientists must consider in the development of data capture and presentation methods, in quantification and interpretation of biological and lifestyle factors. In essence, to ensure precise and reliable data is captured, enabling confidence in cause and effect associations identified, scientists must "...ensure that they conduct their work with honesty and integrity; to ensure that methods and results are reported in an accurate, orderly, timely and open fashion..." [9].

The World Cancer Research Fund [1] and AICR [2] convene an independent panel of world-renowned experts to consider research evidence on modifiable lifestyle factors including food, nutrition, physical activity and body composition and their relevance to both cancer prevention and disease progression. Where research evidence is convincing, the effects of specific factors on the risk of breast cancer development and recurrence is summarised into a series of recommendations, enabling consistent delivery of sound and substantiated advice by professionally governed health care workers. As part of the Continuous Update Project (CUP), newly published research evidence is reviewed and guidance is updated as necessary [1].

Using epidemiology to inform public health strategies

Health promotion campaigns have successfully been used to target changes in diet and lifestyles, where there is a strong evidence-base to rationalise the need for change. For example: smoking cessation and reduced risk of lung cancer [10], folic acid supplementation and the prevention of neural tube defects [11]. Ajzen and Madden [12] theorise that intentions are 'plans of action in pursuit of behavioural goals' and that compliance may be motivated by the strength of the evidence outlining the benefit of changes.

The evidence base outlining how diet and lifestyle choices may influence breast cancer survival statistics is not yet conclusive. The latest WCRF/AICR Report (2007) gives no specific dietary guidelines at all for cancer survivors beyond "... measures that control body weight may help prevent recurrence, at least of breast cancer" and yet patients want to know what they can eat and what they can do to improve their long-term outcomes. Government policies are clearly needed to facilitate this. AICR/ WCRF (2007) quantify that for each 5kg of weight gained, the risk of developing post-menopausal breast cancer elevates by 5% and risks associated with overweight are

not limited to cancer. *The Healthy Lives, Healthy People* White Paper [13] suggested that an obese woman (BMI ≥30 kg/m^2) is almost 13 times more likely to develop diabetes, more than four times more likely to develop high blood pressure and more than three times more likely to have a heart attack than a non-obese woman (BMI <30 kg/m^2). Worryingly, data published by the Health and Social Care Information Centre (2013) highlighted that 65% of UK adults were classified as overweight or obese (BMI >25 kg/m^2) and only 34% of a normal weight in 2011. If the results from the Government 'Our health, your care, your say' report [14] are representative, patients want to modify their behaviour to prevent the recurrence of cancer and increase their overall health to and to avoid co-diagnosis with other non-communicable diseases (e.g., type 2 diabetes, hypertension), but there is a long way to go before this will be achieved.

We must acknowledge that neither a cancer cell nor the environment in which it is located is a static entity. Drugs used in cancer treatments, the hormonal status of the patients, their diets and nutrition are features which could change the outcomes following a breast cancer diagnosis [15]. Ioannidis [4] highlights an apparent inability for promising results observed in randomised controlled trials to be translated into large scale, population studies and acknowledges that a "quick fix" answer cannot be expected. Randomised clinical trials are prohibitively slow and expensive for the investigation risk factors for cancer, and 'controlled' environments are not realistic for the investigation of long-term outcomes. We must therefore rely on the careful design of case control or cohort studies of large populations. Such projects must also rely on existing evidence of influencing factors, both to ensure collection of relevant information, and to enable appropriate statistical analysis of the effect sizes.

Recruiting a fully representative sample of a complete patient group is not without difficulty, however, and socio-economic, ethnic and cultural variability may affect the utility of results obtained. Confounding biases and measurement errors must be carefully considered when interpreting results from epidemiological studies and biological plausibility must be the cornerstone.

DietCompLyf, an observational study of diet, lifestyle and breast cancer outcome, considered the issues outlined above within its design. The heterogeneity of breast cancer diagnoses alongside the variable influences of patient demographics, clinical decision making, molecular and phenotypic features of the cancer are being considered in a cohort of 3,157 UK women with primary invasive (non-metastatic) breast cancer [16]. Patients were recruited onto the study 12 months (±3 months) post-diagnosis and are (or have been) being actively followed up for 5-years, enabling a plethora of data to be captured and quality control checked prior to exploration of whether diet and lifestyle modifications can influence long-term survival rates for breast cancer patients. 'Diet' is being evaluated comprehensively, using patterns of consumption as well as estimation of individual nutrient intakes calculated from records of food only and from 'food and dietary supplement' use. DietCompLyf is one of the largest studies of lifestyle behaviours and breast cancer survival worldwide [17], and the only such study in the UK. While our cohort does not perhaps contain the 100,000 individuals or 50 years of follow up desired by Ioannidis (2013), the integrity of this – like several other – research group is to utilise epidemiological methods carefully, aiming to advance understanding through observation and exploration of our patients' experiences enabling translation of knowledge into influential recommendations for patients. ●

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The Lancet

Risk of venous thromboembolism associated with peripherally inserted central catheters: a systemic review and meta-analysis

Chopra V, Anand S, Hickner A, Buist M, Rogers MAM, Saint S and Flanders SA. The Lancet 2013;382(9889):311-25.

The relative risk of the development of venous thromboembolism from peripherally inserted central catheters (PICC) and other central venous catheters (CVC) is unknown. More evidence should aid appropriate selection of the device and informed consent for a specific patient according to his or her need and preference. A systemic review and meta-analysis of the risk of venous thromboembolism associated with PICCs compared with CVCs has been undertaken. Several databases, including Medline, Embase, Biosis, Cochrane Central Register of Controlled Trials, Conference Papers Index and Scopus were searched. Other studies were identified through manual searches of bibliographies, the internet, and direct contacts (to obtain unpublished data). All human studies published in full text, abstract, or poster form were eligible for inclusion. These were of adult patients of 18+ years who had had a PICC inserted. They were assessed with the Newcastle-Ottawa risk of bias scale. Where there was no comparison group, the pooled frequency of venous thromboembolism was calculated for patients receiving PICCs. In studies comparing PICCs with other CVCs, summary odds ratios (ORs) were calculated with a random effects meta-analysis. Of the 533 identified citations, 64 (12 with a comparison group and 52 without) including 29 503 patients met the eligibility criteria. In the non-comparison studies, the weighted frequency of PICC-related deep vein thrombosis was highest in patients who were critically ill (13·9%, 95% CI 7·7-20·1) and those with cancer (6·7%, 4·7-8·6). Meta-analysis of 11 studies comparing the risk of deep vein thrombosis related to PICCs with that related to CVCs showed that PICCs had an increased risk of deep vein thrombosis (OR 2·55, 1·544·2, $p<0·0001$), but not pulmonary embolism. With the baseline PICC-related deep vein thrombosis rate of 2·7% and a pooled OR of 2·55, the number needed to harm relative to CVCs was 26 (95% CI 13-71). We conclude that PICCs are associated with a higher risk of deep vein thrombosis than CVCs, especially in patients who are critically ill or those with a malignancy. The decision to insert PICCs should be guided by weighing the risk of thrombosis against their benefit.

Reviewer's opinion: The meta-analysis results and comprehensive overview on the subject of "intravenous catheter use and the risk of associated complications" presented by the authors is plausible. Use of these devices has increased many folds in oncology over the last decade, particularly PICC, being easier to insert. After rigorous structured training, the procedure is mostly done by chemotherapy nurses and relatively junior medical staff. Identification of a higher incidence of PICC-associated deep vein thrombosis compared to central venous catheters identified in the meta-analysis could be due to these catheters being longer, increasing venous endothelial trauma, but the risk factors and safety measures need more assessment. Despite the inclusion of several unpublished data in this article, the authors should be congratulated because it is highly unlikely that a randomised controlled prospective study on the subject will be conducted. The evidence presented is compelling and consistent across all the studies included within their meta-analysis. Unfortunately, currently available pharmacological measures do not provide reasonable protection against thrombosis.

Risk assessment, fully informed consent and optimum precautions, like avoidance of misplacement of the tip of the catheter, must be undertaken when these devices have to be inserted. – SU

New England Journal of Medicine

Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma

Motzer R J, Hutson T E, Cella D et al. New England Journal of Medicine 2013;369(8):722-31.

Pazopanib and sunitinib provide a progression-free survival (PFS) benefit compared with placebo or interferon in patients with metastatic renal-cell carcinoma. This randomised trial compared head-to-head, the efficacy and safety of pazopanib and sunitinib as first-line therapy. In this multi-centre, phase III study, 1110 patients with clear-cell metastatic renal-cell carcinoma were randomised in a 1:1 ratio to receive a continuous dose of pazopanib (800 mg once daily; 557 patients) or sunitinib in 6-week cycles (50 mg once daily for 4 weeks, followed by 2 weeks without treatment; 553 patients). The primary end-point was PFS, the study being designed to show that pazopanib was not inferior to sunitinib. Secondary end-points included overall survival, safety and quality of life.

Pazopanib was not inferior to sunitinib with respect to PFS (HR for PFS or death from any cause, 1.05; 95% confidence interval [CI], 0.90 to 1.22), meeting the predefined non-inferiority margin. Overall survival was similar (HR for death with pazopanib, 0.91; 95% CI, 0.76 to 1.08). Patients treated with sunitinib were more (i) fatigue (63 vs. 55%), hand-foot syndrome (50 vs. 29%) and thrombocytopenia (78 vs. 41%); and those treated with pazopanib more often had increased ALT (60 vs. 43%), weight loss, alopecia and change of hair colour. The mean change from baseline in 11 of 14 health-related quality-of-life domains, particularly those related to fatigue or soreness in the mouth, throat, hands, or feet during the first 6 months of treatment, favoured pazopanib ($P<0.05$ for all 11 comparisons). Thus, pazopanib and sunitinib have similar efficacy, but the safety, quality-of-life and patient satisfaction with treatment profiles favoured pazopanib.

Reviewer's opinion: Side effects and its impact on quality of life (QOL) are important considerations for both patients and their clinicians in the management of advanced cancers. It (QOL) takes precedence when different therapies have similar efficacies (response rate, PFS and OS), but significant differences in their side effects for some of the patients. The results of a COMPARZ trial clearly establish the superiority of pazopanib over sunitinib, the reference standard on this front. Both drugs are multi-targeted TKI with similar efficacy, which is reassuring for patients and their clinicians. It allows them to choose the most appropriate agent. However, non-inferiority is not synonymous with equally efficacy. One of the most pertinent points is that pazopanib was superior on 11 out of 14 measures of QOL. Pazopanib has already been recommended by the NICE as first-line treatment for patients in the UK with advanced kidney cancer, since GSK officials had agreed to a 12.5% discount on the list price and possibly a second rebate following the outcome of COMPARZ. Lower medical resources need, e.g. fewer phone calls to clinics and visits to hospitals due to better tolerance, will favourably influence when cost-benefit issue have been reconsidered by the authorities. – SU

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

March

Vascular Access & PICC Training
10 March 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

10th Palliative Care Congress
12-14 March 2014; Harrogate, UK
T: +44 (0)1489 565 475
E: info@compleatconference.co.uk
W: www.pccongress.org.uk

SSO 2014 Annual Cancer Symposium
13-15 March, 2014; Arizona, USA
W: www.surgonc.org

National Breast Oncoplastic Study Day
17 March 2014; London, UK
W: www.royalmarsden.nhs.uk

The Management, Treatment & Future Perspectives of Cancer of Unknown Primary
21-22 March 2014; London, UK
W: www.cupfoundjo.org

Specialist Palliative Care
24 March 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

Bladder cancer
25 March 2014; London, UK
W: www.rcr.ac.uk/oncologyevents
E: conf@rcr.ac.uk

NEW
Annual Marie Curie Palliative Care Research Conference
28 March 2014; London, UK
W: www.rsm.ac.uk/palliative

Pancreatic, Hepatobiliary & Neuroendocrine Tumours
31 March 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

April

Survivorship: Changing Prospects for Cancer
4 April 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

105th AACR Annual Meeting
5-9 April, 2014; San Diego, California
W: www.aacr.org

Intensive Revision Course for MCEM Part A Exam
12 April 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

The Edinburgh MRCS Exam Preparation Course
12-13 April 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 European Congress on Head and Neck Oncology
24-26 April 2014; Liverpool, UK
W: http://echno2014.com/

Gastrointestinal Masterclass
28-29 April 2014; Leeds, UK
W: www.rcr.ac.uk/oncologyevents
E: conf@rcr.ac.uk

May

Skin Cancer of the Head & Neck
1 May 2014; Utrecht, the Netherlands
W: reconstruction-skin-cancer.com

NEW
Current Issues in Palliative Care 2014, 9th national conference
8-9 May 2014; London, UK
W: www.mahealthcareevents.co.uk

NEW
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

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

NEW
Advanced Leadership
19 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

NEW
Association of Breast Surgery Conference & AGM
19-20 May 2014; Liverpool, UK
W: 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

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

NEW
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
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

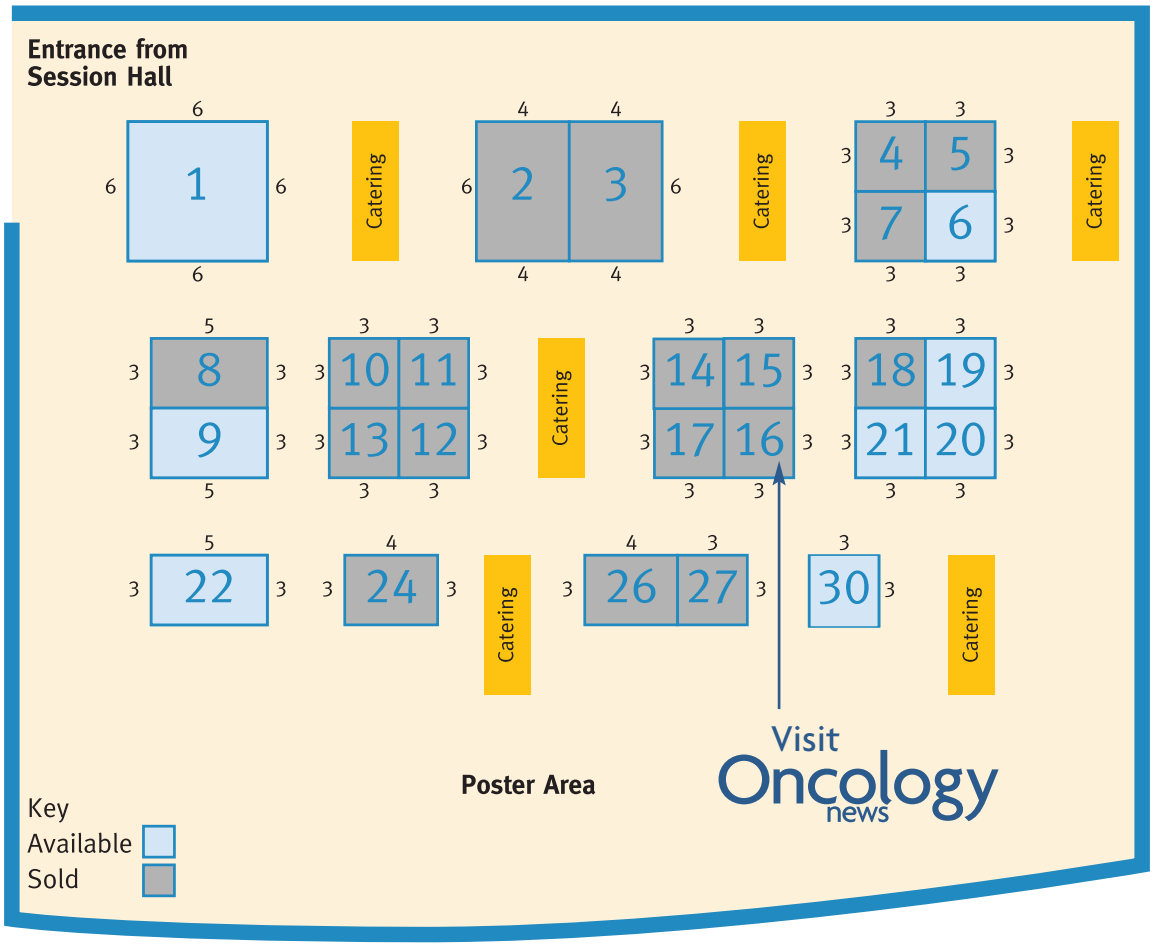
Camstrand Research Conference
17-18 June 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

NEW
ABS Trainees Meeting
19-20 June 2014; Glasgow, UK
W: 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

Exhibition Floor Plan



Company	Booth #
Azanta	26
BAHNO	Table Top
Caris Life Sciences	5
CEL-SCI Corporation	10
Ceredas	7
COOK Medical	17
Depuy Synthes	24
DP Medical Systems Ltd	27
EUSA Pharma (Europe) Ltd.	12
Exmoor Plastics	4
IGEA Medical UK	11
Karl Storz GmbH &Co KG	18
Lumenis	8
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IMPAKT
BREAST CANCER CONFERENCE

IMProving cAre and
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Translational research

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BREAST CANCER TRAINING COURSE

Focus on Translational Research

7-8 MAY 2014
Brussels, Belgium

IMPAKT 2014 CHAIRS:

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THE PRE-IMPAKT EARLY CAREER TRAINING COURSE IS DESIGNED FOR EARLY TO MID-CAREER ONCOLOGISTS AND RESEARCH SCIENTISTS.

IMPORTANT DEADLINES:

26 February 2014	Early registration and training course application
09 April 2014	Late registration and pre-registration closure

Organisers

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GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
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European Society of Breast Cancer Specialists

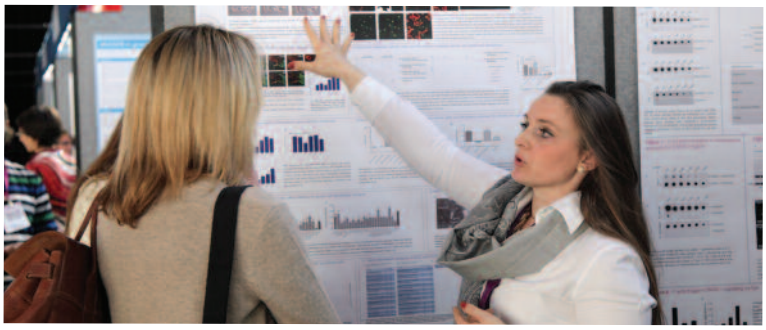
EORTC
European Organisation for Research and Treatment of Cancer

– 10th –
NCRI
Cancer
Conference

2014

2–5 November 2014
BT Convention Centre, Liverpool, UK

Submit your abstract by 4 June 2014



31 March – 4 June
Abstract submission

7 April – 31 July
Earlybird registration

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- Diagnosis and therapy
- Epidemiology and prevention
- Health service research
- Information, patients and the public
- Survivorship and end of life care

conference.ncri.org.uk

Celebrating the 10th NCRI Cancer Conference

BNOS 2014 Liverpool

Contemporary Approaches to Paediatric and Adult Brain Tumours

Wednesday 9th – Friday 11th July 2014

Symposia:
BNOS Main Meeting:
Contemporary Approaches to:
– Clinical Management
– Molecular Characterisation
– In vivo and in vitro models
– Molecular Neuropathology
– Radiology In Adult and Paediatric Brain Tumours

Nursing/AHP Symposium:
Contemporary approaches to clinical care of adult and paediatric patients with brain tumours

- **Abstract submission closes 21st March**
- **Registration opens 1st April**
- **Registration with accommodation – CLOSES – 31st MAY 2014**

British Neuro-Oncology Society

Venue: LJMU The John Lennon Art & Design Building

Accommodation: Vine Court, University of Liverpool or Hotels

The British Neuro-oncology Society is the only UK multidisciplinary society dedicated to advances in research and the treatment of adult and paediatric brain tumours. Our annual meeting attracts delegates from all clinical neuro-oncology specialties (including representatives from neurosurgery, neurology, neuroradiology, neuro-oncology and neuropathology), clinical nurse specialists, charities and basic scientists leading the field in neuro-oncology research.

For programme and meeting details see www.bnos.org.uk.

WE ARE MACMILLAN. CANCER SUPPORT

University of Salford MANCHESTER

The Christie School of Oncology

The Changing Prospects for Cancer

New models of aftercare for those living with and beyond cancer

Friday 4th April 2014

The Lowry, Media City, Pier 8, Salford Quays, M50 3AZ

Introduction

As the National Cancer Survivorship Initiative (NCSI) vision for cancer survivorship begins to become a reality for patients, professionals and commissioners, this conference will explore some of the fundamental issues and controversies that are beginning to emerge.

The conference will bring delegates together to debate possible solutions.

Suitable For:	Everybody welcome, including clinicians in NHS services including cancer, primary and community based services, commissioners, and managers involved in service delivery and improvement
Study Day Fee:	£150 or £125 Early Bird (If booked before Monday 3rd March 2014)
Further Info:	Visit www.christie.nhs.uk/school-of-oncology or e-mail education.events@christie.nhs.uk

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

Association of Breast Surgery Conference & AGM

Date: 19-20 May 2014. Venue: Liverpool, UK. **Preview**

The Association of Breast Surgery Conference & AGM will be held on the 19th & 20th May 2014 at the ACC Liverpool. The ABS was founded in 2010 and is continuing to grow and enhance its reputation as the voice of Breast Surgery in the UK, representing healthcare professionals treating malignant and benign breast disease for the benefit of their patients.

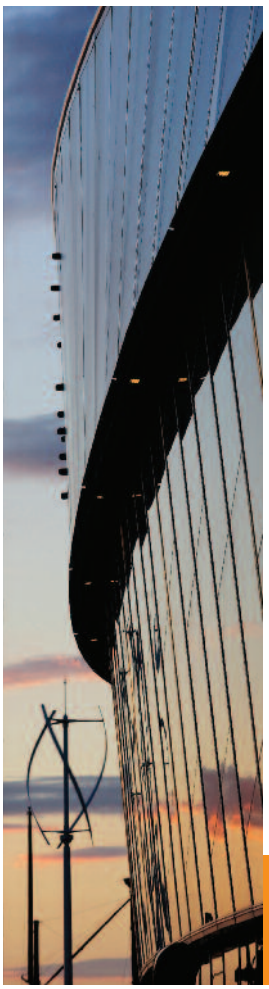
The ABS Conference & AGM is the Association's main meeting of the year and in 2013 attracted 850 delegates and 40 exhibitors. The meeting is multidisciplinary and is attended by surgeons, nurses, oncologists, radiologists, QA and audit staff.

Guest Lecturers for 2014 include:

- Prof Kelly Hunt, MD Anderson Cancer Center, Houston, Texas ***Local-regional therapy in the setting of neoadjuvant chemotherapy***
- Prof Emiel Rutgers, Netherlands Cancer Institute, Amsterdam
  Is there an increasing role for PET-CT scanning in the management of breast cancer?

Symposia include:

- Management of breast cancer in the older patient: Age is just a number
- Moving forward with familial breast cancer



- Addressing overtreatment
- Oncoplastic breast surgery
- Biological factors in breast cancer behaviour and treatment
- Update on axillary management
- The reality behind information giving and treatment choice
- New technologies and techniques
- Clinical research and professional development
- Survivorship
- Nursing hot topics
- Putting learning into nursing practice
- Commissioning, tariffs and coding explained

There will also be the annual presentation of the NHS BSP & ABS Audit of Screen Detected Breast Cancers in a session focusing on breast cancer audits and individual surgical performance.

Abstract submission for the conference has closed with over 300 abstracts being submitted. There will be submitted paper sessions, including a BJS Prize session, and over 180 poster presentations.

The Annual Dinner will be held at St George's Hall on Monday 19th May, allowing members and non members to socialise with colleagues from across the UK and elsewhere. A drinks reception will be held at the Bluecoat on the evening of Sunday 18th May for delegates travelling to Liverpool the night before the conference.

Visit: www.associationofbreastsurgery.org.uk or email Jackie Spencer-Smith on jackiespencersmith@absgbi.org.uk

WIN 2014 Symposium

Date: 23-24 June 2014. Venue: Paris, France. **Preview**

The next annual WIN Symposium promises to become an exceptional global event entirely dedicated to breakthrough biomarker investigations and combination therapies for cancer. Major developments in precision cancer medicine will be addressed in sessions featuring basic and clinical cancer research on:

- Molecular analysis of immune cells and immunotherapy, with keynote lecturer Guido Kroemer, (France)
- What can we learn from hemato-oncology?, with keynote lecturer Bob Löwenberg, (Netherlands)
- Innovative therapeutic initiatives and models of cooperation: Denis Lacombe (Brussels); Jean-Charles Soria (France)
- Tumour cell plasticity and drugable targets: special keynote lecture by Robert Weinberg (USA)
- Combination of targeted therapies, with keynote lecturers: Hans Clevers (Netherlands); René Bernards, (Netherlands)
- New findings in fundamental mechanisms in pediatric solid and liquid cancers, with keynote lecturer Stefan Pfister (Germany)
- Blood and body fluids – non-invasive investigations in oncology, with keynote lecturer Leroy Hood (USA)

Scott P. Serota, President and CEO of Blue Cross and Blue Shield Association (BCBSA), will deliver the opening address on June 23. Mr. Serota has served BCBSA as president and CEO since 2000.

16th International Symposium on Pediatric Neuro-Oncology

Date: 28 June – 2 July 2014 Venue: Singapore **Preview**

The International Symposium on Pediatric Neuro-Oncology (ISPNO) is the major biennial global meeting of the multi-disciplinary international community of professionals involved in the research, diagnosis, treatment and rehabilitation of infants and children with brain tumours.

ISPNO has enjoyed consistent growth since its first meeting in 1986 with over 800 delegates drawn mostly from oncology, neurosurgery and radiation oncology. 16th ISPNO in 2014 will mark the third meeting of ISPNO in the Asian region, as well as the first time it returns to Asia since the 2004 meeting in Japan. The ISPNO meeting organisers are delighted to hold this meeting in Singapore in conjunction with the 8th St. Jude-VIVA Forum in Pediatric Oncology

This year is the first time ISPN (International Society of Pediatric Neurosurgery), the ESPN (European Society of Pediatric Neurosurgery), and WFNS (World Federation of Neurosurgical Societies) have collaborated in developing themes and content for multidisciplinary sessions aimed at boosting participation from both regional pediatric neurosurgeons and leaders in the international pediatric neurosurgery community.

It is also the first time the Pediatric Radiation Oncology Society (PROS), has formally joined the International Advisory Board to lead opinions and assist in the design of multidisciplinary sessions during the main ISPNO meeting. This meeting is expected to provide a unique opportunity to showcase the latest innovations in radiation oncology and diagnostic imaging as these disciplines are essential elements of therapeutic planning in patients with CNS tumours.

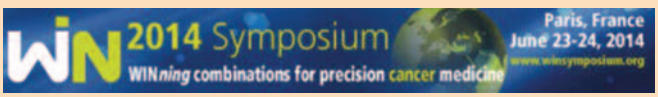
Throughout the entire symposium, attendees will also engage in dialog regarding new surgical treatments, innovative research and advances in pediatric neuro-oncology in a dynamic and interactive forum designed to significantly expand the knowledge base of attendees and further enhance overall patient care worldwide.

16th ISPNO in Singapore

Widely regarded as the leading conference destination in Asia, Singapore offers a safe and enriching experience in a bustling cosmopolitan setting with countless culinary and cultural experiences! Singapore is Asia's leading medical hub with a global reputation as a medical convention and training center, a fast-growing basic and clinical research hub and a center for regional referrals.

Held in Suntec Singapore Convention and Exhibition Centre (Suntec Singapore) from the 28 June – 02 July 2014, the 16th ISPNO will showcase the leading international advances in basic, translational and clinical research and also recent advances in addressing the global burden of pediatric central nervous system (CNS) tumours.

For more information on ISPNO 2014, please visit www.ispno2014.com.



The symposium's main themes – biomarker research and combinations of targeted agents for cancer – were identified on the basis of the observation that most patients' tumours are driven by multiple molecular aberrations that cannot adequately be controlled by a single anticancer agent. The major challenge is to identify and test smart combinations of targeted agents capable of blocking different pathways and molecular targets at the same time. Recent results of clinical studies and translational research will be discussed at the Symposium, including recent and ongoing studies of immunological agents and targets.

Scientists are welcome to submit abstracts of their research within the scope of the WIN 2014 Symposium and get the opportunity to present and discuss their research findings in a setting with global experts in cancer research and therapeutic innovation. The deadline for abstract submission is May 1, 2014. Go to www.winsymposium.org for more information, online registration and abstract submission.

The WIN Symposium is an annual meeting, attracting a broad variety of professionals in cancer research and patient management from around the globe. The Symposium is offered by WIN Consortium, the Worldwide Innovative Networking (WIN) Consortium (www.winconsortium.org) in personalised cancer medicine, which was initiated in 2010 with leadership from Institut Gustave Roussy (France) and The University of Texas MD Anderson Cancer Center (USA).

For more information about the WIN Symposium please visit www.winsymposium.org.

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

SonoSite embarks on a new era in training and education

SonoSite continues to lead the way in ultrasound education and training, opening a new UK Education Centre at Great Marlings, Luton, in October 2013. The purpose-designed training facility boasts a comfortable lecture theatre and superbly equipped training rooms, allowing delegates to gain valuable ultrasound experience using the most up-to-date equipment.

Courses cover a broad range of disciplines – including anaesthesia, critical care, emergency medicine, interventional procedures, musculoskeletal applications and visual medicine workshops – and practical demonstrations are supplemented with hands-on practice sessions, providing the perfect opportunity for participants to discover the potential of pointofcare ultrasound for themselves.

Professor Richard McWilliams, Consultant Interventional Radiologist at the Royal Liverpool University Hospital and director of the inaugural course on ultrasound-guided vascular access, commented: "It was a great pleasure to be course director for the opening session at the new Education Centre. The Centre is very bright and welcoming, and well equipped with the latest ultrasound systems and imaging phantoms,

providing a good environment for teaching and imparting technical skills to course participants."

For more information visit www.sonositeeducation.com/uk

Enhanced patient care at Paul Strickland Scanner Centre with new mCT system

Technology that would streamline workflow and keep dose to the most appropriate level was important to the Paul Strickland Scanner Centre, an independent medical charity based at Mount Vernon Hospital in London delivering specialist cancer care. That is why it has opted for a Biograph™ mCT hybrid PET-CT system from Siemens Healthcare.

The Biograph mCT is a hybrid PET-CT system that utilises Combined Applications to Reduce Exposure (CARE), optimising image quality at the right dose level. Combined with Fully Assisting Scanner Technologies (FAST), which simplifies and automates previously time consuming and complex procedures, the Biograph mCT is able to reduce dose and increase patient throughput.

"As a charity and one of the first centres in the UK to deliver PET scans to NHS district general hospitals, it is our aim to provide the community with the latest and most efficient imaging systems," states Margaret Sullivan, Chief Executive of the Paul Strickland Scanner Centre. "Patient comfort as well as confident diagnoses is our priority."

For more information contact Siemens Healthcare UK, T: +44 (0)1276 696 000, W: www.medical.siemens.com

Provectus's PV-10 path to initial approval in US now clear per FDA meeting minutes

Provectus Biopharmaceuticals, Inc. announced recently that it had received the official minutes from the Type C meeting held with the FDA's Division of Oncology Products 2 in December, 2013. The purpose of the meeting was to determine which of the available paths that Provectus's novel investigational oncology drug PV-10 will take in pursuit of initial FDA approval and commercialisation. PV-10, a 10% solution of rose bengal disodium, is designed to selectively target and destroy cancer cells without harming surrounding healthy tissue, while inducing a secondary tumour-specific immune response. As a result of this meeting, Provectus will submit data from its Phase 2 study in a formal breakthrough therapy designation (BTD) request this quarter, and should receive a decision within 60 days of receipt of that request.

With the passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) in July 2012, the Food and Drug Administration (FDA) was given powerful expedited tools to speed patient access to innovative medicines for serious or life-threatening conditions Food and Drug Administration Safety and Innovation Act (FDASIA)). FDASIA initiatives such as breakthrough therapy designation are designed to accelerate approval for new drugs that show preliminary clinical evidence of a large treatment effect. A key feature of BTD authorises the Agency to take steps to ensure that the design of the clinical trials are as efficient as practicable, when scientifically appropriate, such as by minimising the number of patients exposed to a potentially less efficacious treatment. Requests for BTD are reviewed and granted or rejected within 60 days of receipt. As Provectus has previously reported, based on rapid tumour destruction in a positive Phase 2 trial in melanoma patients receiving PV-10 (protocol PV-10-MM-02), input from the Agency regarding the current development plan was sought. Agency guidance (Frequently Asked Questions: Breakthrough Therapies) encourages sponsors to seek such advice prior to formal request for designation.

For further information visit www.pvct.com

More patients at Leeds Teaching Hospitals NHS Trust receiving advanced radiotherapy

A few months after Elekta unveiled its ground-breaking Versa HD™ system – which unites cutting edge beam shaping and High Dose Rate mode technologies – Leeds Teaching Hospitals installed two of the units, the first entering clinical service in July 2013, and the second in November 2013. Already, the first Versa HD has had a significant impact on clinical workflow. Up to 60 patients per day are scheduled for treatment on the new machine. Treatment slots are booked at 10-minute intervals, so that as many as six patients can be treated per hour.

"Initially, patients undergoing radical prostate radiotherapy have been prioritised for treatment, all with High Dose Rate mode VMAT," says Vivian Cosgrove, PhD, head of radiotherapy physics at Leeds. "In addition, the process to move all SBRT treatments to High Dose Rate mode VMAT has begun. Patients have their SBRT treatment scheduled to a 20-minute time slot on the Versa HD.

In September 2013, over 25 percent of all radical treatments were delivered in the Leeds Cancer Centre using IMRT and VMAT – equivalent to about 90 new patients starting advanced radiotherapy treatment every month. In addition, 20-25 new patients also start an SBRT course each month.

"This volume growth has been greatly enhanced by opportunities to develop the techniques, delivery equipment and workflow on the research accelerators, side-by-side with the clinical service," Dr Cosgrove added.

For further information contact
E: inquiries@elekta.com

Wear A Hat Day – get your hats on, hold an event, and raise money for brain tumour research

Calling all hospitals, clinics, and other medical centres, we're asking you to hold a Wear A Hat Day event on Friday 28th March and raise funds for vital scientific research into brain tumours.

Brain tumours are responsible for more loss of life in children than leukaemia, in women under 35 than breast cancer and in men under 45 than prostate cancer. Despite a decade of campaigning, brain tumours still receive less than 1% of the national spend on cancer research.

With your help we can change this. Wear A Hat Day is a great way to show your support and help raise the crucial funds and awareness needed. Full details are available from www.wearahatday.org, which provides an overview of the campaign, tells you how to register, and carries links to various resources that can be used to help promote and maximise the impact of your Wear A Hat Day event.

For further information contact
T: +44(0)1296 733011 or
E: wearahatday@braintumourresearch.org

First Gamma Knife Centre in South West opens in Bristol

Varian Medical Systems, a leader in radiation oncology equipment and software, has signed an agreement with the UK's National Health Service (NHS) to acquire an NHS-developed cancer care planning tool called the Radiation oncology Planning Online Resource Tool (R-PORT). Varian intends to offer R-PORT to oncology departments globally.

R-PORT has been used in the NHS in recent years to help control costs and manage electronic data. Under the terms of the agreement, Varian Medical Systems will add this tool to its extensive oncology services portfolio and develop and enhance it for worldwide use.

"R-PORT has helped oncology providers within the NHS network to model change management before incurring major costs," says Steve Laws, Varian's EMEA regional director of software sales. "It also measures the results and costs of change management for reporting purposes. It is highly synergistic with Varian's existing software portfolio and builds on Varian's mission to be a 'partner for life' – supporting our customers to deliver world class cancer care."

"At a time of rising costs, uncertainty concerning reimbursement and increasing numbers of cancer patients, healthcare providers worldwide are seeking solutions to help them deliver better patient care," says Scott Brouse, Varian's vice president of Worldwide Site Solutions. "This is a tool that can help Varian support our customers in the fight against cancer."

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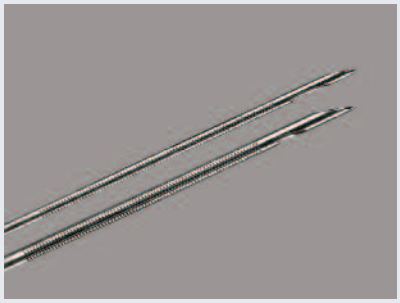
Cook Medical introduces EchoTip® ProCore™ Endobronchial Ultrasound Needle



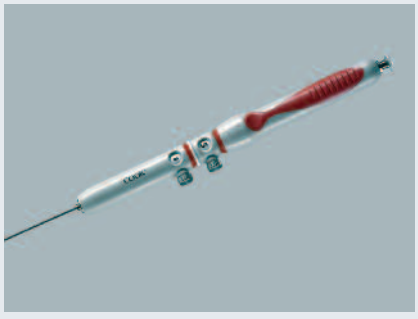
Cook Medical is introducing the first endobronchial ultrasound (EBUS) needle in Europe that can acquire histological samples. The EchoTip® ProCore™ Endobronchial Ultrasound Needle gives physicians the ability to retrieve both cell and tissue samples from lymph nodes or tumours in the pulmonary area.

The EchoTip ProCore EBUS needle is a single-use needle that collects cell and tissue samples in order for a physician to diagnose lung cancer and various mediastinal diseases. The needle can be used for fine-needle biopsy of lesions of submucosal and extramural lesions within or adjacent to the tracheobronchial tree or gastrointestinal tract.

Prior to the availability of the EchoTip ProCore EBUS needle, tissue samples from the pulmonary area could be obtained only by surgical methods. The EchoTip ProCore EBUS needle is designed with a core-trap technology that allows physicians to collect tissue samples through a minimally invasive procedure.

"Cook's ProCore technology has already proven itself in the GI endoscopic ultrasound space," said Barry Slowey, global leader of Cook Medical's Endoscopy division. "We hope that this technology will aid in quick and accurate diagnosis for patients."

For further information visit www.cookmedical.com



Paxman Coolers Ltd appoints a distributor for Australia & New Zealand

Paxman Coolers Ltd, the leading global expert in scalp cooling, has recently announced a distribution agreement for Australia and New Zealand. Paxman Coolers Ltd has signed an exclusive agreement with Regional Health Care Group (RHCG), a leading distributor of medical products in Australia and New Zealand. Paxman Coolers Ltd is dedicated to preventing chemotherapy-induced hair loss and the technology has been successful for thousands of patients throughout the world.

Under the terms of the agreement with RHCG, the Paxman devices will be available to Chemotherapy centres throughout Australia and New Zealand exclusively through RHCG.

"This will be an important addition to our portfolio. Within Australia & New Zealand there are over 15,000 people diagnosed with Breast Cancer alone. Scalp cooling is widely available in the UK and it should become the standard of care for ANZ patients," stated Neil Spence, National Marketing Manager of

Regional Health Care Group (RHCG). "We look forward to combining the Paxman technology with RHCG's extensive distribution network to give patients and care provider's access to the life-changing benefits possible with the Paxman device."

For further information visit www.paxman-coolers.com

Provectus announces PV-10's assessment for drug-drug interaction potential is subject of article published by *Xenobiotica*

Provectus Biopharmaceuticals, Inc., a development-stage oncology and dermatology biopharmaceutical company, and XenoTech, a preclinical CRO and pioneer in collaborative research surrounding in vitro drug metabolism and pharmacokinetics services, announced that an article describing a study to determine the potential of rose bengal disodium to cause drug-drug interactions has been published by *Xenobiotica*, a peer-reviewed scientific journal that publishes comprehensive research papers on pharmacokinetics (the study of distribution, metabolism, disposition and excretion of drugs). The published research indicated that the risk of PV-10 causing clinically relevant drug-drug interactions is likely minimal. PV-10, a 10% solution of rose bengal that is currently under clinical investigation as a novel cancer therapeutic, is designed to selectively target and destroy cancer cells without harming surrounding healthy tissue, minimising the potential for systemic side effects.

The study was undertaken prior to initiation of the now ongoing testing of PV-10 plus sorafenib (cohort 2) in a clinical trial of PV-10 intralesional injection in hepatocellular carcinoma patients taking a stable dose of sorafenib (ClinicalTrials.gov Identifier: NCT00986661). Sorafenib is a competitive inhibitor of cytochrome P450 (CYP) drug metabolism enzymes and is reliant on the UDP-glucuronosyltransferase (UGT) pathway for efficient clearance. CYP and UGT enzymes help to biotransform small lipophilic drugs like sorafenib into water-soluble excretable metabolites.

For further information visit www.pvct.com

Varian spotlights full range of products at Arab Health 2014 in Dubai

Varian Medical Systems recently demonstrated its full range of radiotherapy delivery systems and software at the Arab Health Congress in January 2014. The Varian booth (Sheikh Saeed Hall 1, booth No. S1–C40) featured the company's technology and products for radiotherapy, radiosurgery, brachytherapy, and proton therapy.

At the show, Varian announced a collaboration with Mediclinic International to equip the new Mediclinic City Hospital North Wing radiotherapy department in Dubai, which is expected to start clinical treatments in late 2015.

Full Range of Products

The latest version of Varian's TrueBeam™ platform for fast and precise radiotherapy and radiosurgery were on display, showcasing new image-guidance and precise patient positioning capabilities such as the PerfectPitch™ six-degrees-of-freedom couch, giving clinicians more angles from which to deliver treatments.

Visitors to the Varian booth learned more about the company's new Edge Radiosurgery™ treatment 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.

Varian also unveiled RapidPlan™ for Middle East customers, offering knowledge-based treatment planning capabilities aimed at helping to create complex RapidArc® volumetric modulated arc therapy and intensity-modulated radiotherapy (IMRT) treatment plans.

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Innovative partnerships pave the way for massive new funding programme for brain tumour research

Leading campaign charity Brain Tumour Research has announced ground-breaking collaborative partnerships with three new Brain Tumour Research Centres of Excellence.

The leading institutions embarking on innovative funding partnerships with the charity are:

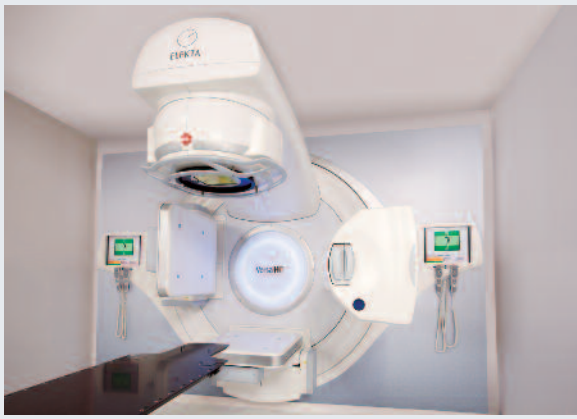
- Queen Mary University of London in collaboration with UCL Institute of Neurology, researching glioblastoma multiforme and identifying effective drug treatments.
- Imperial College Healthcare NHS Trust investigating tumour metabolisms and developing innovative 3D real-time surgical imaging.
- Plymouth University Peninsula Schools of Medicine and Dentistry conducting world-leading research into low-grade brain tumours.

This collaboration will lead to a £20m investment in brain tumour research over the next five years and will establish a network of research centres with secure long-term funding covering the key salaried positions.

The charity will shape research teams and priorities, ensuring all 120+ types of brain tumours are being researched, that the causes of brain tumours are discovered, that complex brain tumour behaviour is understood, and better treatments for all brain tumour patients are developed.

For further information please contact
Katie Abbotts, T: 07810 504380 or
E: media@braintumourresearch.org

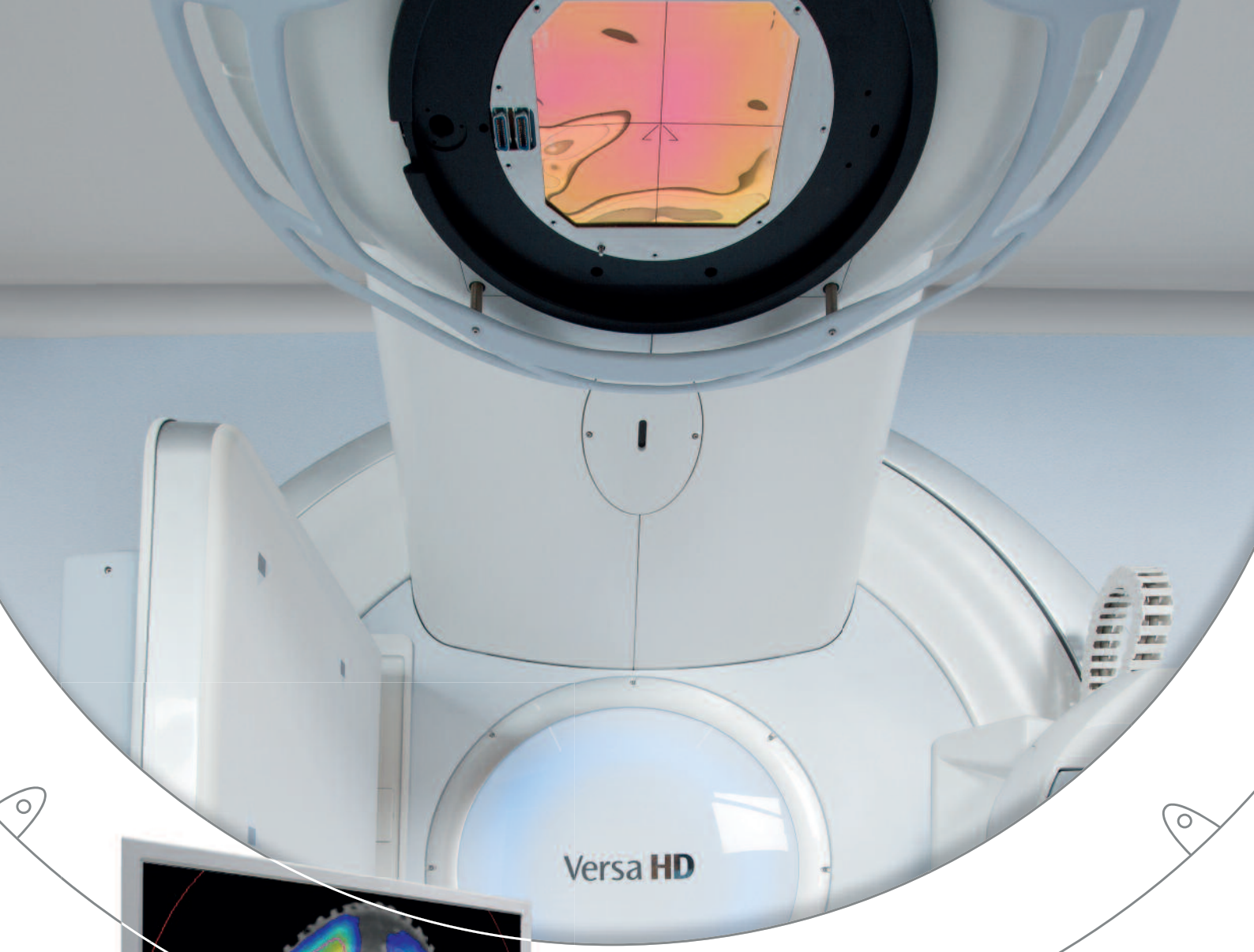
Elekta highlight their product range at ESTRO33

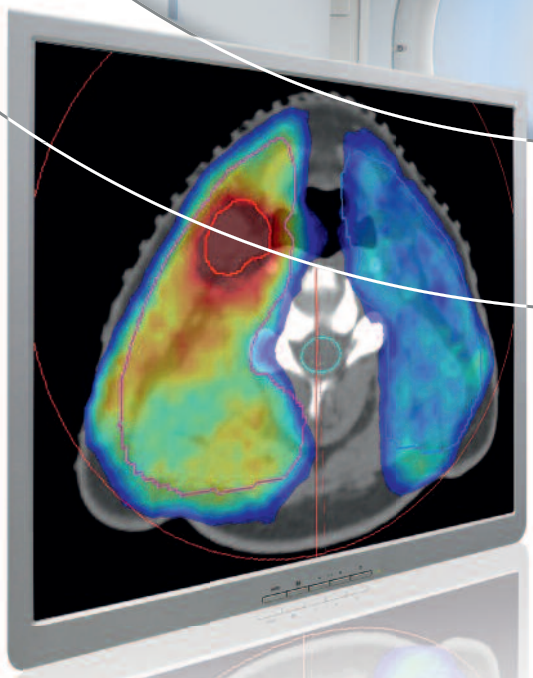


Elekta is a human care company that pioneers significant innovations and clinical solutions for treating cancer and brain disorders. The company develops state-of-the-art tools and treatment planning systems for radiation therapy, radiosurgery and brachytherapy, as well as workflow enhancing software systems across the spectrum of cancer care.

At ESTRO33 Elekta (booth #6200) will demonstrate a comprehensive array of advanced solutions for cancer management. These products include the new Versa HD™ treatment system, Leksell Gamma Knife® Perfexion™ stereotactic radiosurgery system, Monaco® 5 treatment planning system – featuring a new graphical user interface and system architecture – Clarity® Autoscan for real-time soft tissue motion tracking, Identify™ for enhanced patient safety, and the company's advanced solutions for brachytherapy, including the recently launched Esteya® electronic brachytherapy system for treating skin cancer. Elekta's theme for ESTRO33 is "Power of Care" which emphasises the synergy of technology and people working together to support positive patient outcomes.

For further information contact
E: inquiries@elekta.com





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www.VersaHD.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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