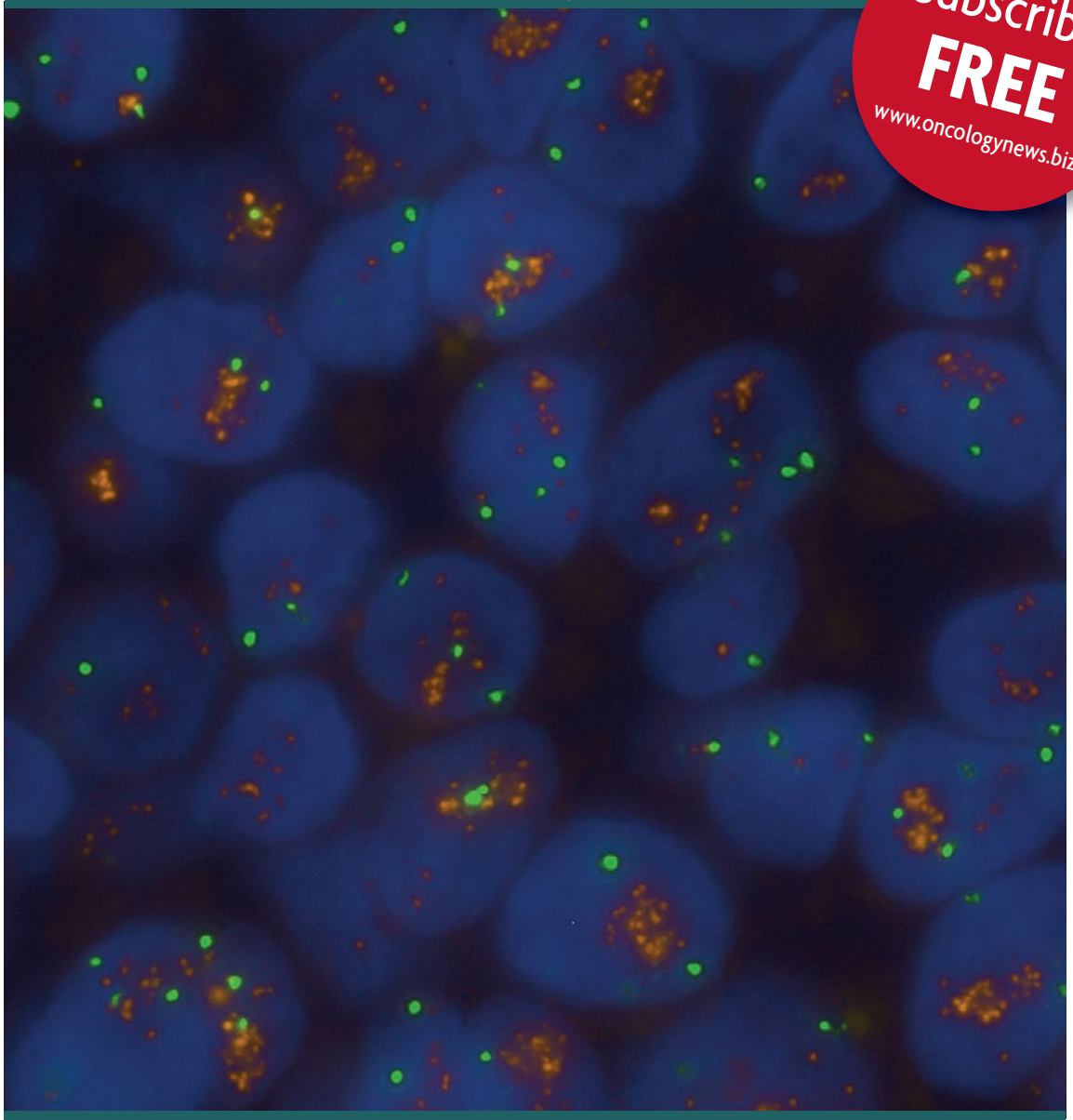
ISSN 1751-4975

Oncology News

Volume 6 Issue 2 : May/June 2011 • www.oncologynews.biz



In this Issue

If you were the patient, which treatment would you prefer?

INTRABEAM® TARGIT Therapy System

TARGIT:

Targeted intraoperative Radiation Therapy with INTRABEAM®.

A Flexible Treatment Platform

Carl Zeiss Ltd
Medical Division

www.zeiss.co.uk

PO Box 78, Woodfield Road
Welwyn Garden City Herts AL7 1LU
Tel: 01707 871231 Fax: 01707 871287
E-mail: medical@zeiss.co.uk

ZEISS

Oral Cavity Cancer in Taiwan – first and second primaries; support for "TOFT"?

Denys Wheatley, Editor.

The habit of betel nut chewing is common in many countries. Its relationship to oral cavity cancer is like that of smoking to lung cancer, but a new study from Taiwan [1] shows that the incidence has risen quite dramatically since 1986, when the incidence was 6 per 100,000 men to 36 per 100,000 in 2007 (1 in 10 men in Taiwan is a habitual betel quid chewer). This recent analysis of over 26,000 cases recorded at the Taiwan Cancer Registry shows that figures like the latter are some 6 times higher than the incidence of oral cancer in the US and other Western countries, where betel chewing is not a habit. In the last 20-30 years there has been no significant improvement in survival rates of patients with oral cavity cancer in Taiwan.

Betel alone is clearly related to the large number of premalignancies - of which about 10% progress to carcinomas - but is also aggravated by smoking and alcohol, amongst other factors. One of the reasons for the poor survival is the high incidence of second primary tumours, which seemed to affect those patients with early stage disease. There was a 3 times greater risk of a betel chewer developing a second primary compared with the figure for the general population; of the total number of cases, around 7% of the patients developed a second primary within the follow-up period. The tendency was for this to occur more in patients who had been diagnosed with a primary tumour before they were 40 years of age, often within the short follow-up period of a year. The increased probability can be due to many factors, including the effects of therapy that the patients received for their primary tumours, which included chemotherapy and irradiation as well as surgery. Not unexpectedly, the sites of the second primaries were closely related to the primaries, the oral-pharynx, naso-pharynx, lung and esophagus being the most likely places, which might suggest some underlying phenomenon regarding the process of carcinogenesis (discussed below). The Taiwan study has nevertheless confirmed similar findings on second primary cancer from two other sources, a UK analysis of almost 60,000 patients [2] and a multi-country study (using 13 registries from European nations, Australia, Canada and Singapore) of almost 100,000 patients [3], which makes it difficult to draw any conclusions about the way in which betel chewing per se influenced second primary tumour development, although an incidence of 7% over a mean follow-up of 3.6 years was very considerably higher than in the multicentre analysis (3.1% in a mean follow-up of 4.9 years). The mean interval between first and second primary tumour diagnosis was also comparable (2-4 years, with a mean of 3.25). The authors of the Taiwan study emphasized the fact that the population they analysed was more homogeneous population than those of the other two large studies mentioned above.

Because of the many contributing factors to the development of cancers of the types being discussed, i.e. the impact of betel chewing, smoking and alcohol, as well as different genetic make-up of the populations and the incidence of other diseases, such as hepatitis, it would be difficult to unravel how each affected the outcome. But since the mucosa of mouth, nose, esophagus and larynx are contiguous, it is not surprising that some have seen this phenomenon as evidence in favour of "TOFT" rather than "SMT". In a recent issue of the BioEssays [4], attention has been drawn to an ongoing debate as to whether the "Tissue Organization Field Theory" has real merit compared with the widely accepted "Somatic Mutation Theory", which has been strongly defended by a second article in the same journal [5]. In truth, both *hypotheses* have been around for a long time, but little support has been given over almost half a century to some of the seminal work of Foulds [6] regarding tumour development, where many cells over a whole area of a tissue might go through progressive stages towards becoming malignant rather than supposing that a single cell, through a series of mutations and alterations, becomes transformed (malignant) to create focally a tumour. Being of the persuasion that hypotheses do not have to be mutually exclusive in life sciences, I can see that both can and probably do operate, as previously discussed in this journal [7]. It would seem much more reasonable to consider that TOFT was the more likely explanation than SMT regarding the matter of second primary cancers in tissues that were also the ones in which the primary tumours were found. But hopefully this topic is now ready for a more open for debate if more are prepared to entertain the possibility that some other mechanism than SMT is involved in carcinogenesis.

References

1. Chen et al. *Incidence and patterns of second primary malignancies following oral cavity cancers in a prevalent area of betel-nut chewing.* (To be published)
2. Wamakulasuriya et al. *Multiple primary tumours following head and neck cancer in southern England during 1961-1998.* J. Oral Pathol. Med. 2003;32:443-9.
3. Chuang et al. *Risk of second primary cancer with head and neck cancers: a pooled analysis of 13 cancer registries.* Int. J. Cancer 123:2390-6.
4. Soto A and Sonnenschein C. *The Tissue Organization Field Theory of cancer: a testable replacement for the somatic mutation theory.* BioEssays 2011;33:332-40.
5. Vaux D. *In defense of the Somatic Mutation Theory of cancer.* BioEssays 2011;33:341-3.
6. Foulds L. *Neoplastic Development.* Academic Press, London, 1969.
7. Wheatley DN. *Carcinogenesis: is there a general theorem?* (Editorial) Oncology News, 2010;5(4):111.

Contents

Volume 6 Number 2 May/June 2011

Meet the Editorial Team

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

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

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

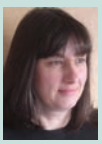
Dr Tom Lynch is Assistant Editor – Imaging, and is a Radiologist and Lead Nuclear Medicine Physician in the Northern Ireland Cancer Centre based at the Belfast City Hospital. Tom specialises in PET/CT scanning and nuclear medicine with a special interest in paediatric nuclear medicine.

Marilena Loizidou is Assistant Editor – Colorectal, and is a Non-Clinical Senior Lecturer in the Department of Surgery, UCL. Her research program focuses on aspects of colorectal cancer and liver metastases, from the basic underlying biology to new potential treatments. The current focus of research is the contribution of the peptide endothelin-1 to tumour growth and progression in the bowel. Additional research areas include breast and bladder cancer.

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

Mo Keshtgar is Assistant Co-Editor - Breast Cancer, and is a Consultant Surgical Oncologist at the Department of Surgery, Royal Free Hospital, London. His main area of interest is minimally invasive approaches in diagnosis and treatment of breast cancer. His research interest is in sentinel node biopsy, intra-operative radiotherapy, quantum dot nanotechnology in breast cancer.

Willie Stewart is Assistant Editor – Neuro-Oncology, he is a Consultant and Lead Neuropathologist based at the Institute of Neurological Sciences, Glasgow and Honorary Clinical Senior Lecturer in the University of Glasgow. His interests include the pathology of high-grade gliomas and developing molecular diagnostic techniques for introduction to routine clinical practice.



Ms Kathleen Mais is Assistant Editor – Nursing, and is a Nurse Clinician in Head & Neck Oncology at Christie Hospital, Manchester. Kathleen qualified as a nurse in Newcastle-upon-Tyne. Kathleen is a nurse-prescriber and runs a nurse-led chemotherapy clinic as well as continuing her work in clinical research.

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

Publisher: Patricia McDonnell

Web: www.oncologynews.biz

Advertising and Editorial Manager: Patricia McDonnell
E: Patricia@oncologynews.biz

T/F: +44 (0)288 289 7023

Design & Production E: design.dept@sky.com
Printed by: Warners Midlands PLC
T: +44 (0)1778 391057

Cover image courtesy of Leica, for further details see p70.

LET'S THINK

IF ONE OF US CAN COME UP WITH AN IDEA TO HELP OUR PATIENTS,
WHAT COULD ALL OF US COME UP WITH?

LET'S WORK

ONCOLOGY FROM BOEHRINGER INGELHEIM

Boehringer Ingelheim

BOEHRINGER INGELHEIM LTD, ELLESFIELD AVENUE, BRACKNELL, BERKSHIRE RG12 8YS
TEL: +44 (0) 1344 424600 · FAX: +44 (0) 1344 741444 · WWW.BOEHRINGER-INGELHEIM.CO.UK

JOB NO: ONC0017 · DATE OF PREPARATION: AUG 2009

The Role of Molecular Techniques in Intra-operative Sentinel Node Analysis in Breast Cancer

Mr Farrokh Pakzad,
National Oncoplastic Fellow, Queen Alexandra Hospital, Portsmouth, UK.

Mr Avi Agrawal,
Consultant Oncoplastic Breast Surgeon, Department of breast and endocrine surgery, Queen Alexandra Hospital, Portsmouth, UK.

Correspondence to:
Mr Farrokh Pakzad,
E: farrokh74@gmail.com

Sentinel lymph node biopsy (SLNB) is now the standard of care in managing patients with clinically node-negative breast cancer. Results from the ALMANAC and NSABP-B32 studies, which compared SLNB to routine axillary lymph node dissection have underlined its many clinical advantages [1,2]. The demonstrable reduction in morbidity includes lower lymphoedema rates, reduced rates of nerve damage, improved functional outcomes to the arm and shorter hospital stay.

Of those undergoing a SLNB, up-to 30% may have a positive sentinel lymph node [1]. There is on going debate as to whether a completion axillary clearance can be avoided in early stage disease. With the paucity of data in this setting, the standard of care in absence of a reliable pre-operative diagnostic tool remains a delayed completion axillary clearance, with resultant longer operative times and potential for increased morbidity, which may delay adjuvant treatment. Clinical and heath economic factors have therefore driven the search for methods of analysing sentinel lymph node(s) intra-operatively, allowing a complete surgical treatment to be carried out in one sitting. Table 1 summarises some of the potential advantages of intra-operative sentinel node (ioSLN).

The two widely investigated and practiced techniques for ioSLN analysis are frozen section analysis and imprint cytology. Both these techniques have been shown to be highly specific in identifying positive lymph nodes (reported specificities of up to 100%). However, they lack sensitivity with reported figures ranging between 57-74% for frozen section and 33-73% for imprint cytology. False negative results occur due to missed micrometastases (tumour foci of 0.2-2mm) and particularly in metastases from lobular carcinoma where the cells are relatively bland and may be difficult to interpret. Although results can be obtained relatively quickly, especially with frozen section analysis, the sample preparation can be labour intensive and relatively costly as it requires a dedicated laboratory technician and a histopathologist. Nonetheless both these pathological techniques have paved the way for the paradigm shift of ioSLN analysis and the advent of molecular techniques that have emerged.

Table 1: Potential advantages of intra-operative sentinel node analysis

- Eliminating the need for a second operation
- Reduced morbidity related to delayed axillary dissection
- Improved patient satisfaction
- Avoidance of delay to adjuvant treatment
- More efficient use of resources =>
  - reduced operative times
  - shorter overall hospital bed stay
  - less use of histopathologist / technician time
  - overall cost saving to the NHS

Molecular techniques for ioSLN analysis

The use of molecular based techniques for SLN analysis is a perfect example of incorporation of translational research in to clinical practice. The two principal technologies for ioSLN analysis use either quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) or one-step nucleic acid amplification (OSNA).

The aim of molecular techniques is to target gene markers that are over-expressed in malignant cells compared to surrounding normal tissue. As yet, there is no single highly specific molecular marker for breast cancer. While multigene assays may confer higher sensitivity, this occurs at the expense of a lower specificity. It appears that two

The two principal technologies use either quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) or one-step nucleic acid amplification (OSNA)

The advantage of molecular techniques is their high level of sensitivity, capable of detecting as few as 10 target gene copies

gene marker assays probably provide the optimal combination but this remains the subject of debate. The two commonly used markers are cytokeratine-19 (CK-19) and mammaglobin (MGB-1), neither of which are ubiquitously expressed in breast cancer but combined have been shown to achieve better sensitivity and specificity than other gene marker pairs [3]. CK-19 is shown to be expressed in over 95% of breasts cancers [4].

The advantage of molecular techniques is their high level of sensitivity, capable of detecting as few as 10 target gene copies. Also, tissue analysis requires homogenisation of the specimen, which theoretically overcomes the challenges of tumour heterogeneity and sampling error associated with histology [5]. However, tissue homogenisation itself is a source of bias in studies where molecular analysis is compared to histology, as the two techniques never examine the same sample. Earlier studies looking at discrepancies between adjacent slides used in histological analysis alone have shown discordance rates of up to 6% between different slices [6]. It is therefore likely that the clinical data published underestimates the true accuracy of molecular techniques as this sampling error is inherently embedded in the methodology. This may be overcome by using protocols where the whole tumour specimen is utilised. However, the lymph node homogenate cannot be reassessed by conventional histological means and there is no data regarding the longevity of stored homogenates for future re-analysis. Therefore if an error or system breakdown occurs, there are limitations as to how the samples can be re-assessed, unlike with stored histological specimens.

Quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR)

The advent of PCR in SLN analysis has stemmed from its experimental use in detecting circulating tumour cells in peripheral blood or bone marrow. As with standard protocols, the technique involves homogenisation of the lymph node, isolation of mRNA, production of cDNA sequences using reverse transcriptase and thermal cycling with DNA polymerase and specific cDNA gene probes to amplify the gene sequence of interest. Labelling the probes with fluorescent markers allows for detection of amplified signals thus giving both qualitative and quantitative data. Quantitative analysis is especially important, allowing estimation of the amount of the target genes above that of a threshold for normal tissues. This has the benefit of improving specificity. The process is fully automated, requiring a single technician and allows several samples to be examined simultaneously. The process is shown to take a median of 32 minutes (range 26-69 minutes) [7].

Several studies to date have reported overall sensitivities ranging between 78-96% and specificities of 92-97% [8]. Quantitative analysis can allow differentiation between macro- and micrometastases, although sampling error may result in reported lower sensitivity in detecting the latter. This requires further validation. Interestingly, qRT-PCR appears to overcome the limitations of histological techniques in detecting metastatic lobular carcinoma. Furthermore, breast carcinomas of special histological type may have focal CK-19 expression, which may lead to false negative results as a consequence of sampling error [4].

As compared to pathological techniques, reported specificities for molecular techniques have been lower. This has raised the question whether these techniques are truly prone to false-positive results. Aside from sampling error, the use of internal controls to safeguard the system from operator or kit error may be a source of contamination that may lead to false positives [8]. However, re-analysing PCR-positive, histology-negative samples using alternative markers have confirmed the presence of metastases in over 70% of cases [5,6]. It is therefore likely that reported specificities are an underestimation.

One-Step nucleic acid amplification (OSNA)

The difference between OSNA and PCR is that gene amplification is by a process of loop-mediated isothermal amplification (RT-LAMP), a method first described by Notomi et al [9]. The technique uses six specific primers for same cDNA target with the primers designed to "loop" the DNA during the amplification process. This results in a magnesium pyrophosphate precipitant, which can be measured using simple photometry and used to quantify the target gene expression. The advantage of OSNA over qRT-PCR is that the isothermic process does not denature the genomic DNA and avoids repeated RNA extraction, thus speeding up the process. It also utilises six primers for the one cDNA target thus overcoming problems of pseudogene interference that may lead to false-positive results. This is especially true as there are three pseudogenes for CK-19 in the human genome [10]. As for this, the OSNA system is designed to detect only CK-19 gene expression and does not require a multigene approach.

Tsujimoto and colleagues described the first application of OSNA in detection of CK-19 expression in sentinel lymph nodes [11]. Their results showed a 98.2% concordance with three-level histological analysis using CK-19 immunohistochemistry, a superior result compared to two-level histology. Later, in a study of 346 lymph nodes, a sensitivity of 95.3% and specificity of 94.7% (97.1% with discordant cases excluded) was reported with OSNA CK-19 compared to histology and immuno-histochemistry as gold standard [12]. Recently a UK multicenter study of 4 centers and 204 patients (the OSNA study group) has reported an overall concordance between OSNA and histology of 96%, sensitivity of 91.7% and a specificity of 96.9% [13]. The median time to process a single SLN was 32 (range 22-97) minutes and 42 (range 30-73) minutes for two nodes. The results were corrected for discordant cases that occurred due to tissue allocation bias (sampling error), which as alluded to earlier is an inherent problem of such comparative studies.

Implementation of the technology and health economic considerations

Molecular ioSLN analysis is now recognised by the NHS Technology Adoption Centre (NTAC) and guidance is provided to assist NHS trusts in implementing these technologies [14]. The OSNA system is available as a single commercial package and can be obtained from Sysmex UK Ltd (www.sysmex-lifescience.com). The only commercially available qRT-PCR kit was the GeneSearch™ Breast Lymph Node (BLN) Assay (Veridex, Johnson & Johnson, USA) but unfortunately due to under-adoption particularly in the USA, the system was

deemed commercially non-viable and globally withdrawn from the market. Recently in the UK, Princess Alexandra Hospital NHS Trust has developed Metasin as an open-source non-profit alternative to GeneSearch™. As yet there are no commercially available kits and therefore setting up the system requires individual procurement of consumables and local clinical/technical expertise (for more information regarding Metasin visit www.metasin.com).

To date, only one published study has examined the health economic implications of ioSLN analysis using the GeneSearch™ system [15]. The estimated per test cost of the molecular assay was £299 as compared to £139 for frozen section and £122 for imprint cytology. The resultant reduction in resource utilisation was shown to be cost effective for primary care trusts and the NHS as a whole. At present there are no national tariffs that cover the cost of ioSLN analysis, thus high capital costs of the technology remain a potential disincentive for individual trusts.

Consclusions

Molecular techniques for ioSLN analysis have been shown to be feasible, effective and accurate for application in the routine clinical setting. Although the implementation of such technologies is associated with high upfront costs, their clinical and health economic benefits are being widely recognised. Despite the strong wave of change in practice, there is a need for more specific research into the clinical impact of utilising highly sensitive molecular tools on stage migration of disease and long-term oncological outcomes. It is however clear that the era of real time molecular based diagnostics and individualised treatment of breast cancer is firmly upon us. ■

References

1. Mansel RE, Fallowfield L, Kissin M et al. *Randomized multicenter trial of sentinel node biopsyversus standard axillary treatment in operable breast cancer: the ALMANAC Trial.* J Natl Cancer Inst 2006;98:599–609.
2. Krag DN, Anderson SJ, Julian TB et al. *Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial.* Lancet Oncol. 2010 Oct;11(10):927-33.
3. Backus J, Laughlin T, Wang Y et al. *Identification and characterization of optimal gene expression markers for detection of breast cancer metastasis.* J Mol Diagn 2005;7:327–36.
4. Alvarenga CA, Paravidino PI, Alvarenga M et al. *Expression of CK19 in invasive breast carcinomas of special histological types: implications for the use of one-step nucleic acid amplification.* J Clin Pathol. 2011 Mar 22. [Epub ahead of print]
5. Blumencranz P, Whitworth PW, Deck K et al. *Scientific Impact Recognition Award. Sentinel node staging for breast cancer: intraoperative molecular pathology overcomes conventional histologic sampling errors.* Am J Surg 2007;194:426–32.
6. Julian TB, Blumencranz P, Deck K et al. *Novel intraoperative molecular test for sentinel lymph node metastasis in patients with early-stage breast cancer.* J Clin Oncol 2008;26:3338–45.
7. Mansel RE, Goyal A, Douglas-Jones A et al. *Detection of breast cancer metastasis in sentinel lymph nodes using intra-operative real time GeneSearch BLN Assay in the operating room: results of the Cardiff study.* Breast Cancer Res Treat. 2009 Jun;115(3):595-600.
8. Layfield DM, Agrawal A, Roche H et al. *Intraoperative assessment of sentinel lymph nodes in breast cancer.* Br J Surg. 2011 Jan;98(1):4-17.
9. Notomi T, Okayama H, Masubuchi H, et al. *Loop-mediated isothermal amplification of DNA.* Nucleic Acids Res 2000;28:E63
10. Hughes SJ, Liqiang X, Raja S et al. *A rapid, fully automated, molecular-based assay accurately analyses sentinel lymph nodes for the presence of metastatic breast cancer.* Ann Surg 2006;243:389–98.
11. Tsujimoto M, Nakabayashi K, Yoshidome K et al. *One-step nucleic acid amplification for intraoperative detection of lymph node metastasis in breast cancer patients.* Clin Cancer Res 2007;13:4807–16.
12. Visser M, Jiwa M, Horstman A et al. *Intra-operative rapid diagnostic method based on CK19 mRNA expression for the detection of lymph node metastasis in breast cancer.* Int J Cancer 2008;122:2562–7.
13. Snook KL, Layer GT, Jackson PA, et al. for the OSNA Study Group. *Multicentre evaluation of intraoperative molecular analysis of sentinel lymph nodes in breast carcinoma.* Br J Surg. 2011;98;527-35.
14. http://www.technologyadoptioncentre.nhs.uk/breast-lymph-node-assay/procurement.html
15. Cutress RI, McDowell A, Gabriel FG et al. *Observational and cost analysis of the implementation of breast cancer sentinel node intra-operative molecular diagnosis.* J Clin Pathol 2010;6:522.

News update

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

Less treatment toxicity for women with HER2 positive advanced breast cancer

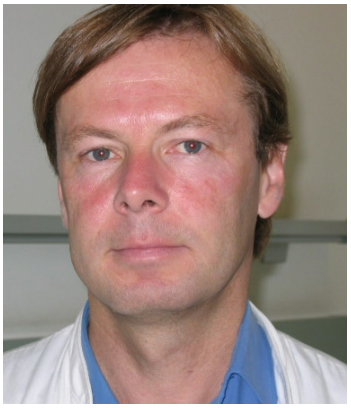
Life prolonging treatment with Herceptin and docetaxel can be difficult because of severe toxicity. Many patients endure nerve disorders, swelling and nail changes in addition to hair loss. One in five women may stop treatment early because of toxicity.

A new study (Andersson M et al. Journal of Clinical Oncology 2011;29:264-71) showed less toxicity when the Herceptin is combined with Navelbine® (vinorelbine) rather than the current standard, docetaxel. This is achieved without compromising survival and enables more women to complete treatment.

In the study 284 women with metastatic or locally advanced HER2 positive breast cancer were randomised to receive either docetaxel or Navelbine, both combined with Herceptin. Women treated with Navelbine experienced significantly less fever and infection, sensory neuropathy, oedema and nail changes. Only 7% of patients discontinued Navelbine-Herceptin due to toxicity whereas 20% of patients treated with docetaxel-Herceptin stopped treatment.

The combination of Navelbine with Herceptin offers additional benefits. Whereas docetaxel and trastuzumab are given by intravenous infusion, Navelbine is also available as a capsule.

For more information please contact nikki.roebuck@pierre-fabre.com



The British Neuro-oncology Society (BNOS) meeting in Cambridge this June marks a milestone in the society's history; this being the 30th annual multidisciplinary meeting of neuro-oncology researchers in the UK. Throughout its existence, Professor Geoff Pilkington has been, and remains, one of the key individuals in the society. Geoff has been at the forefront of neuro-oncology in the UK and internationally since the early 70s. Amongst his career highlights are his involvement in the very earliest studies on stem cells in brain tumours and his work on mechanisms of glioma invasion. Were he not at the forefront of neuro-oncology research Geoff claims he would have been a double internationalist in cricket and rugby union and now enjoying life as a sports journalist; the world of sport's loss has very much been neuro-oncology's gain.

At this year's annual meeting, Geoff will succeed Prof Charles Davis as President of BNOS. To mark this, *Oncology News* has invited Geoff to reflect on the past 30 years (or more) of neuro-oncology research in the UK, through the activities of BNOS and its predecessors, and to provide insight into his vision for neuro-oncology research in the UK.

Geoff J Pilkington, BSc PhD CBiol FSB FRCPath,
Professor of Cellular & Molecular Neuro-oncology, Head, Cellular & Molecular Medicine Research Division.

Correspondence to:
Institute of Biomedical & Biomolecular Sciences, School of Pharmacy & Biomedical Sciences, University of Portsmouth, St Michael's Building, White Swan Road, Portsmouth, UK.
T: +44 (0)23 9284 2116,
www.portsmouth cellularneuroscience.com

BNOS: www.bnos.org.uk

The British Neuro-oncology Society:
Thirty years of endeavour to champion an under-recognised discipline

Researching brain tumours in the 1970s was a somewhat lonesome pursuit, with very few people in the UK engaged in similar activities. Communication with colleagues overseas to discuss mutual interests was also difficult given this was in the pre-internet age. For my part as a young investigator, it was long library sessions and twice yearly British Neuropathological Society conferences, as well as the occasional international conference, which enabled me to learn more about the biology and clinical consequences of this devastating group of neoplasms.

Having moved from the National Hospital for Nervous Diseases (now the National Hospital for Neurology and Neurosurgery), Queen Square, London, I spent nine years at the Middlesex Hospital, then a large teaching hospital in central London. In 1980 things began to change and I moved, with my mentor, Peter Lantos, to the Department of Neuropathology, Institute of Psychiatry, deep in South London and a stone's throw from Kings College Hospital. At this time we had forged an ongoing collaboration on murine models of astrocytoma with David GT Thomas, a consultant Neurosurgeon at Queen Square, and John Darling from David's team, thus beginning a long collaboration and friendship.

In addition, David expressed a strong interest in bringing together UK-based laboratory researchers and clinicians involved in the diagnosis and treatment of the main form of intrinsic brain tumour, known generically as glioma, and to instigate a fairly informal 'club' to meet, present and discuss research and clinical practice. Through his vision, inspiration and enthusiasm, as well as a substantial input from John, the ***British Glioma Group*** was born. In 1981 the first of what would become a series of annual conferences was held at Queen Square and, along with a variety of UK speakers, we were joined by Darell Bigner from Duke University, USA. The group gained impetus and held successful meetings at Southampton and Bristol, organised by Roy Weller and Hugh Coakham respectively. Evidence of increased interest in the meetings was reflected in the attendees list being extended from 44 in 1982 to 85 by 1983.

Professor John L Darling,
Past President of BNOS and a key figure in initiation and development of the Society.

Following the inaugural meeting it became the norm to hold the meetings over a two day period - with the first day beginning with "Bar opens at 6pm" followed by a relaxed dinner. This informality continued through the 1980s. Indeed, it became a sort of jovial tradition during the annual dinner for the local organiser to stand up and announce that, due to the informality of the occasion, there would be no speeches; this was invariably followed by a speech of thanks to all who had helped with the meeting and generally included the presentation of a bouquet of flowers to the organiser's secretary/PA! When I look back and recall Hugh Coakham's virtuoso saxophone performances in the guise of Dr Jazz in 1980s it is clear the template for lavish dinners with ever more entertaining social events and exotic venues of the 21st century had already been set.

These conferences, which were largely research-based, continued to be held at different centres across the UK until 1989 when it was decided to change the name to the ***British Neuro-oncology Group*** in order to encompass tumours other than glioma. Through most of these early years John Darling and I acted as joint treasurer/secretary/organisers until Robin Grant and Tracy Warr took over the responsibilities, while we tried to spread the word of multidisciplinary conferences throughout Europe and further afield. It is, perhaps, gratifying that this format was the first of its kind and more national groups were formed throughout Europe, North America and further afield. Finally, in 2004 the group became the ***British Neuro-oncology Society (BNOS)***, with more structure and purpose. It has continued to grow and prosper rapidly over the ensuing years. We have now met at over 20 different centres and 2011 sees the 30th annual conference, which will be held in Cambridge from 29th June - 1st July and boasts perhaps the most varied and stimulating programme yet.

Over the last 30 years we have entertained some of the key international figures in Neuro-oncology including Lucien Rubinstein, Darell Bigner, Paul Kleihues, Victor Levin and many others. It is of interest to note how the topics covered through the years since 1981 have changed and how concepts and studies have either 'come and gone' or have formed the basis of present practise and research endeavour. For example, in the 1980s there was considerable focus on the application of monoclonal antibodies in both diagnosis and therapy. Stereotactic neurosurgery and both animal and three-dimensional in vitro models also featured in meetings of the '80s.

The 1990s saw a move towards genetic studies, p53-related investigations, novel delivery systems and studies of tumour angiogenesis. We also heard a lecture by Ken Culver in 1993 about the first gene therapy approaches for glioma using HSVtk. There were also presentations on gamma-knife surgery and, with the broadening nature of the group from 'glioma' to 'neuro-oncology', papers were also submitted on schwannoma, meningioma, pituitary tumours and metastases. During this decade the issues of quality of life and indicators of patient performance also came to the fore.

With the advent of the new millennium molecular analyses and the beginnings of a molecular basis for tumour classification were apparent. Loss of heterozygosity 1p19q and MGMT promoter methylation status were main discussion topics through the first decade of the century and issues such as day surgery and cancer stem cells also captured the imagination. The BNOS 2010 meeting in Glasgow brought with it a wonderful presentation on IDH-1 mutations by Andreas Von Deimling, which is perhaps an indicator for the development of further biomarkers which might permit stratification of patients into groups based on likely response to therapy and/or prognosis. However, throughout the years of ***BNOS*** there has been a continued strong interest in radiotherapy, drug sensitivity, neuro-imaging, proliferation control and tumour cell invasion and heterogeneity.

In addition to the changing spectrum of research and clinical practice being presented, the formulation of conferences underwent changes. In 1997 a series of Education Days was introduced which resulted in an extension of the meeting to encompass three days. These sessions have been a huge success over the years. We have now set up a postgraduate forum in which our younger members can present their work and contribute in a very real way to the Society's activities and aims. A Young Investigator award was established in 2010; prizes for best poster and best oral presentations had already been in place since 1998. Other activities within the conference programmes have included open debates on 'hot topics', commercial symposia, ***Association of Neuro-Oncology Nurses (ANON)*** nurse symposia and, over the past three meetings, a neuropathology symposium sponsored by the ***British Neuropathological Society (BNS)***. We now regularly see in excess of 200 delegates at conferences as the scope and quality continually increases. Abstracts are now published in ***Neuro-Oncology*** which reaches a highly appropriate audience of readers.

Throughout the 1980s we were able to rely on the generous support of the Upjohn company's Medical Science Liaison department to help with offsetting the costs of the meeting, but as the meetings became larger and with Upjohn's withdrawal from the UK it became necessary to take on support from various commercial sponsors who have now become indispensible to us in engineering a high quality programme.

Since becoming a Society BNOS no longer simply functions as an organisation with a remit of convening annual conferences. Our membership comes from neurosurgeons, neuroscientists, neurologists, neuropathologists, neuroradiologists, neuropsychologists, neuropsychiatrists, clinical nurse specialists, oncologists, radiotherapists, members of charities and many more disciplines. In this context the Society is central to promoting all branches of medicine related to neuro-oncology and leads the way in enhancing both clinical practice and research through interaction with appropriate national and international bodies.

In David Thomas, John Darling and Charles Davis, I am fortunate to succeed three previous Presidents who have worked enormously hard in developing and professionalising the Society. There is still, however, much to do in order to achieve further professionalisation and recognition of the Society which will involve communication and interaction with other national medical and scientific bodies. However, I do have some specific aims which include encouraging and helping our younger members in their careers, integrating the clinical nurse specialists into the Society in a more substantial way, increasing membership to include all disciplines involved with neuro-oncology in its broadest sense and, in particular, ensuring that paediatric neuro-oncology is a main facet of our strategic planning. With this latter aim in mind, I am pleased to be working with Professor David Walker, himself a paediatric neuro-oncologist, who will become Vice-President of the Society in June. I am also committed to engaging more with mainstream oncology and, to these ends, we are already organising neuro-oncology symposia jointly with NCRI groups to both educate general oncologists about brain tumours and, perhaps more importantly for us, to learn from those with experience in other branches of oncology and cancer research.

I also wish to forge closer relationships with the brain tumour charities which constitute a significant force in furthering the discipline to the benefit of patients and professionals alike and will aim to engage increasingly with the All Party Parliamentary Group in bringing our clinical and research endeavours to the fore.

Brain tumours remain very much the Cinderella of the oncology world; the discipline is under-reported, under-researched and under-funded, but, through BNOS and the united forces of the charity sector, we can change all that.

The BNOS Council is now composed of some 20 members, who represent many sub-disciplines and geographic locations. David Jellinek has played an outstanding and central role as Secretary for several years now and, with Jeremy Rees in place as Treasurer, I am assured of the efficiency and resolve of Council to foster the Society's activities. We have also been extremely fortunate to secure the services of Jenny Loughlin (administrator@bnos.org.uk) as Administrator to the Society. Jenny has been an all-important lynch-pin in our activities over the past few years and has not only kept us in focus but has instigated several new, more professional systems which have enhanced the effectiveness of Council. She has now been joined by our new Communications Officer, Elizabeth Tudball (communications@bnos.org.uk) to whom we wish great success in her new role with ***BNOS***.

Over the next two years I look forward to witnessing sustained growth and development of the Society and am sure that, through increased interaction between professionals, parliamentarians and charities we can increase our research effort with the net result of improved care pathways, quality of life and survival times for patients with all forms of central nervous system tumour. ■

Brain tumours are very much the Cinderella of the oncology world; the discipline is under-reported, under-researched and under-funded, but, through BNOS and the united forces of the charity sector, we can change all that

Gastroenteropancreatic Neuroendocrine Tumours: Advances in Therapy

Dr Maria Gueorguiev,

Centre for Endocrinology, St Bartholomew's Hospital, West Smithfield, London, UK.

Centre for Endocrinology, William Harvey Research Institute, Queen Mary University of London, Charterhouse Square, London, UK.

Correspondence to:
E: M.Gueorguiev@qmul.ac.uk

Professor Ashley B Grossman,

Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Churchill Hospital, Headington, Oxford, UK.

Centre for Endocrinology, William Harvey Research Institute, Queen Mary University of London, Charterhouse Square, London, UK.
E: a.b.grossman@qmul.ac.uk

Epidemiology

Gastro-enteropancreatic neuroendocrine tumours (GEP NETs) have an incidence between 2.5 and 4 per 100,000 population per year, an incidence that has been increasing over the years in the UK. They have traditionally been classified according to their localisation, foregut, midgut or hindgut, with ~10% secreting biologically active hormones. The majority are malignant, with a slowly progressive course. Liver metastases are frequent, and may cause the carcinoid syndrome, whereas some 20-30% of NETs present with distant metastases at diagnosis. In the UK, the 5-year relative survival rate is 42.5% (56.9% for well-differentiated and 7.7% for small-cell carcinoma). Patients with midgut NETs have a better prognosis, while the presence of hepatic metastases results in a 5-year survival rate of 56% from the diagnosis of liver metastases. The new WHO classification (2010) recognises grade 1 and grade 2 NETs, and grade 3 neuroendocrine carcinoma, which should now be used alongside a TNM classification.

Therapy of gastro-enteropancreatic tumours

Resection of the primary tumour or palliative therapies to reduce secondary liver lesions (partial hepatectomy, radiofrequency ablation, selective artery embolisation or chemoembolisation) may prolong survival and induce partial or radiological and clinical responses in 83% and 62% of patients, respectively. There is, however, no effective curative therapy when complete resection is impossible.

Standard cytotoxic chemotherapy is only weakly effective, especially for midgut tumours, and data on the efficacy of interferon-α are controversial. More recently, temozolomide alone or in combination with thalidomide in patients with advanced malignant neuroendocrine tumours (previously treated) has shown an improved response, with stabilisation of disease for the majority and some partial responses, leading to improved survival.

The use of somatostatin analogues (SSA), based on the expression of somatostatin receptors in the majority of GEP NETs, is effective in controlling clinical symptoms related to hormonal secretion in >60% of patients, and reduction of biochemical markers in up to 59% of patients. SSA alone or in combination with interferon-α has resulted in tumour mass reduction in a minority of patients, but in tumour stabilisation in about half of the patients with midgut tumours.

Radionuclide therapy with 131I-MIBG or 90Y-DOTA-Lanreotide, or embolisation with 90Y-labeled microspheres, can achieve variable responses: cure rates of 3-16%, partial responses of 17-84%, with disease stabilisation in 23-63%, and improvement of symptoms in up to 80%.

Recent therapeutic prospects

Somatostatin analogues

The first placebo-controlled phase-IIIb prospective randomised PROMID study showed that octreotide LAR prolongs the time to tumour progression (14.3 versus six months) in patients with metastatic well-differentiated (functional and non-functional) neuroendocrine midgut tumours. Stable disease was observed at six months in 66.7% of patients (versus 37.2% on placebo), with greater benefit to patients with limited hepatic involvement (<10%) [1]. A trial of lanreotide autogel as an anti-tumour agent for non-functioning pancreatic neuroendocrine tumours (PNETs) –the CLARINET study –is nearing conclusion.

A new SSA, SOM230 (pasireotide), with broader affinity for somatostatin receptors sstr 1, 2, 3 and 5, has been used in a phase-II trial in patients with metastatic GEP NETs presenting carcinoid-related symptoms resistant to octreotide LAR (an SSA with affinity for sstr 2 and 5). Control of symptoms was obtained in 27% of patients; 20% had stable disease (SD) at 6 months, and 5% progressive disease (PD) [2]. Lanreotide autogel is an alternative long-acting SSA that can be self-injected.

There is also considerable interest in a serotonin synthesis inhibitor as a novel treatment for the carcinoid syndrome; it may also decrease mesenteric and cardiac valvular fibrosis, with some early results looking promising.

Systemic chemotherapy

Temozolomide, an oral alkylating agent, in combination with capecitabine as first-line chemotherapy in patients with metastatic pancreatic well-moderately differentiated PNETs, achieved an excellent and durable response. The radiographic partial objective response rate (ORR) was 70% of patients, with a median progression free survival (PFS) of 18 months, and two-year survival rate of 92% [3]. However, the number of patients treated was small, and larger trials are awaited.

Peptide receptor radioligand therapy

Recent trials with peptide receptor radioligand therapy (PRRT) have shown improved efficiency in the treatment of advanced GEP NETs.

In a large prospective trial, patients with metastatic carcinoid tumours refractory to octreotide were treated with 90Y-Edotreotide. The median PFS was 16.3 months and overall survival 26.9 months; the median PFS was longer in patients with symptomatic response compared to non-responders (18.2 versus 7.9 months), whereas, 74.4% patients achieved objective tumour response or SD in asymptomatic patients before treatment (17.0 months) [4]. Encouraging results were also observed in patients with advanced inoperable GEP NETs treated with 90Yttrium-DOTATOC or 177Lutetium-DOTATOC. All patients reported a symptomatic response and marked reduction of biochemical parameters [5]. The radiologic responses were complete response (CR) in five patients, PR in 11 patients, SD in 42 (61.8%) patients, and PD in 10 patients, with better responses in pancreatic NETs. The median PFS was 29 months [5].

In a small retrospective study, PRRT (90Yttrium-

DOTATOC or 177Lutetium-DOTATOC/DOTATATE – concomitant SSA therapy in the majority of patients) showed promising results in patients with advanced malignant gastrinomas [6]. The radiologic responses were CR in 1 patient, PR in five patients, SD in five patients (45%), with anti-tumour effect persisting for a median of 14 months; four patients (36%) with PD died – the time to progression (TTP) was 11 months [6].

Molecular targeting agents for endocrine cancer

Due to the overexpression of different components and/or the aberrant activation of several signalling pathways in GEP NETs (IGF-1R, EGFR, VEGF, VEGFR, FGFR, mTOR), and with the advent of molecular targeted cancer therapies, a specific targeted and more powerful approach to the treatment of these endocrine tumours seems to be the ideal basis for future therapies. More efficacious therapeutic approaches arise as combinations of conventional chemotherapy

Table 1. Main clinical trials (Phase II and III) with molecular targeted therapies for GEP NETs

TKI agent	Mechanism of I action of TK	Study phase	Type of tumour, number of patients	Response to therapy (in evaluable patients)	Reference
Imatinib (concurrent OLAR)	EGFR inhibitor	Phase II	Advanced carcinoid tumours* (n = 27)	PR 3.7%; SD 63%; PD 33.3%; PFS 24 weeks; OS 36 mo (median PFS 5.9 mo)	(7)
Gefitinib	EGFR inhibitor	Phase II	Progressive metastatic NETs (carcinoid 57, PNETs 39)	PR 6.8%, SD 37.3%, PFS 64% carcinoid and 13% PNET at 6 mo	(8)
Sorafenib	BRAF, VEGFR2 and PDGFRbeta inhibitor	Phase II	Metastatic NETs (carcinoid 50, PNET 43)	PR 20%, SD 29.3%	(9)
•Sunitinib	VEGFRs and PDGFRs inhibitor	•Phase II	•Advanced NETs (carcinoid* 41, PNETs 66)	•PNET:ORR (PR) 16.7%; SD 68%; PD 7.6%, TTP 7.7 mo Carcinoid*: ORR (PR) 2.4%; SD 83%; PD 2.4%, TTP 10.2 mo	(10)
•Sunitinib versus placebo (concurrent OLAR)		•Phase III, randomised	•PNETs well-differentiated (n = 171)	•PFS 11.4 months vs. 5.5 months placebo; ORR 9.3% vs. 0% placebo; SD 63% vs. 60% placebo; deaths 10% vs. 25% placebo	(11)
Bevacizumab + OLAR (BO) vs. OLAR + pegIFN (OpegI) (Stage I) Bevacizumab + OLAR + pegIFN (BOpegI) (Stage II)	Monoclonal anti VEGF antibody	Phase II randomised, cross-over at 18 weeks for PD all pts	Metastatic NETs (n = 44)	St I: BO: PR 18%, SD 77%, PD 5%, PFS 95% at 18 weeks; OpegI: PR 5%, SD 68%, PD 27%, PFS 68% at 18 weeks St II:overall median PFS 14.4 mo, 1-yr, 2-yr, 3-yr OS rates 93%, 67% and 56%	(12)
Bevacizumab + 2ME2 (concurrent OLAR)	Monoclonal anti VEGF antibody	Phase II prospective	Metastatic carcinoid tumours (n = 31)	Median PFS 11.3 mo Radiologic response 0%: tumour reduction 68%	(13)
Bevacizumab + temozolomide (concurrent OLAR)	Monoclonal anti VEGF antibody	Phase II prospective	Advanced NETs (n = 34) (carcinoid 16, PNET 18)	Biochem response: reduction > 50% in 36% PNETs, 0% carcinoids; radiol response NA	(14)
Bevacizumab + capecitabine + oxaliplatinum	Monoclonal anti VEGF antibody	Phase II prospective	Metastatic or unresectable NETs (n=31 evaluable)	PR23%, SD 71%, PD 6% Median PFS 13.7 mo, 1-year PFS 52%	(15)
MK-0646	IGF-1R inhibitor	Phase II prospective	Metastatic well-differentiated NETs (carcinoid 15, PNETs 10)	SD 20% for > 6 mo	(16)
Temsirolimus	mTOR inhibitor	Phase II	Advanced progressive NETs (carcinoid+ PNET, n=37)	PNET:PR 6.7% and CT: PR 4.8%; TTP 6 mo; 1-year OSR 71.5% (median PFS 6 mo)	(17)
Everolimus + OLAR	mTOR inhibitor	Phase II	NETs low/intermediate (carcinoid 30, PNETs 30)	PR 22%; SD 70%; PD 8% Median overall PFS 15 mo	(18)
Everolimus (E) vs. everolimus+OLAR (EO)	mTOR inhibitor	Phase II	Metastatic PNETs (n = 160)	E: PR 9.6%, SD 67.8%, PD 13.9%, overall median PFS 9.7 mo EO: PR 4.4%, SD 80%, PD 0%, overall median PFS 16.7 mo	(19)
Everolimus vs. placebo (concurrent OLAR)	mTOR inhibitor	Phase III randomised	Advanced PNET (n = 410)	Median PFS 11.0 mo vs. 4.6 mo placebo At 18 mo: 34% pts alive and PFS vs. 9% placebo	(20)
Everolimus + OLAR vs. placebo + OLAR	mTOR inhibitor	Phase III randomised	Advanced NET (well & moderately differentiated) (n = 429)	E+O: median PFS 16.4 mo, P+O: median PFS 11..3 mo	(21)

[PFS progression free survival; PR partial response; CR complete response; SD stable disease; PD progressive disease; OS overall survival; ORR overall objective response rate; OLAR octreotide LAR; pegIFN pegylated interferon; NETs neuroendocrine tumours; GEP NETs gastroenteropancreatic neuroendocrine tumours; PNETs pancreatic neuroendocrine tumours]

and/or molecular targeted agents. Table 1 summarises the current phase-II and phase-III clinical trials with tyrosine kinase inhibitors (TKIs).

EGFR inhibitors

Gefitinib or imatinib, EGFR inhibitors, have shown only modest responses as monotherapy in advanced GEP NETs. The radiologic and biochemical response to imatinib consists mainly of stable disease (up to six months), but a larger proportion of patients have progressive disease [7]. A phase-II trial with gefitinib in 96 patients with islet cell carcinoma and carcinoid showed preliminary results of PR in three patients, SD in 14% and 30% of patients, respectively [8].

Anti-angiogenic therapy

Although the results with sorafenib monotherapy in GEP NETs are limited [9], other anti-angiogenic agents seem to have greater efficacy. The anti-tumour activity of sunitinib (ORR and SD) was more obvious in PNETs compared to malignant carcinoids, with limited median TTP, but similar survival rates (81 and 83%) [10]. A large multicentre, randomised, placebo-controlled phase-III clinical trial with sunitinib continuous daily regimen (prior therapies allowed) in patients with advanced PNETs confirmed the previously observed benefits [11]. There was an improvement of PFS to 11.4 months (versus 5.5 months), with a probability of PFS of 71.3% at six months for sunitinib versus 43.2% for placebo, and an ORR of 9.3% versus 0% favouring sunitib [11]. The study was discontinued early as patients given placebo had more adverse events and deaths, with shorter PFS.

A comparison of the combination of bevacizumab and octreotide LAR with pegylated interferon and octreotide LAR favoured the first approach. A greater objective response (PR + SD) rate (96% versus 73%) and higher 18-weeks PFS (95% versus 68%), with reduction of tumour blood flow seen with functional CT that did not correlate with the tumour response [12], was found. Joint treatment with bevacizumab and 2-methoxyestradiol, both exerting anti-angiogenic effects, of pretreated patients with metastatic carcinoid tumours resulted in prolonged PFS time, although no significant radiologic tumour reduction was detected [13].

In combination with a different chemotherapy regimen, bevacizumab showed promising activity in patients with advanced NETs (carcinoids and PNETs). The trial with concurrent temozolomide is ongoing [14], as is another phase-II trial with capecitabine and oxaliplatinum in metastatic or unresectable NETs [15]. Preliminary results are promising, with higher objective response (PR) 23%, and mainly SD (71%), with median PFS 13.7 months and 1-year PFS of 52% [15].

IGF-1R inhibitor

A phase-II trial with MK-6046, an IGF-1R inhibitor, showed limited anti-tumour activity in patients with well-differentiated NETs, with SD in 20% of patients for six months or longer [16]. This trial was discontinued as this compound was insufficiently efficacious as a monotherapy.

mTOR inhibitors

Temsirolimus, a mTOR inhibitor blocking the IGF-1R and Akt signalling, has given poor response rates [17], everolimus (RAD001), used in combination with SSA in advanced low-intermediate grade NETs, produced a PR in 22% of patients with SD in 70%, with a median overall PFS of 15 months [18]. Everolimus and octreotide showed greater efficacy than everolimus alone in patients with metastatic PNETs after failure of systemic chemotherapy, the median overall PFS being longer (16.7 versus 9.7 months and no PD) [19].

A large multicentre randomised placebo-controlled phase-III clinical trial RADIANT-3 demonstrated prolongation of the progression-free survival (11.4 months versus 4.6 months for placebo) by everolimus in patients with advanced pancreatic low to intermediate grade progressing NETs [20]. Estimates for PFS and patients alive at 18 months were 34% and 9%, respectively, but the median overall survival was not reached [20]. According to RECIST criteria, tumours shrank in 64% versus 21% with placebo [20].

A randomised double-blind phase-III study RADIANT-2 with everolimus combined with octreotide LAR versus placebo and octreotide LAR in patients with advanced progressive well-moderately differentiated NETs reported superior efficacy, prolonging PFS by 5.1 months (16.4 versus 11.3 months), with a 23% reduction in the risk of disease progression [21]. However, the statistical significance depended on whether there was local or central assessment of tumour, and the study remains under analysis.

Conclusions and future challenges

Targeted therapies used in combinations between TKIs or with standard agents (systemic chemotherapy, somatostatin analogues) seem to be the best hope for therapy in these tumours. Several clinical trials assessing the therapeutic effects of different novel TKIs, often combined with somatostatin analogues for the treatment of GEP NETs, are ongoing. The drug-related adverse effects are relatively well tolerated, but dose adjustment may be required.

Both sunitinib and everolimus are now likely to be part of the therapeutic armamentarium for progressive NETs, especially PNETs. Everolimus can be used concurrently with octreotide LAR.

It is also important to determine the therapeutic benefits of TKIs used as neoadjuvant therapy, and effects of the sequential or continuous use of these agents in the long-term. However, it is disappointing that any benefits seen with these agents seem to be limited in time. It is possible that tumour escape might be prevented by combination therapy, either with several targeted agents or with chemotherapy and/or radionuclide therapy. It may be some time before we can truly see long-term remissions.

One issue that needs to be addressed in future clinical trials is the extremely elevated costs of these therapies, which will have to be considered in balance with their therapeutic benefits and improvement in the quality of life. A new quality of life assessment tool specifically designed for NETs should soon be available. All these major challenges will play a determinant role in future therapeutic trends. ■

Key points

- GEP NETs are malignant tumours characterised by slow progression, but once there are advanced metastases, severe comorbidities can result, e.g. mesenteric fibrosis and carcinoid heart disease.
- Patients with functionally active or inactive GEP NETs would benefit from somatostatin analogue therapy for controlling clinical symptoms, but also for reducing tumour growth and metastases.
- Octreotide LAR will only increase progression-free survival in 'midgut' NETs.
- Temozolomide as single agent or in combination with capecitabine in patients with advanced PNETs has proved to be efficacious.
- Proven therapeutic efficacy has been reported for sunitinib in advanced progressive well-differentiated PNETs, and for everolimus in advanced progressive well-moderately differentiated PNETs and low-intermediate grade NETs.

References

1. Rinke A, Müller HH, Schade-Brittinger C, et al. *Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group.* J Clin Oncol 2009;27(28):4656-63.
2. Kvols LK, Oberg K, Glusman JE et al. *Safety and efficacy of pasireotide (SOM230) in patients with metastatic carcinoid tumors refractory or resistant to Octreotide LAR: results of a phase II study.* J Clin Oncol 2006;24 (Suppl 18):Abstract 4082.
3. Strosberg JR, Fine RL, Choi J et al. *First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas.* Cancer 2011;117(1):268-75.
4. Bushnell DL Jr, O'Dorisio TM, O'Dorisio MS, et al. *90Y-edotreotide for metastatic carcinoid refractory to octreotide.* J Clin Oncol 2010;28(10):1652-9.
5. Pfeifer AK, Gregersen T, Grønbæk H, et al. *Peptide Receptor Radionuclide Therapy with (90)Y-DOTATOC and (177)Lu-DOTATOC in Advanced Neuroendocrine Tumors: Results from a Danish Cohort Treated in Switzerland.* Neuroendocrinology 2011;93(3):189-96.

6. Grozinsky-Glasberg S, Barak D, Fraenkel M, et al. *Peptide receptor radioligand therapy is an effective treatment for the long-term stabilization of malignant gastrinomas.* Cancer 2010;117(7):1377-85.
7. Yao JC, Zhang JX, Rashid A et al. *Clinical and in vitro studies of imatinib in advanced carcinoid tumors.* Clin Cancer res 2007;13(1):234-40.
8. Hobday TJ, Holen K, Donehower R et al. *A phase II trial of gefitinib in patients (pts) with progressive metastatic neuroendocrine tumors (NET): A Phase II Consortium (P2C) study.* J Clin Oncol 2006; 24(Suppl 18):Abstract 4043.
9. Hobday TJ, Rubin J, Holen K et al. *MC044h, a phase II trial of sorafenib in patients (pts) with metastatic neuroendocrine tumors (NET): a Phase II Consortium (P2C) study.* J Clin Oncol 2007:25(Suppl 18):Abstract 4504.
10. Kulke MH, Lenz HJ, Meropol NJ, et al. *Activity of sunitinib in patients with advanced neuroendocrine tumors.* J Clin Oncol 2008;26(20):3403-10.
11. Raymond E, Dahan L, Raoul JL, et al. *Sunitinib malate for the treatment of pancreatic neuroendocrine tumors.* N Engl J Med 2011;364(6):501-13.
12. Yao JC, Phan A, Hoff PM, et al. *Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b.* J Clin Oncol 2008;26(8):1316-23.
13. Kulke MH, Chan JA, Meyerhardt JA, et al. *A prospective phase II study of 2-methoxyestradiol administered in combination with bevacizumab in patients with metastatic carcinoid tumors.* Cancer Chemother Pharmacol 2010, In Press.
14. Kulke MH, Stuart K, Earle CC et al. *A phase II study of temozolomide and bevacizumab in patients with advanced neuroendocrine tumors.* J Clin Oncol 2006;24 (Suppl 18):Abstract 4044.
15. Kunz PL, Kuo T, Zahn JM et al. *A phase II study of capecitabine, oxaliplatin and bevacizumab in patients with metastatic or unresectable neuroendocrine tumors.* J Clin Oncol 2006;28 (Suppl 1): Abstract 4104.
16. Reidy DL, Hollywood E, Segal M, Saltz L. *A phase II clinical trial of MK-0646, an insulin-like growth factor-1 receptor inhibitor b(IGF-1R), in patients with metastatic well-differentiated neuroendocrine tumors (NETs).* J Clin Oncol 2010;28 (Suppl 15): Abstract 4163
17. Duran I, Kortmansky J, Singh D et al. *A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas.* Br J Cancer. 2006;95(9):1148-54.
18. Yao JC, Phan AT, Chang DZ, et al. *Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study.* J Clin Oncol. 2008;26(26):4311-8. Erratum in: J Clin Oncol. 2008;26(34):5660.
19. Yao JC, Lombard-Bohas C, Baudin E, et al. *Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial.* J Clin Oncol 2010;28(1):69-76.
20. Yao JC, Shah MH, Ito T, et al. RAD001 in advanced neuroendocrine tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364(6):514-23.
21. Pavel M, Hainsworth JD, Baudin E et al. *A randomized, double-blind, placebo-controlled multicenter phase III trial of everolimus + octreotide LAR vs placebo + octreotide LAR in patients with advanced neuroendocrine tumors (NET) (RADIANT-2).* Ann Oncol 2010;21(Suppl 8):viii4 (Abstract LBA8).

Additional references

1. Modlin IM, Lye KD, Kidd M. *A 5-decade analysis of 13,715 carcinoid tumors.* Cancer 2003;97(4):934-59.
2. Gueorguiev M, Grossman AB, Plowman N. *Endocrine cancer. In Treatment of Cancer,* 2008, Eds Price, P., Illidge, T., Sikora, K. Publisher Chapman & Hall Medical, London
3. Lepage C, Ciccolallo L, De Angelis R, et al. *European disparities in malignant digestive endocrine tumours survival.* Int J Cancer 2010;126(12):2928-34.
4. Ahmed A, Turner G, King B, et al. *Midgut neuroendocrine tumours with liver metastases: results of the UKINETS study.* Endocr Relat Cancer 2009;16(3):885-94.
5. Gupta S, Yao JC, Ahrar K, et al. *Hepatic artery embolization and chemoembolization for treatment of patients with metastatic carcinoid tumors: the M.D. Anderson experience.* Cancer J. 2003;9(4):261-7.
6. Strosberg JR, Choi J, Cantor AB, Kvols LK. *Selective hepatic artery embolization for treatment of patients with metastatic carcinoid and pancreatic endocrine tumors.* Cancer Control 2006;13(1):72-8.
7. Ekeblad S, Sundin A, Janson ET, et al. *Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors.* Clin Cancer Res 2007;13(10):2986-91.
8. Kulke MH, Stuart K, Enzinger PC, et al. *Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors.* J Clin Oncol. 2006;24(3):401-6.
9. Safford SD, Coleman RE, Gockerman JP, et al. *Iodine-131 metaiodobenzylguanidine treatment for metastatic carcinoid.* Results in 98 patients. Cancer 2004;101(9):1987-93.
10. Mukherjee JJ, Kaltsas GA, Islam N, et al. *Treatment of metastatic carcinoid tumours, phaeochromocytoma, paraganglioma and medullary carcinoma of the thyroid with (131)I meta-iodobenzylguanidine [(131)I-mIBG].* Clin Endocrinol 2001;55(1):47-60.
11. Kennedy AS, Dezarn WA, McNeillie P, et al. *Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients.* Am J Clin Oncol 2008;31(3):271-9.
12. Gross DJ, Munetr G, Bitan M et al. *The role of imatinib mesylate (Glivec) for treatment of patientts with malignant endocrine tumors positive for c-kit or PDGF-R.* Endocrine Relat Cancer 2006;13:535-40.
13. Kindmark H, Janson ET, Gustavsson B et al. *Five patients with malignant endocrine tumors treated with imatinib mesylate (Glivec®).* Acta oncologica 2010:49:100-1.

How Translational Science is Changing the Treatment Paradigm in Oncology

Theresa LaVallee,
Director of Translational Sciences Oncology, MedImmune, California, USA.

Correspondence to:
Theresa LaVallee,
E: LaValleeT@MedImmune.com

For the past ten years or more, translational science has been pushing back the frontiers of medical research and oncologists have been its pioneers. Of all the medical disciplines, it is oncology that has taken the tools of translational science and used them most effectively to bring about fundamental changes in the way we treat disease.

Translational tools such as rational drug design, 'in silico' computer modelling, biomarkers and companion diagnostics, have allowed oncologists to begin treating cancer at a genetic and molecular level to go beyond simply focusing on the disease's relatively imprise clinical manifestations.

Some of the newest treatments are able to target genetic pathways and molecular alterations in specific cancers of identified subsets of patients. This raises the prospect of highly personalised medicine in which the right drugs are used in the right patients in the right doses and at the right time.

Such personalised medicine is a timely and logical response to the increasing demands from healthcare systems to become more patient-centred to gain the most effective treatment outcomes and avoid treating patients who will not benefit. The one-size fits all approach to treatment is increasingly viewed as outdated and inappropriate due to the recent appreciation that cancer is not a single disease but many sub-diseases.

The personalised approach may also help stimulate new interest in neglected areas of research. Previous interest in drug development was to only advance compounds that had potential in the 'big four' (lung, colon, breast and prostate cancer). With the new understanding that cancer is a subset of many different patient segments, drug developers can focus drugs on smaller patient populations with the goal of providing more effective treatments and determining utility in early clinical trials.

Indeed there has already been a strategic shift among major pharmaceutical companies away from large clinical trials in unselected patient populations to targeted disease subsets. These companies are also using translational science technology to streamline their early stage research and to make their go/no go decisions on drug development much earlier in the pre-clinical and clinical process.

What is translational science?

Translational science represents a significant shift in focus from the traditional approach to developing new drugs and therapeutic approaches. Originally conceived as a way of facilitating the passage of new molecules from scientific discovery to clinical application, it has now developed into something much more than that.

Translational scientists quickly realised that the 'bench to bedside' model needed to be expanded to incorporate feedback loops through which information would also flow from frontline clinicians back to the laboratory. With information flowing from bench to bedside and back again, research could be better targeted towards the areas in which it would eventually offer the most benefit to patients. Real-time data could be used to adapt trial designs and effective biomarker strategies could increase the success of phase III clinical trials by selecting those investigational molecules with the greatest promise earlier in the development process.

A number of different techniques have been incorporated into this approach.
These include:

- Rational drug design – in which knowledge of the intended biological target is used to direct drug discovery.
- In silico research – in which virtual screening is used to identify potential candidates for therapeutic molecules without the need for expensive and time-consuming laboratory trials.
- Biomarkers – a characteristic that can be measured in response to a biological process, disease or drug treatment such as a protein, DNA, RNA or cell.
  - Pharmacodynamic (PD) marker – a change that can be measured when the drug binds its target (first level of evidence that a drug is doing what it was designed to do).
  - Proof of mechanism (PoM) biomarker – a change that can be measured when the drug binds and inhibits/stimulates the target (second level of evidence the drug is doing what it was designed to do).
  - Proof of principal (PoP) biomarker – a change that can be measured and indicates the drug is affecting the disease (first level of evidence that the drug may be effective).
- Companion diagnostics – in which the identification of biomarkers allows a patient subset to be identified for being included or excluded from treatment due to predicting who will benefit from the drug therapy. Many new oncology agents are now launched together with a specific diagnostic test to identify the target patient population.
- Predictive modelling – in which PD markers are used to monitor the pharmacological response to treatment, allowing clinical outcomes to be predicted and doses optimised at a much earlier stage in drug development.

We, at MedImmune, have developed a unique way of effectively using the promise of translational medicine by incorporating biomarkers early in the development program

Translational science in oncology

Within oncology these translational techniques have been used to produce highly specific treatments that have already benefited thousands of patients in terms of longevity, improved prognosis and raised quality of life.

For instance, when researchers discovered that chronic myelogenous leukaemia (CML) was linked to a chromosomal abnormality known as the Philadelphia translocation, they were able to use rationale drug design to identify a molecule that would inhibit the bcr-abl protein responsible for the leukaemia.

The result was imitanib (Glivec/Gleevec) a drug which has been targeted towards at least two different cancer-causing genetic mutations – bcr-abl and c-Kit mutations benefiting patients with CML –and also patients who test positive for the c-kit genetic mutation in a subset of gastrointestinal stromal tumour (GIST) patients [1].

In the treatment of metastatic colorectal cancer, identifying patient subsets has been greatly advanced by the identification and use of biomarkers. For instance, patients carrying the KRAS mutation have been shown not to respond to the monoclonal antibody cetuximab (Erbitux) and thus, this patient subset should be considered for treatment with other therapies [2].

Companion diagnostics have also resulted in some significant advances in cancer care. For instance, the monoclonal antibody trastuzumab (Herceptin) would not have been viable as a breast cancer treatment if it were not for the diagnostic tests that were developed alongside it to allow identification of the patient subset to treat.

These tests –immunohistochemistry (IHC) or fluorescent in situ hybridisation (FISH) – allow clinicians to identify the subset (around 20%) of patients with invasive breast tumours who exhibit an over-expression of the human epidermal growth factor receptor type 2 (HER2) [3].

In this group of patients trastuzumab improves survival and response to chemotherapy, while the remaining 80% are not suitable for the treatment.

The MedImmune approach: Case study MEDI-575

We, at MedImmune, have developed a unique way of effectively using the promise of translational medicine by incorporating biomarkers early in the development program. Among a number of our exciting drug candidates, we are currently conducting oncology phase II clinical trials of a monoclonal antibody, known as MEDI-575, that targets the platelet-derived growth-factor receptor alpha (PDGFRα) pathway.

PDGFRα is an important cancer target due to its role in regulating transformation, tumour microenvironment, progression and metastasis of solid cancer tumours.

Development of MEDI-575 began in preclinical studies in which we used a targeted approach to develop a human monoclonal antibody to PDGFRα. MEDI-575 was designed to selectively inhibit PDGFRα signalling. An additional characteristic of MEDI-575 is that it does not produce the inhibition of PDGFRβ that has been associated with clinical toxicities, including extra-vascular fluid accumulation.

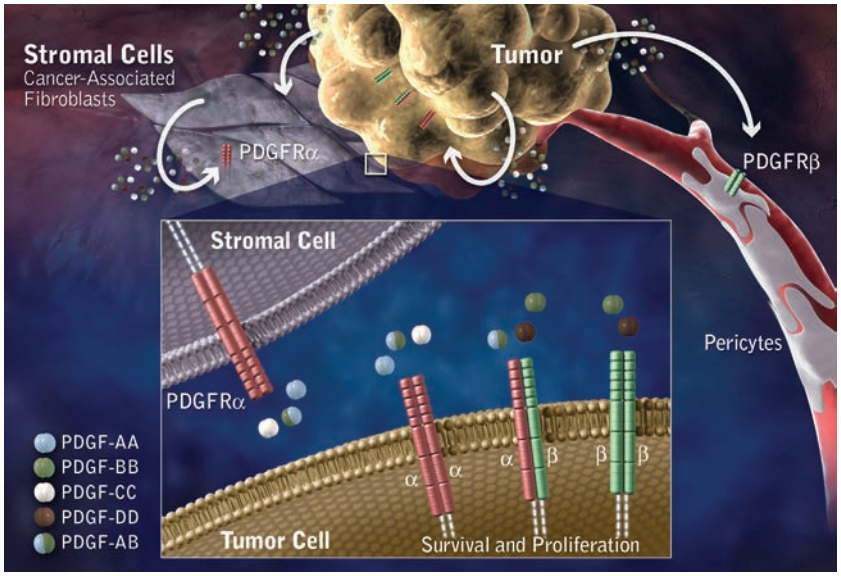


Figure 1: MEDI-575 Mechanism of Action.

In the preclinical development of MEDI-575, a panel of human epitheal tumour cell lines expressing PDGFRα was evaluated for antitumour response to treatment. The H1703 cell line, which has a high protein expression of PDGFRα, was the only epitheal cell line to demonstrate a robust antitumour response to treatment with MEDI-575 in preclinical models. However, when tumour models expressing human PDGFRα in the cancer associated fibroblasts were evaluated; MEDI-575 treatment resulted in antitumour activity in a broad range of models, irrespective of whether or not the tumour cell line itself expressed PDGFRα. Evaluation of human tumours using immunohistochemistry indicated that a number of epitheal tumours have prominent expression of PDGFRα in cancer associated fibroblasts and also have some tumour cell expression (non-small cell lung cancer being one of the best).

Evaluation of MEDI-575 using a panel of human meschymal tumour cell lines (glioblastoma) expressing PDGFRα resulted in significant antitumour activity in several models. Evaluation of human glioblastoma tumours using immunohistochemistry indicated that both primary and recurrent glioblastoma patient samples have a high prevalence of PDGFRα expression.

These preclinical studies led to the development of two working hypotheses that will be tested in Phase II clinical trials following safety, biomarker and dose selection in Phase I:

- That MEDI-575 inhibits tumour growth by its impact on the tumour stroma (cancer associated fibroblasts) that is supporting the tumour growth.
- That MEDI-575 inhibits tumour growth by direct anti-proliferative activity within the tumour cell;

In turn, these hypotheses directly contributed to the design of the current Phase II trials in patients with non small cell lung cancer (NSCLC) and glioblastoma multiforme (GBM).

These human clinical trials use the predictive modeling from the pharmacology and toxicology models developed at the preclinical stage to help us determine the right dosing and schedule in cancer patients.

They are also evaluating the expression of PDGFRα in tumour and stroma (cancer associated fibroblasts) in archival tissue (tumour from the patient when originally diagnosed) and the circulating tumour cells (CTCs – tumour cells in the patient at the time of treatment) for enumeration and PDGFRα expression, to determine if this biomarker can define a particular patient subset that may be more sensitive to MEDI-575. Protein biomarkers in the blood that may be able to identify patients with cancer associated fibroblasts will also be evaluated, as well as biomarkers for tumour cell apoptosis.

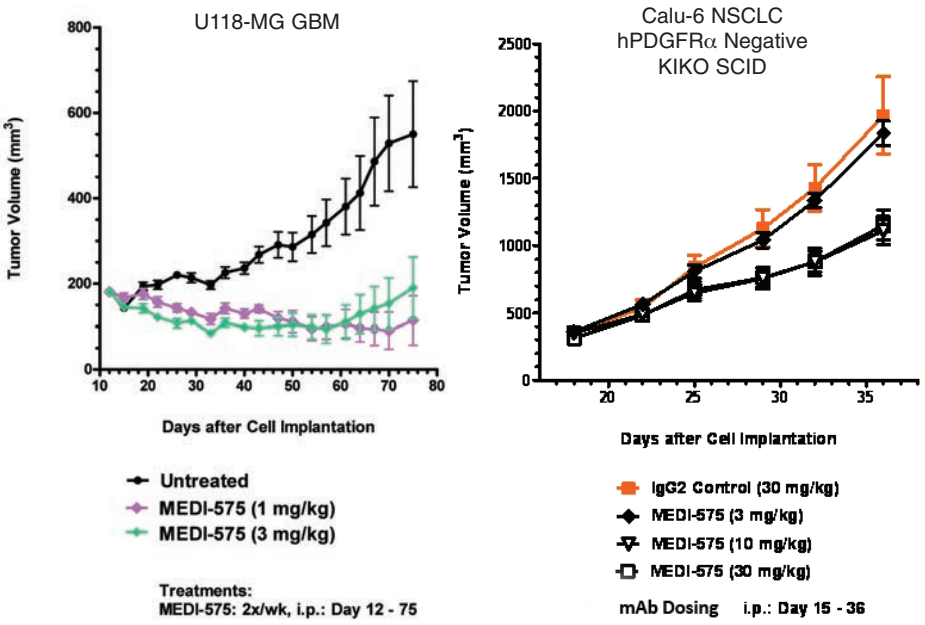
In this way the trials are designed not only to meet regulatory rigour for evaluating safety and efficacy, but also to identify specific molecular features of disease that regulate responsiveness to treatment and improve our understanding of the patient subset(s) that may be best suited for this treatment approach.

Future directions, possible obstacles

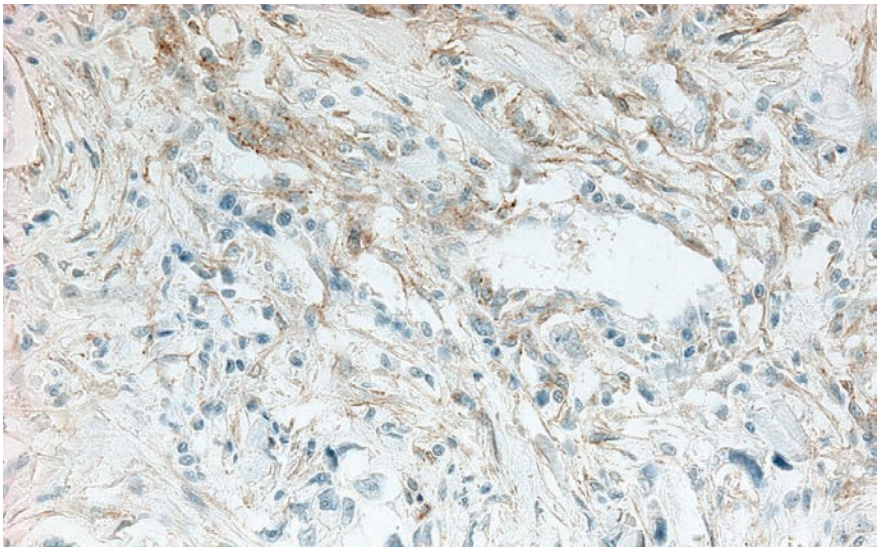
With translational strategies such as that used with MEDI-575 in the development pipeline, the future of oncological therapies appears promising for defining the right patient subsets to treat and enabling us to make go/no go decisions in early clinical development.

Indeed, our growing understanding of the

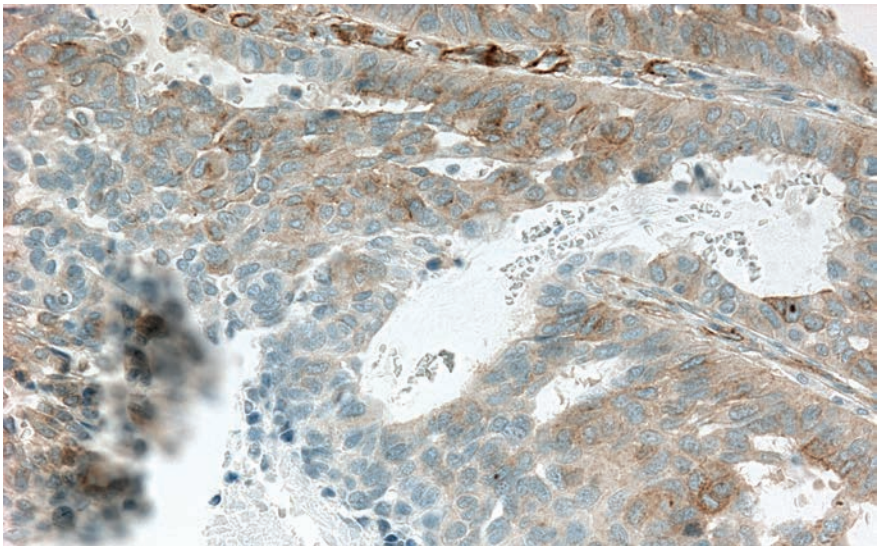
Figure 2: PDGFRα Expression in Human NSCLC Tumours.



PDGFRα expression: Tumour +ve; Stroma +ve



PDGFRα expression: Tumour -ve; Stroma +ve



molecular changes that take place in cancer are leading to new, rationally designed early detection, chemoprevention, and therapeutic strategies. The use of translational science based approaches to use tumour cell lines for pharmacology and predictive modeling, as well as human patient samples for disease linkage studies, allows the design of robust clinical trials to answer specific hypothesis to determine right drug, right target or right drug, wrong target. Moreover, the identification of global gene expression signatures from individual tumours raises the possibility of selecting therapies by molecular typing of individual tumours.

Investigations are also ongoing into a variety of minimally invasive approaches to assess cancer biomarkers such as the methylated or mutated tumour DNA sequences, miRNA, protein signatures and circulating tumour cells in blood or other accessible body fluids with the potential for diagnosis and possibly early detection of cancer.

Clearly, translational science has already achieved many successes both within oncology and beyond. There are however a few dark clouds on the horizon that could impinge on its future success. In an age of increasingly stringent budgetary restrictions there is no doubt that the higher initial costs of translational research programmes could be a major disincentive to investment. There is also a shortage of suitably skilled investigators and a number of administrative and regulatory barriers.

Conclusion

There has been a symbiotic relationship between oncology and translational science in which both have accrued significant benefits. It is a relationship that has resulted in the development of innovative approaches to drug development whose benefits extend well beyond the discipline of oncology itself. At the same time it continues to produce targeted treatments and diagnostic procedures that have extended patient survival, reduced the burden of disease and improved patients' quality of life. Despite some potential barriers to further expansion, the well-stocked research pipeline suggests that translational science and oncology drug development will together continue to develop effective therapies for patients. ■

References

1. *Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours.* Technology Appraisal Guidance 86. NICE 2004
2. American Society of Clinical Oncology 2008 Annual Meeting: Abstract 2. June 1, 2008
3. Kaufman B, et al. *Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomised phase III TAnDEM study.* Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 2009;27(33):5529-37.

Review of Hepatocellular Carcinoma

Douglas L Senecal, PA-C,
Chair of the Medical Research Committee.

Correspondence to:
Blue Faery: The Adrienne Wilson Liver Cancer Association,
Burbank, CA 91505, USA.
T: 1-1478-390-3531,
E: doug@bluefaery.org
W: www.bluefaery.org

Hepatocellular carcinoma (HCC) was reported in ~24,000 patients in 2010 in the United States. The mortality, based on the stage at which the majority of cases were being diagnosed, is such that ~19,000 of these cases were recorded as cancer deaths in 2010, which translates as a five-year survival rate of ~12% [1]. The significance of this is that HCC has become the fastest growing cause of cancer death in the United States [2,3]. This epidemiological pressure can be visualised by the increasing incidence of cirrhosis, driven by the 3.2 million hepatitis C virus-infected patients in the US that rapidly expands the population at risk of developing HCC (Figure 1) [2]. HCC's global impact represents approximately 750,000 cases annually, making it the sixth most common cancer and the third leading cause of cancer death worldwide. Almost 300,000 of these cases are found in China, and about 52,000 in Africa. Over 85% of new HCC cases occur in developing countries [3].

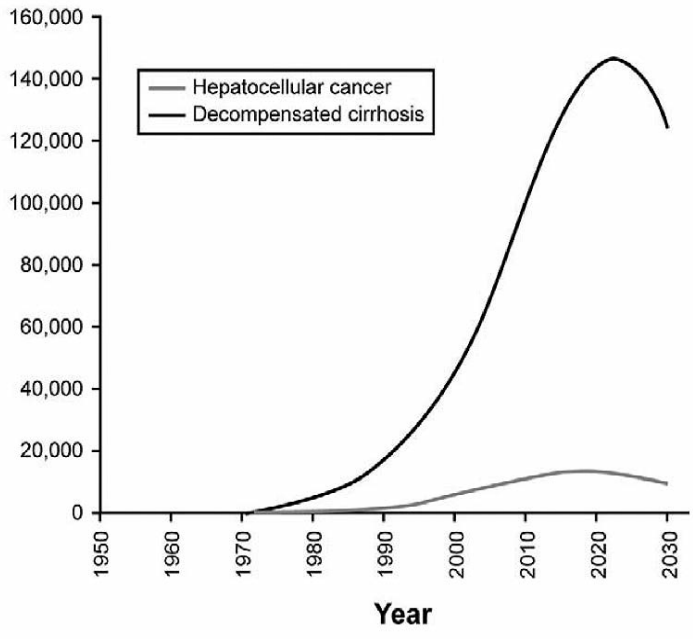
Unfortunately, despite better knowledge about the patients at risk and the increasing number of patients, the current penetration of or adherence to surveillance guidelines is only ~30% in patients who were diagnosed with HCC between 1994-2002 [4]. This seems to have contributed significantly to HCC's poor prognosis, as the vast majority of patients at risk were not actively or appropriately monitored, thus presenting with much later stage disease. Active surveillance of at risk groups is essential, either under the auspices of their primary care providers or at the level of the gastroenterology practice where they are being managed for their chronic hepatitis and/or cirrhosis. Current risk factors for HCC that indicate a patient should undergo surveillance with ultrasound every six months are: established cirrhosis, chronic hepatitis B virus (cHBV) infection and, to a yet to be fully defined degree, non-alcoholic steatohepatitis (NASH) [5].

With respect to treatment, over the last decade, further development in science has led to a broadening of treatment options for the HCC patient. Surgical resection or radio frequency ablation (RFA) in the non-cirrhotic or compensated cirrhotic patient population with HCC confined to the liver offer a five-year survival of around 60% [5]. With the introduction of an appropriate organ allocation measure, such as the Milan criteria (three lesions < 3cm or one lesion < 5cm), the transplant scenario has offered a five-year survival of ~70%, rivaling outcomes in patients transplanted for liver failure [6]. Trans-arterial chemoembolisation therapy (TACE) in patients who are not candidates for resection, RFA, or transplant, and have HCC confined to the liver without vascular invasion, gave a one-year survival of 60-80% [6]. In patients with more advanced HCC that is metastatic and/or invading the vasculature, oral systemic therapy with Sorafenib gave a one-year survival of ~44% [7]. This evidence-based multidisciplinary approach is best represented by the Barcelona Clinic for Liver Cancer (BCLC) Staging and Treatment guideline (Figure 2 overleaf).

HCC represents a current and emerging cancer epidemic in the US that urgently needs the concerted multi-disciplinary attention of the medical community. Given the fact that this is an emerging epidemic in which we have the privilege of foresight, we may be able to make a more significant difference. ■

Blue Faery: The Adrienne Wilson Liver Cancer Association is a 501(c)3 non-profit organisation. Our mission is to prevent, treat, and cure primary liver cancer, specifically HCC, through research, education, and advocacy. Visit our online website at http://www.bluefaery.org

Figure 1: Increasing prevalence of Cirrhosis due to HCV and its impact on HCC prevalence [2].



References

1. ACS Cancer Facts and Figures. 2010. http://www.cancer.org/downloads/STT/Global_Facts_and_Figures_2007_rev2.pdf; 3.
2. Davis G, Alter M, et al. *Aging of the Hepatitis C Virus (HCV) Infected Persons in the United States: A Multiple Cohort Model of HCV Prevalence and Disease Progression.* Gastroenterology 2010;138:513-21.
3. Ferlay J, Shin HR, et al. GLOBOCAN 2008, *Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10* [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr
4. Davila J, El-Serag H, et al. *Use of Surveillance For Hepatocellular Carcinoma Among Patients With Cirrhosis In The United States.* Hepatology 2010, V52, 1:132-41.
5. Bruix, J, Sherman, M. *AASLD Practice Guideline: Hepatocellular Carcinoma. Hepatology 2010, V0:1-35.* Best referenced online at www.aasld.org.
6. Said A and Wells J. *Minerva Medica.* 2009;100:51-68.
7. Llovet JM, et al. *Molecular Therapy in Hepatocellular Carcinoma.* Hepatology, V48-4; 1312-37.

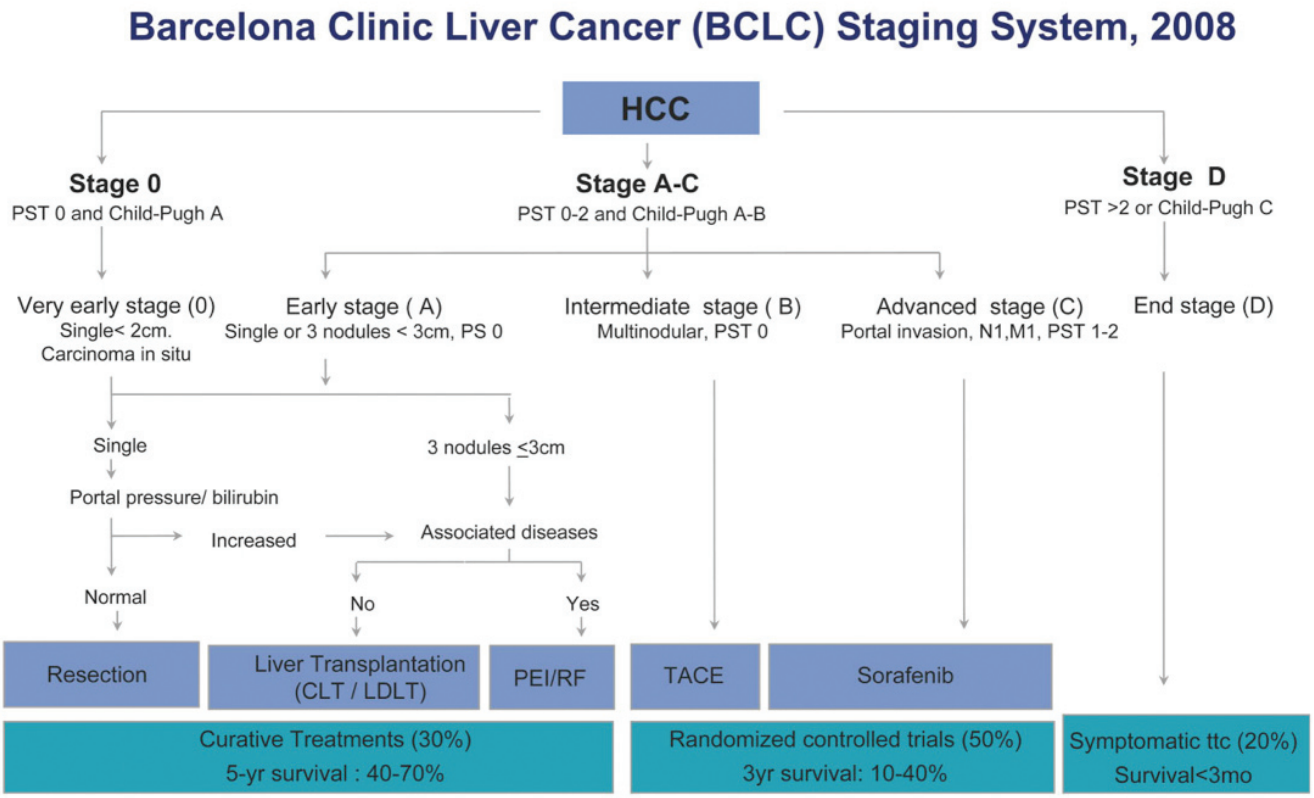


Figure 2: (Current stage-based evidence-based multidisciplinary approach to treating HCC).

Identifying Primary Functions, Goals and Objectives of a Virtual Multi-Disciplinary Advisory Team for Teenagers and Young Adults with Cancer: A Delphi Study

Dr Jo Daniels, BSc ClinPsyD,
Researcher,
Clinical Psychologist.
E: j.daniels@bath.ac.uk

Deirdre Brunton, MSc, BSc (Hons) PGCE, TYA PGcert, RGN,
Teenage Cancer Trust,
Funded TYA Lead Nurse.

Correspondence to:
Deirdre Brunton,
University Hospitals Bristol NHS Foundation Trust,
c/o Level 6, Bristol Royal Children's Hospital,
Upper Maudlin Street ,
Bristol, UK.
T: 0117 34 8292
E: Deirdre.brunton@uhbristol.nhs.uk

This study forms part of a project that was commissioned by the University Hospitals Bristol NHS Foundation Trust Non-medical Research Monies – "Above and Beyond Charity Appeal".

Abstract
The Improving Outcomes Guidance for Teenagers and Young Adults (TYA) with cancer (1) recommends improved access to specialist TYA services. Due to the large area covered by TYA Services in the South West, innovative approaches such as virtual multi-disciplinary teams (MDT) have been developed to achieve IOG standards. However, there is little evidence to help inform in the development of virtual teams. Using a Delphi technique (N = 8), our study set out to identify functions, goals and objectives of a TYA-specific virtual MDT. Findings suggest that they have the potential to adopt a multifaceted role in addressing the clinical needs of patients; developing skills and the knowledge bases of clinicians; and providing a forum that systematically meets the requirement of formal procedures. These findings provide a valuable resource to underpin development of similar teams where there is limited evidence to support this innovative process.

Introduction

In August 2005, NICE published guidance on Improving Outcomes for Children and Young People with Cancer, known as "Improving Outcomes Guidance" [1]. The IOG set out recommendations on how healthcare services for children and young people with cancer should be organised, focussing on the importance of ensuring that the holistic needs of teenagers and young adults (TYA) are met. The key messages of the document indicate that healthcare for this specific population should be inclusive, address their psychological and social needs, recognise the impact of a cancer diagnosis at a crucial stage of development, and be delivered in an accessible way. The document indicates that patients should be discussed at both site-specific MDT meetings and specialist TYA services, adopting a shared-care model of healthcare delivery. Whilst the document outlines potential care pathways and core principles, the operational needs of running a TYA service that can meet all of the IOG standards has fallen to service leads in cancer care.

A core component of guidelines in all of cancer care service is MDT working [2]. However, there are substantial time and resource constraints for a large number of professionals to attend additional meetings required in MDT cancer care [3]. This may be particularly so for the TYA clinical population as both paediatric and adult specialist services input may be necessary in the diagnostic and treatment process. Highly specialised MDT meetings pose a particular difficulty for rural and remote areas or when specialist centres are regional, which may compromise the equality of access and fail to satisfy the guidelines. A major challenge in oncology services is to deliver optimal therapy, when patients often do not live in close proximity to specialist services making it difficult for TYA services to meet IOG guidance [4]. For these reasons, a need has arisen to adopt and develop more innovative approaches, e.g. telemedicine.

Telemedicine emerged in the 1960s, with a steady proliferation of telemedicine and teleconferencing in the delivery of healthcare in the interim. The success of this approach may be attributed to the pivotal role telemedicine has in balancing resources and clinical demands, which is particularly pertinent in delivering healthcare to the TYA clinical population that requires specialist input including oncology, paediatrics, palliative care, nursing, psychology and social work.

However, communicating through technology is likely to produce social barriers, such as the absence of social cues that may hamper the development of a functioning team, [5] particularly when the technology is perceived to make interactions seem 'impersonal' [6]. Due to the reduction of social cues, relationships take longer to form which may directly influence the functioning of the group. Warkentin [7] observed that although previous studies found that virtual teams exchange information less effectively than at face-to-face meetings, this may also reflect how the team has developed as a whole. Once relationships within a team have formed and the team has adapted to the technology, telemedicine may be as effective as face-to-face interactions. Furthermore, it is possible that 'virtual' team work is adversely affected by the interruption of the flow of reciprocal communication due to members having different competency levels using the technology, or simply different speeds of typing or reading [4].

To achieve successful team working, clear shared goals and understanding of roles are imperative [8]. Furthermore, a consistent finding is that good team working is associated with better delivery of services in different work environments [9,10]. Evidence suggests that effective team working needs an established shared team culture, open communication and mutual respect, all of which may be negatively influenced by remote working, social barriers, and technological delays and issues [9,10].

Potential drawbacks in using telemedicine have been identified, despite the distinct advantages in using this medium in both achieving IOG standards and adequately meeting the needs of geographically dispersed specialist population such as TYA. It is important to address these potential difficulties to optimise the use of technological advances. Virtual multidisciplinary teamwork provides an innovative and pragmatic solution to the geographical and logistical difficulties presented in the delivery of healthcare to teenagers and young adults with cancer. Virtual MDTs may be well positioned to offer optimum equitable healthcare to those who are not in close proximity to specialised care. It may also offer accessibility to a range of specialists due to the patient's complexity of needs (e.g. TYA with cancer). However, the success in its solution will be dependent on the operational skills of the team hosting the technology.

Aims of the study

The purpose of this study was to establish the primary functions, goals and objectives of an established virtual TYA Multi-Disciplinary advisory Team (MDaT) through the use of the Delphi technique. The data generated could be used to underpin the development of future virtual or traditional MDTs delivering healthcare for teenagers and young adults with cancer, promoting improved team working, and thus benefitting patient care.

Context: the South West Region TYA MDaT

The TYA MDaT is a secondary approach to determine the unique needs of individual patients. This is a group of clinicians from a range of healthcare disciplines who come to together to discuss a patient between the ages of 16-24 with cancer.

The TYA MDaT team consists of the following professionals: lead TYA nurse; consultant clinical psychologist; social worker; clinical oncologist (TYA lead clinician); paediatric oncologist. These core professions are expected to attend all TYA MDaT meetings, and nominated palliative care and haematology consultants also regularly attend.

Clinicians make their contributions remotely at a specific time-slot using a virtual platform/meeting, so that it is not necessary for referrers or the TYA MDaT to be physically present in the same room for the meeting, facilitating optimum geographical patient treatment and support.

This pilot service innovation is possible through the introduction of an IT platform introduced by a private organisation, ISEEU™ Global Limited. ISEEU is an IT organisation that delivers information security software and expertise to the healthcare sector. Their technology platform supports innovative ways of collaborative, remote working, and adheres to compliance by minimising the data loss risk of sharing valuable confidential data.

Methodology

Delphi methodology is used to obtain relevant and intuitive insight of a panel of experts (in this case of the TYA team) in an anonymous group communication to attain an informed judgment on a topic as systematically as possible [12]. Therefore, due to the new and innovative nature of this virtual TYA team, the technique was the most appropriate for achieving the objective of operationally defining the team functions, goals and objectives.

The method uses a panel of experts in a group communication that usually takes the form of questionnaires or emails, and uses three or more rounds to achieve a consensus view or general agreement. The initial questions posed to the panel are designed to elicit and develop individual responses; in further rounds, responses of all the experts are presented and the experts are required to refine anonymously their views in light of those expressed by other participants as the group's work progresses [12].

Table 1: The primary function of the TYA MDAT

- Register patients on relevant cancer registries/databases
- Forum to discuss psychosocial issues
- Forum to discuss complex cases
- Provide specialist advice for TYA healthcare professionals
- Recommend further support for TYA patients
- Encourage clinical trial recruitment
- Discuss all new and recurrent active TYA patients
- Add value to service that a TYA patient was already receiving
- Improve outcomes of TYA as per Improving Outcomes Guidance
- Clinician peer support
- Improve TYA 'patient experience'
- Promote optimal medical management and care that is developmentally appropriate
- Address psychological and social needs of the patient

Email was used to conduct a three-round Delphi study

Sample

Rowe and Wright [13] suggest that between 2-12 participants is sufficient for a small Delphi study. The aim, therefore, was to recruit all core members of the innovative TYA MDAT of the South West Region.

All core members (N = 8) of the TYA MDAT covering the South West Region were invited to participate and convene as a virtual panel, who remained anonymous throughout. The core members participated in each round. Six out of eight participants were female. The sample included representatives from a multi disciplinary group: Clinical Oncologist, Medical Oncologist, Clinical Psychologist; Paediatric Oncologist; Palliative Care Consultant; Social Worker; and Nursing representatives. They had a shared interest and demonstrated commitment to TYA specific clinical work.

Procedure and data collection

The initial questions of the Delphi were as follows:

1. What should the primary function of the TYA MDAT be?
2. What should the shared goals and aims of the team be?

Participants were asked to generate a free-text response to the questions, which was collapsed into common elements. These elements were compiled within a questionnaire format. Participants were asked to rate their opinion as to whether the element was important to answer the question, rating the element on a five-point Likert scale ranging from one "completely irrelevant – to include would be detrimental" to five "very important – must be included to fully answer the question".

Table 2: Shared goals and objectives of the TYA MDAT

- Meet primary functions of MDAT
- Provide highest level of advice and support on TYA issues
- Improve 'patient experience' of care
- Ensure patients are offered clinical trials where appropriate
- Ensure psychological and social needs TYA patient are
- Engage and support teams providing care for TYA
- Working collaboratively to improve outcomes for TYA
- Ensure patient is offered all appropriate avenues of support
- Involve palliative care where appropriate
- Provide patient-centred care in partnership with service-users
- Deliver/outline provision of best care for TYA
- Achieve Improving Outcomes Guidance standards
- Identify who will action decisions
- Provide developmentally and chronologically specific support
- Identify family needs
- Co-create service with TYA users
- Add to national evidence base of TYA work

Data analysis

Based on previous studies using the Delphi technique to indicate consensus agreement, the panel was required to demonstrate complete agreement or less than one point Inter-Quartile Range (IQR) on the importance of the elements [14].

Results

The primary function of TYA MDAT

Twenty-four elements were extracted from the eight email responses from the first round. This was collapsed to eighteen elements. To develop an agreed definition of the primary functions of the TYA MDAT all elements rated as "fairly important" or "very important", and an inter-quartile range of <0 were retained and stated in Table 1.

The shared goals and objectives of the TYA MDAT

Twenty-seven elements were extracted from the eight email responses from the first round Delphi study. This was collapsed to 17 elements. To develop an agreed definition of the shared goals and objectives of the TYA MDAT all elements rated as "fairly important" or "very important" and an inter-quartile range of <0 have been retained as Table 2.

Discussion

This Delphi study generated thirteen primary functions of the South West Region MDaT. These primary functions fall into three further categories: formal, clinical and professional functions.

Formal function elements include registering patients on relevant databases, encouraging trial recruitment and using the TYA MDaT to 'improve outcomes' as per the IOG guidance. This indicates that the MDaT meetings can be used as a forum to systematically fulfil requirements of the IOG guidance in a coordinated way, e.g. ensuring that all eligible patients in the region are registered on databases and clinical trials.

Clinical function elements are patient-focused and include discussing all new clinical cases to ensure optimum treatment; adding value to the service that the patient is already receiving; promoting optimal medical management and care that is developmentally appropriate; addressing psychological and social needs of the patient and improving patient experience. These functions show potential benefits of telemedicine that are less likely to be achieved through locality-based traditions of MDTs. Due to the increased accessibility of virtual team working, patients referred to the MDaT probably receive higher levels of participation by experts from a range of health professionals, both from their own locality and regional specialist centres. This may increase the quality of treatment and achieve optimum use of TYA-specific services. Team working across the region is also likely to improve communication between local and regional teams, which in turn should promote good team working, and increase awareness of roles and group cohesion – all factors associated with a better delivery of services [11,12].

In the third category, participants generated elements that related to addressing and developing the skills of clinicans using the virtual platform. This category included the following: providing specialist advice for TYA healthcare professionals; clinician peer support; recommending further support for TYA patients; and a forum to discuss complex cases and psychosocial issues.

The shared emphasis on both addressing the needs of the patient and the clinician demonstrates a key function of this particular MDaT - the 'advisory' element of the MDT. The South West TYA MDaT consciously evolved from a traditional MDT in which cases are managed by individual team members to adopting a more advisory role, enabling the team to work collaboratively with others across the region in a coordinated way that should increase the skills of referring clinicians, and disseminate relevant knowledge about TYA-specific resources in the region. By adopting this model, participation might increase as MDaT clinicians can offer advice and expertise without case management responsibility of additional cases, therefore benefitting the patient, the referring clinician and limiting the costs to MDaT clinicians.

Seventeen shared goals and objectives were generated by the TYA MDaT. Elements of the goals/objectives were mainly to ensure achievement of the identified functions of the team and the IOG, as previously discussed. Additional aspects in this section included inter-agency liaison, such as engaging and supporting other TYA services, working collaboratively, providing and co-creating care in partnership with service-users. This suggests that a core theme of the goals/objectives was to promote the use of the TYA MDaT within the broader cancer care context, particularly relating to Patient and Public Involvement (PPI) in services. This has been a priority and a highly valued aspect of service innovation, development and implementation in recent years by the Department of Health [15]. Furthermore, it contributes to a wider evidence base in the treatment of cancer among the TYA population, further benefitting the patient.

The element "identify who will action decisions" indicates the importance of specific roles within the team, echoing previous findings [6]. This suggests that this is an opportunity for development within this relatively new team.

In summary, it is evident that the functions of a MDaT or a TYA MDT are multifaceted. As with traditional MDTs, there are requisite procedures and policies that require adherence; however, emergent themes suggest that developing clinicians' own skills that can be generalised is as high a priority as achieving optimum care for patients. Priority is also given to PPI and the broader context.

Clinical implications

Based on the previous developments of TYA services within the UK, there is no literature available to identify what a potential blueprint of a TYA service team could/should look like. The findings of this study can be used by other TYA teams to formalise their responsibilities and direction of energy when a service is in its earliest stages. It would enable clinicians to consider what solutions might be required to deliver an efficient service to meet the needs of all their TYA patients with cancer, taking into account their unique geographical and demographical requirements. New technological advances, such as an online platform, are core to the delivery of the TYA service, and it is evident that the development of the team around the technological solution is paramount to its effective operation. Delphi has enabled quantification of team goals and direction, in a diplomatic, democratic and statistically reliable way. The process enabled the team to engage with the challenges of virtual team working by using a whole-systems approach for transformational change to deliver a new service that co-exists with a traditional model of care. The purpose of the TYA MDAT is to add value to any experience the teenager and young adult diagnosed with cancer encounters, and the priorities identified using the Delphi technique provide a firm evidence base to deliver a high performance, high quality information and clinical governance compliant service.

Limitations

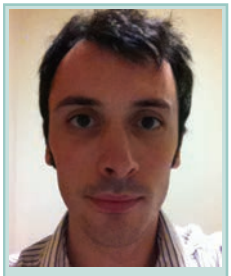
The Delphi study expert panel was sampled from a single TYA MDaT, and therefore may express opinions specific to the operation of this particular team. It may have benefitted the study to involve other experts in other teams as the outcome of the Delphi may have been influenced by the culture and expectations that have developed since the inception of the TYA MDaT in 2009.

However, the information generated from this Delphi study remains a valuable resource to inform future development of similar teams where there is currently limited relevant evidence to support this innovative process. ■

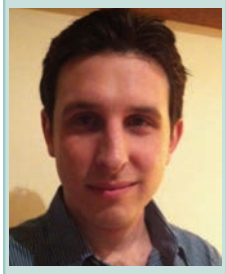
References

1. National Institute for Clinical Excellence (2005) Improving Outcomes in Children and Young People with Cancer.(CSGCYP) accessed from http://guidance.nice.org.uk/CSGCYP.
2. Kunkler IH, Fielding RG, Brebner J, Prescott R, Maclean J, Cairns J et al. *A comprehensive approach for evaluating telemedicine-delivered multidisciplinary breast cancer meetings in southern Scotland.* Journal of Telemedicine and Telecare, 2005;11(1):s71-3.
3. Holland AJ, Soundappan SV, Oldmeadow W. *Videoconferencing surgical tutorials: bridging the gap.* Annual Journal of Surgery 2008;78:297–301.
4. Augestad MK, Lindestmo R. *Overcoming distance: videoconferencing as a clinical and educational tool among surgeons.* World Journal of Surgery 2009;33:1356-65.
5. Olver IN, & Selva-Nayagam S. *Evaluation of a telemedicine link between Darwin and Adelaide to facilitate cancer management.* Telemedicine Journal, 2000;6(2);213-8.
6. Axford AT, Askill C, Jones AJ. *Virtual multidisciplinary teams for cancer care.* Journal of Telemedicine Telecare, 2002;8(2):3-4.
7. Warkentin M, Sayeed L, Hightower R. *Virtual teams versus face-to-face teams: an exploratory study of a web-based conference system.* Decision Sciences, 1997;28(4);975.
8. Stokols D, Misra S, Moser R, Hall K, Taylor B. *The ecology of team science: understanding contextual influences on transdisciplinary collaboration.* American Journal of Preventative Medicine, 2008;35(2s):s96-s115.
9. Gosling S, Westbrook J, Braithwaite J. *Clinical team functioning and IT innovation: a study of the diffusion of a point of care online evidence system.* Journal of American Medical Informatics Association, 2003;10(3);244-51.
10. Borrill C, West M, Shapiro D, Rees A. *Team working and effectiveness in healthcare.* British Journal of Healthcare Management, 2000;6(8):364-71.
11. Adler M and Ziglio E. (1996) *Gazing into the oracle: the Delphi method and it's application to social policy and public health.* London: Jessica Kingsley.
12. McAleer J, O'Loan D,.Hollywood D. *Broadcast quality teleconferencing for oncology.* The Oncologist, 2001;6;459-62.
13. Rowe G & Wright G. (2001). *Expert opinions in forecasting: Role of the Delphi technique.* In J. Armstrong (Ed.), *Principles of forecasting: A handbook of researchers and practitioners*. Boston: Kluwer Academic Publishers.
14. Roos J & Wearden A. (2009) *What do we mean by "socialization to the model"? A Delphi Study*. Behavioural and Cognitive Psychotherapy, 2009;37;341-5.
15. Department of Health (2004) *Patient and Public Involvement in Health: evidence for policy implementation*, London: Department of Health.

Use the Stairs: Fitness Optimisation Before GI Cancer Surgery



Alistair Connell,
Foundation Year 1,
Upper GI Surgery,
Department of General Surgery, GI Division,
University College London Hospitals NHS Foundation Trust.



Gavin Schaller,
Foundation Year 2,
Upper GI Surgery,
Department of General Surgery, GI Division,
University College London Hospitals NHS Foundation Trust.

Khaled Dawas,
Senior Lecturer and Honorary Consultant Upper GI Surgeon,
Department of General Surgery, GI Division,
University College London Hospitals NHS Foundation Trust.

Correspondence to:
Khaled Dawas
khaled.dawas@uclh.nhs.uk

Malignancy involving the gastrointestinal (GI) tract is common. In western populations, colorectal cancers are more prevalent than oesophageal and gastric tumours. The latter two represent the fifth most common cancers diagnosed each year. Typically, they are found in an elderly population, and because their presentation is often late, they account for almost 10% of deaths attributable to cancer. GI cancers are seen most often in men, and increase in incidence with age [1]. As it is more common in the elderly, many patients will have multiple medical co-morbidities, which may increase the risks of surgery. For elective colorectal cancer resections, 30 day mortality may reach 5%; for oesophagectomy and gastrectomy patients, it can be as high as 15% [2].

Historically, our ability to predict which patients will require higher levels of peri-operative care is poor, with recent studies describing a significant number of deaths occurring in patients where transfer to a critical care setting was delayed [3]. GI cancer surgery patients represent one such 'high risk' group. Deciding which patients are at the highest risk could improve outcomes at surgery, and ensure hospital resources are used effectively.

This review seeks to highlight different methods in stratifying risk in GI cancer surgery patients. The effects of both neoadjuvant therapy and surgery on patient fitness will then be discussed.

Means of assessing fitness for surgery

Surgery is a major challenge to the body's physiological systems. Any inability to meet these demands will put an individual at increased risk of morbidity and mortality. Pre-operative assessment aims to ensure that those at high risk receive an appropriate level of peri-operative care [4].

Pre-operative measurements of fitness can take several forms. Questionnaires such as the Duke Activity Status Index (DASI) use questions about the patient's activities of daily living. However, this questionnaire was developed for use in cardiac patients, and it's usefulness in the context of other major surgeries is less well understood. Risk stratification scores are also used, from simple methods (such as ASA grading), to more complex systems (such as the POSSUM index). Interestingly, patients assessed as being high risk in the opinion of their operative surgeon were found to have worse outcomes [5].

More objective assessments of exercise tolerance can take a number of forms; stratifications of risk using an incremental 'shuttle walk' test have been found to correlate with more high-tech exercise tests.

The fitness of high-risk patients may be assessed using echocardiography and spirometry. However, such tests do not reflect the body's ability to deal with the physiological stress that surgery mandates. Stress echocardiography and treadmill exercise tolerance tests have been found to be poor at predicting post-operative ischaemic cardiac events, but they are able to establish which patients are at low risk [6].

In cardiopulmonary exercise testing (CPEX), patients are exercised using a bicycle or treadmill. The intensity of exercise is gradually increased until maximal exertion is reached. Breath-by-breath analysers allow the total oxygen used and carbon dioxide produced by the patient to be calculated. ECG monitoring is typically performed at the same time.

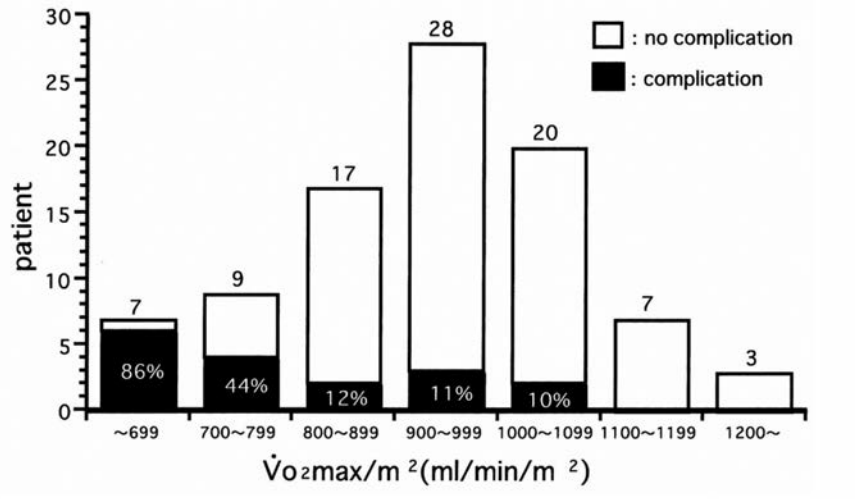


Figure 1: A graph showing cardiopulmonary complication rates following thoracic oesophagectomy as a function of VO_2max.[8]

In the initial aerobic phase of exercise, total expired carbon dioxide increases linearly with oxygen intake, reflecting the CO_2 that is produced aerobically in muscle tissue. As exercise intensity increases, oxygen demand begins to outstrip supply. The product of anaerobic metabolism – lactic acid – is buffered by bicarbonate in the bloodstream. This is seen as a disproportionate rise in exhaled CO_2 relative to oxygen consumption. The point at which this change happens is called the ventilation threshold (VT). An individual's maximum ability to extract oxygen from the air during exercise is termed the 'VO_2max'. Measuring such parameters in exercise is useful, as they act as a surrogate marker for the physiological processes that affect them: gas exchange in the lungs, the fitness of the cardiovascular system, and the performance of the muscles themselves. This point underlies the advantages of CPEX testing over other conventional pre-operative assessment tools; it aims to subjectively assess the body's physiological systems under stress, and in unison. Importantly, it may also be used to guide peri-operative management. For this reason, CPEX testing may be used pre-operatively to assess an individual's fitness for surgery, acting as a proxy for the 'metabolic insult' that surgery represents.

Whilst the utility of CPEX testing in the context of cardiac and major intra-abdominal surgery has been discussed at length, there are far fewer data regarding its usage in GI cancer patients. One study has found a correlation between VO_2max and the rate of cardiopulmonary complications in oesophagectomy patients [7]. This is seen in Figure 1.

However, others have found that CPEX testing was not a useful predictor of post-operative complications in oesophagectomy patients [8]. Similarly, the use of exercise testing in colorectal cancer is poorly understood.

Neoadjuvant treatments

Modern treatment regimes may be multimodal, involving pre-operative chemotherapy and radiotherapy. Whilst they improve survival, such regimes can impact dramatically on quality of life, often leaving side effects long after treatment has finished. They may also have direct effects on cardiovascular fitness; this can be explained in part by side affects such as anaemia and cardiac dysfunction. Indeed, fatigue affects a large proportion of patients undergoing chemoradiotherapy. Other side effects such as nausea may make exercise more difficult. For these reasons, physical 'de-conditioning' in the setting of adjuvant treatments may be expected. This decline in fitness might affect outcome following surgery. However, the detrimental effects of chemotherapy on physical performance can be reduced by structured programs of aerobic exercise during treatment [9].

In a study of colon cancer, an increase in physical activity following diagnosis led to fewer cancer-specific deaths. Exercise has also been found to improve patient-rated outcomes such as depression, anxiety, and quality of life [10].

The effects of surgery

For oesophageal cancer, resection surgery is associated with high rates of morbidity and mortality. Post-operative care may involve long stays in high dependency units, and a lengthy recovery. Techniques involving thoracotomies by necessity collapse a lung. Minimally invasive approaches may have the potential to improve morbidity and the length of hospital stay, and aim to reduce rates of respiratory complications such as pneumonia and atelectesis though this has yet to be proven. Recovery from such complications can be arduous; patients are often frail, and malnourished.

In colorectal cancer patients, 'fast track' post-operative recovery pathways involving the multidisciplinary team have been implemented with the aim of improving care and decreasing complication rates. Studies report a return to pre-morbid physical fitness within one year in colorectal surgery for cancer [11]. However, there is little information on recovery of physical fitness in oesophagogastric (OG) cancer patients.

Means of improving pre-operative fitness and reassessment

Regular exercise may decrease the incidence of colon cancer in population studies, but its effects following diagnosis are less well understood. One study found that increasing levels of exercise after diagnosis improved outcomes in colorectal cancer. High levels of physical activity prior to diagnosis did not appear to have the same effect [12]. The effects of pre-operative exercise regimes on fitness in patients with OG cancer are poorly understood and a study is in place to look at this aspect.

Conclusions

Whilst UK guidelines suggest that all patients diagnosed with GI malignancy should undergo a thorough assessment of fitness, how this should be attained is less clear. Furthermore, there is evidence to suggest that improving physical fitness following diagnosis may have beneficial effects on outcome. Exercise also has a role to play in rehabilitation, and may help limit the detrimental effects of treatment on function and quality of life.

Our knowledge of neoadjuvant therapy and surgical techniques is expanding. However, much of the work surrounding fitness optimisation in the context of malignant disease has focused on breast and lung cancer. In particular, there are few data on oesophageal and gastric cancer patients. Further studies are needed to clarify the best approach to peri-operative assessment and management. ■

References

1. Management of oesophageal and gastric cancer - a national clinical guideline. SIGN guideline 87. Accessed at http://www.sign.ac.uk/pdf/sign87.pdf on 01/03/11.
2. Davies SJ, Wilson RJ. Br J Anaesth. *Preoperative optimization of the high-risk surgical patient.* 2004;93(1):121-8.
3. Pearse RM, Harrison DA, James P, Watson D, Hinds C, Rhodes A, Grounds RM, Bennett ED. *Identification and characterisation of the high-risk surgical population in the United Kingdom.* Crit Care. 2006;10(3):R81.
4. Struthers R, Erasmus P, Holmes K, Warman P, Collingwood A, Sneyd JR. Br J Anaesth. *Assessing fitness for surgery: a comparison of questionnaire, incremental shuttle walk, and cardiopulmonary exercise testing in general surgical patients.* 2008;101(6):774-80.
5. McCulloch P, Ward J, Tekkis PP; ASCOT group of surgeons; British Oesophago-Gastric Cancer Group. *Mortality and morbidity in gastro-oesophageal cancer surgery: initial results of ASCOT multicentre prospective cohort study.* BMJ. 2003;327(7425):1192-7.
6. Davies SJ, Wilson R,. Br J Anaesth. *Preoperative optimization of the high-risk surgical patient.* 2004;93(1):121-8.
7. Nagamatsu Y, Shima I, Yamana H, Fujita H, Shirouzu K, Ishitake T. *Preoperative evaluation of cardiopulmonary reserve with the use of expired gas analysis during exercise testing in patients with squamous cell carcinoma of the thoracic esophagus.* J Thorac Cardiovasc Surg. 2001;121(6):1064-8.
8. Forshaw MJ, Strauss DC, Davies AR, Wilson D, Lams B, Pearce A, Botha AJ, Mason RC. *Is cardiopulmonary exercise testing a useful test before esophagectomy?* Ann Thorac Surg. 2008;85(1):294-9.
9. Dimeo F, Fetscher S, Lange W, Mertelsmann R, Keul J. *Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy.* Blood. 1997;90(9):3390-4.
10. Spence RR, Heesch KC, Eakin EG, Brown WJ. *Randomised controlled trial of a supervised exercise rehabilitation program for colorectal cancer survivors immediately after chemotherapy: study protocol.* BMC Cancer. 2007;7:154.
11. Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, Ladha AB, Proulx C, Vallance JK, Lane K, Yasui Y, McKenzie DC. *Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial.* J Clin Oncol. 2007;25(28):4396-404.
12. Meyerhardt JA, Giovannucci EL, Holmes MD, Chan AT, Chan JA, Colditz GA, Fuchs CS. *Physical activity and survival after colorectal cancer diagnosis.* J Clin Oncol. 2006;24(22):3527-34.

Conference News

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

3rd ICHNO

Date: 24-26 February, 2011. **Venue:** Barcelona, Spain.

The 3rd International Conference on innovative approaches in Head and Neck Oncology (ICHNO) ook place in Barcelona in February 2011. A gentle sun provided a warm multi-disciplinary welcome away from rainy home and Gaudi rapidly became the hallmark of the meeting. The spread of participants was slightly skewed with 33% clinical oncologists, 12% head and neck surgeons, 46% radiation oncologists and 9% from other groups.

We started off with a keynote lecture by Kian Ang who gave an overview of randomised trials and the background for the chosen experimental arms. HPV positive patients do better (or more reliably: HPV negative, P16, do worse) and as in 2009 the question remains: can we decrease treatment and side effects for the prognostically more favorable group? An interesting observation was the continued anti-tumour effect of prolonged Cetuximab administration after chemoradiation.

Kaanders reported on the, overall negative, ARCON trial. In the case of hypoxia Arcon was effective. The Danish group proved the value of a sustained database on trials in head and neck cancer: not surprisingly, but clear from the data, co-morbidity is a determining prognostic factor for patients suffering from head and neck cancer, more so than in other tumour regions. Overall: the days that treatment selection was based upon classic TNM criteria are over. We need to do better than that. P16 positivity, less than 10 pack years... Trials testing more specific tumour criteria with tailored treatment are ongoing.

In the afternoon proferred papers were presented. Dr Takes demonstrated that microarray evaluation better predicts nodal metastasis than conventional investigations. Furthermore, the case was made for nimorazole in combination with radiotherapy especially in hypoxic tumours. Given the few side effects, why isn't it used more widely? Dr Nuyts reported on P16 and HPV-ve patients, they do as well as HPV+ve patients. The question that remains is: Is 80% good enough?

Friday stressed the multidisciplinary approach with technological advances on imaging, radiotherapy, nuclear imaging and robotic surgery. Exciting possibilities emerge for the tiny virtual surgeon. Operating from what would otherwise be impossible positions provides new possibilities with minimal side effects. Care should be taken to select patients without the need for adjuvant treatment.

Imaging gradually improves and diffusion MRI predicts response earlier than conventional MRI. Current PET imaging is 95% FDG based. This is likely to change; more tailored agents can better distinguish between tumour and inflammation.

In the afternoon the swallocopies for wing problem after radiotherapy was addressed. The main factors for late swallowing toxicity are chemotherapy with radiation and the dose to the upper pharyngeal constrictor. Langendijk demonstrated the need for standardisation in delineating the swallowing organs at risk. With different, published, guidelines the dose to the upper pharyngeal constrictor muscle varied from more than 60 to less than 40 Gy. However, a clear improvement in predicted normal tissue complications is possible with swallowing-sparing radiation techniques. Cleverly designed trials are needed to validate this assumption.

Keynote lecture from Kian Ang: "Don't forget the HPV negative patients!" – 650 professionals of radiation oncology participated to the 3rd ICHNO.

Mucositis in radiation remains a large concern. New drugs are being tested in phase II trials to accelerate regeneration of the mucosa. Given the high prevalence and impact on the quality of life this is an important field to watch.

After recurrent cancer, outcome is poor with radiation, surgery or chemotherapy. Surgical salvage treatment for recurrent cancer is possible but with a high complication rate of 72%. Good tumour control results were presented by C Leemans. What is promising is that with proper selection "once irresectable: always unresectable" 49% disease free survival can be achieved, with 31% DFS after chemoradiation. With new stereotactic radiation treatments re-irradiation with hypofractionation seems possible but control rates remain poor. In the case of metastatic disease, polychemotherapy provides higher response rates but no improvement in survival. The addition of anti-EGFR to chemotherapy provides higher response rates especially in the presence of acneiform rash as a treatment side effect.

New targeted agents provide yet more possibilities in treating head and neck tumours. More and more treatment selection will be based upon molecular imaging and predictors for treatment specific outcome. ■

Dr Coen Rasch,
The Netherlands Cancer Institute,
Amsterdam, The Netherlands.

12th International Breast Cancer Conference

Date: 16-19 March, 2011. **Venue:** St Gallen, Switzerland.

Gene expression testing works in Europe

Region specific data, presented at St Gallen, showed that gene expression testing was readily applicable to European patients with early stage breast cancer.

The Oncotype DX breast cancer test, developed by Genomic Health, provides a snap shot of tumour activity at the molecular level by measuring the expression of 21 genes using real time PCR on tumour blocks to measure levels of RNA. Readouts are then fed into mathematical equations to produce the patient's Recurrence Score® (RS), giving a numerical value to the woman's likelihood of benefitting from chemotherapy and experiencing a metastasis over the next 10 years on a scale 0 to 100.

"In the past we've used a one size fits all approach where all women with early stage breast cancer get offered chemotherapy," said Steven Shak, from Genomic Health. "But in reality only four out of 100 women actual benefit, with the remainder experiencing unnecessary toxicity."

The Oncotype X test is widely used in the US (where it was launched in 2004) and is now routinely offered to women with stage I or II node negative and oestrogen receptor positive disease. What has been less clear, however, is whether the Oncotype DX test would be valuable in European health care settings that traditionally use less chemotherapy.

At St Gallen Simon Holt, a surgical oncologist at the Prince Philip Hospital (Llanelli, Wales) presented a prospective analysis of 107 patients who had undergone testing at the South West Wales Breast Cancer Network (abstract P196). The team analysed how many women who had initially been evaluated with the Nottingham Prognostic Index (the current evaluation tool) had treatment decisions changed following evaluation with Oncotype DX technology.

Results showed that 33% of patients in the study had their treatment decisions changed, with 23.6% changing from receiving both chemotherapy and hormone therapy to just receiving hormone therapy and 9.4% changing from just receiving hormone therapy to receiving hormone therapy plus chemotherapy. "From the clinical perspective it's probably more important to identify those patients who'll benefit from chemotherapy," said Holt, adding that patients were quite happy to undergo treatment once they appreciated its importance.

Scalp cooling does not pose a risk for scalp metastases

Scalp cooling offers a "viable and effective method" for preventing hair loss during cancer treatments and does not appear to pose a risk for scalp metastases, concluded a US overview of 83 papers, presented at St Gallen.

Hair loss is a distressing and common side effect of chemotherapy that can be reduced by scalp cooling, the concept being that low temperatures reduce blood flow to the scalp and the metabolism of chemotherapy.

In the overview study Hope Hugo and colleagues, from the UCSF Comprehensive Cancer (San Francisco, California), reviewed 83 papers published between 1972 and 2009 involving more than 4,000 patients and four cooling systems including DigniCap, Penguin, Paxman and Gel Caps.

The investigators found that seven randomised trials (including 12 to 77 patients) reported good hair preservation in 10 to 100% of patients, with six out of seven studies demonstrating a significant improvement for patients randomised to treatments over those randomised to the control group. In 12 non randomised trials, 46 to 100% of patients were reported to have good to excellent hair preservation. The six studies, involving 1593 patients, that evaluated the incidence risk of scalp metastases, showed that 10 patients (0.6%) developed scalp metastases. None, however, was found to be an isolated site of first metastasis. The success of scalp cooling in hair preservation, the investigators found, was dependant on the type of chemotherapy regimen used, with worse outcomes obtained for the combination of anthracyclines and taxanes.

Coffee protects against oestrogen receptor negative breast cancer

High intakes of coffee were found to be associated with a statistically significant decrease in the risk of oestrogen receptor negative (ER negative) breast cancers, concludes a joint Swedish and Singapore study presented at St Gallen (abstract P150).

While previous studies have suggested that high coffee consumption is associated with a modest reduction in breast cancer risk, a meta-analysis of over 500 papers relating the consumption of coffee to cancer in various sites reported a null association with breast cancer risk. "But the complex make-up of chemicals in coffee may differentially affect breast cancer of different oestrogen subtypes," explained Jingmei Li, first author of the study.

For example, trigonelline, a phytoestrogen present in coffee extract, has been suggested to activate oestrogen receptors through an oestrogen-independent mechanism.

In the current study Li and colleagues from the Karolinska Institute (Stockholm) and Genome Institute of Singapore, explored the association between coffee consumption and breast cancer (stratified according to oestrogen receptor tumour subtypes) among 2,818 cases of breast cancer and 3,111 controls.

In the stratified case-control analysis investigators found that the incidence of oestrogen receptor positive breast cancer was 66% less likely to occur among women who drank more than five cups of coffee a day in comparison to those who drank less than one cup. "We found no evidence that coffee consumption increases the overall risk of postmenopausal breast cancer. However, a high daily intake of coffee was found to be associated with a significant decrease in ER-negative breast cancer among postmenopausal women," said Li, adding that further studies are needed to confirm the effects of coffee consumption according to breast cancer subtypes. ■

Janet Fricker, Medical Journalist.

Progress In Vaccination Against Cancer – PIVAC-11

Date: 10-13 October, 2011. **Venue:** Copenhagen, Denmark. **PREVIEW**

We welcome you all to the next PIVAC meeting "The Eleventh International Conference on Progress in Vaccination Against Cancer" (PIVAC-11) which will be held from 10th-13th October 2011, in Copenhagen, Denmark. The meeting will cover all aspects of therapeutic cancer vaccinations, and retain a relaxed and informal atmosphere for scientific discussions and interactions. PIVAC-11 will be held at the Radisson Blu Royal Hotel in the centre of Copenhagen, a convenient location in the heart of Copenhagen, the Radisson Blu Royal Hotel is regarded as the city's most harmonious high-rise.

The meeting will be up to a maximum of 100 participants and will provide much scope for close interactions among attendees in addition to offering an exciting programme of presentations.

Invited Speakers:
Hinrick Abken, Cologne, Germany
Else Marie Agger, Copenhagen, Denmark
Jim Allison, New York, USA tbc
Mads Hald Andersen, Herlev, Denmark
Sjoerd van der Burg, Leiden, Holland
Chen Dong, Texas, USA
Lindy Durrant, Nottingham, UK
Leisha Emens, Baltimore, USA
Victor Engelhard, Virginia, USA
Tom Gajewski, Chicago, USA
Federico Garrido, Granada, Spain
Cécile Gouttefangeas, Tübingen, Germany
Patrich Hwu, Texas, USA tbc
Joseph Lustgarten, USA
Sue Ostrand-Rosenberg, Baltimore, USA
Graham Pawelec, Tübingen, Germany
Anne Marie Rasmussen, Oslo, Norway
Ton Schumacher, Amsterdam, Holland
Barbara Seliger, Halle, Germany
Andy Sewell, Cardiff, UK
Jolanda de Vries, Nijmegen, Holland

Two EACR Poster Prizes of 100 EUR will also be awarded and certificates presented at the Conference Dinner and Awards Ceremony.

The Trade Exhibition will be open throughout on Tuesday 11th and Wednesday 12th October 2011 in room "Eggett" directly opposite the Meeting Auditorium "Svanen". We look forward to welcoming you to Copenhagen.

Scientific Organising Committee
Per thor Straten
Graham Pawelec
Lindy Durrant

For further information visit:
www.eacr.org/pivac11/index.php
or T: +44 (0)115 9515114
E: kathryn.wass@nottingham.ac.uk

14th World Conference on Lung Cancer

Date: 3-7 July, 2011. **Venue:** Amsterdam, The Netherlands. **PREVIEW**

On behalf of the International Association for the Study of Lung Cancer (IASLC) and the Local Organising Committee we are pleased to invite you to the 14th World Conference on Lung Cancer, taking place from in July 2011 at the RAI Amsterdam Exhibition and Convention Centre, Amsterdam, The Netherlands.

The World Conference on Lung Cancer is the leading global forum for Lung Cancer and will welcome more than 7,000 experts from a wide range of disciplines from all regions of the world. The Amsterdam Conference will continue the extraordinary success of previous meetings in Seoul and San Francisco, and will provide a legacy and foundation for those to come in Sydney in 2013 and Denver in 2015.

The groundbreaking programme encompasses exciting discoveries in prevention, imaging and early detection of lung cancer, novel approaches to molecular biology and pharmacogenomics of lung cancer and their effect on personalised lung cancer treatment as well as many other topics at the cutting edge of thoracic oncology. Results from recent clinical trials related to mesothelioma and thymoma, new palliative care options for individuals with lung cancer as well as the efficacy of tobacco control methods being used throughout the world will be discussed.

The 14th WCLC will provide a wonderful forum for you to explore innovations and advances in the treatment of lung cancer, and to meet and interact with colleagues and leaders in the field of thoracic oncology.

A special Young Investigator's Session will be held on 3rd July which is specifically designed for those in the early stages of their career. Hands-On Training Sessions are a brand new addition to the outstanding Programme. These courses will take place on Sunday, 3rd July and provide a fantastic opportunity to receive one-on-one guidance from leading international experts. Repeated self performances using various systems and models will guarantee a wonderful and valuable learning experience.

Amsterdam is home to some of the world's most acclaimed artistic works and offers a great variety of historical and cultural treasures. There are plenty of ways for visitors of any age to explore Amsterdam and there is something for everyone to enjoy. We hope you will join us for a symphony of outstanding science.

14th World Conference on Lung Cancer
IASLC

Important Dates:
Abstract Submission Deadline – 25 February 2011
Early Registration Deadline – 1 April 2011
Regular Registration Deadline – 20 May 2011

Please visit the Conference website at www.2011worldlungcancer.org for further information.

Diary of Events

If you would like an event listed in the Oncology News diary please send the relevant information to E: Patricia@oncologynews.biz by June 5th, 2011.

May

NEW

UK Cutaneous Lymphoma Annual General Meeting
5 May, 2011; Manchester, UK
W: www.christie.nhs.uk/pro/education/events
E: education.events@christie.nhs.uk

3rd IMPAKT Breast Cancer Conference
5-7 May, 2011; Brussels, Belgium
T: +41 (0)91 973 19 94
F: +41 (0)91 973 19 18
E: impakt@esmo.org
W: www.impakt.org

GEC-ESTRO-ISIORT Conference
7-10 May, 2011; London, UK

11th Biennial Conference on Physics and Radiation Technology for Clinical Radiotherapy
8-12 May, 2011; London, UK

EIOF ESTRO International Oncology Forum Clinical Perspectives in Radiation Oncology
8-12 May, 2011; London, UK
W: www.estro.org

Student Nurse Study Day: Developing Clinical Practice Skills
11 May, 2011; London, UK
T: +44 (0)207 808 2921
E: conferencecentre@rmh.nhs.uk
W: www.royalmarsden.nhs.uk/conferences

ASGBI 2011 International Surgical Congress: 21st Century Surgery
11-13 May, 2011; Bournemouth, UK
W: www.asgbi.org.uk

National Mortuary Conference
12 May, 2011; Manchester, UK
E: education.events@christie.nhs.uk
W: www.christie.nhs.uk/pro/education/events

Acute Cancer Care (6 day course)
12, 19, 26 May, 2, 9 & 23 June, 2011; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W: www.royalmarsden.nhs.uk/school

NEW

Non-Malignant Study Days - COPD Study Day
13 May, 2011; Middlesex, UK
E: anni.hall@nhs.net

Lymphoedema in Cancer Care – Blended Learning
Weekly e-learning activities commence 16 May 2011 + practical workshops on 14 & 15 June, 2011; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W: www.royalmarsden.nhs.uk/school

The Operon Model and its impact on modern molecular biology
17-20 May, 2011; Paris, France
W: www.eacr.org/meetings.php

EMSOS 2011, the 24th Annual Meeting of the European Musculo-Skeletal Oncology Society and 12th Symposium of the EMSOS Nurses/AHP Group
18-20 May, 2011; Ghent, Belgium
W: www.emsos2011.be or www.emsos.org

BACR Meeting: Cancer Epigenetics
19 May, 2011; London, UK
W: bacr.org.uk
E: bacr@leeds.ac.uk

NEW

British Gynaecological Cancer Society Scientific Meeting
19–20 May, 2011; Cardiff
E: BGCS@in-conference.org.uk

NEW

UK Management of Testes Cancer Meeting
20 May, 2011; Glasgow, UK
Lesley Forsyth
T: +44(0)131 623 4728
F: +44(0)131 623 4503
W: www.sign.ac.uk

NEW

Radiotherapy Study Day 6-Research your future
21 May, 2011; Middlesex, UK
E: anni.hall@nhs.net

Casley-Smith Update (Unaccredited)
24-26 May, 2011; Glasgow, UK
Mrs Margaret Sneddon, Programme Director,
T: +44 (0)141 330 2071/2072,
E: lymph@glasgow.ac.uk
W: www.gla.ac.uk/departments/nursing/

NEW

Symptom Control at End of Life
25 May, 2011; Middlesex, UK
E: anni.hall@nhs.net

Clinical Leadership in Cancer Care (5 day course)
25 May, 8, 22 June, 6 & 20 July 2011; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W: www.royalmarsden.nhs.uk/school

NEW

1st National Conference of the Independent Association of Nurses in Palliative Care (IANPC)
26 May, 2011; Lancaster, UK
E: heather@compleatconference.co.uk or W: ianpc.org

IDIBELL Cancer Conference (ICC) on Metastasis and Angiogenesis
26-27 May, 2011; Barcelona, Spain
W: www.eacr.org/meetings.php

June

Innovative Practice in Neuro-Oncology
2 June, 2011; London, UK
T: +44 (0)207 808 2921
E: conferencecentre@rmh.nhs.uk
W: www.royalmarsden.nhs.uk/conferences

American Society of Clinical Oncology (ASCO) Annual Meeting
3-7 June, 2011; Chicago, Illinois, USA
W: www.asco.org/annualmeeting

Chemotherapy in Cancer Care (5 day course)
6, 7, 8, 23 & 25 June 2011; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

NEW

Radiotherapy Study Day 6 - Research your future
21 May, 2011; Middlesex, UK
E: anni.hall@nhs.net

Managing Complicated Lymphoedema Casley-Smith DLT (3 parts)
8-10 June, 2011; Glasgow, UK
Mrs Margaret Sneddon, Programme Director,
T: +44(0)141 330 2071/2072,
E: lymph@clinmed.gla.ac.uk
W: http://www.gla.ac.uk/departments/nursing/

NEW

3 Day Assessing & Managing Symptoms at EoL
9+29+30 June, 2011; Plymouth, UK
Marilyn Prowse
T: +44(0)1752 436763
E: marilyn.prowse@stlukes-hospice.org.uk

World Conference on Interventional Oncology 2011
9-12 June, 2011; New York, NY, USA
W: www.wcio2011.com

BAHNON National Study Day
10 June, 2011; Cardiff, Wales
Annette Beasley
E: Annette.Beasley@wales.nhs.uk
T: +44(0)29 207 43479

Breast Cancer Care
13-17 June 2011; London, UK
T: +44 (0) 20 7808 2900 E: school@rmh.nhs.uk W. www.royalmarsden.nhs.uk/school

NEW

Palliative Care Day 2, All AHP
14 June, 2011; Middlesex, UK
E: anni.hall@nhs.net

Smoking Cessation and the Cancer Patient
17 June, 2011; London, UK
T: +44 (0)207 808 2921
E: conferencecentre@rmh.nhs.uk
W: www.royalmarsden.nhs.uk/conferences

NCRI Cancer Conference 6 - 9 November 2011

Plenary speakers

Michael Hall (Switzerland)

Michael Stratton (UK)

Hans Clevers (The Netherlands)

Maria Blasco (Spain)

Harald zur Hausen (Germany)

Jeffrey Settleman (USA)

Murray Brennan (USA)

Sir Mike Richards (UK)

Eva Grunfeld (Canada)

John Potter (USA)

The Conference is the major forum in the UK for showcasing the **best British and international cancer research**, bringing together the **leading experts across all disciplines** with a compelling mix of **high-quality plenary speakers, symposia and parallel sessions**, including **focused satellite meetings and workshops.**

Also featuring symposia on

Cancer screening and prevention
Hosted by Robert Steele

Epithelial mesenchymal transition
Hosted by Nicholas Hastie

Living with and beyond cancer
Hosted by Peter Selby / Julia Brown

Predictive models of human cancer
Hosted by David Tuveson

Metabolism and cancer
Hosted by Eyal Gottlieb

The diagnostic and therapeutic potential of the tumour microenvironment
Hosted by Thorsten Hagemann

Epigenetics and cancer
Hosted by Peter Adams

Stratified medicine
Hosted by Alan Ashworth

Important dates for the 2011 NCRI Cancer Conference

Abstract submission opens:
Monday 21 March

Abstract submission deadline:
Friday 13 May

Registration opens:
Wednesday 1 June

Late breaking abstract submission opens:
Monday 11 July

Earlybird registration deadline
Monday 1 August

Late breaking abstract deadline:
Wednesday 31 August

Online registration deadline:
Friday 30 September

NCRI Cancer Conference commences:
Sunday 6 November

BNOS
British Neuro-Oncology Society

UNIVERSITY OF CAMBRIDGE
Cambridge University Hospitals NHS
NHS Foundation Trust

BNOS 2011

Targeting Heterogeneity & Individualising Therapy

29th June - 1st July

Annual Meeting & Teaching Programme

Homerton College, Cambridge

neurooncology.org.uk/bnos2011

Further details from:
Dr Colin Watts
BNOS 2011 LOC Chair
Department of Neurosurgery
Cambridge University Hospitals NHS Foundation Trust. Cambridge, UK
Email: nos2011@addenbrookes.nhs.uk

WIN Worldwide Innovative Networking in personalized cancer medicine

REGISTRATION ONLINE
WWW.WINCONSORTIUM.ORG

JULY 6th–8th 2011

Palais des Congrès, Paris [France]

3rd WIN Symposium

in personalized cancer medicine

A forum for open discussion in which your expertise and input is crucial

Dr. John Mendelsohn. President of the MD Anderson Cancer Center and Chairman of WIN Consortium

2011: Gateways to efficacy of cancer diagnostics and therapeutics

> Evidence for efficacy of targeted therapies
> Improving efficacy of biomarker-driven clinical trials
> Discovering new targets and predictive biomarkers
> Combinations of targeted drugs
> Advances in technology, bioinformatics and systems biology

Poster/ abstract submission deadline **May 15th 2011**

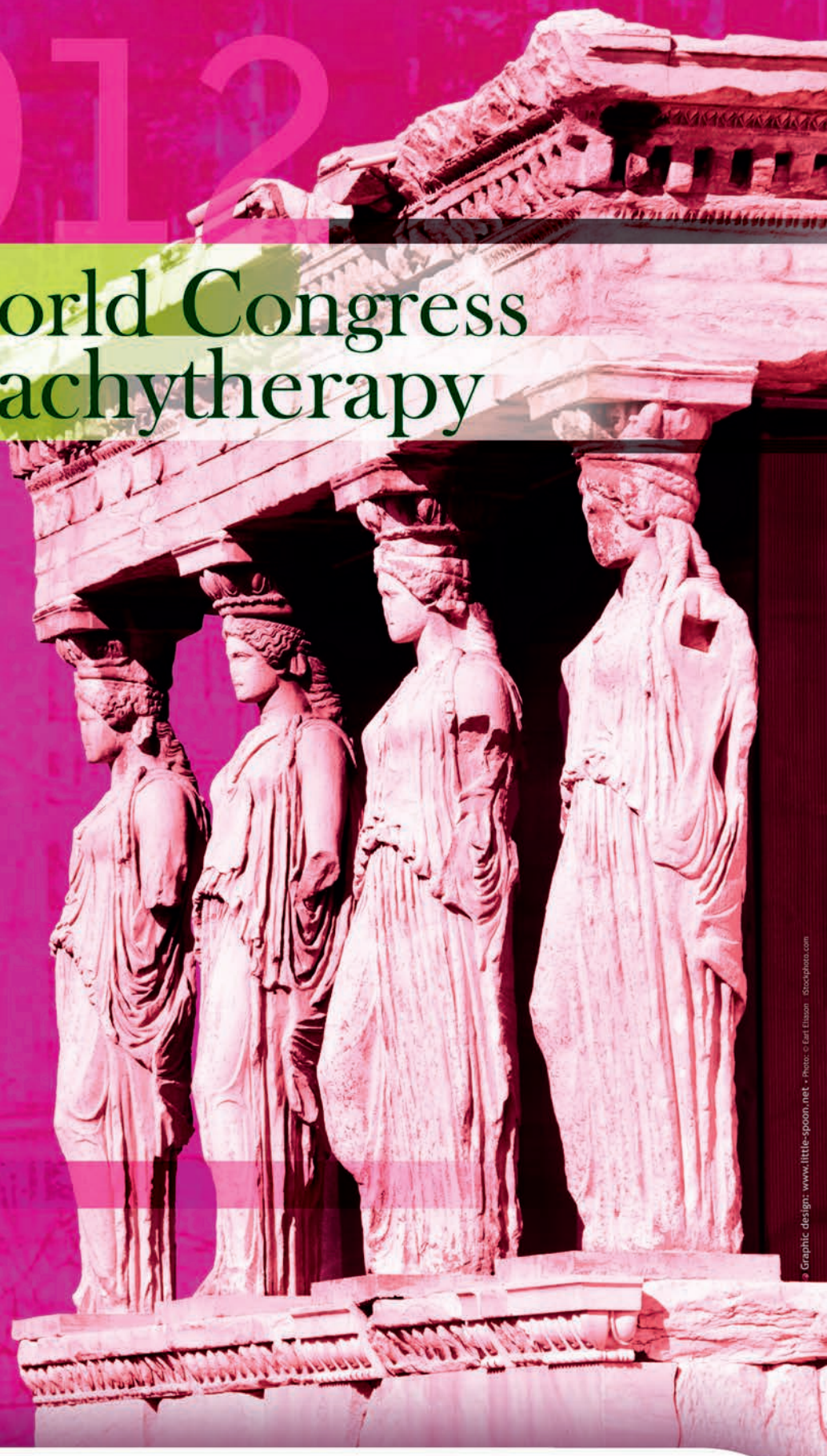
ACTREC · Ben-Gurion University of the Negev · Fondazione IRCCS Istituto Nazionale dei Tumori · Shanghai Cancer Center Fudan University · GE Healthcare · Hospital de Barretos · VHIO Vall d'Hebron Institute of Oncology · Hadassah

Institut de cancérologie Gustave Roussy Villejuif · www.igr.fr · Fundeni Clinical Institute for Digestive Diseases · King Hussein Cancer Center · life technologies · National Breast Cancer Foundation, Inc. · National Cancer Centre Singapore SingHealth · Oncology Institute I. Chiricuta Cluj-Napoca - Romania

Sage Bionetworks · Agilent Technologies · Segal Cancer Centre at the Jewish General Hospital · Semmelweis University Faculty of Medicine Budapest · The Chaim Sheba Medical Center at Tel Hashomer - Est. 1948 The Hospital of Israel · UMF · The University of Texas MD Anderson Cancer Center Making Cancer History®

2012

World Congress of Brachytherapy



May
10-12
2012
Athens
Greece

WWW.ESTRO.ORG

Journal Reviews

Head & Neck

Perceptual characteristics of tracheoesophageal speech production using the new indwelling Provox Vega voice prosthesis: A randomised controlled crossover trial

This is a novel approach taken by the Speech therapy dept from Brisbane, Queensland, Australia to look into new voice prosthesis. Provox Vega Indwelling prosthesis (Atos Medical, Horby, Sweden) is a new, one way valve with the housing and valve made out of medical grade silicone rubber and a radioopaque valve seat made out of fluoroplastic. The device is optimised to improve the airflow characteristics and provide enhanced protection for the valve flap from esophageal mucosa. The objective of the study was to determine if the design enhancements incorporated into the new Provox Vega Indwelling Voice prostheses result in any positive benefits in vivo. Using a randomised, crossover study design, and 31 participants using tracheoesophageal speech post-laryngectomy completed a 3-week trial of the Provox Vega and a comparator device. The comparator device was Blom-Singer Classic Indwelling prosthesis. Main outcome measures included patient perceptions of vocal effort and quality using each device, and perceptual judgments of voice quality produced. The majority of patients (72%) indicated the Provox Vega gave them overall better voice quality and 52% felt they required less effort to phonate. Voice samples produced with the Provox Vega were also perceived by listeners to be significantly ($p<0.05$) less strained, easier to understand, produced with less effort, and the better speech sample overall. Results support that the aerodynamic improvements incorporated in the design of the new Provox Vega facilitate enhanced voice and speech qualities. This outcome can be attributed to enhanced airflow properties of the new device. There is also need for further trials to find the best indwelling prosthesis. – MD

Ward EC, Hancock K, Lawson N, van As-Brooks CJ.
Head & Neck • 2011:33(1);13-19.

Voice-related quality of life (V-RQOL) outcomes in laryngectomees

Laryngeal cancer and its treatment have a direct and significant impact on quality of life of patients, especially to post-treatment voice loss. This study compared the Voice-Related Quality of Life (V-RQOL) outcomes specific to three different post-laryngectomy voice rehabilitation methods i.e. electrolaryngeal speech, oesophageal speech and tracheoesophageal speech. Our goal as surgeons is for optimal speech outcome. The study is a retrospective review of 75 patients with laryngectomy from the institute (Dept of Otolaryngology, Division of Head & Neck Oncology and Reconstructive Surgery, Schulich School of Medicine and Dentistry, University of Western Ontario) V-RQOL questionnaire database. The database included 18 electrolaryngeal speech (ELS), 15 esophageal speech (ES), and 42 tracheoesophageal speech (TES) patients. Pairwise comparisons of V-RQOL outcomes showed that TES was perceived to be better than ELS ($p<.001$). ES was perceived as better than ELS, but this was driven by a difference in the total and social–emotional V-RQOL scores ($p<0.05$). There was no significant difference between TES and ES groups. ELS showed a positive correlation with time after surgery and older age. Patients using TES had similar V-RQOL outcomes compared to ES and both performed significantly better than ELS. For ELS, the total V-RQOL score was better with longer time after surgery and older age. The study is limited by its retrospective nature. However the study gives an interesting conclusion. It indicates that ES when achievable is a viable option and can give good outcomes. Outcome is also dependant on patient dedication and speech therapist. – MD

Moukarbel RV, Doyle PC, Yoo JH, Franklin JH, Day A, Fung K.
Head & Neck • 2011;33(1):31-6.

Tumour volume as prognostic factor in chemoradiation for advanced head and neck cancer

Background: Tumour volume is an important predictor of outcome in radiotherapy alone. Its significance in concomitant chemoradiation (CCRT) is much less clear. We analysed the prognostic value of primary tumour volume for advanced head and neck squamous cell carcinoma (HNSCC) treated with CCRT.

Methods: Three hundred sixty patients treated with definitive CCRT for advanced HNSCC were selected. The pretreatment MRI or CT scan was used to calculate the primary tumour volume. Median follow-up was 19.8 months.

Results: The average primary tumour volume was 37.0cm^3 (range, 2.1–182.7cm^3; median, 28.7cm^3). Multivariate analysis showed a significant effect of tumour volume on local control. The hazard ratio for a local recurrence increased by 14% per 10cm^3 volume increase (95% CI, 8% to 21%). There was no significant independent effect of T and N status on local control.

Conclusion: For advanced HNSCC, tumour volume is more powerful for predicting outcome after CCRT than TNM status.

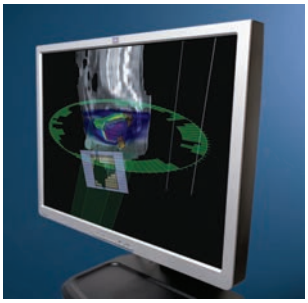
Reviewers view: HNSCC is a cause of considerable morbidity and mortality. These days role of CCRT is well established and has become important and standard in the treatment locally advanced HNSCC. Predictors of outcomes are not clear. On several occasions TNM information has failed to predict response. This paper shows the importance of primary tumour volume as an important prognostic factor and a predictor for disease control and survival in patients with advanced HNSCC treated with CCRT. For advanced tumours, conventional TNM staging is an insufficient prognostic indicator of outcome after a multimodal treatment strategy. This can be used in pretreatment patient selection, thereby improving treatment results and avoiding unnecessary toxicity. – MD

Knegjens JL, Hauptmann M, Pameijer FA, Balm AJ, Hoebers FJ, de Bois JA, Kaanders JH, van Herpen CM, Verhoef CG, Wijers OB, Wiggenraad RG, Buter J, Rasch CR.
Head Neck • 2011:33(3):375-82.

News update

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

St James's Institute of Oncology first in the UK to use new VMAT radiation technique



St. James's Institute of Oncology, Leeds is the first radiotherapy centre in the UK to employ a new treatment procedure using Nucletron's Oncentra VMAT (Volumetric Modulated Arc Therapy). The new method was introduced into clinical routine at the end of 2010. VMAT reduces treatment time and may significantly reduce the risk of serious side effects for patients.

Dr Vivian Cosgrove, leading physicist, Radiotherapy Department, St. James's Institute of Oncology, says, "We achieve shorter treatment time by moving the linac continuously around the patient during radiation. At the same time, we can change the speed of this movement, strength of radiation and shape of the radiation field throughout the procedure. In conventional IMRT treatment, radiation can be given only from certain angles. During the move from angle to angle, the beam has to be switch off again and again."

For further information visit:
www.nucletron.com
E: helen.hanratty@uk.nucletron.com
T: + 44 (0)7764 831828.

Leeds Teaching Hospitals NHS Trust Pass 100th Patient Milestone for Treatment for Lung Cancer

Setting the pace for lung SBRT, clinicians at St. James's University Hospital are gaining more confidence at seeing and hitting lung tumours, a difficult task before the introduction of advanced technology. For many of the more than 100 patients treated, doctors have used Symmetry™ motion management software, new imaging technology from Elekta that enables clear visualisation of moving targets.

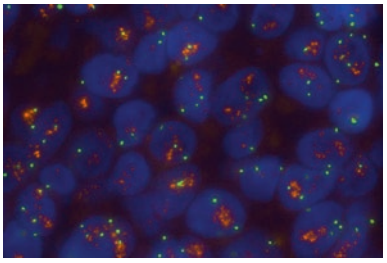
"For certain patients – those with lung tumours that move a large amount during breathing – Symmetry has been incredibly useful," says John Lilley, physicist at St. James's, part of Leeds Teaching Hospitals NHS Trust.

"The standard 3D volume imaging system on our Elekta Synergy® system is great for imaging targets that remain still, but moving objects become blurred," he explains. "However, by taking the 4DCT planning scan – which shows the 'envelope' of space within which the tumour is moving – and matching that to

Symmetry reconstructions, which show the tumour's position during the breathing cycle, we can easily localise moving tumours."

For further information contact:
Patrick Greally, Elekta Ltd,
T: +44 (0)1293 654 462,
E: Patrick.Greally@elekta.com
W: www.elekta.com/symmetry.

Leica Microsystems Releases Fully Automated HER2 FISH Test



Breast Cancer Specimen stained with the Leica HER2 FISH System showing amplification of the HER2 gene.

Leica Microsystems has announced the European release of the fully automated Leica HER2 FISH System for the Leica BOND advanced staining system. The Leica HER2 FISH System combines the use of the gold standard PathVysion® HER2 FISH probes, supplied by Abbott Molecular Inc, with Leica's industry-leading BOND automated platform.

Automation of labour intensive FISH techniques reduces process variation while offering walk-away convenience. Samples can be processed continuously, saving valuable hands-on time and allowing rapid reporting of patient results. This fully automated system uses an optimised ready-to-use Leica HER2 FISH reagent kit with a robust BOND protocol to produce consistent, high quality stained slides. The system enhances the laboratory workflow, increasing efficiency and enabling the laboratory to provide a responsive service to their clinicians and clients.

For further information contact:
Sarah Barnett, Theranostics Product Manager, Leica Biosystems Newcastle Ltd,
T: +44 (0)191 215 0567,
F: +44 (0)191 215 1152,
E: sarah.barnett@leica-microsystems.com
W: www.leica-microsystems.com

Nucletron UK successfully gains ISO 14001 accreditation

Nucletron UK, a leading provider of state-of-the-art radiotherapy solutions for cancer treatment has recently been awarded an SIO 14001 Certificate. ISO 14001 is a voluntary environmental management system, which requires constant commitment to environment planning and improvement.

Simon Richardson, Quality & Operations Manager at Nucletron UK comments, "ISO 14001, which is in addition to our ISO 901 certification, is a significant accomplishment for us, as it allows us to reduce the environmental impact of our products and provide a safer, healthier place in which to work. Nucletron in the UK takes quality issues very seriously and it is high on our agenda. As a responsible organisation we seek to achieve high standards, particularly in the handling of radiation oncology materials."

ISO 14001 is an internationally recognised accreditation. Its key requirement is that an environmental policy exists within the organisation, and is fully supported by the senior management of the company.

For further information visit:
www.nucletron.com
E: helen.hanratty@uk.nucletron.com
T: + 44 (0)7764 831828.

Mr Simon Richardson, Quality & Operations Manager at Nucletron UK.

Launch of relocatable radiotherapy treatment suite

Radiotherapy treatment in the UK and Europe is being transformed with the launch the modular, relocatable, stand-alone radiotherapy treatment suite, Pioneer™.

Julie Mead, Clinical Director of OSL said: "Pioneer reduces the risk and costs for hospital trusts. It can be moved closer to areas of patient need as they are identified over time and there's no need to undertake lengthy, costly bunker building projects."

The Pioneer is positioned on a pre-constructed concrete pad with access to utilities. The suite has changing rooms for patients, a reception and waiting area and treatment room housing a TomoTherapy HD.

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

New TimestripPlus™ shows when +8°C is breached

New TimestripPlus™ 8° temperature indicators can show at a glance whether your vaccine or medication has breached the recommended temperature level of +8°C and for how long.

TimestripPlus™ indicators are easy to use, simply activate at room temperature and apply the disposable indicator to your temperature sensitive item using the adhesive backing. Store the item below 8°C and the indicator will remain inactive. As soon as the temperature of the item rises above 8°C, a colour will travel along the view window. If a product is returned to a refrigerated environment and the temperature falls back to below 6°C, the indicator will stop. In addition TimestripPlus™ gives you the confidence to reallocate any unused medications that are returned to pharmacy, reducing waste and saving time. Helapet are the exclusive distributor of TimestripPlus™ for the NHS. TimestripPlus 8 deg has been independently validated for accuracy in both temperature and time.

For more information and FREE SAMPLES call 0800 0328 42.

1st Varian High Dose Rate Brachytherapy Afterloader in China

Jilin University No. 1 Hospital is now offering state-of-the-art treatment using GammaMed® brachytherapy afterloader from Varian Medical Systems. Brachytherapy treats cancer by placing radioactive sources directly into or next to the area requiring treatment, enabling clinicians to deliver a high dose with minimal impact on surrounding healthy tissues.

Doctors at Jilin said early brachytherapy treatments would focus on cervical and rectal cancers, explaining the decision to install Varian machines was based on the company's reputation for advanced systems and excellent service, as well as a desire to integrate the hospital's brachytherapy offering with its external beam systems, which are also supplied by Varian Medical Systems."

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

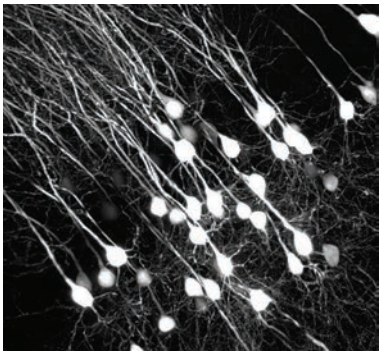
Nikon introduces streamlined A1 MP imaging system

In response to demand, Nikon has developed a streamlined version of its groundbreaking A1R MP multiphoton confocal imaging system. The new A1 MP scanner has been developed for simplified, cost-effective multiphoton imaging, whilst maintaining the sensitivity and quality of the highly respected A1R MP system. Multiphoton imaging is becoming increasingly popular for cell-friendly, dynamic live cell and deep tissue imaging. Budgetary constraints have, historically, prevented some laboratories from realising the full potential of this exciting technique.

Fluorescence detection is undertaken by Nikon's highly sensitive NDD detectors (Non Descan Detectors). The scanner is capable of frame rates up to 10 fps, depending on image size and can easily be upgraded to true spectral imaging using Nikon's renowned spectral detector.

The A1 MP imaging system can be used in conjunction with Nikon's upright FN1 microscope and inverted Nikon Ti-E microscope, where it can also be combined with a TIRF system and incorporated with the award winning Perfect Focus System for long term, deep tissue imaging with unsurpassed clarity and stability.

For more information on Nikon microscopes contact Nikon Instruments,
T: +44 (0)208 2471718,
E: info@nikoninstruments.eu
W: www.nikoninstruments.eu/



Fixed neuronal cells of mouse brain expressing eGFP. Image courtesy of Dr Satoru Kondo, Dept. of Cellular Neurobiology, Graduate School of Medicine, University of Tokyo, Japan.

Quick and easy test for colorectal cancer

The launch of the new ScheBo® • M2-PK Quick™ 'rapid test' brings benefits for doctors, patients and biomedical laboratory staff. Quick and easy to perform on a small 'one-off' stool sample, this is a sensitive and specific non-invasive test which facilitates the identification of those who require further investigation for colorectal cancer, polyps or other significant gastrointestinal diseases. The ScheBo® • Quick-Prep tubes provided in the test kit are a convenient method for patients to collect a small faecal sample and return it for testing. A positive M2-PK test result should be followed by appropriate further investigation (e.g. colonoscopy) for diseases of the gastrointestinal tract. Because M2-PK is a biomarker of altered glucose metabolism typical for colorectal and other cancers it can detect both bleeding and non-bleeding tumours and polyps, without imposing pre-test restrictions on the patient's diet or medication.

For further information contact: Ivor Smith, ScheBo Biotech UK Ltd,
T: +44 (0)1256 477259,
E: i.smith@schebo.co.uk

Managing complexity

so you can focus on what matters

Advanced therapies made easier

Radiotherapy techniques are becoming increasingly sophisticated, requiring more time and skill to ensure safe delivery. By simplifying the variables in planning, patient setup, treatment verification, and delivery, Elekta gives you greater confidence to define and raise the standard of human care. Visit us at elekta.com/experience.

Experience the Elekta Difference

ELEKTA