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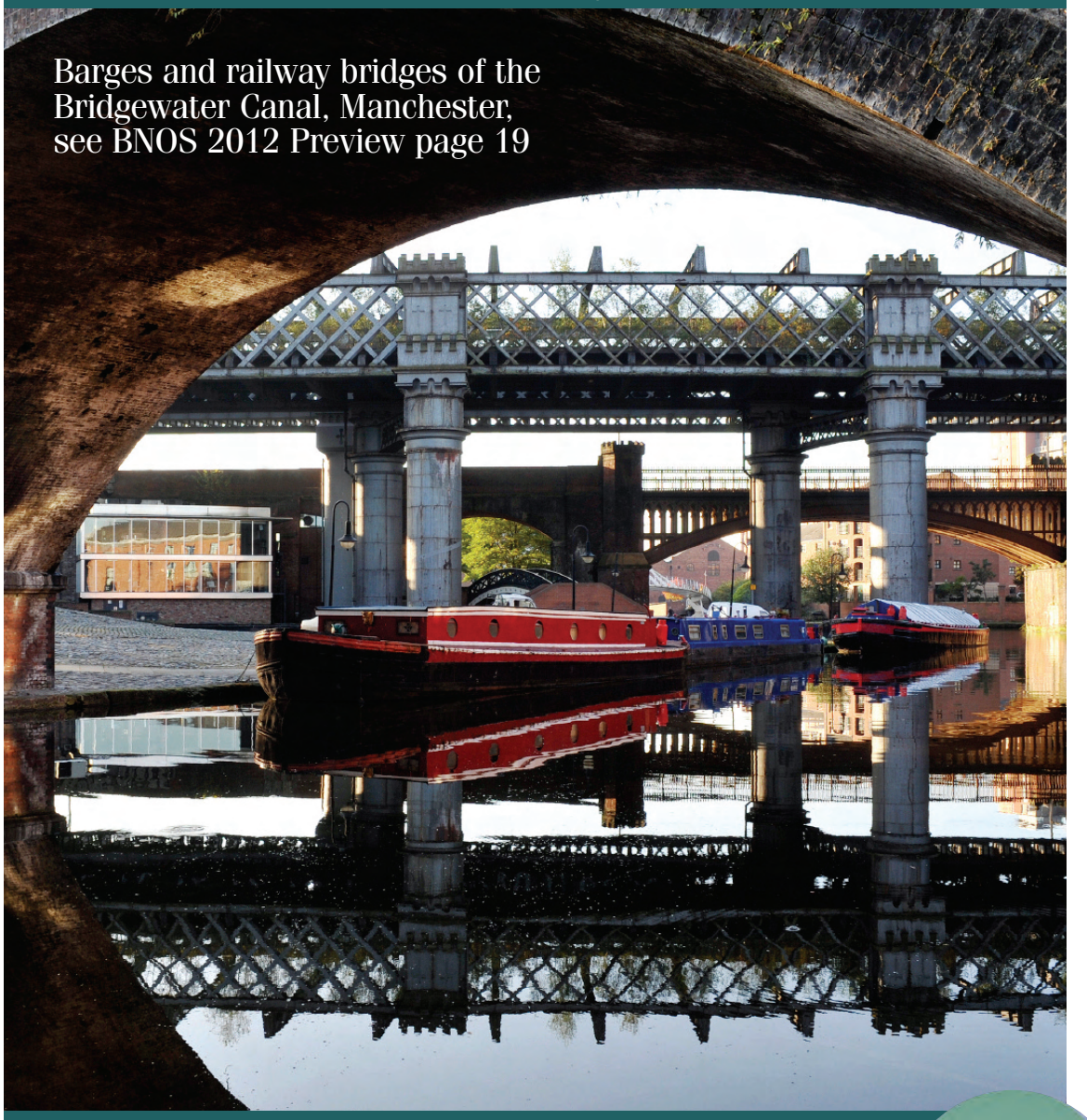

Barges and railway bridges of the Bridgewater Canal, Manchester, see BNOS 2012 Preview page 19

In this Issue

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Invasiveness of Cancer Cells Revisited

Brian L Pipes

Richard J Ablin

Metastatic cancer, unlike benign tumour growth, can be conceptualised as a second independent cancerous disease emerging from a primary tumour. Metastatic cancer dissemination, discussed in a recent editorial by Denys Wheatley [1], is 'the scourge of cancer'. Despite decades of investigations into the processes, the underlying mechanisms of cancer promotion remain disputed. The growing consensus is that chronic inflammation plays a major role [2], but there is no consensus on the key molecular mechanisms responsible. Although the concept of cancer stem cells is now well established, their exact identity and origins remains unclear [3]. A better understanding of the mechanisms involved in the initiation of metastatic disease could lead to more effective treatment modalities, and most importantly, novel means of preventing the development of metastatic cancer.

Recent studies by Shiozawa et al. [4,5] ascertaining the precise location metastasising prostate cancer (PCa) favours bone marrow, which is a fundamental advance in our understanding of the metastatic development. Aside from suggesting novel clinical interventions in metastatic disease, the findings give some insights into the fundamental mechanisms underlying the origin of metastatic cells. In advanced PCa, ~70% of the cases develop bone metastases as opposed to other tissues [6]. The reason PCa preferentially targets a precise microenvironment within the bone marrow remains unclear [7]. Shiozawa et al. [4] found that metastasizing PCa cells compete directly with haematopoietic stem cells (HSC) for the same niche as HSC, but the molecular basis for this, e.g. the chemoattractants and attachment factors involved, remains unclear. This astounding similarity between HSC and metastatic PCa cell behavior invites questions such as: can we take advantage of it to improve current treatment for PCa? And, is this similarity more than just functional, which may be merely the result of random genetic evolution and selection of unstable PCa cells, or are metastatic PCa cells fundamental in some way related to bone marrow stem cells [8]?

The hypothesis that metastatic cells are derived not from (as is commonly believed) local cancerous tissues, but rather from cells of the haematopoetic system has gained some support [9-11], in which it has been shown that circulating bone marrow derived cells (BMDC) contribute to the progression of cancers (e.g. gastric, breast) to the metastatic state. The identity of this BMDC is disputed, with some strongly favouring macrophages, and others supporting stem cells of haematopoetic or mesenchymal origin, as also the mechanisms involved. Chronic inflammation, whether the result of infection, wounding, or even unrepairable genetic damage (see the recent *New York Times* headline [12] featuring the research of Baker et al. [13]), leads to the recruitment of circulating BMDC, which help local cells repair/replace damaged tissues. If the damage persists, the ongoing repair signals may eventually drive exhausted BMDC cells into a catastrophic last attempt at tissue repair/replacement by cell-cell fusion, in which they acquire the phenotype of a metastatic cell – widespread deregulated dissemination and growth. Yet these putative new metastatic cells retain much of their original phenotype – they continue to functional like circulating BMDC that home to their original niches. Regarding PCa, Shiozawa et al. [4,5] suggest that a circulating peripheral HSC that has a role in tissue repair is the BMDC from which metastatic PCa cells originate. Further work should show how a peripheral HSC recruited to a site of chronic inflammation in a hyperplastic prostate becomes dysfunctional and metastatic, while also acquiring prostate epithelial characteristics (Houghton and Wong [9] suggest some scenarios).

Whether the homing of PCa metastatic cells to bone marrow HSC microniches is due to an acquired HSC functional similarity, or a reflection of their origin from HSC, better knowledge of their behaviour could help improve PCa treatment. One possibility might address a clinical dilemma of PCa in which an apparently cured patient (via prostatectomy) is left with a substantial chance of delayed development of bone metastases (sometimes many years later). We can speculate that metastasised PCa cells in the bone remain quiescent, typically like HSC, while occupying the HSC niche. Perhaps, in this dormant state PCa cells remain undetected for years until something activates their proliferation or mobilises them. This dormancy might contribute to chemoresistance, another problematic feature of metastatic PCa because most cytotoxics kill only cycling cells. An improved chemotherapeutic treatment might chemically mobilise metastatic PCa cells from the HSC niche, as is commonly done in HSC transplant settings prior to chemotherapy, rendering PCa cells sensitive to chemotherapeutic agents. A caveat is that mobilisation should preferably target PCa cells and not HSC.

Beyond envisaging new treatments, the possibility that HSC-like metastatic PCa cells arise from an inflammation-driven promotion process (e.g. BMDC fusion with prostate epithelial cells) suggests that metastasis might be prevented by suppression of chronic inflammation [14]. An alternative or complementary approach would focus on interfering with the process cell fusion [15]. These novel approaches require much further research.

brian.pipes@gmail.com
ablinrj@email.arizona.edu

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Contents

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* Locally advanced or metastatic breast cancer that has progressed following use of at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments[1]

Reference **1.** Halaven Summary of Product Characteristics. 2011 **2.** Cortes J *et al. Lancet* 2011; 377: 914 -23.

Date of preparation: May 2011 Job code: Eribulin-UK2053

Nano-Mediated Gene Delivery:

a revolutionary treatment to deliver cytotoxic nitric oxide to breast tumours

Dr Helen McCarthy,
Senior Lecturer in Experimental Therapeutics
School of Pharmacy,
Queen's University Belfast.

Prof Tracy Robson,
Chair in Experimental Therapeutics,
School of Pharmacy,
Queen's University Belfast.

Correspondence:
School of Pharmacy,
Queen's University Belfast,
97 Lisburn Road,
Belfast BT9 7BL, UK.

Breast cancer has become the most common female malignancy in the UK, accounting for almost a third of all new diagnoses. Unfortunately the current options for disseminated disease, involving chemo- and hormone therapy, are mainly palliative because of the development of hormone refractory or chemotherapy resistant cells that have a propensity to disseminate to distant bone sites. For women in this position the outcome is bleak. Thus, there is a desperate need for better treatment options for those with this disease. Gene therapy has been identified as a possible option for the treatment of metastatic disease [1,2].

Nitric oxide ($NO^{\bullet}$) is a highly reactive free radical with a lipophilic nature that can easily diffuse through cell membranes and tissues when present in high concentrations [3]. $NO^{\bullet}$ is produced by nitric oxide synthase enzymes, of which there are three isoforms: neuronal NOS (nNOS), endothelial NOS (eNOS) and inducible NOS (iNOS). The iNOS isoform can generate up to 1000 fold greater quantities of $NO^{\bullet}$ than either nNOS or eNOS. High levels of $NO^{\bullet}$ confer many of the ideal characteristics of an anti-cancer molecule, which include inhibition of angiogenesis and metastasis, radio- and chemosensitisation coupled with the induction of apoptosis. Therefore $NO^{\bullet}$ is ideally placed to augment current conventional cancer treatments.

iNOS Gene Therapy

We have previously utilised an iNOS gene expression plasmid in a gene therapy approach where iNOS expression was controlled through transcriptional targeting using a broad spectrum of promoters. For example the use of the externally radiation-inducible WAF-1 promoter to control iNOS expression resulted in high levels of $NO^{\bullet}$ mediated cytotoxicity in a range of tumour cell lines and radiosensitisation (with sensitizer enhancement ratios (SERs) 1.6-2.5) in rodent and human tumour models both *in vitro* and *in vivo* [4]. These effects were also achieved using clinically-relevant fractionated radiation *in vivo* [5]. We have also controlled expression of the iNOS gene using the tumour specific human osteocalcin promoter (hOC). The main transcription factor that activates the hOC promoter is RUNX2. Furthermore, those tumours that have a propensity to metastasise to bone sites have been shown to have elevated levels of RUNX2 [6]. The hOC-iNOS plasmid has shown exquisite specificity for both androgen independent prostate cancer and oestrogen independent breast cancer cells *in vitro* coupled with cytotoxicity comparable to that of constitutively expressed iNOS [7]. *In vivo* data has also confirmed the potency of hOC-iNOS gene therapy in a mouse xenograft model of human prostate (PC-3) cancer; multiple intra-tumoural injections slowed tumour growth dramatically and lead to some complete responses. On average, tumour growth was delayed by 59 days compared to vector only controls. This data thus supports the premise that tumour-specific promoters can effectively drive iNOS monotherapy giving long term tumour control [8]. Given that metastatic breast tumours have also been shown to have high levels of RUNX2, hOC-iNOS gene therapy could be delivered to patients with this disease.

The data generated thus far with iNOS gene therapy *in vivo* has been via intra-tumoural injection, limiting the clinical potential of this therapy to accessible primary tumour sites, since to date, there are no safe and suitable delivery vehicles to facilitate systemic gene delivery to distant metastases. For systemic administration of therapeutic genes, a suitable vector for clinical applications should have low cytotoxicity, be non-immunogenic, have a high transfection efficiency at the target site and be cost effective. Unfortunately, all currently-available vectors have significant limitations. For example high transfection efficiency can be achieved by liposomes but there are problems with size heterogeneity of the particles and direct cytotoxicity [9]. Cationic polymers are robust and biocompatible but they have poor gene-transfer efficiency [9]. The high efficiency and recombinant engineering possibilities of viral vectors give them the delivery edge, but safety and toxicity issues have limited their use for systemic gene therapy [9]. Therefore the ideal delivery system should have the biocompatibility of polymers, efficiency of liposomes and the engineering capability of viruses.

Figure 1: The Designer Biomimetic Vector is a fusion protein comprised of several discrete sequences that include: NLS - Nuclear Localisation Signal, DCM – DNA condensing motif, EDM - Endosomal Disruption Motif, CS - Cathepsin Substrate and TP-Targeting Peptide. The iNOS plasmid (piNOS) is condensed by the DCM.

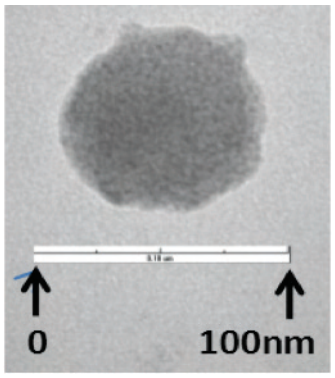

Figure 2: A representative Transmission Electron Microscopy image of the size and shape of a typical DBV/piNOS nanoparticle.

Designer Biomimetic Vectors

The perfect delivery vector should be designed to overcome several biological barriers associated with gene delivery. Such biological barriers include stability in the circulation, extravasation to the target tissues, cellular entry, endosomal disruption and active transport to the nucleus. Several peptide sequences already exist in nature that can perform some but not all of these functions. For example the TAT peptide can penetrate cells, the SPKK repeating motif in Histone 1 can condense DNA, the influenza virus HA2 can disrupt endosomes and the Rev protein from the HIV-1 virus is an excellent nuclear localisation signal [9]. One of the key components for successful gene delivery is to actively transport the DNA across the nuclear membrane to the nucleus where it can be transcribed and then translated into the active protein. A functional nuclear localisation signal (NLS) is critical for maximising gene expression. In the absence of such a NLS, the DNA will only enter the nucleus during cellular division when the nuclear membrane dissolves, and this significantly reduces the transfection efficiency. Advances in genetic engineering facilitate the biosynthesis of such functional motifs and enable the design of vector architecture at a molecular level. Using such technology, Designer Biomimetic Vectors (DBV) can be created that are essentially fusion proteins. These bio macromolecules are designed to mimic viral characteristics in order to overcome the biological barriers associated with gene transfer. They are comprised of several discrete motifs, each with a single function.

As a proof of principle we utilised a Designer Biomimetic Vector to deliver the iNOS gene to breast cancer cells. The DBV has a DNA condensing motif (DCM) obtained from the adenovirus mu peptide [10], a ZR-75-1 breast cancer cyclic targeting peptide (TP) for specific delivery of the nanoparticles [11], an endosomal disruption motif (EDM) that mimics the influenza virus fusogenic peptide [12] and a nuclear localisation signal (NLS), rev, obtained from the human immune-deficiency virus type-1 [13]. In addition, a cathepsin D substrate (CS) is also engineered within the DBV structure to facilitate dissociation of the targeting peptide from the vector inside endosomes, where cathepsin D is abundant (Figure 1) [14]. This DBV fusion protein was expressed in Escherichia coli BL21 (DE3) pLysS cells and was shown to have a molecular weight of 22.8 kDa. Nanoparticles were formed when the DBV was added to the iNOS DNA at a range of N:P ratios (N:P is the molar ratio of nitrous atoms of the DBV vector to phosphates in pDNA). We reported that the DBV was able to neutralise the charge of the iNOS plasmid from N:P ratios 8 upwards and formed spherical nanoparticles < 100 nm between N:P ratios of 4-10, which is the ideal range for cellular entry (Figure 2). When the DBV/iNOS nanoparticles were placed on the ZR-75-1 breast cancer cells there was significant cellular toxicity that could be attributed to the production of NO• as evidenced by the Griess test whilst the DBV/GFP control nanoparticles did not induce any cell death. Furthermore, this approach also resulted in a considerable NO• induced bystander effect, with the DBV/iNOS nanoparticles killing in excess of 66% of breast cancer cells with less than 20% transfection efficiency [15].

Although NO• donor drugs have also been shown to elicit significant anti-cancer effects, systemic administration of such compounds raises considerable physiological concerns associated with hypotension. Transcriptionally targeting the iNOS plasmid with the hOC promoter in combination with the DBV delivery system offers a distinct advantage by sparing normal tissue damage. Furthermore, at a molecular level the controlled expression of NO• to the tumour's site will have several beneficial effects, which include: reactions with super oxide and oxygen resulting in oxidation, deamination and alkylation of DNA; the production of dinitrogen trioxide which reacts with zinc thiolates reducing the efficiency of DNA repair proteins such as Poly ADP Ribose Polymerase; inhibition of Hypoxia Inducible Factor 1 transcription (HIF-1) which in turn down regulates the MDR-1 (multidrug resistance gene) which can reduce associated chemo-resistance; and inhibition of the anti-apoptotic factor, NF-κB, which leads to a reduction in the expression of many other pro-tumour factors such as MMP1, 3, 9, VEGF, survivin and BCL2. Furthermore, despite being highly diffusible, NO• only has a very short half-life of 2-4 seconds, which should alleviate any concerns regarding normal tissue damage at adjacent sites.

The future success of this treatment now depends upon the immunogenicity of the nanoparticles and formulation into a freeze dried pharmaceutical product that can be reconstituted and administered without a reduction in efficacy. Studies are on-going to address both of these questions and preliminary results are encouraging. The evidence indicates that iNOS gene therapy could become a valuable tool as an adjuvant cancer therapy but the clinical success of such a product will undoubtedly be dependent on the continued evolution of novel bio-inspired delivery systems, such as the designer biomimetic vector. ■

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Journal Reviews

Neuro-Oncology

Prognostic variables in oligodendroglial tumours

Combined loss of heterozygosity of 1p and 19q (LOH) is associated with an improved prognosis and response to chemoradiotherapy in anaplastic oligodendrogliomas. Previous studies have suggested a correlation of LOH with 'classical' oligodendroglial histology (round nuclei, perinuclear haloes and a vascular capillary network). Isolated 19q loss is frequently observed in high grade astrocytic tumours however, its prognostic significance is unclear. In this study the authors investigated the significance of a variety of prognostic factors including 1p19q status, tumour location and tumour histology in a single institution. 95 adult patients (58 male 37 female) diagnosed with an oligodendroglial tumour (WHO Grade II to IV – oligodendrogliomas, oligoastrocytomas and glioblastomas with an oligodendroglial component) were included in the study. Tumour histology was reviewed independently by 3 neuropathologists including the presence or absence of gemistocytic cells and calcifications. Microsatellite PCR and FISH analysis was undertaken for the assessment of 1p19q status. The median age of presentation was 43 years (range 42-47) with 69% of patients presenting with seizure and 16% with headache. 63% of tumours arose in the frontal region. 64% were WHO Grade II, 32% Grade III and 6% Grade IV. Median overall survival was not calculated for all groups due to the short follow up period. The 1 year survival was 96% (89-98) and 5year survival 69% (58-78) for all tumours (WHO Grade II to IV). All 6 patients diagnosed with GBMO died during the observation period with median overall survival 14 months. Favourable prognostic factors including seizures (associated with Grade II tumours), female gender, frontal location, WHO Grade II, classical histology, absence of gemistocytes and loss of 1p/19q. LOH was observed in 55% of cases and interestingly 10% (9 patients) showed isolated 19q loss. This was associated with a poor outcome with median overall survival 24 months (8-94 months) and was associated with WHO Grade III tumours, temporal location and non-classical histology. Stratification based on 1p19q status revealed the best outcomes in those with LOH regardless of the presence of classical histology, followed by those with no LOH and the least favourable outcomes in those with isolated 19q loss ($P<0.001$).

Reviewer's opinion: This single centre retrospective study highlights a variety of prognostic and predictive factors in oligodendroglial tumours. Stratification is possible on the basis of 1p 19q status with isolated 19q loss conferring the least favourable prognosis. Interestingly, in this study 1p19q loss appears to be an independent prognostic variable regardless of the histological appearance of the tumour. – SB

Prognostic variables in oligodendroglial tumours: a single institution study of 95 cases.
Scheie D, Meling T, Cvancarova M, Skullerud, Mork S, Lote K, Eide T, Helseth H, Beiske K.
NEURO-ONCOLOGY
2011;13(11):1225-33.

Journal of Clinical Oncology

Validation of a Quantitative Gene Expression Assay in Stage II Colon Cancer

Adjuvant chemotherapy with 5-fluorouracil (5-FU) based regimens is effective in significantly reducing recurrence rates in completely resected stage III colon cancer. Controversy exists regarding the benefits in stage II disease. Most clinicians will only offer it to patients with certain high risk features (T4 stage, vascular invasion, obstruction, perforation, inadequate lymph node harvest &c.). A Quantative gene expression assay was developed using four adjuvant chemotherapy studies. 761 candidate genes were assessed for their relationship to the risk of recurrence and the benefit from adjuvant 5-FU chemotherapy. Algorithms for a recurrence score and a treatment score were derived and validated using paraffin-embedded tumour tissue from the QUASAR study. The recurrence score was validated but the treatment score was not, perhaps due to the heterogeneity of trials supplying data to develop the assay. Aside from the recurrence score, T4 stage and mismatch repair deficiency were the strongest predictors of recurrence. The absolute benefits from adjuvant chemotherapy appeared to range from 2-7%, with the lower estimate in good prognosis patients (T3, MMR deficient). The final suggestion is that patients defined with very high risk of recurrence (T4, MMR proficient) and very low risk of recurrence should be considered for adjuvant therapy/no therapy respectively, but that the patients inbetween would gain extra clinical utility from the use of the recurrence score derived from the use of the gene expression assay.

Reviewer's opinions: : This is a fascinating paper. The devil is in the detail. A thorough read of the methods and results serves as an excellent tutorial in the difficult science of prognostic & predictive markers in cancer. It illustrates the strengths and weaknesses of such a strategy and adds support to prognostic factors already widely used (T stage, lymph node harvest, lymphovascular invasion and MMR status) as well as posing some interesting questions regarding the use of the recurrence score. Essential reading for anyone involved in the decisions on adjuvant therapy in colon cancer. – SG

Validation Study of a Quantitative Multigene Reverse Transcriptase-Polymerase Chain Reaction Assay for Assessment of Recurrence Risk in Patients with Stage II Colon Cancer.
Gray RG, Quirke P, Handley K, Lopatin M, Magill L, Baehner FL, Beaumont C, Clark-Langone KM, Yoshizawa CN, Lee M, Watson D, Shak S and Kerr DJ.
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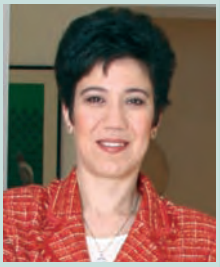
Aspirin in the Prevention of Colorectal Cancer – is it really worth it?

Dr Christos Kallis, MBBS, BSc,
Foundation Year 1 trainee, North Central Thames Deanery.

Dr Georghios Kallis, MBBS, BSc, MSc,
Core Surgical trainee year 2, West Midlands Deanery.

Mohamed Elsharif, MSc,
Surgical science student University Collage London.



Marilena Loizidou,
Non-Clinical Senior Lecturer in the Department of Surgery, UCL.

Correspondence to:
Dr Marilena Loizidou,
Royal Free,
9th floor,
Department of Surgery, UCL
Pond Street,
London, NW3 2QG UK.

Colorectal cancer (CRC) remains the third most common cancer type in both men and women and the second most common cause of cancer-related deaths in the western world. Incidence increases with age and the disease is mainly diagnosed in people over 60 years old. The aetiology is variable and includes a combination of both genetic factors and other modifiable risk factors, like obesity and diet.

Aspirin is one of the most commonly prescribed drugs worldwide and its benefits in the prevention of cardiovascular disease have been extensively researched and are widely accepted. However, more recently there has been increasing interest in the possible use of aspirin in the primary and secondary prevention of cancer pathologies, more specifically colorectal cancer.

This article gives a brief overview of the molecular mechanisms of action of aspirin in the prevention of CRC and presents the latest evidence from relevant clinical studies.

Mechanisms of action

Although not fully elucidated, suggested antineoplastic mechanisms of action for aspirin include both cyclooxygenase (COX)-dependent and COX-independent pathways. COX regulates the rate-limiting step in the conversion of arachidonic acid to prostanglandins and related eicosanoids. Two isoenzymes, COX-1 and COX-2 are well characterised; COX-1 is constitutively expressed in most tissues, whereas COX-2 formation is induced by inflammatory cytokines, growth factors, oncogenes and tumour promoters. COX-2 overexpression has been reported in most adenomatous polyps and colorectal carcinomas compared to normal colon tissues and therefore COX-2 has become implicated in colorectal tumourigenesis. The anti-tumour mechanism of aspirin action is thought to be associated with the inhibition of COX-2 mediated synthesis of prostaglandin E2 (PGE2), which has several downstream effects, including: (i) inhibition of tumour angiogenesis and proliferation, (ii) attenuation of COX-2-mediated activation of co-carcinogens and (iii) generation of aspirin-triggered lipoxins which inhibit cell proliferation [1]. A role for COX-1 has also been proposed and studied in animal models, however this needs further evidence and clarification.

Additionally, aspirin is believed to affect COX-independent pathways involved in physiological processes, such as apoptosis and angiogenesis that are central to the development of malignancies. A well-documented molecular event, is the modulation by aspirin of the transcription factor nuclear factor kappa B (NFκB) signalling pathway. Both *in vitro* and *in vivo* studies have shown that activation of this pathway by aspirin results in increased apoptosis in neoplastic epithelial cells, but not in normal intestinal mucosa [2].

Given the proven benefit of aspirin in clinical studies, one might assume that elucidation of the exact mechanism of action is not of primary significance. However, a better insight into the mechanisms involved might serve to answer current uncertainties with regards to the correct dosing, duration and frequency of administration for optimal effect.

The effect of aspirin on colorectal cancer risk

The compelling analyses of cancer outcomes from randomised control trials (RCTs) which were originally designed to investigate the beneficial effects of aspirin on cardiovascular disease, combined with reports on malignant disease prevention with the use of anti-inflammatory drugs from as early as the 1980s, have brought renewed interest in the role of aspirin as a chemopreventive agent in colorectal cancer.

The strongest early evidence was collected from observational studies, primarily in the United States, and this provided the baseline for the analysis of existing data in the more recent and powerful systematic reviews and meta-analyses.

A meta-analysis of 19 case-control studies and 11 cohort studies demonstrated an inverse relationship between the use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) and CRC risk [3]. This result was further substantiated in a more recent analysis by Rothwell and colleagues, who linked data from cardiovascular-prevention RCTs to show a reduction of 24% in the 20-year risk of CRC and of 35% in CRC-associated mortality with aspirin doses between 75 and 500mg/day; and with more benefit from longer duration of intake [4]. The data pooled were derived from four trials, each of them enrolling subjects in excess of 1,000.

However, two commonly cited RCTs, the Physicians' Health Study and the Women's Health Study, found no reduction in CRC incidence in patients receiving low dose aspirin (325mg and 100mg on alternate days, respectively) [5,6]. The discrepancies from the studies above could be accredited to a number of factors: (i) the sample was not representative of the general population, as in both the latter studies the participants were healthcare professionals, (ii) the follow-up period was relatively short and (iii) treatment was given every other day.

The protective effect of aspirin was also examined in the prevention of adenomas, the pre-cancerous lesions which give rise to colorectal carcinomas. Adenomas can be a useful substitute endpoint in studies, since their development occurs over a noticeably shorter period of time compared to carcinomas. A RCT by Sandler and colleagues, demonstrated that daily intake of 325mg of aspirin in patients with a history of non-metastatic CRC following resection of the primary tumour led to a 35% (RR = 0.65; 95% CI = 0.46-0.91) reduction in the risk of recurrence of adenoma or carcinoma at three years [7]. This result was further supported by a meta-analysis of three more RCTs that investigated the effect of aspirin in nearly 3,000 patients with a previous history of CRC or adenoma. Here, a 17% reduction (RR = 0.83; 95% CI = 0.72-0.96) in

recurrence of any colorectal adenoma over a median period of 33 months following randomisation was reported [8].

Moreover, the effects of aspirin were also extrapolated to patients with inherited conditions associated with CRC, namely familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) (also known as Lynch syndrome). The Colorectal Adenoma / Carcinoma Prevention Programme 1 (CAPP1 study) assessed the efficacy of aspirin 600mg/day and/or resistance starch 30g/day in patients with FAP [9]. This RCT demonstrated that treatment with aspirin for more than one year led to a significant decrease in colorectal polyp size compared to non-aspirin treatment, but did not show a significant reduction in polyp number. High dose aspirin (600mg/day) was also investigated in a study involving 746 HNPCC carriers. This study reported a non-significant decrease in incidence of CRC (RR = 0.87; 95% CI = 0.39-1.96) and adenoma (RR = 1.03; 95% CI = 0.75-1.41) at two and a half year follow-up [10]. However, significant decrease in the period to first HNPCC carcinoma was demonstrated at four year follow-up. The effects of lower doses of aspirin on these genetic conditions need further investigation.

The use of aspirin has also been connected to lower mortality from CRC. In one of the meta-analyses conducted by Rothwell and colleagues on 6 RCTs with data related to CRC, there was a reported 59% reduction in the risk of death due to cancer (Hazard Ratio (HR) = 0.41; 95% CI = 0.17-1.00, P = 0.05), evident five years after the start of aspirin treatment [11]. This effect has also been confirmed to different extents by several other observational studies.

The effect of dose and duration of aspirin intake

Despite the convincing evidence linking aspirin to CRC prevention, there is a lack of agreement about the balance of risks and benefits of long-term aspirin use, in view of its known side effects such as gastrointestinal bleeding and haemorrhagic stroke, especially in individuals with low risk of cancer development.

Dose-related effects on cancer prevention have been reported in a meta-analysis of 20-year follow-up of five RCTs, where typical amounts of aspirin used for the prevention of vascular disease (75-325mg/day) did not show a significant difference in benefits when compared to higher doses (1,200mg/day) [4]. Conversely, there is also evidence supporting a dose-dependent effect. For example, Cole and coworkers analysed two trials comparing low dose (81-160mg/day) and high dose aspirin (300-325mg/day) and demonstrated a decrease in the risk of recurrence of colorectal adenomas with the lower doses [8].

Since the adverse effects of aspirin appear to be dose-related, knowledge of the minimal effective dose of aspirin is of paramount importance. A recent case-control study by Din et al examined 2,279 incident CRC cases and 2907 controls [12]. The results collated from questionnaires completed by the subjects, demonstrated that the lowest daily dose of aspirin used clinically, 75mg, was associated with a decrease in CRC incidence. This was evident after one year, but significant after five years of use.

Additional to the question of the optimum aspirin dose, there is debate on the correct duration of intake. The prevailing notion is that long-term use of aspirin is required to reduce the risk of CRC. This has indeed been strongly supported by several observational and clinical trials. The meta-analyses of RCTs carried out by Rothwell and colleagues showed that there was a direct relationship between the duration of aspirin therapy at any dose between 75 to 325mg/day and CRC incidence [4,11]. Furthermore, an analysis by Cuzick and colleagues of seven cohort studies involving 5,146 women, reported that use of aspirin over approximately 20 years resulted in a significant reduction of CRC risk by 15% (RR = 0.85; 95% CI = 0.78-0.92) [13]. In the same report, analysis based on 11 case-control studies involving 9,232 men estimated that long-term use of aspirin over about 20 years was associated with a decrease in CRC risk by 41% (RR = 0.59; 95% CI = 0.54-0.64) [13].

More studies would be required to better define the best combination of aspirin dose and duration for maximal effect in prevention of CRC development.

Conclusion

In light of the fact that large numbers of patients are already long-term users of aspirin due to the increasing incidence of cardiovascular disease, the ability to provide a dual benefit for these patients who may also be at risk of developing colorectal cancer holds a strong appeal.

Given the growing body of evidence to support that even low doses of aspirin are associated with a reduction in the risk of colorectal cancer, re-evaluation of the risks and benefits, as well as cost-effectiveness of the use of aspirin as a strategy for primary and/or secondary prevention of colorectal cancer is warranted. This would also require the appraisal of its cost-effectiveness, either in comparison or in combination with the existing National Health Screening Programme in the UK.

The use of aspirin as chemoprevention for colorectal cancer will undoubtedly form part of clinical guidelines in the future. However, for national health institutes to embrace its effectiveness and benefits, there has to be more extensive research in order to provide the evidence base and decisions for the optimal dose, duration and frequency of administration. ■

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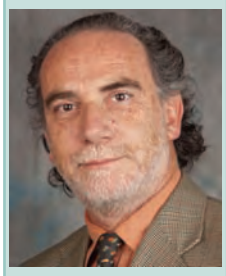
Geriatric Oncology: a problem and solution

Vikram Swaminathan, MD,
Southport District General Hospital.



Riccardo A Audisio, MD, FRCS
Honorary Professor – University of Liverpool
Consultant Surgical Oncologist – St Helens Teaching Hospital.

Correspondence:
Riccardo A Audisio,
St Helens Teaching Hospital,
Marshalls Cross Road,
St Helens,
WA9 3DA, UK.
T: +44 (0)1744 646689.

The dilemma

The worldwide population of the elderly is growing at its fastest rate ever. The United States Census Bureau calculated that there were over half a billion over-65s in 2008. This number is estimated to more than double by 2040 to 1.3 billion. As a result, 14% of the world's population will be of retirement age. Since people are living longer and having fewer children, it is expected that the number of elderly will soon outnumber the young for the first time in human history. This ageing of the world population is combined with a longer life expectancy and increasing healthy-life expectancy of almost 10 years at age 65 in most European countries (stretching beyond 15 years in Scandinavia). With the exception of 18 countries termed by the United Nations 'demographic outliers' [1], this process is occurring in every country and region worldwide.

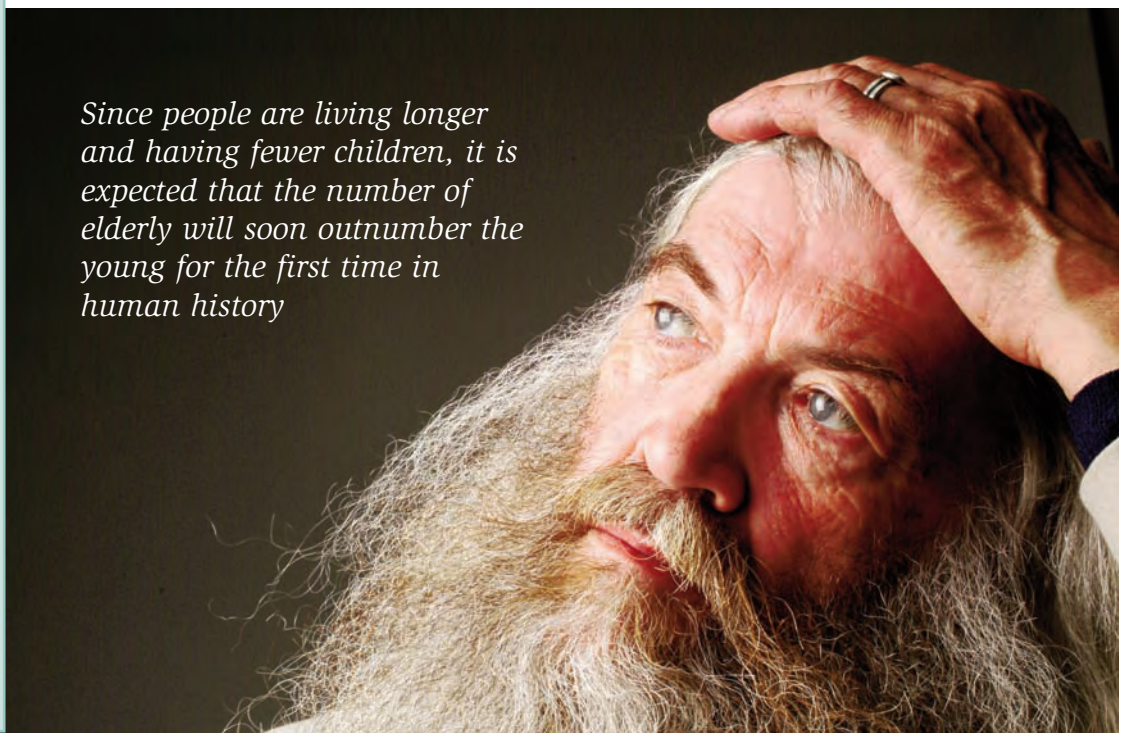
Even though anyone can develop cancer, it is known that the risk of acquiring cancer increases with age; cervical cancer being the only exception to this rule. This has huge implications and deep socio-economical consequences. Assuming that the cost of treatment will grow annually at a 2% rate, the largest increases in cost will be for breast cancer at 32% and prostate cancer at 42%, simply because more people will be living longer with these diseases [2]. The cost of treating breast cancer remains relatively low (compared to other tumour types) but this cancer will incur the highest costs by 2020 in the US ($20.5 billion) as many more women will be alive with the disease.

Definition of 'old'

In the scientific literature, a threshold of 70 years is commonly used when classifying the 'elderly', with the term 'oldest olds' referring to the population above age 80. The above 80 year olds also happens to currently be the fastest growing age sub-group. Most developed world countries accept the chronological age of 65 years as a definition of 'elderly' or older person. While this definition is somewhat arbitrary, it is often associated with the age at which one can begin to receive pension benefits. There is no United Nations (UN) standard numerical criterion for 'elderly' at present; the UN agreed cut-off is 60 + years of age when referring to the older population. The literature refers to 70 as an age threshold. Due to our ageing population as well as to the expanding healthy-life expectancy, it is not unrealistic to focus on the > 75 for the years to come.

Geriatric oncology

Older cancer patients have different needs than younger adults with the disease. Treatments for older adults need to consider many different issues. These patients may be less able to tolerate certain cancer treatments due to pharmacokinetics/dynamics. They may also have a decreased reserve and other comorbidities, resulting in the presence of current polypharmacy even before the inclusion of any additional therapy for the cancer. In addition this older age group may have functional problems, or difficulty with activities of daily living. This combined with any lack of access to transportation, social support or financial resources could result in reduced compliance to state-of-the-art treatments. Another common problem for the elderly cancer patient is malnutrition, which is due to the coexistence and/or potentiation of the metabolic alterations related to sarcopenia with underlying cancer cachexia. Both processes lead to loss of body weight, lean body mass, and reduced muscle function, as well as a progressive deterioration of many systems and organs. These changes give a low quality of life and poor adaptation to stress. Although neither sarcopenia nor cancer cachexia may



cause a state of simple starvation, there is evidence of excessive malnourishment among older patients. Adequate nutritional intake is the condition sine qua non which can make any attempt at aggressive oncologic therapies possible [3]. Any of these differences will greatly impact treatment planning and the individualisation of therapeutic options, thus the understanding of what any treatment may imply can be hampered. Ignoring or withholding these aspects is an ageist approach.

Most importantly, the volume of scientific evidence currently available to support any of these specific issues is greatly limited, due to almost all treatments designed being tested by randomised clinical trials, preferentially using much younger cohorts of patients, perhaps because of all these differences just mentioned earlier. It has thus become an oncological priority to expand the use of older cohorts of patients in cancer research, due to the different challenges this particular cohort presents with regards the management of cancer.

A close collaboration with geriatricians over the last 10 years has allowed better understanding of the interaction between geriatric syndromes and cancer management. The identification of frailty has been encouraged when treating onco-geriatric patients. In an ideal world this could be incorporated through a Comprehensive Geriatric Assessment (CGA). This is time-consuming and impossible to fit into our busy clinical practice. Accordingly, quicker tools have thus been developed (GFI, VES13, TUG) with the purpose of screening older cancer patients for frailty. Anagraphic age is not sufficient to characterise these patients [4].

The past

Sizeable evidence has been collect over the previous decades confirming that the standard of care for older patients is inferior. This is attributed to many factors, from delayed diagnosis and minimal staging, to the substandard treatment of these individuals. Unavoidably this results in a reduced cancer-specific survival. Figures are noted to be consistent across all geographic areas [5]. The reason behind this substandard performance rests on our lack of knowledge and inability to provide appropriate tailored treatment. This involves the risk of either over-treating frail patients or under-treating fit ones. Understandably, physicians were prepared to risk a less aggressive strategy and under-treat older patients in order to avoid excessive treatment-related morbidity or even mortality. About 15,000 older cancer patients in the UK die prematurely from cancer each year due to this ageist approach. A clear example is the management of breast cancer in older women. Since the introduction of endocrine treatment in the early 80's, several surgeons have prescribed primary endocrine treatment even on patients who were deemed sufficiently fit to receive a surgical operation. It has been computed that this ageist attitude has resulted in 2,000 excess deaths/year in the UK.

The present

Action has been taken to amend the inequality in treatment between age groups. In 2008, the Deutsche Kreshilfe priority programme allocated 8 million Euros towards therapeutic studies in patients of advanced age or who were medically unfit. A year later, the French National Cancer Institute allocated 2 million Euros toward research projects on older cancer patients. This generated resources for the Oncodage Study which developed the G8, an 8-item screening tool that was tested on a prospective cohort of 364 cancer patients aged > 70 years. A threshold of 14 has been identified (90% sensitivity, 60% specificity). The preliminary results were subsequently validated on 1,650 patients from 23 French cancer and geriatric units. Sensitivity of G8 was superior to VES13 (76.6%, 95%CI [74.0%; 79.0%] vs 68.7%, 95%CI [65.9%; 71.4%]), although its specificity was inferior (64.4%, 95%CI [58.6%; 70.0%] vs 74.3%, 95%CI [68.8%; 79.3%]). When G8 and VES13 were used together (giving at least one abnormal test), sensitivity increased to 86.6%, but specificity decreased to 53.2%.

In the UK, The National Cancer Equality Institute, well supported by an All Parliamentary task-force, has been essential in moving forward in the country the field of Oncogeriatrics. Macmillan Cancer Support joined forces with the Department of Health to fund studies on older cancer patients with a grant of £1 million and full support from AgeUK. The one-year pilot programme will introduce new ways of evaluating an older person for cancer treatment, giving short-term practical support for older people undergoing cancer treatment, and addressing any age discrimination that has been highlighted with cancer services. These beneficial developments are presently on-going, although, the indirect benefit of raising awareness has already succeeded. It is also encouraging to know that numerous researchers across Europe have adopted frailty assessment tools into the day-to-day management of older patients with cancer. Geriatric Oncology over time has been raised from a minor area of scientific interest, to a newly introduced and widely available novel approach.

The future

As numerous studies have been established, it is only a matter of time till the results will be made available and an accurate screening for vulnerability is close to hand. The momentum has generated vivid interest, with ASCO dedicating sessions to this topic. A Geriatric Oncology subspecialty has been set up in 10 USA institutions who are recipients of a Geriatrics/Oncology Training Program Development Grant. Similar examples are also seen across Europe; a Diplome Universitaire d'Oncogeriatrie is awarded by three French Institutions. These programs aim to provide optimal cancer care for senior adults and help patients to overcome the special challenges that this population faces in battling the disease. Onco-geriatric education is essential for physicians as well as nurses: EONS has a well established Curriculum for cancer in older people. The International Society of Geriatric Oncology (SIOG) has been crucial to progress in this field. SIOG was founded in 2000 with a purpose to advance the art, science and practice of oncology in elderly patients, and disseminate knowledge in order to maintain a high common standard of healthcare in elderly cancer patients. The SIOG also aims to improve research in the field of geriatric oncology and promote education in order to ensure a high standard of qualification for health professionals, maintain liaison with other medical and health professionals associations, cancer leagues, universities and, where appropriate, the pharmaceutical industry. Numerous task forces have been organised to summarise the current field of evidence and state of the art approaches of onco-geriatrics. The SIOG is intending to draft guidelines as soon as hard data is made available from presently on-going research. ■

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Prof Jeffrey S Tobias, MD, FRCP, FRCR,

Professor of Cancer Medicine, University College London, and Consultant in Clinical Oncology at UCL Hospitals, London, UK.

Targeted therapy using the INTRABEAM® system: a new option in cancer treatment

During the history of cancer treatment, therapeutic interventions have gradually become less invasive. A perfect example of this development is intraoperative targeted therapy using the INTRABEAM® system created by Carl Zeiss. The INTRABEAM® radiotherapy system offers a new treatment option in many oncologic indications.

How the method works

Targeted therapy and tumour control form the design and the treatment philosophy behind the INTRABEAM® platform. Following tumour resection and without the need for time delay, the sterile applicator of INTRABEAM® is positioned directly in the tumour bed to deliver the highest radiation dose exactly where it is needed most. Accelerated electrons of the INTRABEAM® X-ray source strike a gold target at the tip of a 10 cm long drift tube, resulting in the emission of low-energy X-rays (50 kV) in an isotropic dose distribution. The relative biological effectiveness (RBE) of radiation increases with decreasing photon energy. A higher ionization density increases the RBE and low-energy X-ray radiation results in a high RBE and consequently leads to an efficient tumour cell killing.[1,2] Moreover, the radiation emitted by INTRABEAM® is characterized by a steep dose fall-off in the periphery which avoids irradiation of healthy tissue.[3]

Rationale of INTRABEAM® in cancer treatment

Fortunately, radical surgical methods for many cancer indications have largely been replaced by less invasive surgery approaches, which can be viewed as risk-adapted strategies. INTRABEAM® can also be considered a risk-adapted strategy for radiotherapy. While breast cancer is the most common indication for intraoperative radiotherapy with INTRABEAM®, the system has been successfully used in many other solid tumours including tumours of the brain and the gastrointestinal system as well as bone metastases, a new and very promising indication. Besides curative settings, INTRABEAM® can be very effectively used for tumour recurrence when therapeutic options are limited. Further radiation is normally restricted by the intolerance of normal tissue that has already been irradiated, while surgery is limited by the closeness of vital structures such as vessels and nerves. With INTRABEAM® it is often possible to deliver a restricted dose escalation since these structures can be spared. Additionally, if the primary tumour cannot be removed completely, INTRABEAM® offers new local treatment opportunities.

Breast cancer

Breast cancer is the best-established indication for intraoperative radiotherapy using INTRABEAM®. In patients with good prognostic factors (T1-3, N0-1, M0), INTRABEAM® can completely replace external beam radiotherapy. Data from a multinational, randomized clinical study (TARGIT-A) prove that for selected patients with a favourable prognosis, targeted intraoperative radiotherapy (TARGIT) with INTRABEAM® is equivalent to conventional external radiotherapy. TARGIT is well tolerated, and no statistically significant difference in the total rate of side effects between TARGIT and external beam radiation was detected.[4] Patients who are not suitable for single intraoperative treatment with INTRABEAM® can nevertheless benefit when intraoperative therapy with INTRABEAM® is delivered as a boost, replacing the external boost at the end of external beam radiation. Study data show lower rates of recurrences when the boost is administered intraoperatively with INTRABEAM® when compared with external boost application.[5]

Treatment of spinal metastases

For the many patients who develop spinal metastases during the course of their cancer, percutaneous kyphoplasty and vertebroplasty are valuable treatment options. By using intraoperative radiotherapy with INTRABEAM® during kyphoplasty or vertrebroplasty, the metastasis can be sterilized and simultaneously stabilized, a process resulting in significant pain relief. The first clinical trials using this approach have yielded very promising results. The method was technically feasible with an intraoperative risk profile comparable to kyphoplasty alone and a shorter treatment duration for patients, compared with conventional radiation therapy.[6,7]

Brain tumours and cerebral metastases

Postoperative irradiation of brain tumours and cerebral metastases is often delayed due to wound healing problems and long patient recovery times following the operation. INTRABEAM® offers a cost-efficient and immediate treatment following open surgery which can replace partial / whole brain irradiation and mitigate toxicity in these now longer surviving patients. Furthermore, a substantial number of studies have proven the value of INTRABEAM® in the treatment of brain and cerebral tumours in both children and adults.[8-11]

Gastrointestinal cancer

Frequently, a complete resection of gastrointestinal cancer is not possible, meaning that cancer cells remain present in

the tumour bed or in neighbouring structures. Intraoperative radiotherapy with INTRABEAM® can improve local control of colorectal tumours in the case of local recurrence or locally advanced tumours.[12] The efficaciousness of INTRABEAM® has also been demonstrated in the setting of laparoscopic hemicolectomy in patients with colon cancer and gastrectomy in patients with gastric cancer.[13,14]

Oral cancer

First study data have convincingly demonstrated that delivering a boost radiation intraoperatively with INTRABEAM® has potential advantages in the treatment of oral cancers.[15] After resection, the margins of the tumour can be sterilized immediately which may have a positive impact on the local recurrence rate. Additionally, the numerous vital structures in this region can be spared due to the steep fall-off of the low-energy radiation emitted by INTRABEAM®. An anatomical miss is unlikely since the applicator can be positioned directly in the tumour bed.

Endometrial cancer

In endometrial cancer – the most common malignancy of the female genital tract – the use of INTRABEAM® is also feasible and has some potential advantages compared to most commonly used 192Ir high-dose rate (HDR) afterloading, which is highly expensive, due to necessary changes in the radioactive source and complex radiation protection requirements. By comparison, INTRABEAM® can be used in non-shielded spaces with no radioisotopes involved. Results from the first clinical trials evidence has shown that it is possible to create a homogeneous cylindrical dose distribution similar to 192Ir HDR afterloading, suggesting that INTRABEAM® could be used effectively in this common female cancer.[16]

Conclusion

The INTRABEAM® radiotherapy system offers a new and versatile treatment option in many oncologic indications. With very solid clinical evidence in breast cancer treatment the opportunities of INTRABEAM® are also applicable to other solid cancers as well as bone metastases.

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HPV Related Head and Neck Cancer:
The clinical, radiological and prognostic implications


Imaging section is edited by Dr Tom Lynch

Authors
Jolyne O'Hare[1], Michael Moran[2], David P Stewart[1], Fionnuala Houghton[1]

1. Cancer Centre, Belfast City Hospital, Belfast
2. CCRCB Queens University Belfast

There is an increasing body of literature, in keeping with the rising incidence, on human papillomavirus (HPV) and its causative role in cancers of the cervix, vulva, vagina, anal canal and penis. More recently, HPV has been associated with squamous cell cancers of the head and neck (HNSCC). This review focuses on HPV related HNSCC, which is most often manifested in the oropharynx. Patients with HPV related HNSCC are typically younger, with reportedly lower levels of alcohol intake and tobacco usage than patients whose cancers are caused by other mechanisms, such as p53 mutations. The outcome for HPV oncogenic driven HNSCC, in terms of local control and overall survival, are markedly better [1]. They are a specific subset with distinct clinical, histological and now radiological features that will be discussed in more detail.

HPV

There are over one hundred subtypes of HPV, and a new subtype is defined when certain regions of the virus (E6, E7 and L1) domains display less than 90% homology with another variant. Such viruses are small nonenveloped double stranded DNA viruses. In some cases HPV can cause benign papillomas. The oncogenic genotype of HPV can cause malignant skin or mucosal transformation. The first documented evidence of HPV in head and neck cancer dates back to 1985. The first meta-analysis was performed in 1998, in which McKaig et al reviewed 1205 patients with head and neck cancer and found 416 cases were HPV DNA positive, an incidence of 34.5% [2].

The proportion of HPV related tumours varies greatly depending up the site of primary tumour, with HPV positivity found most often in the tonsil. A German study demonstrated this with the rate of HPV positive tumour of tonsillar tumours reaching 76% [3]. There are a number of theories regarding this. One theory is that the HPV 16 viral infection specifically targets the reticulated epithelium that lines tonsillar crypts. Within the genome, the HPV DNA dysregulates the expression of oncoproteins E6 and E7. The E6 protein leads to degradation of p53 through ubiquitin mediated proteolysis. p53 is therefore lost, preventing cell cycle arrest at the G1 phase and induction of apoptosis, which allows the host DNA to repair. The loss of p53 tumour suppressor protein leads to genomic instability. E7 protein binds to and inactivates the retinoblastoma (Rb) protein causing the cell to enter S phase, leading to cell cycle disruption, proliferation and malignant transformation.

The incidence of HPV positive tumours of the tonsil has also been highlighted in a Swedish study, with 23% of tumours carrying the HPV DNA compared with 93% in more recent times [4].

Glombitza et al compared HPV status of primary tumours with their secondary lymph node metastases and found that, in keeping with literature, there is an increased risk of developing lymph node metastasis should the primary test positive to HPV DNA. The authors also found a concordance in HPV status between the primary and secondary tumours. Conversely there were no cases of HPV positive lymph nodes in the presence of a HPV DNA negative primary [3].

HPV testing

There are a number of reasons to test for HPV, and although current treatment for HPV positive cancers is no different from other HNSCC, HPV status has a role in prognositication for patients. It is also emerging as a valid biomarker for the presence and progress of disease. Knowing the HPV status of a tumour can encourage more accurate tumour staging and possibly in the future lead to selective treatment. There are a number of methods used to test for HPV related tumours. The gold standard detection method is polymerase chain reaction (PCR) based detection of the E6 oncoprotein expression in frozen tissue samples. PCR testing from frozen tissue samples requires a high level of technical skill however, and is dependent on adequate amounts of DNA being provided for analysis. p16 immunostaining is another, less expensive method for testing for HPV 16 infection; however testing for this alone is not sufficient to determine HPV status with confidence.

In HPV positive tumours, transcription of the viral oncoprotein E7 inactivates Rb protein, which leads to upregulation of p16 to levels that can be detected by immunohistochemistry. There are disadvantages for using p16 as a surrogate for HPV positivity. Namely, detection of p16 can also indicate disruption of the Rb pathway by other causes and p16 is also elevated when other HPV subtypes are involved, therefore is not deemed to be specific to HPV 16. DNA in situ hybridisation is another method to test for HPV and could be tested along with p16 immunostaining to improve accuracy of detection [5].

Clinical appearances

Clinically, with HPV associated carcinomas the primary tumour is often small, with large cystic multi-level lymph nodes. These cystic lymph nodes have a tendency to appear on a very rapid basis. It has been hypothesised that the cysts occur with the changes in a pseudocyst resulting in degradation of cellular components and breakdown of keratin. In general terms HPV positive tumours are thought to classically have small primary tumours with large advanced nodal disease. Anatomically, primary tumours are more likely to occur in the oropharynx and have non-keratinsing histology. There is a trend for such tumours to occur in younger patients [6].

Radiological appearances

The radiological appearances of HPV related HNSCC have been investigated and similar features have been identified. Goldberg et al undertook a retrospective review of patients who underwent neck dissections for head and neck lymph node metastasis between 2002 and 2004. One hundred patients were identified and each histological sample was reviewed for evidence of HPV DNA. The appearance on CT scan and MRI was classified into solid/necrotic or cystic. The authors found that 20% of all lymph nodes on imaging were cystic by their criteria. These criteria included round or ovoid structure with homogeneous features and thin walls (Figures 1 & 2). The majority of these patients had evidence of HPV DNA within the primary disease or the lymph node metastasis. Specifically, biologically active HPV was found in the majority of tonsil or base of tongue tumours. Not all HPV positive primary tumours caused cystic nodal appearances however; it was shown that HPV DNA was found in most of the cystic neck nodes tested [7].

Figure 1

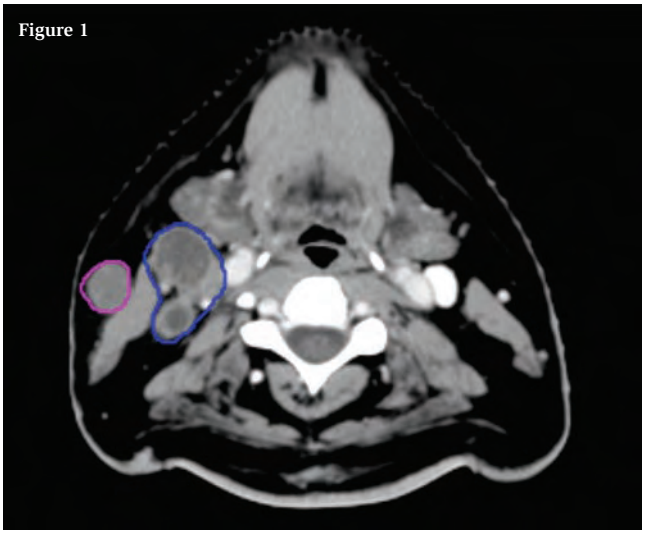


Figure 2

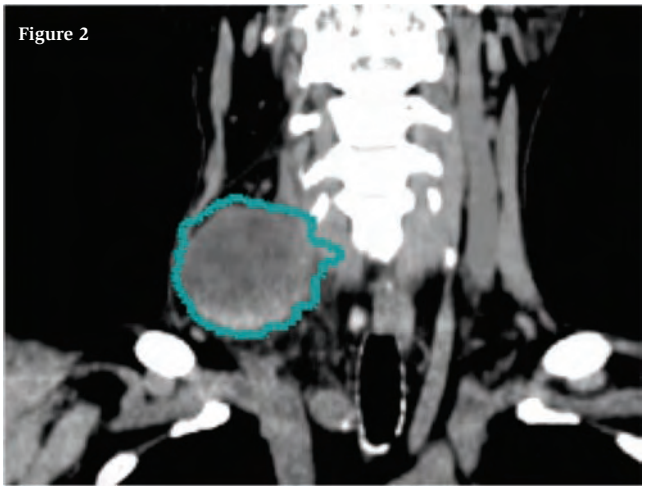
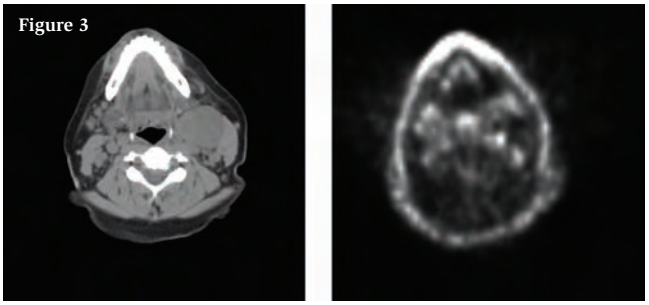


Figure 3



Clinical implications of cystic lymph nodes

Fine needle aspiration (FNA) is used in HNSCC routinely. The sensitivity of FNA within lymph nodes of the head and neck has been recorded at 92% with a positive predictive value of 100%. There are higher false negative rates associated with cystic lymph nodes than those with solid metastasis. False negative rates of FNAs within this subset are documented between 30–50%. This is thought to be due to the absence of cellular features within the cyst [7]. Accurate investigations for the purposes of staging in HNSCC are crucial for devising treatment plans. Excision biopsy of large cystic lymph nodes is therefore recommended. A study by Haerle et al. in 2010 looked at the use of 18 FDG PET compared with CT and contrast enhanced CT and contrast enhanced 18 FDG PET. In summary the authors found a correlation between the maximal standardised uptake value (SUV max) of the metastatic lymph nodes and the degree of necrosis. The higher degree of necrosis appears to lead to a lower SUV max [8] (Figure 3). This could have implications for detection of lymph node metastasis, however it remains that the most accurate method for staging is histological. Contrast enhanced imaging has shown superior results over non-contrast.

Patterns of metastasis

A Canadian study looked at a cohort of patients retrospectively from 2003 to 2009, comparing HPV positive and HPV negative tumours in terms of synchronous primaries and distant metastasis. This group found that HPV positive tumours were less likely to have synchronous primary tumours. There was also no difference in distant metastasis rates in either group. However the HPV positive subset were more likely to have multiple visceral metastasis and unusual sites of metastasis such as skin metastases, paraspinal metastasis, axillary metastasis and brain metastasis [9].

Management and prognosis

The standard management for locally advanced head and neck cancers is either surgery with post operative radiotherapy with or without chemotherapy or concurrent chemoradiation alone. There are a number of characteristic features that infer a better prognosis to standard treatment. These include non-smokers, low alcohol intake, no comorbidities and good performance status.

The distinct entity of HPV positive HNSCC has a better prognosis than HPV negative tumours. This may be in part due to increased sensitivity of these tumours to chemotherapy and radiation and a functional p53 gene [5]. Attempts have also been made to stratify tumours according to HPV status, smoking history and tumour stages, but although this looks promising, it has yet to be validated prospectively.

Treatment toxicity, both in regard to acute and long-term effects, can be extremely debilitating. It is not yet known if the therapeutic ratio can be altered with the aim to maintain overall survival and local control rates with a reduction in late morbidity.

Summary

HPV related head and neck cancer is a distinct disease entity. The HPV status of a patient is a prognostic indicator of overall survival and may predict response. Clinically and radiologically the cervical lymph node metastases of these tumours appear to demonstrate unique cystic features with lower glucose uptake on PET. Further studies investigating the therapeutic ratio of treatments are required before standard treatments can be altered. ■

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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

World Cancer Day 2012 - Uniting in the fight

Date: 4 February, 2012.

Spearheaded by International Union for Cancer Control (UICC) and its members, Saturday 4 February saw the world unite in the global fight against cancer. Taking place nearly six months after the first UN High-level Meeting on non-communicable diseases (NCDs) and the signing of the Political Declaration, World Cancer Day 2012 aimed to showcase that it is only by every person, organisation, and government individually doing their part, that the world will be able to reduce premature deaths from cancer, and other NCDs, by 25% by 2025.

Why is World Cancer Day important? Cary Adams, UICC Chief Executive Officer explains, "Put simply, because the global cancer epidemic is huge and set to rise. At UICC, we are committed to delivering the targets of the World Cancer Declaration, but we know that this can only be achieved through strategic partnerships with our members, as well as other institutions interested in fighting cancer. It is this shared mission that makes World Cancer Day all the more important. February 4 represents an annual opportunity to coordinate our efforts to ensure that globally everyone recognises that they can play a part in fighting cancer."

Under the banner Together it is possible, approximately 250 different events to mark the awareness day were held across the world. Events ranged from the hosting of local cancer information stands to activities on a much larger scale including; lighting up the CN Tower in Toronto (The Canadian Partnership Against Cancer) and the Empire State Building in New York (American Cancer Society), and building a giant human LIVESTRONG wristband in the main square in Mexico City (LIVESTRONG).

To harness the power of social media in generating awareness, a dedicated World Cancer Day 2012 application on Facebook, developed by UICC and US charitable organisation Stand Up to Cancer (http://apps.facebook.com/worldcancerday/), was launched to allow users to make their personal commitment to reducing their cancer risk. Tweeters were also encouraged to use the hash tag #worldcancerday to pledge their support to the day, a mission that was boosted by support from a variety of influential health groups, personalities and celebrities.

"Through the hard work of individuals and the global cancer community, World Cancer Day 2012 has reached an audience of over 130 million people worldwide. I would like to personally thank all those who got involved for their invaluable support", commented Cary. "UICC looks forward to keeping cancer high on the global health agenda at the upcoming World Cancer Congress in August, the focus of which will be translating the benefits of knowledge gained through research and practice to those living with and affected by cancer." ■

For information on the World Cancer Congress, or to register, please visit www.worldcancercongress.org

BAHNO Annual Scientific Meeting 2012

Date: 26-27 April, 2012 . **Venue:** London, UK. **PREVIEW**

The British Association of Head and Neck Oncologists Annual meeting is a regular fixture on the Medical events calendar – occurring on the last Friday in April. Over the last 10 years this has been held at the Royal College of Physicians in London. This outstanding venue is equally matched by the outstanding hospitality and catering.

For 2012, the meeting has been extended to include a second day to enable us to have a Joint meeting with the British Society for Oral and Maxillofacial Pathology.

The theme of the meeting is Prognostic and predictive biomarkers in Head and Neck Oncology.

Day one involves a Head and Neck quality assurance discussion; there will also be a key note lecture from Professor J Wright from Dallas Texas entitled – Reflections on the WHO classification of Odontogenic tumours and finally a case based panel discussion.

Day two has two free paper sessions; a case based panel discussion on sarcomas; a DAHNO update; the Blair Hesketh Lecture is to be given by Professor David Sidransky from John Hopkins in Baltimore USA and the meeting is concluded with the ever popular and highly entertaining debate.

This year the subject is "This house believes that the use of molecular biomarkers for p16 and HPV, to deliver personalised treatment of Head and Neck cancer, should be the standard of care". There will also be a poster display. As in previous years, the number of submissions far exceeds the number of spaces available and this has raised the standard of abstracts.

The meeting is open to all medical professionals who work in the field of Head and Neck Oncology and this most definitely includes allied health professionals and Head and Neck nurses and the organization representing them – BAHNON. It is an excellent opportunity to listen to cutting edge presentations and meet colleagues. Finally there will be a trade exhibition incorporating all up to date products used in the management of this difficult condition. On behalf of BAHNO and BSOMP we would like to invite you to the meeting and hope you will find it rewarding. ■

Further details can be found on our website www.bahno.org.uk

BNOS 2012 Annual Conference 'Challenges and Controversies'

Date: 27-29 June, 2012. **Venue:** Manchester, UK. **PREVIEW**

The British Neuro-Oncology Society (BNOS) has gone from strength to strength over the last 30 years and the annual meeting is a unique opportunity for colleagues from many different disciplines to exchange ideas and share their experience.

We are in the process of putting together what we hope will be a stimulating and memorable meeting and look forward to welcoming you all in 2012. It is said there are three aspects which make a conference memorable:

- The first is a motivational programme – the 2012 conference with the theme 'Challenges and Controversies' offers an extensive and informative programme with the very best speakers, from both the UK and overseas, on the most relevant clinical topics. Delegates, from all fields of Neuro-oncology are expected to attend the conference, which will also include a Neuro-oncology Nursing Forum. Poster presentations will be on display throughout the conference.
- The second is great social events – the social programme begins on Wednesday evening with an informal buffet and drinks reception with the main conference dinner being held at Old Trafford, the home of Manchester United, and the largest football ground in the UK. Preceding the dinner, delegates will have the opportunity to take a tour of this iconic stadium and visit the club museum, which blends exhibits with interactive experiences.
- And finally, a vibrant location – Manchester is one of the most dynamic and lively places in Europe, a place with an illustrious past that is always at the cutting edge of what's new – in fact singer Ian Brown once said 'Manchester has got everything except a beach'.

The conference will take place from Wednesday 27th June to Friday 29th June, 2012 at the Manchester Conference Centre.

BNOS is delighted to have the following sponsors for the 2012 conference Brainlab, Medac, Archimedes, Forth Medical, Leica, Seren, Cavendish Implants, IBTA and Oncology News. ■

For further information or to book please visit the BNOS website www.bnos2012.co.uk
T: +44 (0)161 665 5886 or E: enquiries@bnos2012.com

Awards & Appointments

GSK UK Oncology CASE PhD Scholarship

GSK recently announced the winner of the first GSK UK Oncology CASE (Collaborative Award in Science and Engineering) PhD Scholarship – set up as part of its commitment to working in partnership with academia to further the development of oncology research and support oncology healthcare professionals in the UK.

The winner was: Melania Capasso (pictured), from the Centre for Cancer & Inflammation, Barts Cancer Institute – a Cancer Research-UK Centre of Excellence, Queen Mary University of London for her proposal 'Investigating the voltage-gated proton channel HVCN1 as a target for lymphoma treatment'. The scholarship will commence in October 2012.

Commented Melania: "It is very exciting to receive this award at a time when funding for research is less available. It is great to have more collaborative projects between

industry and academia. This funding will allow us to gain a greater insight into common blood cancers such as lymphoma and chronic lymphocytic leukaemia that remain incurable with current treatment. Hopefully it will lead to a new cure to take to the clinic."

Commenting on the entries, judging panel member Alan Ashworth said: "Joint industry-academic research efforts are vital in the quest for furthering scientific progress – especially in the current climate. With this award, GSK have created an exciting opportunity to support and showcase cutting-edge UK research and it was fascinating to be involved in the judging process. All the finalist proposals were outstanding in their potential to further scientific progress in cancer research so choosing the final winner was a difficult decision." ■

To have your Event featured in this section, or to write a report on a meeting you have attended contact Patricia McDonnell – E: patricia@oncologynews.biz

Diary of Events

To have your event listed in the Oncology News diary E: Patricia@oncologynews.biz by April 5th 2012.

March

NEW
Late Effects in Cancer Survivors - 4th biennial Sheffield meeting
8-9 March 2012; Sheffield, UK
E: lateeffects@sheffield.ac.uk

NEW
10th International Congress on Targeted Anticancer Therapies
8-12 March 2012, Amsterdam, The Netherlands
W: www.esmo.org/events/targeted-anticancer-therapies-tat-2012.html E: tat@mccm.nl
T: +31 88 0898100

ESMO Conference on Sarcoma & GIST
9-10 March 2012; Milan, Italy
W: www.esmo.org/events/sarcoma-gist-2012-conference.html
E: conference@esmo.org
T: +41 (0)91 973 19 26

NEW
Oncology Imaging – PET, CT, MRI, Diffusion: What all Oncologists Need to Know
12 March 2012; London, UK
W: www.royalmarsden.nhs.uk/studydays
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921/ 020 7808 2924

Palliative Care in Cancer
12, 13, 14, 15 & 16 March 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Stem Cell Transplantation in Cancer
12, 13, 14, 15 & 16 March 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Chemotherapy in Cancer Care
12, 13, 21, 22 & 23 March 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

NEW
Sylvia Lawler prize meeting
14 March 2012; London, UK
Ruth Threadgold,
T: +44 (0)20 7290 3942
F:+44 (0)20 7290 2989
E: oncology@rsm.ac.uk

9th Palliative Care Congress
14-16 March 2012; Newcastle, UK
W: www.pccongress.org.uk
T: +44(0)1489 565475

BTOC 11 – Biological Therapy of Cancer
14-16 March, 2012;
Munich, Germany
http://www.bdaoncology.org/pages/pv.asp?p=bda5

NEW
NCCN 17th Annual Conference: Clinical Practice Guidelines and Quality Cancer Care
14-18 March 2012; Hollywood, Florida, USA
W: http://www.nccn.org

NEW
Target Controlled Infusion Practicum
15-16 March 2012; London, UK
W: www.royalmarsden.nhs.uk/studydays
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921/ 020 7808 2924

Current Status and Future Directions of SPECT/CT Imaging
16 March 2012; London, UK
E: conference@bir.org.uk

Genito-Urinary Cancer Care
19, 20, 21, 22 & 23 March 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Clinical Trials in Cancer Care
19, 20, 21, 22 & 23 March 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

NEW
Skin Cancer StudyDay – A perspective on Melanoma
21 March 2012; Middlesex, UK
E: anni.hall@nhs.net

NEW
BIR: Medico-Legal Training CPD Opportunity
22 March 2012; London, UK
British Institute of Radiology
E: admin@bir.org.uk

NEW
18th Annual Blood-Brain Barrier Consortium Meeting
22-24 March 2012; Stevenson Washington, USA
W: http://www.soc-neuro-onc.org/en/cev/67

SSO 2012 Annual Cancer Symposium
22-25 March, 2012;
Orlando, FL, USA
W: www.surgonc.org/

Marie Curie Annual Palliative Care Research Conference
23 March 2012; London, UK
T: +44(0)207 091 4153
E: Oswin.Taylor@mariecurie.org.uk

Psycho-Social Impact of Cancer
26, 27, 28, 29 & 30 March 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Lung Cancer Care
26, 27, 28, 29 & 30 March 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Using Physical Assessment and Clinical Reasoning to Assess Cancer Patients
Taught days over 17 weeks commencing 27 March 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

NEW
Lymphoma Education Day
27 March 2012, London, UK
T: + 44 (0)1296 619425
E: helen@lymphomas.org.uk
W: www.lymphomas.org.uk

NEW
brainstrust Meet Up to mark Brain Tumour Awareness Month
27 March 2012, London, UK
W: www.meetup.com/brainstrust/ or Meg E: meg@brainstrust.org.uk

103rd AACR Annual Meeting
31 March – 4 April, 2012;
Chicago, Illinois
W: www.aacr.org/

April

NEW
Molecular Mechanisms of Targeted Cancer Treatments
2 April 2012; London, UK
W: www.royalmarsden.nhs.uk/studydays E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921/ 020 7808 2924

The Sciences of Cancer Care
3, 4, 10, 11 & 16 April 2012;
London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Lymphoedema: Assessment and Management
4-6 April, 2012; Newcastle, UK
Mrs Margaret Sneddon,
Programme Director,
T: +44 (0)141 330 2071/2072,
E: lymph@glasgow.ac.uk
W: http://www.gla.ac.uk/departments/nursing/

NEW
Nutrition and the Cancer Patient
12 April 2012; London, UK
W: www.royalmarsden.nhs.uk/studydays
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921/ 020 7808 2924

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.

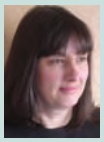
Dr Tom Lynch is Assistant Editor – Imaging, and is a Radiologist and Lead Nuclear Medicine Physician in the Northern Ireland Cancer Centre based at the Belfast City Hospital. Tom specialises in PET/CT scanning and nuclear medicine with a special interest in paediatric nuclear medicine.

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.

Panel of Journal Reviewers

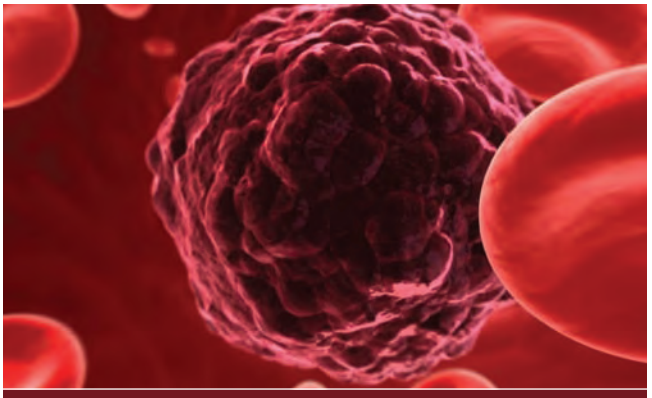
Dr Sarah Bell, Specialty Trainee Neuropathology, Southern General Hospital, Glasgow MRC Clinical Research Training Fellow, University of Glasgow, UK.

Mr Mriganka De, FRCS (ORL-HNS), Consultant ENT Head & Neck/Thyroid Surgeon, Derby Royal Hospital, UK.

Ms Helen Evans, Senior Lecturer in Cancer Nursing, Institute of Nursing and Midwifery, University of Brighton, UK.

Dr Simon Grumett, BSc MBChB MRCP PhD, Consultant & Honorary Senior Lecturer in Medical Oncology, Royal Wolverhampton Hospitals NHS Trust & University of Birmingham, UK.

Richard Novell, MChir FRCS, Consultant Coloproctologist, The Royal Free Hospital, London, UK.



2012 NCRI Cancer Conference

BT Convention Centre, Liverpool, UK

4-7 November 2012

cancer conference ncri national cancer research institute

The NCRI Cancer Conference is the leading international oncology meeting in the UK and delivers a pioneering programme showcasing high-quality data and a multi-disciplinary approach to cancer research from basic research to prevention, diagnosis, treatment and survivorship.

The world-renowned speakers and excellent networking opportunities attract around 2,000 delegates representing the whole oncology field from researchers and data managers to clinicians, nurses and policy makers.

PLENARY SPEAKERS

Kenneth Anderson (USA)
Robert G. Bristow (Canada)
Eduardo Bruera (USA)
Judy Garber (USA)
William Hahn (USA)
Lee J. Helman (USA)
Harpal S. Kumar (UK)
Michael Marmot (UK)
Joan Massagué (USA)
Neal Rosen (USA)

ALSO FEATURING SYMPOSIA ON

The Royal College of Radiologists' symposium
Hosted by Fergus Macbeth (UK)

Cancer evolution
Hosted by Gerard Evan (UK)

Cancer in the developing world
Hosted by Ian Magrath (Belgium)

The challenges of drug development
Hosted by Susan Galbraith (UK)

Cancer susceptibility
Hosted by Bruce Ponder (UK)

Palliative and supportive care
Hosted by Irene Higginson (UK)

Tumour immunology
Hosted by Adrian Hayday (UK)

The tumour microenvironment
Hosted by Margaret Frame (UK)

IMPORTANT DATES FOR THE 2012 NCRI CANCER CONFERENCE

Abstract submission opens
Monday 2 April

Abstract submission closes
Tuesday 5 June

Registration opens
Friday 1 June

Late breaking submission opens
Wednesday 1 August

Earlybird registration closes
Tuesday 31 July

Late breaking submission closes
Tuesday 28 August

Online registration closes
Sunday 30 September

Conference
Sunday 4 - Wednesday 7 November

Please check the Conference website for further information and updates on additional plenary speakers, parallel sessions and workshops

www.ncri.org.uk/ncriconference

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.

HCG Ahmedabad is first hospital in India to deliver treatments using TrueBeam™

A 65-year-old breast cancer patient has become the first person in India to be treated using the fast and precise TrueBeam™ radiotherapy treatment system from Varian Medical Systems. In a treatment carried out at HCG (Health Care Global) Ahmedabad, the patient received accelerated partial breast irradiation which allowed her treatment course to be completed in a week instead of the usual five weeks required with previous Varian technology.

"The patient was saved from visiting hospital for five full weeks," says radiation oncologist Dr Vivek Bansal. "As the TrueBeam treatment involved high dose rates delivered twice a day, the clinical team needed to be certain that the intended dose was delivered to the right area. A high degree of accuracy and good quality imaging helped ensure successful completion of the treatment."

Dr Bansal said shorter treatment times, high quality imaging, and greater throughput were all significant benefits for patients and the clinical team at HCG Ahmedabad. The center, which added radiotherapy to existing surgical and chemotherapy services a month ago, is the first private cancer hospital in Ahmedabad offering both diagnostic and treatment facilities for cancer under one roof. Its patients come from across Gujarat and neighbouring states of Rajasthan and Madhya Pradesh, as well as from outside India.

For further information contact:
Neil Madle, Varian Medical Systems,
T: +44 (0)7786 526068,
E: neil.madle@varian.com
W: www.varian.com

Leeds Teaching Hospitals accelerates cancer care with Elekta's Monaco Planning Software

IMRT and VMAT delivery techniques have dramatically reduced treatment times for thousands of patients. An obstacle to offering VMAT to more patients is the time it takes to create a plan. Physicians at St James's University Hospital – the first UK centre to use Monaco® VMAT clinically – have been able to significantly reduce VMAT planning times, increasing the potential to offer this therapy to more patients.

"Our referrals for radiation therapy are increasing considerably," says St James's head of radiotherapy physics Vivian Cosgrove, PhD. "If we can plan complex radiotherapy quickly and deliver treatment more efficiently with VMAT, then we can treat more patients and derive more benefit from our treatment machines."

Elekta VMAT delivers treatment in one or more continuous high-speed arcs around the patient, enabling the radiation dose to precisely conform to a tumor by modulating the radiation beam's intensity in multiple small volumes.

"Monaco has transformed our IMRT service," he noted. "After contouring, we can complete a complex head-and-neck plan in two to three hours – two to three times quicker than other planning systems we have used."

For further information contact: Patrick Greally, Elekta Limited,
T: +44 (0)1293 654 462,
E: Patrick.Greally@elekta.com

Stago's STA-R Evolution® key to blood services at Leicester

Clinicians at one of New Zealand's leading University Hospitals of Leicester NHS Trust relies on Stago's STA-R Evolution® instruments for measurement of blood coagulation parameters. Joanne Melbourne, Deputy Laboratory Manager in blood sciences, explained: "We provide blood services across three different sites and have six STA-R Evolution instruments spread between them. Five of the systems are used for routine tests such as fibrinogen and D-dimer, and the remaining instrument is dedicated to the more specialised coagulation tests. When purchasing new coagulation instrumentation, a crucial consideration is that the system must be able to link to a track at our main site – Leicester Royal Infirmary – but also be capable of working as a stand-alone system at our smaller sites. STA-R Evolution fulfilled all these roles."

"Because we operate over a large site with a lot of staff, it was also important to be able to train people quickly and easily; the STA-R Evolution's user-friendly touch screen plays a key role in this, enabling straightforward operation. We have had the instruments for almost four years now, and in that time have developed a very good relationship with Stago and found the STA-R Evolution to be very robust."

For more information, please contact:
Diagnostica Stago UK Ltd,
T: +44 (0)845 054 0614,
F: +44 (0)845 054 0625,
W: www.stago-uk.com

Radiometer's Blood Gas Handbook now available for iPhone® and iPad®

Radiometer's classic publication, The Blood Gas Handbook, is now available as an app for Apple's iPhone, iPod touch® and iPad. Blood gas status plays a key role in assessing the condition of critically ill patients, and this easy-to-use app aids the clinician in evaluating arterial oxygen status based on comprehensive blood gas analysis, including oximetry, and a closely related parameter, lactate.

The evaluation of blood gas parameters can be divided into subgroups – oxygen status, related metabolic parameters and acid-base status – and, as each subgroup consists of several parameters, the volume of data requiring interpretation can be overwhelming. As well as providing guidance and continuous access to information to assist the clinician with this task, Radiometer's interactive app allows users to add and edit their own reference intervals and to include notes for individual parameters. The blood gas app also has a search function, the capability to zoom in on images, and allows import and export of user-defined notes and reference intervals via iTunes®. A description of the parameters available on Radiometer's blood gas analysers, plus guides to their evaluation, is also provided.

Radiometer's blood gas app supports both English and Danish, and is available worldwide as a free-of-charge download from the Apple App Store. To date, there have been over 17,000 downloads of the blood gas app.

To find out more, please contact sales@radiometer.co.uk, or download Radiometer's blood gas app at the Apple App Store.

Varian exhibited TrueBeam™ Treatment System at Dubai World Trade Centre

Varian Medical Systems, a world leader in radiotherapy, exhibited its family of advanced treatment machines and integrated software solutions at the 2012 Arab Health Congress and Exhibition in January 2012. The Varian exhibit (Sheikh Saeed Hall, Booth No. S3-E40) focused on latest developments and future innovations in Varian's complete line of medical linear accelerators – including the fast and precise TrueBeam™ system – along with Eclipse™ treatment planning software, ARIA® oncology information software, proton therapy systems, brachytherapy solutions, and its full range of X-ray tubes and digital image detectors.

Rolf Staehelin, Varian's director international marketing for EMEA and APAC said, "Varian is the clear market leader in radiotherapy and radiosurgery in the Gulf Corporate Council (GCC) countries and is at the forefront of technology advances that help clinicians benefit patients by delivering faster and more efficient treatments."

Designed to advance the treatment of lung, breast, prostate, gynaecologic, liver, head and neck, intracranial and other types of cancer, Varian's TrueBeam™ system was engineered from the ground up to treat tumors with unprecedented speed and accuracy. It features a multitude of technical innovations that dynamically synchronize imaging, patient positioning, motion management, and treatment delivery. With its High Intensity Mode, TrueBeam machines can deliver very high doses quickly and accurately, more than twice as fast as earlier generations of Varian technology.

For further information contact:
Neil Madle, Varian Medical Systems,
T: +44 (0)7786 526068,
E: neil.madle@varian.com
W: www.varian.com

Zeiss Intrabeam® installed at The Princess Alexandra Hospital, Harlow

Clinical Oncologist Dr Julian Singer and the breast team at St Margaret's Hospital, have installed the state of the art radiotherapy equipment, IntraBeam®, into the operating theatres at Princess Alexandra Hospital. This machine is able to deliver Intra-operative Radiotherapy (IORT).

This is a radically new concept for early breast cancer treatment, whereby a single dose of radiotherapy is delivered directly into the breast following the removal of a tumour before the completion of the operation

For women with smaller breast cancers, IORT avoids women having repetitive radiotherapy sessions over a three to six weeks period. In most cases travelling long distances to a radiotherapy centre is unnecessary.

The procedure is called TARGeted Intra-operative radiotherapy (TARGIT). This procedure has been on trial for over a decade by breast cancer teams around the world with extremely favourable results recently published in The Lancet. Further research trials are underway for women with larger breast cancers and Dr Singer will be linked up with the research team at University College Hospital London.

For further information visit:
w: www.Zeiss.co.uk

East Yorkshire charity secures funds to order Biograph mCT

The Daisy Appeal, a local charity that aims to improve treatment and research opportunities in cancer and heart disease for the people in the Hull and East Yorkshire region, has helped to secure funds for the purchase of a Biograph™ mCT from Siemens Healthcare. It will be installed along with a cyclotron into the purpose built Medical Research Centre at Castle Hill Hospital, part of Hull and East Yorkshire Hospitals NHS Trust, and aims to be operational by spring 2013.

The mCT hybrid combines cutting-edge CT technology with HD•PET to provide a new depth of information and will assist the Medical Research Centre with earlier patient diagnosis and greater accuracy in treating cancer, heart disease and neurological diseases including dementia.

"Thanks to invigorated fund raising in the local area we are now in a position to sign a contract with Siemens Healthcare and begin the exciting steps in taking delivery of the Biograph mCT system for go-live in early 2013." explained Nick Stafford, Founder and Chairman of the Trustees at the Daisy Appeal and Professor of Otolaryngology & Head and Neck Surgery, at Hull and East Yorkshire Hospitals NHS Trust.

For further information visit:
www.siemens.co.uk/healthcare

Paxman scalp-cooling equipment

Paxman is the World's leading manufacturer of scalp-cooling equipment for the prevention of chemotherapy-induced hair loss. The innovative ORBIS system is the very latest in scalp-cooling technology and has the backing of leading oncologists from across the globe. This revolutionary hair loss prevention system is responsible for helping thousands of people throughout the world not only to keep their hair but to maintain their dignity whilst undergoing chemotherapy.

Scalp cooling works by lowering the temperature of the scalp immediately before, after and during the administration of chemotherapy drugs. This in turn reduces the blood flow to the hair follicles, thus preventing or minimising damage, meaning that hair loss is not inevitable.

Hair loss is a well-documented side-effect of many chemotherapy regimens. It is often devastating and the fear of hair loss has even been known to cause patients to refuse treatment.

The Paxman system is widely available in NHS and private hospitals throughout the UK and in the past 12 months the company has seen success in more than 20 new markets across Europe, Russia, the Middle East, the Far East and the Americas.

For further information visit:
www.paxman-coolers.com

Brain cancer patient receives first TrueBeam STx treatment in Asia at BGS Global Hospitals in Bangalore

Doctors at BGS Global Cancer Institute in Bangalore have begun delivering advanced radiotherapy treatments using the first clinical Varian TrueBeam™ STx medical linear accelerator in Asia. A 57-year-old female patient with a brain metastasis received whole brain radiotherapy and this will be followed by stereotactic radiosurgical boosts to the lesion using the fast and precise system.

"The whole procedure, the imaging and treatment, was completed within five minutes," says Dr Nirmala Srikantia, senior consultant and chief of radiation oncology services at BGS Global Cancer Institute. "TrueBeam STx gives our oncologists the flexibility to deliver multiple high precision treatments such as this while minimising the time required and, potentially, the inconvenience to the patient."

Global Hospitals has acquired three TrueBeam STx systems for its sites in Bangalore, Chennai and Mumbai, because of the rapidly increasing cancer incidence in these major population centers, along with the strength of the neuroscience departments in those hospitals.

For further information contact:
Neil Madle, Varian Medical Systems,
T: +44 (0)7786 526068,
E: neil.madle@varian.com
W: www.varian.com

Test may help reduce unnecessary repeat prostate biopsies

Gen-Probe have announced that the US Food and Drug Administration (FDA) has approved its PROGENSA® PCA3 (Prostate Cancer gene 3) assay, the first molecular test to help determine the need for repeat prostate biopsies in men who have had a previous negative biopsy.

"When used in conjunction with other diagnostic information, our PROGENSA PCA3 assay provides clinically important information that helps physicians and their patients make better, more informed decisions about one of the most vexing problems in prostate cancer diagnosis," said Carl Hull, Gen-Probe's Chairman and Chief Executive Officer. "From a commercial perspective, this is the third of four potential US regulatory approvals that we expect to generate a significant new sales growth cycle for the Company."

The PROGENSA PCA3 assay is indicated for use in conjunction with other patient information to aid in the decision for repeat biopsy in men from 50 years of age who have had previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on the current standard of care, before consideration of PROGENSA PCA3 assay results. A negative PROGENSAPCA3 assay result is associated with a decreased likelihood of a positive biopsy. A prostate biopsy is required to diagnose cancer.

For further information visit:
W: www.gen-probe.com

Nucletron offers an all-in-one solution for LDR and HDR prostate brachytherapy

Users treating prostate cancer are now able to access both LDR and HDR brachytherapy together with advanced Robotic delivery technology on a single platform.

For LDR treatments, Oncentra Seeds is a best-in-class brachytherapy system that integrates the latest developments in treatment planning with unique robotic implant technology. Nucletron's prostate solution considerably improves needle and seeds placement accuracy, resulting in superior treatment outcomes.

Advantages of this unique robotic implant technology include eliminating any manual handling of seeds, minimising unnecessary radiation exposure to staff and precise reproducible seed delivery. This results in the right dose being delivered to the right place, guaranteeing reliable and accurate treatment delivery.

Integrated in a compact mobile cart, Oncentra Seeds provides convenient access to workspace and network connections. Oncentra Seeds supports any type of seeds and application method, complete with customised isotopes and template types. This flexibility makes the Oncentra Seeds adaptable to any environment.

The seedSelectron™ is a unique robotic seeds delivery device designed to improve the permanent seed implantation process. It automatically delivers radioactive seeds to accurately match the planned seed configuration according to the latest and online adopted treatment plan.

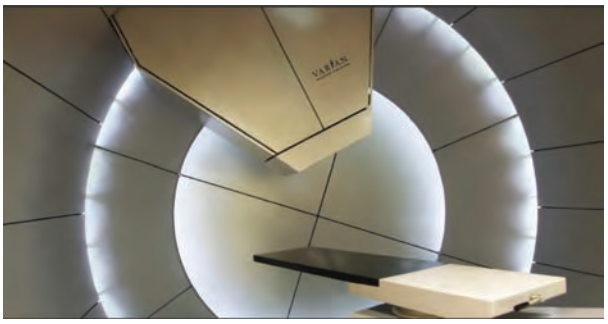
For further information contact:
Patrick Greally, Elekta Limited,
T: +44 (0)1293 654 462,
E: Patrick.Greally@elekta.com

Varian Books $77 Million order to equip Proton Treatment Center in Saudi Arabia

Varian Medical Systems recently announced it has booked a $77 million order with Saudi Particle Therapy Centre LLC to equip a new proton therapy facility at the King Fahd Medical Center in Riyadh, Saudi Arabia. Varian will equip the new center with a ProBeam™ system for five treatment rooms as well as two TrueBeam™ medical linear accelerators. Equipment delivery and installation is expected to commence in spring 2013 and patient treatments are scheduled to begin in late 2014. The agreement will also include a multi-year service contract that should commence as the installation is completed.

"We are honoured to have been selected to supply our equipment and software for this prestigious new facility, which will make life-saving proton therapy treatments available for the first time to cancer patients in this region," says Tim Guertin, Varian's chief executive officer. "This is an exciting step forward for our Varian Particle Therapy business."

Proton therapy makes it possible to treat certain types of cancer more precisely and with potentially fewer side effects than with conventional radiation therapy. With proton therapy, the risk of damage to healthy tissues is reduced. The method can be applied



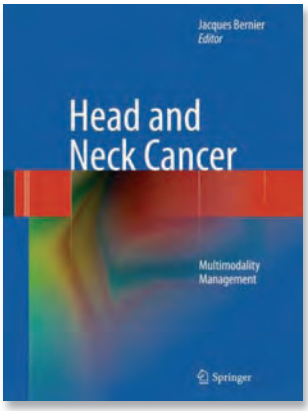
for many of the most common types of cancer and offers advantages when treating tumors close to radiosensitive tissues.

For further information contact:
Neil Madle, Varian Medical Systems,
T: +44 (0)7786 526068,
E: neil.madle@varian.com
W: www.varian.com

Book Reviews

Head & Neck Cancer – multi modality management

Edited by: Jacques Bernier. Published by: Springer. ISBN: 978-1-4419-9463-9. Price: £162.00.



This book is aimed at all members of multidisciplinary teams involved in assessing and managing head and neck cancer. This is the first edition of the book. It is considerably detailed and therefore more informative. As it says on preface that in the last two decades the management of head and neck cancer has been characterised by a number of profound mutations – triggered by the willingness of oncologists to reshape significantly their conceptual approaches to locally advanced diseases and facilitated by the advent of new, more active drugs. The potentialities of functional imaging, significant progress in conservative surgery and reconstructive surgery, the acknowledge role of concurrent chemoradiation, investigational use of combined therapies for organ preservation and advent of targeted therapies are among the main tracks along which the fundamental changes in philosophy of management in this group of disease has been observed. This book addresses the necessity to move towards the goal of having more holistic approach taking into account of quality of life after treatment. The book also gives very good account of usefulness of translational research in head and neck oncology. As a surgeon, I feel the book is concentrating more on non-surgical management aspect. This in one sense is good as we are embarking on 21st century medicine.

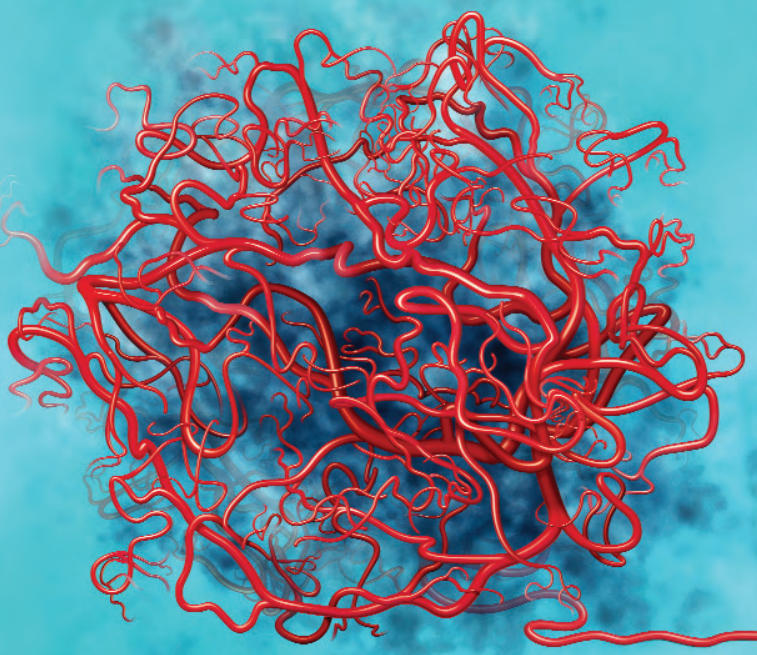
The book is divided into fifty chapters. All the chapters incorporate most up to date information and provide a succinct overview of various topics. The surgical sections discusses the various surgical treatments, however, the reader must be aware that its not and neither is it intended to be an operative manual guide. As expected, the book is quite heavy on non-surgical aspects of management of head and neck cancer. The non-surgical aspect of the book provides an excellent understanding of the whole spectrum of head and neck cancer management which from a surgeon's point of view is very useful in achieving a greater understanding of head and neck cancer management.

In summary, this text is well written, in a clear style and gives us a clear overview of not only the scientific and clinical but also the quality of life aspects of management of head and neck cancer. The chapters are easy to read and understand with the text assuming little prior knowledge. I would recommend this book to all members of multidisciplinary team involved in assessing and managing head and neck cancer irrespective of level and stage of training. ■

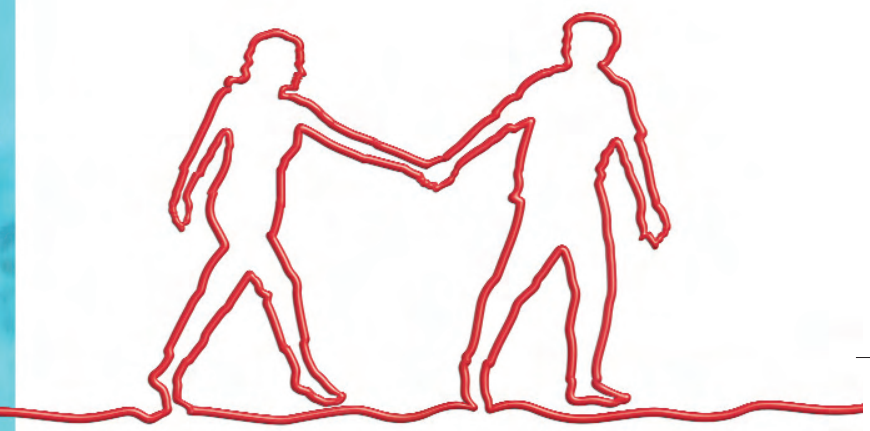
Reviewed by Mr Mriganka De
Consultant ENT Head & Neck/Thyroid Surgeon,
Derby Royal Hospital, UK.

Roche

New licence in ovarian cancer



The first new treatment option for advanced ovarian cancer in 15 years[1]



Avastin in combination with front-line chemotherapy, and continued as maintenance therapy for up to 15 months, offers significant PFS gains versus standard chemotherapy alone[2,3,4]

PRESCRIBING INFORMATION

Refer to Avastin Summary of Product Characteristics (SPC) for full prescribing information. **AVASTIN® (bevacizumab) 25mg/ml concentrate for solution for infusion. Indications:** In combination with carboplatin and paclitaxel for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer. **Dosage and Administration:** Single use vials (25mg/ml bevacizumab) as 100mg/4ml or 400mg/16ml. Physicians experienced in antineoplastic medicines should supervise Avastin administration. *Ovarian cancer:* 15 mg/kg every 3 weeks in addition to carboplatin and paclitaxel chemotherapy for up to 6 cycles, then as monotherapy until disease progression or for a maximum of 15 months. *Administration times; initial dose:* 90 minute IV infusion; *second dose:* 60 minute IV infusion if initial dose well tolerated; *subsequent doses:* 30 minute IV infusion if second dose well tolerated. Do not administer as IV push or bolus or mix with glucose. Dose reduction for adverse events not recommended. If indicated, discontinue or temporarily suspend therapy. Not recommended in children or adolescents. No dose adjustment in the elderly. **Contraindications:** Hypersensitivity to bevacizumab, Chinese hamster ovary cell products, recombinant human or humanised antibodies or any excipients. Pregnancy. Lactation. **Precautions:** *Gastrointestinal (GI) perforation;* risk may be increased; permanently discontinue in patients developing GI perforation. *Fistulae;* permanently discontinue in tracheo-esophageal fistula or any Grade 4 fistula, consider discontinuation in non-GI fistula. *Wound healing;* do not initiate for at least 28 days following major surgery or until surgical wound has healed; withhold for elective surgery. *Hypertension;* control pre-existing hypertension prior to initiation. Monitor blood pressure during therapy and treat as per SPC: permanently discontinue if medically significant hypertension remains uncontrolled or for hypertensive crisis/ encephalopathy. *Reversible Posterior Leukoencephalopathy Syndrome (RPLS);* should RPLS develop, confirm by imaging, treat symptoms and discontinue Avastin. RPLS signs include: seizures, headache, altered mental status, visual disturbance or cortical blindness with/without associated hypertension. *Proteinuria;* test prior to and monitor during treatment. Permanently discontinue if Grade 4 proteinuria (nephrotic syndrome) develops. *Arterial thromboembolism* including cerebrovascular accidents, transient ischaemic attacks and myocardial infarctions, especially if prior history or elderly: permanently discontinue if arterial thromboembolic events develop. *Venous thromboembolism* including pulmonary embolism; discontinue in Grade 4 thromboembolic events and monitor where ≤Grade 3. *Haemorrhage, especially tumour-associated haemorrhage;* discontinue permanently if Grade 3/4. Caution in patients with congenital bleeding diathesis, acquired coagulopathy or during anticoagulant therapy. *Patients with CNS metastases;* monitor and discontinue treatment if intracranial bleeding occurs. *Congestive Heart Failure (CHF);* caution in patients with clinically significant cardiovascular disease or pre-existing CHF. *Neutropenia;* fatal infection with or without severe neutropenia in combination with myelotoxic chemotherapy. *Hypersensitivity reactions/infusion reactions;* close observation recommended during and following bevacizumab administration. If a reaction occurs, discontinue infusion and administer appropriate medical therapies. Systematic premedication not warranted. *Osteonecrosis of the jaw (ONJ);* has been reported. Consider dental examination and preventive dentistry before starting Avastin. Caution when Avastin and bisphosphonates are administrated simultaneously or sequentially, avoid invasive dental procedures if possible. *Ovarian failure:* may occur. Consider fertility preservation strategies in women of child-bearing potential. **Drug Interactions:** Risk of microangiopathic haemolytic anaemia (MAHA) when combined with sunitinib malate (50mg daily). Reversible on discontinuation of both agents. Fatal infection with or without severe neutropenia, mainly with platinum- or taxane-based therapies for metastatic or recurrent non-small cell lung cancer and metastatic breast cancer. Safety and efficacy with concomitant radiotherapy not established. **Pregnancy and Lactation:** Contraindicated. No data on use in pregnancy; may inhibit foetal angiogenesis. Women of childbearing potential must use effective contraception during treatment and for 6 months after last dose. Discontinue breast-feeding during treatment and for 6 months after last dose. **Side-effects and Adverse Reactions:** For full listings please refer to the Avastin SPC. *Serious reactions, very common:* Leucopenia, thrombocytopenia, neutropenia and febrile neutropenia. Peripheral sensory neuropathy. Hypertension. Diarrhoea, nausea, vomiting. Venous thromboembolic events. Asthenia, fatigue. *Serious reactions, common:* Anaemia. Sepsis, abscess, infection. Dehydration. Cerebrovascular accident, syncope, somnolence, headache. Supraventricular tachycardia, CHF. Arterial thromboembolism, deep vein thrombosis, haemorrhage, including pulmonary haemorrhage. Pulmonary embolism, dyspnoea, hypoxia, epistaxis. Ileus, intestinal perforation and obstruction, abdominal pain, GI disorder, stomatitis. Palmar-plantar erythrodysaesthesia syndrome. Muscular weakness, myalgia, arthralgia. Proteinuria, urinary tract infection. Pain, lethargy, mucosal inflammation. Dysphonia. *Serious reactions, uncommon/rare/very rare:* Fistulae. RPLS (with or without associated hypertension). Hypertensive encephalopathy. *Serious reactions (frequency not known):* pulmonary hypertension, nasal septum perforation, renal thrombotic microangiopathy clinically manifested as proteinuria, gastrointestinal ulcer, hypersensitivity/ infusion reactions with possible co-manifestations: dyspnoea/difficulty in breathing, flushing/ redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting, ONJ, gall bladder perforation. *Other, very common:* Wound healing complications. Anorexia. Dysgeusia, dysarthria. Eye disorder, lacrimation increased, rhinitis. Rectal haemorrhage, constipation. Ovarian failure. Exfoliative dermatitis, dry skin, skin discolouration. Pyrexia. Any of the above may become serious. Elderly; increased risk of severe leucopenia and thrombocytopenia; neutropenia, nausea, headache, diarrhoea, fatigue, or arterial thromboembolic events. Laboratory abnormalities – refer to SPC. **Legal Category:** POM. **Presentation and Basic NHS Cost:** Pack of one 100mg vial: £242.66. Pack of one 400mg vial: £924.40. Excluding VAT. **Marketing Authorisation Numbers:** 100mg/4ml: EU/1/04/300/001; 400mg/16ml: EU/1/04/300/002. **Marketing Authorisation Holder:** Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, United Kingdom. Registered in England No. 3028626. **Avastin is a registered trade mark. Date of Preparation:** October 2011. **RXUKMED100068. References:**

1. European Medicines Agency, European Public Assessment Report (EPAR). Available at: http://www.ema.europa.eu/ Accessed November 2011 (search). **2.** Avastin Summary of Product Characteristics. Accessed www.medicines.org.uk/emc **3.** Burger RA *et al. J Clin Oncol* 2010; **28**: 18s, (suppl; abstr LBA1). **4.** Burger RA *et al. J Clin Oncol* 2011, **29**: (suppl; abstr 5023).

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Leading angiogenesis inhibition

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk

Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre on: 01707 367554.

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