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IN THIS ISSUE

Honest Answers, Sound Advice: A Young Person's Guide To Cancer

This is the first edition of Honest Answers, Sound Advice: A Young Person's Guide to Cancer, produced by Teenage Cancer Trust, a UK charity dedicated to improving the quality of life and chances of survival for the seven young people aged 13 to 24 diagnosed with cancer every day.

The resource was developed by the charity, along with expert reviewers including doctors, nurses, psychologists, youth support coordinators and, most importantly, young people with cancer. Generous funding support was also received from The Queen's Trust, along with help and support from CanTeen Australia.

The ring-bound, compact, guide was created in response to research carried out by a patient insight specialist. This discovered that young people felt there was a lack of consistent information made available to them, tailored to their age group and that dealt with the physical and mental impact of cancer and gave advice on how to keep their lives on track.

The guide covers a variety of topics, which take a patient from diagnosis, through treatment, and beyond. The creators of the guide have thought about what information a young person really needs. Coloured tags handily divide the book into six different sections: Finding Out, Med Stuff, Heart Stuff, Life Stuff, Beyond Cancer, and Handy Stuff.

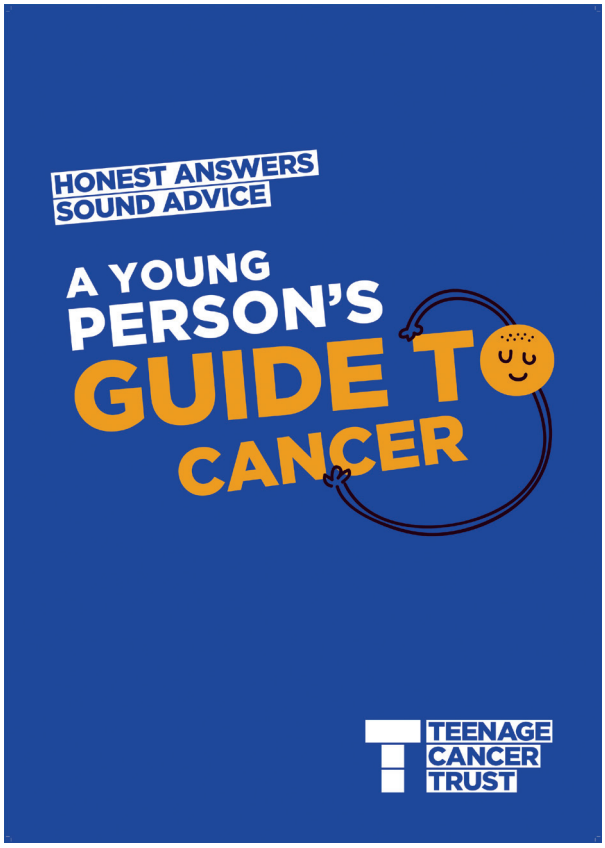
'Finding Out' covers the moment of diagnosis, providing advice and comfort on how to deal with hearing the news. The guide provides responses to questions that a young person might have, and gives advice on how to ask further questions. It also includes cautionary advice about Google, while acknowledging that a patient will almost certainly consult the internet on diagnosis.

'Med Stuff' is the longest and most comprehensive section. It outlines different types of cancer, treatment, clinical trials, and side-effects in simple and honest language. It also includes practical advice about sex, addressing issues that a young person might not wish to discuss with their clinical team.

'Heart Stuff' focuses on the wide-ranging emotional impact that a cancer diagnosis can have on a young person. It contains advice, such as not to bottle up feelings, while acknowledging that different people react differently. A section on 'Coping Strategies' has a wide range of tips and information on who to talk to, while the pages on body image provide emotional support as well as tips on what to expect and how to weather the physical bodily changes.

'Life Stuff' covers relationships with friends, family, boyfriends and girlfriends. The pages on school, studying and work offer practical advice on managing these aspects of life, on taking time out, and also on returning to work or education after time off. A section on legal and money matters clearly outlines the young person's rights and provides a list of useful organisations who can help.

'Beyond Cancer' contains advice about life after treatment. It has a section on late side effects and an honest section on re-diagnosis.



'Handy Stuff' includes an extensive glossary of all the cancer terms. It even contains cards that can be ripped out and given to others to explain experiences and emotional needs.

The guide has been well received by the young people who have used it so far. Emily, 17, who finished treatment for Acute Lymphoblastic Leukaemia in October said:

"It is a great guide and, even though I have not been recently diagnosed, it was helpful to read the section about finishing treatment.

"I would have found it really helpful and comforting if I had received it when I was diagnosed, so I think it would be a good idea if as many newly-diagnosed patients as possible receive a copy. I really think it would be a great help to them.

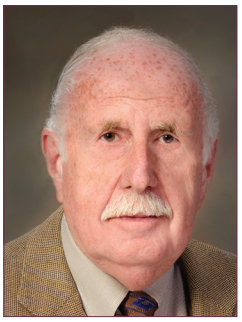
"I read through the guide and found so many times that my thoughts and feelings and reactions to being diagnosed were identical to those in the book, which meant a lot – obviously I'm not alone and my reactions were completely normal!"

The guide, which adheres to the strict quality guidelines of The Information Standard, is a free resource, currently given to patients receiving treatment on a Teenage and Young Adult cancer unit. However, the guide is also available more widely and anyone interested can request their copy by emailing support4you@teenagecancertrust.org

TEENAGE CANCER TRUST

www.teenagecancertrust.org

Toward the realisation of immunotherapy for cancer



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To paraphrase the recent popular media, there is a buzz of excitement throughout industry thought leaders and to a lesser extent in academia on personalised (also precision) medicine (PM) and immune checkpoint inhibitors (ICI) among other advances, that many have credited for the coming of age of immunotherapy for cancer.

I have previously addressed PM, and therein the role of the immune system as a personalised therapeutic intervention, in an earlier Editorial [1] and Geanta more recently considered additional aspects of PM in ON [2]. Therefore, it only seems appropriate that as emerging cancer therapeuses, buoyed by ICI, are being increasingly utilised to target the immune system stimulating an antitumour response that, we take a cursory look at some of the factors taking us toward the possible realisation of immunotherapy for cancer.

With increasing knowledge how to regulate and direct the immune response a key factor in the use of immunotherapy unlike chemotherapy and other treatments is that the immune system has exquisite sensitivity and specificity and has traditionally held promise for eradicating, if not controlling, cancer locally and systemically, sparing normal tissue and with minimal sequelae. Furthermore, the immune system may leave behind a long-term memory serving to protect the patient from subsequent disease. Presently, to my knowledge there is no treatment regimen for cancer that can claim such specificity of memory.

Among many questions arising out of very early independent endeavors to the use of BCG augmentation and cryoimmunotherapy (development of an immune response following in situ cryoablation [reviewed in 3]) were: i) can we predict who will benefit vs. be harmed, i.e., when will it work and ii) how do we monitor the patient's response. Evolving therefrom was the concept of "immunostaging" –a method of assessing a patient's immune status before and after immunotherapy [3]. Just as cancer is clinically staged and graded, immunostaging is essential in consideration of the development and treatment of cancer. Obviously (but in the beginning only to a sanguine few) immunotherapy is based on the premise tumours are antigenic, but essential, the patient has to possess the innate (or augmented) ability to respond, i.e., immunocompetancy, to the tumour. Of growing importance as clinical trials of immunotherapy have increased, immunostaging paved the way toward recognising the bidirectional nature of the immune response, i.e., which was tumouricidal (beneficial) vs. tumour enhancing (harmful), and the necessity to down regulate the tumour enhancing effects of T suppressor cells via cyclophosphamide. After some time, the realisation of the importance of immunostaging, or some paradigm thereof, including expanded realisation of the role of the tumour microenvironment (early-on considered by the author), have appeared in several articles [reviewed in 4].

With the advent of improvements in criteria toward patient selection as to who will benefit from immunotherapy, questions and challenges continue in regard to how do we monitor the immune response and determine its clinical efficacy.

Traditional Response Evaluation Criteria in Solid Tumours (RECIST) and WHO Criteria for evaluation, e.g., of radiologic and chemotherapeutic responses, wherein effectiveness noted by tumour shrinkage translate to patient benefit have been found to be misleading with immunotherapy. For example, some lesions may even increase in size before regressing. Herein, biopsy has shown lymphocytic infiltration rather disease progression. These, and other observations have resulted in an alternative Immune-Related Response Criterion (irRC) [5]. The benefit of using irRC correctly captures responses in patients, who benefit from immunotherapy that are missed with conventional criteria. Of note, immune agents may require additional time to achieve measureable or sustained clinical effects. Absence of this knowledge can lead to inaccurate interpretation of the beneficial effects of immunotherapy.

Mentioned at the outset ICI, a new approach to immunotherapy combines several immunological agents to prime an antitumour response and prevent suppression of existing new responses.

Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) was the first ICI to be clinically targeted. Normally, following T-cell activation, CTLA-4 is upregulated on the plasma membrane where it functions to down regulate T cell function. Appreciation of CTLA-4 as a negative regulator of immunity led to the demonstration that antibodies to CTLA-4 resulted in antitumour immunity. Antibodies targeting CTLA-4, e.g., ipilumumab, have shown clinical responses in melanoma patients and other malignancies [6]. A second ICI of clinical interest is programmed cell death-1 receptor (PD-1) and ligands PDL-1 and PDL-2. PD-1 is a negative regulator of T cell activity at various stages of the immune response when it reacts with its two ligands PDL-1 and PDL-2. Antibodies that disrupt PD-1 have entered clinical development, e.g., pembrolizumab and nivolumab have been approved for melanoma [6].

Albeit, without a doubt, ICI have substantially improved the successful prospect of immunotherapy, they are not without associated toxicities [7]. Termed immune-related adverse events (irAEs), they are typically transient, but occasionally can be severe or fatal. The most common and important irAEs are dermatologic, diarrhea/colitis, hepatotoxicity and endocrinopathies. They are suggested to be associated with general immunological enhancement, transient immunosuppression with corticosteroids and TNF-alpha antagonists.

Extensive, if not exhaustive, studies have demonstrated an irrefutable interrelationship between immunity and cancer, bringing us to the present state toward the future realization of immunotherapy for cancer.

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New therapeutic approaches for the treatment of brain tumours

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Glioblastoma Multiforme (GBM) is the most common type of primary malignant brain tumour in adults, accounting for 54% of all gliomas. Approximately 0.59 to 3.69 GBM cases per 100,000 of the population are diagnosed annually worldwide. GBM is also one of the most lethal brain tumours, with only one-third of patients surviving for one year and less than 5% living beyond five years with an average survival of 12 to 15 months [4]. Therefore, the development of new and effective therapies for brain tumours, and GBM in particular, is a priority. While a number of key challenges exist, there are also promising treatment strategies being developed which could hold real hope for the future.

When considering the development of new therapies, the first challenge is to ensure that the drug reaches its target within the brain. The blood brain barrier (BBB) prevents the entrance of many small drugs, in addition to larger molecules which have a therapeutic effect on the tumour cells, from entering the brain. One approach is to develop drugs attached directly to carrier proteins which bind to specific components of the BBB to facilitate their entry into the brain. A similar approach for targeting drug delivery is to load the drug into lipid vesicles which express the carrier protein in the outer membrane which can also transfer across the BBB [6]. Two particular receptor proteins have shown particular promise. The transferrin receptor (TfR) is expressed at a low level in most human tissues but at a high level in brain capillary epithelial cells. Therefore, drugs which are conjugate to the transferrin protein (Tf) can cross the BBB more readily, resulting in an increase in brain levels of a drug. This can also be achieved using Tf-containing liposomes [9]. A second target is the low-density lipoprotein (LDL) receptor. Again, these are expressed at a high level in the BBB epithelium and also in glioma cells. The angiopep-2 protein, which binds to the LDL, can increase drug uptake into the brain and initial pre-clinical experiments have demonstrated that liposomal membranes containing angiopep-2 can readily be taken up into the brain and deliver small marker peptides into glioma cells [1].

Integrins are cell-surface proteins involved in communication between cells which are over-expressed on tumour cells. Although there are a number of potential peptide ligands which may target integrins, the most promising to date is the [c(RGDfK)] tripeptide. When it is attached to the surface of liposomes, it increases their uptake into tumour cells. One study reported an increase in the uptake of the drug paclitaxel which is currently used to treat ovarian, breast, lung and other non-brain tumours. This demonstrates that the development of an appropriate drug delivery strategy will increase the library of drugs that may be used to target brain tumour cells [10]. A similar drug, cilengitide,

also binds to cell surface integrins and has undergone investigation. While this showed potential anti-tumour activity in pre-clinical models, a phase II clinical trial did not demonstrate any efficacy, either alone or when administered with temazolamide. This discrepancy highlights the challenge in translating the results obtained in pre-clinical studies into the clinical arena.

The second challenge is to develop drugs that are effective in killing the tumour cells as some GBM cells have a particularly high resistance to currently employed radio- and chemotherapy approaches. A subclass of cells, termed GBM initiating cells (GIC), play a key role in the process of tumour initiation and sustained growth, and so represent a potential drug target. The bone morphogenic protein (BMP) is one of a group of compounds associated with the inflammatory response within the brain which reduces glioma cell growth and makes them more susceptible to conventional chemotherapy, including temozolamide. Early clinical studies have reported that glioma cells which themselves express higher levels of endogenous BMP, have a better clinical prognosis. However, the pre-clinical studies that have been carried out to date have used direct intracranial injections of the protein which would not be routinely clinically appropriate. A similar target is the CD133 protein which is expressed on cancer stem cells (CSCs) which are associated with increased tumour malignancy. Peripherally administered liposomes containing antibodies to CD133 bind and are taken up into tumour cells, leading to a significant increase drug levels within the cells [8]. CD133 has also been used as a target using the emerging chimeric antigen receptor (CAR-T) cell approach. These cells have been engineered to express the CD133-specific antigen to target and ultimately kill CD133-positive CSCs, both in vitro and in a pre-clinical model [11]. Interestingly, the promising results using the CAR-T technology is associated with the entry of the immune cells into the brain, thus questioning the dogma that the brain is an immune privileged site.

Activation of the epidermal growth factor receptor (EGFR) increases glioma cell proliferation and tissue invasion, and its expression is upregulated in up to 50% of glioblastoma cells. The tumour-specific mutation EGFRvIII is also expressed in glioblastoma cells, making it an appealing therapeutic target. A number of strategies have been developed to inhibit receptor activation and therefore decrease tumour cell proliferation and penetration. Liposomes which contain an agent directed against EGFR, cetuximab, were reported to enhance their uptake and accumulation within the cells, although this was not observed in tumours which only expressed the EGFRvIII mutation, thus highlighting the potential selectivity of such cell-targeted approaches. A vaccine targeted against EGFRvIII receptor variant, rindopepimut, is currently undergoing phase II clinical trials with initial positive reports [3]. CAR-T cells have also been engineered to target both the EGFR and EGFRvIII epitopes and intracranial injections in pre-clinical models have reported positive results [5].

Another growth factor that has been identified as a therapeutic target is the vascular endothelial growth factor (VEGF) which binds the VEGF-R receptor to activate cell growth. This is expressed particularly by higher grade glioblastmas and is indicative of a poor treatment outcome. A study using the VEGF-R inhibitor, axitinib, has reported promising pre-clinical results [7]. However, a trial of an antibody directed against the VEGF peptide, bevacizumab, was unsuccessful in initial clinical trials. a subsequent analysis of the data suggested that a sub-group of patients demonstrated a positive response, so this warrants further research to be able to identify those who will respond to the therapy [2]. However, a clinical trial combining bevacizumab with rindopepimut represents an approach using complementary immunological approaches targeted against two proteins. Early results have reported potential clinical benefits [3].

In conclusion, while the library of existing treatments for brain tumours remains extremely limited at present, new technological approaches may provide the next-generation of therapies that will be more effective against brain tumours. This will address the key current challenges including access of the treatments to the tumour and the identification of new therapeutic targets which will be effective against the heterogeneous populations of brain tumour cells.

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Prostate Cancer and Quality of Life:

Q&A with Alison Birtle, Consultant Clinical Oncologist And Honorary Clinical Senior Lecturer at Lancashire Teaching Hospital

Why is there an increasing focus on health-related quality of life (HRQoL) in the management of men with advanced prostate cancer?

Before 2004, we could do little for men with advanced prostate cancer, apart from offer symptomatic relief. Then results were published from the TAX 327 study, which compared docetaxel and mitoxantrone, both given with prednisone, for hormone-refractory advanced prostate cancer. Median survival was 16.5 months with mitoxantrone, 18.9 months with docetaxel every 3 weeks and 17.4 months with weekly docetaxel.[1] For the first time, we could demonstrate a survival advantage in advanced prostate cancer. Since then, a growing number of treatments means that men with advanced prostate cancer can potentially remain well with a good HRQoL for a long time. In effect, advanced prostate cancer is increasingly a chronic condition. So, we have to minimise side effects and maximise HRQoL for as long as possible.

What are the main problems that undermine HRQoL in men with metastatic castration resistant prostate cancer (mCRPC)?

In my experience, pain and fatigue often have the greatest impact on HRQoL in men with mCRPC. Chronic pain, which is often generalised, can undermine HRQoL, while acute, localised pain may be the first sign of progression. Fatigue can also have a marked impact on HRQoL. Within 6 months, men with advanced prostate cancer can go from still managing to go for a long walk to being just about able to get around the corner to the shops. They'll still be at performance status 1, but the impact of the change in their physical performance on their HRQoL can be marked. It's important that we understand our patients' goals and what affects their HRQoL so that we can plan treatment accordingly.

How do you assess HRQoL in the clinic?

I tend to focus on key drivers of HRQoL in men with mCRPC. I ask about weight. Cancer teams often tend to become fixated on weight loss and cachexia. Hormonal treatments can, however, result in weight gain that undermines HRQoL and which can contribute to the metabolic syndrome associated with androgen deprivation. Controlling the metabolic syndrome may be important for long-term survival as we move towards treating advanced prostate cancer as a chronic disease.

I also ask men with advanced prostate cancer about body image, breast tenderness and depression, and to rate their pain. I tie questions about the fatigue to fixed events to aid recall. Rather than, for example, asking how their current energy level compares to 'six months ago', I ask the patient to compare to, for instance, Christmas or Easter. Recently, I have started collecting these data and looking at trends over time and with different therapies.

Do you use HRQoL scales?

HRQoL scales are valuable in clinical studies, but they are not really useful in a busy clinic. For example, in a study, a research nurse is on hand to help volunteers complete the questionnaire. We don't have the resources for this or the time to evaluate formal HRQoL questionnaires in a routine clinic. They're just too unwieldly for the real world.

In addition, specific instruments – such as the prostate module for the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 or Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire – include domains about issues such as urinary function that are much more relevant for early prostate cancer than for men in the advanced, palliative setting.

On the other hand, I use visual analogue scales for pain and the Brief Pain Inventory, which can be easily completed even in a busy clinic. But these look at only one aspect of HRQoL.

How can treatment influence HRQoL?

In the palliative setting, we are looking for treatments that improve HRQoL. Indeed, while side effects are common, chemotherapy can improve HRQoL. In the TAX 327 study, for example, 22% and 23% of men reported improvements in their HRQoL with docetaxel every three weeks or weekly respectively, compared to 13% with mitoxantrone.[1] Despite side effects, docetaxel improved all HRQoL domains including weight loss, appetite, pain, physical comfort, and bowel and genitourinary function.[1]

TAX 327 showed that men felt better on chemotherapy despite the side-effects. I now tell patients that about 30% of men with advanced prostate cancer feel better on chemotherapy, and that the improvement in pain control and HRQoL can emerge rapidly, in some cases after the first cycle. Some patients, however, really want an oral treatment and infusions would comprise their HRQoL unacceptably. We have to respect patients' views and tailor treatment accordingly.

Do the cancer teams' and the patients' views of HRQoL differ?

Inevitably, we tend to focus on overall survival even when treating mCRPC. However, the 'Prostate Cancer: Living, not Just Surviving' report developed by Janssen and national patient organisations, revealed, for example, that UK men living with prostate cancer are more likely to worry about intimacy problems with their partner (43%) and the practical impact on their family routine (36%) than dying (27%).[2] In general, we are aware of these issues and tailor treatment accordingly. There can, sometimes, be a discordance between patients and professionals.

For example, a patient receiving palliative treatment will focus excessively on their Prostate Specific Antigen (PSA) levels. We explain that if they feel better, if their pain is gone, if their energy levels are higher, then the PSA levels are less important. Indeed, a significant number of patients show a marked mismatch between PSA levels and the severity of symptoms or the impact on HRQoL. On the other hand, I would never persist with a treatment that caused significant side effects even though the PSA levels improved dramatically.

How do you think HRQoL assessment will develop?

Uro-oncology clinical nurse specialists (CNSs) will probably take on more of the 'routine' assessment of men with prostate cancer, including evaluating HRQoL. We see patients with advanced prostate cancer every 4-6 weeks, and the increasing number of men living longer with the disease places an unsustainable burden on doctors. A uro-oncology clinical nurse specialist sits in on my clinical appointments, is familiar with the HRQoL domains that we collect and then follows up with patients during independent clinics, referring men to me when needed. Having a uro-oncology clinical nurse specialist is a huge advantage.

This feature was drafted by a medical writer funded by Janssen UK. Dr Birtle guided and reviewed the content and has not received payment for her involvement. For more information about Janssen UK, please visit www.janssenpro.com

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Key findings from the 'Prostate Cancer: Living, Not Just Surviving' report developed by Janssen and national patient organisations

- Only 13% of HCPs (n=80) feel that they have sufficient resources to address the quality of life issues that affect their prostate cancer patients.[2]
- Over half (55%) of UK men with prostate cancer (n=103) surveyed state that they are so tired, they no longer feel able to take the regular exercise that 81% of HCPs agree could lessen the physical impact of prostate cancer.[2]
- Only 24% of men surveyed could recall receiving advice from a HCP on exercise.[2]
- 60% of HCPs say they do not always proactively provide advice to patients on ways to improve their physical and emotional wellbeing.[2]
- Fatigue has the biggest negative impact, particularly in metastatic patients (100%) and patients on medication such as hormone treatment, chemotherapy and steroids (88%).[2,3]
- The biggest worry for men living with prostate cancer is intimacy problems with their partner (43%). Fear of death was only the fifth biggest worry (27%), with men also revealing greater worries about the practical impact on their family routine (36%), feeling ill (30%) and the emotional impact on their family (29%).[2]

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A method for accurate spatial registration of PET images and histopathology slices

Positron emission tomography (PET) is an imaging technique used for the assessment of tissue of interest via administration of radiopharmaceutical commonly known as tracer. A newly developed tracer for PET imaging should be validated by comparison with the gold standard of histopathology imaging before it can add value for clinical purposes, for example, diagnosis, prognosis and response to treatment. The tracer validation studies may become more meaningful if the quantitative comparison between the PET and histopathology images comes from spatially corresponding regions.

An image processing technique called 'image registration' is used to establish spatial alignment between two image datasets. An image registration example between two datasets is shown in Figure 1. The registration between tomographic and three dimensional (3D) histopathology data have been previously shown to obtain satisfactory results [1,2]. However, the process involved in obtaining 3D histopathology data is expensive and not always feasible in routine pathology settings.

The registration between PET and histopathology slices become challenging when the sectioned specimen is non-parallel, non-contiguously cut and non-mega-block sized (i.e. standard sized) because systematic sectioning of a specimen provides thickness estimates of the sectioned slices, contiguous sectioning minimises the errors in reconstructing histology volume and mega-block sized slices provides tissue boundaries for matching with blockface/tomographic data. We present a registration methodology for an accurate spatial alignment between PET and histopathology data obtained in routine pathology settings such that the sectioned slices may be non-parallel, non-contiguously cut and of standard block sized.

Data from males with histo-pathologically proven advanced squamous cell carcinoma of the head and neck (SCCHN) cancer was used. Relevant patient permissions and regulatory approvals were obtained. Subjects underwent 64Cu-copper-II-diacetyl-bis (N4-methylthiosemicarbazone) 64Cu-ATSM PET-CT (computed tomography) scan a week before the surgery. Pimonidazole was administered a day before the laryngectomy. The spines of the black sea urchins were used as the fiducial markers which were inserted into the fresh specimen thereafter fixed in formalin and scanned CT *ex-vivo*. Specimen was sliced and blockface images of the tissue blocks were obtained. From these thick tissue blocks, a subsection of tissue from the tumour region was extracted for the preparation of histopathology slides and digitised using a light microscope (Figure 2).

The total registration errors between

Figure 1: An example of rigid registration where Image2 is translated and rotated to spatially align with Image1.

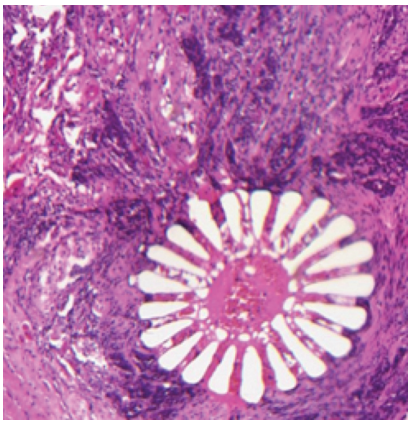

FIGURE 2: A 5-µm thin pimonidazole stained histopathology slice with spine of black sea urchin that was cut orthogonally and scanned under a light microscope at a resolution of 1 µm/pixel.

Authors


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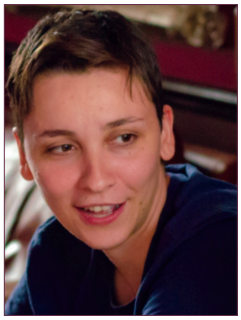
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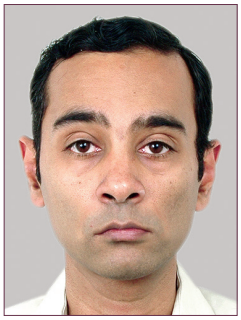
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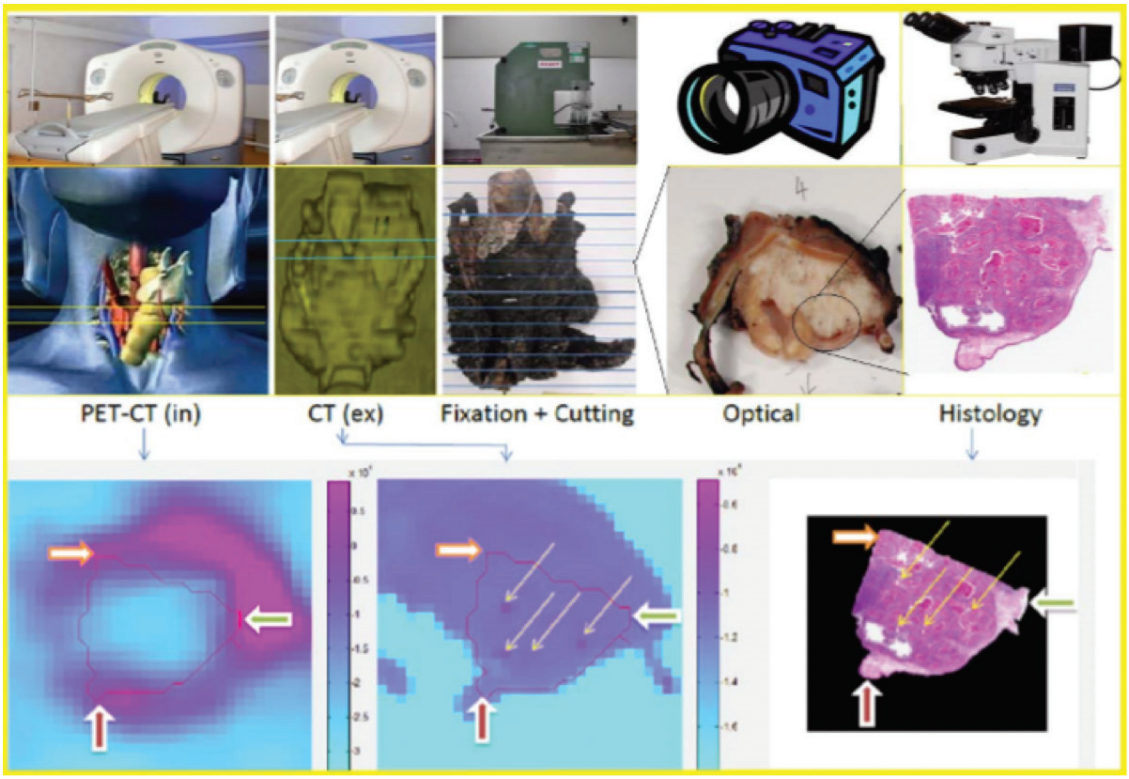

Figure 3: The top row shows (from left to right) a PET scanner, CT scanner, band-saw used to slice larynx, optical camera and a light microscope. The middle row shows images of PET-CT *in-vivo*, CT *ex-vivo*, images of *ex-vivo* specimen fixed and sliced images taken with a camera and histology sample digitised using a light microscope. The bottom row shows registered images of PET, CT *ex-vivo* and histology. Regions in PET and CT *ex-vivo* that correspond to histology are marked with red outline. Yellow markers show the sea urchin spine markers on CT *ex-vivo* and histology images.

PET and histopathology were reported as square root of the sum of the squares of the errors from the individual steps, namely, PET to CT *in-vivo*, CT *in-vivo* to CT *ex-vivo* and histopathology to CT *ex-vivo*. The registration results reported in Figure 3 were prepared using PMOD software (PMOD Technologies Ltd., Zurich, Switzerland), Matlab (The MathWorks, Inc, Natick, USA) and ImageJ open source software. A detailed methodology is presented in Puri et al [3]. The work was previously presented at the National Cancer Research Centre conference [4] and a Workshop on Imaging in Stratified Cancer Treatment at the Newcastle University [5].

An example of PET and histology registered to CT *ex-vivo* are shown in Figure 3. The total registration error between PET and histology slices was approximately 3±0.7mm assuming 1mm alignment accuracy between PET and CT. The registration error between CT *in-vivo* and CT *ex-vivo* was 2.66±0.66mm where the registration was performed using anatomical landmarks. The registration error between CT *in-vivo* and CT *ex-vivo* was 1.41±0.05mm where the same step was repeated using segmented larynx in three datasets only. The registration error between histology and CT *ex-vivo* was 0.86±0.41mm using fiducial markers.

When the specimen is systematically cut in parallel consecutive slices, the thicknesses are known and the identification of the z-axis level between the 2D histology and the 3D image can be performed by counting [6]. However, not all pathology departments have equipment required to perform parallel sectioning and would require deviation from the local pathology laboratory protocol. The proposed method affected the routine pathology workflow with a simple extra step, i.e. the insertion of the fiducial markers, which was done by the specimen handling staff. The optical images and recorded anatomical information from the pathology records were used to identify the


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approximate level of each tissue blocks on the *ex-vivo* CT before the inter marker distances were used to choose the final CT *ex-vivo* slice for registration.

The blockface images are mainly used for shrinkage correction [7], our choice of rigid (only) registration obviated the exclusion of histology-to-blockface step. Excluding the use of blockface images avoided the errors from three different steps namely, (1) reconstructing blockface volume, (2) CT *ex-vivo* to blockface registration and (3) histology-to-blockface registration. It was anticipated that the combined registration error from these three steps may be similar to the one obtained from not correcting for shrinkage.

The use of PET-CT scanner was a major advantage. This is because an intermediate high resolution CT *ex-vivo* of the larynx specimen served as the reference dataset that corresponded well with the CT *in-vivo* data (from PET-CT scanner) and also with the histopathology slice that included boundaries, edges and fiducial markers.

The *in-vivo* and *ex-vivo* CT alignment was performed using point-based registration and also with bone segmentation based registration which obtained lower registration errors. This was probably due to the large pre-registration errors of 2.54±0.42mm in manually identifying the corresponding pair of landmarks. Consequently, manual point based registration should be avoided in each of the registration step whenever possible. The segmentation-based registration may allow an automated implementation of this methodology with a potential to facilitate radiotherapy planning studies.

This study suffers from a number of limitations. This work is a specific case where tumour is surrounded by the larynx cartilage that may prevent any unexpected deformation of the tumour during surgery, fixation and slicing procedure. Another limitation is that the quantitative comparison between the two

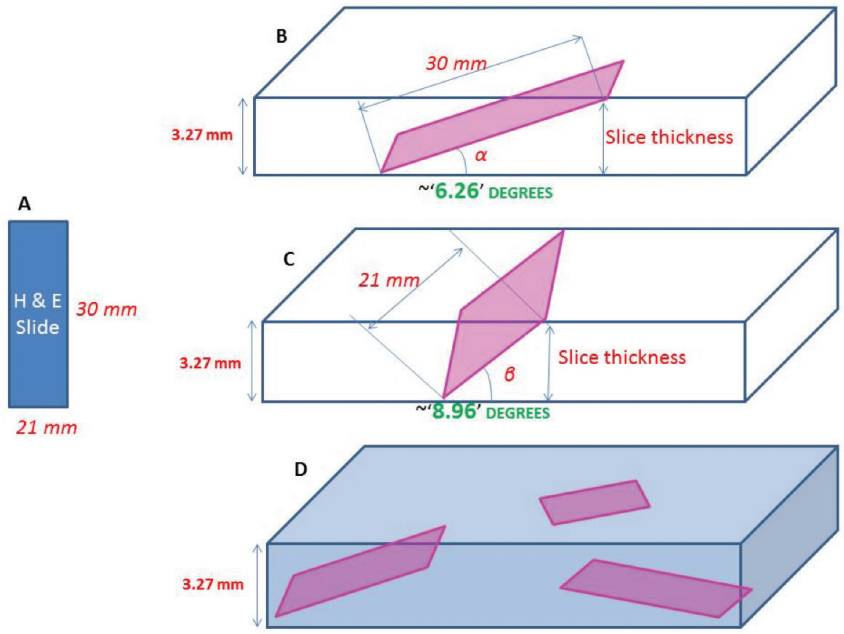

FIGURE 4 (A): Shows the dimensions of a histopathology slide used in routine pathology settings and in our study. (B) Shows the calculation of maximum angle a slide can make within a single PET slice along its long side. (C) Shows the calculation of maximum angle a slide can make within a single PET slice along its short side. (D) The few possible ways in which the histo-pathology may truly correspond to a corresponding spatial location in a PET image. However, since PET image slice anyways represent an average of 3.27mm thick spatial space, correction within this space of single PET slice would be meaningless. The inclination correction of the histopathology slides would be more meaningful if the inclination is greater than 6.26 degrees considering the spatial resolution of the PET scanner is greater than the thickness a PET slice.

datasets may be largely dictated by partial volume errors as the ratio between PET and histopathology slice thickness is 654 (i.e. 3.27mm/5μm). Therefore, obtaining contiguous histopathology slices from each tissue block may be more appropriate for radiotracer validation studies albeit controversial due to the logistics and cost involved. Another limitation was the assumption about inclination between histology and CT *ex-vivo* which was considered less than 8.96 degrees (Figure 4). The Figure 4 shows the difficulty in correcting histopathology for inclination if It belongs to only one CT slice since each slice represent an average over 3.27mm space with a loss of true information within that cuboid like region representing a single PET slice (Figure 4B and 4C). A true inclination correction may be appreciable only when one histopathology slice belongs to two or more PET-CT slices.

Due to the differences in true inter-marker distances on CT *ex-vivo* and histology, it may be more appropriate to first correct the histology for shrinkage using blockface images and then measure the inclination. However, a simple alternative would be to acquire CT images of the tissue blocks to provide an accurate thickness estimates and to reconstruct a 3D volume from sliced tissue blocks.

In conclusion, we have developed and assessed a method for aligning PET and histopathology slices obtained in routine pathology settings such that the slices may be non-parallel, non-contiguously cut and non-mega-block sized in male larynx with advanced SCCHN cancer. The average registration error between PET and histopathology was 3.0(SD:0.7)mm which is better than the 6.00mm full-width half maximum spatial resolution of the PET scanner.

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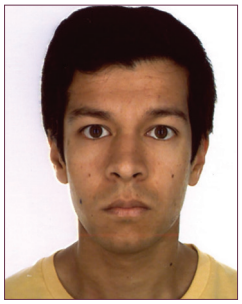
Changing expectations of surgery for oesophageal cancer



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Oesophageal cancer has traditionally posed a significant challenge for clinicians; however evidence demonstrates that patient outcomes have consistently improved with time. The National Oesophago-Gastric Cancer Audit (NOGCA) was set up in 2006 to improve the quality of care received by this patient population in England and Wales.

The 2014 NOGCA reported on 22,832 patients data collected over a two year-period [1]. This revealed reduced 30 and 90 day mortality for oesophagectomies at 2.4 and 4.4% respectively, compared to 3.8 and 5.7% from the 2010 report. One third of patients undergoing oesophagectomy developed an inpatient postoperative complication – most frequently respiratory – reflecting no significant change from 2010.

In the USA, the Surveillance, Epidemiology and End Results Program (SEER) of the National Cancer Institute has shown a progressive improvement in 5-year relative survival for oesophageal cancer from 12.1% in 1990 to 20.1% in 2011 [2].

There is a multifactorial basis for these advances including: (i) centralisation of oncology and surgical services; (ii) development of novel staging investigations; (iii) precise patient selection and anaesthetic assessment of fitness for surgery; and (iv) incorporation of neoadjuvant chemotherapy/chemoradiotherapy into treatment regimes.

Background

Oesophageal squamous cell carcinoma (SCC) remains the predominant histological subtype of oesophageal cancer worldwide, however in several Western countries including the UK and USA, the incidence of oesophageal adenocarcinoma has rapidly risen to exceed that of SCC. Oesophageal cancer represents the sixth leading cause of cancer-related mortality and is the eighth most common cancer worldwide.

Diagnosis

Early detection of the symptoms and signs of oesophageal cancer is paramount in maximising patient survival, as the best outcomes are achieved for patients with early stage disease.

Tobacco use and excessive alcohol consumption are strongly linked with oesophageal SCC [3]. Barrett's oesophagus, symptomatic gastro-oesophageal reflux disease and obesity [4] represent key risk factors for oesophageal adenocarcinoma. Patients with these risk factors require a lower threshold for further investigation.

Classical symptoms include progressive dysphagia and weight loss. Advanced disease may present with cough, recurrent lower respiratory tract infections or hoarseness as a result of tracheobronchial invasion or recurrent laryngeal nerve palsy.

Oesophagogastroduodenoscopy (OGD) is the initial investigation to establish the diagnosis through biopsy and evaluate the macroscopic extent of proximal and distal tumour invasion.

Staging

Once the diagnosis is confirmed, staging investigations are undertaken to define the small population of patients with operable disease. A CT scan of the chest, abdomen and pelvis is initially performed to provide information regarding local spread, lymph node involvement and the presence of metastases. The introduction over the last decade of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), endoscopic ultrasound (EUS) and diagnostic laparoscopy have enhanced the accuracy of this process.

FDG-PET

The primary role of FDG-PET is to identify occult metastases which therefore preclude curative resection. A prospective multicentre trial demonstrated that FDG-PET identified biopsy-proven distant metastases in at least 4.8% of patients with no evidence of metastatic disease on standard workup [5]. FDG-PET revealed metastases in an additional 3.7% of cases, though these lesions were not pathologically confirmed. This imaging modality may also be useful in assessing the response to induction chemotherapy, thereby highlighting patients who will benefit from completion of neoadjuvant chemotherapy prior to oesophagectomy [6].

EUS

Endoscopic ultrasound allows accurate assessment of the depth of tumour infiltration through the oesophageal wall, as well as providing information on nodal status. EUS delivers greater sensitivity but lower specificity than CT or FDG-PET for the identification of regional lymph node metastases [7]. Its performance is enhanced by the addition of EUS-guided fine needle aspiration for cytological differentiation between reactive and malignant lymph nodes. Furthermore, EUS demonstrates higher sensitivity for the detection of coeliac lymph node metastases than CT [7].

EUS examination is limited by its depth of penetration of approximately 5cm and the potential inability to traverse tight malignant strictures leading to an incomplete examination.

Diagnostic laparoscopy

Laparoscopy (and/or thoracoscopy) provides greater accuracy than FDG-PET for the identification of distant metastases, particularly for lesions less than 1 cm in diameter. It also confirms lymph node metastases with superior sensitivity than CT, EUS or MRI [8]. Simultaneous peritoneal fluid cytology can detect malignant cells, providing evidence of peritoneal dissemination in the absence of macroscopic metastases. However this procedure necessitates general anaesthesia, engenders potential morbidity and is more expensive than noninvasive techniques.

Management

Mucosal tumours

Endoscopic mucosal resection and/or ablation are increasingly employed for the treatment of Barrett's oesophagus with high-grade dysplasia and squamous cell carcinoma or adenocarcinoma limited to the mucosa (T1a). Observational studies have shown that with adjustment for patient and tumour factors, those who received endoscopic treatment had similar overall survival-times when compared to patients treated with surgical resection [9]. However a recent systematic review regarding endoscopic and surgical management of mucosal and submucosal disease revealed positive resection margins in 33% and local recurrence in up to 17% of patients treated endoscopically [10]. Although mucosal tumours are considered low risk for lymph node involvement, surgical resection specimens of mucosal tumours revealed multifocal neoplasia, lymphovascular invasion or nodal metastases in a third of patients prompting some to suggest that endoscopic therapy should be reserved for patients at high surgical risk [11]. However, in experienced hands this remains a very effective treatment for early disease.

Locally advanced disease

Tumours that have invaded through the muscle layer (>T2) with lymph node involvement are defined as locally advanced. Current optimal management consists of neoadjuvant chemotherapy or chemoradiotherapy combined with oesophagectomy. The introduction of neoadjuvant therapy has improved the outcomes for this stage of disease. Meta-analysis of ten randomised controlled trials (RCT) comparing preoperative chemotherapy versus surgery alone for resectable thoracic oesophageal cancer, revealed a survival advantage and significantly higher rate of complete (R0) resection with chemotherapy [12]. A further meta-analysis demonstrated that perioperative chemotherapy for adenocarcinoma of the lower oesophagus, gastro-oesophageal junction and stomach conferred a 9% absolute improvement in survival at five years: from 23% for patients treated with surgery alone to 32% for those who received perioperative chemotherapy [13].

Advanced and recurrent disease

Patients with metastatic or disseminated oesophageal cancer are considered to have advanced disease. Symptomatic relief from obstructive symptoms can be achieved with endoscopic stenting or intraluminal brachytherapy. Palliative chemotherapy agents are selected based on predicted response, performance status and toxicity profile. Two small RCTs have compared chemotherapy with best supportive care for metastatic disease and did not demonstrate any survival benefit [14].

Recent interest has focused on the human epidermal growth factor receptor 2 (HER2) oncogene as a potential target. The prevalence of HER2 positive disease in patients with oesophageal cancer is 26%, with a significantly higher rate within the squamous cell carcinoma population [15]. A recent meta-analysis of patients with oesophageal cancer demonstrated a decreased average survival rate of 7 months for cases with HER2 positive disease [15]. The randomised controlled Phase III ToGA trial [16] comparing the monoclonal antibody trastuzumab and chemotherapy versus chemotherapy alone for advanced or metastatic gastric and gastro-oesophageal cancer, revealed a 2.7 month improvement in median overall survival for patients treated with trastuzumab. It is hoped that similar results will be observed within the oesophageal cancer population.

Surgical Management

Centralisation of the treatment of patients with oesophageal cancer is thought to improve outcomes. A meta-analysis assessing the relationship between surgeon or hospital volume and outcomes following oesophagectomy identified a significant pooled estimate effect size in favour of high volume settings for both postoperative mortality and survival [17]. Similar results were seen for high volume surgeons though these did not reach statistical significance.

The precise surgical approach is determined by the location of the tumour. These include the two-stage Ivor Lewis oesophagectomy with combined abdominal and right transthoracic access, as well as the thoracoabdominal approach and the three-stage McKeown oesophagectomy involving a laparotomy, thoracotomy and cervical anastomosis. Transhiatal oesophagectomy can also be performed for distal tumours.

Minimally invasive surgical techniques are being increasingly employed in an attempt to mitigate the otherwise significant potential morbidity incurred with open oesophagectomy. Single-lung ventilation in the lateral decubitus position together with a painful thoracotomy wound are thought to contribute to atelectasis and subsequent pulmonary complications [18]. In contrast, the thoracoscopic stage of the minimally invasive oesophagectomy is typically performed in the prone position with only partial right lung collapse. There is currently little evidence of significant differences in outcomes compared to open surgery.

Enhanced recovery after surgery (ERAS) pathways streamline care in the postoperative period. In the context of oesophagectomy these have been shown to reduce length of stay with associated cost savings [19]. A recent systematic review and pooled analysis of studies comparing outcomes between conventional postoperative care and ERAS suggested reduced incidence of anastomotic leak and pulmonary complications with no significant change in postoperative mortality or rate of readmission [20]. Enteral feeding is initiated at an early stage as part of ERAS to meet patients' nutritional requirements, although controversy persists regarding the optimal postoperative point at which it should be initiated.

Conclusion

Oesophageal cancer poses a significant challenge even when treatment is initiated at an early stage. Advances in staging techniques allow more accurate

classification of patients to better inform treatment choices. Anaesthetic assessment of fitness for surgery precisely selects patients capable of withstanding an oesophagectomy. This targeted patient selection inherent to current practice forms a key part of raising the expectations of oesophageal surgery. It is only offered to patients who will both benefit from the intervention and who can be expected to make a good postoperative recovery.

Parameters of effective surgical treatment are improving as evidenced by the 2014 NOGCA data, and the application of minimally invasive surgical techniques is expected to enhance the postoperative recovery phase. The integration of oncological and surgical advances is hoped to contribute to the continued progress in the management of this complex disease.

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VE-cadherin – a biomarker for metastatic breast cancer

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The cadherins are a superfamily of calcium dependant cell surface transmembrane glycoproteins, whose functional role is cell adhesion at adherens junctions (and desmosomes) via between 5 and 34 Ca2+binding extracellular domains consisting of repeats of approximately 110 residues. In addition to this, however, cadherins are also involved in tissue morphogenesis, general cytoskeletal organization and initiating signalling cascades in response to adhesion [1,2]. Cadherins fall into two broad categories: classical, type 1, which includes E-cadherin (CDH1) and N-cadherin (CDH2), and type 2, which includes vascular endothelial cadherin (CDH5) and K-cadherin (CDH6); involved predominantly in homophilic cadherin binding at adherens junctions and heterophilic binding at desmogleins and desmocollins [3].

Vascular endothelial (VE)-cadherin (VEC; also CD144 or cadherin 5) is coded for by the CDH5 gene at 16q22.1 in humans, and was first shown to be expressed by endothelial cells [2,4). This has a number of functions: firstly, it is essential for endothelial cell adhesion as it is predominantly located at adherens junctions in contrast with N-cadherin, which is found in similar levels in endothelial cells, but diffused over the entire cell surface; secondly, a host of agents, including vascular endothelial growth factor (VEGF) stimulate phosphorylation of the intracellular component of VEC, leading to increased endothelial permeability; thirdly, VE-cadherin has been shown to interact with the platelet–endothelial cell adhesion molecule (PECAM/CD31), facilitating endothelial tube formation [1,5,6] Work by Bittner et al. [7] revealed that VE-cadherin is overexpressed in aggressive cutaneous- and uveal melanoma cells and an extension of this work by Hendrix et al. [8] showed that downregulation of VE-cadherin in aggressive melanoma cells resulted in reduced vasculogenic mimicry (thus possibly having an impact on the tumour's ability to grow). VE-cadherin may be involved in the progression of a variety of cancers primarily through angiogenic processes and the role of VE-cadherin in this context merits further investigation.

VE-cadherin, is a glycoprotein and contains seven possible glycosylation sites, all of which are subject to N-linked glycosylation [9,10]. Aberrant glycosylation has been identified as a hallmark of a variety of carcinomas, both invasive and non-invasive early cancers. Most investigations focusing on the glycosylation of cadherins, however, have been limited to E-cadherin, where a number of researchers (including in our group) has shown aberrant glycosylation of this glycoprotein in cancer development and growth [11-14]. VE-cadherin, therefore, is uncharted territory with respect to altered glycosylation and associated links to cancer. This is yet another aspect of this glycoprotein that requires further investigation.

Work carried out at the Breast Cancer Research laboratory at the University of Westminster aimed to add to the literature in terms of examining VE-cadherin as a possible biomarker for breast cancer. Immunofluorescent studies of three cell lines (SKBR3, MCF7 and BT474) using PHA-L and anti-VE-cadherin antibody yielded some interesting results (Figure 1). BT474 displayed

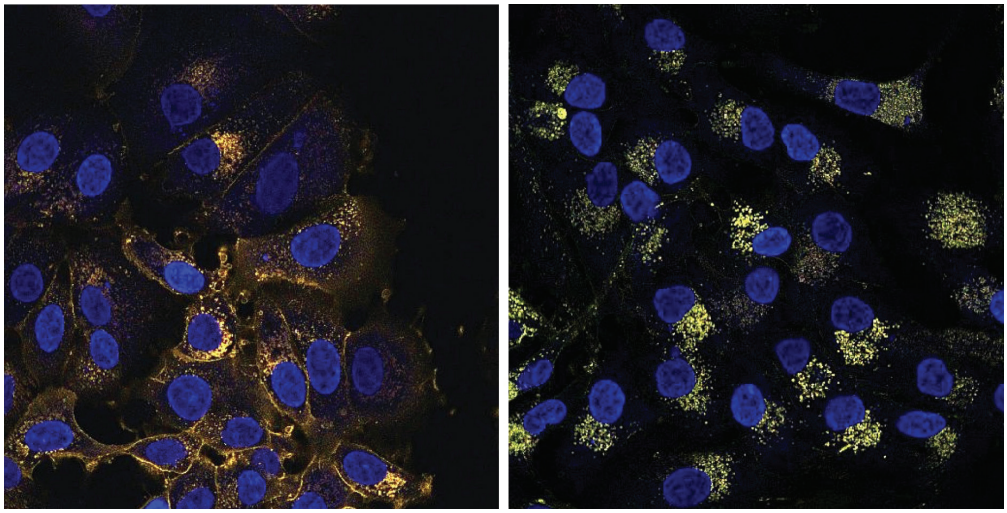

Figure 1- Confocal microscopy images of overlays of MCF7 cells stained with with anti VE-cadherin antibody (Texas Red-conjugated) and the carbohydrate binding protein PHA-L (FITC-conjugated) [left]. Staining with same agents on BT474 [right].

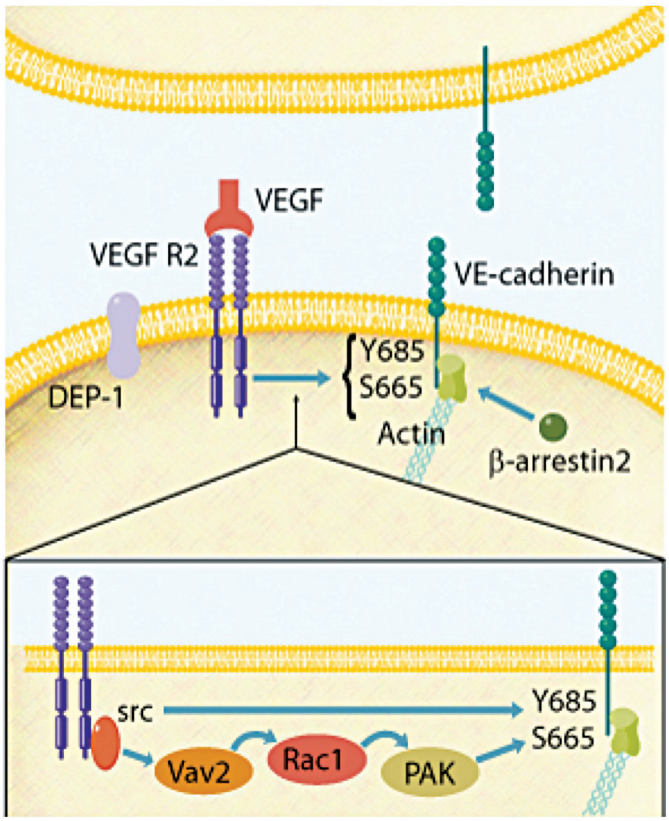

Figure 2: Diagrammatic illustration of the mechanism of VEGF-VEGF R2-VE-cadherin interaction. Note the activation of the Vav2-Rac1-PAK pathway by Src recruited by activated VEGF R2. This ultimately causes β-arrestin binding at VEC, leading to clathrin-dependant endocytosis.

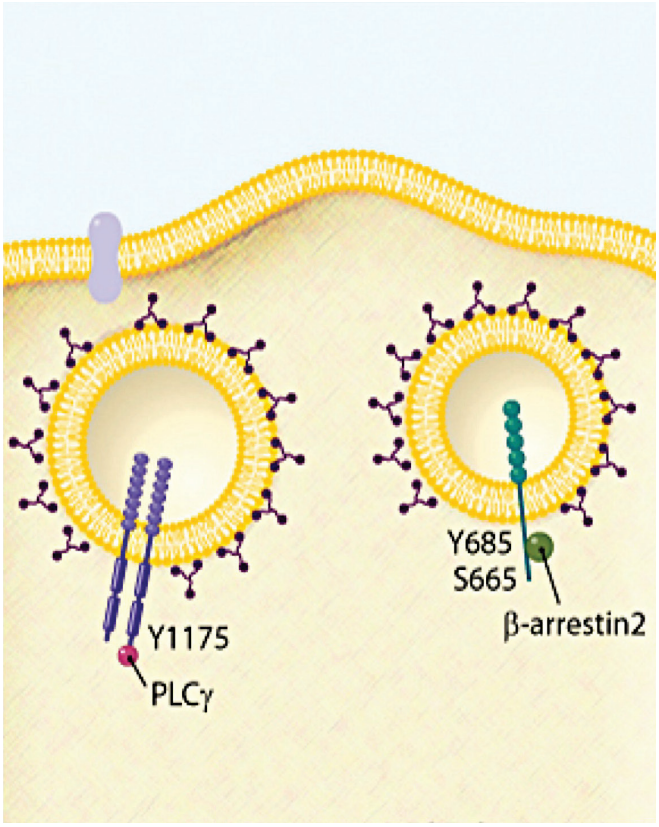

Figure 3: Illustration of clathrin-coated endocytosis of both VEGF R2 (left/purple) and VE-cadherin (right/green). Note the PLCϒ (associated with metastasis) bound to the phosphorylated Y1175 residue on VEGF R2.

R&D Systems, n.d. Regulation of VE-Cadherin and VEGF R2 by VEGF. [online] Available at: http://www.rndsystems.com/cb_detail_objectname_sp07_RegulationVE-CadherineVEFGR2.aspx

little VE-cadherin on the cell surface and intracellular binding of both the anti VE-cadherin antibody and lectin (and thus, limited levels of cell membrane glycosylated VE-cadherin) whilst MCF7 cells showed both cell membrane and intracellular binding of the anti VE-cadherin antibody and the lectin. The observations fit with the phenotypic growth pattern of the BT474 cells which grow in clumps and patches, presumably with relatively weak adherens junctions. MCF7, on the other hand, has definite presence of glycosylated VEC at points of cell adhesion. Given the previously mentioned role for VE-cadherin in cell adhesion; in VE-cadherin positive cells it is unusual to detect other types of cadherins this may account for the concentration of VE-cadherin observed at the cell junctions in the MCF7 cells in particular [5].

A glycoproteomic study using serum samples collected as part of the DietCompLyf study breast cancer cohort found VE-cadherin to be elevated in the serum from patients with metastatic breast cancer [15-16]. The results provided a different but related perspective to the experimental results above. Notably, that the mean serum VE-cadherin levels in study subjects in whom distant metastatic recurrence (REC) occurred was significantly higher than for those with no sign of recurrence (NSR; ~9.33ng mL^{-1} vs. ~5.33ng mL^{-1}). Serum levels of VEGF were shown to have elevated mean average levels in REC sera (~58pg mL^{-1} vs. 25pg mL^{-1}).

VEGF is an important endothelial-cell specific angiogenic factor that induces tyrosine phosphorylation in endothelial cells leading to the the disruption of cell adhesion and thus paves the way for the vascular permeability required for the various processes involved in angiogenesis e.g.: the 'sprouting' and migration of endothelial cells from existing capillaries into spaces [17]. VE-cadherin was found to be elevated in patients with ER+ve cancers exhibiting vascular invasion into the tumours and appears to offer utility as serum a biomarker of metastasis in this group of individuals [16].

The mechanism of interaction between VEGF and VE-cadherin (Figure 2) has been elucidated and has shown to be through a VEGF binding event at the VEGFR2 receptor, causing activation of the Src-Vav2-Rac1-PAK pathway, in turn leading to the phosphorylation of certain key Tyr residues on VE-cadherins [18]. This phosphorylation results in β-arrestin-dependent endocytosis of VE-cadherin into clathrin-coated vesicles, thus reducing cell adhesion due to reduced levels of VE-cadherin at the cell surface [18]. Furthermore Lampugnani et al. [19] showed that VE-cadherin binds to activated VEGF R2 preventing endocytosis of VEGF R2 (Figure 3) allowing a junction-associated transmembrane tyrosine phosphatase, DEP-1, to inactivate it after a period of time. Endocytosis prevents DEP-1 phosphatase-mediated inactivation, as DEP-1 cannot carry out its activity on internalised vesicle-contained proteins. All of this has implications for breast cancer biology including:

- a reduction in the strength of cell adhesion: in a rapidly-replicating tumour, this may result in an increased chance of metastasis,
- increase in vascular permeability: facilitating the growth of new blood vessels into the tumour mass, providing oxygenation and nutrients for tumour growth and further metastasis, and,
- decreased VE-cadherin-VEGF R2 binding:

resulting in VEGF R2 endocytosis, and, since DEP-1 can no longer inactivate it, the activated vesicle-enclosed receptor continues signalling via pathways such as that initiated by PLCϒ, a metastasis-associated protein [20].

This is a cyclical set of processes that may lead to a self-sustaining positive-feedback loop. Indeed, this effect has been observed, to a certain degree, in work performed by (among others) Weis et al. [21]. Thus, increased levels of serum VEGF, with correspondingly elevated levels of VE-cadherin is emerging as a key marker of metastatic breast cancer.

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Meet the Editorial Team

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

WIN 2016 Symposium – Innovative Approaches to Improve Cancer Patient Outcomes

Date: 27-28 June, 2016. **Venue:** Paris, France. **Preview**

Worldwide innovative networking in personalized cancer medicine

Under the chairmanship of Josep Tabernero (Vall d'Hebron, Barcelona, Spain), the 8th WIN Symposium will present an exceptional scientific program under the overarching theme "Innovative Approaches to Improve Cancer Patient Outcomes". The central question addressed during the two days of the symposium will be: How can the smarter use of innovative therapies improve the survival of greater numbers of cancer patients? Or in other words: What is hampering the translation of the great promise of new targeted and immunological cancer therapeutics into significantly improved survival for large groups of cancer patients?

World-class experts in the field of personalized medicine in oncology from academia, industry, cancer research and patient advocacy organizations will address these questions in four plenary sessions:

- New tools for early diagnosis, selecting therapies and monitoring
- Innovative clinical trials to substantially improve outcome
- Relevant models and critical preclinical data before moving to the clinic
- Translation of big data into clinical opportunities

The WIN Symposium will be opened by a representative of patient advocacy organizations who will present the patient's perspective of improved outcomes in cancer: Francesco de Lorenzo, European Cancer Patient Coalition, Belgium. Each of the four thematic sessions will feature a renowned keynote lecturer: Andrea Califano, Darwin Health, USA; William Sellers, Novartis, USA; Leroy Hood, Institute for Systems Biology, USA; and Bruce E. Johnson, Dana-Farber Cancer Institute, USA, respectively. Speakers will not only address recent scientific advances, but will also discuss controversies about the best way forward and challenges facing them in the various domains of cancer research reviewed during the meeting.

The annual WIN Symposium is the only event of its kind that enables all stakeholders in cancer care, from academia and industry, to present and discuss their latest advances. It is also the forum that enables true debates on challenging and controversial subjects facing cancer researchers and innovators in cancer therapy.

The WIN Symposium is offered by WIN Consortium (www.winconsortium.org), a not-for-profit global collaboration of leading academic, industry and health plan that develop cutting edge concepts to impact survival for cancer patients. Consortium members launch breakthrough global projects and trials designed to better address the complexity of the disease.

For further information visit: www.winsymposium.org

9th International Conference and 1st Global Adolescent and Young Adult Cancer Congress

Date: 5-7 December 2016. **Venue:** Edinburgh, UK. **Preview**

Registration for Teenage Cancer Trust's 9th International Conference which is also the 1st Adolescent and Young Adult (AYA) Global Cancer Congress is now open. The event will be held in the centre of Edinburgh at the iconic Assembly Rooms, from 5-7 December, 2016.

The full programme for this momentous event, which will see talks given by a host of expert speakers from across the globe, is complete and has been finalised.

The Congress will build on the success of the previous eight Teenage Cancer Trust International Conferences and the relationships that have developed through worldwide advances in AYA cancer treatment and services. A Global Accord has been developed between three charities, Teenage Cancer Trust, Teen Cancer America and CanTeen Australia, creating a truly collaborative approach. Hosting will rotate between the charities, with the 2017 conference to be held in the US, and 2018 in Australia.

Sam Smith, Head of Nursing and Clinical Services, at Teenage Cancer Trust and Conference Chair, said: "This conference is dedicated to improving care, treatment and sharing best practice in this unique field. We encourage healthcare professionals from across the world including oncologists, haematologists, epidemiologists, research scientists, psychologists, nurses, social workers, youth workers and allied health professionals to join us for this historic global gathering in adolescent and young adult cancer. By working together we feel we can achieve so much more."

The Global Congress will help to direct the attention of international clinical and healthcare communities and will be a powerful stimulus for looking for innovative and effective solutions in adolescent and young adult cancer care. Bringing the international community together will help sustain and develop the specialty of adolescent and young adult cancer. It will also provide support and expertise to those in the early stages of service development and drive quality improvements in practice and care of young people with cancer.

For further information visit: www.teenagecancertrust.org/conference

Myeloma Academy Roadshows 2016

Preview

This year Myeloma Academy officially launches its Myeloma Academy Roadshows programme; a series of provocative and educational, free evening events for doctors and nurses. Borne from a pilot event in 2015, the Myeloma Academy Roadshows have been developed in consultation with doctors and nurses, with the aim of assisting healthcare professionals support the needs of myeloma patients in a challenging and ever-changing healthcare environment.

Featuring separate events for doctors and nurses the series will take place in three locations across the UK – Edinburgh, Birmingham and London. Each session will be led by a facilitator and will include an expert panel of international keynote speakers and faculty who will address current and future challenges, and opportunities in myeloma research, treatment and care.

The series aims to offer a platform for practical discussion with colleagues where no topics are off limits. Debate and powerful round table discussions will have an entirely UK patient-centred focus. Each event will feature a number of different elements which are aimed at developing a narrative around a range of issues and topics:

The plenary lecture – delivered by a key opinion leader in myeloma, these topical lectures will focus on an aspect of myeloma treatment and management that is considered to be of significant importance to healthcare professionals working in a myeloma environment.

The debate – an important part of the programme, the debate will be delivered by two national key opinion leaders within myeloma. It will consider an area of myeloma management that is currently unanswered where there may be varying opinions, controversies and/or where practice varies.

Round table discussion – bringing faculty members together to discuss topical aspects. Topics vary from research and treatment to delivery of care, access to treatment for patients, and regional challenges and issues. The audience will be invited to comment and question the panel.

The Myeloma Academy Roadshows will also include sessions that focus on innovation in research and clinical practice, and audience Q&A.

The programme offers small, intimate events aimed at developing and empowering discussion around treatment and care of myeloma patients. All events are free and places are limited.

For further information visit: myeloma-academy.org.uk

14th Annual BTOG Conference 2016

Date: 27-29 January 2016. **Venue:** Dublin, Ireland. My Experiences by Amit Paik, Core Surgical Trainee, University Hospitals of Leicester NHS Trust.

Having had the chance to work as a surgical SHO in a tertiary referral centre, I've had the opportunity to share the journey our lung cancer patients take. I've witnessed the anxiety patients suffer whilst planning for surgical intervention and the relief they feel post operatively. Most of all though, it is their determination to overcome adversity that is most inspiring.

This exposure prompted me into looking at thoracic surgery as a career. A huge part of this emerging speciality surrounds rapid pace being made in the management of thoracic oncology.

Having previously attended other cardiothoracic conferences, I've always felt a very small part of such meetings, more reserved to standing by a research poster. However, BTOG, with its origins from Leicester, was described by my colleagues as being a smaller, friendlier meeting. Intrigued, I submitted my abstract and awaited the chance to visit Dublin.

Foremost, the BTOG bursary available proved invaluable in providing financial support to attend the meeting, allowing my study budget to breathe a sigh of relief.

From first impressions, you realise that the meeting itself is actually quite compact. Sure, there's enough room to hold debates and presentations, but allowing everyone to stay and work within a single hotel raises a unique opportunity to get to know people around you. In effect, it becomes a fantastic venue to network.

I found everyone exceptionally friendly and approachable, often finding myself asking questions from senior oncologists over topics presented. Surprisingly, there were a good number of fellow juniors amongst the delegates, again providing opportunity to share ideas over how best to get the most out of training programmes.

The talks themselves were wide ranging; from discussing on-going cutting edge clinical trial to aid in the management of mesothelioma to utilising specialist nurses in providing support to lung cancer patients. It most definitely allowed me to broaden my horizons and appreciate the wide ranging roles that exist across thoracic oncology.

Finally, the evening meal on the Thursday night provides yet another opportunity to mingle and chat with delegates, this time in a much more informal manner. Personally, the opportunity proved to be invaluable in gathering advice ideas for further clinical research and how best to tackle the next career hoop jump. There's even an award ceremony to celebrate the best projects presented at the meeting.

All in all, BTOG provides a fantastic opportunity to meet peers and seniors across a wide range of roles within the thoracic oncology field. The meetings were engaging and delegates approachable. I would most highly recommend to my peers.

Almost 800 attended this multi-disciplinary conference. BTOG 2016 provided important opportunities for education, scientific exchange and networking and welcomed speakers, chairs and delegates from the UK, Ireland, Europe, India, Canada, the USA and Australia.

For further information visit: http://www.btog.org/

BTOG Lifetime Achievement Award 2016 presented at BTOG 2016 is Professor Sam Ahmedzai

Left to right: Sam Ahmedzai and Matthew Hatton.

Professor Ahmedzai is Emeritus Professor in the Medical School at University of Sheffield, with 30 years' experience of being a consultant physician in palliative medicine. His research covers - cancer pain and opioid drugs; symptom management in advanced diseases; holistic needs and quality of life assessment; improving supportive care services for cancer and chronic disease patients; advocating patient and public involvement in cancer research. He chairs the UK National Cancer Research Institute's Clinical Studies Group on Supportive and Palliative Care. He also chairs the NICE guideline for care of the dying adult and the Royal College of Physicians of London's national audit of end of life care. He is NIHR national specialty lead for cancer research outside the acute hospital. He is editor in chief of Current Opinion in Supportive and Palliative Care and of the Oxford Textbook series on Supportive Care.

The award was presented by Dr Matthew Hatton, Consultant and Honorary Reader in Oncology, Weston Park Hospital, Sheffield. Dr Hatton says, "It was an honour to present this award on behalf of BTOG to Sam Ahmedzai, who has been a very active member of BTOG over the past 14 years. Over that time I have been working with him in Sheffield and seen that he has been able to change the thinking of a speciality from one offering terminal/palliative care to one offering supportive/palliative care with the development of the supportive care team for cancer and non-cancer patients alike. Through his involvement with BTOG and other national bodies he has been able to spread this thinking beyond the boundaries of South Yorkshire influencing and improving the care of many, many patients with lung cancer".

Three cancer charity supporters have won Halifax Giving Extra Awards

Three cancer charity supporters from across the UK have won Halifax Giving Extra Awards in their local communities. The winners are amongst the 66 local winners recognised by their local panel, for their services to cancer charities:

- Martin Lawrence, from Doncaster
- Bobbie Cass, from Yiewsley, West London
- Tom Hacker, from Wakefield

Now in its third year, the Halifax Giving Extra Awards reward people who bring communities together and help them thrive. Charity fundraisers, sports coaches, community volunteers and many more have been recognised for the contribution they make.

Martin Lawrence

Bobbie Cass

Tom Hacker

Martin Lawrence: nominated by Karen Merton for his charity fundraising activities over the years, including the creation of The Eve Merton Dreams Trust, in memory of his mum. Martin has been a charity fundraiser for many years, organising football tournaments and fundraisers with his work colleagues. When his mum, Eve Merton, died from Ovarian Cancer in 2011 Martin, and his family and friends, created The Eve Merton Dreams Trust. The ambition of the charity was to help people in Doncaster suffering from terminal cancer to create some final positive memories with their loved ones. Further information about the charity can be found at www.evestrust.co.uk

Bobbie Cass: nominated by Bren Fisher, manager of the Community Cancer Centre in Yiewsley. Bobbie has been volunteering at the Community Cancer Centre since it opened 20 years ago, supporting countless patients suffering with cancer.

Bobbie said: ""I was surprised but also delighted to win a Halifax Giving Extra Award. It was such an honour to just be nominated, so I am hugely proud to have actually won."

Tom Hacker: nominated by Katie Hodkin, for raising almost £100,000 in the past seven years for Macmillan and cancer charities. Since Tom lost his mother to cancer in 2001 he has been inspired to raise as much money as possible to help support other people going through similar experiences with the money raised helping to contribute to local facilities such as the Macmillan Cancer Support and Information Centre at Pinderfields Hospital, Wakefield.

Tom has completed three significant charity challenges amongst the many fundraising activities undertaken, including: walking from John O'Groats to Land's End in 28 days; cycling the same distance in just five days; and completing six marathons in six days, running coast to coast. He is currently exploring ideas about what his next major challenge could be.

The 66 local Halifax Giving Extra Award winners will each receive £300 in Supercheque vouchers. Each one of the 66 local winners will then be put forward to be chosen as one of our seven regional winners. Regional winners will be announced by the end of February and will each receive £5,000 to make a further difference in their community.

Journal of Clinical Oncology

Pemetrexed Plus Cisplatin Versus Gemcitabine Plus Cisplatin According to Thymidylate Synthase Expression in Nonsquamous Non-Small-Cell Lung Cancer: A Biomarker-Stratified Randomized Phase II Trial

Sun JM, Ahn JS, Jung SH, et al. J Clin Oncol. 2015; Aug 1;33(22):2450-6.

Purpose: We investigated whether thymidylate synthase (TS) expression is a predictive marker for the clinical outcome of pemetrexed/cisplatin in patients with nonsquamous non-small-cell lung cancer.

Patients and Methods: Eligible patients were tested for TS expression by immunohistochemistry and stratified into either a TS-negative or a TS-positive group. After stratification, patients in each group were randomly assigned (1:1 ratio) to receive either pemetrexed/cisplatin or gemcitabine/cisplatin for a maximum of six cycles until disease progression. The primary end point was evaluation of the interaction between TS groups and treatment allocation for objective response rate.

Results: Of 321 enrolled patients with nonsquamous non-small-cell lung cancer, 315 received at least one dose of study chemotherapy and were analyzed. By investigator assessment, response rates were 47% for the pemetrexed/cisplatin arm and 21% for the gemcitabine/cisplatin arm in the TS-negative group and 40% and 39%, respectively, for the TS-positive group (interaction P=.0084). By independent reviewers, response rates of pemetrexed/cisplatin and gemcitabine/cisplatin were 39% and 21%, respectively, in the TS-negative group and 40% and 48% in the TS-positive group (interaction P=.0077). The median progression-free survival times for the pemetrexed/cisplatin and the gemcitabine/cisplatin arms were 6.4 and 5.5 months, respectively, in the TS-negative group and 5.9 and 5.3 months in the TS-positive group (interaction P=.07).

Conclusion: With regard to response rate and progression-free survival, pemetrexed/cisplatin was superior to gemcitabine/cisplatin in the TS-negative group but not in the TS-positive group, indicative of TS expression as a potential predictive marker. Additional prospective studies involving larger cohorts are warranted to confirm the predictive role of TS expression.

Reviewer's comments: The application of personalised/stratified medicine to the treatment of advanced malignancies has the potential to herald a new era in oncology and already drugs targeted against specific oncogene products have made a major impact – for example vemurafenib in B-RAF mutant melanoma, erlotinib in EGFR mutant non-small cell lung cancer (NSCLC) and vandetanib in RET mutant medullary thyroid carcinoma. However, the development of predictive biomarkers for benefit from conventional cytotoxic chemotherapy remains an important unmet need particularly in view of the potential for major toxicity with such treatment. In the first-line treatment of advanced NSCLC, histology determines the most appropriate chemotherapeutic partner for a platinum agent with pemetrexed being preferred for non-squamous cancers and docetaxel or gemcitabine for squamous cancers. Pemetrexed is a folate antagonist whose cellular targets include the enzyme thymidylate synthase and it is now thought that differential expression of TS (higher in squamous cancers) may explain the differential responses of non-squamous versus squamous cancers. This study tested the hypothesis that within the adenocarcinoma subset of NSCLC, levels of TS expression predict the survival benefit of cisplatin/pemetrexed chemotherapy (as compared with cisplatin/gemcitabine). TS expression was assessed by immunohistochemistry with a cut-off for positivity of 10% of tumour cells. The study was performed in Korea and nearly half of patients were female and a sizeable proportion were lifelong non-smokers harbouring EGFR mutations or ALK rearrangements. Cancers in females, never-smokers and with EGFR mutations were over-represented in the TS-negative group. Using the 10% threshold, half of patients were TS negative. In the TS negative subset, response rate to pemetrexed was over double that of gemcitabine with no difference in the TS positive subset. A similar, but more modest, differential benefit was observed in terms of median progression-free survival. Regardless of chemotherapy regimen, the level of TS expression was prognostic with a hazard ratio for mortality of 3.34 in patients with TS expression in greater than 30% tumour cells. It is also noteworthy that median overall survival was around 2 years in this study, significantly longer than in 'Western' NSCLC populations treated with chemotherapy likely attributable to the high prevalence of EGFR mutations and the high rates (over 80%) of subsequent erlotinib/gefitinib. – AR

Combined BRAF and MEK Inhibition with Dabrafenib and Trametinib in BRAF V600-Mutant Colorectal Cancer

Corcoran RB, Atreya CE, Falchook GS, et al. Journal of Clinical Oncology 2015; Dec 1; 33(34):4023-9.

Purpose: To evaluate dabrafenib, a selective BRAF inhibitor, combined with trametinib, a selective MEK inhibitor, in patients with BRAF V600–mutant metastatic colorectal cancer (mCRC).

Patients and Methods: A total of 43 patients with BRAF V600–mutant mCRC were treated with dabrafenib (150 mg twice daily) plus trametinib (2 mg daily), 17 of whom were enrolled onto a pharmacodynamic cohort undergoing mandatory biopsies before and during treatment. Archival tissues were analyzed for microsatellite instability, PTEN status, and 487-gene sequencing. Patient-derived xenografts were established from core biopsy samples.

Results: Of 43 patients, five (12%) achieved a partial response or better, including one (2%) complete response, with duration of response > 36 months; 24 patients (56%)

achieved stable disease as best confirmed response. Ten patients (23%) remained in the study > 6 months. All nine evaluable during-treatment biopsies had reduced levels of phosphorylated ERK relative to pretreatment biopsies (average decrease ± standard deviation, 47% ± 24%). Mutational analysis revealed that the patient achieving a complete response and two of three evaluable patients achieving a partial response had PIK3CA mutations. Neither PTEN loss nor microsatellite instability correlated with efficacy. Responses to dabrafenib plus trametinib were comparable in patient-derived xenograft–bearing mice and the biopsied lesions from each corresponding patient.

Conclusion: The combination of dabrafenib plus trametinib has activity in a subset of patients with BRAF V600–mutant mCRC. Mitogen-activated protein kinase signaling was inhibited in all patients evaluated, but to a lesser degree than observed in BRAF-mutant melanoma with dabrafenib alone. PIK3CA mutations were identified in responding patients and thus do not preclude response to this regimen. Additional studies targeting the mitogen-activated protein kinase pathway in this disease are warranted.

Reviewer's comments: With a combination of conventional cytotoxic chemotherapy, anti-EGFR (in RAS and BRAF wild-type cancers) and anti-angiogenic therapies, median life expectancy for advanced colorectal cancer (CRC) now exceeds 2 years. However, the subgroup of cancers driven by a BRAF codon 600 mutation derives far less benefit from standard therapy and has an inferior prognosis (less than 1 year). BRAF mutant colorectal cancer is typified clinically by female preponderance, right sided tumours and frequent distal nodal and peritoneal metastases and genetically by high micro-satellite instability, low chromosomal instability and promoter hypermethylation. Despite the proven survival benefit of selective inhibitors of the mutant, constitutively-active BRAF kinase in metastastic melanoma, single-agent vemurafenib or dabrafenib have no meaningful clinical activity in in BRAF mutant CRC. This phase I/II study, of 43 patients, used the combination of dabrafenib and trametinib to inhibit the MAP kinase pathway simultaneously at 2 'nodes' and incorporated pre-treatment and on-treatment biopsies for translational research. 80% of patients were female, 50% had 3 or more metastatic sites and 51% had received 3 or more lines of systemic therapy. There was evidence of efficacy with one patient, who was treatment-naïve, achieving a durable complete response, two-thirds of patients achieving disease control and 37% exhibiting a greater than 10% reduction in disease volume. In the 9 patients with paired biopsies available, there were significant reductions in phospho-ERK levels after 15 days of treatment, but these were smaller in magnitude than those achieved with single-agent dabrafenib in melanoma. The molecular analyses on archival tumour tissue suggested that PIK3CA mutation, PTEN loss or TGF-βpathway mutations may be associated with response. The median progression-free-survival in this study was 6 months less than that achieved with first line therapy in melanoma and the challenge will be to identify and target resistance mechanisms. 2 potential resistance mechanisms are upregulation of PI3K and EGFR pathways and these are being targeted with combinations such as panitumumab, dabrafenib and trametinib. Patient derived mouse xenograft were established in 4 of 5 patients and these may be useful tools to further dissect resistance mechanisms. – AR

New England Journal of Medicine

Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma

Schaapveld M, Aleman BMP, van Eggermond AM, et al.
N Engl J Med, 2015; 373:2499-511;December 24, 2015.
DOI: 10.1056/NEJMoa1505949

Background: Survivors of Hodgkin's lymphoma are at increased risk for treatment-related subsequent malignant neoplasms. The effect of less toxic treatments, introduced in the late 1980s, on the long-term risk of a second cancer remains unknown.

Methods: We enrolled 3905 persons in the Netherlands who had survived for at least 5 years after the initiation of treatment for Hodgkin's lymphoma. Patients had received treatment between 1965 and 2000, when they were 15 to 50 years of age. We compared the risk of a second cancer among these patients with the risk that was expected on the basis of cancer incidence in the general population. Treatment-specific risks were compared within the cohort.

Results: With a median follow-up of 19.1 years, 1055 second cancers were diagnosed in 908 patients, resulting in a standardized incidence ratio (SIR) of 4.6 (95% confidence interval [CI], 4.3 to 4.9) in the study cohort as compared with the general population. The risk was still elevated 35 years or more after treatment (SIR, 3.9; 95% CI, 2.8 to 5.4), and the cumulative incidence of a second cancer in the study cohort at 40 years was 48.5% (95% CI, 45.4 to 51.5). The cumulative incidence of second solid cancers did not differ according to study period (1965–1976, 1977–1988, or 1989–2000) (P=0.71 for heterogeneity). Although the risk of breast cancer was lower among patients who were treated with supra-diaphragmatic-field radiotherapy not including the axilla than among those who were exposed to mantle-field irradiation (hazard ratio, 0.37; 95% CI, 0.19 to 0.72), the risk of breast cancer was not lower among patients treated in the 1989–2000 study period than among those treated in the two earlier periods. A cumulative procarbazine dose of 4.3 g or more per square meter of body-surface area (which has been associated with premature menopause) was associated with a significantly lower risk of breast cancer (hazard ratio for the comparison with no chemotherapy, 0.57; 95% CI, 0.39 to 0.84) but a higher risk of gastrointestinal cancer (hazard ratio, 2.70; 95% CI, 1.69 to 4.30).

Conclusion: The risk of second solid cancers did not appear to be lower among patients treated in the most recent calendar period studied (1989–2000) than among those treated in earlier periods. The awareness of an increased risk of second cancer remains crucial for survivors of Hodgkin's lymphoma. (Funded by the Dutch Cancer Society.)

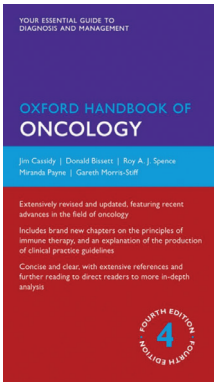
Reviewer's opinion: It is heartening to know that with improving knowledge and better management strategies, the majority of unfortunate individuals who develop Hodgkin's lymphoma can now expect to be cured and survive longer. However, it brings new concerns of late side effects and the increased risk of a second malignancy. With time, due to better selection of chemotherapy (for example declining use of alkylating agents) and radiotherapy (precise limited

volume radiotherapy delivery using complex treatment planning) there has been an improvement in morbidity and reduction in life threatening treatment related risks such as haematological disorders and injury to organs (heart, lungs and bones).

Unfortunately, even after 40 years of their primary treatment, the risk of developing secondary solid cancers remains high in Hodgkin's lymphoma survivors compared to the general population, with the cumulative incidence reaching 48.5%. In this Dutch study, the median age of the patients was 28.6 years at the time of diagnosis and the treatment for Hodgkin's lymphoma included radiotherapy for 27.3%, chemotherapy for 12.1% and combination for 60.5%. According to the findings of this study, the risk of developing late onset second cancer has not diminished over time despite changing treatment. The cumulative incidence of a second cancer was 33.2% at 30 years and 48.5% at 40 years, as compared with the expected cumulative incidence of cancer in the general population of 9.6% and 19.0% respectively. Similar to lung cancer, breast cancer accounted for more than 40% of the excess risk. Surprisingly, as compared with mantle field, less extensive field was not associated with a decline in the risk of breast cancer. This could be due in part to the increased early detection of breast cancer through screening and a reduction in the use of alkylating agents. Remarkably, the cumulative incidence of secondary gastrointestinal cancers (stomach, pancreatic, or colorectal cancers) did not change appreciably over time. The biggest challenge for the professionals is to provide comprehensive information on the late risks, continued careful monitoring and an urgent need to design, evaluate and implement safer personalised treatment strategies for patients diagnosed with Hodgkin's lymphoma. – SU

Oxford Handbook of Oncology 4th Edition

Editors: Jim Cassidy, Donald Bissett, Roy AJ Spence, Miranda Payne, Gareth Morris-Stiff. Published by: Oxford University Press. ISBN: 978-0-19-968984-2. Price: £34.99.



This 873 page handbook is the 4th edition of the very popular text on oncology. Originally designed to fit in the pocket of a " white coat" this book is essential reading for the oncology trainee in particular though will be of use to doctors at other levels as well as to other members of the oncology team.

This edition has been revised and updated to reflect the developments on oncology over the last 5 years. This book follows the same pattern as the third edition; though now includes chapters on the principles of immune therapy and an explanation of the production of clinical practice guidelines. This practical guide examines the background of cancer; aetiology and epidemiology of cancer as well as surgical oncology the "Principles of treatment" section; discusses the various treatment modalities. The chapter on principles of symptom control in palliative care was well written, informative and will be of use daily on the ward.

This book presents the information in a well organised, evidence based manner, allowing the clinician confidence in the decision making process. The general management options of malignancy are covered including the role of biological and targeted therapies.

Part 4 looks at the individual tumour sites. This section covers the key points of the common and, less common tumour types. The chapters were very informative and comprehensive in their detail and included Management of Carcinoma of the Unknown primary and haematological malignancies. Recent advances in the use of monoclonal antibodies and small molecules therefore, providing a more personalised treatment approach are discussed; bringing the reader up to date with the latest available treatment options.

The chapters are concise and practical making good use of bullet points for brevity and clarity, tables and flow diagrams present the information clearly. Examples of further reading are given at the end of each chapter.

Part 5 " Emergencies in Oncology" covers the usual emergency situations such as spinal cord compression and superior vena caval obstruction, however the radiotherapy details were very scanty considering the high incidence and burden of these conditions.

Part 6 " The way forward" examines novel therapeutic strategies, gene therapy and genetic immunotherapy for cancer and biomarkers for cancer.

In summary, I found the handbook easy to read and a good way to refresh one's knowledge quickly. I would recommend this handbook, reasonably priced about £30.

Dr Karin Baria, Retired Consultant Oncologist

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13 April	**Cytotoxic Medication Study Day for Paediatric Nurses new to Cytotoxic Treatment (£100)**	ID: 572
05-06 May	**Foundations Oncology Skills for Nurses new to working in Paediatric and Adolescent Cancer Care (£200)**	ID: 547
18 May	**Advances in Nutritional Care of the Cancer Patient (£100)**	ID: 550
26 May	**Paediatric Neuro-Oncology Study Day (£120)**	ID: 553
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05 Jul	**Targeted Treatments of Haematological Cancers (£150)**	ID: 552
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17 Mar	**Molecular Pathology in oncology – Hot topics (Early Bird only 50 places available - £100/ Standard - £150)**	ID: 542
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7 Oct	**The 9th Annual Royal Marsden Breast Cancer Meeting: Hot Topics in Breast Cancer (Full Delegate - £180/Trainees and CNSs - £120)**	ID: 545
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01-02 Nov	**Royal Brompton Practical Nuclear Cardiology Course (£200)**	ID: 589
11 Nov	**The 8th Annual Royal Marsden Head and Neck Conference (Full Delegate - £180/Trainees and CNSs - £120)**	ID: 546
12 Nov	**Sentinel lymph node biopsy in mucosal and cutaneous head and neck cancer: Why, when and how? (£125)**	ID: 585
17 Nov	**Neuro-Endocrine Tumour: The Evolving Horizon (Full Delegate - £180/Trainees and CNSs - £120)**	ID: 575
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For further information please email: conferencecentre@rmh.nhs.uk
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International Symposium on Pediatric Neuro-Oncology 2016

Dear Colleagues and Friends of the Pediatric Neuro-Oncology Community.

The 17th International Symposium on Pediatric Neuro-Oncology (ISPNO) in 2016 is taking place from 12th - 15th June in the vibrant and cosmopolitan city of Liverpool. The venue for the conference is the award winning Liverpool Convention Centre set on a delightful waterfront that has achieved world heritage.

The biennial ISPNO meeting has become the pre-eminent event in the field of Pediatric Neuro-Oncology, being the only global meeting of the multi-disciplinary international community of professionals involved in the research, diagnosis, treatment and rehabilitation of infants, children and young people with Central Nervous System tumours.

ISPNO 2016 Liverpool will feature:

- A full programme of plenary and poster sessions, keynote talks and round table discussions covering all the main aspects of CNS tumours in children and young people.
- A day dedicated to Neuro-oncological surgery - with leading international experts in Pediatric Neurosurgery.
- A full day neuro-oncology nurses meeting and a reception for nurses hosted by The Brain Tumour Charity.
- A pre-meeting Education day with state of the art lectures given by world-class clinicians and scientists.
- An open meeting of Posterior Fossa Society.
- A Family Day.

We will offer a memorable networking and social program with the Welcome Reception at the brilliantly designed waterside Museum of Liverpool, a fantastic gala dinner and optional social events at the Cavern Club – home of the Beatles – or a Latin themed evening.

- **Please register as soon as possible** to take advantage of our **early registration rates** which end on the **25th March 2016**
- Tickets for the gala dinner and optional events are limited, so don't miss out!
- A full range of hotels can be booked all of which are within walking distance of the Liverpool Convention Centre.
- All details regarding the conference, the provisional programme, invited speakers and how to register are available at **www.ISPNO2016.com**.

We look forward to welcoming the International Pediatric Neuro-Oncology community to Liverpool.

Together we will create an incredible meeting. With Very Best Wishes

Professor Barry Pizer
Chair of the Local Organising Committee of ISPNO 2016 - Liverpool.

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

Varian Honored Among World's 100 Most Sustainable Corporations for Second Year Running

Varian Medical Systems have been honoured for its commitment to sustainability with inclusion on a prestigious list of the world's most sustainable companies for the second year in a row. Varian remains the highest ranked US healthcare equipment company among the Corporate Knights Global 100 Most Sustainable Corporations list, announced during the World Economic Forum at Davos, Switzerland.

"We are proud to be recognised once again for our commitment to sustainability and this will spur us on to continually improve our efforts," says Dow Wilson (pictured), Varian's chief executive officer. "Our company's mission is to help save lives around the world and we seek to do this in ways that benefit the communities in which we operate."

"The inclusion of Varian in the Global 100 ranking for the second time in a row is a reflection of its continuous dedication to sustainability," said Michael Yow, director of research at Corporate Knights. "Once again, Varian is an industry leader in terms of sustainability performance and disclosure."

The 2015 Varian Sustainability Report can be found here: https://www.varian.com/about-varian/citizenship

Provectus Biopharmaceuticals confirms first patients dosed in trials of PV-10 for melanoma

Provectus Biopharmaceuticals, Inc confirmed in January 2016 that patients have been dosed in both its Phase 3 clinical trial of PV-10, Provectus' novel investigational drug for cancer, for Stage III locally advanced cutaneous melanoma and its Phase 1b/2 clinical trial of PV-10 in combination with Merck's anti-PD-1 therapy KEYTRUDA® (pembrolizumab) in patients with Stage IV melanoma. In addition, the Company confirmed that it continues to enroll patients in all of its active oncology studies.

Eric Wachter, Chief Technology Officer of Provectus, said, "With patients starting treatment in both of these studies, the clock is ticking to interim results and ultimately the completion of these studies. Our recruitment activities are moving ahead and we are hopeful that these studies will play critical roles in demonstrating effectiveness and safety of PV-10 in melanoma."

PHASE 3 STUDY

The Phase 3 study is an international multicenter, open-label, randomised controlled trial (RCT) of single-agent intralesional (IL) PV-10 versus systemic chemotherapy to assess treatment of locally advanced cutaneous melanoma in patients who are BRAF V600 wild-type and have failed or are not otherwise candidates for ipilimumab or another immune checkpoint inhibitor. Subjects in the PV-10 arm receive IL PV-10 to all of their melanoma lesions. Subjects in the comparator arm receive the investigator's choice of dacarbazine or temozolomide as determined by investigator preference and/or local availability of the agent.

For more details on the study, please visit https://www.clinicaltrials.gov/ct2/show/NCT02288897.

PROVECTUS BIOPHARMACEUTICALS, INC.

Provectus Biopharmaceuticals announces immunology data on PV-10 in colon cancer, presented at 11th Annual ASC Meeting

Provectus Biopharmaceuticals, Inc have announced that an abstract discussing the immunologic effects of PV-10 on colon cancer cells was presented at the 11th Annual Academic Surgical Congress in February 2-4, 2016, at the Hyatt Regency in Jacksonville, Florida.

The abstract, titled "PV-10 Induces Potent Immunogenic Apoptosis in Colon Cancer Cells," was presented by Dr AV Maker. It is co-authored by NM Kunda, J Qin and G Qiao, working out of the University of Illinois at Chicago, Division of Surgical Oncology, Department of Surgery, College of Medicine, Chicago, IL, USA. The team of authors also includes B Prabhakar of the University of Illinois at Chicago, Department of Microbiology & Immunology, College of Medicine, Chicago, IL, USA. Dr Maker belongs to both departments.

The abstract can be found at: http://www.asc-abstracts.org/abs2016/2-01-pv-10-induces-potent-immunogenic-apoptosis-in-colon-cancer-cells/

PROVECTUS BIOPHARMACEUTICALS, INC.

A New Chapter for Genesis Care in the UK

Following its acquisition by Australia's largest provider of radiotherapy services, Cancer Partners UK has become Genesis Care. It has also launched its ninth centre in the UK, West Malling Diagnostic & Treatment Centre, in Kent.

With a focus on delivering early diagnosis, unparalleled patient care and rapid access to treatments, including chemotherapy and world-class radiotherapy, the new centre follows a similar model to the company's latter two in Milton Keynes and Oxford.

Paul McPartlan, who has recently been appointed UK General Manager, says: "I am looking forward to the benefits Genesis Care will deliver for cancer patients, with a focus on innovation, the sharing of global best practice and investment in the latest technology and treatment techniques. In addition, we are really looking forward to collaborative working with our NHS partners, so that we can provide the best possible results for patients across the UK, closer to their home and workplace.

"I'm also excited at the opportunities it will bring to our staff. Sharing best practice across all job roles, greater learning, and a real focus on research and development means they will be able to play a significant part in the company's growth."

For further information please contact:
Beth Rankine T: +44 (0)7809 603 751
E: beth.rankine@genesiscare.co.uk
W: www.genesiscare.co.uk

GenesisCare

Brain Tumour Research have moved

National charity Brain Tumour Research has relocated to headquarters in central Milton Keynes. Since inception in 2009 the charity has enjoyed a period of remarkable growth and its previous base in rural Buckinghamshire became no longer fit for purpose for a charity striving to make a real difference for those diagnosed with the biggest cancer killer of children and adults under 40.

The charity's eye catching branding and strong key messages have been incorporated into an office space that motivates staff and volunteers alike and provides visitors with an inspirational vision of the charity's ambitions.

A launch event in January was attended by the Mayor of Milton Keynes, Iain Stewart MP for Milton Keynes South and representatives of the city's business community who were all able to hear from principal scientists at the dedicated brain tumour research centres that the charity funds. They were also able to see how the new office space enables staff and volunteers to fulfil the orders pouring in for

badges, wristbands and other merchandise as we approach the UK's premier brain tumour awareness event Wear A Hat Day which this year is Thursday March 24th.

For further information visit:
http://www.braintumourresearch.org/ or
E: info@braintumourresearch.org

Old red dye shows promise as new cancer foe

PROVECTUS BIOPHARMACEUTICALS, INC.

Modern cancer drugs supercharge immune systems, target specific gene mutations and pack modified viruses into vaccines. Amid the increasing sophistication, one investigational treatment stands out for its simplicity.

Rose Bengal, a cheap industrial chemical that turns yarn and food bright red, has been used as a diagnostic staining agent for some time. Now, some scientists are looking at its potential to fight various forms of cancer.

At the forefront is Provectus Biopharmaceuticals Inc, which is testing a reformulated version of the industrial dye on melanoma, the deadliest form of skin cancer. The company reported promising results in a small melanoma study.

While some doctors are encouraged by the research, government approval is years off and not guaranteed. The company must replicate its early results on a bigger scale, and a US Food and Drug Administration decision is not expected before 2019.

Rose Bengal's potential against cancer was discovered by accident. The salt was first patented in 1882 as a wool dye and has been used for years as a diagnostic stain in tests for jaundice in newborns and to detect eye damage.

In 1998, scientists who later founded Provectus were looking for a safe photoreactive agent to use in an investigation of lasers against cancer. Rose Bengal fit the bill.

As it turned out, the Rose Bengal solution appeared to work on its own to dissolve tumours when directed injectly into them, recalled Provectus Chief Technology Officer Eric Wachter, a former scientist from Oak Ridge National Lab who co-founded the company. "It made the lasers obsolete."

For further information visit:
www.pvct.com

Provectus Biopharmaceuticals announces data on PV-10 and co-inhibitory blockade to be presented at AACR Annual Meeting 2016

Provectus Biopharmaceuticals, Inc announced that data on intralesional PV-10 and co-inhibitory blockade in a melanoma model will be presented at the American Association for Cancer Research's ("AACR") Annual Meeting 2016 on Wednesday, April 20, 2016, from 8 am to 12 Noon Central Standard Time.

The poster presentation is titled "T Cell Mediated Immunity after Combination Therapy with Intralesional PV-10 and Co-Inhibitory Blockade in a Melanoma Model." Scheduled for presentation at Section 26 of the exhibition area, the data are from a team of researchers at the H Lee Moffitt Cancer Center in Tampa, led by Dr Shari Pilon-Thomas.

The AACR Annual Meeting 2016 is being held at the Ernest N Morial Convention Center in New Orleans, Louisiana, from April 16-20, 2016.

The complete press release is available at www.pvct.com/pressrelease.html?article=20160224.1 on the Provectus website: www.pvct.com

PROVECTUS BIOPHARMACEUTICALS, INC.

Provectus Biopharmaceuticals initiating Phase 1 study of PV-10 in neuroendicrine tumours metastatic to liver

Provectus Biopharmaceuticals, Inc are initiating a protocol titled, "A Phase 1 Study to Assess the Safety, Tolerability and Effectiveness of PV-10 Chemoablation of Neuroendocrine Tumours (NET) Metastatic to the Liver in the Reduction of Biochemical Markers and Symptoms Caused by Secretory Products."

The 12-patient phase 1 study will run up to 48 months with interim data anticipated at the half-way point of the two-cohort study. Patients in the first of the two successive cohorts will receive PV-10 to a single NET tumour in their liver, while patients in the second cohort may receive PV-10 to multiple NET tumours. Timothy Price, MD will serve as principal investigator for the study at The Queen Elizabeth Hospital in Woodville, South Australia.

Dr Price explained, "The primary endpoint of our study will be assessment of safety and tolerability of PV-10 in the treatment of these metastatic NETs. Our secondary endpoints address preliminary efficacy, disease symptoms and biomarkers, and include assessments of Objective Response Rate (ORR) of injected and uninjected tumours; change in tumour biomarkers (somatostatin receptor expression, chromogranin A and 5-hydroxyindole acetic acid); change in NET symptoms assessed by standard quality of life instruments; and possible change in peripheral blood mononuclear cells (PBMCs)."

For further information, please visit https://www.clinicaltrials.gov/ct2/show/NCT02693067. The study is expected to open for enrollment in March 2016.

Beating Bowel Cancer announces details of London Patient Day

Beating Bowel Cancer's 11th annual London Patient Day will take place on Saturday 16 April at The Royal College of Surgeons, London.

The event offers bowel cancer patients, their carers and colorectal clinical nurse specialists a day of support, education and inspiration.

The programme will include a selection of talks by eminent health professionals and interactive workshops on every aspect of living with bowel cancer. They include:

Mr Peter Dawson – Consultant Colorectal Surgeon, Chelsea & Westminster NHS Foundation Trust, presenting on: "Advances in bowel surgery"

Dr Jonathan Hoare – Consultant Gastroenterologist, St Mary's Hospital, Imperial NHS Trust, presenting on "What can be done down the scope? What colonoscopy can contribute to the management and prevention of bowel cancer"

Dr Robert Thomas – Consultant Oncologist, Bedford & Addenbrooke's Hospitals, presenting on "Lifestyle after cancer - self-help strategies".

The exhibition hall will include all kinds of goods and services that improve quality of life for bowel cancer patients.

If you know of any patients who would benefit from attending, or you are a colorectal clinical nurse specialist who is interested, please visit: www.beatingbowelcancer.org/patient-day-london-2016 for further details and to register for the day.

Provectus Biopharmaceuticals awarded patent extending protection of the PV-10 manufacturing process

Provectus Biopharmaceuticals, Inc announced several leadership changes following the resignation of one of its Co-Founders and its Chairman and CEO, H Craig Dees, PhD.

Provectus believes that this patent, wholly owned by Provectus and conferring coverage to at least 2031, will provide further protection around the proposed commercial process for manufacturing PV-10. Investigational drug product generated using this proprietary technology is being used in all ongoing clinical trials of PV-10, including the pivotal phase 3 trial in melanoma (NCT02288897).

Provectus' efforts to bring this process development to fruition were supported by Cambrex Charles City, Inc, a subsidiary of Cambrex Corporation, a life sciences company that provides products and services that accelerate and improve the development and commercialisation of new and generic therapeutics.

Dr Kurt Kiewel, Director of R&D at Cambrex Charles City, said, "We feel fortunate to bring the depth of our experience in custom development and API manufacturing to support promising investigational products like PV-10. It has been our pleasure to work with the innovative scientists at Provectus to help advance this potential new cancer treatment toward the market."

The complete press release is available at www.pvct.com/pressrelease.html?article=20160301.1

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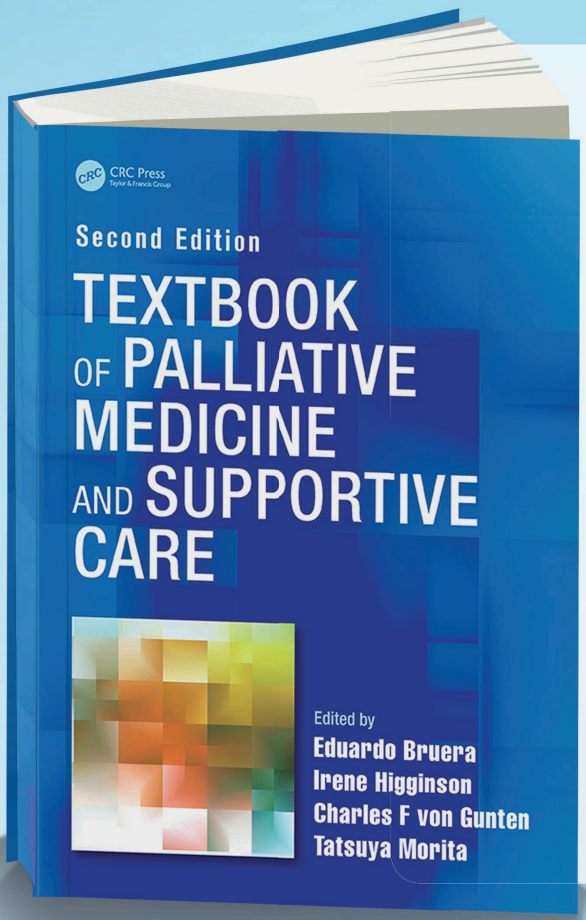

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—British Journal of Hospital Medicine

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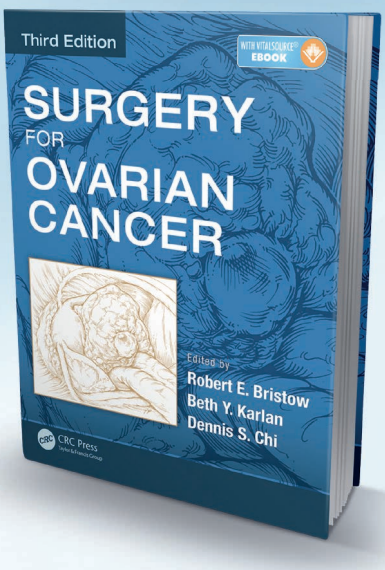

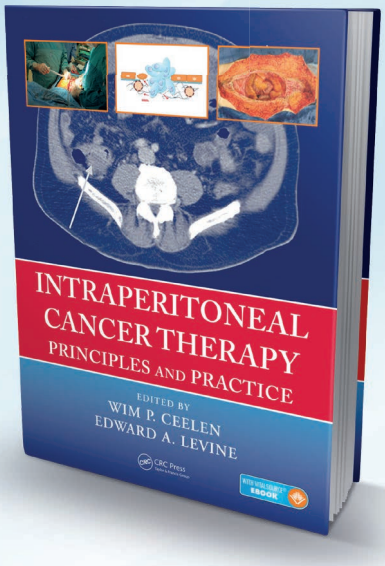

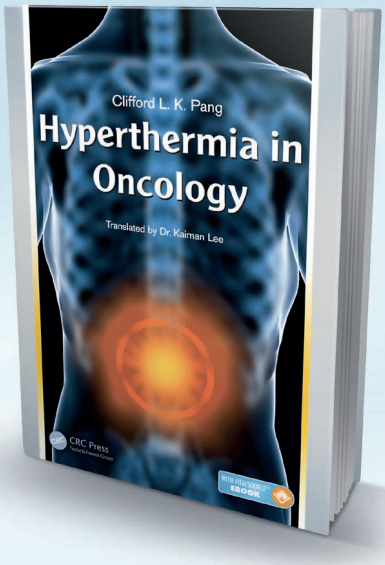

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