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

Denys Wheatley
Editor

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

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

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

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

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

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2. Smithers DW. *Cancer - an Attack on Cytologism.* The Lancet. 1962;1(7228):493-9.

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Reports from the 50th America Society of Clinical Oncology (ASCO) Annual Meeting

Date: May 30 to June 2 2014; Chicago, Illinois, USA. Author: Janet Fricker, Medical Journalist.

Overall survival benefits for upfront chemotherapy in metastatic prostate cancer

Adding docetaxel to androgen deprivation therapy (ADT) improved survival in men with newly metastatic prostate cancer, reported the CHAARTED trial.

"The benefit is substantial and warrants this being a new standard treatment for men who have [extensive] disease and are fit for chemotherapy," said Christopher Sweeney, the study presenter from the Dana Farber Cancer Institute, Boston. ADT alone is the standard first-line treatment for hormone-sensitive prostate cancer, with chemotherapy initiated at progression to resistance. The CHAARTED trial set out to address the question of whether adding chemotherapy to ADT upfront would prolong survival for men with metastatic prostate cancer compared with ADT alone.

In the study between July 2006 and November 2012 Sweeney and colleagues randomized 790 men with newly diagnosed hormone-sensitive metastatic prostate cancer to standard ADT or to ADT plus a maximum of six cycles docetaxel. Approximately two thirds of patients had high-volume disease, with either extensive bone metastases or visceral disease.

Results showed after a median follow-up of 29 months, 136 patients in the ADT arm had died versus 101 in the group that received ADT and chemotherapy. The median overall survival was 44 months in the ADT group versus 57.6 months for the combination therapy group (HR 0.61, 95% CI [0.47, 0.80]; p=0.0003).

Among men with high volume disease the results were even more striking – the median overall survival was 32.2 months for the ADT group versus 49.2 months for the combination therapy group (HR 0.60, 95% CI 0.45-0.81, P=0.0006). The median overall survival for the subset with low-extent disease has yet to be reached.

Regarding toxicity, 6% of men receiving the chemo hormonal regimen experienced febrile neutropenia, 1% experienced significant effects on sensory nerves and 1% on motor nerves, and one patient died as a result of treatment.

"This is one of the biggest improvements in survival we have seen in a trial involving patients with an adult metastatic solid tumour," said Sweeney.

The new treatment paradigm, he added, will entail earlier, multidisciplinary care involving collaborations between urologists and oncologists.

Reference
Sweeney C, et al. *Impact on overall survival with chemo hormonal therapy versus hormonal therapy for home-sensitivity newly metastatic prostate cancer: An ECOG-led phase III randomized trial.* ASCO 2014, J Clin Oncol 32:5s, 2014 (suppl; abstr LBA2)

Dual blockade does not deliver benefits in HER 2 positive breast cancer

Adding lapatinib to trastuzumab and chemotherapy after surgery for HER2 positive breast cancer made no difference to disease free survival or overall survival, but significantly increased toxicity, concluded the phase III ALTTO trial.

The results came as a surprise to experts who had anticipated that ALTTO would confirm the positive results of the earlier NeoALTTO study which sin the neoadjuvant setting showed that the combination of lapatinib and trastuzumab achieved a significantly better pathological complete response than trastuzumab alone.

"This is a serious disappointment, not just for the investigators, but for the entire field. It is difficult to mount any enthusiasm for combined blockade of HER2 in the adjuvant setting, at least with the combination used here," said discussant George Sledge, from Stanford University.

The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial was designed to test the hypothesis that dual blockade of HER2 using two anti-HER2 agents would provide greater benefit than single anti-HER2 therapy following surgery. In the study 8,381 women from 946 medical centres in 44 countries with newly diagnosed early-stage HER2-postive breast cancer were randomly assigned to trastuzumab alone (n=2097), lapatinib alone (n=2,100), trastuzumab plus lapatinib sequentially (n=2091), and trastuzumab and lapatinib concurrently (n=2093).

Results at four years show disease-free survival was 86% with trastuzumab alone, 88% with concurrent trastuzumab and lapatinib and 87% with sequential trastuzumab then lapatinib. The lapatinib alone arm was stopped early due to futility.

Adverse events more frequently reported in the lapatinib plus trastuzumab arm than the trastuzumab arm included diarrhoea (75% versus 20%), rash (55% versus 20%) and liver problems (23% versus 16%).

Despite the marginal performance of lapatinib in ALTTO, Martine Piccart-Gebhart, the co study director and study presenter from the Jules Bordet Institute, Belgium, said that the results for trastuzumab in early stage breast cancer, where it achieved a four year disease free survival rate of 86% and four year overall survival rate of 94%, had been heartening.

"A key lesson of this trial is that we need robust clinical trials in a specific disease setting to fully assess and understand the value of new treatment regiments," said Edith Perez, co study director from the Mayo Clinic Cancer Center , Jacksonville, Florida.

Reference
Piccart-Gebhart M, et al. *First results from the phase III ALTTO trial (BIG 2-06; NCCTG[Alliance] NO63D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T L), or their combination (T+L) in the adjuvant treatment of HER2-postive early breast cancer (EBC).* ASCO 2014, J Clin Oncol 32:5s, 2014 (suppl; abstr LBA4)

Immunotherapy takes centre stage in melanoma

Data on three separate drugs presented at ASCO underlined the way immunotherapy is reshaping the treatment of melanoma. The explosion in treatment is happening across the board, not just in metastatic melanoma (the combination of nivolumab and ipilimumab, and pembrolizumab), but also in locally advanced cutaneous melanoma (PV-10).

In the first study Mario Sznol, from the Yale School of Medicine, explored the combination of ipilimumab and nivolumab in 94 patients with inoperable stage II or IV melanoma who had undergone up to three prior systemic therapies [1].

Nivolumab and ipilimumab are antibody drugs that target and block two different 'gatekeepers' or checkpoints (PD-1 and CTLA-4, respectively) on T cells, disarming the tumour's defences against the immune system and boosting the immune system's ability to fight melanoma.

Results showed overall 41% (22 out of 53 patients) responded to the treatment and 17% (nine) achieved complete remissions. Furthermore, 42% of the patients had a greater than 80% tumour reduction by week 36, and responses were durable with 18 of 22 responses (82%) ongoing at the time of the analysis. Across doses, the one-year and two-year median overall survival rates were 85% and 79% respectively, and the median survival duration 39.7 months.

"Just a few years ago, median survival for patients diagnosed with advanced melanoma was as little as a year or less, and only approximately 20-25 % survived two years, so it's truly remarkable that we're seeing a median survival over three years in this trial," said Sznol, adding that even in the latest era of targeted and immunotherapy agents, the median survival is on average about 16-18 months with any new treatment alone.

In the second study Antoni Ribas, from the University of California in Los Angeles, enrolled 411 patients with metastatic melanoma that had spread to the skin, lungs or other major organs (221 with prior ipilimumab treatment and 190 who had not previously received ipilimumab) to receive pembrolizumab [2].

Pembrolizumab is an investigational, selective, humanized monoclonal anti-PD-1 antibody, designed to block the interaction of PD-1 on T cells and to reactivate anti tumour immunity.

The study included seven different cohorts with different eligibility and three different dosing regimens for single-agent pembrolizumab.

Results showed that overall 34% of patients experienced tumour response (assessed by Independent Review), including 28% of the 221 patients whose disease had progressed on prior ipilimumab and 40% of the 190 patients not previously treated with ipilimumab.

The median PFS among ipilimumab naïve patients from all dosing schedules was 24 weeks (95% CI, 16-48), and 51% achieved 24-week PFS. The median PFS among the cohort previously treated with ipilimumab was 23 weeks (95% CI, 14-24), and 44% achieved 24-week PFS.

"This is probably the biggest phase 1 trial ever conducted in oncology. We were excited to see that pembrolizumab was effective in previously untreated patients as well as in those who had multiple prior therapies, including ipilimumab," said Ribas.

In the third study, which took place in locally advanced cutaneous melanoma, Sanjiv Agarwala, from St Luke's Hospital and Health Network, Bethlehem, Pennsylvania, explored a subgroup of 54 patients from a phase 2 study who had most or all of their lesions injected with PV-10 [3].

PV-10, a 10% solution of Rose Bengal that was originally used as an agent to stain necrotic tissue in the cornea, has been developed to selectively target and destroy cancer cells through intralesional injection, reducing the potential for systemic side effects.

In the original phase 2 study between October 2007 and May 2010, 80 patients with locally advanced cutaneous disease refractory to a median of six previous interventions, were recruited from seven centres to receive up to four treatment cycles of injections with intralesional (IL) PV-10. Furthermore, up to two 'bystander' lesions were identified that underwent biopsy to confirm melanoma, but did not receive treatment. The current abstract explored the subgroup of patients who had all or most of their lesions injected, leaving out patients with more advanced disease where substantial numbers of lesions went untreated.

Results show that for the 28 patients who had all their existing melanoma lesions injected with PV-10, the overall response rate was 71% (CI 51-87%) with 50% achieving a complete response (CI 31-69%). Furthermore, when the 28 patients who had all their lesions injected were analysed together with 26 patients who had two lesions left untreated (to investigate bystander effects) a complete response was achieved in 232 of the 363 injected lesions (64%).

"These sub-group analyses show response to PV-10 is maximized when all lesions get treated. The level of response observed in this heavily pre treated or refractory patient population with locally advanced cutaneous melanoma is noteworthy since, unlike those with more advanced disease, these patients have limited treatment options now or on the horizon," said Eric Wachter, the Chief Technology Officer at Provectus, who co-developed PV-10.

Additionally, data reported from a pilot clinical trial in eight patients showed that one to two weeks after PV-10 injection patients had increases in peripheral blood T cells, including CD8+ ($p=0.03$), CD4+ ($p=0.06$), CD3+ ($p=0.03$), and NKT ($p=0.05$) [4]. "This data provides a rationale for combination trials of PV-10 with check point protein inhibitors, such as ipilimumab, pembrolizumab and nivolumab. PV-10 might offer the perfect way to prime the immune system," said Jeffrey Weber, the senior author from Moffitt Cancer Center.

Following the presentation Provectus announced that a phase 3 trial of PV-10 to generate sufficient data for a new drug application (NDA) is expected to start accrual in the second half of 2014.

Reference

1. Mario Sznol. "Survival, response duration, and activity by BRAF mutation status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) an ipilimumab concurrent therapy in advanced melanoma. ASCO 2014, J Clin Oncol 32:5s, 2014 (suppl; abstr LBA9003)
2. Antoni Ribas. "Efficacy and safety of the anti-PD1 monoclonal antibody MK-3475 in 411 patients (pts) with melanoma (MEL)." ASCO 2014, J Clin Oncol 32:5s, 2014 (suppl; abstr LBA9000^)
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Lenvatinib offers new hope for refractory thyroid cancer

Lenvatinib extended progression free survival (PFS) in patients with treatment-refractory thyroid cancer, reported the phase III SELECT study.

"We are confident that, based on our findings, lenvatinib will eventually become a standard treatment for radioiodine-resistant thyroid cancer," said Martin Schlumberger, the lead author from University of Paris Sud, France.

Although differentiated thyroid cancer is generally curable with surgery and radioactive iodine 5% to 15 %of patients develop radioactive iodine resistance. The result is that they have few treatment options and 10 year survival rates of just 10%. Lenvatinib is an oral tyrosine kinase inhibitor that blocks several targets, including VEGFR1-3, FGFR 1-4, PDGFRβ, KIT, and RET.

In the SELECT study, 392 patients with advanced, radiation-resistant, iodine resistant differentiated thyroid cancer that had progressed during one year were randomized 2:1 to lenvatinib (n=261) or placebo (n=121). Patients assigned to placebo were allowed to cross over and receive lenvatinib on disease progression.

Results showed that the median progression free survival was 18.3 months for patients assigned to lenvatinib versus 3.6 months for those assigned to placebo (HR 0.21, 95% CI 0.14-0.31 P<.0001). The median overall survival has yet to be reached.

Approximately 65% of patients experienced tumour shrinkage in the lenvatinib arm compared to only 3 % in the placebo arm.

The five most common side effects of lenvatinib were high blood pressure, diarrhoea, decreased appetite, decreased weight and nausea. Although side effects necessitated dose reductions in 78.5 % of patients, the benefits of lenvatinib persisted with decreased dose, Schlumberger noted."This new drug is extremely efficient, and though toxicities were considerable they can be managed with dose modification," he said.

Lenvatinib is also currently being explored in phase II and III clinical trials as a potential treatment for liver, lung, and kidney cancers and other types of solid tumours.

Reference

1. Schlumberger M, et al. A phase 3, multicenter, double blind, placebo-controlled trial of lenvatinib (E7080) in patients with 131I-refractory differentiated thyroid cancer (SELECT). ASCO 2014, J Clin Oncol 32:5s, 2014 (suppl; abstr LBA6008)

British Neuro-Oncology Society

July 2014

Dear Delegate

The British Neuro-Oncology Society is delighted to offer you this year's annual meeting programme in Liverpool, entitled "Contemporary approaches to paediatric & adult brain tumours". This meeting has been expertly organised by Carol Walker and Andrew Brodbelt to whom we owe a debt of gratitude for their hard work and dedication.

BNOS is offering three days of conference activity linking the opportunity for syndicates and groups to meet, an education day and 1½ days of intensive scientific communication about the management of cancer within the brain.

Cancer affects the brain of humans at all ages; in childhood nearly 25% of all primary cancers arise in the brain; in adulthood, whilst only 2% of primary cancers arise in the brain, up to 40% of all cancers may be complicated by brain metastases, the startling effect that brain cancer is the biggest cancer killer, up to 40 years of age, thereby justifying this conference as a priority in the scientific and clinical calendar.

We are fortunate this year in being strongly sponsored by charity and commercial partners. We have a number of keynote presentations by leaders in their field; we are able to make an award to our Young Investigator of the Year, Dr Ruman Rahman, and we will be offering prizes for the best posters and presentations.

Socially, the Organising Committee has arranged a dinner in the Lutyens Crypt of the Metropolitan Cathedral in Liverpool, a stunning setting for our Annual Dinner.

We welcome you to Liverpool! We want your ideas on how to improve BNOS for the future, we invite you to become involved with the BNOS organisation through our sub-groups, and we look forward to working with you over the next three days.

Yours sincerely

David A. Walker.

David A Walker (Chair)
On behalf of Carol Walker & Andrew Brodbelt – Local Organising Committee

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Computer-Aided Detection of Colorectal Lesions: Current and Future Directions

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Early detection of colorectal cancer significantly increases the likelihood of successful treatment. In many cases, detection and removal of pre-cancerous adenomatous polyps will prevent colorectal cancer from forming in the first place. The most accurate approaches to detect colorectal lesions (polyps and cancers) involve imaging. However, imaging the colon results in large quantities of data that must be analysed by a human reader and can therefore result in errors. Computer-aided detection (CAD) applies automated image analysis algorithms to identify and draw the reader's attention to suspicious pathology in the image data. This article provides an overview of different CAD approaches developed for colorectal lesion detection and gives some perspective on emerging technologies in the field.

Screening for colorectal disease

Worldwide, colorectal cancer is the second most common cancer in women and the third most common cancer in men [1]. The majority of colorectal cancer cases occur in developed countries. Despite the high prevalence, colorectal cancer is largely preventable through early detection and treatment. Colon cancer arises from pre-cancerous polyps, which typically grow slowly, of the course of years. Because of this slow growth, the colon can be screened for lesions, and detected polyps safely removed via a polypectomy procedure. Colorectal cancer screening programmes are proven to be effective [2] and have been adopted by many healthcare systems.

One of the key challenges to successful implementation of a screening programme is patient engagement. Despite concerted efforts to enrol patients, uptake remains low, with less than 60% in the UK [3] for individuals meeting the enrolment criteria. For patients that are screened, effective detection is paramount. There are chemical tests such as the faecal occult blood test (FOBT) or the faecal immunochemical test (FIT) that respond to the presence of occult (not visible) blood in the faeces. Alternatively, stool DNA tests [4] look for abnormal genetic material present in the stool. While a positive result with one of the above tests may result from a lesion, there are numerous sources of false positives. Therefore further testing is typically done with imaging; usually with video endoscopy or computed tomography (CT) colonography.

Imaging exams come in several forms, and are normally applied to the colon after cathartic cleansing. Flexible sigmoidoscopy is a procedure that examines the rectum and lower colon with a sigmoidoscope, a flexible tube roughly 60 centimetres long that includes a light source and video camera at the tip that transmits video to a monitor viewed by the gastroenterologist whilst manoeuvring the camera. Colonoscopy, in contrast, uses a longer camera that can traverse the entire colon during the examination. A key advantage of these procedures is that if pathology is detected, it can biopsied or removed using surgical tools that are part of the scope. However, some patients prefer to elect a less invasive examination. CT colonography (CTC) images the insufflated colon using CT series of the patient in the prone and supine position. The 3D images are then reviewed by a reader on a workstation using advanced visualisation software. Recently, there has been considerable interest in capsule endoscopy, which images the colon using a single-use miniaturised camera that is swallowed by the patient and transmits images to a data recorder as it moves through the body. The images are later retrieved and reviewed for the presence of pathology. Whilst CTC and capsule endoscopy can identify polyps, a subsequent colonoscopy may be required for polypectomy.

The role of CAD

CAD has its history in the study of radiologic errors. Concern over the misinterpretation of radiologic images dates back to at least the 1940s [5]. This laid the groundwork for error reduction through computerised image analysis. In early CAD research, there was the belief that the computer would replace the human interpretation of images. However, given the challenges in interpreting subtle pathology, along with the high standards required for clinical use, success with fully automated CAD was limited. Today the prevailing

view is that CAD is best deployed to assist the human interpretation of images. The CAD field had a watershed moment in 1998 with the US Food and Drug Administration (FDA) cleared the first commercial CAD system, designed by R2 Technology for breast mammography. Since then, CAD has seen considerable growth into clinical practice.

A typical colonoscopy procedure lasts approximately 30 minutes; roughly half of this time will be spent examining the video feed for the lesions. Assuming 60 frames per second video common to progressive scan systems, the gastroenterologist may view up to 50,000 video frames. Given this large amount of data, it is possible that lesions are missed due to perceptual errors resulting from fatigue, distraction, or variable conspicuity of an abnormality. Similarly, a CT colonography can generate over 1000 images (of 512 x 512 pixels) for each patient position. The primary objective of CAD then is to assist the reader to reduce the false negatives that would otherwise be overlooked. However, another important consideration is the role of false positives, which should be minimised to reduce additional patient work-up. An ideal CAD system is therefore both sensitive and specific, that is, it should detect a high number of lesions without generating many false positives.

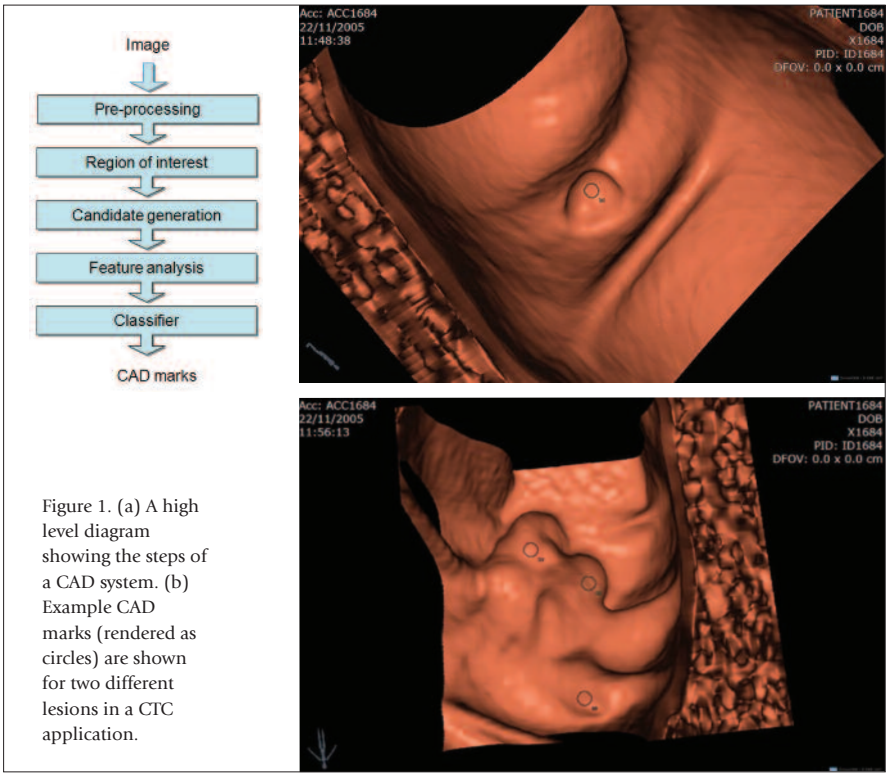

Figure 1. (a) A high level diagram showing the steps of a CAD system. (b) Example CAD marks (rendered as circles) are shown for two different lesions in a CTC application.

CAD techniques

A depiction of modern CAD system is given in Figure 1a. First, image pre-processing algorithms may be applied, for example, to denoise the data. A region of interest within the image is determined, often through segmentation. This step limits the subsequent processing (and resulting detection) to a subset of the data, such as the colon, and not adjacent organs, in CTC. Next, a candidate generation step finds a set of possible lesions in the image. Candidate generation is designed to be highly sensitive, and therefore may include many non-lesions as well. For each candidate, a set of features is extracted from the image. Good features are those that discriminate between lesions and non-lesions, and are often composed of image intensity or colour (if available), texture, and shape. Finally, a classifier based on a supervised machine-learning algorithm is used to filter out the non-lesion candidates. The candidates that remain form a set of CAD marks that are superimposed on the image to draw the reader's attention to suspicious regions in the image. Examples of CAD marks in a CT colonography application are presented in Figure 1b.

In the literature, several CAD systems for video endoscopic examination of the colon have been proposed [6-10], and often rely on shape, textural, and/or colour cues for detection of lesions. Shape-based methods take advantage of the fact that sections of polypoidal lesions often project as curved sections into the image, and have distinctive edges [7, 9, 10]. Texture-based methods [6, 8] exploit the roughness or pit pattern [11], related to the morphology, size, and distribution of mucosal pits. Finally, colour-based methods [6, 7] look for chromatic differences between lesions and non-lesions; for example, due to bleeding, lesions may have a more reddish hue. Arguably the most useful deployment of an endoscopic CAD (EndoCAD) system is to provide real-time [7] clinical support to the endoscopist, by processing the live video feed and inserting CAD marks to highlight suspicious regions. Due to real-time requirements, this necessitates computationally efficient algorithms. With the advent of capsule endoscopy into clinical practice, there has been research in adapting similar EndoCAD techniques to capsule endoscopy data [12]. A key difference between these techniques is the frame rate, which is considerably lower in capsule endoscopy.

Computer-aided detection systems for CT colonography have made considerable impact in clinical practice since early research prototypes were first developed in the 1990s. In the literature there are a number of CAD systems that have been researched [13-16] and commercial systems are now available. CTC CAD systems primarily rely on shape features that result from protruding geometry [14] from the colonic wall, and can be captured using differential geometric features like shape index [13] or the second principal curvature [15]. CAD systems used in CTC workflows are deployed as a second reader, meaning the human reader first reviews the CT images without CAD and makes a note of any findings. Then, the CAD is activated, and the reader reviews the CAD marks to see if CAD identified any lesions that were missed on their first read. Using CAD in this way reduces automation bias so that reader does not overly focus on the CAD marks during their initial read of the data.

Emerging directions

The scope of CAD continues to expand as new imaging systems become available. A potentially fruitful area involves 3D reconstruction of the mucosal surface from in-vivo imaging. Whilst approaches

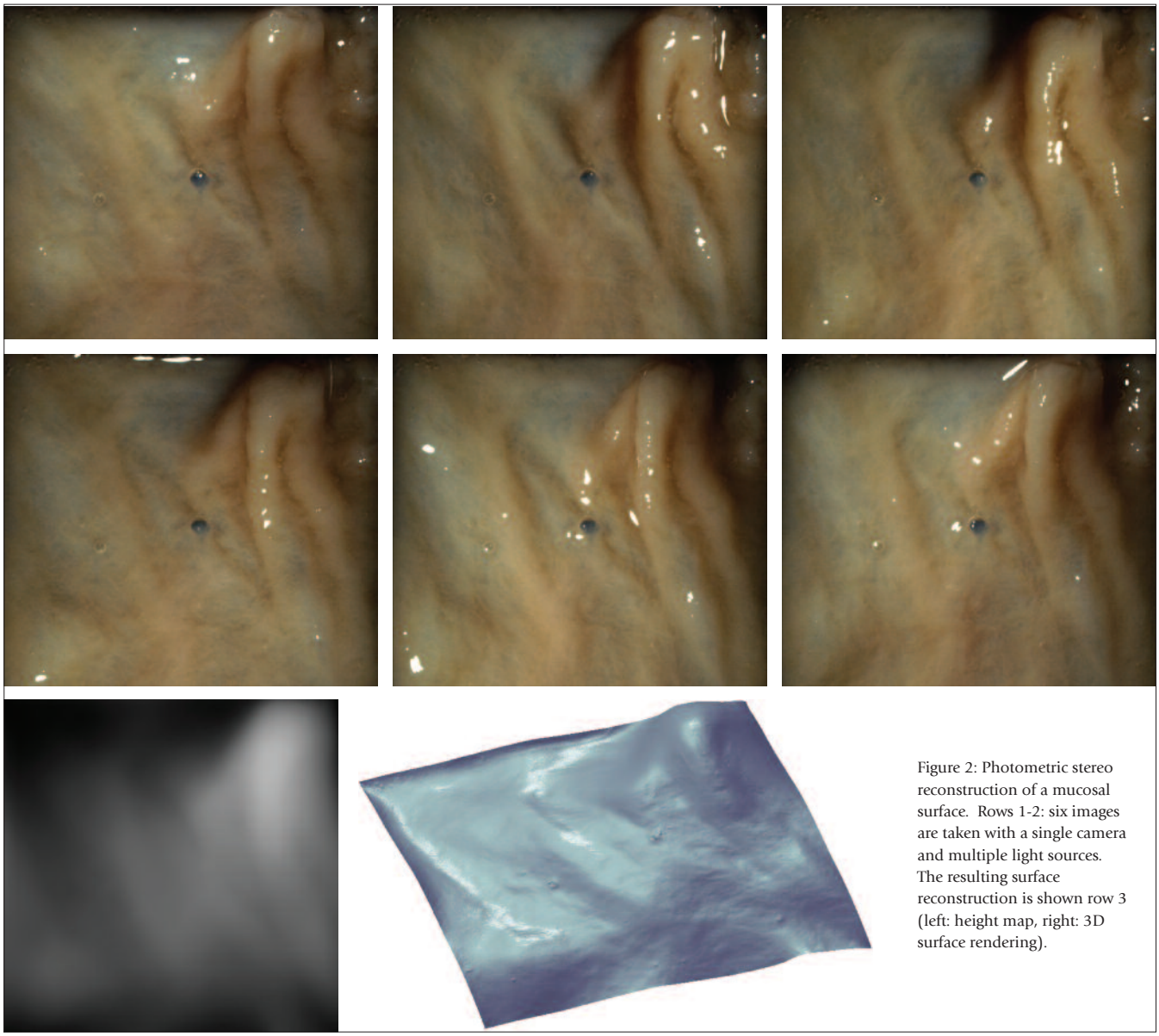

Figure 2: Photometric stereo reconstruction of a mucosal surface. Rows 1-2: six images are taken with a single camera and multiple light sources. The resulting surface reconstruction is shown row 3 (left: height map, right: 3D surface rendering).

using stereovision, structure from motion and structured light have been proposed, photometric stereo [17, 18], which uses a single camera and multiple light sources to reconstruct 3D surface topography has promise due to its real-time reconstruction and high resolution. An example is shown in Figure 2. By taking advantage of the shape information, it is possible to combine some advantages of the 3D shape-based analysis of CT colonography CAD with the colour and texture-based analysis of EndoCAD approaches. However, performing precise 3D reconstruction of a highly reflective mucosal surface in a narrow confined space poses difficult engineering challenges.

In CT colonography, there is considerable interest in developing CAD for reduced, or even non-cathartically prepared patients [19], as this preparation is seen as a factor contributing to lower patient engagement rates. CAD systems designed for this application must differentiate lesions from residual waste in the colon, which is a difficult problem even with the use faecal tagging agents [20]. Extension of existing CAD techniques to alternative imaging such as low-dose CT [21] or dual-energy CT [22] have been proposed. Recently, there has been notable research activity on further resolving polyps from non-polyps by taking advantage of both CT series (prone and supine) through spatial registration [23, 24]. Non-polyps such as stool are mobile, and move considerably relative to the colon when the patient is repositioned in the scanner.

Finally, there is growing research activity in going beyond pure detection, and into computer-aided diagnosis and treatment. The classification of a polyp as hyperplastic or adenomatous can affect the surveillance interval for patient follow-up. Typically, this diagnosis is done by a histopathologist who examines excised tissue under a microscope. However, recent studies [25] have argued for an in-vivo classification during colonoscopy to reduce healthcare costs. The diagnosis can be achieved using a variety of imaging techniques, for

example using white light endoscopy [26], or narrow-band imaging [27], which uses two frequencies of light to enhance the surface detail of the mucosa. In regards to treatment, computer-assisted navigation is an emerging topic. If a lesion is detected on a pre-interventional CT image, a possible navigational aid could help guide the endoscopist to the lesion when performing a colonoscopy. This is particularly challenging problem as it requires registering the CT image to a live video feed during colonoscopy, and the colon itself will deform significantly between the two procedures.

Outlook

The future of CAD for colonic lesion detection is bright. One hurdle to CAD reach has been the complex regulatory environment for CAD devices, particularly in the USA. However, with the recent clearance of computer-aided detection systems for CT colonography by the FDA, there is now precedent and a better understanding of regulatory requirements, so additional commercial systems are expected in the future. Further academic research taking advantage of advances in image formation, image analysis, and machine learning will advance the accuracy of CAD and bring it to new clinical applications. ●

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The Patient Experience of Traversing the Complex Rectal Cancer Pathway

This pathway is not straight forward in that each person from rural Northland, New Zealand, may have as many as 12 different groups of health professionals involved in their care. In this article I will focus on the treatment journey and the patient experience, and hope to impart some understanding of how confusing it can be for patients setting out on this pathway, 200 km or more away from home. In this article I plan to:

1. Discuss the Standards of Service Provision for Patients with Bowel Cancer in New Zealand
2. Consider the NZ Health and Disability Commission Vision
3. Consider the question, 'Have we met the needs of the consumer?'

In the latter part of this article, I examine the consumer perspective by talking to a patient and share these findings in order to assist with the planning of future services.

So, why is rectal cancer so important?

Associate Professor Diana Sarfati from the Department of Public Health, University of Otago, Wellington, summarised the data at the Rectal Cancer summit held in Wellington in August 2013. Rectal cancer is a major health issue for New Zealand: 3000 colorectal cancers are diagnosed every year and 1/3 are rectal cancers. New Zealand death rates from colorectal cancer rank among the highest in the world: in 2009 there were 300 deaths from rectal cancer [1, 6].

She also identified inequities in outcome for New Zealanders. Maori are more likely to develop cancer and die from cancer than non-Maori across all NZ deprivation deciles: between 1981 and 2004 the incidence of colorectal cancer remained stable for non-Maori but increased significantly for Maori. Maori also have a 33% poorer survival from colorectal cancer than non-Maori, are less likely to receive adjuvant chemotherapy, and experience lower quality of care [2, 5].

In order to address some of these issues, the National Tumour Standards for Bowel Cancer in New Zealand were born. The standards were developed by the National Bowel Tumour Standards working group chaired by Professor Frank Frizelle, a colorectal surgeon with the Canterbury DHB. The group consisted of a multidisciplinary team of professionals working in the area of colorectal cancer in N.Z. The final draft was published in December 2013 by the Ministry of Health: it can be found on the Ministry website www.health.govt.nz or through the Northern Cancer Network at www.northerncancernetwork.org.nz

The new standards describe the care and services a person with colorectal cancer should have access to, no matter where they live in NZ. Their aim is to improve consistency of care for people with colorectal cancer across all NZ District Health Boards, in particular improving outcomes for those living away from the main centres. The standards are built around the person's journey rather than traditional "silos" of hospital oncology care.

The standards recognise the need for evidence-based practice, and were initially developed by referring to established national and international guidelines, particularly the UK Department of Health Guidelines. The working group had access to expert advisors, including Maori and consumer health experts, and there was wide consultation with key stakeholders and relevant professional organisations.

The standards document has a list of contents as below, but I will enlarge upon only two areas for consideration [3].

1. **Timely access to services**
2. Referral and communication
3. Investigations, diagnosis and staging
4. Multidisciplinary care
5. Supportive care
6. **Care coordination**
7. Treatment
8. Follow up and surveillance
9. Clinical performance monitoring and research.

Timely access to services:

A suspicion of cancer or a cancer diagnosis is very stressful for the patient and family. It is really important that patients are given timeframes and that they know how quickly they are going to receive treatment, are managed through the pathway and that they experience well coordinated service delivery.

1. New patients referred urgently with a high suspicion of cancer are required to have their first specialist assessment or colonoscopy within 14 days.
2. Patients with a confirmed diagnosis of bowel cancer must receive their first cancer treatment within 31 days of the decision to treat.
3. Patients needing radiotherapy or chemotherapy must receive their first treatment within four weeks of the decision to treat.
4. Patients referred urgently with a high suspicion of bowel cancer must receive their first cancer treatment within 62 days [4].

Care coordination:
In order to support patients through this pathway of care, each patient has a nominated single point of contact, in the form of a Clinical Nurse Specialist, to accompany them throughout the care trajectory which for many traverses different departments, two or three hospitals and numerous health professionals. So one of the key messages here is that the standards are developed around the 'person's journey' through the continuum of care.

The New Zealand Health and Disability Commission Vision

In 2013 Anthony Hill, the N.Z. Health and Disability Commissioner, visited Northland, New Zealand, and spoke to us about his vision for health and disability services in N.Z. He also shared with us some of the findings of the Mid-Staffordshire report that was released in the UK in 2012 and the learning points arising from the report. I want to consider his vision as we review the complex rectal cancer pathway.

That vision is a consumer-centred system, a system built on the concepts of seamless service, consumer engagement, transparency and an empowering culture, which promotes and protects the rights of health and disability services consumers, as set out in the Code of Health and Disability Services Consumers' Rights.

A consumer-centred system is about engagement: an engaged consumer is an empowered consumer. The opposite, as was found in the Mid-Staffordshire report, is not listening to patients' stories.

A consumer-centred system is about seamless service: the complexities of modern medicine demand that clinicians no longer work as 'cowboys', working alone in their specialist field, but work within teams. We need to be more like pit-crews at the V8 races where the crew know their roles and work together as a team to get those tyres changed.

A consumer-centred system is about transparency: sharing information and being open to criticism and to new ideas. In Mid-Staffordshire there was a failure to share information and a defensive approach to criticism.

A consumer-centred system is about culture: a culture of taking responsibility for the care you deliver and always taking notice of the patient's concerns and feelings of isolation.

Recurring themes in the Mid-Staffordshire Report are lessons for each of us:

- Get the basics right
- Read the notes
- Ask the questions
- Talk to the patient
- Listen to the patient and the patient's family
- Ensure continuity of care
- Take responsibility for the care you deliver

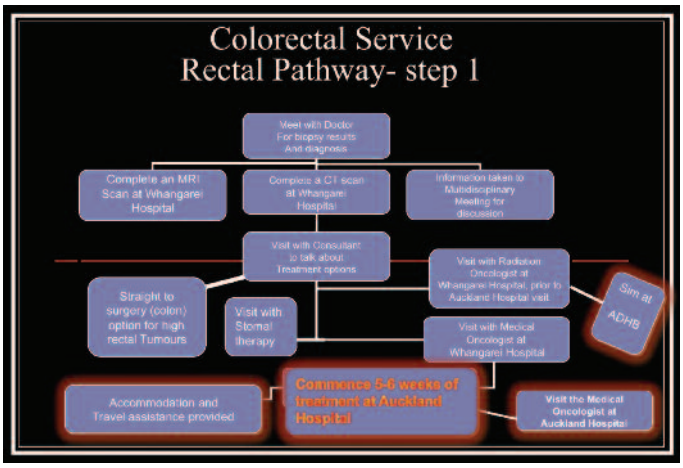
So, for those with a new diagnosis of rectal cancer, do we provide a service built around the person's journey and is it a consumer-centred service?
Let's look at the rectal cancer pathway, and the multiple people and places encountered over the course of investigation, diagnosis and treatment.

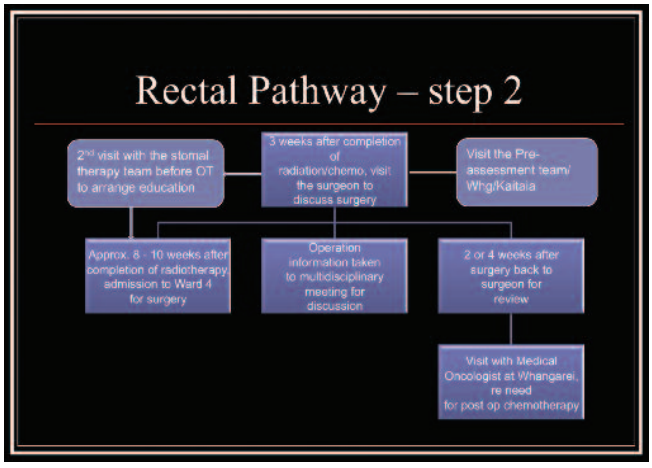
- Referral to secondary services
- Surgical clinic team
- Endoscopy team
- Colorectal team including the stoma therapy team
- Radiology team
- Northland DHB Radiation and Medical Oncology team
- Transport and accommodation team
- Auckland DHB Radiation and Medical Oncology team
- Pre-assessment team
- Surgical ward team

The diagrams overleaf demonstrate the pathways of care that each rectal cancer patient receiving neo-adjuvant radiotherapy and chemotherapy is required to progress through to ensure the best possible outcome.

Rectal Cancer Pathway – Part 1 and Part 2

Have we met the needs of the consumer? Have we directed our care at the person's journey and provided seamless care as recommended in the Standards of Service Provision and by the Health and Disability Commission? I asked Sarah, a patient with rectal cancer, about her experiences.





How do you feel you coped with this complex pathway of care?
I feel I coped well considering the side effects of treatment and the fact I was three hours from home for a period of nearly six weeks. I would like to say it was the people around me who helped me to cope – the staff in both hospitals who explained everything so clearly for me, and my family and friends who were with me all the way.

Can you take your mind back to the time when you were given the diagnosis and comment on the attitudes and support of the health professionals around you at that time?
I felt supported and respected by all the health professionals, the nurses, the doctors. I did have one area of concern though, and that was when I was at the end of my treatment and a nurse spent time with me explaining about the use of vaginal dilators and the need to continue this at home. I was totally unprepared for this as none of the written information or the verbal discussions I had had with staff had mentioned this at all. I do think a paragraph about this needs to be added to the information booklet.

Did you feel your concerns were listened to?
Generally, yes, especially when I had concerns around transport and accommodation at the treatment centre. However, I experienced terrible diarrhoea and dehydration from the treatment and needed to be admitted to the oncology ward. I tried many times to describe how ill I felt, but there seemed to be a real delay in getting a bed in hospital.

What support services were you given access to?
I was referred to the cancer liaison nurse from the Cancer Society and she visited me at home and helped me come to terms with the cancer, and she also helped me to explain the treatment to my family who live overseas.

Thinking now about your 6 weeks of combined chemotherapy and radiotherapy treatment in Auckland – how did you feel about the coordination of that part of the journey?
It was very well coordinated, with appointments and accommodation and travel.

So, would you use the word seamless?
Yes, I was informed each step of the way, and given written information to help me. When I was in the ward, I found it difficult to cope as my family really thought I was dying, and that was upsetting. At the same time my brother was admitted to the ward on the floor below, so I had extra concerns.

Talking to patients like Sarah has helped us to recognise the impact of this complex rectal cancer pathway on the person and family undertaking the journey through treatment and beyond. She shared with us her experience of a well coordinated pathway of care and her feelings of great support from the team around her. I'd like to take this opportunity to thank the team who deliver this consumer centred care to those people with colorectal cancer from Northland NZ.

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Meet the Editorial Team

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

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

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

Mr Richard Novell is Assistant Editor – Gastrointestinal Section, and is a Consultant Colorectal Surgeon at the Royal Free Hospital. He was a member of the Court of Examiners of the Royal College of Surgeons for eight years and has been an advisor to NICE, NCEPOD and CORESS, the Confidential Reporting System in Surgery.

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

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

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

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

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

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

International Liaison Committee

Mikhail Yu Reutovich, Abdominal Oncology Department, NN Alexandrov National Cancer Center of Belarus, Minsk, Belarus.

Joining the Editorial Board

Richard Novell will join the Editorial Board as the Assistant Editor for the Gastro Intestinal Cancer section. Mr Novell qualified in medicine from Cambridge University in 1981, having studied at Sidney Sussex College, Cambridge and the Middlesex Hospital. He was awarded the FRCS in 1986 and was appointed to the Royal Free Hospital, where he remained for the next eight years as Registrar, Research Fellow and Senior Registrar. He was awarded the degree of Master of Surgery from Cambridge University in 1993. The following year he was appointed as a Consultant Colorectal Surgeon at the Luton & Dunstable Hospital, where he remained for 12 years. In 2004 he was appointed Honorary Senior Lecturer at University College London Medical School, and in 2006 he moved back to the Royal Free Hospital where he practices today.

He has served on the Councils of the Association of Coloproctology and the Section of Coloproctology of the Royal Society of Medicine since 1998 and is currently President of the Section of Coloproctology. He was a member of the Court of Examiners of the Royal College of Surgeons for eight years and has been an advisor to NICE, NCEPOD and CORESS, the Confidential Reporting System in Surgery. He has published over 40 articles on surgery and is the Senior Editor of *Kirk's General Surgical Operations* (6th Edition, 2013).

Sir David Lane

Trusting in Talent

How Daniel K Ludwig's formula for success has fuelled four decades – and counting – of top-notch cancer research

By Sir David Lane, PhD, Scientific Director

Soon after the US government issued its declaration of war on cancer in 1971, Daniel K Ludwig, then among the world's wealthiest businessmen, announced he would use nearly all his international holdings to join the campaign. The same principles that had guided his successful career in commerce, he believed, could be gainfully applied to the formidable challenge of conquering cancer. "Success in any complex enterprise," he wrote, "consists in bringing the best minds to bear on each problem, in providing the best resources possible, and in putting each concept into practice whenever and wherever the opportunities are most favourable."

Mr Ludwig, who died in 1992, was on to something. Over the past 42 years, scientists affiliated with his eponymous organisation—a global network of research centers known today as Ludwig Cancer Research—have made several landmark contributions to cancer biology and therapy. This is no accident. Ludwig's model for supporting such work has, from the outset, been predicated on finding top-notch scientists and giving them the steady support they require to take risks and develop their best ideas. Mr Ludwig expected that the research network established in his name would span the globe and that its discoveries would be swiftly translated into preventive and therapeutic interventions. The Ludwig community is thus a highly collaborative global enterprise that supports basic and applied science. To convert the fruits of such research into novel diagnostics and therapies, it also maintains a team of scientists who specialise in the preclinical development of small drug molecules and a team dedicated to clinical trial management. Ludwig has, through this model, not only advanced fields to which researchers have flocked—such as cellular signaling and genomics—but kept neglected areas of research alive to potent effect.

Breaking the mould: cancer immunotherapy

Most notable in that regard is Ludwig's pioneering contribution to cancer immunotherapy, which was initially driven by the late Lloyd Old, scientific director and chairman of the Ludwig Institute for Cancer Research. Over a storied scientific career spanning five decades, Old led several studies that transformed cancer biology. His laboratory discovered the tumour necrosis factor (TNF [1]), and he was among the researchers who isolated [2] and extensively characterized p53, a tumour suppressor that is mutated in half of all cancers. But, perhaps most notably, Old came to be recognised as the founding father of modern tumour immunology and immunotherapy.

In the 1960's and early 70's, most researchers believed the immune system could detect and attack tumours. But a study published in 1976 argued, convincingly, that spontaneous mammalian tumours of all types are not immunogenic—leaving the possibility of cancer immunotherapy in doubt for many years. Old, however, continued to conduct research that would ultimately shore up the theoretical foundations of the strategy: the immune surveillance hypothesis, which holds that the immune system routinely detects and suppresses incipient cancers, and that such selective pressure fuels the evolution of tumours.

At the same time, a team of scientists led by Thierry Boon at Ludwig Brussels pursued research that would revive the moribund field of cancer immunotherapy [3]. Over the course of some 15 years, the Brussels team—which had previously disproved the notion that tumours are non-immunogenic—painstakingly isolated the genes for antigens that made mouse tumours vulnerable to immune clearance. They used the techniques and insights developed in those studies to patiently (these were pre-genomics days) hunt down the first antigens from human tumours, the MAGE family of antigens [4]. While the vaccines based on their discovery are still being explored in large-scale trials for melanoma [5], the discovery itself rejuvenated a field that thrives today as one of the most promising new therapeutic strategies.

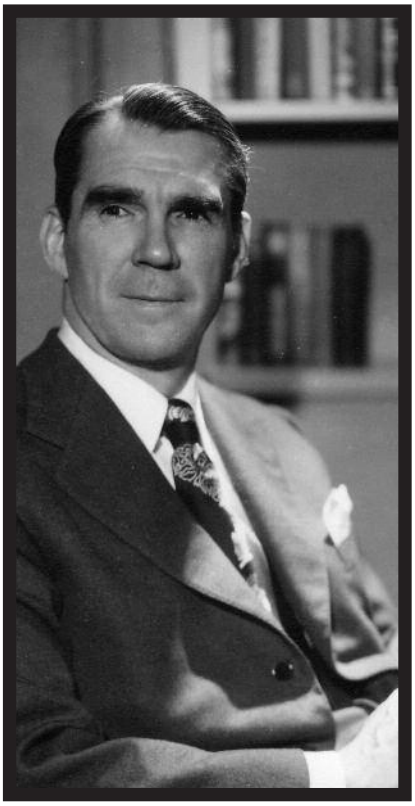
In the early 1980's, Ludwig researchers in Melbourne, Australia, contributed separately to immunotherapy through their discovery [6] of the granulocyte-monocyte colony-stimulating factor

(GM-CSF). The factor has helped many patients recover from chemotherapy and is today being fielded as a component of several experimental cancer therapies.

Building on the notion that vaccines could be devised against cancer, Ludwig scientists were conducting laboratory and epidemiological research in the 1980's on infectious agents, especially human papillomavirus (HPV), contributing to the confirmation of HPV's causative role in cervical cancer. Ludwig researchers in São Paulo subsequently ran one of the largest epidemiological studies of HPV infection, finding that persistent—though not transient—HPV infection dramatically increases cervical cancer risk. Their findings prepared the ground for the development of the HPV vaccine [7], and Ludwig researchers led the first trial that demonstrated its clinical efficacy. More recently, work by the São Paulo team helped convince the US Centers for Disease Control and Prevention to endorse the HPV vaccination of boys and young men to prevent oral, anal and other cancers.

Today, cancer immunology, including vaccine development and modulation of the anti-cancer immune response, remain hallmarks of Ludwig research. For example, Ludwig Stanford researchers in California have found that CD47, a protein overexpressed on cancer stem cells as they progress into a highly malignant state, transmits a "don't eat me" signal to macrophages [8], undermining a key element of the immune system's cancer surveillance. CD47 appears to be over-expressed in every type of cancer the researchers have so far assessed, and an antibody against the protein induces a highly effective macrophage attack on a variety of tumours in mice. A humanized version of the antibody will soon be fielded in clinical trials.

Ludwig scientists at Memorial Sloan Kettering in New York, meanwhile, are exploring a number of ways to alter the immunosuppressive tumour microenvironment and boost the activity of cytotoxic T cells. They played a leading role in the clinical development of the anti-CTLA-4 antibody ipilimumab [9], and recently pioneered its combination with an anti-PD-1 antibody named nivolumab for the treatment of advanced melanoma [10]. The impressive results from this trial were among the factors that prompted



Science to name immunotherapy the "breakthrough of the year" in 2013.

Attacking from all angles: discovery, technology, and clinical application

Cell signaling

Cancer, as we now know, is a complex disease and Ludwig has championed many other approaches to tackling the fundamental challenges of treating malignancies. Its support for basic research has provided grist for tools to prevent cancer and improve the odds of detecting it early, when it is more readily cured. Similarly, Ludwig's fundamental research into tumour biology has led to the discovery of signaling pathways required for cancer cell proliferation, which have been mined for the design and development of novel targeted therapies. Its emphasis on basic biology has likewise led to the development of drugs to sabotage the vascular and lymphatic supplies essential to tumour survival, while ongoing work on the heterogeneity and spread of malignancies is feeding strategies to specifically target cancer stem cells and block metastasis.

The organisation has, for example, participated intensively in the identification of key signaling pathways and the development of targeted therapies on the basis of these studies. Ludwig researchers in the UK discovered and extensively characterized members of the phosphatidyl inositol 3 kinase (PI3K) family of proteins and led the elucidation of their functioning in cell signaling [11] and cancer. Drugs based directly on their findings are currently being assessed in clinical trials for breast and lung cancer, and many related therapies now under development owe their existence to this body of work.

Ludwig also conducted a coordinated global program to study angiogenesis and lymphogenesis, without which solid tumours would not grow to more than a couple of millimeters in size. This project culminated in the identification of two of the four platelet-derived growth factors (PDGF), three of the four known vascular endothelial growth factors (VEGFs) and a novel VEGF-receptor (VEGFR-3), and the elucidation [12] of their functions in tumourigenesis and metastasis. These findings have inspired the design of therapies currently in development [13].

Another major triumph of Ludwig's collaborative approach in the area of signal transduction was the development of an antibody specific to the overexpressed epidermal growth factor receptor (EGFR) [14]; such overexpression occurs in many types of cancer. The antibody also binds a mutated form of the receptor (EGFRvIII) that is found exclusively on a range of cancer cells and renders them resistant to many EGFR-inhibiting therapies. In describing how this antibody binds EGFRvIII and overexpressed EGFR, Ludwig researchers discovered a major mechanism of aberrant growth factor receptor activation, opening the door to the development of a novel class of therapeutic antibodies that specifically target structurally distinct receptors. The antibody they developed is currently in clinical trials for the treatment of glioblastoma multiforme (GBM) and other cancers.

In a major therapeutic advance based on cellular signaling, Ludwig Harvard researchers have led the development of a new kinase inhibitor, regorafinib [15], to treat gastro-intestinal stromal tumours

(GIST) that have become refractory to first-line targeted therapies. Their approach has already benefited many patients, pointing to the importance of understanding how signaling networks and proteins adapt to make cancers drug-resistant.

The cancer genome

Based on the flexible and long-term support provided through Mr Ludwig's gifts to cancer research, Ludwig scientists have for decades led the investigation of changes in the cancer genome and the molecular mechanisms that drive such phenomena, including defects in mismatch repair and chromosome segregation. Recent research in the latter arena conducted at Ludwig San Diego has, for example, disproved the prevailing model for how cells determine that the separation of sister chromatids during mitosis will result in an equal number of chromosomes in their daughter cells, and shown how the process actually occurs [16].

Harnessing recent advances in large-scale DNA sequencing, scientists at Ludwig Johns Hopkins in Baltimore, Maryland, have pioneered sequencing of the complete gene repertoire and the full complement of genes expressed in a variety of devastating cancers, including those of the head, neck, colon and breast, as well as GBM [17]. Publically available data they have generated are being parsed worldwide for clues to the design of novel cancer diagnostics and therapies.

The Baltimore team is also applying its genomics expertise to develop novel diagnostics for the detection of circulating DNA from tumour cells, paving a route to the early detection and improved management of cancers [18]. They have, further, devised a "PapGene" test for the early detection of uterine and ovarian cancers using DNA collected in pap tests [19]. Ludwig Stanford too has developed a blood-based test for circulating DNA, one that they recently showed detects stage 2 and later lung cancers with high accuracy, and stage 1 lesions roughly half the time [20].

Complementing the genome sequencing studies at Johns Hopkins, other Ludwig scientists have developed technologies that are providing new insights on how regulation of the human genome drives cancer. For example, scientists at Ludwig San Diego have developed technologies now being applied to advance whole-genome analyses of great relevance to basic cancer research, drawing up genomic maps of enhancer elements and charting histone modifications and other epigenetic changes that accompany normal development and carcinogenesis [21].

Researchers at Ludwig Stockholm, meanwhile, have developed powerful new methods for massively parallel whole-genome expression analyses in single [22] cells. These technologies are advancing knowledge of the complex variety of cells within tumours and the various roles they play in sustaining malignancies. These techniques have also provided deep insight [23] into basic biological phenomena, such as the variable penetrance of both normal and pathological phenotypes.

Cancer cell biology

Today, while some Ludwig scientists focus on developing novel cancer interventions, others continue to contribute prodigiously to the basic science of cancer initiation and progression. At Ludwig MIT in Cambridge, Massachusetts, researchers are probing cancer stem cell biology [24] and developing detailed models of the molecular processes that drive metastasis [25], which accounts for more than 90% of cancer-related deaths. At Ludwig Oxford, researchers have found a set of key regulators of p53 and are unraveling the mechanisms by which they control the tumour suppressor's activity and are themselves regulated in healthy and cancerous cells.

Aside from its intrinsic value, basic research is the scientific foundation on which new therapies are constructed. It is such work that helped Ludwig researchers raise immunotherapy from its status as insignificant stepchild of clinical oncology to its brightest prospect. This would not have been possible without the confidence and long-term support Ludwig gave its researchers as they methodically laid the groundwork for immunotherapy. With the freedom to pose daring questions and fastidiously vet their hypotheses, it is likely Ludwig and its researchers will author many similar breakthroughs in the years to come. ●

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A single centre, retrospective evaluation of five-year service:
Parenteral nutrition in haematology & oncology patients

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Cancer patients experience many obstacles preventing them from maintaining an adequate nutritional intake. This includes consequences of the disease itself (e.g. bowel obstruction) and side effects from treatments (e.g. vomiting due to chemotherapy, malabsorption secondary to graft vs. host (GvHD) reaction). Weight loss and malnutrition during all stages of the cancer process can have devastating effects on the quality of life (QOL), increasing length of hospital stays and decreasing survival [1].

Some controversy has surrounded the use of parenteral nutrition (PN) in patients, especially regarding decisions of when to commence it, the associated costs, the length of time needed for set-up of home PN (HPN), and appropriate cessation in end of life care [2], which may account for its under-utilisation in the UK. Initiation of PN tends to occur when patients have already experienced significant weight loss and muscle wasting [3]; however, it is much more effective if initiated at a point when these change are detected so as to prevent or halt malnutrition.

The use of PN in oncology patients (especially in the home setting) is a developing area in the UK despite research showing that it is safe and effective when prescribed by a trained team [4] and administered by a competent person. Many countries in Europe and the US are further ahead in PN with oncology patients, accounting for a much higher proportion of their HPN, i.e. up to a third compared to only 7% in the UK [5].

Bozzetti et al. [2] found that PN in oncology patients can have a positive affect on nutritional status, aid treatment and prolong functional ability, which all contribute to an improved QOL. These are important considerations for patients undergoing treatment whether curative, palliative or end of life. Shang et al. [6] also concluded that PN can have positive effects on survival, body composition and QOL. Patients should not be denied PN due to disease [7]; it should be considered on an individual basis, taking into account benefits vs. burden.

We have undertaken an evaluation of UK dietetic service, investigating the use of PN in oncology patients, which highlighted that the perceived barriers to providing PN and HPN are unchanged and thus its use continues to be low. HPN was never or very rarely used with the length of HPN set-up ranging from 10 days to 6 weeks. Several centres were unable to provide a HPN service, which meant that patients had to be transferred to other hospitals, often taking them further away from family and support, often delaying their discharge.

A previous small service review of our patients with active solid cancer between April 2009 and March 2011 showed that their perceived barriers were mostly unfounded, and that successful and safe HPN could be achieved within 14 days. The upward trend in the use of PN on all our oncology wards over the past 5 years prompted a wider evaluation at our centre to include both solid and haematological cancers.

Methods

All adult oncology and haematology patients receiving PN between April 2009 and March 2014 were identified from PN logs. Retrospective data was collected from dietetic notes and the electronic patient data system (HISS), which included:

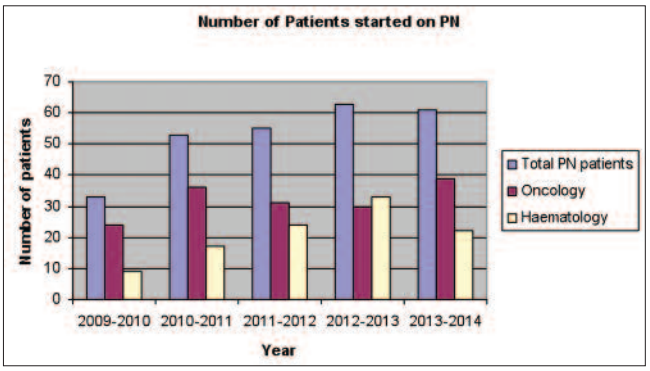
- Diagnosis and indication for PN
- Date PN started and finished (length of time on PN)
- Reason for stopping PN
- Date of decision for HPN and length from this date until discharge with HPN
- Date HPN was discontinued
- Date of death where applicable

Results

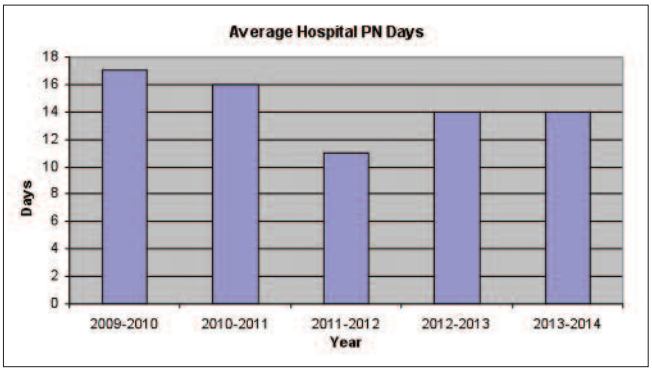
A combined total of 264 oncology and haematology patients were given parenteral nutrition during the period from April 2009 and March 2014. Females accounted for just over half the population group. Ages ranged from 16 to 91years, the average being 57.6years.

Years	2009 - 2010	2010 - 2011	2011 - 2012	2012 - 2013	2013 - 2014	2009 - 2014
Female	20 (60%)	26 (49%)	24 (44%)	39 (62%)	33 (55%)	142 (54%)
Male	13 (40%)	27 (51%)	31 (56%)	24 (38%)	27 (45%)	122 (46%)
Ave age	54.3	59.2	58.5	55.1	59.9	57.6
Youngest	18	16	18	16	22	16
Oldest	77	91	82	79	86	91

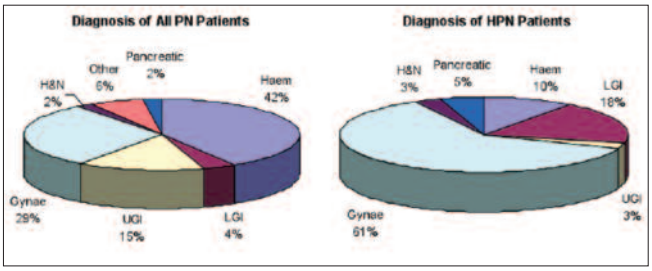
Use of PN in oncology/haematology has doubled in the past five years.



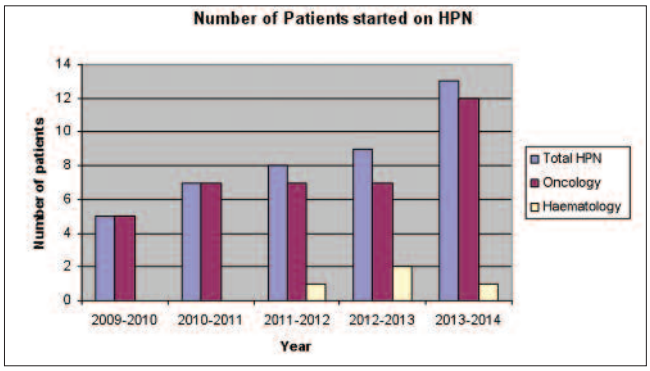
The largest increase was seen in haematology oncology, with only 9 patients receiving PN in 2009-10 rising to 33 patients in 2012-13, with total numbers involved increasing only 2 fold.
The average number of days on PN decreased from 17-14.



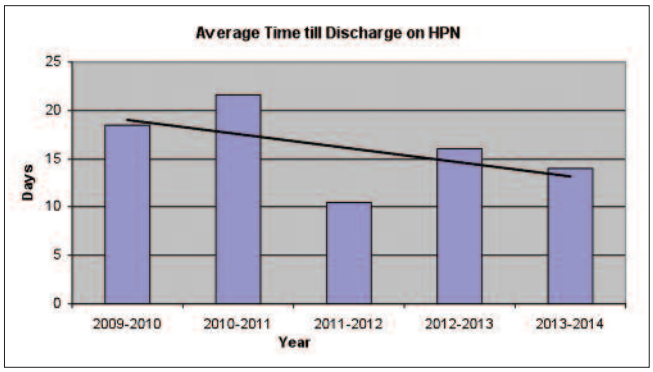
Main diagnosis for starting PN: haematology: 108 in 5 years and gynae-oncology 77 in 5 years.
Main diagnosis for HPN: gynae-oncology patients accounted for 24 out of 39 in 5 years.



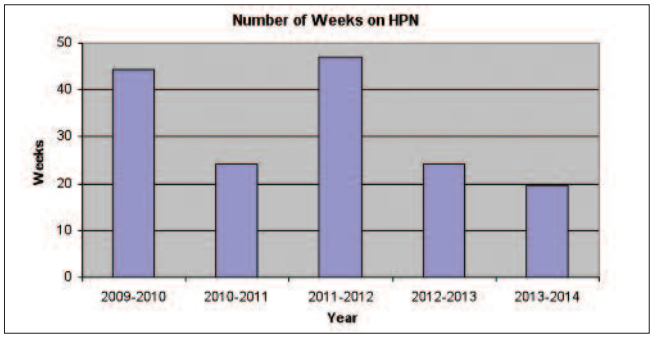
Use of HPN in the combined oncology/haematology group has more than doubled over the past 5 years (see above table) . Oncology HPN doubled from 5 to 12 patients.



There is a decreasing trend in number of days from the date HPN is approved until discharge. The shortest time to discharge with HPN was 8 days during 2011-12, with the longest being 32 days in 2010-11. Average length from HPN decision to discharge in 2013-14 was 14 days, a fall of 4.5 days from 2009-10.



Length of time on HPN – 3 days to 30 months, average time 32 weeks.



Reason for stopping PN	2009 -2010	2010 - 2011	2011 - 2012	2012 -2013	2013 - 2014	Total
Surgery / resolving Small Bowel Obstruction	1	1	0	2	1	5
Improved GvHD is above	0	0	1	1	0	2
Death	4	6	6	7	11	34
Ongoing	0	0	1	0	1	2

Discussion

An anticipated increase in overall use of PN in both the oncology and haematology cases was observed. Increased PN can be attributed to a combination of factors:

- Increased number of patients receiving treatment at our centre, e.g. haematology has increased by 36% in the past 5 years with a 52% increase in patients undergoing allogeneic transplants.
- Greater understanding of nutritional concerns in post-transplant GVHD has been a contributor to increasing numbers of haematology patients receiving PN.
- Positive outcomes from earlier patients on PN, leading to greater willingness to refer for parenteral support, e.g. inpatients with small bowel obstruction being supported on PN, allowing them to be better prepared for surgery; palliative ovarian cancer patients being supported on HPN for 2.5 years.
- Overcoming perceived barriers to PN and HPN use. A previous review showed that concerns over decision when to stop PN in palliative patients and length of time to discharge on PN were unfounded, which has led to greater acceptance of its use in palliative oncology patients.
- Greater involvement of the dietitians to assess and offer appropriate nutritional advice, encouraging suitable referrals.

Irrespective of increasing numbers, the average days on PN has decreased from 17 to 14, which may be due to earlier initiation of enteral nutrition. Patients with complex nutritional issues are able to be discussed at a weekly feeding issues multi-disciplinary team meeting which allows experts to examine the case, initiate plans and expedite placement of enteral feeding tubes.

We feel that the increasing experience of our teams has resulted in greater awareness of those patients who will benefit most from HPN, which has helped lead to their numbers doubling during the review period. Additional contributing factors to the increase may be greater acceptance of HPN in the palliative setting and a better understanding of it use by oncology teams.

Length till discharge on HPN had previously been identified as a barrier to its use; however, this and previous reviews have shown it can be achievable in 14 days from the date HPN is approved (even as short as 8 days in some cases). When examining reasons for delays in discharge, these were not due to problems surrounding HPN, but to unsuccessful treatment plans, changes in the clinical circumstances and/or insufficient care plans being in place for discharge.

As expected in an oncology setting, the main reason for stopping HPN was due to end of life care and death (80%), with only a small portion of patients being able to return to oral/enteral nutrition due to resolving obstructions or improving GvHD. Length of time on HPN decreased over the last 5 years from 11 months in 2009-10 to 5 months in 2013-14, suggesting patients are closer to the death when accepted for HPN. Although one patient only benefited from a few days of HPN, the majority of patients have been supported for several months at home (average of 8 months), thus prolonging expected life. QOL has not been assessed, and therefore comments on improvement are only through anecdotal evidence and the assumption that increased time spent at home is advantageous during the last stages of life. Perceived benefits of HPN could be decreased with frequent readmissions; however, our nutrition team works closely with home-care companies to minimise PN complications. Over the review period only 2 HPN patients had to be admitted with line infections.

Concerns raised by medical teams over difficulties surrounding the decision of when to stop HPN proved unsubstantiated. The decision in the majority of cases has been led by patients' wishes in conjunction with their families, GPs and the palliative care team. In our experience, ceasing HPN at the end of life has been uneventful, usually occurring within a few days before death.

Conclusion

An increasing trend in the use of PN and HPN in oncology and haematology patients has been possible through effective team work, overcoming barriers, observing benefits and increasing awareness. Communication between numerous teams is essential for effective and efficient nutrition support, with the benefits to the patient being at the forefront of decision making. While we know HPN discharges can be effectively managed in 14 days, some patients experience delay due to miscommunication between teams and delays in treatments. There is potential to improve decision-making and streamline our processes, with the development of clear guidelines and protocols that help to ensure all patients receive safe and efficient discharge, allowing them more time spent at home. ●

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ACKNOWLEDGEMENTS

Thanks to Tracy Papworth and Helen Lawrence for their help.

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

SIOG 2014 Conference

Date: 23-25 October 2014. Venue: Lisbon, Portugal. **Preview**

The International Society of Geriatric Oncology is proud to invite you to its annual meeting in Lisbon, Portugal from October 23-25, 2014.

The mission of the SIOG conference is to bring together international experts in geriatric oncology to present the latest evidence based research in the care of older adults with cancer.

The worldwide population is aging, and cancer is a disease of aging. Thus, there is an anticipated rise in the number of older adults with cancer. In order to provide high-quality, evidence-based care for this growing group of individuals, it is essential to meld the principles of Geriatrics and Oncology. This year, SIOG celebrates its mission by bringing together multidisciplinary experts in cancer and aging via its annual conference theme, "Bringing Two Worlds Together: Oncology and Geriatrics."

This meeting will bridge the gap of best practices between geriatrics and oncology featuring multidisciplinary sessions on hard tumours, haem malignancies, new therapies, geriatric assessment, supportive care needs and an educational forum dedicated to nurses. This year, our Partnership Session will promote the new SIOG collaboration with the European Geriatric Medicine Society (EUGMS) involved in the planning of this conference and in the development of other educational on-going projects. A Young SIOG Mentorship session dedicated to younger participants will be articulated around the following questions: how to start a research in GO; how to apply to fellowship programmes and how to submit papers for publications...

Special sessions dedicated to the Young Investigators and to the Nursing & Allied Health Professionals for the selection of the related awards will also be organised.

The sessions will address updated Geriatric Oncology issues around the following tracks:
Track 1: Solid Tumours in the Elderly
Track 2: Haem Malignancies in the Elderly
Track 3: New Therapies and Basic Science
Track 4: Nursing, Supportive Care and Geriatric Assessment
Track 5: Advocacy and Socio-Economical Issues
There is no doubt that your active participation, support, enthusiasm and your willingness to share your best and newest research results with the participants will make this 14th event a memorable meeting.

Lisbon is a very exciting city, combining a rich history with a modern and dynamic life. This Lisbon is in fact the image of Portugal, a small country but where many discoveries can happen. Scientific activity and health care after the revolution of April 1974 have gained an important role in society.

Further information on the SIOG 14th Annual Conference is available on www.siog.org

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

2014

July

International Conference on Teenage and Young Adult Cancer
7-8 July 2014; London, UK
Sarah Wallace
T; +44 (0)20 7612 0709 or
E: sarah.wallace@teenagecancertrust.org

BNOS
9-11 July 2014; Liverpool, UK
W: www.bnos.org.uk

2014 Joint Annual Scientific Meeting of the British Gynecological Cancer Society and the NCRI
10-11 July 2014; London; UK
W: http://bgcsconference.com

5th IFHNOS World Congress
26-29 July 2014; New York, USA
W: www.ifhnos2014.org

August

6th Latin American Conference on Lung Cancer
21–23 August 2014; Lima, Peru
W: www.lalca2014.org

September

2nd International Medical Student Cancer Conference
6-7 September 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events,
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

NEW ENTRY
RCR Annual Scientific Meeting 2014
8-10 September 2014; London, UK
W: www.rcr.ac.uk

NEW ENTRY
1st National Cancer Pain Update
12 September 2014; London, UK
W: www.mahealthcareevents.co.uk

Endometrial Cancer Conference
12 September 2014; London, UK
W: www.royalmarsden,nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

ASTRO's 56th Annual Meeting
14-17 September 2014;
San Francisco, USA
W: www.astro.org

3rd Annual Cancer Vaccines Conference
15-16 September 2014; London, UK
E: events@smi-online.co.uk

Advanced Clinical Practice Cardiovascular Masterclass
16 September 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

VIII Congress of Oncologists and Radiologist from the ex-USSR countries
16-18 September 2014; Kazan, Republic of Tatarstan, Russia
W: www.kazan2014.com

Still Confused about Feeding Tubes?
18 September 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

Targeted Treatments of the Digestive System
22 September 2014; London, UK
W: www.royalmarsden.nhs.uk

TYA/Paediatric Study Day
23 September 2014; London, UK
W: www.royalmarsden.nhs.uk

Upper GI Study Day
25 September 2014; London, UK
W: www.royalmarsden,nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

ISSC - Sexual Consequences of Cancer Treatment
26-27 September 2014; London, UK
W: www.royalmarsden.nhs.uk

NEW ENTRY
14th National Conference of FHNO (Foundation for Head and Neck Oncology)
26-28 Sep 2014; Chandigarh, India
W: www.fhno2014.com

39th ESMO Congress
26-30 September 2014, Madrid, Spain
W: www.esmo.org/events/madrid-2014-esmo-congress.html
E: congress@esmo.org
T: +41 (0)91 973 19 26

Teenagers and Young Adults with Cancer 10th Anniversary Conference: Working Together
30 September 2014; Leicester, UK
W: www.tyac.org.uk
E: info@tyac.org.uk

October

NEW ENTRY
7th Annual ERUOHNC
1-3 October 2014; Poznan, Poland
E: ehnc@wco.pl

NEW ENTRY
Head and Neck Cancer Dysphagia Workshop
3 October 2014;
Amsterdam, The Netherlands
W: www.dysphagiarehab.com

7th Annual EUROHNC
1-3 October 2014; Poznan, Poland
T: +48 61 88 50 929
E: ehnc@wco.pl

Neuro-Oncology Conference
2 October 2014; London, UK
W: www.royalmarsden.nhs.uk/neuroconference

Targeted Treatments for Haematological Cancers
2 October 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

7th Annual Royal Marsden Breast Cancer Meeting: Hot Topics in Breast Cancer
3 October 2014; London, UK
W: www.royalmarsden.nhs.uk/breastmeeting

Anaesthesia for Major Surgery Conference
7 October 2014; London, UK
W: www.royalmarsden.nhs.uk/anaesthesia

Lymphoma Study Day
7 October 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

Manchester Melanoma Surgical Meeting
9 October 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

11th Meeting of the European Association of NeuroOncology
9-11 October 2014; Turin, Italy
W: www.eano.eu

Bladder and Testicular Cancer Conference
10 October 2014; London, UK
W: www.royalmarsden.nhs.uk

ORBS Technical Meeting 2014
10-11 October 2014; Nottingham, UK
W: www.orbsmeetings.com
E: admin@orbsmeetings.com

Royal Brompton Chest Radiography Study Day
11 October 2014; London, UK
W: www.royalmarsden.nhs.uk

NEW ENTRY
Clinical trials workshop
14 October 2014; London, UK
W: www.rcr.ac.uk/oncologyevents
E: conf@rcr.ac.uk

Royal Marsden Palliative Care Update
15 October 2014; London, UK
W: www.royalmarsden.nhs.uk

Anaesthesia for Major Surgery: What's New
16-17 October 2014; London, UK
W: www.royalmarsden,nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

NEW ENTRY
Lymphoma Masterclass for nurse specialists
17 October 2014, London, UK
E: h.mee@lymphomas.org.uk or
W: www.lymphomas.org.uk

Haematology Nursing: Acute Lymphoblastic Leukaemia
20 October 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

Oral Care Conference 2014
22 October 2014; Hertfordshire, UK
W: www.OralCare.org.uk
T: +44 (0)1438 840135

NEW ENTRY
International Society of Geriatric Oncology (SIOG)
23-25 October 2014; Lisbon, Portugal
W: www.siog.org

November

NCRI Cancer Conference
2-5 November 2014; Liverpool, UK
W: conference.ncri.org.uk

Gynaecological Cancers Study Day
5 November 2014; London, UK
W: www.royalmarsden.nhs.uk

Psychotherapeutic Issues in Cancer Care
6 November 2014; London, UK
W: www.royalmarsden.nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

7th Royal Marsden Pain and Opioid Conference
7 November 2014; London, UK
W: www.royalmarsden.nhs.uk/painconference

9th International Head & Neck Cancer Quality of Life Conference
13-14 November 2014; Liverpool, UK
Christopher Evans
E: christopher.evans@aintree.nhs.uk
T: +44(0)151 529 6342

6th Annual Royal Marsden Head and Neck Conference
14 November 2014; London, UK
W: www.royalmarsden.nhs.uk/headneckconference

NEW ENTRY
The Møller Centre, Cambridge
17-19 November 2014; Cambridge, UK
W: www.rcr.ac.uk/oncologyevents
E: conf@rcr.ac.uk

Gynaecology: Ovarian Cancer
17 November 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

Molecular Pathology & Targeted Treatments: Non-Small Cell Lung Cancer
18 November 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44 (0)161 446 3773 or
E: education.events@christie.nhs.uk

NEW ENTRY
myRhinoplasty - Aesthetics meets Reconstruction
19-21 November 2014; London, UK
Aesculap Academia
T: +44 (0)114 2259057
F: +44 (0)114 2259119
E: academia.bbmuk@bbraun.com

Skin Cancer Conference: a GP Focus
21 November 2014; London, UK
W: www.royalmarsden,nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

Haematology Management Study Day
24 November 2014; London, UK
W: www.royalmarsden.nhs.uk

NEW ENTRY
Management for Oncologists
24-26 November 2014; London, UK
W: www.rcr.ac.uk/oncologyevents
E: conf@rcr.ac.uk

Palliative Care: Management of Breakthrough Cancer Pain
26 November 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

Supporting Workers with Cancer Study Day
27-28 November 2014; London, UK
W: www.royalmarsden.nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

December

Molecular Mechanisms of Targeted Cancer Treatments
2 December 2014; London, UK
W: www.royalmarsden.nhs.uk

Advances in the Nutritional Care of Cancer Patients
9 December 2014; London, UK
W: www.royalmarsden,nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

Biology of Cancer & Targareted Treatments for Solid Tumours
10-11 December 2014; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44(0)161 446 3773 or
E: education.events@christie.nhs.uk

2015

January

National Head & Neck Study Day
19 January 2015; London, UK
W: www.royalmarsden.nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

13th Annual BTOG Conference 2015
28-30 January 2015; Dublin, Ireland
BTOG
T: +44 (0)116 250 2811
F: 44 (0)116 250 2810
E: dawn.mckinley@uhl-tr.nhs.uk
W: www.btog.org

February

EUROGIN 2015 International Multidisciplinary Congress
4-7 February 2015; Seville, Spain
E: admin@eurogin.com
W: www.eurogin.com/2015

Breast cancer meeting
10 February 2015; London, UK
W: www.rcr.ac.uk/oncologyevents
E: conf@rcr.ac.uk

5th ICHNO
12-14 February 2015; Nice, France
W: www.estro.org

ISSC – Sexual Consequences of Cancer Treatment
27-28 February 2015; London, UK
W: www.royalmarsden,nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

March

Cancer Care in China
9-23 March 2015
W: www.jonbainestours.co.uk

Paediatric Palliative Care Study Day
10 March 2015; London, UK
W: www.royalmarsden.nhs.uk
E: conferencecentre@rmh.nhs.uk
T: +44 (0)20 7808 2921

Organised by

BJN British Journal of Nursing | International Journal of Palliative Nursing | UKONS Oncology Nursing Society

National Cancer Pain Update

Multidisciplinary Care for Cancer Pain in 2014

Royal College of General Practitioners
London, 12th September 2014

Highlights will include:

- Chemotherapy-induced painful neuropathy Dr Paul Farquhar-Smith
- Psychological approaches to cancer pain management Emma Elliott
- Is the WHO pain ladder still relevant? Dr Andrew Davies
- Breakthrough cancer pain Dr John Zeppetella
- Overview and epidemiology of cancer pain Jo Thompson
- Barriers to pain control Wendy Oldenmenger

To book your place:
Call us on +44(0)20 7501 6786
www.cancerpainupdate.co.uk

RCR The Royal College of Radiologists

RCR asm 2014

ANNUAL SCIENTIFIC MEETING 2014

Tuesday 9 September 2014, The Barbican, London

Building on the success of last year's event the Annual Scientific Meeting will feature an oncology lecture stream entitled **Chemoradiation: Current strategies and future directions** The day includes a variety of sessions, a keynote lecture, learning and research presentations, a panel debate, cancer staging workshops, an industry exhibition and the College AGM.

Topics include chemoradiotherapy for the treatment of lung cancer; overcoming radioresistance with targeted agents and hypoxia modification and radiotherapy which will be delivered by high-profile speakers from across the UK.

This year's cancer staging workshop topics are head and neck; prostrate MR; Breast MRI and lymphoma. There will also be a workshop on brain tumour diagnostics.

Delegates can keep up to date with the programme and access learning points and references through the conference app. www.rcrasm2014.com.

Attendance at the meeting will earn delegates 5 RCR CPD credits.

For details of the full three day programme, venue, and accommodation and to book a place, please visit:

www.rcr.ac.uk/asm

10th NCRI Cancer Conference

2014

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

Earlybird rates end 31 July 2014

31 July
Earlybird registration deadline

1 - 25 August
Late breaking abstract submission

Join us at the 10th NCRI Cancer Conference

The largest cancer research meeting in the UK

Hear from over 150 experts on topics including:

- Drug discovery
- Imaging
- Immunotherapies
- Localised therapies
- Molecular pathology
- Primary care
- Prevention
- Radiation therapy
- Targeted therapies

View the full programme and register at conference.ncri.org.uk

Celebrating the 10th NCRI Cancer Conference

BTOG 2015

13th Annual BTOG Conference 2015

Wednesday 28th - Friday 30th January 2015 – Dublin

IMPORTANT DATES

Poster submission opens	1st August 2014
Poster submission deadline	1st October 2014
(please note this date will not be extended)	
Registration and hotel booking opens	1st September 2014

The conference updates all attendees on state of the art management of lung cancer and mesothelioma, increases understanding on the nature of clinical practice and research and seeks to develop new national and international clinical research studies.

BTOG is a multi-disciplinary group for professionals involved with thoracic malignancies.

BTOG aims to improve the care of patients with thoracic malignancies through multidisciplinary education, developing and advising on guidelines for patient care and facilitating and nurturing clinical trial ideas into full protocols. Chair: Dr Sanjay Popat

BTOG Secretariat

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BTOG 2015 Information is available on the website:

www.BTOG.org

New England Journal of Medicine

Final Trial Report of Sentinel-Node Biopsy versus Nodal Observation in Melanoma

Donald Morton, John Thompson, Alistair Cochran, et al. for the MSLT Group. New England Journal of Medicine; 370:599-609; February 13, 2014.

Background: Sentinel-node biopsy (SNB), a minimally invasive procedure for regional melanoma staging, was evaluated in a phase 3 trial. **Methods:** We evaluated outcomes in 2001 patients with primary cutaneous melanomas randomly assigned to undergo wide excision and nodal observation, with lymphadenectomy for nodal relapse (observation group), or wide excision and SNB, with immediate lymphadenectomy for nodal metastases detected on biopsy (biopsy group). **Results:** No significant treatment-related difference in the 10-year melanoma-specific survival rate was seen in the overall study population (20.8% with and 79.2% without nodal metastases). Mean10-year disease-free survival rates were significantly improved in the biopsy group, as compared with the observation group among patients with intermediate-thickness melanomas, defined as 1.20 to 3.50 mm (71.3±1.8% vs. 64.7±2.3%; hazard ratio for recurrence or metastasis, 0.76; P=0.01), and those with thick melanomas, defined as >3.50 mm (50.7±4.0% vs. 40.5±4.7%; hazard ratio, 0.70; P=0.03). For patients with intermediate-thickness melanomas, the 10-year melanoma-specific survival rate was 62.1±4.8% for those with metastasis versus 85.1±1.5% for those without metastasis (hazard ratio for death from melanoma, 3.09; P<0.001). For patients with thick melanomas, the respective rates were 48.0±7.0% and 64.6±4.9% (hazard ratio, 1.75; P=0.03). Biopsy-based management improved the 10-year rate of distant disease-free survival (hazard ratio for distant metastasis, 0.62; P=0.02) and the 10-year rate of melanoma-specific survival (hazard ratio for death from melanoma, 0.56; P=0.006) for patients with intermediate-thickness melanomas and nodal metastases. Accelerated failure-time latent-subgroup analysis was used to account for the nodal status was initially found only in the biopsy group, and significant treatment benefit persisted. **Conclusions:** Biopsy-based staging of intermediate-thickness or thick primary melanomas provides important prognostic information and identifies patients with nodal metastases, who may benefit from immediate complete lymphadenectomy. Biopsy-based management prolongs disease-free survival for all patients and prolongs distant disease-free survival and melanoma-specific survival for patients with nodal metastases from intermediate-thickness melanomas.

Reviewer's opinion: Thickness of the malignant melanoma lesion has been used as a guide in its primary surgical management for over 3 decades. Patients with intermediate-thickness lesions have a higher risk of anatomical lymphatic drainage area nodal metastases. In contrast, low-thickness (<1 mm) lesions are rarely associated with nodal metastases and thick lesions (>4.0 mm) invariably have synchronous, occult distal metastases. Therefore, theoretically patients with both low-thickness or thick lesions would not benefit from early lymphadenopathy – the former group because of the low incidence of regional nodal metastases and the latter group because of the high risk of synchronous occult distant metastases. This hypothesis has been the scientific basis for the use of sentinel lymph node biopsy and early therapeutic lymphadenectomy in intermediate-thickness group leading to substantial improvement in 10 year disease-free survival.

The final results of the Multi-Center Selective Lymphadenopathy Trial (MSLT-1) comparing SLN biopsy with a watch-and-wait approach (only removing nodes once palpable) in melanoma corroborate the profound prognostic significance of micro-metastasis detection by SNB in intermediate-thickness (20%) as well as 290 patients with thick lesions (40%) defined in this study as >3.5 mm. The 10 year DFS was clearly better for the intermediate rather than delayed lymphadenectomy group of patients with intermediate-thickness as well as thick lesions. However, there were no significant treatment-related differences in the 10-year melanoma-specific survival advantage for patients with intermediate-thickness or thick melanoma groups.

These long-term follow-up results from a randomised international clinical trial provide strong evidence to support the use of SNB in patients with intermediate-thickness or thick primary melanoma. The 10-year follow-up results of this trial led by the SNB pioneer, the late Donald Morton, should put the controversy surrounding the role of SNB and early lymphadenectomy to rest. Clearly, the patients should be informed about the advantage of PFS from this approach which, unfortunately, does not translate into significant gain in overall survival (81.4% vs 78.3%; P = 0.18). The accompanying editorial supports the practice of SNB in lesions ≥ 1.2 mm, but lack of any long-term survival gain and extra cost will provide legitimate ammunition to its critics. No doubt the procedure provides accurate and important staging information. – SU

Bevacizumab plus Radiotherapy–Temozolomide for Newly Diagnosed Glioblastoma

Chinot O L, Wick W; et al. New England Journal of Medicine; 370; 709-722: Feb 20, 2014.

Background: Standard therapy for newly diagnosed glioblastoma is radiotherapy plus temozolomide. In this phase 3 study, we assessed the effect of the addition of bevacizumab to radiotherapy–temozolomide for the treatment of newly diagnosed glioblastoma. **Methods:** We randomly assigned patients with supratentorial glioblastoma to receive intravenous bevacizumab or placebo, plus radiotherapy and oral temozolomide for 6 weeks. After a 28-day treatment break, maintenance bevacizumab or placebo, plus temozolomide was continued for 6 4-week cycles, followed by bevacizumab monotherapy or placebo until the disease progressed or unacceptable toxic effects developed. The co-primary end-points were investigator-assessed PFS and overall survival. **Results:** A total of 458 patients were assigned to the bevacizumab group and 463 patients to the placebo group. The median PFS was longer in the bevacizumab group than in the placebo group (10.6 months vs. 6.2 months; HR 0.64; P<0.001). The benefit with respect to PFS was observed across subgroups. Overall survival did not differ significantly between groups (HR 0.88; P = 0.10). The respective overall survival rates with bevacizumab and placebo were 72.4% and 66.3% at 1 year (P = 0.049) and

33.9% and 30.1% at 2 years (P = 0.24). Baseline health-related quality of life and performance status were maintained longer in the bevacizumab group, and the glucocorticoid requirement was lower. More patients in the bevacizumab group than in the placebo group had grade 3 or higher adverse events (66.8% vs. 51.3%) and grade 3 or higher adverse events often associated with bevacizumab (32.5% vs. 15.8%). **Conclusions:** The addition of bevacizumab to radiotherapy–temozolomide did not improve survival in patients with glioblastoma. Improved PFS, maintenance of baseline quality of life and performance status were observed with bevacizumab. However, the rate of adverse events was higher with bevacizumab than with placebo.

Reviewer's opinion: The presence of extensive (florid) angiogenesis is considered to be responsible for aggressive behaviour and poor prognosis of glioblastoma. Adjuvant post-operative chemo-radiotherapy has brought limited success with an average survival of 15 months. Use of anti-angiogenetic agent, like bevacizumab, is a natural instinct. Several phase 2 trials showed dramatic and encouraging response leading to its approval in the management of relapsed cases. These unprecedented results led to the use of bevacizumab in 2 randomised placebo controlled phase 3 trials (RTOG 0825 and AVAglio) on its use in primary adjuvant settings and the results of these trials have been simultaneously published as above. Looking at the results published by the 2 groups, one cannot fail to notice many similarities, such as trial design, patient characteristics, and primary and secondary end-points. Both trials have reported similar PFS of 3-4 months, which was their primary end-point. However, neither group of investigators reported any survival advantage with the addition of bevacizumab. This could be due to crossover to bevacizumab after relapse, although other (unknown) factors may be important in this outcome.

Although the PFS is a standard measure of efficacy, clinical benefit measured by quality of life, symptom control, performance status and neurocognitive function are important criteria in justifying the use of an additional therapy. The results of these trials clearly diverge in their contrasting observations. It is difficult to attribute these differences to the different methods of data collection and analysis. The extent of surgical resection, quality of supportive care and genetic make-up may have been important and influenced the final outcome. Review of the data by independent investigators may resolve the true benefit from the primary use of bevacizumab on quality of life seen in the AVAglio trial. Identification of a biological marker predictive of a response to bevacizumab, robust imaging, better patient selection and availability of newer molecular agents needs to be tested in future trials for any significant impact on the treatment outcome in this difficult tumour. – SU

Ceritinib in ALK-Rearranged Non–Small-Cell Lung Cancer

Alice T. Shaw, Dong-Wan Kim, Ranee Mehra et al; New England Journal of Medicine; 370:1189-97 March 27, 2014

Background: Non–small-cell lung cancer (NSCLC) harbouring the anaplastic lymphoma kinase gene (ALK) rearrangement is sensitive to the ALK inhibitor crizotinib, but resistance invariably develops. Ceritinib (LDK378) is a new ALK inhibitor that has shown greater antitumor potency than crizotinib in preclinical studies. **Methods:** In this phase 1 study, we administered oral ceritinib in doses of 50 to 750 mg once daily to patients with advanced cancers harbouring genetic alterations in ALK. In an expansion phase of the study, patients received the maximum tolerated dose. Patients were assessed to determine the safety, pharmacokinetic properties, and antitumor activity of ceritinib. Tumours were biopsied before ceritinib treatment to identify resistance mutations in ALK in a group of patients with NSCLC who had had disease progression during treatment with crizotinib. **Results:** A total of 59 patients were enrolled in the dose-escalation phase. The maximum tolerated dose of ceritinib was 750 mg once daily; dose-limiting toxic events included diarrhea, vomiting, dehydration, elevated aminotransferase levels and hypophosphatemia. This phase was followed by an expansion phase in which an additional 71 patients were treated for a total of 130 patients. Of the114 patients with NSCLC who received at least 400 mg ceritinib per day, the overall response rate was 58% (95% confidence interval [CI], 48 to 67). Of the 80 patients previously receiving crizotinib, the response rate was 56% (95% CI, 45 to 67). Responses occurred in patients with various resistance mutations in ALK and some without detectable mutations. Of the patients with NSCLC who received at least 400 mg of ceritinib per day, the median progression-free survival was 7.0 months (95% CI, 5.6 to 9.5). **Conclusions:** Ceritinib was highly active in patients with advanced ALK-rearranged NSCLC, including those who had had disease progression during crizotinib treatment, regardless of the presence of resistance mutations in ALK.

Reviewer's opinion: The management of NSCLC has been rapidly changing over the last decade. Thanks to the better understanding of their molecular profile, underlying molecular mechanisms of tumour progression and successful targeting of the driver mutations due to availability of new targeted agents, their management outcome has also changed for the better. After EGFR mutation, ALK translocation/rearrangement is the other driver that has been successfully targeted. Crizotinib, a multi-targeted tyrosine kinase inhibitor of c-Met, ALK and ROS1, has recently been made available through national CDF to patients in the UK. This has resulted in routine testing of the tumour tissue for selection of the ALK translocation harbouring tumours and treatment with crizotinib. Although the clinical responses have been dramatic and high, it is almost always short-lived (median PFS 8-10 months). The Achilles heel of such cancer is the development of acquired resistance. It could be due to ALK amplification, development of ALK mutation or bypass tracks and/or other unknown resistance mechanisms. Moreover, at first progression, many cells remain oncogene addicted. New second generation ALK inhibitors (Ceritinib, AP26113, Alectinib) are already undergoing clinical trial and the above phase 1 trial results on ceritinib is encouraging, being several times more potent than crizotinib. Higher levels of the drug in the plasma may inhibit the oncogenic activity, along with blockage of the gatekeeper mutation gene L1196M due to its unique chemical structure in these individuals. Early evidence of activity in the CNS sanctuary site is good news for patients. Sequencing of the available agents, optimum dose and strategies to overcome resistance to 2nd generation agents remains an important challenge. These results need to be duplicated in the ongoing phase 3 expanded access program before routine use of this agent can be established in the management of ALK positive tumours. – SU

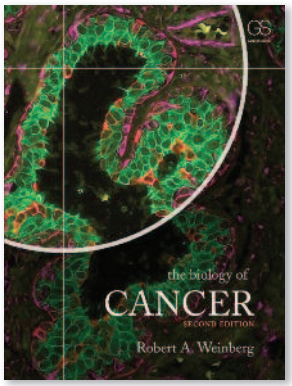
New Journal Reviewers

Ankit Rao MRCP PhD is a Clinical Lecturer in Oncology at the University of Birmingham and Honorary Specialty Registrar in Medical Oncology at University Hospital Coventry and Warwickshire NHS Trust. He qualified from Birmingham University and has done clinical training in the West Midlands, Hertfordshire and North London. His main interests include translational research in particular tumour immunology and immunotherapy related to melanoma, renal cell carcinoma and non-small cell lung cancer and Epstein-Barr virus associated malignancies. He is also interested in medical education and writes MRCP(UK) written examination questions. He has contributed towards a chapter entitled 'Dendritic cell vaccination' in the textbook 'Gene Therapy of Cancer'. He aims to always put the patient at the centre of their care. Ankit will review the *Journal of Clinical Oncology* for *Oncology News*.

Xinchao Pan, PhD is currently a Postdoctoral researcher in the Department of Internal Medicine (Nephrology) and Molecular Biology at the UT Southwestern Medical Center. She did research work to study the signaling mechanism of cell apoptosis and metastasis in mouse hepatocytes during my undergraduate training. Dr Pan started to investigate the cellular and molecular mechanisms of kidney development, polycystic kidney disease and kidney cancer from 2010 in UT Southwestern Medical Center. Her additional research interests include other urogenital cancers. She got postdoctoral fellowship award from the National Kidney Foundation from July 2011 to Jun 2013. Xinchao will review the journals *Cancer* (Wiley-Blackwell) and *Cancer Cytopathology* (Wiley-Blackwell).

The Biology of Cancer 2nd Edition

Author: Robert Allan Weinberg. ISBN: 978-0-8153-4219-9 (hardback); ISBN: 978-0-8153-4220-5 (paper back). Publishers: Garland Science, Taylor & Francis Group. Price: £57.00.



Cancer is a constantly evolving field of medical science. Desire to understand the behaviour of the tumour and overcome the disease, the biology of cancer research has grown at a tremendous pace. The scientific literature has progressed to the understanding of molecular and cellular mechanism of the development and spread of cancer. The modern technology of genetic profiling has revolutionalised the field and has advanced to a stage where sequencing of the entire tumour cell genomes within days has become a practical reality. For practicing physicians, recent advances have opened new horizons in cancer management Therefore, the understanding of the molecular complexities of malignancy has become even more essential with the possibility of personalised medicine on the horizon. Cell signaling technology has led to the possibility of multiple key signaling pathways thought to be responsible for carcinogenesis, identification of genetic alterations and development of even larger number of anti-signaling molecular agents.

The book is organised into 16 structured chapters, with significant change of the contents compared to the previous edition. The initial chapters successfully lay the foundation of the current molecular science and establish the background concepts of the subject in a clear logistic fashion. The principles of cancer biology are presented in an organised, clear and detailed manner. Numerous schematic drawings and clear coloured pictures in every chapter greatly help to understand the complex subject and theoretic logics behind the novel concepts. To develop additional interests and develop wider discussions among the readers, "sidebars and supplementary sidebars" have been provided frequently along with thought questions and suggested additional readings. The list of abbreviations, glossary and the index provided are clear and accurate. The DVD-ROM provided with the book includes the book's art program, a selection of movies with narration, audio files of mini-lectures by the author, supplementary sidebars and a Media guide. Clearly, not only it is an authoritative text book on the complex biology of cancer, it serves an invaluable reference document for individuals working in biomedical laboratories as well as professionals involved in day to day management of cancer in the clinics.

Dr Sunil Upadhyay, Consultant Oncologist, Castle Hill Hospital, Hull, UK.

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

SonoSite's NanoMaxx® helps enhance palliative care

Woking and Sam Beare Hospices in Surrey have recently invested in a SonoSite NanoMaxx® point-of-care ultrasound system, enhancing palliative care services for its patients. Dr Fiona Bailey, medical director and consultant in palliative medicine, explained: "We have used ultrasound for a number of years and find it very beneficial, particularly for abdominal investigations. Diagnosis is easier, and it enables us to perform treatments such as the insertion of an ascitic drain in a safe and efficient manner."

"We purchased the NanoMaxx a few months ago to replace an older instrument. Its touch screen operation and pre-programmed settings make the system very user friendly, and the image quality is a big improvement on our previous instrument. As a hospice, our role is to treat patients wherever they are. Many of our patients are quite frail, and the NanoMaxx's small size, portability and robustness are a particular benefit. Although the system is kept on a stand in the hospice, it is easily detached and transported if we need to use it at another site."

For more information contact:
FUJIFILM SonoSite, Ltd T +44 (0)1462 444 800,
E :ukresponse@sonosite.com
W: www.sonosite.com

Provectus Biopharmaceuticals to discuss outline of Phase 3 Clinical Trial of PV-10 to treat melanoma on conference call

Provectus Biopharmaceuticals, Inc have announced that it held a conference call on Thursday, June 19, 2014, at 4pm Eastern Daylight Time.

Management discussed the outline of the Company's proposed Phase 3 study of PV-10 in the treatment of melanoma, developments in the use of PV-10 in other cancer indications, as well as PH-10 and news regarding its use. A digital replay is available by telephone until August 19, 2014, and may be accessed by dialing 877-660-6853 from the US or 201-612-7415 for International callers, and using the Conference ID#13584727. Management also discussed its potential plans to monetize its PV-10 and PH-10 assets with various contemplated license and co-development transactions.

For additional information about Provectus Biopharmaceuticals please visit: www.pvct.com

Innovative medical app set to deliver quicker cancer care across Merseyside and Cheshire

The Clatterbridge Cancer Centre is leading the way as the first NHS Trust in the UK to launch ONCOassist, a new mobile app for medical professionals, which will centralise all information around cancer care. The user-friendly technology will assist with faster diagnosis and help to deliver even more precise treatments for patients.

The app is only the third worldwide to get CE approval – the safety gold standard for medical apps – and will provide a one-stop solution for cancer care at the touch of a button. Cancer specialists will have immediate access to relevant information for all cancers, including managing the side-effects of existing treatments and advice on new drugs – something which has never before been accessible from one digital location.

Jo Upton, Skin Cancer Advanced Nurse Practitioner at The Clatterbridge Cancer Centre, who has been involved in the development of this new technology, commented: "We constantly need to be looking at new ways of providing patients with the highest quality of care as smoothly and promptly as possible, keeping waiting times to an absolute minimum. The app will offer rapid and convenient access to treatment protocols, which is essential for the safe delivery of cancer treatments."

For further information Email: Isobel.Pritchard@finncomms.com

Provectus Biopharmaceuticals Inc appoints Brendan O'Brien to strategic advisory board

Provectus Biopharmaceuticals, Inc recently announced that it has appointed Brendan O'Brien to its strategic advisory board. Brendan O'Brien, age 48, is currently VP of Strategic Planning & Analysis for North American Pharmaceuticals at Sanofi. In this role, he is responsible for business planning and strategy development; he leads both the three-year strategic planning and one-year operating planning processes for Sanofi US, the North American affiliate of Sanofi SA.

Brendan started his career in healthcare, working for ten years in sales, marketing and planning for managed care organisations in the Pacific Northwest. In 1998, he moved on to work in pharmaceuticals at Smithkline Beecham Pharmaceuticals in London, UK where he directed development of strategic plans for 14 European markets. From there, Mr O'Brien went to Pfizer spending the next 13 years in roles with increasing levels of management responsibility in many European countries, including managing director/general manager of Pfizer's country organizations in both Slovakia and Romania.

Mr O'Brien received his B.A. degree cum laude from Bowdoin College in Brunswick, ME, and he holds a Master's degree in Business Administrationfrom London Business School in London, UK.

For further information contact:
W: www.pvct.com

Varian Medical Systems Scores Highly on 2014 Newsweek Green Rankings

Varian Medical Systems, a world leader in radiotherapy systems and software, has been rated among the greenest companies in the United States by the influential Newsweek Green Rankings for 2014.

"We're proud to be recognised for our commitment to sustainability and this will spur us on to continually improve our efforts," says Dow Wilson, 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 which benefit the communities in which we operate."

Newsweek evaluated up to 800 of the

largest publicly-traded companies by market capitalization, in the U.S. and globally. The rankings measure sustainability performance in energy, carbon, water, and waste, as well as a new criterion measuring 'reputation'. Ranked #51 on the US list, Varian was one of just a few companies rated 100 percent in the reputation category.

Varian operates globally but has significant United States production facilities in Palo Alto, CA, Las Vegas, NV, and Salt Lake City, UT. Varian makes a yearly submission to the Carbon Disclosure project and publishes an annual Sustainability Report measuring its performance against defined goals.

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

Provectus Biopharmaceuticals Inc is listed on NYSE MKT

Provectus Biopharmaceuticals, Inc have announced that its shares of common stock have been listed on the NYSE MKT. Shares began trading on the NYSE MKT on Friday May 16, 2014. The company's ticker symbol will remain "PVCT" but it will withdraw its shares from quotation on the OTCQB concurrent with listing its shares on the NYSE MKT.

Dr Craig Dees, PhD, CEO of Provectus Biopharmaceuticals, Inc said, "Listing on the NYSE MKT is a huge milestone for Provectus Biopharmaceuticals, and I take a great deal of personal satisfaction from this news. I believe that this will enhance our shareholder value as well as broaden our shareholder base and heighten our corporate profile in the capital markets."

NYSE MKT is a fully integrated trading venue within the NYSE Euronext community and leverages the NYSE's advanced and innovative market model to offer a premier venue for listing and trading the stocks of small companies. The venue utilises the trading, connectivity and routing technologies of the NYSE platform and offers superior price discovery, superior liquidity and reduced trading volatility. Listed companies benefit from issuer-selected Designated Market Makers (DMM) that utilize world-class NYSE trading systems to discover and improve prices, dampen volatility, add liquidity and enhance value. In addition, NYSE MKT-listed companies gain access to the brand visibility and are eligible for the issuer services enjoyed by the NYSE Euronext community.

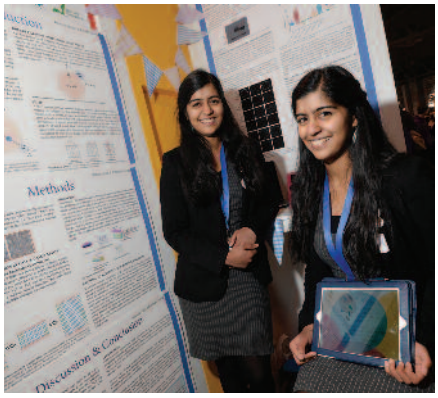
For further information contact:
W: www.pvct.com

PROVECTUS BIOPHARMACEUTICALS, INC.

Britain's brightest young scientists to take part in RSM medical innovations summit

Some of the UK's brightest young scientists took part in the Royal Society of Medicine's Medical Innovations Summit on Saturday 5 July. Eighteen-year old twin sisters Ameeta and Aneeta Kumar, winners of the UK Young Scientist of the Year competition, described their project to develop a diagnostic tool for identifying cancerous tumours at an early stage of development. Beating off competition from 4,000 other entries, the pair are now both considering a career in medicine.

Also in her teens, Amber McCleary explained how the anti-bacterial and healing properties of the copper-infused pyjamas she and inventor Paula Ward produced last year quite possibly saved the life of a new mother who had acquired MRSA from a caesarean section wound. Amber presented at the summit with consultant obstetrician and gynaecologist Mr Abdul Sultan who is leading a trial of the effectiveness of copper at Croydon University Hospital.



In all 12 innovations were presented at the event. For more information about the entrepreneurs and innovators presenting at the RSM's Medical Innovations Summit visit:

http://www.rsm-medicalinnovations.com/summer-summit.aspx

Plotsker brings Pharma, breast cancer expertise to Provectus Biopharmaceuticals

Provectus Biopharmaceuticals, Inc has appointed Jacob M Plotsker to its strategic advisory board. Mr Plotsker, age 46, is currently Director of IUS Strategy and Lifecycle Management at Bayer Healthcare. Jacob started his career as a staff accountant at Deloitte & Touche.

Mr Plotsker currently serves on the board of directors of Emisphere Technologies, a publicly traded drug delivery technology company. From 2008 to 2014, he served on the board of directors of Sharsheret, a national 501(c)(3) not-for-profit organisation providing support and resources to young women living with breast cancer. He served as President of Sharsheret from 2009-2012.

Mr Plotsker said, "I am excited at becoming a member of the Provectus Strategic Advisory Board. The Company is at a very important juncture in its development. PV-10's pending application for breakthrough therapy designation is an important milestone for the product and the Company. As the Company continues to advance the development of PV-10, the preparation for commercialization will take on an increasingly important role. I look forward to leveraging my experience to benefit patients in need of new therapies and contributing to Provectus' future success."

For information please visit: www.pvct.com

PV-10 Data Presented at the ASCO Annual Meeting Defines Path Forward for Provectus Biopharmaceuticals, Inc.

Provectus Biopharmaceuticals, Inc. announced recently that data on its investigational agent PV-10 for intralesional (IL) treatment of solid tumors were featured in two presentations in the Poster Highlights Session, Melanoma/Skin Cancers, on June 2, 2014 during the American Society of Clinical Oncology (ASCO) annual meeting in Chicago, IL.

The first highlighted abstract, presented by Sanjiv S. Agarwala, MD, of the St. Luke's Cancer Center, Bethlehem, PA, entitled "Efficacy of intralesional rose bengal in patients receiving injection in all existing melanoma in phase II study PV-10-MM-02" (abstract 9027), may be viewed at: http://abstracts.asco.org/144/AbstView_144_132320.html.

The second highlighted abstract, presented by Amod A. Sarnaik, MD, of Moffitt Cancer Center, Tampa, FL, entitled "Assessment of immune and clinical efficacy after intralesional PV-10 in injected and uninjected metastatic melanoma lesions" (abstract 9028), may be viewed at: http://abstracts.asco.org/144/AbstView_144_132288.html.

Eric Wachter, Ph.D., Chief Technology Officer of Provectus, observed that these results delineate two development paths to generate data sufficient for a new drug application (NDA) for PV-10 in melanoma.

Dr. Wachter concluded, "Our focus this year will be initiation of the phase 3 randomized controlled trial. We also expect to begin the more exploratory combinatorial work that potentially addresses the needs of patients with more advanced metastatic disease."

For further information contact:
W: www.pvct.com

New brain tumour research presented to MP's

On July 1st the national charity Brain Tumour Research bought together leading research scientists in the field alongside patients and their families, to meet MP David Willetts, Minister of State for Universities and Science at the House of Commons. The Minister was asked for clarification around funding flows and the need for a complete register of research taking place in the UK.

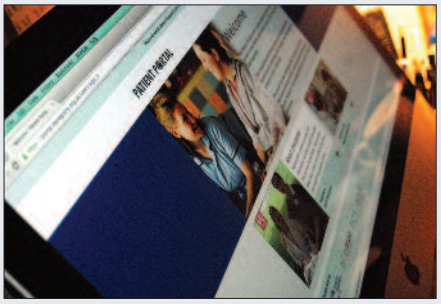
Also presented to MP's was an update to the groundbreaking National Research Funding report, issued by the charity in July last year, presenting new stark facts about the impact of the disease.

Startlingly, one in 50 people who die under the age of 60 years are dying from brain cancer. Just as shockingly, 71% of those who die of a brain tumour will be under 75 years old, compared to 47% for all cancers.

Sue Farrington Smith, Chief Executive of Brain Tumour Research, said: "We know funding into brain tumours needs to increase to around £30-35million a year over a ten-year time frame. At the current rate of spend, it could take 100 years to find a cure!"

For further information visit:
www.braintumourresearch.org

Cancer Patient Portal expands to new Centres



After promising patient uptake during an initial pilot at four hospitals, brainstrust, the National Cancer Registration Service (NCRS) and Cancer Research UK (CRUK) are expanding a new information service (the Patient Portal) to other centres.

The organisations believe online access to Registry held information will help patients become more involved in their care, find it easier to search for information about their condition and have better conversations with their clinical teams and carers about their condition.

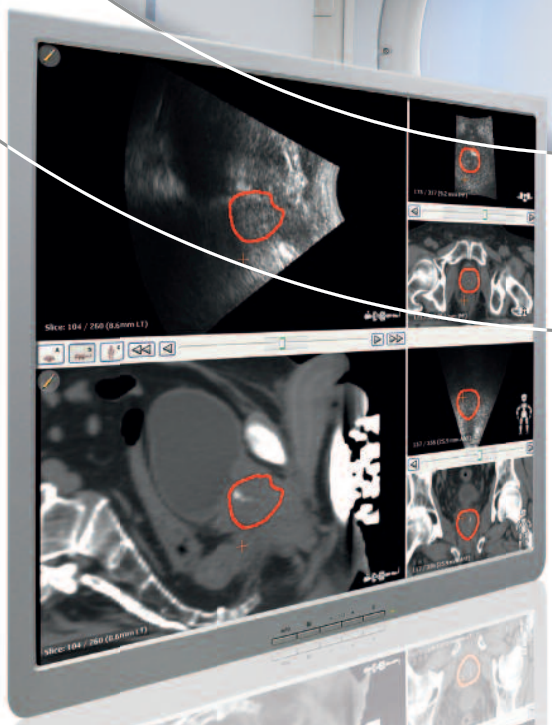
Michael Chapman, Project Director at CRUK says "We have shown that brain tumour patients can access their cancer registry records securely, online at four large hospitals, and the patient uptake rate is promising. We're now looking to increase the number of users to allow us to better evaluate demand and understand whether this approach can be implemented across a wider patient base. As such we are seeking enquiries from hospitals who, like us, believe that access to personal information can drive engagement and understanding."

Taking part involves:

- Offering the portal to patients either in clinic or by post.
- Maintaining a log of numbers of patients approached.
- Confirming the identity of patients who request access to records and activating their account.
- Providing feedback on implementation to inform evaluation..

If you or colleagues would like more information about participating please contact Julie Temple: Julie.Temple@cancer.org.uk.

The Patient Portal is available at www.myregistry.nhs.uk



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