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Special NCRI Issue

In this Issue

ARE YOU MAKING THE MOST OF US?

You know and trust Macmillan Cancer Support for excellent palliative care. But did you know that most of the people we help today don't need palliative care? And that we offer many other kinds of free support that you may be interested in for your patients?

Before, during and after cancer

Today, people are coming to us for support before, during and, increasingly, after cancer.

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Mary, living with cancer

Conference Digest

Reports from the European Society for Medical Oncology (ESMO) Congress 2012

Date: 28 September – 2 October 2012 Venue: Vienna, Austria.

International survey shows cancer patients will delay treatment to benefit from biomarker-led treatment

Prof Tejpar

Almost three-quarters of patients with metastatic colorectal cancer (mCRC) would be willing to delay starting treatment for two weeks or more in order to undergoing biomarker testing to benefit from targeted effective therapy, revealed an international survey reported at ESMO 2012.

The survey interviewed 811 patients diagnosed with different types of cancer in the last five years using telephone-based questionnaires. The patients included 164 with late-stage breast cancer, 157 with stage III/IV non-small cell lung cancer and 490 with metastatic colorectal cancer from Argentina, China, France, Germany, Italy, Spain and the UK.

Results revealed that 73% of the mCRC patients would be willing to delay starting treatment by two weeks or more in order to be prescribed treatment that is targeted and effective. Two weeks is the average turnaround time for KRAS testing results to be reported, which guides decisions on treatment with KRAS inhibitors. Nearly one-third of patients (31%) said they would be prepared to wait 'as long as it takes' to benefit from personalised therapy. And 73% would be willing to undergo a re-biopsy if necessary.

"KRAS testing and other biomarker tests can be beneficial in the management of patients, and it would be useful to have these tests conducted as early as possible," said lead author Professor Sabine Tejpar (University Hospital Gasthuisberg, Leuven, Belgium).

Further results showed that 66% of the whole group of cancer patients surveyed would be willing to delay treatment if this helped to select the most effective drug. More than two-thirds (69%) would be willing to undergo additional tumour biopsies and 91% would allow hospitals to retain their tumour samples for future research.

"It was really striking participants were willing to allow hospitals to retain their tumor samples even if this didn't directly relate to their own treatment. It shows they want to advance research and help others with the disease," said Professor Tejpar.

But results revealed a need for raising awareness about personalised medicine. Almost one-third (32%) of patients surveyed were unaware that tests are available for certain cancers to determine the best treatment for different individuals. Breast cancer patients were the most well informed about testing, with 62% thinking testing might be possible, compared with 52% with colorectal cancer and 48% with non-small cell lung cancer. ■

Susan Mayor PhD, Medical Journalist.

Crizotinib improves outcomes in ALK-positive lung cancer

The tyrosine kinase inhibitor crizotinib nearly doubles progression-free survival in patients with advanced ALK-positive lung cancer compared to standard chemotherapy, according to a phase III study.

The global study randomised 347 patients with ALK-positive lung cancer already treated with chemotherapy to crizotinib or standard single-agent chemotherapy with pemetrexed or docetaxel. Results showed that crizotinib prolonged progression-free survival to a median of 7.7 months compared to 3.0 months with chemotherapy (hazard ratio 0.49; $p < 0.0001$). The overall response rate was also significantly higher with crizotinib (65% vs 20%; $p < 0.0001$).

"This study is the first head-to-head comparison of crizotinib with standard chemotherapy in this patient group," said Dr Alice Shaw (Massachusetts General Hospital Cancer Center in Boston, USA), reporting the findings. She added: "These results establish crizotinib as the standard of care for patients with advanced, previously treated, ALK-positive lung cancer."

The study is not yet mature enough to assess impact on overall survival. However, many patients randomised to chemotherapy crossed over to crizotinib, which will make it difficult to assess the effect on overall survival. Side-effects were more frequent with crizotinib, but Dr Shaw said that, despite this, patients on the targeted therapy reported improved quality of life.

The independent discussant, Dr Enriqueta Felip (Vall d'Hebron University Hospital in Barcelona, Spain), said the results are of great clinical relevance. "Crizotinib, an oral drug, is more effective than standard chemotherapy in previously treated lung cancer patients with a specific molecular alteration, ALK. After the worldwide implementation of targeted therapy in lung cancer patients defined by another molecular alteration - EGFR mutation, this is the second group of lung cancer patients to clearly benefit from a therapy directly targeting a molecular alteration. The results of this study represent a significant step towards individualised therapy in lung cancer patients." ■

Susan Mayor PhD, Medical Journalist.

New studies confirm one-year treatment with trastuzumab in breast cancer

Prof Pivot

Giving combination chemotherapy after standard radiation therapy delays tumour growth and extends survival in patients with anaplastic oligodendroglial tumours, according to results from a phase III study from the European Organisation for Research and Treatment of Cancer (EORTC).

Two studies confirmed that the optimal duration of treatment with trastuzumab (Herceptin) is one year in women with HER-2 positive early breast cancer.

Latest results from the HERA trial, led by the Breast International Group (BIG) since 2001, showed that one year of treatment with trastuzumab is as effective as two years of treatment. After finishing primary therapy with surgery, chemotherapy and radiotherapy, women with early HER-2 positive breast cancer were randomised to trastuzumab every three weeks for one year, two years, or observation. The hazard

ratio for disease relapse for women in the two-year treatment arm versus the one-year arm was 0.99. The overall survival rate in the two groups was similar (HR 1.05; p = 0.6333).

"The key message is that one year of treatment with trastuzumab remains the standard of care for HER-2 positive early breast cancer patients," said Professor Richard Gelber (Dana-Farber Cancer Institute, Boston, USA). The benefit in disease-free survival and overall survival in women treated with one year of trastuzumab compared to those given no trastuzumab that had been reported previously remained stable after a median of eight years' follow-up.

A second study carried out by the French National Cancer Institute compared six months with 12 months of trastuzumab therapy in women with HER-positive early breast cancer. "The trial results were inconclusive for the non-inferiority hypothesis," said Professor Xavier Pivot (Université de Franche Comté, France). But he said there was a trend in favour of 12 months treatment for the overall population. ■

Susan Mayor PhD, Medical Journalist

PV-10 delivers benefits in cutaneous melanoma

Injecting cutaneous lesions in stage III-IV melanoma patients with PV-10 (Rose Bengal) delivered sustained high response rates, reported an open label phase 2 study. The results, presented at the ESMO meeting, confirm the robust response that can be achieved with PV-10 first seen in a preliminary report in 20 patients presented in 2010.

The use in melanoma of Rose Bengal, an agent used to stain necrotic tissue in the cornea, was discovered by Provectus Pharmaceuticals Inc (Knoxville, Tennessee, USA) while exploring formulations for use in photodynamic cancer therapy. The company discovered that PV-10, a formulation developed for administration directly into solid tumours, destroyed tumours without needing light activation.

After intralesional injection, PV-10 accumulates selectively in the lysosomes of cancer cells eliciting autolysis. "PV-10 also appears to produce a bystander effect where it triggers an immune response causing spontaneous regression of nearby melanoma tumours that haven't been injected," said study presenter Dr Sanjiv Agarwala, from St Luke's Hospital, Bethlehem, Pennsylvania.

In open label single arm trial, which took place at seven centres in Australia and the USA, 80 patients with stage III-IV melanoma received up to four courses of PV-10 injected in up to 20 cutaneous or subcutaneous lesions on the extremities and, or torso. For each patient a bystander lesion was identified that underwent biopsy to confirm melanoma, but did not receive treatment.

Results showed that an objective response rate (OR) was achieved in 51% of subjects' targets lesions (25% complete response and 26% partial response). Furthermore, disease control (combined Complete, Partial and Stable Response) was achieved in 69% of lesions. Additionally, when bystander lesions were monitored, 33 % of subjects received an OR in bystander lesions, while 50% achieved disease control in these lesions. Injection site pain, edema and injection site vesicles were the most common reported side effects.

The abstract also intriguingly included MRI scans of two patients treated with PV-10 showing regression of lung metastasis. "It was an interesting observation but we will need a randomized study to demonstrate the effect," commented Dr Agarwala.

The findings are guiding a planned Phase 3 trial of PV-10 which will include around 180 subjects with Stage IIIB-IIIC disease. ■

Janet Fricker, Medical Journalist.

International Collaborations: an essential and noble manner to advance scientific research to the bedside (bench to bedside)

Guest Edited by
Dr Helen L Fillmore, PhD
Cellular & Molecular Neuro-oncology,
School of Pharmacy & Biomedical Sciences,
University of Portsmouth
Portsmouth, UK.

Clinicians and scientists in the neuro-oncology field seldom have the opportunity to celebrate discoveries which bring about cures for patients with brain tumours, even less in the case of high grade gliomas or other aggressive brain tumours. However, in the case of the most common childhood brain tumour, medulloblastoma, perhaps it is time to consider a small celebration with hopes that bigger celebrations are near. Medulloblastomas are still the most common malignant paediatric brain tumour and although many are 'cured' this comes at a high cost with survivors suffering with low quality of life issues due to the aggressive nature of the treatment. The issue has been that this type of tumour is complex (like many others) and currently patients with good prognosis are grouped together with those with poor outcomes receiving the same aggressive treatment. This has been based on diagnostic histopathological classification of biopsy material. Although this information is critical in the design of treatment, it does not include the molecular components that might better define the precise nature of medulloblastoma.

Based on the impressive scientific strides with regard to the molecular understanding of medulloblastoma (as discussed in this issue), there is great hope that when this information is incorporated into the day to day clinical, diagnostic and stratification setting, children with this type of brain tumour will receive more 'personalised' therapy based upon the molecular signature of the tumour. Please see the Donovan article (p148) in this issue to understand our excitement about the potential to reduce toxicity and to focus on and develop specific targeted therapies for the most aggressive subtype of medulloblastoma.

There is great hope that clinicians involved in the diagnosis, treatment and care of children with brain tumours will integrate the molecular analysis into their clinical practices. There is no question that there is much to be done and challenges remain. However there is another reason to celebrate. This scientific achievement is a direct result of an international and multidisciplinary effort. The co-ordinated effort for international leaders in this field to come together to provide a current consensuses is extremely impressive [1,2]. Scientists working on the molecular profiling of patient material recognised the tremendous work done with preclinical models and the scientists working on preclinical models have incorporated the genomic information from patient tissue. Understanding childhood brain tumours, especially medulloblastoma, will continue to improve and, at a fast pace. I am certain that those that are leading the way will continue to push the field forward aggressively. For the moment, however, this type of collaboration is worth celebrating.

At this time, thanks to the incredible co-ordinated effort by many, we now know that it is possible to improve the stratification in patients in order to reduce toxicity to those who have good prognosis and to begin to develop novel specific targeted therapies for those with a poor prognosis. Although many challenges remain and there is much more work to be done, especially in terms of the least understood and most aggressive medulloblastoma subtypes, we celebrate those in this field who have provided the rest of us with an example of how an international effort can lead to enormous gains in the knowledge of a particular tumour. Well-done! ■

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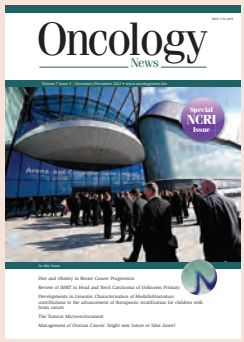

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Diet and Obesity in Breast Cancer Progression

Naomi Johnson,
MSc in Public Health Nutrition at the University of Westminster.
For her dissertation, Naomi accessed data from the DietCompLyf Study.

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The prevalence of obesity in the UK trebled between 1980 and 2002 [1] and although the rate of this incline is slowing, prevalence continues to rise (see Figure 1) [2]. The 2011 Health Survey for England (HSE) reports that in 2009 almost a quarter of adults (22% men, 24% women ages 16 or over) were classified as obese (BMI ≥30kg/m^2) and a further 44% of men and 33% of women were overweight (BMI 25-30kg/m^2) [3].

Pathophysiology of lymphoedema

The influence of poor dietary and lifestyle choices on these statistics is well recognised, yet public health guidance aiming to tackle the situation is not yet impacting on population statistics sufficiently, therefore incidence of chronic diseases typically associated with overweight and obesity have not declined. Specific to breast cancer, several authors [e.g., 4,5] emphasise the risks associated with overweight and obesity on development of breast cancer in post-menopausal women. In the Pooling Project of Diet and Cancer, a significant protective effect was observed in pre-menopausal women; however, this was driven by effects observed in women with high BMI levels (BMI ≥31kg/m^2) and as these individuals represent only 4% (n = 30) of the available sample, this association cannot be considered conclusive [6]. Obesity is implicated in a detrimental way in all women when prognosis following diagnosed breast cancer is considered. Protani and colleagues (2010) reported in their systematic review that women who gain weight or are overweight after diagnosis have an increased risk of recurrence and mortality compared to their lighter-weight counterparts, an observation also reported elsewhere and illustrated in Figure 2 [7-9].

Greater understanding is therefore required to understand how weight gain – seen typically in response to treatment of breast cancer – can be minimised to reduce associated risks on long-term survival and recurrence.

The DietCompLyf Study has been designed to answer questions like these. Run by the Against Breast Cancer Research Unit at the University of Westminster (and supported by the NCRN), DietCompLyf was designed to investigate the role of diet, lifestyle factors and use of complementary therapies in breast cancer survival. Just under 3,400 female patients recruited from 56 NHS hospitals across the UK are contributing detailed information over a five-year period. Data collected includes information on diet (assessed annually using food frequency questionnaires, and twice – years two and four – using seven day food diaries), lifestyle choices and clinical information relating to diagnosis and treatment, as well as annual blood and urine samples. Papers illustrating the complexity of this project design are in preparation for publication. For more details, see: http://www.westminster.ac.uk/research/a-z/against-breast-cancer.

The richness of data collected in the DietCompLyf Study (and its precision following repeated and detailed quality control procedures) has enabled exploration of the influence of treatment on women's weight following primary breast cancer diagnosis. At this time, all women participating in the study have completed at least two years of data collection. These details are used here to gain a firmer understanding of the frequency and magnitude of weight changes experienced by UK women diagnosed with grade I-III invasive primary breast cancer, and also to explore the demographic of women identified as being more vulnerable to weight changes.

Analyses presented here were conducted using data collected from 3270 women, with an average age of 54 (26-76) years. Weight changes are

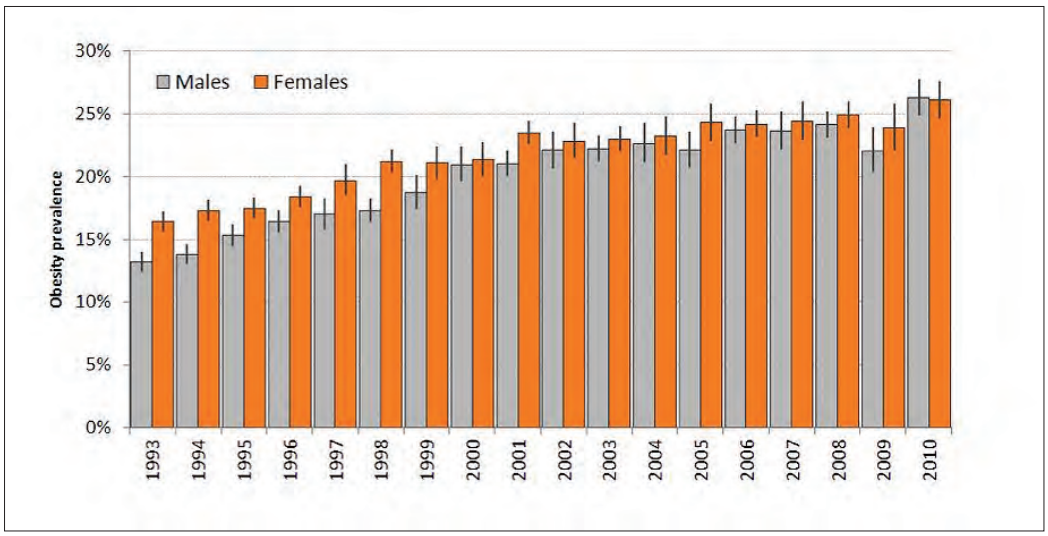

Figure 1. Trends in adult (ages 16 years and over) obesity (BMI ≥ 30 kg/m2) prevalence in the Health Survey for England

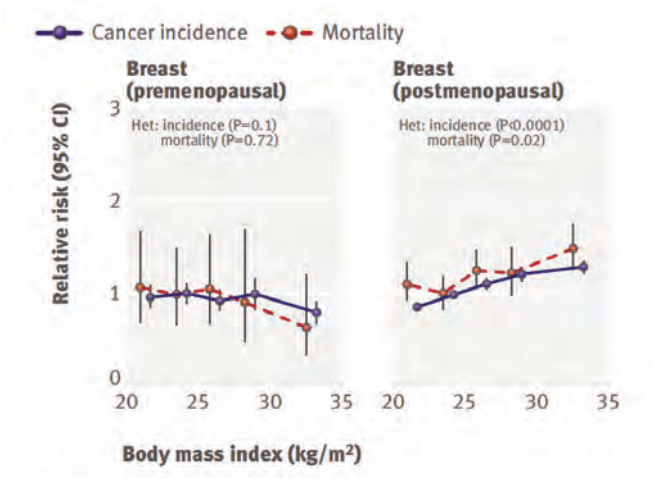

Figure 2. Breast cancer incidence and mortality according to body mass index. Data from the Million Women Study (Reeves et al., 2007) [9]

summarised using comparisons of information recorded on medical notes at diagnosis and weight measured at year one (i.e. recruitment onto DietCompLyf, a date 9-15 months since diagnosis and following completion of all – except continued hormonal - treatment) and at year two of follow-up. Weight information was collected from medical records at diagnosis, measured at recruitment, and self-reported at year two. Details including the patient's cancer treatment (adjuvant chemotherapy, hormonal therapy and radiotherapy) age at diagnosis, menopausal status, tumour stage and ethnicity are summarised to describe differences between those women who gained weight, and those who did not. Although information on physical activity and dietary changes implemented post-diagnosis were collected, neither were utilised in these initial, exploratory analyses. Comparisons between groups were conducted using independent sample t-tests (gender), linear regression (age and BMI), one-way analysis of variance (ANOVA: menopausal status, tumour stage, ethnicity) and univariate analysis of variance (associations between weight change and those variables which were found to be significantly related to weight change in the tests mentioned above) were performed using the statistical software SPSS (Statistical Package for the Social Sciences) version 19.0. All tests were performed using a significance level of $p \leq 0.05$.

Results – summarised in table 1 – highlight that women in the DietCompLyf Study tend to experience weight gain following breast cancer diagnosis. Independent associations were found for weight gain (one year from base-line) and chemotherapy ($p = 0.011$). Despite the expectation that hormonal treatment may induce early menopause as a consequence of its use in treatment, and therefore that the use of this therapy might be associated with subsequent weight gain, no associations were identified here (baseline to year one $p = 0.404$, baseline to year two $p = 0.106$). The average weight increase observed in the first year was 1.72kg, a figure acknowledged to be considerably higher than gains typically observed by adults [10]. Linear regression analyses demonstrated an increase in percentage weight change with decreasing age at both year one and year two ($p \leq 0.001$). Associations between weight gain and menopausal status and with tumour grade were also found. However, after adjustment for age (which remained an independent significant variable for weight changes at both time points analysed) these associations were no longer significant. Percentage weight changes were considerably higher in the first year (2.73%) compared to the second (from baseline, average elevation of 0.54%) post diagnosis, suggesting that this may be a more vulnerable stage within the treatment process.

The effects of treatment on weight changes following breast cancer diagnosis have long been acknowledged [11], yet because survival statistics have improved alongside incidence rates, the implications of this knowledge have not yet been fully explored. As a side-effect of cancer treatment, weight gain has more relevance than its acknowledged relationship with poor self-image and quality of life, psychological and social burdens or reduced mobility in post-treatment breast cancer patients [12]. Evidence in fact suggests that a 13% increase in breast cancer specific mortality ($p = 0.01$) and a 12% increase in all cause mortality ($p = 0.004$) is associated with every 5kg gained post diagnosis ($p = 0.01$) [13]. Weight gains between 2.5 to 6.2kg have been reported following treatment for breast cancer, with significant weight gain occurring in as many as 50-96% of patients during treatment [14, 15]. Modification of these gains is required to slow mortality rates.

Some studies suggest that the degree of weight gain varies dependent on the type of treatment used [16]. Weight gain is a commonly reported side-effect of chemotherapy, and yet no clear association is apparent on the impact of hormonal therapy or radiotherapy on weight (associations confirmed here). Various theories exist to explain this. Hyperphagia is thought to occur in an attempt to diminish nausea brought on by chemotherapy as well as depression, or as a result of increased appetite due to steroid use [17]. Weight gain has also been attributed to psychosocial problems linked with diagnosis and treatment, rather than the chemotherapy treatment itself [18]. Fatigue is also a commonly reported side-effect, and through links with reduced energy expenditure and resultant increases in body fat, has been associated with diabetes, cardiovascular disease and poorer prognosis in breast cancer cases [19, 20]. Chemotherapy induced weight gain has also been shown to be indicative of sarcopenic obesity [21]. While therapies used are effective in cancer control, their longer-term consequences may require careful consideration.

Adiposity is a behaviourally modifiable risk factor. Understanding what may lead to weight changes/ gain would enable increased awareness of who is vulnerable and of how such changes can be prevented. Our primary analysis of DietCompLyf data (data not presented) confirms reports elsewhere that certain sub-groups of

Table 1. Diversity of treatment methods used by women in the total DietCompLyf sample (n=3236) (data presented as counts, frequencies)

Characteristic		Frequency (n)	Percentage (%)	Most common types	Frequency (n)	Percentage (%)
	No	464	14.2			
Hormonal treatment	Yes	2772	84.8	Tamoxifen	1846	56.5
				Arimidex	579	17.7
				Herceptin	166	5.1
				Femara/ Letrozole	97	3.0
Adjuvant chemotherapy	No	1628	49.8			
	Yes	1613	49.3			
Post-operative radiotherapy	No	523	16			
	Yes	2742	83.9	*Treatment details for some participants missing from original data.		

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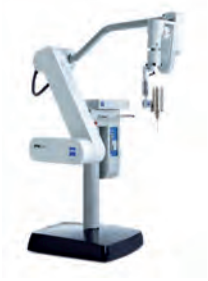

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Table 2. The relationship between menopausal status, tumour grade and percentage weight change from diagnosis to 1 and 2 years after breast cancer diagnosis

Post diagnosis (years)	Characteristic		N	Mean	Std. Deviation	95% confidence interval lower	upper	F	p value
1	Menopausal status	Pre-	586	3.59	7.08	3.02	4.17	15.22	0.000
		Peri-	456	3.57	6.75	2.95	4.19		
		Post-	1979	2.19	6.42	1.91	2.47		
2		Pre-	377	1.67	8.09	0.85	2.49	19.99	0.000
		Peri-	321	2.37	9.13	1.37	3.37		
		Post-	1414	-0.24	7.32	-0.62	0.14		
1	Tumour grade	I	520	2.62	6.46	2.07	3.18	5.90	0.003
		II	1483	2.35	6.74	2.00	2.69		
		III	1197	3.24	6.77	2.85	3.62		
2		I	349	0.90	7.70	0.09	1.71	2.71	0.067
		II	1050	0.15	7.71	-0.32	0.62		
		III	776	0.95	8.14	0.37	1.52		

breast cancer patients are more susceptible to weight gain. Women with a BMI in the normal range, pre-menopausal women and those in younger age groups at diagnosis gain more weight than their comparators, and risk is increased with chemotherapeutic treatment [22, 23, 24]. The long-term effects of treatment on these groups require greater consideration to inform determination of appropriate management strategies.

It is expected that findings from the DietCompLyf Study will contribute to the existing evidence base on the role of diet, lifestyle and treatment factors on survival and recurrence outcomes in breast cancer. An aim of this study is to increase openness in paths of communication between patients, doctors and policy makers, achieved by using research findings which explore means of improving survival opportunities. Clearer nutritional and public health guidance is required to support health professionals giving advice to patients, and also to support those patients vulnerable to weight changes, especially those already vulnerable to weight issues and those most susceptible to them. This early analysis suggests that treatment choice must reflect the cancer diagnosis and vulnerability of patients to weight gain due to the established long-term effects of weight gain on clinical outcomes. If only affecting treatment by addition of dietetic support to manage expected weight gain, such an achievement could enable patients to positively influence their own prognosis.

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Review of IMRT in Head and Neck Carcinoma of Unknown Primary

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Cervical lymph node metastases comprise 2-9% of head and neck malignancies, with the main histological group being squamous cell carcinomas (SCC) from occult head and neck primary cancer [1]. One of the characteristics of head and neck SCC is that its progression tends to be loco-regional with a relatively low rate of distant metastases, and therefore the overall goal of treatment of cervical lymph node metastases is to reduce the chance of nodal relapse and prevent emergence of a primary. However, the exact treatment algorithm remains a topic of debate. The best treatment for head and neck cancers of unknown primary (HNCUP) remains uncertain due to the lack of evidence from randomised trial. Unfortunately the proposed EORTC/RTOG randomised trial addressing radiotherapy in HNCUP was closed due to poor recruitment, and therefore retrospective studies, with their limitations, are relied on to guide management.

In patients who present with cervical lymph node metastases, clinical investigation is undertaken to identify the primary site. This involves a thorough history and physical examination, examination under anaesthetic with targeted biopsy of any suspicious sites, blind biopsies of common sites, including consideration of bilateral tonsillectomy, and imaging with CT, MRI and PET scanning.[1] Options for treatment include surgical neck dissection alone, neck dissection followed by postoperative radiotherapy, or upfront radiotherapy, with or without concurrent chemotherapy. The optimal treatment must always balance the benefits against the potential toxicity of different treatment modalities. Neck dissection and RT are equally effective at treating N1 disease; however combined modality treatment should be recommended in N2 and N3 disease [1].

Radiotherapy

Radical radiotherapy aims to eradicate the maximum number of tumour cells while sparing the normal tissues in the process. Conventional radiotherapy has used rectangular or simply shaped beams to treat a wide area of tissue to a high dose, which – although successful in covering the tumour volume – led to significant toxicity due to irradiation of large volumes of normal tissue. Severe side effects limit the total dose that can be delivered, and breaks in treatment may be needed or even admission to hospital, potentially reducing the chance of effective tumour control. Approximately two-thirds of patients treated with conventional treatment will suffer acute grade 2 or worse toxicity [2], with its significant impact on quality of life. A significant numbers of patients also suffered late radiotherapy effects, such as osteoradionecrosis of the jaw, strictures, hoarse voice, mucosal damage and lymphoedema.

In contrast, conformal radiotherapy aims to reduce the dose to the normal tissues or critical structures by shaping the dose distribution. This is done by a variety of methods, from shaping beams with multi-leaf collimators to adding additional beams and altering the radiation fluence. Thus increasingly complex isodose patterns can be produced, with correspondingly increased time required for radiotherapy planning and calculation.

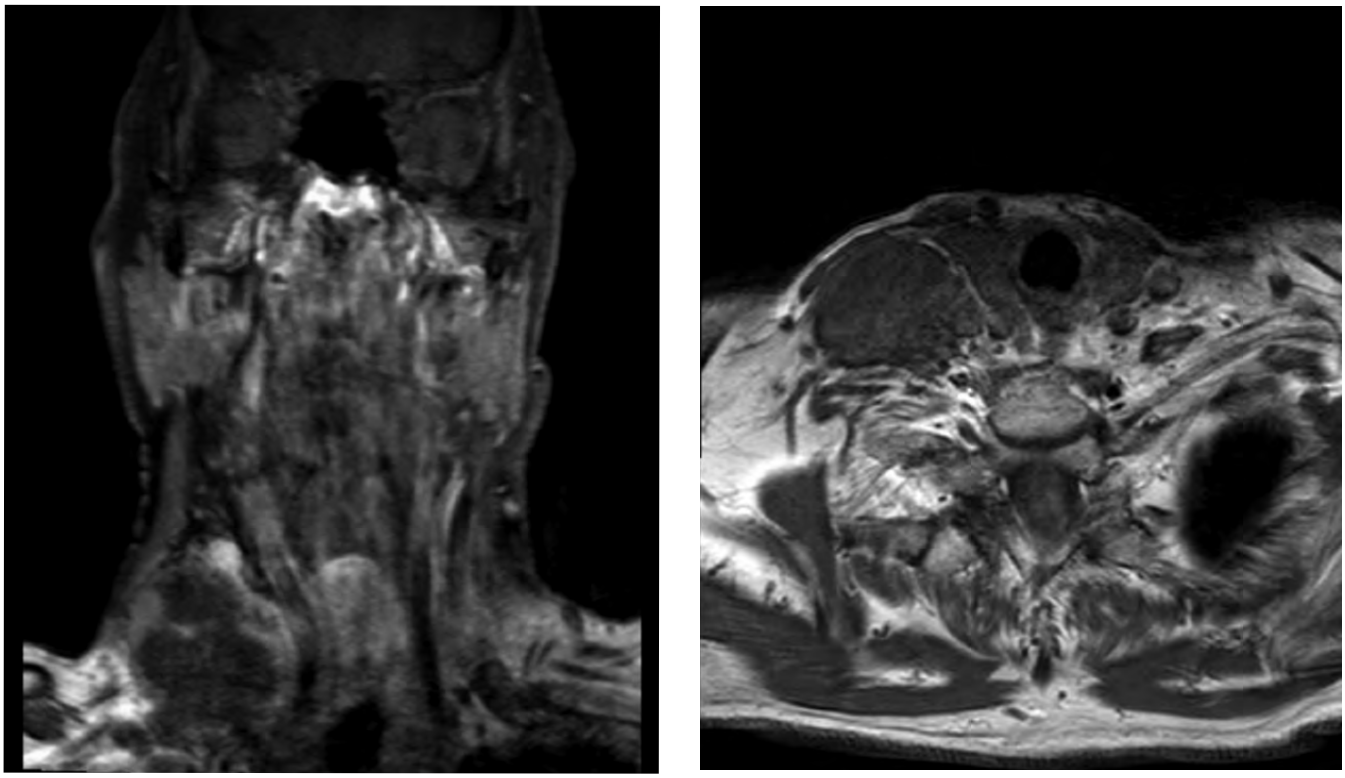
Intensity modulated radiotherapy (IMRT) is a form of conformal treatment that uses multiple fluence modulated beams, resulting in isodose distributions that more closely follow the required contours defined by the clinical oncologist. Uniquely, IMRT can also achieve concave dose distributions, which have previously been unobtainable. The clinical target volume (CTV) of head and neck patients often involves a target in the midline and nodes surrounding it. This leads to a typically 'horseshoe' shaped volume that is notoriously difficult to irradiate with a uniform dose. With IMRT, the CTV (and corresponding planning target volume, PTV) can be homogenously treated to a high dose whilst keeping the critical structures, such as the spinal cord, within specified dose tolerances. IMRT also allows differential dosing to areas with different risk of disease, so CTV-1 may encompass gross nodal disease, CTV-2 areas at high risk of microscopic disease,and CTV-3 areas at lower risk of microscopic disease. Radiation doses delivered using IMRT for HNCUP vary between centres and researchers, but doses given to gross nodal disease are between 66-70 Gy in 30-35#, uninvolved nodal areas 54-64Gy, mucosal irradiation 50-64Gy, and post-operatively involved areas are treated with 60-66Gy. [3-10]

Target volume

The chance of an emerging primary is more likely if post-operative mucosal radiotherapy is not given [11]; however, its effect on overall survival is less clear, particularly in early stage disease. However, radiotherapy has a major role in advanced disease, both in the post- operative setting and as primary treatment possibly concurrently with chemotherapy.

The key question in radiotherapy planning for HNCUP is what the target volume should encompass. Several researchers have recommended treatment of the bilateral neck and pharyngeal mucosa over unilateral neck irradiation as there is decreased incidence of an occult primary emerging [11]. Another retrospective study found that there was no difference in loco-regional control or survival between unilateral and bilateral neck plus pharyngeal mucosa irradiation. However, both loco-regional control and survival were improved by 3D conformal treatment or IMRT over conventional RT [7].

As well as deciding on whether to treat the bilateral neck or not, a decision also has to be made about how much of the mucosa should be irradiated. As the oro-pharynx contains the most common sites for possible primary sites in HNCUP, some researchers advocate sparing the larynx and hypopharynx, i.e. the critical structures for swallowing and speech that are easier than the oropharynx to evaluate so that there is less chance of missing a small primary. Some suggest that non-smokers and those with level I-II nodes are more suitable for sparing of the larynx and hypopharynx [9]. IMRT can be used to spare these structures, whilst also sparing the parotids and reducing the incidence of xerostomia [10].



Right level III/IV lymph node mass, no primary. Axial and Coronal views.

Intensity modulated radiotherapy can reduce the radiation dose to important normal tissues such as the parotids, spinal cord, ear structures, brainstem and temporal lobes. In a single centre experience treating pan-mucosal and bilateral neck (including larynx and hypopharynx), severe late xerostomia was significantly reduced from 58% using standard treatment to 11% using IMRT, and dependence on PEG feeding at 6 months was reduced from 42 to 11% [3].

The National Comprehensive Cancer Network guidelines for HNCUP [12] reflect the fact that there is no clear consensus regarding treatment and little trial evidence. The guidelines consider observation as an option after surgery for N1 disease without extracapsular spread; they also consider sparing the larynx is an option if nodal involvement is level I to upper level IV.

Role of Positron Emission Tomography (PET)

Numerous small studies have investigated the use of FDG-PET in HNCUP for more accurately delineating the radiotherapy target volume and thus reducing toxicity. These studies have evaluated FDG-PET after conventional work-up by panendoscopy or CT/MRI imaging.

Overall sensitivity, specificity and accuracy rates of FDG-PET in detecting HNCUP were 88, 75 and 79%, respectively, with FDG-PET detecting a further 25% of tumours not apparent after conventional work-up [13]. FDG-PET also detected undiagnosed metastatic disease in 27% of patients (16% regional and 11% distant). Studies have also demonstrated a low specificity and high false positive rate of 39% in the tonsils, and a low sensitivity was also seen with base of tongue and hypopharynx tumours (21% and 8.3%, respectively). High false-positive rates in tonsillar tissue may be associated with increased cellular metabolism in inflammatory lesions with enhanced FDG uptake in benign tonsils overlapping with the range found in malignancies. The most common site of false negative FDG-PET uptake is in the base of tongue, the reduction in sensitivity being attributed to the high baseline FDG uptake in this area as a result of swallowing and speech. As such, negative FDG-PET findings at this site require further clinical investigation.

Concurrent chemo-radiotherapy

The role of chemotherapy is less clear, particularly as control of a T0 primary is excellent with radiotherapy alone, and therefore the benefits of chemotherapy are small with significant additional toxicity. The additional toxicity is seen not only as increased acute mucositis and dermatitis, but as late toxicity. Of particular note, concurrent chemo-

radiotherapy appears to be associated with a significant oesophageal stricture rate, with 46% of patients requiring oesophageal dilatation in one series [6]. The most widely accepted indications for concurrent chemo-radiotherapy post-operatively appear to be extra-capsular spread. When radiotherapy rather than surgery is the primary treatment, more advanced nodal disease (N2-3) is considered an indication for addition of chemotherapy.

Survival

Follow-up times for most of the studies using IMRT for HNCUP is relatively short and therefore not all can report on 5-year survival rates. For those with shortest follow-up times, 2-year overall survival rates range from 74 to 92% [6, 8, 10], those that report 5-year rates ranging from 71 to 89% [5, 9], and disease-free survival from 85 to 88%. One study reported a 3-year overall survival of 100% [4].

Conclusion

Head and neck cancer of unknown primary encompasses a heterogeneous group of patients, with no single target volume being suitable for all patients. All clinical examination and imaging information should be considered when deciding which areas to irradiate. IMRT can reduce normal tissue toxicity, particularly allowing parotid sparing; it also spares laryngeal and hypopharyngeal structures while giving adequate coverage of the most common primary sites in the oro-pharynx. The evidence available for IMRT treatment of HNCUP comes from a heterogeneous group of small retrospective studies making conclusions as to the best target volume difficult to draw. However, IMRT can reduce both acute and late radiation effects without reducing loco-regional control or overall survival, with some evidence to suggest an improved outcome. Larger prospective studies are required to help to clarify the target volume that should be irradiated, and obtain longer term survival and toxicity data.

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Developments in Genomic characterisation of Medulloblastomas:

Contributions to the advancement of therapeutic stratification for children with brain cancer

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Brain tumours are the leading cause of cancer-related deaths in children, with medulloblastoma representing the most malignant tumour. An embryonal neuroepithelial tumour arising in the cerebellum, medulloblastoma can also be found rarely in other neuro-axis locations, notably as metastatic nodules along the spinal cord and occasionally in supratentorial locations. Despite advances in chemotherapy and radiation treatment, 40% of children experience tumour recurrence, and 30% will die from the disease [1]. Current classification schemes for medulloblastoma are based on clinical features and morphological pathology/histology (Figure 1). Pathological grading ranges from medulloblastoma with extensive nodularity, classic medulloblastoma, desmoplastic/nodular, large cell, to anaplastic medulloblastoma. Clinical risk stratification (including dissemination beyond primary site, three years of age or less, or extent of resection) is also used in treatment planning. Seventy percent of children with at least one of these measures are expected to have a five-year event-free survival following very aggressive surgery, radiation and chemotherapy whereas the five-year survival rate for patients with clear dissemination of tumour with aggressive treatment is below 50% [reviewed in 2]. The use of risk stratifications along with advances in chemo and radiation therapy has led to considerable improvements; however the assumption that all children's tumours within a risk group behave the same is a limiting issue. For example, patients with tumours classified as average or standard risk with good outcomes often suffer a low quality of life due to neurological and endocrinological sequelae as a result of their treatment. Considerable side-effects persist especially in children under the age of seven [2].

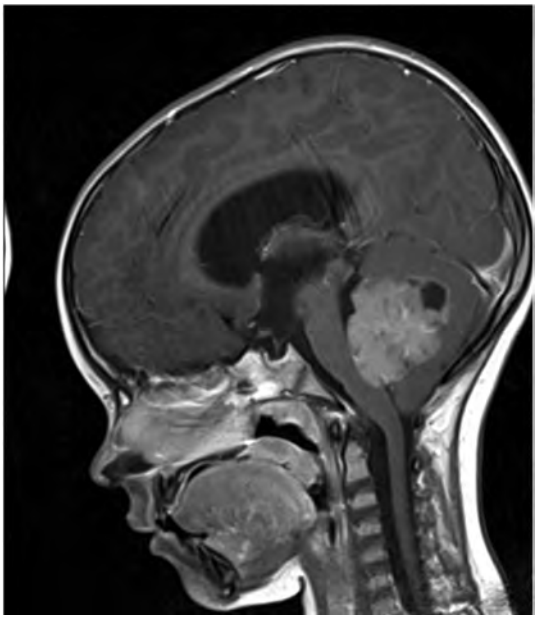
Advancing patient stratification

Over the past decade information on molecular signalling pathways driving medulloblastoma pathobiology has drastically improved through genomic approaches. Evidence from transcriptional profiling studies conducted by several research groups around the world has led to the initial molecular classification for medulloblastomas and consists of four main subgroups named WNT, SHH, Group 3 and Group 4. These four core subgroups have distinct demographics, transcriptomes, somatic genetic events, and clinical outcomes [3]. These molecular classifications have reconceptualised the heterogeneity which is present within the pathological subgroups by highlighting the role of key developmental signalling pathways in medulloblastoma pathogenesis. Excellent long-term prognosis, with survival rates often exceeding 90% is associated with the WNT subgroup [3]. To date, nearly all medulloblastomas in the WNT group display classic histology and frequently harbour BETA CATENIN (CTNNB1) mutations. CTNNB1 is a vital piece in this developmental signalling pathway. When considered as a whole, the occurrence of medulloblastoma is more frequent in males, however in the WNT group the ratio is approximately 1:1 male:female, presenting at all age groups but less common in infants [3]. As the majority of WNT group sufferers survive, it is probable that over-treatment with current therapies is occurring which can be devastating as mentioned above.

The SHH group is named aptly from the Sonic hedgehog (SHH) signalling pathway. SHH signalling is critical during early brain development, with excessive SHH activity in the cerebellum being responsible for tumourgenesis in this subgroup. In excess of 30% of all human medulloblastomas display evidence of aberrant SHH pathway activation. Inhibition of the SHH pathway at the level of the receptors, although transiently beneficial is impeded by rapid development of drug resistance, a trait distinct in SHH-associated-tumour-bearing mice [4].

Unfortunately, patients that fall into the least understood subgroups (groups C and D) also have the worst prognosis. Group C medulloblastoma display large cell/anaplastic morphology, exhibit overexpression and amplification of the c-MYC proto-oncogene, are highly aggressive, frequently invade (via the neuro-axis) and carry an extremely poor patient prognosis. The fact that ectopic overexpression of c-MYC can cause medulloblastoma cell lines to adopt an anaplastic phenotype, plus the fact that high c-MYC levels are associated with poor clinical outcome suggests that c-MYC facilitates a

The relatively successful outcome for medulloblastoma patients over the past decade and the molecular profiling of this group of paediatric tumours have hailed new hope for neuro-oncology researchers and clinicians alike. The use of such profiles to help identify therapeutic targets as well as to reduce toxicity in treatment regimens will, we hope, be mirrored in the research effort and similar outcome improvement in other groups of malignant central nervous system tumours in both children and adults.



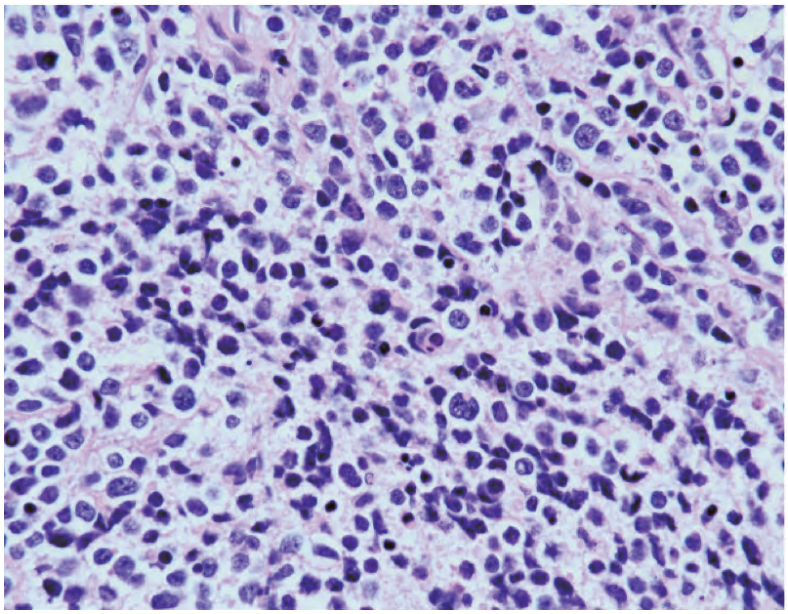


Figure 1: Current classification schemes for medulloblastoma are based on clinical features, morphological pathology and clinical risk stratification (dissemination beyond primary site, three years of age or less, or extent of resection). In figure 1A (left), an MRI indicates a cerebellar mass as well as an enlargement of the lateral and third ventricles, this information along with histology (Figure 1B, anaplastic medulloblastoma) and clinical features are used to help direct therapy. With recent considerable medical research advances in understanding the molecular pathology involved in driving medulloblastoma tumourgenesis there is a renewed hope for improved disease risk stratification schemes that will help identify new therapeutic targets as well as reduce toxicity in treatment regimens [3]. Images were obtained from colleagues, Gary Tye, MD, Joann Tillet, RN and Knarik Arkun MD of Virginia Commonwealth University.

pivotal role in the biology of this subgroup [5]. The fourth subgroup, group D, is currently characterised by neuronal and glutaminergic signalling [6]. The molecular pathogenesis of group D is currently unclear, although it is common in all age groups. In both subgroups C and D, leptomeningeal dissemination (spread of tumour cells along the cerebral spinal fluid channels, leading to development of metastatic tumour nodules within the spinal cord) is frequent. Leptomeningeal spread is a marker of poor prognosis, present in 40% of paediatric medulloblastoma at diagnosis and the majority of cases at the point of recurrence [7]. At present, children with metastatic medulloblastomas are administered radiation to the entire developing brain and spinal cord followed by an intensive chemotherapy routine; needless to say this results in detrimental effects on the developing nervous system.

Clearly great strides have been made in the molecular understanding of medulloblastoma. The research achievements made by scientists around the world in the past few years are very impressive and are just barely touched on in this short article. Based on these exciting discoveries, we now know that it is possible to better stratify patients in order to reduce toxicity to those who have good prognosis and to begin to develop novel specific targeted therapies for those with a poor prognosis. Challenges remain and include the incorporation of new molecular markers using biologically-based therapies, the incorporation of molecular tissue analysis to aid with stratification (sub group assignment) and therapy, and unite this knowledge with the day to day clinical care of medulloblastoma patients. Medulloblastomas are still associated with extensive mortality rates, and those that survive, endure long-term side-effects and complications that significantly affect their quality of life. Although there are many issues to address, the good news is that this global collaborative research effort resulted in significant advances in our knowledge concerning medulloblastomas and clinicians are now poised to work internationally in clinical trials and to translate this knowledge into better treatments for children with medulloblastoma. ■

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The Tumour Microenvironment

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Genetic changes that mark cells as potentially cancerous are being discovered with the new technologies of sequencing and the determination of specific mRNAs being expressed in each cancer. Cancers with similar phenotypes, e.g. non-small cell carcinomas of the lung, may have disparate genetic changes that result in different responses to drugs. One aspect of tumour formation and progression that has not been sufficiently addressed are the effect of normal tissues surrounding a tumour and the microenvironment itself on growth and invasion. The stroma is not perhaps so 'normal' and can play a part in the progress of a cancer. In 1889, Paget [1] hypothesised that the tumour was like a seed and the microenvironment the soil; for optimum growth the tumour needed the soil of the microenvironment, as emphasised by the predilection of certain sites for metastasis. It has recently been shown that the genetic profile of the stroma can predict clinical outcome in breast cancers [2]. The activity of its fibroblasts, referred to as cancer-associated fibroblasts (CAFs) that differ from fibroblasts found associated with normal epithelial tissue, may affect tumour growth and behaviour [3] A number of markers have been identified that might differentiate CAFs from normal fibroblasts, but none so far can do so unambiguously.

While the genetic profile of the stroma can sometimes predict outcome [2], genetic signatures have been acquired from the whole stroma, not for any particular cell type, but recent investigations have been following the role of inflammatory cells. There is little doubt that the immune response can be protective, since immuno-suppressed individuals have a high incidence of some tumours, e.g. cervical cancer and haematological malignancies. However, there is also evidence that the immune response can promote cancer development [4]. An important component is Signal Transducer and Activator of Transcription 3 (STAT3), upregulated in many cancer types, which helps to transcribe cytokines and growth factors (e.g. IL6 and vascular endothelial growth factor A, respectively) that interact with cells in the stroma to increase immune cell infiltration. Tumour-associated macrophages may be important in being pro-tumorigenic, since they produce growth and angiogenic factors that stimulate tumour growth [5]. Therefore, cross-talk between the tumour and the surrounding stroma may result in immune cell infiltration and production of pro-tumorigenic factors. Whether the immune cells can be targeted as a therapeutic approach is unclear, since as already mentioned, the immune response can be protective. The challenge will be to differentiate the protective aspects of the immune response from the pro-oncogenic for improved anti-tumour therapy.

We have been investigating the interaction of oro-pharyngeal cancer cells with stromal fibroblasts. Three-dimensional organotypic culture techniques are being used that recapitulate the stratified epithelium, the type found in the oro-pharyngeal region. Epithelial cells from the oral cavity or human foreskin were used to produce epithelium, with the oral and foreskin fibroblasts being embedded in collagen to represent the stroma. In this model, fibroblasts in the collagen affect the differentiation of stratified epithelium [6], and the invasive potential of transformed cells [7]. The model was particularly helpful in investigating a number of other aspects. In experiments investigating the effects of retinoblastoma protein (RB) on neighbouring cells, short-hairpin RNAs (shRNA) were used to deplete Rb in the embedded fibroblast cells to follow their effect on the epithelium. The epithelium cells here were human keratinocytes expressing E6 and E7 from human papillomavirus type 16 (HPV16), the commonest cause of cervical cancer but also increasingly being implicated in oro-pharyngeal cancer. When encountering control fibroblasts or fibroblasts transduced with a control shRNA (i.e. one that does not recognize any cellular mRNA), the keratinocytes did not invade the collagen, whereas the Rb-depleted fibroblasts resulted in the epithelial cells invading the collagen in a quite dramatic fashion. The process was further stimulated by the overexpression of keratinocyte growth factor or fibroblasts growth factor 7 (KGF/FGF7), produced by the fibroblasts as a result of Rb depletion. How does an increase in KGF/GFG7 induce invasion of the epithelial cells? It appears that KGF/FGF7 interacts with its receptor, fibroblast growth factor receptor 2b (FGFR2b), on the epithelial cells. This activation by KGF/FGF7 binding results in signals being sent through via the AKT pathway, eventually upregulating matrix metalloproteinases (MMP), in particular MMP-1. Degradation of collagen fibres by MMP-1 assists epithelial cell invasion, a process that can be inhibited by either depletion of MMP-1 or any of the components downstream of the FGFR2b receptor (e.g. AKT or the transcription factor Ets2).

Regarding the clinical implications, samples from 35 oro-pharyngeal cancers were tested to see if Rb was inactivated in the stromal fibroblasts next to the cancer cells, since it is unlikely that Rb would be depleted. Rb can be physiologically inactivated by

cancer-associated fibroblasts (CAFs) that differ from fibroblasts found associated with normal epithelial tissue, may affect tumour growth and behaviour

hyper-phosphorylation. Using 2 different antibodies to recognise the phosphorylated amino acids on the Rb protein, we found that most stroma fibroblasts in the tumours contained hyper-phosphorylated Rb, unlike fibroblasts from normal connective tissue of the same patient that had active Rb. The tumour cells had high levels of activated Ets2 and MMP-1, indicating that the pathways seen in vitro were active in tumour tissue. Inactivation of Rb was independent of whether the oro-pharyngeal cancer was HPV positive or negative, as had also been seen in the stroma of cervical cancers. As well as influencing the growth and invasion of tumours, new data suggests that the microenvironment can alter the drug sensitivity of tumours. Two studies [8, 9] have shown that the release of growth factors, in this case hepatocyte growth factor (HGF), from the fibroblasts led to resistance to the BRAF inhibitor, PLX4032 (vemurafenib), in BRAF-mutant melanoma cells through stimulation of alterative signalling pathways in the tumour cells. Thus the microenvironment not only impacts tumour growth, invasion and response to chemotherapy, but is an important part of the whole process of cancer growth, spread and treatment.

Are stromal fibroblasts surrounding a tumour different from those fibroblasts associated with normal epithelial tissue? In normal tissues, the epithelium and the underlying stroma communicate with each other to ensure the controlled growth of the epithelium; where this equilibrium is disrupted, e.g. in wound healing, stromal fibroblasts respond by controlling epithelial cell growth and repair [10]. However, this response is induced by signals from the epithelium through release of interleukin-1 (IL-1). In the cancer scenario, it is unclear what signal tumour cells are sending to the stromal fibroblasts that inactivate Rb and the subsequent induction of KGF/FGF7, with the consequences described above. In the normal stratified epithelium, e.g. skin, IL-1-alpha and -beta are released by the epithelial cells, which induces KGF/FGF7, and this in turn stimulates proliferation in the epithelium to maintain homeostasis. Is this homeostasis disturbed in cancers or are other signalling pathways involved in tumour cells? These are questions we hope to answer in unravelling 'the seed and soil' concept in cancer.

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Management of Ovarian Cancer: Bright New Future or False Dawn?

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The proportion of UK women surviving five years after diagnosis of ovarian cancer has improved by only 5% since 1995 [1], yet, there is great optimism as new treatment strategies emerge that may genuinely improve the outlook of patients.

Current management and recent advances

For the past 15 years, the standard initial management of ovarian cancer has been primary debulking surgery followed by six cycles of platinum (carboplatin or cisplatin) and paclitaxel chemotherapy. The superiority of regimes containing both platinum and taxane emerged in the mid-1990s [2]. This remains standard management for the minority of women presenting with early stage ovarian cancer (stages I and II),

A marked change in management of advanced disease has recently emerged, with debulking surgery deferred until after three cycles of primary/neoadjuvant chemotherapy. The hypothesis is that these three cycles should reduce the bulk of tumours and increase the likelihood of complete macroscopic resection. The EORTC55971 trial compared conventional management with primary chemotherapy and interval surgery in 670 women with advanced disease. Women undergoing primary chemotherapy were more likely to have no visible residual disease after debulking. However, this did not translate into a survival advantage [3], although surgical morbidity was significantly lower in the primary chemotherapy group. Thus, it was concluded at the recent 4th Ovarian Cancer Consensus Conference that the use of primary chemotherapy in advanced ovarian cancer is an appropriate international standard in clinical trials [4].

Another advance has been the use of dose-dense fractionated paclitaxel with carboplatin as first-line chemotherapy. The Japanese JGOG3016 trial randomised 637 women to receive either standard post-operative chemotherapy or the dose-dense regime. Initial results were extremely encouraging, with a highly significant increase in progression-free survival (PFS) in favour of the dose-dense arm (28 vs 17 months, hazard ratio 0.71; $p = 0.0015$) [5]. The data presented at ASCO 2012 also showed a significant improvement in overall survival.

The activity of bevacizumab in the first line treatment of ovarian cancer is attracting much attention. Two large randomised phase III trials, GOG218 [6] and ICON7 [7], showed improved PFS when bevacizumab was included with carboplatin and paclitaxel chemotherapy, and also when given as single agent maintenance for up to 15 months. The women who benefited most were those with the poorest prognosis (residual tumour following primary surgery and/or stage IV disease). In ICON7, the PFS curves showed non-proportional hazards, with most benefit at the end of bevacizumab maintenance treatment, but diminishing thereafter. With license approval in both the EU and USA, bevacizumab is the first new drug in initial ovarian cancer management for 15 years.

Bevacizumab can also improve PFS when added to chemotherapy in relapsed disease that is either platinum-sensitive [8] or platinum-resistant [9]. Some questions remain, however, regarding the most appropriate dose (7.5 or 15mg/kg), with potentially huge cost implications for the NHS. It is also unclear in which setting bevacizumab would be most appropriate (first-line, platinum-sensitive relapse or platinum-resistant relapse), whilst no reliable predictive biomarkers of benefit are available.

As a drug with undoubted activity in ovarian cancer, bevacizumab is the first of many targeted agents that may enter the oncologist's armamentarium over the next few years.

State of the scientific basis

It is now universally appreciated that the disease called 'ovarian cancer' for the past 40 years is, in fact, at least five different diseases linked only by a common anatomical location [10]. Thus, the maxim of 'one-treatment-regime-for-everyone' is increasingly untenable [11]. Oncologists must, therefore, strive towards customising treatment for each patient, perhaps with different treatments being used for the different subtypes.

High Grade Serous Type

The most common type of ovarian cancer is high grade serous, accounting for two thirds of all cases and disproportionately presenting at an advanced stage (up to 90% of stage IIIc/IV patients have high grade serous pathology). Women with inherited germline mutations in BRCA1 and BRCA2 also overwhelmingly develop high grade serous ovarian cancer compared to other subtypes.

The first key revelation is that high grade serous disease does not actually arise in the ovary, but in the distal fallopian tube [12]. The second is that a near-universal molecular abnormality has been identified - mutations in the tumour suppressor gene, TP53, are seen in >95% of all high grade serous cases [13]. This frequency was confirmed by the Cancer Genome Atlas (TCGA) consortium, which subjected 489 of these tumours to an array of genomic analyses [14].

Not unexpectedly, TCGA also uncovered further fascinating data. For many years, it was thought that inherited ovarian cancer resulting from BRCA1 and BRCA2 mutations was rare (<5% of cases). However, TCGA suggested that ~15% of cases arose in women with inherited BRCA1/2 mutations, a figure subsequently confirmed by others [15,16]. This has huge implications for women and their families – there may be many more women at genetic risk of ovarian cancer than previously thought, many of whom will have no obvious family history of breast or ovarian cancer.

Mutations in BRCA1/2 cause a defect in a cell's ability to repair DNA damage using the process of Homologous Recombination (HR). This has two

consequences: cells lacking BRCA1/2 function will acquire multiple unrepaired genetic abnormalities that might eventually produce cancer; however, the malignant cells that arise are exquisitely sensitive to DNA-damaging drugs. Thus, ovarian cancer caused by mutations in BRCA1 or 2 responds very well to platinum-based chemotherapy and overall survival is significantly better than sporadic ovarian cancers [17]. In addition, BRCA1/2-mutated cancers can also respond to a novel group of anti-cancer drugs, called PARP inhibitors, which induce irreparable DNA damage by blocking a separate repair pathway [18,19].

TCGA has also shown that abnormalities in other HR genes are common in high grade serous cancer: up to 50% of tumours have some form of HR pathway defect. The same frequency was observed in a separate study using a functional assay of HR activity in primary tumour cells [20]. The implication of these studies is that up to half of women with high grade serous ovarian cancer may benefit from PARP inhibitor treatment. Indeed, one large study has already demonstrated that women with relapsed disease show a dramatic increase in PFS when treated with a PARP inhibitor following platinum-based chemotherapy [21].

Overall, three great challenges in high grade serous ovarian cancer exist – first, to develop specific therapies for TP53-mutated cancers, which is the universal feature of this disease; second, to continue developing PARP inhibitor therapy, with a simple test to identify tumours with defective HR; third, and the most difficult, to identify the abnormalities underpinning the 50% of high grade serous tumours with normal HR – these cases respond less well to conventional chemotherapy and have a poor prognosis.

Other subtypes of ovarian cancer

Low grade serous cancer, despite its name, is very different from high grade. Mutations in TP53 are very rare and HR pathway genes are invariably intact. Low grade serous cancers can arise from borderline or low-malignant potential tumours, which are more frequent in younger women, and they tend not to respond to conventional platinum-based chemotherapy. Their pattern of growth could be described as slow but inexorable.

However, distinct and targetable abnormalities have now been identified. The most commonly mutated genes are B-Raf, KRas and NRas, which lie in a common pathway, with the kinase MEK acting as key effector. The potential for MEK inhibitors in the treatment of low grade serous tumours will be explored in the LOGS trial, run in both the UK and the USA, which will compare single agent MEK inhibitor with conventional chemotherapy in 250 women with relapsed disease. Most importantly, all women will have a biopsy of their relapsed cancer as they start treatment, so that correlations can be made between tumour biology and response to treatment. This idea of taking new biopsies is a vital new paradigm in modern clinical trials; only by having a sample of cancer that is contemporaneous with the treatment being given can researchers hope to understand the biology of the disease.

Another rarer type of ovarian cancer is Clear Cell Carcinoma (CCC). In European populations, it accounts for approximately 10% of tumours, although in Japan it is as high as 30%. CCC has a fearsome reputation because advanced disease is almost completely resistant to platinum-based chemotherapy. However, CCC is much more likely to present at very early stages and the survival of patients with stage I CCC is extremely good [22].

At a biological level, two key features have recently emerged. Many cases of CCC, as well as another type of ovarian cancer called endometrioid, arise on a background of endometriosis, and mutations in the gene ARID1A are highly frequent [23]. ARID1A encodes a protein called Baf250a, which is a key component of a complex remodelling chromatin that influences gene expression by regulating the gross 3-dimensional structure of DNA. Mutations in this complex are seen in other cancers [24], but novel ARID1A/Baf250a-specific therapies need to be developed.

A more targetable abnormality in CCC is increased activity of the inflammatory cytokine, interleukin-6 (IL-6), together with HIF1α, a gene that regulates cellular responses to low oxygen concentration [25]. Clinical trials of IL-6 inhibitors have already been undertaken in ovarian cancer [26], and a new trial of nintedanib, a drug that should inhibit the downstream effects of IL6-HIF1α activity in women with relapsed CCC, will start in the UK in 2013.

Summary

For many years, ovarian cancer has only had one active drug, based on platinum. However, the next decade should see significant improvements in the outlook for patients. Five key points need to be considered:

1. Ovarian cancer covers many diseases, the commonest of which probably does even not arise in the ovary.

2. We need specific treatments for the different subtypes, starting with subtype-specific clinical trials. The one-size-fits-all era both in treatment and clinical trials must end. Trials will have to be smaller, run rapidly and have rigorous clinical and scientific endpoints.

3. New targets for therapy are required. Although BRCA1 and IL-6 are exciting, there are multiple other abnormalities present that require elucidation and the possible uncovering of new therapeutic targets.

4. Tumours adapt and become resistant to therapy. High grade serous disease is particularly heterogeneous; intrinsically resistant clones of tumour may exist at diagnosis. It is essential that further samples of tissue are taken when tumours relapse to identify changes that have occurred during treatment and relapse.

5. Ovarian cancer is relatively rare and international effort is required to combat it. No individual research team can defeat this disease.

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Advancing the multidisciplinary treatment of colorectal liver metastases

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Colorectal cancer (CRC) is the third most common cancer in the UK, with some 40,000 new cases each year [1]. It also remains the second most common cause of cancer death in the UK, despite advances in treatment [1].

Approximately 20–25% of CRC patients have liver metastases at presentation, and over 30% of the remainder go on to develop liver metastases [2]. The presence or absence of liver metastases is the primary determinant of survival [2]—their presence accounts for at least two thirds of all CRC deaths [3]. Indeed, in patients with liver-limited metastases, it is progression of the liver disease (rather than the primary CRC) that determines overall life expectancy [2].

For optimal management of liver metastases, it is important to involve all appropriate specialists in the multidisciplinary team (MDT) caring for patients with CRC. Guidelines for the management of CRC from the Association of Coloproctology of Great Britain and Ireland recommend that fit patients with resectable or potentially resectable liver metastases should be reviewed in the MDT with a hepatobiliary (HPB) surgeon and colorectal oncologist "to evaluate operability and to decide on a combined plan of management to optimise the chance of achieving complete resection of all metastatic disease" [4].

This article focuses on the rationale for advancing the multidisciplinary treatment of colorectal liver metastases, and on the improvements in outcomes that can be achieved. It is based on a meeting held at The Royal Marsden Hospital (Fulham) in February 2012, attended by more than 130 oncologists, HPB and gastrointestinal surgeons, clinical nurse specialists and other members of colorectal and HPB MDTs.

Liver resection: a potentially curative approach

An analysis of the 114,155 patients with CRC who underwent surgery in England between 1998 and 2004 reported an improvement in survival with liver resection [5]. Over that period, 3,116 patients (2.7%) underwent one or more hepatic resection. In line with expectations, 5-year survival of patients with unresected stage 4 CRC (i.e. mCRC) was considerably worse than for patients who underwent hepatic resection, 9% [95% CI 8.4-9.6] versus 44.2% [95% CI 42.4–46.1], respectively. Patients with stage 4 disease who underwent liver resection had 5-year survival rates comparable to those with stage 3 disease.

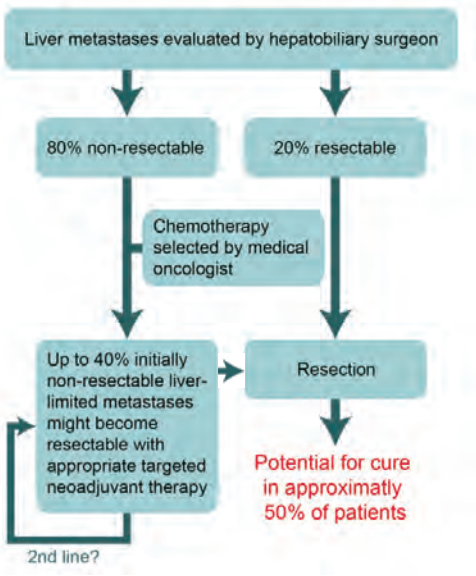

Figure 1: Resectability of liver metastases in CRC [Adapted from 7].
To achieve the best outcomes for patients, liver surgeons and medical oncologists must be involved from the outset in the multidisciplinary care of patients with colorectal liver metastases.

Because liver resection is a potentially curative approach to the management of colorectal liver metastases (Figure 1) [6], an increase in the proportion of patients eligible for such an intervention is an important goal. With approximately 85% of patients with colorectal liver metastases considered unresectable at presentation, the use of conversion therapy to shrink unresectable metastases may increase the proportion eligible for subsequent resection [7,8].

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Table 1. Doublet chemotherapy plus cetuximab in patients with unresectable mCRC

Study	Eligibility criteria	Biomarker defined subgroup	Regimen	KRAS WT population		Unresectable liver-only mCRC		
				n	ORR (%)	n (% of trial population)	ORR (%)	R0 resection rate (%)
Anti-EGFR agents								
CRYSTAL [16] (Phase III)	Unresectable mCRC	KRAS WT	FOLFIRI FOLFIRI + cetuximab	350 316	39.7 57.3	72 (21) 68 (22)	44.4 70.6	5.6 13.2
OPUS [16] (Phase II)	Unresectable mCRC	KRAS WT	FOLFOX FOLFOX + cetuximab	97 82	34.0 57.3	23 (24) 25 (31)	39.1 76.0	4.3 16.0
CELIM [18,19] (Phase II)	Unresectable CRC liver metastases	KRAS WT	FOLFOX/ FOLFIRI + cetuximab	67	70.0	67 (100)	70.0	33.0

CRC: Colorectal cancer; FOLFIRI: Irinotecan, leucovorin, fluorouracil; FOLFOX: Oxaliplatin, folinic acid, fluorouracil; mCRC: Metastatic colorectal cancer; ORR: Overall response rate; WT: Wild-type. Please refer to the publications for details of dose and schedule.

Who should be considered for liver resection?

The criteria for resection of CRC liver metastases have changed in recent years [9,10]. A meta-analysis has shown that seven factors traditionally associated with poor prognosis (poorly differentiated primary tumour, node-positive primary tumour, liver tumour >5 cm diameter, >1 liver metastases, positive resection margin, extrahepatic disease and raised carcinoembryonic antigen level) show a significant relationship with poor survival post-resection, but the effect is modest and does not necessarily preclude surgery [11].

While these prognostic factors may prove useful when considering therapeutic options, a new definition of resectability is required. It has been proposed that resection can be carried out if complete removal of all liver metastases will leave at least 30% of remnant liver [2]. Using this criterion, three categories of patients can be defined [12]:

- Easily resectable
  - Complete resection is likely with tumour-free margins
- Marginally resectable
  - Tumour-free margins unlikely
  - Small liver remnant
  - Concomitant resectable extrahepatic metastases
- Definitely unresectable
  - Widespread hepatic disease
  - Unresectable extrahepatic metastases
  - Multiple metastatic sites

Conversion therapy to increase resectability

Analysis of six studies of neoadjuvant treatment in patients with unresectable colorectal liver metastases has suggested a correlation between tumour response and subsequent resection rates [8]. Studies of neoadjuvant dual combination chemotherapy have found response rates of 48–60%, and R0 resection rates of 10–33% [8,13-15]. Efficacy can be improved when anti-epidermal growth factor (EGF) receptor therapy, cetuximab, is combined with the chemotherapy regimen (see Table 1) [16-19]. For example, compared with doublet chemotherapy alone, a combination of cetuximab and doublet chemotherapy resulted in improved response rates (70–76% vs 39–44%) and R0 resection rates (13–16% vs 4–6%) in subset analyses of patients with KRAS wild-type liver-limited disease [16].

A phase II study designed to explore the response and resection rates of cetuximab in combination with doublet chemotherapy in patients with unresectable colorectal liver metastases, reported response and R0 resection rates of 70% and 33%, respectively, in patients with KRAS wild-type disease [18,19]. The addition of cetuximab was not associated with increased peri-operative complications when compared with other studies reporting liver resection in this setting [18].

Studies of cetuximab-based neoadjuvant treatment were appraised in the development of guidance from the National Institute for Health and Clinical Excellence (NICE) on the first-line treatment of mCRC [17]. For patients considered fit enough to undergo resection of the primary tumour (and removal of liver metastases should they become resectable), NICE recommends treatment with cetuximab (within its licensed indication) in combination with FOLFOX (5-fluorouracil [5-FU], folinic acid and oxaliplatin) or FOLFIRI (5-FU, folinic acid and irinotecan). After a maximum of 16 weeks of neoadjuvant treatment, patients should be reassessed for potential liver resection.

The addition of anti-vascular endothelial growth factor (VEGF) therapy, bevacizumab, to doublet chemotherapy in a randomised controlled trial setting has not shown an increase in response

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Table 2. Doublet chemotherapy plus bevacizumab in patients with unresectable mCRC

Study	Eligibility criteria	Biomarker defined subgroup	Regimen	ITT population		Unresectable liver-only mCRC		
				n	ORR (%)	n (% of trial population)	ORR (%)	R0 resection rate (%)
Anti-VEGF agents								
NO16966 [20,21] (Phase III)	Unresectable mCRC	No	FOLFOX/ XELOX + placebo	701	38*	207 (29.5)	NA	11.6
			FOLFOX/ XELOX + bevacizumab	699	38*	211 (30)	NA	12.3
BOXER [22] (Phase II)	Poor risk CRC liver metastases	No	CAPOX + bevacizumab	45	78	30 (65)	NA	10

*Independently assessed. CRC: Colorectal cancer; CAPOX/XELOX: Oxaliplatin, capecitabine; FOLFOX: Oxaliplatin, folinic acid, fluorouracil; ITT: Intention to treat; mCRC: Metastatic colorectal cancer; NA: Not available; ORR: Overall response rate. Please refer to the publications for details of dose and schedule.

rates with a corresponding increase in resection rates (Table 2) [20,21]. A phase II, single arm study has explored the use of bevacizumab in combination with CAPOX (capecitabine, oxaliplatin) in patients with unresectable colorectal liver metastases (n=30) or upfront resectable liver metastases with a synchronous primary (n=15). A total of 3 patients with unresectable liver metastases underwent an R0 resection [22].

Triplet chemotherapy has been shown to achieve response rates of 71% [24] and R0 resection rates of 26-36% in patients with colorectal liver metastases initially considered to be unresectable [23, 24]. Single arm studies have investigated the addition of either cetuximab [25] or bevacizumab [26] to triplet chemotherapy producing response rates and R0 resection rates in the range of 79-80% and 40-60%, respectively (Table 3). Trials are on-going evaluating triplet therapy plus a targeted antibody in this setting to improve on response and resection rates further.

Importance of the liver MDT

Despite the importance of potentially curative hepatic resection for patients with colorectal liver metastases, analysis of resection rates in the UK has shown wide geographical variation [5]. Across cancer networks, there was a four-fold difference (1.1–4.3%), with a ten-fold difference between individual hospitals (0.7–6.8%). While some variation may reflect differences in patient populations, there may also be disparities in clinical practice and service organisation.

A cancer network has examined the issue of variability in care delivery in an audit of patients with mCRC who survived resection of primary CRC, and were treated with palliative chemotherapy and not liver resection [27]. Of 110 patients in this category during 2009, 37 were discussed at a HPB MDT and 73 patients were not, i.e. the decision to move to palliative care did not involve an HPB surgeon. Of the 73 patients not seen by the HPB MDT, 20 had multisite disease and the decision to offer palliative care was considered appropriate. However, there were 53 patients with liver-limited disease, for whom the guidelines recommend discussion by the HPB MDT [1,4].

After independently reviewing radiology reports and imaging for these 53 patients, six HPB surgeons scored the resectability of the liver metastases [27]. One patient was excluded because all the reviewers reported the imaging to be of insufficient quality. The reviews of the remaining 52 patients showed consistency in evaluation between the surgeons (kappa score 0.577). In 33 of the 52 cases (63%), the majority of reviewers considered that resection was possible.

Examination of liver resection rates in various studies highlights the role of HPB surgeons in the MDT caring for patients undergoing conversion treatment for unresectable colorectal liver metastases. Despite similar response rates to cetuximab plus chemotherapy for KRAS wild-type, unresectable, liver-limited disease (70–79%), there was marked variability in the liver resection rate (13–60%) reported in clinical studies [16,18-19,25]. Where the decision on initial and subsequent resectability was determined without the involvement of an HPB surgeon, the rate of liver resection after neoadjuvant treatment was 13–16% [16]. Where the decision rested with an MDT involving an HPB surgeon, the liver resection rate was 33–60% [18-19,25].

Conclusion

Liver metastases are common in patients with CRC [2], and the leading cause of mortality [3]. Hepatic resection is potentially curative [6], so increasing the proportion of patients eligible for surgical treatment is key to improving outcomes. Multidisciplinary treatment, including

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Table 3. Triplet chemotherapy in patients with unresectable mCRC

Study	Eligibility criteria	Biomarker defined subgroup	Regimen	ITT population		Unresectable liver-only mCRC		
				n	ORR (%)	n (% of trial population)	ORR (%)	R0 resection rate (%)
Triplet chemotherapy alone								
Falcone et al [23] (Phase III)	Unresectable mCRC	No	FOLFIRI FOLFOXIRI	122 122	34* 60*	42 (34) 39 (32)	NA NA	12 36
Ychou et al [24] (Phase II)	Unresectable CRC liver metastases	No	FOLFIRINOX	34	70.6	34 (100)	70.6	26.5
Anti-EGFR agents								
Masi et al [26] (Phase II)	Unresectable mCRC	No	FOLFOXIRI + bevacizumab	57	77	30 (53)	80	40
Anti-VEGF agents								
POCHER [25] (Phase II)	Unresectable CRC liver metastases	No	Chrono-IFLO + cetuximab	43	79.1	43 (100)	79.1	60

*Independently reviewed. CRC: Colorectal cancer; FOLFIRINOX/FOLFOXIRI/Chrono-IFLO: Oxaliplatin, irinotecan, leucovorin, fluorouracil; FOLFIRI: Irinotecan, leucovorin, fluorouracil; ITT: Intention to treat; mCRC: Metastatic colorectal cancer; NA: Not available; ORR: Overall response rate. Please refer to the publications for details of dose and schedule.

advice from an HPB surgeon, is required from the outset to ensure accurate assessment of the initial resectability of liver metastases.

It is estimated that approximately 15% of patients with liver-limited disease are resectable with curative intent at the time of detection [7]. Use of first-line conversion therapy for patients with initially unresectable liver-limited disease may allow subsequent resection in a further 24–54% of patients [8]. Studies of neoadjuvant regimens suggest that the addition of the EGF receptor antagonist cetuximab to doublet chemotherapy (FOLFOX or FOLFIRI) in patients with KRAS wild-type disease improves response rates and resection rates versus doublet chemotherapy alone [16]. Based on these findings, NICE recommends the combination of cetuximab and FOLFOX or FOLFIRI for use in the neoadjuvant treatment of unresectable colorectal liver metastases [17].

Through the implementation of guidelines on MDT management and conversion therapy, outcomes for patients with mCRC may be improved, and inequalities reduced.

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Panel: Biomarkers and targeted agents

The use of biomarkers has opened up an era of personalised medicine, in which the likelihood of a patient's response to a targeted agent is evaluated before the therapy is given. Tumour biomarkers may reflect oncogenic mediators that are turned on during cancer development, or tumour-suppressor factors that are turned off in cancer.

There are a number of hurdles to the development of clinically useful biomarkers, notably:

- A good understanding of the disease pathology and the targeted agent
- Establishment of the prognostic and predictive effects of potential biomarkers, using disease models and clinical trials, and requiring interaction between pharmaceutical companies and regulatory bodies, adequate funding and effective research networks

These hurdles have been overcome for the biomarker, KRAS, now validated to predict the response of mCRC to cetuximab-based therapy. Analysis of patients with tumours characterised by KRAS wild-type mutational status showed a significant benefit in efficacy to cetuximab monotherapy compared with best supportive care, versus no significant treatment effect in patients with mutated KRAS [28].

KRAS encodes a protein essential to the EGF-receptor signalling mechanism [28]. Approximately 40% of CRC tumours have one or more activating mutation in exon 2 of this gene, which may make the cells unresponsive to EGF receptor inhibitors, such as cetuximab.

Clinical message:
Test CRC tumours to identify patients with KRAS wild-type status; if they have (or develop) metastatic disease, these patients may benefit from cetuximab therapy

Further work is underway to refine the biomarkers for prediction of response to cetuximab therapy. Not all KRAS mutations are alike. Although nearly 80% of mutations in KRAS occur in codon 12 (e.g. G12D, 32.5% of mutations; G12V, 22.5%; G12C, 8.8%; others, 14.9%), mutations in codon 13 (G13D) account for 19.5% [29]. Interestingly, in contrast to mutations in codon 12, data suggest that mutations in this codon may not be predictive for resistance to cetuximab-based therapy [30].

Not all patients with KRAS wild-type respond to cetuximab. This may be due to the impact of genes for other elements of the EGF-receptor signalling pathway, receptor ligands and other related receptors in the same family of receptors (e.g. human epidermal growth factor receptor 2 [HER2] and human epidermal growth factor receptor 3 [HER3]) [31]. However, currently these biomarkers have no practical use in clinical practice as they have yet to be validated.

Clinical message:
Other potential biomarkers to target the use of cetuximab are not yet validated for clinical use

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Conference News

Are you organising an annual meeting or conference which you would like to tell our readers about? Or would you like to write a report on a meeting or conference of particular interest? If so, contact Patricia McDonnell at Oncology News on T/F: +44 (0)288 289 7023, E: patricia@oncologynews.biz

European Society for Medical Oncology Congress 2012

Date: 28 September – 2 October 2012 **Venue:** Vienna, Austria.

A record breaking 16,394 delegates attended the European Society for Medical Oncology (ESMO) Congress 2012 in Vienna, making it the largest congress yet held. The focus of the meeting was personalised treatments for cancer, but leading oncologists warned that progress towards matching treatment to tumour characteristic for individual patients would be stifled unless regulations governing clinical trials are changed to facilitate rather than block clinical research.

"At the moment we are in the era of 'stratified' medicine for cancer, not yet personalised medicine," ESMO president Professor Martine Piccart (Jules Bordet Institute, Brussels, Belgium) told the meeting. "For personalised medicine, we need to know more than simply that a person's tumour has particular biological characteristics. We also need to know whether drugs targeted at those characteristics will actually work for individual patients."

In her opening address, Professor Piccart said that there is unprecedented opportunity for making rapid advances in the prevention, diagnosis and treatment of cancer. ESMO's vision to accelerate progress against cancer includes education, clinical and translational research, partnerships and a particular focus on young oncologists. But she warned that the society is very concerned about the huge bureaucracy currently involved in running clinical trials. "We hope that the new EU clinical trials directive due to come into force in 2016 will facilitate research rather than making it even more complex," she said.

The value of supporting cancer research in Europe was underlined by the strength of the studies reported at ESMO 2012. More than 2000 abstracts were presented during the congress, representing an increase of 30% from the last meeting in 2010. These included results from more than 100 phase III studies. "We're optimistic that among these will be practice-changing breakthroughs that will lead to new treatments and improved patient outcomes in the not too distant future," said ESMO Scientific Chair Professor Josep Tabernero (Vall d'Hebron University Hospital, Barcelona, Spain).

Highlights reported at the meeting included an international survey showing that cancer patients would be willing to delay treatment for up to two weeks in order to undergo tumour biomarker testing and use of personalised therapy. A study with the ALK inhibitor crizotinib revealed significant benefits in the 10% of lung cancer patients with an ALK translocation. New studies also reported on the optimal duration of treatment, with a French study with the HER-2 targeted agent trastuzumab (Herceptin) in women with HER-2 positive early breast cancer suggesting that a shorter six-month period of treatment is less effective than the standard 12 months while a second study showed that extending treatment for two years did not significantly improve outcomes.

Prof Martine Piccard.

Prof Josep Tabernero.

ESMO is lobbying about another new EU directive in development that will have a potentially important impact on clinical trials: the new Data Protection Regulation, currently in draft form. "In cancer research, we need to be able to share data," explained ESMO Scientific Chair Professor Josep Tabernero (Barcelona, Spain). ■

"For personalised medicine, we need to know more than simply that a person's tumour has particular biological characteristics. We also need to know whether drugs targeted at those characteristics will actually work for individual patients"

31st Annual Meeting of the British Neuro-oncology Society 2012

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

This year marked the 31st Annual Meeting of the British Neuro-oncology Society (BNOS), held at the Manchester Conference Centre in the heart of the city centre. BNOS has gone from strength to strength over the last 30 years and this year's annual meeting certainly lived up to previous expectations, with a dynamic programme ranging from new concepts in basic science to the latest initiatives in clinical trials.

The meeting was proceeded with an education day which gave a comprehensive overview of vast progressions in brain tumour research, including a riveting lecture from Professor Susan Short, Leeds Institute of Molecular Medicine, entitled 'The Brain Tumour Patient's Pathway: Key research questions at each stage'. Not only did the education day ensure plenty of basic science and clinical diversity, it also witnessed the first Postgraduate Forum in the form of an open discussion. Three junior investigators (Dr Laura Donovan, Dr Nel Syed and Mr Paul Brennan) presented up-to-date controversies within the neuro-oncology field resulting in engaging debates.

The quick fire 5 minute poster orals and short oral presentations were excellent ways for investigators to disseminate an overview of their work to an audience not always familiar with basic science or clinical practises. The exceptional array of presentations kept these sessions innovative and ensured that there was a plethora of compelling discussions to be had over the evening entertainment, including dinner at, and an 'access all areas' tour of Old Trafford.

Other highlights from the meeting included an outstanding British Neuropathological Society keynote lecture – 'Molecular Diagnosis of Gliomas' – from the current President of the Society for Neuro-oncology, Professor Kenneth Aldape, University of Texas MD Anderson Cancer Centre, providing a concurrent overview of current molecular profiling techniques from bench to bedside. Furthermore, Professor Normand Laperriere, University of Toronto, delivered an exceptional keynote lecture entitled 'Optimal Management of Elderly Patients with Glioblastoma'.

BNOS 2012 certainly delivered an exciting and diverse array of topics ranging from 'Epigenetic Reprogramming of Glioblastoma-derived Stem Cells' to 'Mechanism of Memory loss and Management Options' to 'Animal Model Findings in Medulloblastoma'. Following the dynamic programme from this year's BNOS I left enthused and motivated with fresh ideas and itching to get back to the bench. I am already looking forward to the 32nd Annual Meeting scheduled to be held at the University of Durham, 10th-12th July 2013, see www.bnos.org.uk for more information. ■

Dr Laura K. Donovan,
BNOS post-graduate rep and Senior Research Associate,
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Portsmouth, UK.

Awards & Appointments

Dr Schilsky Awarded Society for Translational Oncology's Pinedo Prize

The Society for Translational Oncology (STO) is pleased to announce that Dr Richard L Schilsky, MD, Professor of Medicine and Section Chief of Hematology/Oncology at the University of Chicago Department of Medicine, has been named recipient of the 2012 Bob Pinedo Cancer Care Prize. The award recognises Dr Schilsky's clinical and research leadership in the areas of gastrointestinal cancers and cancer pharmacology coupled with his compassionate care of cancer patients.

This year's Pinedo Prize of $50,000 was presented at the Third Annual STO meeting, hosted by UNC Lineberger Comprehensive Cancer Center at the Rizzo Center in Chapel Hill, N.C., October 20-21, 2012. Dr Schilsky delivered the keynote lecture, "Publicly Funded Clinical Trials and the Future of Cancer Care". The 2012 Pinedo Prize Lecture will be published by The Oncologist, STO's official journal.

An internationally recognised expert on gastrointestinal malignancies, Dr Schilsky is also a leader in the development and evaluation of new treatments for cancer. He is past Chairman of the Cancer and Leukemia Group B (CALGB), a national cancer clinical trials group sponsored by the National Cancer Institute and former chair of the Board of Scientific Advisors of the National Cancer Institute and of the Oncology Drugs Advisory Committee of FDA. ■

New Editorial Board member

Farrokh Pakzad is to join the Oncology News Editorial Board as Assistant Editor – Skin Cancer. He will co-ordinate a new Skin Cancer section in subsequent issues. Farrokh completed his higher surgical training in London, during which he was selected onto the highly competitive National Oncoplastic Fellowship program. He was awarded a MD from University College London for his thesis on the role of molecular imaging using PET in solid cancers. 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. He is currently a locum Consultant Oncoplastic Surgeon at Royal Surrey County Hospital.

Meet the Editorial Team

BTOG 2013

11th Annual BTOG Conference 2013

Wednesday 23rd January 2013 to Fri 25th January 2013
The Burlington Hotel, Dublin, Ireland

Pictured at BTOG 2012, Prof Ken O'Byrne, BTOG President

IMPORTANT DATES

Poster Abstract Submission Opens Online	1st September 2012
Registration Opens Online	1st September 2012
Hotel Booking Opens	1st September 2012
Poster Abstract Submission Deadline	31st October 2012

BTOG aims to improve the care of patients with thoracic malignancies through multidisciplinary education and encouraging the development of clinical and scientific research.

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BTOG 2013 Information is available on the website:

www.BTOG.org

Book Reviews

Targeted Therapy in Non-Small Cell Lung Cancer

David E Gerber, Published by: Oxford University Press, ISBN: 978-0-19-974308-7, Price: £9.99.

This interesting little handbook, published in 2010, provides a very good overview of the current (well current in 2010) state of the art in targeted therapy in non-small cell lung cancer (NSCLC). The book is concise and accurate. It starts with a very good overview comparing and contrasting monoclonal antibodies (mabs) and protein kinase inhibitors (nibs) and giving a fascinating insight into the nomenclature of mabs (for example -ximab denotes a chimeric antibody, -zumab a humanised antibody and mumab a fully human antibody). The book is an excellent aide-memoire of the relevant trials in the development of targeted therapy in NSCLC from 2004-2009, with all the pivotal trials summarised and well referenced.

The book does have some disadvantages. Targeted therapy is a rapidly evolving field. This book becomes out of date quickly and has an understandable US bias.

For example Gefitinib is not licenced in the US, but is standard first line therapy for EGFR mutation positive patients with NSCLC in the UK. Clinical and toxicity data is only provided for drugs commonly used in the US. Even with these caveats, this is a very useful pocket guide for those attempting to get this rapidly evolving field into focus and to understand the pivotal papers that underpin the more recent advances. It will be especially useful reading for oncologists and related healthcare professionals new to the fields of systemic lung cancer therapy. ■

Reviewed by Dr Simon Grumett, PhD FRCP
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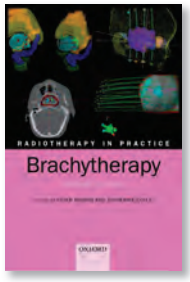
Radiotherapy in practice: Brachytherapy – 2nd Edition

Editors: Peter Hoskin and Catherine Coyle, Published by: Oxford University Press, ISBN: 978-0-19-960090-8, Price: £44.99.



This specialist text is aimed at the clinician both in training and practising radiotherapy, as well as physicists, dosimetrists, radiographers, and nurses. This updated version provides practical guidance on the use of brachytherapy; the delivery of radiation in or close to the tumour. This book was written as a practical guide to the use of brachytherapy in current practice.

Each chapter provides the reader with a good background in the physics and dosimetry of the technique, followed by information on its use in common disease sites. The first three chapters are concerned with the physics of brachytherapy. Chapter 4 discusses all aspects of radiation safety; essential knowledge for all those involved in brachytherapy treatments. The next eight chapters, discuss the role of brachytherapy in various tumour sites.

Chapter 7 is a well written and comprehensive chapter. It discusses low dose rate seed brachytherapy, from volume definition, implantation of sources, dose prescription and post implant dosimetry. Temporary high dose rate afterloading brachytherapy for localised prostate cancer section discusses HDR brachytherapy as a boost treatment following external beam radiotherapy. The implant procedure is detailed in a stepwise fashion, with the aid of photographs. Dosimetry, prescription, and outcome of treatment including side effects are described.

Chapter 8 discusses the use of brachytherapy in the palliative management of bronchus and oesophageal carcinomas. The pros and cons of treatment, the implant procedure, are easy to follow, as is the volume definition and dose prescription. Chapter 10, written by PJ Hoskin and A Sun Myint takes the reader through the implant procedure, for both LDR iridium wire, pulsed dose rate PDR or HDR afterloading. The operative procedure is described along with implant reconstruction and dosimetry. The dose prescriptions, treatment delivery are clearly stated.

The chapters concerning other tumour sites are equally well written, with good use of photographs, diagrams and references. In conclusion this book is a valuable practical guide for those involved in the provision of brachytherapy services. ■

Reviewed by Dr Karin Baria, Consultant Clinical Oncologist
Lincoln County Hospital, UK.

Journal of Clinical Oncology

Ipilimumab in Advanced Non-Small-Cell Lung Cancer

Two hundred and four patients with stage IIIB/IV NSCLC were randomised to carboplatin/paclitaxel plus ipilimumab or placebo. Ipilimumab is a monoclonal antibody targeting the CTLA-4 receptor on cytotoxic T lymphocytes (CTL). It was the first drug to demonstrate a survival advantage in metastatic melanoma in over 40 years and acts by modulating CTL's to attack tumour cells. Patients received ipilimumab/placebo on two different schedules and responding patients continued on maintenance ipilimumab/placebo. Response was assessed by immune-related response criteria and modified WHO criteria as is usual with ipilimumab studies. The study met its primary end point for phased ipilimumab (HR=0.72, p=0.05) but not for concurrent ipilimumab (HR=0.81, p=0.13). Phased ipilimumab had the most impressive results with an response rate of 32% (placebo 18%), median overall survival of 12.2 months (placebo 8.3 months) and grade 3/4 immune-related toxicity in 15% (placebo 6%). The authors conclusion was that phased ipilimumab plus carboplatin/paclitaxel improved PFS, ORR and mOS when compared to placebo and is worthy of further investigation.

This is a very interesting paper for several reasons. Immunotherapy has long been thought to be effective in renal cell cancer and melanoma, but lung cancer has not been thought to be an immunogenic tumour. This paper provides evidence that a potent immunotherapy drug (in other tumour types) improves outcomes in lung cancer. Perhaps immunotherapy does have a future in lung cancer after all. The paper does, of course, have limitations. It is a small phase II study and a three way randomisation impacts on the statistical power adversely. There appeared to be some patients entered with extensive stage SCLC, further muddying the waters. The phased ipilimumab arm performed best, but the concurrent arm also had a HR less than one and hence may have failed due to small numbers rather than lack of efficacy. The toxicities from ipilimumab were similar to those seen with the drug in melanoma (although possibly less severe in this smaller study). Overall this study probably raised more questions than it answers but it may herald a new dawn for immunotherapy in advanced lung cancer. This seems especially valid given the tantalising data for the immunotherapy drug PD-1 in lung cancer presented at ASCO this year and published in the New England Journal of Medicine in July. This paper certainly supports the idea that further investigation is warranted into the role of this drug in advanced lung cancer. The questions still remain over which schedule and which dose? – SG

Lynch TJ, Bondarenko I, Luft A, et al.
Ipilimumab in Combination with Paclitaxel and Carboplatin as first-line treatment in stage IIIB/IV Non-small-cell-lung cancer: Results from a randomized double-blind, multicenter phase II study.
JCO 2012; June:30(17):2046-54.

Indoor Tanning and Skin Cancer

This cohort study followed more than 70 000 women in the Nurses' Health Study 2 (NHSII), a large American cohort with more than 20 years follow up. The study reported that there was a dose-response relationship between the use of tanning beds and the development of basal cell carcinoma (BCC) (HR=1.15, p<0.001), squamous cell carcinoma (SCC) (HR=1.15, p=0.03) and malignant melanoma (MM) (HR=1.11, p=0.13). The association was stronger for the development of BCC if the tanning bed use was before the age of 25 (HR=1.73, p<0.001). The associations were robust after controlling for possible confounding factors.

This paper confirms the findings from several previous smaller studies and meta-analyses. The use of indoor tanning devices significantly increases the risks of skin cancer of all types, especially for those who use them before the age of 25. Basal cell carcinoma had the strongest association, but the risks of squamous cell carcinoma and melanoma (the most lethal form of skin cancer) are also increased. Interestingly, the authors have concluded that the data suggests that the carcinogenic effects of UVA and UVB radiation are similar, and hence the assertion from the indoor tanning industry that newer UVA predominant tanning beds are safer is untrue. Although the increased risk of melanoma was not as great in this study, other studies have demonstrated larger hazard ratios for the development of melanoma associated with indoor tanning and this is especially noteworthy as the incidence of melanoma is increasing rapidly, and once metastasised it is a rapidly lethal cancer in most cases. Tanning devices work by causing DNA damage leading to melanocyte activation and transfer of melanin to keratinocytes causing the desired tan. Endorphins are released during this process, which may explain the addictive nature of tanning. Radiation exposure from tanning beds can be greater than that from natural sources and the International Agency for Research on Cancer (IARC) has described tanning devices are definitely carcinogenic to humans. This study, well designed and analysed, confirms that assertion and adds to the considerable volume of data demonstrating the dangers this industry poses, especially to young skins. - SG

Use of Tanning Beds and Incidence of Skin Cancer.
Zhang M, Qureshi A, Geller A, Frazier L, Hunter D & Han J.
J Clin Oncol 2012; May: 30 (14);1588-93.

Diary of Events

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

2012

November

Palliative Care Research: A Vision for the Future
1 November 2012; Manchester, UK
W: www.christie.nhs.uk/school-of-oncology/education-events
T: +44 (0)161 446 3773
E: education.events@christie.nhs.uk

5th Royal Marsden Pain and Opioid Conference
2 November 2012; London, UK
W: www.royalmarsden.nhs.uk/painconference
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921/ 020 7808 2924

NCRI Cancer Conference
4-7 November 2012; Liverpool, UK
T: +44 (0)20 3469 5453
E: ncriconference@ncri.org.uk
W: www.ncri.org.uk/conference

24th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics
6-9 November 2012; Dublin, Ireland
W: www.ecco-org.eu/Home/Conferences/Conferences/EORTC_NCI_AACR%202012.aspx

Gynaecological Cancers Study Day
7 November 2012; London, UK
W: www.royalmarsden.nhs.uk/gynaestudy
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921/ 020 7808 2924

Responding to the needs of young people with cancer Workshop
8 November 2012; Middlesex, UK
E: anni.hall@nhs.net

Global Post Laryngectomy Rehabilitation Academy course
8-9 November 2012; Rome, Italy
W: www.gpracademy.com
E: info@gpracademy.com

NEW
Oncoplastic Breast Surgery – A Day for CNSs and Nurse Practitioners
9 November 2012; London. UK
W: www.royalmarsden.nhs.uk/oncoplastic
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921

'Going for Gold in Palliative Care' Conference
9 November 2012; Watford, UK
E: anni.hall@nhs.net

Management issues in Haematological Disorders of Children and Adults
12 November 2012; London, UK
W: www.royalmarsden.nhs.uk/haemmanagement
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921/ 020 7808 2924

NEW
TYAC Winter Education Day: Loss
14 November 2012; Coventry, UK
T: 0116 2494483 E: info@tyac.org.uk
W: www.tyac.org.uk

Central Venous Catheters
15 November 2012; Middlesex, UK
E: anni.hall@nhs.net

17th Annual Scientific Meeting of the Society of Neuro-Oncology (SNO 2012)
15-18 November 2012;
Washington, DC, USA
W: www.soc-neuro-onc.org/

4th Annual Head and Neck Conference
16 November 2012; London, UK
W: www.royalmarsden.nhs.uk/studydays
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921/ 020 7808 2924

Non-Medical Prescribing Study Day
20 November 2012; London, UK
W: www.royalmarsden.nhs.uk/nonmedicalprescribing
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921/ 020 7808 2924

Nutrition and the Cancer Patient
21 November 2012; London. UK
W: www.royalmarsden.nhs.uk/nutrition
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921

NEW
Joint ITMIG-APLCC meeting: 3rd International Thymic Malignancy Interest Group Annual Meeting
25-26 November 2012;
Fukuoka, Japan
W: www.aplcc2012.org

NEW
5th Asia Pacific Lung Cancer Conference
26-28 November 2012;
Fukuoka, Japan
W: www.aplcc2012.org

NEW
"Oncology Drug Development in Practice"
November 27-30, 2012;
Amsterdam, The Netherlands
W: http://congressbydesign.com/oncology-drug-development-course/oddp-2012-educational-program

Molecular mechanisms of targeted cancer treatments
29 November 2012; London, UK
W: www.royalmarsden.nhs.uk/molecular Henry Coleman,
E: Henry.Coleman@rmh.nhs.uk

Joint BACR/SM development of cancer medicines
29 November 2012; London, UK
W: www.bacr.org.uk or
E: bacr@leeds.ac.uk

Toxicity of Chemotherapy
29 November 2012; Manchester, UK
www.christie.nhs.uk/pro/education/events,
T: +44(0)161 446 3773
E: education.events@christie.nhs.uk

Global Post Laryngectomy Rehabilitation Academy course
29-30 November 2012;
Amsterdam, The Netherlands
www.gpracademy.com
E: info@gpracademy.com

December

Melanoma Study
3 December 2012; London, UK
W: www.royalmarsden.nhs.uk/melanoma
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921/ 020 7808 2924

Targeted treatments for haematological cancers
4 December 2012; London, UK
W: www.royalmarsden.nhs.uk/targetedtreatment Henry Coleman,
E: Henry.Coleman@rmh.nhs.uk

Global Post Laryngectomy Rehabilitation Academy course
6-7 December 2012; Moscow, Russia
www.gpracademy.com
E: info@gpracademy.com

The Tumour Stroma and Disease Progression - Targeted Therapies and Treatment Response
7 December 2012; London, UK
British Institute of Radiology
E: admin@bir.org.uk

Essential Communications Skills (Time to Listen)
7 December 2012; Middlesex, UK
E: anni.hall@nhs.net

Mandatory Chemotherapy Update for Trained Nurses
11 December 2012; Middlesex, UK
E: anni.hall@nhs.net

2013

January

Pancreatic & Hepatobiliary Cancer
14 January 20123 Manchester, UK
www.christie.nhs.uk/pro/education/events,
T: +44(0)161 446 3773
E: education.events@christie.nhs.uk

NEW
Teleconference: Principles of medical treatment for younger women
17 January 2013; London, UK
T: 0845 092 0802
W: www.breastcancercare.org.uk/training
E: nursetraining@breastcancercare.org.uk

After all the Treatment: The delayed effects of disease and treatment interventions on individuals who have had a Head and Neck Cancer
21 January 2013; London, UK
W: www.royalmarsden.nhs.uk/headandneck
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921/ 020 7808 2924

An Introduction to Acute Oncology
21 January 20123 Manchester, UK
www.christie.nhs.uk/pro/education/events,
T: +44(0)161 446 3773
E: education.events@christie.nhs.uk

Lymphoedema: Application of Core Skills and Knowledge (Level 3)
21 January 2013; Glasgow, UK
Margaret Sneddon,
T: +44(0)141 330 2072
E: lymph@glasgow.ac.uk

Lymphoedema Specialist Practice (Level 4 and M)
21 January 2013; Glasgow, UK
Margaret Sneddon,
T: +44(0)141 330 2072
E: lymph@glasgow.ac.uk

Endometrial Cancer
22 January 2013 Manchester, UK
www.christie.nhs.uk/pro/education/events,
T: +44(0)161 446 3773
E: education.events@christie.nhs.uk

Molecular pathology and targeted treatments for urological cancers
23 January 2013; London, UK
W: royalmarsden.nhs.uk/studydays
Henry Coleman,
E: Henry.Coleman@rmh.nhs.uk

Joint 34th EORTC-PAMM – BACR Winter Meeting
23-26 January 2013; Cardiff, Wales
W: www.bacr.org.uk or
E: bacr@leeds.ac.uk

11th Annual BTOG Conference 2013
23-25 January 2013; Dublin, Ireland
www.BTOG.org

February

International Conference on Innovative Approaches in Head and Neck Oncology
7-9 February 2013; Barcelona, Spain
www.estro-events.org

NEW
Teleconference: Menopausal symptoms – what can we suggest to our patients?
20 February 2013; London, UK
T: 0845 092 0802
W: www.breastcancercare.org.uk/training
E: nursetraining@breastcancercare.org.uk

2012 NCRI Cancer Conference Trade Exhibition

List of confirmed exhibitors (as of 21st October 2012)

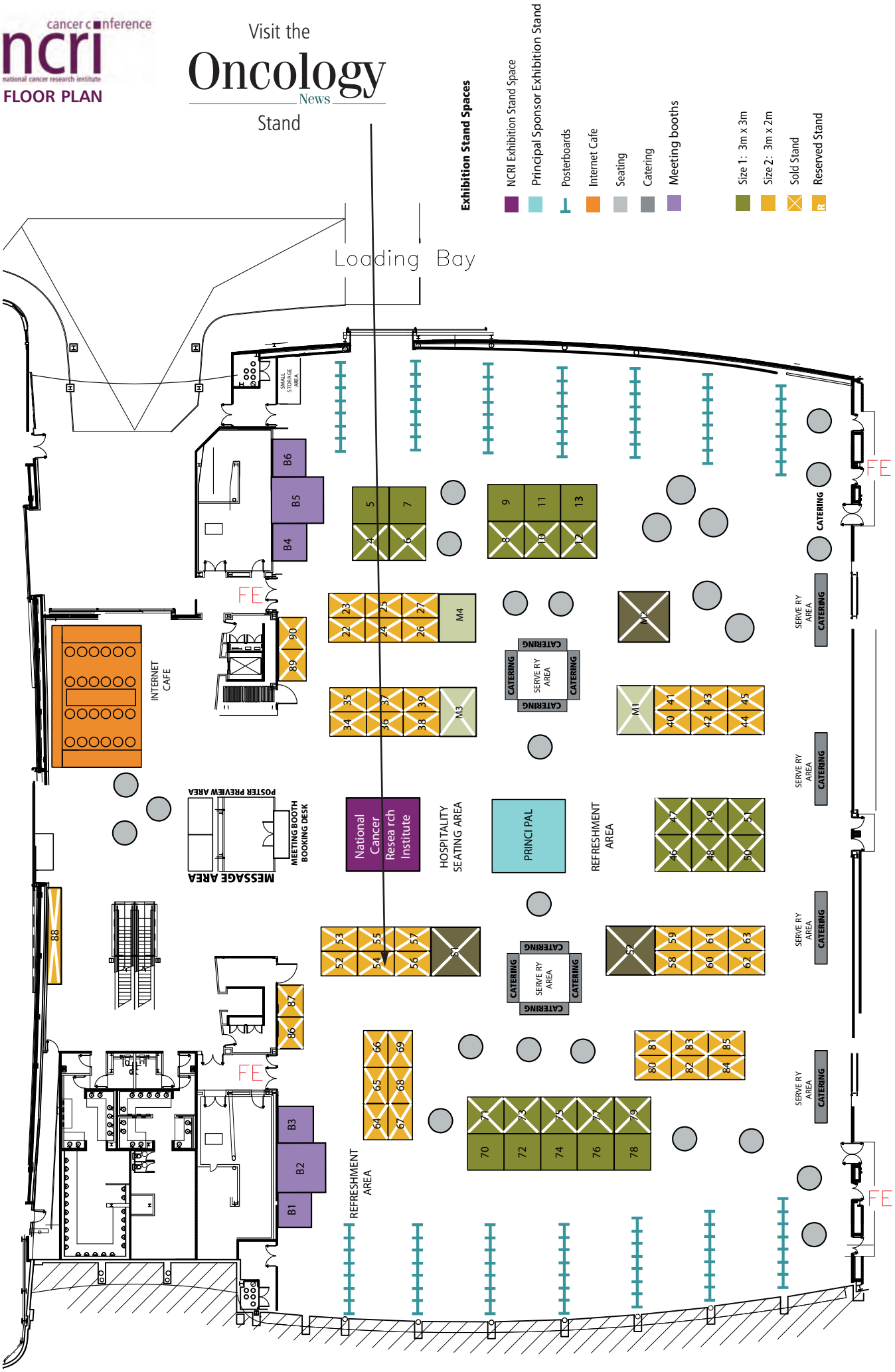
Exhibitor	Stand
Abcam Plc	08
Affymetrix	82
AICR (Association for International Cancer Research)	65*
Aldevron Freiburg	26*
American Peptide Company Inc	58
Amsbio	56
Barts Cancer Institute	04
Bioline Reagents Ltd	71
Bristol-Myers Squibb	35*
British Association for Cancer Research (BACR)	87
Cancer Clinical Trials Unit Scotland (CaCTUS)	37
Cancer Research Technology Ltd	59
Cancer Research UK	S2
Charles River UK Ltd	79
College of Radiographers	89
Consumer Liaison Group	38
Enzo Life Sciences (ELS)	AG40
Essen Bioscience Ltd	53
Eurogentec	83
Fluidigm Europe B.V	51*
FluidX	66
GlaxoSmithKline	M2
Greiner Bio-One	47
Integrated DNA Technologies	22
Lab Mode Ltd	49*
Labtech International Ltd	84*
Leukaemia Care	43*
LI-COR Biosciences UK Ltd	69
Liverpool Cancer Research UK Centre	12
Macmillan Cancer Support	S1
Manchester Cancer Research Centre	46
Marie Curie Cancer Care	80
MDS UK Patient Support Group	41*
NanoString Technologies	48
National Cancer Action Team	52*
New England Biolabs	81
Newcastle Cancer Centre	90*
NIHR Cancer Research Network (NCRN)	36
Oracle Health Sciences	07*
Paxman Coolers Ltd	45*
Pierre Fabre	27
Porvair Filtration Group	55*
Promega UK Ltd	63
Qiagen	06
RainDance Technologies	57
Roche Applied Science	23*
Roche Products Limited	Principal
Roy Castle Lung Cancer Foundation	25
Science & Technology Facilities Council (STFC)	10
Sequenom GmbH	44
Sirtex Medical Europe GmbH	67*
Source Bioscience Plc	39*
Takara Bio Europe	42*
Target Ovarian Cancer	61*
Tebu-Bio Ltd	62*
The Francis Crick Institute	50
The Royal College of Radiologists	86*
TissueGnostics GmbH	M3
Tutela Monitoring Systems	85*
UCL Cancer Institute	M1
University of Southampton Clinical Trials Unit	24
Varian Medical Systems UK Ltd	64*
VH Bio Ltd	68
Wales Cancer Bank	75
Wales Cancer Research Network	73
Wales Cancer Trials Unit	77
Warwick Clinical Trials Unit	60
Wheaton	34
Wisepress	88

(* New exhibitors)

cancer conference
ncri
national cancer research institute

FLOOR PLAN

Visit the Oncology News Stand



News update

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

Varian Publishes 2012 Sustainability Report

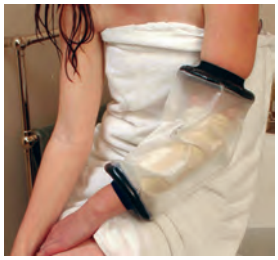
Varian Medical Systems, a world leader in radiotherapy and X-Ray imaging technology, is announcing the publication of its 2012 Corporate Social Responsibility report, detailing the company's policies and achievements in extending care, protecting resources and helping to save lives. The Varian Sustainability Report 2012 has been produced as part of a wider company investment to continually improve sustainability performance and transparency.

"In our inaugural report last year we made a commitment to produce annual updates so we could measure our achievements against defined sustainability goals," said Tim Guertin, president and chief executive officer of Varian Medical Systems. "Companies such as ours have a responsibility to achieve our business goals in a socially and environmentally responsible manner. While we continue to develop better therapeutic capabilities for fighting cancer and other diseases as well as better components for X-Ray imaging and for cargo screening, we continually strive to do so in ways which extend access to advanced care, improve clinical outcomes, optimize safety and make a positive impact on the communities where we operate."

Two years ago, Varian commenced a company-wide undertaking to examine sustainability performance and identify challenges and opportunities to be addressed over time. This effort involved the close participation of senior leaders from all divisions, key geographies, and core functions.

Varian's Sustainability Report 2012 is available to download at: http://www.varian.com/us/corporate/corporate_citizenship/corporate_social_responsibility.html

Patients can now shower without the fear of getting their PICC line wet



LimbO has been serving professionals and patients for the last seventeen years with our waterproof protectors for casts and dressings. We are currently the UK's leading manufacturer in waterproof limb covers and are proud of our excellent customer service and fast delivery times. You can find our information in over 700 hospitals and clinics including orthopaedics, podiatrist, diabetes clinics, and oncology units.

LimbO range of waterproof protectors are a PVC cover strengthened with nylon thread. We use a soft neoprene seal which is designed not to restrict blood flow but to create a friction barrier against water.

We also manufacture PICC line covers (known as M65 and M75) so patients can now shower without the fear of getting the PICC line wet. The two seals grip above and below the limb joint to form a watertight sleeve which will last throughout the patient's treatment.

For more information: T: +44 (0)1243 574694, W: www.limboproducts.co.uk
E: sales@limboproducts.co.uk

Lord Lieutenant of West Sussex Presents Queen's Award for Enterprise to Elekta

Her Majesty's Lord Lieutenant of West Sussex officially presented The Queen's Award for Enterprise 2012: International Trade to Elekta, a leading global medical technology company dedicated to oncology and neuroscience clinical advancements. Dignitaries representing The Queen, West Sussex County Council, Crawley Borough Council and local Crawley MP, The Rt. Hon. Henry Smith, attended the ceremonial presentation.

The Queen's Award, confirmed in April 2012, is the UK's highest accolade for business success, and acknowledges continuous improvement in Elekta's overseas sales. Elekta's steady growth of exports is calculated at 131 percent over the last six years. In addition to The Queen's Award presentation, the official party toured Elekta and participated in an informal reception.

"The presentation of The Queen's Award was a celebration of the skill and commitment of our staff and the support of valued customers at home and overseas," says Bill Yaeger, Executive Vice President Elekta Oncology. "Crawley is world renowned as the home of the digital linear accelerator, and we are pleased that Elekta's employees and clinical partners can be proud of The Queen's Award and in our tradition of improving the lives of individuals with cancer."

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

Siemens announces plans for UK syngo training facility

Siemens Healthcare is to open a UK based training facility for syngo®.via customers at its headquarters in Frimley, Surrey.

Siemens Healthcare is to open a UK based training facility for syngo®.via customers at its headquarters in Frimley, Surrey. The Siemens syngo.via Training Academy will enjoy state-of-the-art training facilities for the provision of specialist IT and Clinical Application training courses. The aim is to support Siemens' installed customer base to enhance their experience and knowledge with the solution's capabilities, including efficient and structured workflows, plus networking images across modalities, mobile devices or web browsers.

Over 60 syngo.via systems are currently installed in the UK alone, and the increased demand for targeted training has prompted Siemens to establish plans for a national training base. This ensures customers can have easy and cost effective access to specialist training without the need for expensive international travelling. The Siemens syngo.via Training Academy is planning to hold its first training courses in the autumn and Siemens will contact its customers with a timetable once the schedule has been finalised.

syngo.via is a multi-modality advanced visualisation solution that automatically prepares cases for reading and reporting according to condition-specific requirements. As part of the syngo family of products from Siemens Healthcare, syngo.via can either be used as a standalone device or integrated with a variety of other applications from the range, such as syngo.plaza PACS.

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

Brain Tumour Research inviting prospective centres to partner with us

We are delighted to announce that the continued growth of the charity Brain Tumour Research and our family of member charities brings us closer to achieving our mission of raising at least £7 million per annum in order to support seven centres of dedicated brain tumour research across the UK. We are proud to now be in a position to build on the encouraging results we are seeing through funding the centre at the University of Portsmouth, to be able to contribute further to accelerating progress in brain tumour research in the UK, by inviting prospective centres to partner with us, so that together we can continue to make a clinical difference and most importantly improve the outcomes for brain tumour patients.

It is our strategic goal at this stage to support the development of dedicated centres of brain tumour research by providing funding towards programmes of research. This will enable sharing of knowledge through critical mass and will promote the future sustainability of brain tumour research in the UK instead of funding individual project grants. Our criteria for selection includes: centres where brain tumour research is already being carried out, where the lead investigator has a track record of brain tumour research including peer-reviewed publication, where the programme of research is unique and shows evidence of collaboration with other centres.

We are looking to support the development of a further one or two centres dedicated to brain tumour research with a programme that demonstrates a balance of projects which may include studies on high and / or low grade tumours, specific tumour types, affecting adults, children or both.

We are asking investigators to submit a one page (500 words) summary of your plans, outlining the programme of research that will be undertaken and demonstrating how your centre matches our criteria and can meet our conditions, supported by relevant documentation, and sent to me by email to sue@braintumourresearch.org by Friday 2nd November 2012.

If you require further the information pack or would like to discuss this further please do not hesitate to contact me on 01296 733011.

Yours in hope
Sue Farrington Smith
Director, Brain Tumour Research

Brain Tumour Research
Funding the fight

UK Center Combines Elekta's Agility Beam-shaping Solution with Fast VMAT Delivery

Less than three months after beginning clinical use of their Elekta Agility™* 160-leaf MLC, physicians at The James Cook University Hospital have achieved another benchmark – their first use of Agility to deliver radiation therapy employing VMAT. The ability to accelerate both beam shaping and beam delivery with Agility and VMAT cut 57 seconds off the beam delivery time of the patient, a 61-year-old male with prostate cancer.

The patient received his first treatment fraction, a single 200-degree VMAT arc, which took just 83 seconds to deliver. In comparison, a three-field 3D conformal treatment would have taken 140 seconds, a 40.7 percent reduction in beam delivery time. When factoring in image guidance, the total treatment time-savings was 72 seconds.

"This was our first experience with VMAT and it went very well," says Christopher Walker, Head of Radiotherapy Physics at The James Cook University Hospital. "The treatment speed not only reduces the likelihood that the patient will move and that the internal organs will shift position, but it also contributes to faster patient throughput. With Agility / VMAT we expect to be able to treat five patients per hour."

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

**Agility is CE marked but not available for sale or distribution in all markets. Please contact the local Elekta representative for details.*

Cancer Centre Uses High Intensity Mode on Varian TrueBeam

Clinicians at Beatson West of Scotland Cancer Centre in Glasgow have commenced brain radiosurgery treatments that enable patients to spend less time on the treatment table while aiding precision by minimising the chance of movement during treatment. Doctors at the Centre have begun delivering the pioneering treatments using a TrueBeam™ STx linear accelerator from Varian Medical Systems.

A 71-year-old female with breast cancer that metastasised to her brain received treatment for two small brain metastases – just 5mm and 6mm in diameter – in a single treatment. "Reducing the time the patient spends on the treatment couch reduces the opportunity for movement during the treatment, which helps enhance precision." said clinical oncologist Dr Brian Clark.

In addition to the High Intensity Mode, the first treatment utilised Varian's RapidArc® technology for dose delivery. RapidArc makes it possible to complete a precise treatment by delivering dose continuously during just one or two rotations of the machine around the patient. During treatment, the beam is continually reshaped to conform the dose to the size, shape, and location of the tumour and minimise the dose to surrounding healthy tissue. By using a two-arc approach and delivering the dose at 2400 monitor units per minute doctors were able to deliver the full prescribed radiosurgery dose of 25 Gy within a single session, with a "beam on" time of five minutes.

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

NCRI – Essen BioScience – Stand No 53

Essen BioScience Inc, a global provider of life science research tools and services, will be showing its new live-cell imaging system the IncuCyte ZOOM™, as well as an expanded line of novel CellPlayer™ reagents specifically developed by Essen for use on the platform.

A unique aspect of the IncuCyte is the ability to acquire images automatically from within the user's own cell culture incubator, enabling around-the-clock observations without removing the cells from their physiological environment. Integrated software provides full quantification of the real-time biological processes under observation. New features on the ZOOM include multi-fluorescent colours, support of multiple magnifications, enhanced phase contrast processing and more speed. With a strong focus on cancer applications new CellPlayer™ reagents, assays covering migration, invasion, apoptosis, cytotoxicity, angiogenesis, proliferation and the IncuCyte Zoom are an invaluable fully-integrated solution for quantitative long-term kinetic biology.

To learn more about the approach we call Live Content Imaging visit us at NCRI stand 53 or W: www.essenbio.com

Latest on alternative treatment for malignant ascites

New data on the treatment of malignant ascites with Removab® (catumaxomab) showed maintenance of quality of life during therapy and an improvement after treatment. This may be attributed to the improvement of ascites symptoms and the fact, that the majority of patients had no therapeutic ascites puncture until their death. [1]

As Hani Gabra, Professor of Medical Oncology, Imperial College London says: "Drainage of malignant ascites by paracentesis is an invasive procedure that is strictly palliative. Treatment effect is of short duration and requires repeated paracenteses. For a condition such as this the therapeutic options are limited and it is good to have an alternative to consider."

Contact nigel.foulkes@fresenius-biotech.com, call 07800 708485 or visit www.removab.com for further details about Removab®, an alternative treatment for malignant ascites in patients with EpCAM-positive carcinomas.

1. Lordick F et al. Maintenance of quality of life in patients with malignant ascites during treatment with the trifunctional antibody catumaxomab: results from the phase III b CASIMAS trial. ESMO 2012; abstr. 1596P

Varian's 'GPS for the Body' Real-Time Tracking System

Clinicians at the Harley Street Clinic in London are using the Calypso® 'GPS for the Body' system from Varian Medical Systems to provide real-time tracking of tumours during prostate cancer radiotherapy treatments.

"This really is the gold standard for real-time tracking and we are finding that as patients learn about the system, an increasing number are requesting that we make use of Calypso transponders during their treatments," said Neil Livingstone, treatment superintendent. "We hope that an increase in precision may help minimise radiation to healthy tissue while giving our clinicians additional confidence to deliver higher doses."

At the Harley Street Clinic, clinicians are using the real-time tracking capabilities of Calypso to reduce the amount of healthy tissue exposed to the treatment beam. Three Calypso transponders are inserted into the prostate, where they provide continuous real-time information. The position of the markers is tracked continuously throughout a treatment session to help keep the beam on target. If the targeted area moves outside the treatment beam, the treatment is automatically halted.

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

NCRI – Paxman – Stand No 45 Saving hair, preserving dignity, retaining confidence

As a UK based Company with a national and international presence Paxman continues to be the preferred and most used scalp cooling system within the United Kingdom.

The revolutionary Paxman hair loss prevention system is responsible for helping thousands of cancer patients to maintain an outwardly 'normal' appearance whilst undergoing their chemotherapy treatment.

Our mission of continuous advancement in scalp cooling technology ensures patients worldwide can attain the best possible results, keep their hair and maintain their dignity at this difficult time. It is well documented that chemotherapy-induced hair loss has a negative impact on patients' psychosocial wellbeing and anything that can help maintain a positive attitude is to be encouraged.

Help raise awareness and join our campaign for scalp cooling to be offered as the standard treatment practice for all applicable cancer patients undergoing chemotherapy in the UK!

For further information visit:
www.paxman-coolers.com www.coolheadwarmheart.co.uk
@Paxmancoldcap
@CHWHcampaign

paxman

Cool head warm heart
Cold Cap Hair Retention During Chemo

Made in Britain

Give BTR Christmas Cards, Host a Christmas Gift Party… Give Hope

Brain Tumour Research Christmas Cards start from just £3 per pack of 10, providing another opportunity to help improve outcomes for the thousands of patients and their families living with the diagnosis of a brain tumour.

You can ask for a mixed box of Christmas Cards to sell or host a Christmas gift event. Request a donation in return for drinks or supper sell Christmas cards, jewellery, clothes and gifts, and hold a raffle.

Proceeds are approx £2 per pack and go directly to funding much needed brain tumour research and help find a cure for this most devastating of diseases, which kills more children and adults under the age of 40 than any other cancer.

W: www.braintumourresearch.org
or E: sarah@braintumourresearch.org.
To send personalised Christmas cards, visit www.charitychristmascards.com, up to 50p per card is given directly to Brain Tumour Research. Choose your design, select the card, personalise it, preview, select quantity, add to order and choose Brain Tumour Research as your selected charity on the order form… It's that simple.

...twice the leaves at twice the speed

Agility is not licensed for sale in all markets. Please contact your local Elekta representative for details.

With Agility™, it's reality.

As the ultimate device for advancing modern radiotherapy, Elekta's Agility MLC precisely sculpts radiation with 160 high-resolution leaves across a 40 cm x 40 cm field. Capable of managing the broadest spectrum of therapies, Agility also boasts ultra-fast leaf movements with extraordinarily low leakage to maximize the potential for advanced techniques such as SRS, SRT and VMAT.

4513 371 0993 03:12

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ELEKTA