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Oncology News

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Brain Tumour Research - Wear A Hat Day, see page 60 for further details

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Because more than one pathway promotes angiogenesis

isn't it time to consider inhibiting more than one pathway?[1–4]

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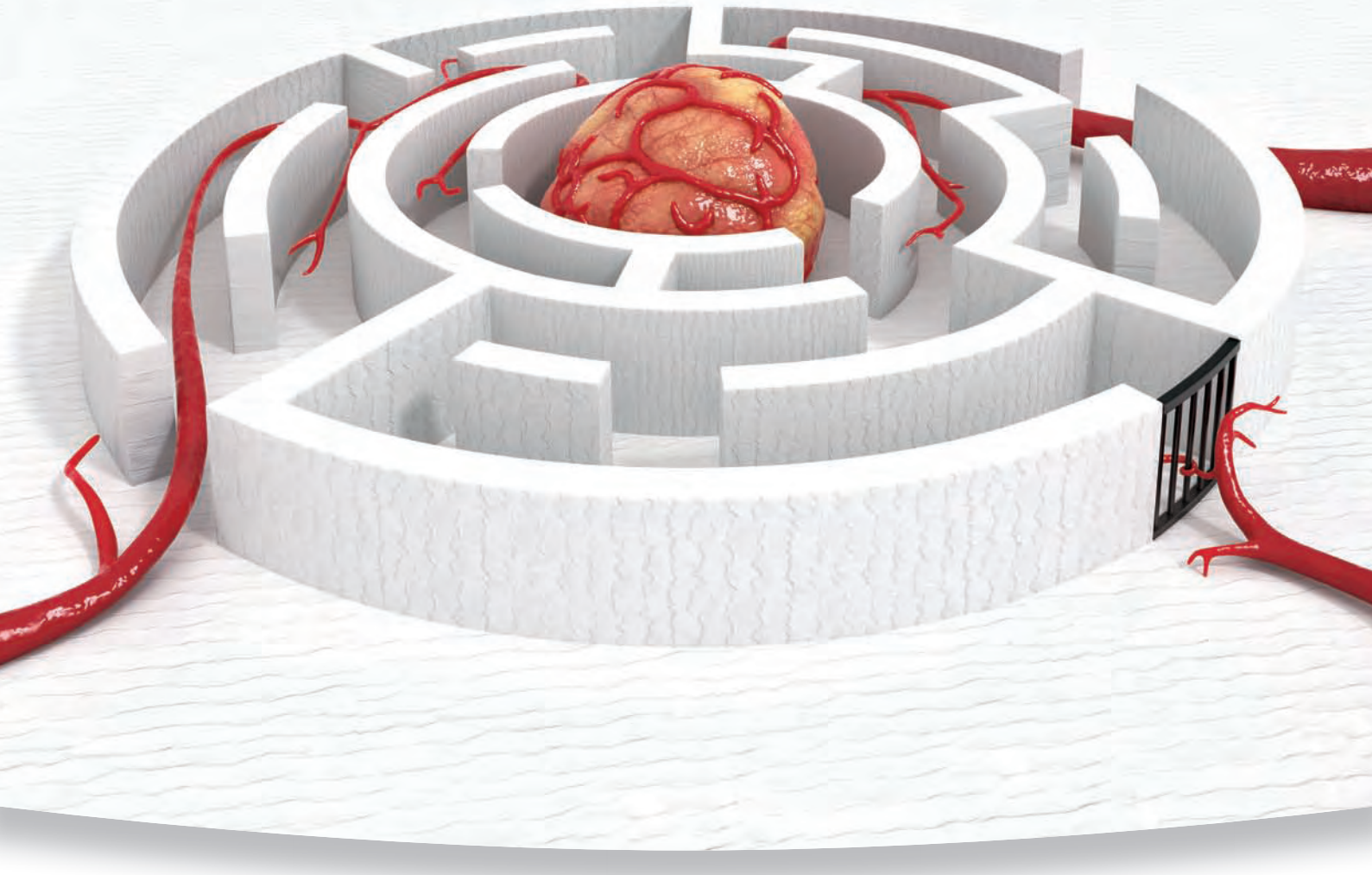

References:
1. Fischer C, Jonckx B, Mazzone M, et al. *Cell*. 2007;131:463–475.
2. Ellis LM, Hicklin DJ. *Clinical Cancer Research*. 2008;14:6371–6375.
3. Eichholz A, Merchant S, Gaya AM. *OncoTargets and Therapy*. 2010;3:69–82.
4. Taylor AP, Rodriguez M, Adams K, et al. *Int J Cancer*. 2003;105:158–164.

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REGENERON SANOFI

Cancer During Pregnancy

Denys Wheatley, Editor.

In searches on the web for information on medical conditions, the two at the top of the list are 'pregnancy' and 'cancer', according to data released by PRNewswire. But how many searches are for a combination of two medical conditions; very few indeed. Other recent press releases from the proceedings of the American Association for Cancer Research and the European Breast Cancer Conference, however, deal with these self-same discriminators together! One of the important recommendations has been that obstetricians, gynaecologists, other doctors and maternity care specialists need to be increasingly aware that cancer can arise during pregnancy, and that detecting and diagnosing it from symptoms over and above the changes of pregnancy itself might make things more difficult, with extra caution being needed in the techniques chosen for diagnostic purposes. Greater surveillance is therefore called for, and pregnant women also need to be given more information/education to know that cancers can and do arise during pregnancy, so that they should also be alerted to the possibility that any suspicious (pathological) change, such as the sudden growth, spread or ulceration of a breast lesion, needs to be divulged. It is not necessarily that pregnancy per se affects the incidence of cancers developing, but it is possible that pregnancy can turn some incipient cancers into overt ones.

The next salient point relates to age. Since women are now deferring child-bearing for a decade or more compared with the situation 20-30 years ago, they are more likely to develop cancer in the same way as the non-pregnant age-matched population. Apart from breast cancers, other cancers found in pregnant women are of the ovary, haematological malignancies, cervical cancer and melanomas. The less common types of tumours seen include gastrointestinal, urological and lung cancers [1]. However, the possibility of cancer developing during gestation has to be kept in perspective as the incidence is very low, most estimates being about 0.1% (1:1000). Malignant ovarian tumours, for example, might occur in only 3-5% of this small proportion [reviewed in 2,3].

How pregnancy itself might impact on the biological behaviour of tumours remains an interesting subject for further research, and may reveal a whole spectrum of differences, for example, because the oestrogen receptor status of developing breast tumours might range widely. In this regard, one particularly relevant observation is that breast cancer cases diagnosed during pregnancy tend, by a factor of 2.5, which is not insignificant, to be of more advanced stages than those arising in non-pregnant women of the same age.

It is clear that pregnancy affects cancer, and it must be as true that cancer affects pregnancy. Equally, the action of chemotherapeutic interventions is likely to be different in many women during pregnancy than in non-pregnant women. But there is not just one life to deal with here; the effects of treatment of any kind on the foetus must be very carefully considered. There is clear evidence from some quarters that certain drugs should be avoided, e.g. trastuzumab and tamoxifen [2], and others that appear to be safer have been recommended [4,5]. Dose levels need to be carefully adjusted and the effects closely monitored on mother and foetus. The treatment schedule must also be carefully planned, preferably after 14 weeks of gestation, because there are times during development when the foetus is particularly vulnerable, such as during brain growth and the development of neuronal co-ordination, because these processes are saltatory rather than continuous [6].

Finally, with regard to outcomes, overall and disease-free survival rates for pregnant women with breast cancer are disappointingly about 20% lower than in non-pregnant controls with breast cancer [6]. Pregnancy can be fraught with many problems, and cancer contributes a small but added complication that in future needs to be kept firmly in mind.

References

1. Pavlidis N. *Cancer and pregnancy: what should we know about the management with systemic treatment of pregnant women with cancer?* Eur J Cancer. 2011; 47 Suppl 3:S348-52.
2. Amant F, Loibl S, Neven P, Van Calsteren K.Lancet. *Breast cancer in pregnancy.* Lancet 2012 11;379:570-9.
3. Hoellen F, Reibke R, Hornemann K, Thill M, Luedders DW, Kelling K, Hornemann A, Bohlmann MK. *Cancer in pregnancy. Part II: treatment options of breast and other non-gynecological malignancies.* Arch Gynecol Obstet. 2011;284:1481-94. Epub 2011, Aug 20.
4. Berveiller P, Veyrie N, Rouzier R, Carbonne B, Mir O. *Anti-cancer agents for breast cancer treatment during pregnancy.* J Surg Oncol. 2011;104:560.
5. McGrath SE, Ring A. *Chemotherapy for breast cancer in pregnancy: evidence and guidance for oncologists.* Ther Adv Med Oncol. 2011 3:73-83.
6. Ali SA, Gupta S, Sehgal R, Vogel V. Breast J. 2012;18:139-44. *Survival outcomes in pregnancy associated breast cancer: a retrospective case control study.*

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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

12th Meeting of the International Society of Geriatric Oncology

Date: October 25-27, 2012. **Venue:** Manchester, UK. **PREVIEW**


Riccardo Audisio

Building on the success of the 2011 SIOG Congress in Paris, the 12th Congress is to be held in October in Manchester, UK. It is the first time the International Society of Geriatric Oncology has visited the United Kingdom and special celebratory arrangements have been set in place. The UK has a high reputation for charity work; it is for this reason that voluntary bodies will be taking an active part during this year's event and so will the Department of Health, which has been extremely sensitive to the issues of discrimination and inequalities, establishing NCEI (National Cancer Equalities Initiative) and promoting research in the field of geriatric oncology (GO).

Top profile researchers in the field will be in attendance to disclose their findings and debate controversial issues. This is internationally recognised as "the" meeting where the oncogeriatric community gathers and discusses. Basic scientists, medical-, surgical- and radiation-oncologists, geriatricians, nurses, anaesthetists, charity workers and politicians will be there with the common purpose of improving cancer management in older patients.

According to our tradition, the scientific programme will focus on issues relevant to clinical practice, and the congress will open with updates on surgery, medical oncology, radiation oncology, geriatrics and nursing.

A round table will follow on the biology and the multimodal management of lung cancer. International speakers will then discuss targeted therapies for breast cancer while a second parallel session is entirely dedicated to melanoma in older patients.

Mental problems are highly prevalent amongst senior patients, affecting treatment planning and communication, consenting and compliance to treatment. It is for this reason that a full session will focus on the treatment of people with dementia, where several high-profile geriatricians will present and discuss.

Poor recruitment of older patients into clinical trials has been widely noticed; this is relevant to surgical patients, the medically treated, radiotherapy series and so no. The result is the unfortunate lack of evidence-based knowledge for this age group. A whole workshop will discuss the enrolment of older cancer patients into randomised clinical investigations.

Two symposia will close the first day, one on post-operative pain and the other on nutrition, with world-renowned speakers in attendance.

A social dinner will facilitate discussion and a friendly, collegial interaction between the variegated onco-geriatric community. The presence of outstanding geriatric champions is foreseen.

The second day will open with proffered papers, followed by a workshop on the implementation of a geriatric oncology clinic in our daily practice.

The session on 'muscle, cancer and ageing' will discuss the complex interaction between sarcopenia, compliance with chemotherapy, the reversion of muscular loss through exercise and pharmacological intervention.

Special issues relevant to the treatment of haematological malignancies in older patients will be the topic of an entirely dedicated session during which international speakers will confront their views and discuss practical problems.

A broad outlook at the epidemiology of geriatric oncology, its associated costs and implications on the community will complete the morning.

After the lunch break, a parallel session will debate on CGA, frailty and intervention: screening tools will be discussed and confronted and the latest CPEx findings on older cancer patients will be presented.

A second session will be centred on prostate cancer, it's high prevalence, surgical treatment, newly developed medications and patients' real expectations.

A report from SIOG task forces will summarise recent findings, most of which have been recently submitted for publication to high impact-factor journals.

A session designed to present and debate the central support from charities and the Department of Health will put together stakeholders such as Macmillan, AgeUK, Breakthrough Breast Cancer and leaders form the National Cancer Equalities Initiative.

The congress will close with the Paul Calabresi Award and a conclusive presidential speech.

Proffered papers from delegates will be presented every day and posters will display experiences and facilitate the discussion; the best one be rewarded with a prize.

Meet-the-Professor sessions will deal with career development of geriatric oncology and with ways to set up a multidisciplinary GO team.

For the very first time SIOG will be running a restricted meeting on basic science issues. This will take place on Thursday 25th October and will involve 100 researchers. This workshop is intended as a brainstorming opportunity for aging and cancer researchers to facilitate collaborative bedside to bench to bedside research, and to identify funding strategies.

Topics open for debate will be cell senescence, immuno-senescence and cancer. Barriers to research and limitations of funding on this topic will be collegially debated, taking into account models such as the use of mTOR inhibitor trials to learn about aging and its interaction with cancer. This unprecedented research debate will assist in identifying the path for future research and fundraising.

We have all by now realised how many elderly patients we are dealing with in our busy clinical practice. Those who have an interest in optimising their clinical performance and tailoring treatment plans to every individual patient according to his/her frailty, rather than to the mare anagraphic age, are mostly welcome to contribute to the debate in Manchester, for the 12th SIOG International Congress. ■

Riccardo Audisio, Scientific Chair, SIOG President.

2nd National Conference of the Independent Association of Nurses in Palliative Care incorporating the AGM

Date: 14 June, 2012. **Venue:** Manchester, UK. **PREVIEW**

This conference is open to all health and social care professionals who care for people with a life limiting illness. It is not restricted to members of the association.

Following the success of the association's first conference in 2011 the IANPC can confirm that Elaine Owen, End of Life Care Lead, Acute and Specialist Services at Cheshire and Merseyside Clinical Networks, has accepted the invitation to present the keynote address: Societal engagement with death and dying at this year's conference.

Other sessions:

- ACP in dementia: reducing burdensome interventions in the last year of life - Dr Becky Bancroft Consultant Geriatrician, Liverpool
- What patients want from ACP? - Dr Phil Swarbrick, Medical Director, Ulverston
- Deciding right – a regional approach to making care decisions in advance - Dr Claud Regnard, Consultant in Palliative Care Medicine, Newcastle-upon-Tyne
- Taking ACP forward - Les Storey, National Lead, Preferred Priorities for Care, National End of Life Care Programme
- Workshop sessions will cover: Having the conversation - interactive communication skills - Elaine Stevens, Chairperson IANPC and Ethical and legal issues in advance care planning - Susan Jackson, University of West of Scotland
- The AGM of the IANPC will be held during the lunch break for all IANPC members

The aims of the Association are:

- To promote equity of access to high quality palliative care for people with advanced progressive disease regardless of diagnosis or place of care
- To promote palliative nursing education through the provision of educational events
- To inform international, national and local palliative care strategies, policies and systems of care
- To share good nursing practice through a dedicated website and an electronic newsletter
- To protect vulnerable dying people by rejecting the need for assisted dying ■

INDEPENDENT ASSOCIATION OF NURSES IN PALLIATIVE CARE IANPC

Further details of the association and the full conference programme can be found on the IANPC website www.ianpc.org or E: kate@compleatconference.co.uk

Awards & Appointments

Global award for cancer drug success

A multidisciplinary team from The Institute of Cancer Research (ICR) and The Royal Marsden Hospital has won a prestigious global award for its success in taking new cancer drugs from concept to patients. This is the first time the American Association for Cancer Research (AACR) Team Science Award has been won outside the US.

The AACR said its decision was based on "the tremendous impact this team has had in preclinical and clinical studies of cancer therapeutics".

The Team members are from the Cancer Research UK Cancer Therapeutics Unit at the ICR, which discovers new drugs, and the Drug Development Unit at the ICR and The Royal Marsden, which progresses drug candidates into clinical trials.

The AACR highlighted the team's world-leading discovery of 16 innovative drug candidates over the past six years, and the progression of six of these drugs into Phase I clinical trials, along with the discovery and development of abiraterone acetate. This new treatment for advanced prostate cancer, which is now licensed in the UK and the US, was an "outstanding example of how a highly functioning translational team can rapidly translate a biologic hypothesis into a new cancer therapeutic."

"Overall, the work carried out by this multidisciplinary team over the last six years provides an outstanding example of the non-profit

cancer drug discovery and development model that they have pioneered, as well as exemplifying a meritorious ability to collaborate productively with industry to accelerate patient benefit," the AACR Award citation said.

Award Team leader Professor Paul Workman, Director of the ICR's Cancer Research UK Cancer Therapeutics Unit, says: "We are thrilled that we have been able to make a real and ongoing impact on the lives of cancer patients."

The prize was presented on April 1 during the AACR Annual Meeting. ■

$10 million boost for efforts to personalise prostate cancer treatment


Professor Johann de Bono

Professor Johann de Bono from The Institute of Cancer Research (ICR) and The Royal Marsden has been selected as part of a global prostate cancer "Dream Team" given $10 million to drive the development of personalised treatment for this disease.

Stand Up to Cancer, the Prostate Cancer Foundation and the American Association for Cancer Research chose Dream Team members from five leading prostate cancer clinical research centres in the US and London.

"We have made great strides forward in developing new drugs to treat men with prostate cancer, along with the technology needed to examine the DNA faults causing these cancers. This project represents the next step – a global effort to combine these two advances to create a truly personalised approach to treating prostate cancers," Professor de Bono said. "This collaboration should make a real and lasting difference to the way we care for men with advanced prostate cancer."

In recent years a number of new drugs have been shown to extend life for men with advanced prostate cancer, including several that Professor de Bono and his colleagues at the ICR and The Royal Marsden helped develop. Genetic differences between prostate cancers can affect the way they react to treatments. The Dream Team therefore aims to devise tests that can help doctors determine which of these new options – and future experimental drugs - will best benefit their patients.

Over their three-year project, the Dream Team will systematically scan the genomes of patients with advanced metastatic cancer. They will look for gene alterations that are more common in patients who respond to therapies, as well as alterations in patients who develop resistance to the drugs. Ultimately, they hope to identify a panel of biological markers that doctors can use to make sure treatments are targeted specifically to their patient's cancer and to successfully develop further treatments. ■

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Primary CNS Lymphoma – current barriers to improving prognosis and predicting outcome

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Primary CNS lymphoma (PCNSL) is a rare high grade non-Hodgkin's lymphoma representing around 5% of all primary brain tumours [1,3]. Patients typically present in their 50's or 60's with clinical features of an expanding intracranial mass lesion. There also appears to be a slight male predominance in presentation. For the overwhelming majority of patients, overall survival remains poor, partly due to often poor performance status at diagnosis and difficulties tolerating the neurotoxic effects of chemoradiotherapy, with median survival rates around 10-20 months [2]. Unlike systemic diffuse large B cell lymphoma (DLBCL), the pathophysiology of PCNSL is poorly understood. In this article we discuss the clinicopathological features of PCNSL, the limitations in current management and the emergence of potential prognostic markers similar to those routinely assessed in systemic DLBCL.

Changing incidence and risk factors

Until the late 1990's, the incidence of PCNSL had been steadily increasing over the preceding 20 years [3]. The reasons for this still remain unclear, with the steady rise now no longer so evident and current incidence rates stable around 2.7-2.8 per million population in the immune competent [4]. Immunosuppression is well-recognised as a major risk factor in the aetiology of PCNSL, and prior to the introduction of highly active antiretroviral therapy (HAART), the incidence rate of PCNSL in the HIV positive population was several thousand fold higher than in the general population, probably accounting for some of this observed increase. Since HAART however, these rates have fallen considerably [5]. Widespread use of immunosuppressant drugs in autoimmune diseases and for post-transplant immunosuppression has also been implicated in this rise in PCNSL [6]. Of note, whilst the majority of cases of PCNSL are Ebstein-Barr virus (EBV) negative, in the immune compromised EBV may be found.

Clinical features

Given the aggressive nature of the disease there is usually a short interval between onset of symptoms and diagnosis with the specific clinical features encountered depending on the regions of CNS involvement. The majority of cases present with a focal neurological deficit (70%); sequelae of raised intracranial pressure (33%) and seizures (14%) are also common at presentation [7]. In those patients with ocular disease, only half present with visual symptoms such as floaters, blurred vision or reduced visual acuity, therefore specific examination of the eye is a requirement of full staging of the disease. In addition, diagnosis can be delayed as ocular disease can often mimic other more common conditions such as posterior uveitis.

Table 1: A summary of the staging investigations recommended by BNOS [10].

STAGING INVESTIGATIONS FOR PCNSL
HIV serology
Examination of eyes (slit lamp, ophthalmoscopy +/- biopsy)
CSF for protein/glucose/cytology/molecular studies
Bone marrow aspirate and trephine
CT chest/abdomen/pelvis
Testicular ultrasound – elderly males

The typical radiological appearance of PCNSL is a deep enhancing periventricular or subependymal mass with homogenous enhancement and without central necrosis. On MR, these often appear as isointense or hypointense lesions on T2 weighted imaging, with the frontal lobes as the most commonly involved region along with corpus callosum and basal ganglia. Lesions are typically solitary but can be multifocal, particularly in end stage disease or in immunocompromised patients. 10% of cases present with leptomeningeal involvement, which is an unusual feature and often reflects a late stage in the course of the disease. This can mimic other more common meningeal lesions such as meningiomas. Whilst the radiological appearances can be distinctive, PCNSL lesions can mimic other diagnoses, including high grade glioma, metastases or infective/inflammatory lesions. Therefore, a stereotactic or image guided open biopsy with intraoperative neuropathological assessment is required to histologically confirm the diagnosis. Resection is not advocated as it is well established that it does not alter overall survival [2].

Corticosteroids are usually the first line therapy following diagnosis as they significantly reduce symptoms related to raised intracranial pressure and mass effect by reducing oedema and inducing apoptosis of tumour cells. Because of this, they can potentially induce 'radiological' tumour regression (the 'disappearing tumour') and affect the quality of histological material for assessment. The general advice is therefore to avoid giving steroids prior to biopsy unless there is an urgent clinical need. However, a recent study of 109 patients by Porter et al showed similar rates of repeat biopsy in patients who received pre-operative steroids compared to those who did not [8], suggesting this may not be as severe a problem as previously thought. In our experience the diagnostic yield is usually high regardless of prior treatment.

Once histological diagnosis is established, a number of staging investigations are recommended by the International PCNSL Collaboration Group [9],

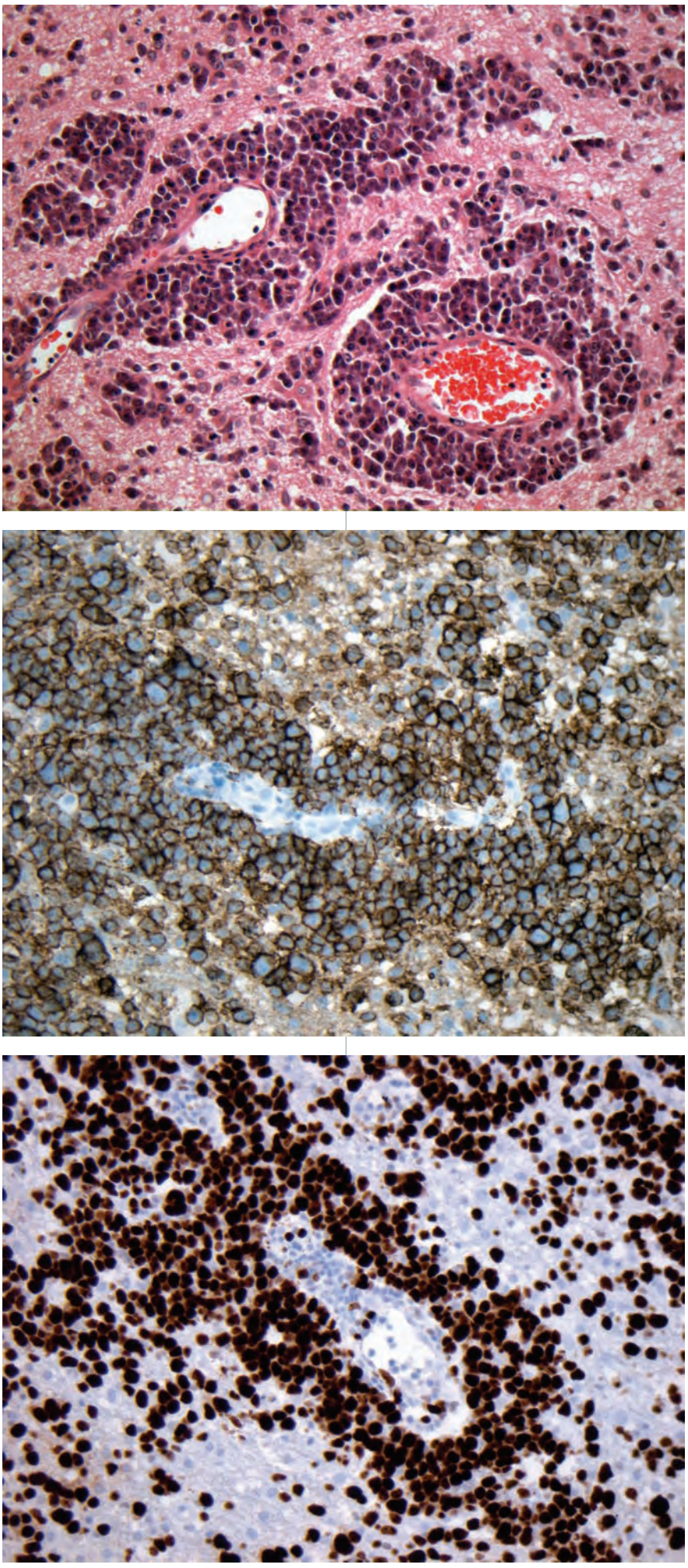

Figure 1: Shows medium to large tumour cells with rounded irregular nuclei and limited cytoplasm infiltrating neural tissue and showing characteristic perivascular 'cuffing' (a; H&E x20). Immunocytochemistry shows positivity for the pan-B cell marker CD20 (b; x20) and a high proliferation index (c; Ki67 x20).

all of which have been highlighted in the recent British Neuro-oncology Society (BNOS) Rare Brain/ CNS Tumour Guidelines on Primary CNS Lymphoma. These investigations are summarised in Table 1 and are aimed at excluding systemic disease and fully assessing the extent of CNS involvement. A CT chest, abdomen and pelvis should be carried out along with bone marrow examination to exclude CNS spread of systemic lymphoma. Given the potential for synchronous ocular or leptomeningeal involvement, eye examination and CSF assessment is recommended. Testicular ultrasound should be performed in elderly males due to the high propensity for testicular lymphomas to spread to the CNS. As HIV infection is a risk factor for the development of PCNSL, an HIV test should also be carried out in all patients following informed consent. Although FDG-PET is well-established in the management of systemic lymphoma, its exact role in PCNSL is yet to be established. Up to 12% of cases initially thought to be confined to the CNS are found to have synchronous systemic involvement on subsequent investigations [11].

Histopathological features

The overwhelming majority (over 95%) of PCNSL are high grade B cell lymphomas of diffuse large B cell type (DLBCL). Low grade lymphomas, such as lympho-plasmacytic lymphoma and marginal zone lymphoma, rarely present in the CNS. Approximately 2% of PCNSLs are of T cell lineage and show a predilection for the posterior fossa. The remainder of lymphomas presenting in the CNS are extremely rare, such as Burkitt lymphoma, anaplastic large cell lymphoma, lymphoid granulomatosis and Hodgkin's lymphoma, which often presents as leptomeningeal lesions late in the course of the disease (i.e. secondary spread).

Macroscopically, PCNSLs are space occupying lesions with an ill-defined boundary and greyish/yellow cut surface. Histologically, medium to large tumour cells with rounded nuclei and limited cytoplasm diffusely infiltrate the parenchyma and show an angiocentric pattern of spread, forming a characteristic perivascular 'cuff' of tumour cells (Figure 1). The tumour cells are associated with occasional reactive T cells, reactive astrocytes and microglia with stains for reticulin revealing increased perivascular

deposition. Necrosis is often present, particularly following steroid treatment. As the majority of PCNSLs are of B cell origin, they stain positively with pan-B cell markers CD20 and CD79a. The majority of PCNSLs are also positive for BCL2, BCL6 and MUM-1. The proliferation rate is usually high, with around 70-90% of tumour cells positive for the proliferation marker Ki67.

PCNSL – a distinct entity from systemic lymphoma?

PCNSL cells are postulated to recapitulate late/post germinal centre B cells however the exact origin of this neoplastic clonal population remains unclear. At a morphological level, the neoplastic cells of PCNSL are indistinguishable from those of systemic DLBCL. However, PCNSL is an extremely infiltrative tumour with a characteristic angiocentric pattern of growth; a pattern not normally found in other organs involved by DLBCL. There is high expression of growth factors such as IL-4 and XBP-1 within endothelial cells of tumour associated vessels which may be responsible for the angiocentric pattern of growth observed in PCNSL [12].

Diagnostic molecular pathology plays a major role in the diagnosis and prognostication of systemic lymphomas, however the same is not yet so for PCNSL. The role of oncogenes and transcription factors in the molecular pathogenesis of PCNSL is poorly understood, however there is growing evidence that PCNSL may have a molecular profile distinct to systemic DLBCL. The commonest aberrations observed are deletions or hypermethylation of CDKN2A which expresses p14ARF [13]. Array Comparative Genomic Hybridisation studies have also shown that loss of heterozygosity of 6q may be associated with poorer outcome in PCNSL, similar to outcomes in other systemic lymphomas [14]. IgH gene rearrangements may also be more frequent in PCNSL than in other lymphomas. Further studies characterising this disease at a molecular and cytogenetic level and correlation with clinical outcome are urgently required.

Following validation in a number of studies, systemic DLBCL is now routinely subtyped into two broad prognostic groups according to their positivity for the immunocytochemical markers CD10, BCL6 and MUM-1 (Figure 2) [15]. There is also a third group ('type 3') which is less well defined. Systemic DLBCL's which show a 'germinal centre' (GC: CD10+, BCL6+, MUM1+/-) phenotype have improved five-year survival rates when compared to 'non-germinal centre' (NGC: CD10-, BCL6+/-, MUM1+) phenotypes. Furthermore, BCL2 is known to confer a poorer survival in patients with NGC

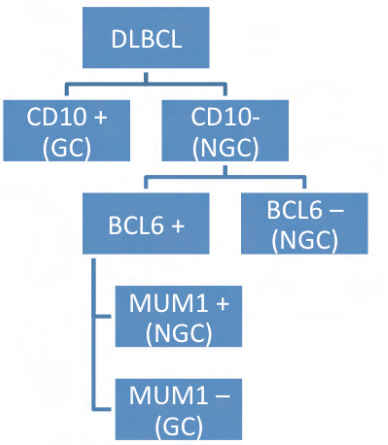

Figure 2: DLBCL's are subtyped into Germinal centre (GC) and Non germinal centre (NGC) phenotypes according to their positivity for CD10, MUM-1 and BCL6. (Adapted from Hans et al [15]).

phenotype. To date, the evidence for similar prognostic groups in PCNSL is somewhat limited. Some studies suggest a prognostic advantage in GC subgroups similar to DLBCL [16], however other studies have failed to show this benefit. One explanation is that the majority of PCNSLs appear to have a NGC phenotype with higher BCL2 and MUM1 expression when compared to DLBCL and therefore comparison to GC groups in small studies is flawed. There is also some evidence that BCL-6 is associated with a more favourable outcome in PCNSL [17]. Again, further work is required in a larger cohort of patients independently to assess these subtypes in PCNSL and correlate with clinical outcome.

Current management and potential barriers to improving outcomes

Similar to most other forms of lymphoma, PCNSL is sensitive to both radiotherapy and chemotherapy. Radiotherapy alone increases survival from around two months (untreated) to 11-18 months [18,19]. The most effective chemotherapeutic agent is methotrexate, improving survival to over 30 months [20,21], with high doses required to achieve adequate penetration of the blood brain barrier. Over the last decade optimal treatment has been regarded as methotrexate-based combination chemotherapy followed by radiotherapy [22,23], though this carries significant morbidity, including age-related dementia, limiting this aggressive approach to only the fittest patients, generally those less than 60 years old. This severe neurocognitive toxicity has prompted the investigation of the possibility of deferring radiation in those responding well to primary chemotherapy, which appears to be a successful approach with no detriment to survival [24].

Because of many factors including the advanced age of many patients and levels of fitness / comorbidity, the individual management of PCNSL varies significantly and population survival statistics remain poor. Unifying management strategies across different centres and countries is an important but difficult goal to achieve in this rare disease. Three main factors can be identified as potential barriers. Firstly, the CNS is a unique site to treat with problems related to poor blood brain barrier penetration of potentially active drugs and the neurotoxicity associated with both chemotherapy and radiotherapy. Secondly, because of this rarity, clinical trials are often underpowered, and cross-trial comparisons limited by heterogeneity. Steps have been taken to ameliorate this, as in the last twelve months guidelines on standardising investigation, management and outcome measures have been released by both the British Neuro-Oncology Society and the International PCNSL Collaborative Group [9] which will hopefully aid in the design of future studies. Finally the pathophysiology of PCNSL is yet to be fully defined both in terms of pathological subtyping and the development of useful prognostic molecular markers.

Given the rarity of the diagnosis and the poor but heterogeneous survival outlined above, identifying prognostic factors to tailor treatment is an important ambition. A number of prognostic models have previously been proposed incorporating combinations of age, performance status, serum lactate dehydrogenase (LDH) level, CSF protein concentration, and involvement of deep brain regions (periventricular regions, basal ganglia, brainstem, cerebellum), multifocal, or meningeal disease. In addition to individualising care through consideration of these factors, treatment decisions must also be multi-disciplinary.

Conclusions

In conclusion, PCNSL is a rare, aggressive B cell lymphoma with outcomes remaining poor for the majority of patients. PCNSL remains a challenge to treat oncologically due to the balance between disease control and minimising neurotoxicity. Current research efforts include a need to focus on improving our understanding of the pathology of PCNSL, in particular identifying specific molecular features which may aid in diagnosis and predicting prognosis. Furthermore, the initiation of large, multicentre and ideally multinational clinical trials should help to standardise optimal management. ■

References

1. Rubenstein J, Ferreri AJ, Pittaluga S. *Primary lymphoma of the central nervous system: Epidemiology, pathology and current approaches to diagnosis, prognosis and treatment.* Leuk Lymphoma 2008;49(1):43-51.
2. Reni M, Ferreri AJM, Garancini MP and Villa E. *Therapeutic management of primary central nervous system lymphoma in immunocompetent patients: results of a critical review of the literature.* Annals of Oncology 1997;8:227-34.
3. Olson JE, Janney CA, Rao RD, Cerhan JR, Kurtin PJ, Schiff D, et al. *The continuing increase in the incidence of primary central nervous system non-Hodgkin lymphoma: a surveillance, epidemiology, and end results analysis.* Cancer [Internet]. 2002;95(7):1504–10.
4. Hoffman S, Propp JM, McCarthy BJ. *Temporal trends in incidence of primary brain tumors in the United States, 1985-1999.* Neuro-oncology 2006;8(1):27-37.
5. Besson C. *Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy.* Blood 2001;98(8):2339-44.
6. Schabet M. *Epidemiology of Primary CNS Lymphoma.* Journal of Neuro-Oncology. 1999;43(3):199-201.
7. Bataille B, Delwail V, Menet E, Vandermarcq P, Ingrand P, Wager M, et al. *Primary intracerebral malignant lymphoma: report of 248 cases.* Journal of Neurosurgery. 2000;92(2):261–6.
8. Porter A, Giannini C, Kaufmann T, Lucchinetti CF, Wu W, Decker PA, Atkinson JLD, O'Neil BP. *Primary central nervous system lymphoma can be histologically diagnosed after previous corticosteroid use: a pilot study to determine whether corticosteroids prevent the diagnosis of primary central nervous system lymphoma.* Annals of Neurology 2008;62:662-7.
9. Abrey LE, Batchelor TT, Ferreri AJM et al. *Report of an international workshop to standardize baseline evaluation and response criteria for primary central nervous system lymphoma.* J Clin Oncol 2005;23:5034-43.
10. BNOS Rare Brain and CNS Tumours Guidelines. In collaboration with the National Cancer Action Team. *Guidelines on the diagnosis a nd management of primary CNS and intra-ocular Lymphoma.* [Internet]. Available from: www.bnos.org.uk
11. Ferreri AJ, Reni M, Zoldon MC, Terreni MR, Villa E. *Importance of complete staging in non hodgkins lymphoma presenting as a cerebral mass lesion.* Cancer 1996;77(5):827-33.
12. Rubenstein JL, Fridlyand J, Shen A, Aldape K, Ginzinger D, Batchelor T, et al: *Gene Expression and Angiotropism in Primary CNS Lymphoma.* Blood 2006;107:3716–23.
13. Kadock C, Treseler P. *Molecular Pathogenesis of Primary CNS Lymphoma.* Neurosurg focus 2006;21(5):61-7.
14. Nakamura M, Shimada K, Ishida E, Konishi N: *Histopathology, pathogenesis and molecular genetics in primary central nervous system lymphomas.* Histol Histopathol 2004;19:211–9.
15. Hans CP, Weisenburger DD, Greiner TC et al. *Confirmation of molecular classification of diffuse large B cell lymphoma by immunohistochemistry using tissue microarray.* Blood 2004; 103(1): 275-82.
16. Rubenstein JL, Fridlyand J, Shen A, Aldape K, Ginzinger D, Batchelor T, et al. *Gene expression and angiotropism in primary CNS lymphoma.* Blood 2006;107(9):3716–23.
17. Braaten KM, Betensky RA, Leval LD, Okada Y, Hochberg FH, Louis DN, et al. *BCL-6 Expression Predicts Improved Survival in Patients with Primary Central Nervous System Lymphoma BCL-6 Expression Predicts Improved Survival in Patients with Primary Central Nervous System Lymphoma 1.* Clinical Cancer Research. 2003;3:1063–9.
18. Nelson D, Martz K, Bonner H, Nelson J, Newall J, Kerman H, et al. *Non-Hodgkin's lymphoma of the brain: Can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315.* . Int J Radiat Oncol Biol Phys. 1992;23:9–17.
19. Shibamoto Y, Ogino H, Hasegawa M, Suzuki K, Nishio M et al. *Results of radiation monotherapy for primary central nervous system lymphoma in the 1990s.* International Journal of Radiation Oncology Biology Physics. 2005;62(3):809–13.
20. Glass J, Gruber ML, Cher L, Hochberg FH. *Preirradiation methotrexate chemotherapy of primary central nervous system lymphoma: long-term outcome.* Journal of Neurosurgery. 1994;81(2):188–95.
21. O'Brien P, Roos D, Pratt G, Liew K, Barton M, Poulsen M, et al. *Phase II Multicenter Study of Brief Single-Agent Methotrexate Followed by Irradiation in Primary CNS Lymphoma.* J. Clin. Oncol 2000;18(3):519.
22. Laack NN, O'Neill BP, Ballman KV, O'Fallon JR, Carrero XW, Kurtin PJ, et al. *CHOD/BVAM Chemotherapy and Whole-Brain Radiotherapy for Newly Diagnosed Primary Central Nervous System Lymphoma.* International journal of radiation oncology, biology, physics. 2011;81(2):476–82.
23. Thiel E, Korfel A, Martus P, Kanz L, Griesinger F, Rauch M, et al. *High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial.* The lancet oncology. 2010;11(11):1036–47.
24. Correa D, DeAngelis L, Shi W, Thaler H et al. *Cognitive functions in survivors of Primary CNS Lymphoma.* Neurology 2004;62:548-55.

Update on Multi-Gene Tests in Breast Cancer

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Complex biomarkers in breast cancer

The development of pathology tests to define prognosis and predict treatment response has been a major focus of breast cancer research for many years. A simple Pubmed search lists over 25,000 articles on biomarkers in breast cancer. Only a handful of biomarkers are in everyday use. Steroid hormone receptors and HER2 are notable examples. Both are prognostic factors, the former favourable and the latter adverse. Both predict response to targeted treatments and it is this that has led to their routine measurement in virtually all cancers. What is currently missing is an accessible and robust method of predicting the sensitivity of individual cancers to chemotherapy. The new generation of multi-gene tests promises to change this.

Multi-gene tests, also known as complex biomarkers or multi-parameter assays were first developed in the early 2000's. The type and use of contemporary multi-parameter assays is shown in Figure 1. Early microarray studies in breast cancer lead to the development of the intrinsic classification and to the first multigene prognostic signature. The 70 gene signature, now better known as the MammaPrint assay was derived by studying RNA from stored frozen tumour samples from 98 patients with clinical outcome data. By contrast the Oncotype DX test was developed using a technology that allowed extraction of RNA from the formalin-fixed paraffin-embedded (FFPE) samples found in all routine pathology labs. The final assay measures 21 genes by quantitative RT-PCR, which were selected from a pool of 250 candidates. The output of both MammaPrint and Oncotype DX is a numerical score which is related to the risk of future development of distant relapse. Both tests are performed commercially in centralised laboratories.

To date Oncotype DX has been studied exclusively in ER postive and mostly node negative tumours whilst validation studies for MammaPrint have included a much more heterogeneous population. These studies have been discussed in three systematic reviews [1-3]. The overall conclusion was that Oncotype DX was further down the validation pathway than MammaPrint. The requirement for fresh tumour tissue by MammaPrint has been widely considered an obstacle to its adoption into UK clinical practise but as it has very recently been adapted for FFPE specimens, this may change.

Predicting chemotherapy benefit

Oncotype DX test was first described in a retrospective study of archival tumour samples from the NSABP B-14 study [4]. NSABP B-14 was a randomised trial of adjuvant tamoxifen in both pre- and post-menopausal patients with ER positive and node negative disease. Out of 2,167 tamoxifen-treated patients in the main trial, 668 were included in this initial validation study of Oncotype DX. The results showed that the Recurrence Score (RS) analysed as a continuous variable correlated with the risk of distant recurrence at 10 years. When the recurrence score was used to divide patients into the now well-known 3 risk categories of low (RS < 18) intermediate (RS 18-30) and high (RS≥31), the risk of distant recurrence in the groups was 6.8%, 14.3% and 30.5% respectively. In a multivariate analysis of other prognostic factors, only RS and high tumour grade were independently significant.

The outcome of trials of chemotherapy vs. no chemotherapy in women with ER positive disease who were also treated with tamoxifen has been analysed retrospectively according to RS. NSABP B-20 had 2 chemotherapy arms with CMF and MF chemotherapy in women with node negative disease; 2299 patients were randomised of whom 45% were under 50. The Oncotype DX study[5] included 651 of these patients and combined the 2 chemotherapy arms. The SWOG-8814 study compared CAF chemotherapy and tamoxifen given either consecutively or concurrently with tamoxifen alone in 1588 post-menopausal women with node positive disease. The Oncotype DX study included 367 (40%) patients from the sequential chemotherapy and control arms [6].

Both analyses showed that there was a clear benefit for chemotherapy in the high risk group and none in the low risk group. The intermediate risk groups both appeared to have intermediate chemotherapy benefit that failed to reach statistical significance. When RS was treated as a continuous variable the magnitude of chemotherapy benefit increased continuously as RS increased. Although the authors were unable to define a threshold score for chemotherapy benefit, in both studies, a score of 25 was associated with a reduction in the absolute risk of distant recurrence of 3-4%. Crucially in neither study did stage influence the prediction of chemotherapy benefit so women with more advanced stage but a low RS did not benefit from chemotherapy despite their worse prognosis [6,7].

The MammaPrint assay categorises patients into low-risk and high-risk groups. The assay has been extensively validated as a prognostic test for patients with both ER negative and positive disease and has been shown to re-classify a significant proportion of tumours categorised as low or high risk using Adjuvant! [see [1-3]]. There is currently very little evidence to show that MammaPrint is able to predict chemotherapy sensitivity and none from analyses of randomised controlled trials.

Newer testing technologies

A number of additional multi-gene tests have been developed by both academic groups and commercial organisations. Although many are poorly validated and remain experimental, a small number have significant evidence to support their clinical utility, particularly in ER positive tumours. Most of the better validated assays have been developed commercially and are either available or in the process of being developed for clinical use. Table 1 summarises assays that have either been described, are in current use or are in development.

Broadly there are two groups of multi-gene assays (Figure 1). As in the case of MammaPrint and Oncotype DX, the majority offer a simple numerical estimate of risk for all breast cancer; most are strongly influenced by steroid hormone sensitivity, HER2 and proliferation. The main output from the second group is information about the sub classification of breast cancer, usually the intrinsic subtype. The best established of this second group is PAM50 [8]. Multi-parameter assays are also divided by their input material. The older tests all RNA-based but some of the newer tests, notably IHC4 [9] use immuno-histochemistry and have been termed extended immunohistochemistry tests. A brief description of some of the newer tests follows.

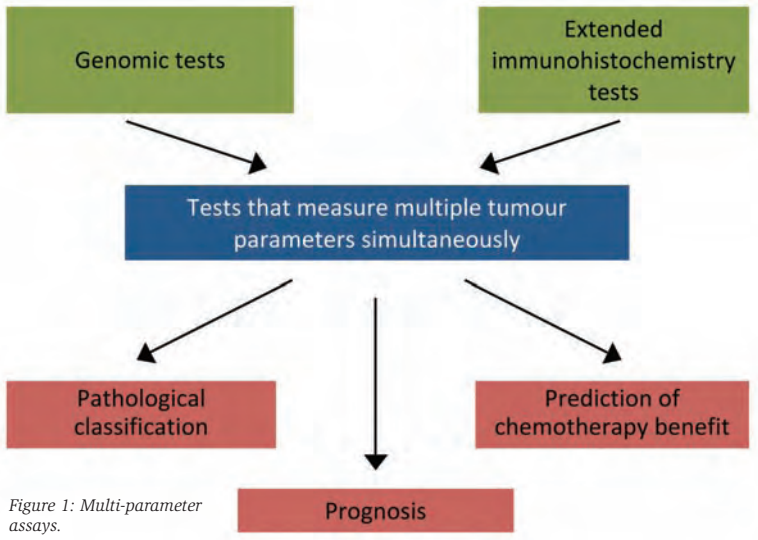

Figure 1: Multi-parameter assays.

Risk predictors

Mammostrat: The Mammostrat assay relies on immunohistochemical analysis of five markers using a proscribed and validated scoring approach. First described in 2006, this assay was validated across multiple retrospective institutional and clinical trial cohorts, including the NSABP14 & 20 trials [10]. Recent evidence from the TEAM trial [11] suggests this assay also provides information on residual risk in patients treated with aromatase inhibitors.

Breast Cancer Index: BCI is a 7-gene RT-PCR assay which combines the 5-gene molecular grade index and the HOXB13:IL17BR ratio, a measure of estrogen sensitivity [12]. The output, a continuous risk-score grouped into three

Table 1: Summary of multi-parametric tests for breast cancer.

Assay (Investigators or Company)	Details of Multi-parametric assay	Test Material	Test Output	Status
Perou and Sorlie (academic)	The original description of the intrinsic classification using 495 genes (the most highly cited papers in breast cancer).	Fresh/frozen	category	research tool
Oncotype DX (Genomic Health Inc)	A 21 gene qRT-PCR expression assay (using 16 cancer related and 5 normalisation genes)	FFPE	risk score	available (EU & N America)
MammaPrint (Agendia)	A proprietary 70 gene microarray based expression signature.	fresh & FFPE	risk score	available (EU & N America)
Rotterdam signature (academic)	76 gene microarray based expression signature, not yet commercially available.	Fresh/ frozen	risk score	research tool
PAM50 (ARUP Laboratories & nanoString Inc)	A 50 gene expression assay using RT-PCR or the nanoString system.	FFPE	subtyping & risk score	available (N. America)
Theros Breast Cancer Index (Biotheranostics)	A proprietary 7 gene qRT-PCR expression assay	FFPE	risk score	available (N. America)
Blueprint (Agendia)	A microarray based assay used in conjunction with MammaPrint	fresh & FFPE	subtyping	available (EU & N America)
Genomic Grade (Ipsogen)	Quantitative immunohistochemical assay for proliferation markers reflecting grade	FFPE	risk score	available (N. America)
Randox Breast Cancer Array (Randox Ltd)	A 23 gene assay using bio-chip technology	fresh & FFPE	subtyping	in-development
IHC4 (HistoRx & non-proprietary)	Quantitative immunohistochemical assay for ER, PgR, Her2, Ki67	FFPE	risk score	academic
Mammastrat (GE Healthcare)	A 5 gene immunohistochemical assay.	FFPE	risk score	available (EU & N America)
NPI plus	A 10 gene immunohistochemical assay.	FFPE	risk score	in-development

qRT-PCR=quantitative reverse transcriptase polymerase chain reaction. FFPE=formalin-fixed paraffin-embedded. ER=estrogen receptor, PgR=Progesterone receptor. Ki67 is a proliferation marker.

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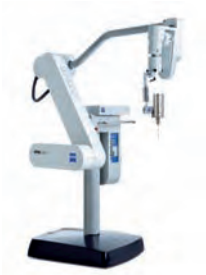

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Table 2: Ongoing RCT's of prediction of chemotherapy by multi-parameter assays

Study	Testing Technology	Population characteristics	Test result for chemo. randomisation	Trial size	Country	Start date	Likely analysis date
TAILORx	Oncotype DX	ER+ HER2- N0	RS 11-25	11,248 (cohort)	USA, Canada	2006	2015
MINDACT	MammaPrint	ER+ N0-1	Discordant MammaPrint vs Adjuvant!	6,600 (cohort)	EU	2006	2015?
RxPONDER	Oncotype DX	ER+ HER2- N1	RS ≤25	4,000 (rand)	USA, Canada	2011	2017
OPTIMA	adaptive	ER+ HER2- N1-2	Randomise to test vs. no test (initially RS)	3,640/ 5,460 (rand)	UK	2012	2020?

risk categories has been shown to be prognostic. Analysis of the historic Stockholm study shows that BCI predicts tamoxifen benefit [13] but as yet there is no data on prediction of chemotherapy benefit.

IHC4: HC4 relies on quantitative immunohistochemistry. There is long-standing evidence that the conventional IHC markers, ER, PgR, HER2 and Ki67 are able to identify patients at increased residual risk following endocrine therapy. Cuzick et al recently described an algorithm which integrated this data into a viable predictor of residual risk in postmenopausal women with ER positive disease who had participated in the ATAC trial [9]. Of potential great importance, the prognostic information provided by IHC4 was equivalent to that from Oncotype DX, which was also measured in the same patient population. This is not surprising since Oncotype DX is strongly influenced by the expression of genes that relate to steroid hormone and HER2 sensitivity and to proliferation. Although there is no data on the use of IHC4 as a predictive biomarker, the similarity with Oncotype DX suggests that this assay should have similar utility to Oncotype DX at a fraction of the cost. The critical unanswered question is: are routine pathology labs, which are equipped to perform the assay capable of performing it with acceptable accuracy and QA?

Intrinsic subtype

PAM50: Following the pivotal publication by Perou and collaborators [14,15] of the molecular classification of breast cancer intrinsic subtypes, development of a simple molecular assay for clinical determination of these subtypes has been a key objective. The development of PAM50, a multiplex PCR assay using 50 genes to identify molecular sub-types of early breast cancer followed a similar path to Oncotype DX [8]. More recently the assay has been ported to the NanoString platform (www.nanostring.com) and is currently being developed for clinical validation in a number of retrospective clinical trial cohorts. Therefore, rapid progress in the understanding of the utility of this approach is likely in the near future.

A numerical risk score has also been developed using the PAM50 gene set [8]. Recently evidence has been presented that this, like Oncotype DX and IHC4, is able to predict residual risk in the ATAC trial with good correlation between all 3 assays [16]. Other assays, particularly MammaPrint have also been shown to correlate with PAM50 in the I-SPY1 trial [17].

One of the key issues hindering the adoption of intrinsic subtyping as a practical platform to use in breast cancer management is the lack of a standardised definition. In addition to PAM50, a variety of definitions based on immuno-histochemistry have been proposed, notably that of Nielson and collaborators [18] and more recently an assay based on expression of three genes has been described [19]. PAM50 in contrast to these assays does not use ER and HER2 expression as rigid parameters for defining subtype boundaries. Thus a small but significant proportion of luminal cancers defined by PAM50 do not express ER whilst some basal-like cancers do [8]. There is some evidence to suggest that the subtype takes precedence over receptor expression but this needs verification in large scale studies before a standard definition of intrinsic subtype can be adopted.

Are they ready for prime time?

As a result of the NSABP-B20 analysis, in 2007 the American Society of Clinical Oncology made a practice guideline recommendation for the use of Oncotype DX. This has led to its widespread adoption in North America where it has been performed on over 120,000 patients during the past three years at a cost of $400m. Economic evaluations conducted from a US, Canadian and Japanese perspective in women with ER positive node negative breast cancer all conclude that Oncotype DX is cost-effective in those jurisdictions. The cost of the test (currently $4,075 in the US) is covered by Medicare and by many other health care provider groups. It is also increasingly supported by private UK health insurers who regard it as cost effective technology if it can identify patients who will not benefit from expensive (private sector) chemotherapy. A recent economic analysis of the SWOG-8814 data translated in to a UK setting suggested that Oncotype DX is probably cost-effective for this patient group treated in the NHS [20]. NICE will complete an appraisal of Oncotype DX and related technologies for ER positive HER2 negative node negative patients in summer 2012. As much less chemotherapy is given to this group in the NHS than in North America, it is unclear whether Oncotype DX will be cost-effective in this setting in the NHS.

Standing back from the growing pressures to adopt multi-gene tests for making chemotherapy decisions, is there now a convincing case for their routine use for patients with ER positive disease? The trial data that support the use of Oncotype DX is from just over 1000 women. Confidence intervals are consequently large and the prediction of the magnitude of chemotherapy benefit at any particular RS values is highly uncertain. Clearly additional research into all technologies is required. Four prospective RCT's (Table 2) are currently in progress (or about to start) which collectively will resolve many of the current uncertainties.

TAILORx, which assesses Oncotype DX guided chemotherapy in a node-negative population is expected to report initial results in 2015. A second Oncotype DX based trial (RxPONDER) for node positive patients opened to recruitment in 2011. Both studies test all consenting patients and randomise patients to chemotherapy or not within a window of Oncotype DX Recurrence Scores. In both studies patients with a RS >25 are ineligible for randomisation. In the MINDACT study, likely to report in 2015, all patients have a

MammaPrint assay and are randomised to chemotherapy or not when there is discordance between clinically and test assessed recurrence risk. OPTIMA is a UK study with an adaptive design for patients with 1-9 nodes or tumours >30mm diameter. The preliminary (feasibility) phase will open in summer 2012 and will randomise patients to standard treatment with chemotherapy or to have treatment decided according to an Oncotype DX test. The preliminary phase will inform the detailed design of the main study.

It is anticipated that the results of these studies will validate the use multi-gene tests as predictive assays, allow the test thresholds to be better defined and enable a proper economic evaluation of the tests. In the meantime technology develops apace. It likely that assays to identify sensitivity to specific cytotoxics will appear in the near future. The rapidly falling cost of DNA sequencing is likely to result in an entirely new generation of tests and to open a new era of personalised cancer medicine of which the current multi-gene tests represent the first steps. ■

References

1. Marchionni L, Wilson RF, Marinopoulos SS, Wolff AC, Parmigiani G, Bass EB, et al. *Impact of gene expression profiling tests on breast cancer outcomes.* Evid Rep Technol Assess (Full Rep). [Review]. 2007 Dec(160):1-105.
2. Smartt P. *A comparison of gene expression profiling tests for breast cancer: Health Services Assessment Collaboration (HSAC)2010.* http://www.healthsac.net/publications/publications.php?t=2
3. Ward S, Scope A, Rafia R, Pandor A, Harnan S, Evans P. *Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management.* 2012. http://guidance.nice.org.uk/DT/4/DAR/pdf/English
4. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. *A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.* N Engl J Med. 2004 Dec 30;351(27):2817-26.
5. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. *Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer.* J Clin Oncol. 2006 Aug 10;24(23):3726-34.
6. Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh IT, et al. *Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial.* Lancet Oncol. 2010 Jan;11(1):55-65.
7. Tang G, Cuzick J, Costantino JP, Dowsett M, Forbes JF, Crager M, et al. *Risk of recurrence and chemotherapy benefit for patients with node-negative, estrogen receptor-positive breast cancer: recurrence score alone and integrated with pathologic and clinical factors.* J Clin Oncol. 2011 Nov 20;29(33):4365-72.
8. Parker JS, Mullins M, Cheang MC, Leung S, Voduc D, Vickery T, et al. *Supervised risk predictor of breast cancer based on intrinsic subtypes.* J Clin Oncol. 2009 Mar 10;27(8):1160-7.
9. Cuzick J, Dowsett M, Pineda S, Wale C, Salter J, Quinn E, et al. *Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer.* J Clin Oncol. 2011 Nov 10;29(32):4273-8.
10. Ross DT, Kim CY, Tang G, Bohn OL, Beck RA, Ring BZ, et al. *Chemosensitivity and stratification by a five monoclonal antibody immunohistochemistry test in the NSABP B14 and B20 trials.* Clin Cancer Res. 2008 Oct 15;14(20):6602-9.
11. Bartlett JMS, Bloom KJ, Goldstein NS, van de Velde CJH, Ross DT, Seitz RS, et al. *Mammostrat(R) as an Immunohistochemical Multigene Assay for Prediction of Early Relapse Risk in Postmenopausal Early Breast Cancer: Preliminary Data of the TEAM Pathology Study.* Cancer Res. 2011 April 26, 2011;70(24 Supplement):P3-10-33.
12. Ma XJ, Salunga R, Dahiya S, Wang W, Carney E, Durbecq V, et al. *A five-gene molecular grade index and HOXB13:IL17BR are complementary prognostic factors in early stage breast cancer.* Clin Cancer Res. 2008 May 1;14(9):2601-8.
13. Jerevall PL, Ma XJ, Li H, Salunga R, Kesty NC, Erlander MG, et al. *Prognostic utility of HOXB13:IL17BR and molecular grade index in early-stage breast cancer patients from the Stockholm trial.* Br J Cancer. 2011 May 24;104(11):1762-9.
14. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. *Molecular portraits of human breast tumours.* Nature. 2000;406(6797):747-52.
15. Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, et al. *Repeated observation of breast tumor subtypes in independent gene expression data sets.* Proc Natl Acad Sci. 2003 July 8, 2003;100(14):8418-23.
16. Dowsett M, Lopez-Knowles E, Sidhu K, Pineda S, Cowens JW, Ferree S, et al. *Comparison of PAM50 Risk of Recurrence (ROR) Score with OncotypeDx and IHC4 for Predicting Residual Risk of RFS and Distant-(D)RFS after Endocrine Therapy: A TransATAC Study.* Cancer Res. 2011 Dec 15;71(24 supplement):108s.
17. Esserman LJ, Berry DA, Cheang MC, Yau C, Perou CM, Carey L, et al. *Chemotherapy response and recurrence-free survival in neoadjuvant breast cancer depends on biomarker profiles: results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657).* Breast Cancer Res Treat. 2011 Dec 25. doi: 10.1007/s10549-011-1895-2
18. Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, et al. *Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer.* J Natl Cancer Inst. 2009 May 20;101(10):736-50.
19. Haibe-Kains B, Desmedt C, Loi S, Culhane AC, Bontempi G, *Quackenbush J, et al. A three-gene model to robustly identify breast cancer molecular subtypes.* J Natl Cancer Inst. 2012 Feb 22;104(4):311-25.
20. Hall PS, McCabe C, Stein RC, Cameron D. *Economic evaluation of genomic test-directed chemotherapy for early-stage lymph node-positive breast cancer.* J Natl Cancer Inst. 2012 Jan 4;104(1):56-66.

Synchronous Chemo-radiation in Early Stage Breast Cancer: A Review of the World Literature

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In 1996 a study published in the *New England Journal of Medicine* by Recht and colleagues [1] from Boston, USA, suggested that delaying radiotherapy until after chemotherapy may lead to a higher rate of local recurrence (14 v 5%; Table 1). However, delaying chemotherapy until after radiotherapy may result in an increased rate of distant metastases (32 v 20%). A subsequent overview by Huang et al [2] showed a five-year local recurrence rate of 6% when radiotherapy was given first compared with 16% when delivered after chemotherapy. This paper was criticised because it omitted several key studies. Notably, it was written in 2003 before the update from the Boston group [3], which showed that the initial differences observed in the Recht et al study had disappeared with longer follow-up (Table 1). There seems to be no randomised data to suggest that there is any advantage in giving radiotherapy prior to the delivery of chemotherapy.

Table 1. Results from the Boston Group

	Site of First Recurrence			
Follow-up	**5 years [1]**		**11 years [3]**	
	Local	**Distant**	**Local**	**Distant**
RT⇒CT	5%	32%	13%	32%
CT⇒RT	14%	20%	15%	26%

This begs the question as to whether there is any advantage in giving synchronous chemo-radiation to the standard treatment of chemotherapy followed by radiotherapy. To date three studies have been formally published, two from France (Table 2).

The largest of these is the Arcosein trial [4], in which patients were randomised to either six cycles of 5-fluorouracil, mitoxantrone, and cyclophosphamide (FNC) with either concurrent or sequential radiotherapy. The study showed no difference in overall five-year disease-free survival or loco-regional free survival, but there was a five-year loco-regional free survival advantage to the synchronous group in a very small sub-group of node-positive patients (synchronous arm: 97%, seven recurrences; sequential arm: 91%, 17 recurrences; $p = 0.02$). In terms of local recurrences there were 7.3% in the sequential arm and 4.5% in the synchronous arm (see Table 2). Significantly increased toxicity occurred in the synchronous arm, both in terms of acute skin reaction and late effects including fibrosis, telangiectasia and breast atrophy.

The second study by Rouëssé and colleagues [5] used two different chemotherapy regimes, 5-fluorouracil, epirubicin and cyclophosphamide (FEC) for the sequential arm and FNC for the concurrent radiation arm. They found no difference in disease-free survival between the two arms, but there was a benefit in local control in the synchronous arm of 3% (nine recurrences) versus 7% (20 recurrences), $p = 0.047$. The benefit was seen predominantly in patients who had undergone a lumpectomy. Again there was an increase in acute skin toxicity, cardiac toxicity, myelotoxicity and telangiectasia. There was an increased risk of second malignancies in both studies, including leukaemia in both arms. [N.B. mitoxantrone-containing chemotherapy regimens are no longer used in the adjuvant treatment of breast cancer.]

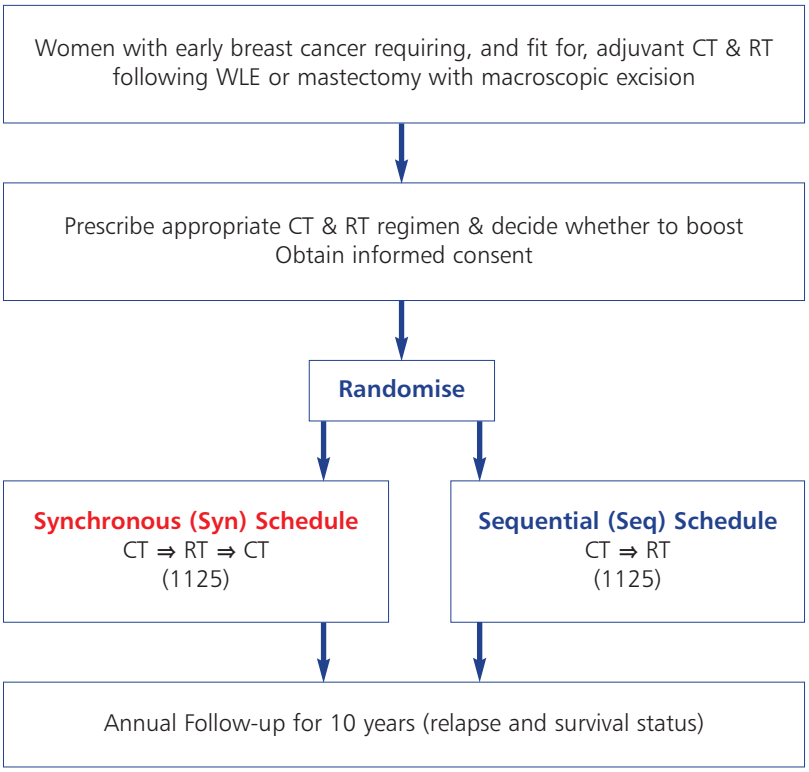
Arcangeli et al. [6] also published a randomised trial, using cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy. Only 206 of the planned 400 patients were entered into the trial because of poor recruitment and there were only two events in each arm. Interestingly, however, there were no significant cases of acute skin toxicity or radiation pneumonitis despite using concurrent full doses of radiation and chemotherapy treatment.

From these studies and the Cochran overview [7],

Table 2. Five Year Local Recurrence Rates Reported in Randomised Trials of Sequencing of Chemo-radiation in Early Breast Cancer

	Arcosein [4]	**Rouëssé et al. [5]**	**Arcangeli et al. [6]**
	n=716	n=650	n=206
Sequential CT⇒RT	7.3% (n=25)	7.0% (n=20)	2.0% (n=2)
Synchronous CT⇒RT⇒CT	4.5% (n=16)	3.0% (n=9)	1.9% (n=2)
Notes: Type synchronous CT & RT Chemotherapy regimen Radiotherapy schedule	Concomitant FNC 50Gy in 25F	Concomitant Seq FEC & Syn FNC 45-50Gy in 20-25F	Concomitant CMF 50Gy in 25F & boost

Figure 1. SECRAB Trial Design.



synchronous chemo-radiation in early stage breast cancer had not been considered beneficial. The preliminary results of the SECRAB (Sequencing of Chemotherapy and Radiotherapy in Adjuvant Breast cancer) trial presented at European Cancer Congress in September 2011 changed this perception [8].

SECRAB was a prospective, UK, multicentre study in which patients were randomised to synchronous or sequential therapy (Figure 1). Patients could only be treated with CMF or anthracycline (A or E) followed by CMF. A variety of different radiotherapy schedules were used and, for simplicity, were split into those of three weeks duration (15 fractions) or > 3 weeks (> 15 fractions).

Of the 2,296 recruited women, and with a median follow-up of 8.8 years, we found 63 and 41 local relapses in the sequential and synchronous arms, respectively. Five-year local relapse rates were 5.1% for the sequential arm compared with 2.8% for the synchronous arm. Synchronous treatment was significantly beneficial, with a 35% reduction in the risk of local recurrence (HRSyn = 0.65, 95% CI: 0.44, 0.96; p = 0.03) [8].

There was an increase in acute skin toxicity and telangiectasia in patients treated with synchronous treatment, this was seen mainly in patients having > 3 weeks of radiotherapy. However, there was no difference in other late effects, including pneumonitis, lymphoedema, rib fracture, brachial plexopathy, severe subcutaneous fibrosis and cardiac events [9]. There was no difference in dose intensity of chemotherapy [9], quality of life [10] or overall survival (83% synchronous arm v 82% for the sequential arm) [11]. We await results of cosmetic evaluation before this can be considered a standard treatment.

These results are applicable to CMF containing regimes. It may be time to look again at how to combine radiotherapy with regimens such as E-CMF, E-T-CMF, A-CMF or A-T-CMF (where T represents taxane), which seem to be at least as effective as standard FEC or FEC-T, but have the advantage that synchronous chemo-radiation could be used as part of the treatment protocol. ■

References

1. Recht A, et al., *The Sequencing of Chemotherapy and Radiation Therapy after Conservative Surgery for Early Stage Breast Cancer* New England Journal of Medicine, 1996;334:1356-61.
2. Huang J, et al., *Does Delay in Starting Treatment Affect the Outcomes of Radiotherapy? A Systematic Review.* Journal of Clinical Oncology, 2003;21(3):555-63.
3. Bellon J, et al., *Sequencing of Chemotherapy and Radiation Therapy in Early-Stage Breast Cancer: Updated Results of a Prospective Randomized Trial* Journal of Clinical Oncology, 2005;23(9):1934-40.
4. Toledano A, et al., *Phase III Trial of Concurrent or Sequential Adjuvant Chemoradiotherapy After Conservative Surgery for Early-Stage Breast Cancer: Final Results of the ARCOSEIN Trial.* Journal of Clinical Oncology, 2007;25(4):405-410.
5. Rouesse J, et al., *A phase III randomized trial comparing adjuvant concomitant chemoradiotherapy versus standard adjuvant chemotherapy followed by radiotherapy in operable node-positive breast cancer: Final results.* International Journal of Radiation Oncology*Biology*Physics, 2006;64(4):1072-80.
6. Arcangeli G, et al., *A phase III randomized study on the sequencing of radiotherapy and chemotherapy in the conservative management of early-stage breast cancer.* International Journal of Radiation Oncology*Biology*Physics, 2006;64(1):161-7.
7. Hinkley B, Francis D, and Lehman M, *Sequencing of Chemotherapy and Radiation Therapy for Early Breast Cancer (review).* The Chocrane Database of Systematic Reviews. 2006;4:John Wiley & Sons Ltd.
8. Fernando I, et al., *Synchronous Chemo-Radiation Can Reduce Local Recurrence In Early Stage Breast Cancer: Results Of The SECRAB Trial. ISRCTN: 84214355.* European Journal of Cancer, 2011;47(Supl 2): Abstract 2BA.
9. Fernando I, et al., *Acute and Late Toxicity Results from the SECRAB Trial: The Optimal SEquencing of Adjuvant Chemotherapy (CT) and RAdiotherapy (RT) in Early Breast Cancer (EBC).* Cancer Research 2010;70(24): Supl: 352S Abstract P4-11-05.
10. Fernando I, et al., *Effect Of Synchronous Chemo-Radiation On Quality Of Life: Results From The SECRAB Trial. ISRCTN: 84214355.* European Cancer Congress, 2011;Abstract Number 5.122.
11. Fernando I, et al., *SECRAB: The Optimal SEquencing of Adjuvant Chemotherapy (CT) and RAdiotherapy (RT) in Early Breast Cancer (EBC), Results of a UK Multicentre Prospective Randomised Trial.* Cancer Research 2010;70(24 Supl):Abstract S4-4.

Chemoradiation in breast cancer: A new treatment option?

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Intraperitoneal Hyperthermo-Chemo-Perfusion in Treating Resectable Gastric Cancer: First Experience in Belarus

Overview and aims

Peritoneal carcinomatosis alongside other gastrointestinal malignancies is a common cause of death in patients with gastric carcinoma. It is a major problem encountered after serosa-invasive gastric carcinoma surgery. Despite recent advances in surgical procedures and adjuvant chemotherapies [1,2], no satisfactory outcomes have been reported, because of residual micrometastases and/or free-floating carcinoma cells present in the peritoneal cavity. The area of serosal tumour invasion has been shown to be positively correlated with the detection rate of intra-peritoneal cancer cells [3]. Furthermore, extensive lymph node dissection itself may be responsible for opening lymphatic channels, thereby spreading viable tumour cells [4]. Also, at the time of laparotomy, gastric carcinoma cells have been detected in the abdominal cavity, even in patients with no peritoneal metastases detected microscopically prior to surgery [5].

Hyperthermia has been developed as an anticancer therapy and employed clinically for its direct cytotoxic effect and synergy with some types of chemotherapeutic drugs. Hyperthermia also increases the depth of penetration of these drugs into tumour tissue. It mainly represents the pharmacodynamic features of drug-heat interaction (changes of the kinetics of the primary mode of drug action) [6].

Koga et al [7] were among the first to use Intraperitoneal Hyperthermo-Chemo-Perfusion (IHCP) as a prophylactic treatment for peritoneal recurrence after gastric cancer surgery. Since they released their data, a fairly large number of reports have been published demonstrating a successful application of IHCP in preventing peritoneal dissemination in gastric cancer patients. For example, administration of mitomycin C (MCC) based IHCP in combination with cisplatin (30mg MMC + 300mg cisplatin, 42-43°C, 60 minutes) helped increase the five-year survival in gastric cancer patients to 61% as compared with 42% in the control group [8]. Applying a similar IHCP regimen, Scaringi and colleagues [9] reported an increase in median survival to 23.4 months and that in median delay to recurrence to 18.5 months.

It was also established that the exclusion of cisplatin from the perfusate had no effect on the outcome of treatment. Using an IHCP regimen comprising 10mg/L MMC in 3-4L of infusate at 43-44°C for 120 minutes, Fujimoto et al [10] found that the four-year survival rate in the IHCP group was 76% against 58% in the control group. Similar results were reported using a dose of 10 mg/m^2 MMC at 43-44°C with a perfusion time of up to 90 minutes, which resulted in a 75% five-year survival rate. Interestingly, IHCP administration did not lead to an increase in complications or mortality [8,10,12].

According to the meta-analysis published by Xu and colleagues, the cohort of trials from Asian countries exhibited a trend towards a more significant curative effect than those from non-Asian countries [13]. It should be noted that there were few studies of IHCP efficacy conducted in Europe [9,14], and their results were mixed. That prompted us to conduct our own study.

Here, we report our preliminary results of a prospective randomised trial study of 68 patients with serosa-invasive gastric carcinoma carried out to evaluate the effect of surgery plus IHCP in the prevention of peritoneal metastases.

Patients and methods

Between 2008 and 2011, 68 patients with gastric cancer (stage stage II-IIIC, III-IV Borrmann type) were randomly assigned to two groups at the time of surgery. 39 patients underwent IHCP combined with radical gastrectomy plus D2 lymph node dissection (IHCP group). Twenty-nine patients underwent radical gastrectomy plus D2 lymph node dissection without IHCP (control group). There were 26 males and 42 females (age range – from 24 to 70). Patients over the age of 70 were not considered suitable for IHCP because of the anticipated incidence of serious complications. There were no significant differences in tumour location and pathologic type between patients treated with and without IHCP.

IHCP technique: IHCP was performed after gastrectomy/alimentary tract reconstruction and

IHCP appears to be helpful in decreasing peritoneal dissemination and has a potential for improving the survival rate among radically operated gastric cancer patients

wound closure. One inflow catheter (30F) was positioned beneath the left hemidiaphragm. Three outflow catheters (32F) were placed in the subhepatic area, in both the true and false pelvises. Temperature probes were placed on the inflow and outflow catheter tips. IHCP was administered for one hour with an automatic IHCP device (HT-1000 Thermochem (ThermaSolutions, Inc., USA)). Perfusate used was Ringer's solution (5-6L) mixed with cisplatin 50mg/m^2 + doxorubicin 50mg/m^2, warmed to an inflow temperature of 42°C.

Postoperative disease progression was detected by a combination of physical examination, periodic diagnostic imaging, computed tomography and ultrasonography. Disease progression with the development of peritoneal dissemination was detected by performing second-look laparoscopy. Chemotherapeutic side effects were assessed using CTCAE v 3 score.

Statistical analysis: Survival curves were calculated by the Kaplan-Meier method and compared by using the log-rank test. Student's t-test and Fisher's test were used to determine significant differences. The differences were judged to be significant at p value of less than 0.05.

Results

There was no difference between the two groups in the complication rates: 15.4% in the ICHP group and 6.9% in the control group (p = 0.45) (Table 1).

Gastrojejunal anastomotic leak occurred in two patients from the IHCP group leading to their death. Postoperative mortality rate was 5.1%. Development of gastrojejunal anastomotic leak in the IHCP group and its absence in the control group may be attributed to the influence of the IHCP procedure per se on the temperature of metal staples forming the anastomosis. In our view, an increase in their temperature could in some way contribute to such failure. No fatality was suffered by the control group.

IHCP-related complications: Evaluation of IHCP toxicity showed neither toxic complications of III-IV degree nor haematological toxicity (according to CTCAE v 3). IHCP-specific complications were observed, namely, postoperative fever of unclear genesis rising to 38°C and more and persisting for over three days. That complication was observed in two IHCP-treated patients and required administration of anti-inflammatory therapy.

As compared with the control group, the IHCP group showed a heightened degree of endogenous intoxication (up to III degree) with subsequent normalisation of laboratory test indicators by the tenth day after the surgery. The degree of endogenous intoxication in the control group was less pronounced (I-II degrees) and normalisation occurred earlier – from three to seven days after the surgery. An increase in endogenous intoxication in both groups was reversible and had no effect on the length of patient stay in hospital.

Table 1. Postoperative morbidity rate

Complications	IHCP group	Control group	P value
Gastrojejunal anastomotic leak	5.1% (2 patients)	-	0.5
Postoperative pneumonia	10.3% (4 patients)	6.9% (2 patients)	1.0
Overall morbidity rate	15.4% (6 patients)	6.9% (2 patients)	0.45

Table 2. Recurrence pattern among radically operated patients with gastric cancer

Recurrences	IHCP group	Control group	P value
Peritoneal metastases	12.8% (5 patients)	27.6 % (8 patients)	0.21
Hematogenous metastases	7.7% (3 patients)	6.9% (2 patients)	1.0
Disease progression	20.5% (8 patients)	34.5% (10 patients)	0.28
Time to development of peritoneal dissemination after surgery	6.9±1.12 months	10.6±0.98 months	0.02

Recurrence pattern with disease progression: Among the 68 patients, recurrences developed in 18 patients (Table 2).

No loco-regional recurrences were observed in either group. Remote results analysis showed a tendency toward a more frequent disease progression in the control group than in the IHCP group: 10 patients (34.5%) v 8 patients (20.5%), respectively (p = 0.28), in particular, trending toward a more frequent development of peritoneal dissemination: 27.6% v 12.8%, respectively (p = 0.21). The difference in the frequency of peritoneal dissemination appeared to be statistically unreliable (p > 0.05) and this may be due to the small number of observations in the groups. At the same time peritoneal dissemination also appeared to develop earlier in patients without IHCP: 10.6 ± 0.98 months v 6.9 ± 1.12 months in the IHCP group (p = 0.02). In contrast, we noted survival improvement in the IHCP-treated group.

Survival analysis: The follow-up period varied from 1 to 34 months. Overall 1-year survival (Kaplan-Meier) for the IHCP group was 0.952 ± 0.0465 [95% CI 0.866 – 1]; that for the control group was 0.667 ± 0.1111 [95% CI 0.481 – 0.924] [log-rank: chi2 on 1df = 4.9, p = 0.0312].

Discussion

Our trial results are in agreement with studies conducted by researchers in Europe and Asia that have shown a positive effect of IHCP on reducing peritoneal dissemination rates [8,9,11-13].

However, there are also reports about a lack of IHCP efficacy in managing peritoneal dissemination. Thus, according to a non-randomised study undertaken in the Medical University of Yokohama, Japan, there was a decrease in the frequency of peritoneal relapse: 50% in the IHCP group against 67.7% in the control group, with p > 0.05 [15]. The perfusate used in this trial comprised 150mg of cisplatin plus 15mg of MMC plus 150mg of etoposide administered at 42-43°C for 40 minutes. This study showed some decrease in the five-year survival rate (49% in the IHCP group v 56% in the control group) and an increase in the number of complications, including respiratory (73% v 19%, p < 0.0001) and renal failures (7% v 0%, p < 0.03). Based on these findings, it was concluded that IHCP was ineffective as a prevention method. A similar conclusion about IHCP inefficiency was drawn by Samel et al [14]. Their study comprised nine patients treated with cisplatin and MMC as IHCP agents. They reported a 66% postoperative morbidity that included kidney failure, pancreatitis and anastomotic failure. Furthermore, the disease progressed into carcinomatosis in 55% of cases and led to the death of these patients. These researchers concluded that the IHCP application results in an increase in postoperative complications and appears to be incapable of preventing or delaying disease recurrence in patients with advanced stomach cancer.

It is notable that all of the above-referenced studies [14,15], both testifying to the efficacy of IHCP or to lack of it, employed MMC or a combination of MMC and cisplatin in IHCP solutions.

As cisplatin is known to be fairly toxic irrespective of methods of administration, we opted for a combination of a reduced dosage of cisplatin to mitigate its side-effects and an increased dosage of doxorubicin to retain synergy of these two

drugs. Even so, we observed that the number of complications in the IHCP group exceeded that in the control group: 15.4% against 6.9%, respectively, although this difference appears statistically unreliable with $p > 0.05$. However, it should be noted that the complications observed in the IHCP group were mainly postoperative pneumonias which in itself is not attributable to the IHCP effect. Thus, in our estimate such an approach does not affect chemotherapy tolerance, nor does it compromise the treatment effect.

Given the difference of views on the efficacy of IHCP in treating radically operated gastric cancer patients, there is a need for further studies to evaluate the effect of IHCP with regard to peritoneal dissemination.

Conclusions

Based on the results of our trial study and the above cited studies, we can draw the following conclusions:

1. IHCP appears to be helpful in decreasing peritoneal dissemination;
2. IHCP has a potential for improving the survival rate among gastric cancer patients;
3. Further prospective studies based on a larger cohort of patients are needed to fully assess the potentialities of IHCP as a preventive treatment of gastric cancer associated with a high risk of peritoneal dissemination. ■

References

References

1. Cunningham D, Allum WH, Stenning SP et al. *Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer* // N. Engl. J. Med.- 2006.- Vol. 350.- P. 11-20.
2. Macdonald JS, Smally SR, Benedetti J et al. *Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction* // N.Engl. J. Med.- 2001.- Vol. 345.- P. 725-30.
3. Kaibara N., Sumi K., Yonekawa M et al. *Does extensive dissection of lymph nodes improve the results of surgical treatment of gastric cancer?* // Am. J. Surg.- 1990.- Vol. 159.- P. 218-21.
4. Liano A.-D., Yarnoz C., Aguilar R. et al. *Rationale for gastrectomy with D2 lymhadenectomy in the treatment of gastric cancer* // Gastric Cancer. – 2008. – Vol. 11. – P. 96-112.
5. Hayes N., Wayman J., Wadehra V. et al. *Peritoneal cytology in the surgical evaluation of gastric carcinoma* // Brit. J. Cancer. – 1999. – Vol. 79(3/4). – P. 520-4.
6. Ceelen W.P. (editor) *Peritoneal carcinomatosis: a multidisciplinary approach*. – Springer, 2007.- 533p.
7. Koga S., Hamazoe R., Maeta M. et al. *Prophylactic therapy for peritoneal recurrence of gastric carcinoma by continuous hyperthermic peritoneal perfusion* // Cancer.- 1988.- Vol. 61.- P. 232-7.
8. Yonemura Y., de Aretxabara X., Fujimura T. et al. *Intraoperative chemohyperthermic peritoneal perfusion as an adjuvant to gastric cancer: final results of a randomized controlled study* // Hepatogastroenterol.- 2001.- Vol. 48.- P. 1776-82.
9. Scaringi S., Kianmanesh R., Sabate J.M. et al. *Advanced gastric cancer with or without peritoneal carcinomatosis treated with hyperthermic intraperitoneal chemotherapy: a single western center experience* // Eur. J. Surg. Oncol.- 2008.- Vol. 34. - P. 1246-52.
10. Fujimoto S., Takahashi M., Muton T. et al. *Succeful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma* // Cancer.- 1999.- Vol. 85.- P. 529-34.
11. de Roover A., Detroz B., Detry O. et al. *Adjuvant hyperthermic intraperitoneal peroperative chemotherapy (HIPEC) associated with curative surgery for locally advanced gastric carcinoma.* An initial experience // Acta Chir. Belg.- 2006.- Vol. 106, No. 3.- P. 297-301.
12. Kim J.-I., Bae H.-S. *A controlled clinical trial of serosa-invasive gastric carcinoma patients who underwent surgery plus intraperitoneal hyperthermo-chemo-perfusion (IHCP)* // Gastric Cancer.- 2001.- Vol. 4.- P. 27-33.
13. Xu D.-Z., Zhan Y.-Q., Sun X.-W. et al. *Meta-analysis of intraperitoneal chemotherapy for gastric cancer* // World J. Gastroenterol. – 2004. – Vol. 10 – P. 2727-30.
14. Samel S., Singal A., Becker H. et al. *Problems with intraoperative hyperthermic peritoneal chemotherapy for advanced gastric cancer* // Eur. J. Surg. Oncol.- 2000.- Vol. 26.- P. 222-6.
15. Kunisaki C., Shimada H., Nomyra M. et al. *Lack of efficacy of prophylactic continuous hyperthermic peritoneal perfusion on subsequent peritoneal recurrence and survival in patients with advanced gastric cancer* // Surgery.- 2002.- Vol. 131, No. 5.- P. 521-8.

The Genome Doctor, a Whole-Genome Sequencing Approach to Cancer

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The enthusiasm of the clinical cancer research community has been renewed by clinically relevant demonstrations of molecular profiling arising from "whole genome sequencing" (WGS), leading to novel approaches of "personalised" cancer treatments. However, critics question the merits of such large-scale, expensive, time-consuming, data-harvesting, and descriptive approaches, citing the paucity of improvement in outcomes. We address here the challenges and potentials in the clinical application of whole-genome sequencing for cancer.

Why a whole genome sequencing approach to cancer?

Cancers ultimately result from the pathological impact of aberrations in DNA sequence. Human anomalous DNA sequences derive from exposure to mutagens, virus, inflammation, and even spontaneous mutation, and perpetuates through replication, resulting in the accumulation of tumour promoting alterations in the DNA sequence. An unbiased genome-wide mutation detection approach to cancer can identify somatically acquired sequence variants and functional mutations and thereby identify critical genes uniquely relevant to the development of a specific patient's cancer. This strategy will ultimately provide the paradigm for the detection of germline mutations in non-neoplastic human genetic diseases through genome-wide mutation detection approaches, which may fundamentally revolutionise cancer prevention and treatment through personal medicine.

Technology advancements make whole genome sequencing affordable

The Human Genome Project (HGP) applied a highly labour intensive process called Sanger sequencing to identify the original DNA sequences. The HGP launched in 1990 and formally completed the first draft sequence of an entire human genome in 2003([1,3]. The cost of HGP was about 5 billion dollars [4,5]. Since 2005, however, a new technology, called 'next-generation sequencing' or 'massively parallel sequencing,' has emerged and replaced Sanger sequencing [6]. This cut down not only the cost, but the time to complete the genome sequencing. For example, Complete Genomics Incorporation has developed a genome sequencing platform that achieves high accuracy and significantly reduced cost (currently > $10,000) with the ability to detect rare variants within 10 days [7]. Competition has motivated several companies to predict that within the very near future, delivery of a complete WGS project can be completed within 24 h with a cost of $1,000! [8,9]. These developments have prompted scientists to conceive the concept of using whole-genome sequencing in everyday clinical decision-making for personalized medicine [10].

In the USA, NIH has funded three institutions to apply WGS to studying human diseases – Baylor College of Medicine, the Broad Institute of Harvard and MIT, and the Washington University. In the United Kingdom, the Sanger Centre has decided to sequence the whole genome to study certain highly important diseases [11-15]. In Germany, Korbel and colleagues have published paediatric medullo-blastoma genome data [16]. All of these sequencing centres have included a focus on cancer, applying the whole genome approach. We will discuss several recent publications to address the challenges and potentials for WGS for cancer.

The Washington University approach to acute myeloid leukaemia

Washington University researchers have published a series using the WGS approach to describe acute myeloid leukaemia (AML) [17-22]. They reported a new mutation in a gene called DNMT3A that may help identify patients with high risk of recurrent AML. They successfully used WGS to tailor a personalised treatment plan for a woman with a rare subtype of AML that responded well to a specific targeted therapy, sparing her from more aggressive stem-cell transplantation [23]. Her disease subtype could only be definitively identified through whole-genome sequencing.

The Johns Hopkins University approach to breast and colorectal cancers

At the Johns Hopkins University, Vogelstein and colleagues have published the consensus coding sequences of human breast and colorectal cancers from 11 breast and 11 colorectal cancer patients [24]. This group expanded the study by including analysis of the sequences of 20,857 transcripts from 18,191 human genes, including the great majority of encoding proteins. Any gene in the tumour that was mutated, but not in normal tissue from the same patient, was analysed in 24 other tumours. Selected genes were further analysed in 96 colorectal cancers to improve the definition of their mutation frequency and aid subsequent bioinformatic analyses [25]. They also found a new pathway for pancreatic neoplasia by identifying recurrent mutations at codon 201 of GNAS [26]. The data was derived from analyses of 113 patients with intraductal papillary mucinous neoplasm. KRAS and GNAS mutations can be used in the diagnosis and prognosis of patients with cystic pancreatic lesions.

Clinical Potential of WGS in Cancer Therapy

Vogelstein and colleagues have defined the first genomic landscape of two of the most common human cancers, breast and colon [24]. The majority of their identified 189 cancer-associated genes were not known to be mutated in tumours, prior to these results it was thought that the average tumour harboured 90 mutated genes. Unexpectedly, no gene was consistently mutated in either breast or colorectal tumours. Thus the number of mutations occurring during the evolution of human tumours is greater than previously estimated. The level of complexity suggests a two-step approach to cancer genome: first, a discovery screen, and second, a validation screen.

Discovery Screen

In the past, most cancer-causing mutations have been discovered by foci analysis, often providing to be driver genes that control cell division. Current research indicates that these early efforts barely glimpsed the big picture. The whole genome approach has identified not only known colorectal tumour genes (TP53, APC, KRAS, SMAD4, FBXW7, EPHA3, SMAD2, and TGFBRII), but concomitantly uncovered their pathogenesis of other forms of cancer (GNAS, NF1, and RET) [25]. The approach also indicated other inherited cancer syndromes (familial adenomatous polyposis, neurofibromatosis, Li-Fraumeni syndrome, juvenile polyposis and multiple endocrine neoplasia).

Validation Screen

The Discovery screen (WGS) can guide the validation screen (functional studies) by focusing on genes that may play a role in human cancers. The validation screen may be able to identify mutations that initiate, evolve, and maintain tumours in model systems [27,28]. Recent studies using abnormalities detected in cancer mouse models to study previously unknown genetic lesions in human cancer uncovered a list of high priority targets, which can be further validated as therapeutic targets [29]. Such comparative oncogenomic approaches should prove more rational and cost-effective.

Clinical relevance of the genomic approach

Verhaak and colleagues [30] have published a framework for integrated genomic analysis that identifies clinically relevant subtypes of glioblastoma characterised by abnormalities in PDGFRA, IDH1, EGFR, and NF1. They catalogued recurrent genomic abnormalities in glioblastoma multiforme (GBM). Their gene expression-based molecular classification of GBM led to the construction of four subtypes – proneural, neural, classical and Mesenchymal, based on integrated multidimensional genomic data (patterns of somatic mutations and DNA copy number). Aberrations and gene expression of biomarkers (EGFR, NF1, and PDGFRA/IDH1) define the classical, mesenchymal, and proneural subtypes, respectively. Gene signatures of normal brain cell types show a strong relationship between subtypes and different neural lineages. Additionally, the response to conventional aggressive clinical therapy differs by subtype, with the greatest benefit in the Classical subtype and no benefit in the proneural subtype.

Challenges

Currently 90% of drugs fail in cancer patients. The relatively small number of new genes common to tumours reinforces concerns about the cancer genome approach. In the Johns Hopkins study, despite previously unknown mutated genes being discovered, the functional consequences of most of these and their actual role in tumourigenesis are unknown; even with that knowledge, we remain a long way from identifying new therapeutic targets.

Large-scale efforts

Vogelstein and his colleagues analysed 13,023 genes to define the best studied genes in the human cancer genome. His 29-member team resequenced the protein-coding regions of the genes in 11 breast cancer samples and 11 colon cancer samples and found about 800,000 possible mutations. The team then redefined functional mutations in 189 cancer-associated genes by removing errors, normal variants, and changes that did not alter a protein.

Heterogeneity

All these studies show that cancer mutations exhibit daunting complexity and heterogeneity. A major issue in looking at the whole genome for cancer is that so many of the mutations known to date are not common to patients with a single type of cancer. Furthermore, many lie in areas of the genome where their unknown function and/or significance is unknown. Vogelstein's team found that the average breast or colon tumour has 93 mutated genes, with at least 11 thought to be cancer-promoting. Their work yielded a total of 189 'candidate' cancer genes. The cancer genes differ between colon and breast cancers, suggesting that more steps or pathways leading to tumourigenesis cancer than previously conjectured.

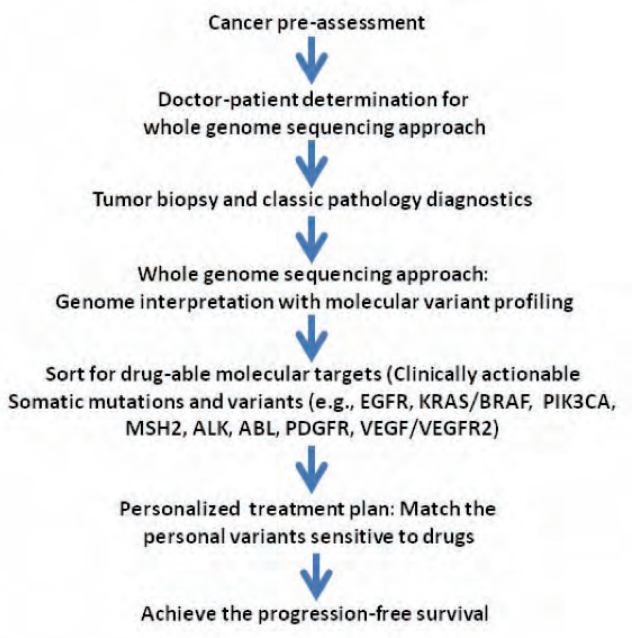

Figure 1. The genome doctor's diagnostics and treatment flowchart.

Complex statistical analysis

While Sjöblom et al. [31,32] reported 189 genes with an apparent statistically significant excess of mutations in breast and colorectal tumours, Rubin and Green [32] used a different set of criteria for statistical analysis for the same cancer genomic data and identified only a handful of previously known cancer genes (TP53 in breast cancer, and APC, KRAS, TP53, SMAD4, and FBXW7 in colorectal cancer). Thus, they concluded that this genome approach did not implicate any additional cancer genes beyond the handful known from previous studies.

Eric Lander's group at MIT/Harvard, after correcting the statistical analysis and using a background mutation rate that better fit their data, reported that these 189 novel cancer genes did not reach a 90% probability of being relevant to colon or breast cancer [33]. Forest and Cavet [34,35] argued against point probabilities algorithm that was used in the original paper [24] and they suggested using P value-based algorithm to reanalyse the same set of data. Their analysis led to definition of only six (instead of 122) candidate cancer genes (CAN genes) in breast cancer and 28 (instead of 69) CAN genes in colorectal cancer.

Addressing the above criticism, the original study group introduced two experimentally derived concepts – candidate cancer genes (CAN genes; driver mutation genes) versus passenger mutation genes [34]. They argued that driver mutation genes identified by Sjöblom et al. [35] mutated at higher rates than the experimentally determined passenger mutation rate. Thus, they advocated that the focused functional studies are essential for determining cancer treatment strategies as guided by WGS approach, which can help identify those mutated genes that likely are subject to study in model organisms.

Cost

The US Cancer Genome Atlas is an ambitious $1.5 billion federal project to search systematically for genes mutated in dozens of cancer types [36]. The Hopkins study alone costs about $5 million [37]. The cost per whole-genome sequence has rapidly dropped over the past three years. At Washington University, the 2008 AML study cost just over $1.5 million; over a third of it was devoted simply to developing the bioinformatics required to compare the tumour and normal genomes, whereas today, the cost is only $10,000.

A novel platform, generating an average of 45- to 87-fold coverage per genome and identifying 3.2 to 4.5 million sequence variants per genome has been developed [7]. Validation of one genome data set demonstrates a sequence accuracy of about 1 false variant per 100 kilobases. The high accuracy, affordable cost of $4400 for sequencing consumables, and scalability of this platform enables complete human genome sequencing for the detection of rare variants in large-scale genetic studies.

Reducing the cost with continuing improvements in speed and accuracy led researchers to move from few patients-based proof-of-concept studies to larger projects to determine the impact of rare genetic mutations on potential responses to treatment and outcome predictions. The Washington University researchers have sequenced the complete tumour and normal genomes of 150 patients. Washington University estimated a complete panel of current genome tests can cost up to $10,000 per patient, and that cost will rise as new prognostic genes are discovered and added to the panel of molecular profiling.

Future Directions

Current consensus argues for a two-stage experimental approach to cancer genome research, a discovery sequencing screen followed by a validation functional screen (Figure 1). Sequencing data can, in general, only point to candidate genes worthy of further functional study. Sequence data can only identify genes that are mutated at unusually high rates [25]. In general, such data cannot determine whether the higher rate is the result of higher intrinsic mutability or positive selection during tumourigenesis. At most, sequencing data should be used to prioritise candidate cancer genes on the basis of their mutation characteristics and frequency.

A whole genome approach to cancer identifies the genetic alterations in cancers on a genome-wide scale. The resulting compendium of genetic changes in individual tumours provides new opportunities for diagnosis and treatment of cancer in each patient. However, this approach raises significant new challenges in understanding the roles that these mutations actually play in cancer. Such an understanding is essential for patients with the mutations to have dramatic benefits. ■

References

1. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, Devon K, Dewar K, Doyle M, FitzHugh W et al: *Initial sequencing and analysis of the human genome.* Nature 2001, 409(6822):860-921.
2. Venter JC: *A part of the human genome sequence.* Science 2003, 299(5610):1183-4.
3. Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, Smith HO, Yandell M, Evans CA, Holt RA et al: *The sequence of the human genome.* Science 2001, 291(5507):1304-51.
4. Cravchik A, Subramanian G, Broder S, Venter JC: *Sequence analysis of the human genome: implications for the understanding of nervous system function and disease.* Arch Neurol 2001, 58(11):1772-8.
5. Metzker ML: *Sequencing technologies - the next generation.* Nat Rev Genet 2010, 11(1):31-46.
6. Mardis ER: *A decade's perspective on DNA sequencing technology.* Nature 2011, 470(7333):198-203.
7. Drmanac R, Sparks AB, Callow MJ, Halpern AL, Burns NL, Kermani BG, Carnevali P, Nazarenko I, Nilsen GB, Yeung G et al: *Human genome sequencing using unchained base reads on self-assembling DNA nanoarrays.* Science 2010, 327(5961):78-81.
8. Davies K: *The $1000 genome: The revolution in DNA sequencing and the new era of personalized medicine.* . New York: Free Press; 2010.
9. Bayes M, Heath S, Gut IG: *Applications of Second Generation Sequencing Technologies in Complex Disorders.* Curr Top Behav Neurosci 2012.
10. Roach JC, Glusman G, Smit AF, Huff CD, Hubley R, Shannon PT, Rowen L, Pant KP, Goodman N, Bamshad M et al: *Analysis of genetic inheritance in a family quartet by whole-genome sequencing.* Science 2010, 328(5978):636-9.
11. Bignell GR, Greenman CD, Davies H, Butler AP, Edkins S, Andrews JM, Buck G, Chen L, Beare D, Latimer C et al: *Signatures of mutation and selection in the cancer genome.* Nature 2010, 463(7283):893-8.
12. Garnett MJ, Edelman EJ, Heidorn SJ, Greenman CD, Dastur A, Lau KW, Greninger P, Thompson IR, Luo X, Soares J et al: *Systematic identification of genomic markers of drug sensitivity in cancer cells.* Nature 2012, 483(7391):570-5.
13. Greenman C, Stephens P, Smith R, Dalgliesh GL, Hunter C, Bignell G, Davies H, Teague J, Butler A, Stevens C et al: *Patterns of somatic mutation in human cancer genomes.* Nature 2007, 446(7132):153-8.
14. Pleasance ED, Cheetham RK, Stephens PJ, McBride DJ, Humphray SJ, Greenman CD, Varela I, Lin ML, Ordonez GR, Bignell GR et al: *A comprehensive catalogue of somatic mutations from a human cancer genome.* Nature 2011, 463(7278):191-6.
15. Stephens PJ, McBride DJ, Lin ML, Varela I, Pleasance ED, Simpson JT, Stebbings LA, Leroy C, Edkins S, Mudie LJ et al: *Complex landscapes of somatic rearrangement in human breast cancer genomes.* Nature 2009, 462(7276):1005-1010.
16. Rausch T, Jones DT, Zapatka M, Stutz AM, Zichner T, Weischenfeldt J, Jager N, Remke M, Shih D, Northcott PA et al: *Genome sequencing of pediatric medulloblastoma links catastrophic DNA rearrangements with TP53 mutations.* Cell 2012, 148(1-2):59-71.
17. Ding L, Ley TJ, Larson DE, Miller CA, Koboldt DC, Welch JS, Ritchey JK, Young MA, Lamprecht T, McLellan MD et al: *Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing.* Nature 2012, 481(7382):506-510.
18. Ley TJ, Mardis ER, Ding L, Fulton B, McLellan MD, Chen K, Dooling D, Dunford-Shore BH, McGrath S, Hickenbotham M et al: *DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome.* Nature 2008, 456(7218):66-72.
19. Mardis ER, Ding L, Dooling DJ, Larson DE, McLellan MD, Chen K, Koboldt DC, Fulton RS, Delehaunty KD, McGrath SD et al: *Recurring mutations found by sequencing an acute myeloid leukemia genome.* The New England journal of medicine 2009, 361(11):1058-66.
20. Tomasson MH, Xiang Z, Walgren R, Zhao Y, Kasai Y, Miner T, Ries RE, Lubman O, Fremont DH, McLellan MD et al: *Somatic mutations and germline sequence variants in the expressed tyrosine kinase genes of patients with de novo acute myeloid leukemia.* Blood 2008, 111(9):4797-808.
21. Walter MJ, Payton JE, Ries RE, Shannon WD, Deshmukh H, Zhao Y, Baty J, Heath S, Westervelt P, Watson MA et al: *Acquired copy number alterations in adult acute myeloid leukemia genomes.* Proceedings of the National Academy of Sciences of the United States of America 2009, 106(31):12950-5.
22. Xiang Z, Zhao Y, Mitaksov V, Fremont DH, Kasai Y, Molitoris A, Ries RE, Miner TL, McLellan MD, DiPersio JF et al: *Identification of somatic JAK1 mutations in patients with acute myeloid leukemia.* Blood 2008, 111(9):4809-12.
23. Link DC, Schuettpelz LG, Shen D, Wang J, Walter MJ, Kulkarni S, Payton JE, Ivanovich J, Goodfellow PJ, Le Beau M et al: *Identification of a novel TP53 cancer susceptibility mutation through whole-genome sequencing of a patient with therapy-related AML.* Jama 2011, 305(15):1568-76.
24. Sjoblom T, Jones S, Wood LD, Parsons DW, Lin J, Barber TD, Mandelker D, Leary RJ, Ptak J, Silliman N et al: *The consensus coding sequences of human breast and colorectal cancers.* Science 2006, 314(5797):268-74.
25. Wood LD, Parsons DW, Jones S, Lin J, Sjoblom T, Leary RJ, Shen D, Boca SM, Barber T, Ptak J et al: *The genomic landscapes of human breast and colorectal cancers.* Science 2007, 318(5853):1108-13.
26. Wu J, Matthaei H, Maitra A, Dal Molin M, Wood LD, Eshleman JR, Goggins M, Canto MI, Schulick RD, Edil BH et al: *Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development.* Sci Transl Med 2012, 3(92):92ra66.
27. Li SC, Jin Y, Loudon WG, Song Y, Ma Z, Weiner LP, Zhong JF: From the Cover: *Increase developmental plasticity of human keratinocytes with gene suppression.* Proc Natl Acad Sci U S A 2011, 108(31):12793-8.
28. Li SC, Loudon WG: *A novel and generalizable organotypic slice platform to evaluate stem cell potential for targeting pediatric brain tumors.* Cancer Cell International 2008, 8:9 (page 1-11).
29. Chng WJ: *Limits to the Human Cancer Genome Project?* Science 2007, 315(5813):762; author reply 764-5.
30. Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, Miller CR, Ding L, Golub T, Mesirov JP et al: *Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1.* Cancer Cell 2010, 17(1):98-110.
31. Rubin AF, Green P: *Comment on "The consensus coding sequences of human breast and colorectal cancers".* Science 2007, 317(5844):1500.
32. Rubin AF, Green P: *Mutation patterns in cancer genomes.* Proc Natl Acad Sci U S A 2009, 106(51):21766-70.
33. Getz G, Hofling H, Mesirov JP, Golub TR, Meyerson M, Tibshirani R, Lander ES: *Comment on "The consensus coding sequences of human breast and colorectal cancers".* Science 2007, 317(5844):1500.
34. Chng W, Loeb L, Bielas J, Strauss B, Sjöblom T, Jones S, Wood L, Parsons D, Lin J, Barber T et al: *Limits to the human cancer genome project?* Science 2007, 315:762-4.
35. Stein LD: *The case for cloud computing in genome informatics.* Genome Biol 2010, 11(5):207.
36. Kaiser J: *GENOMICS: Tackling the Cancer Genome.* Science 2005, 309 (5735): 693
37. Kaiser J: *Cancer. First pass at cancer genome reveals complex landscape.* Science 2006, 313 (5792):1370.

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Journal Reviews

Neuro-Oncology

Intraoperative MRI for optimal glioblastoma resection

The extent of surgical resection in glioblastoma (GBM) may be an independent predictor of overall survival, however this remains a controversial issue. Intraoperative imaging methods such as ultrasound, 5-aminolevuleinic acid (5-ALA) guided resection and MRI aim to improve the rates of gross total resection (GTR) in glioma. Furthermore, combining intraoperative MRI (iMRI) with advanced imaging methods such as functional MRI, diffusion tensor imaging and PET allows for identification of eloquent areas of the brain and therefore aids in surgical planning. In this study the authors used these techniques to assess extent of resection and clinical outcome in a cohort of patients with GBM. 135 patients with GBM (mean age 59.3) were included in the study and underwent surgery with iMRI guidance. Following iMRI, 88 patients were found to have residual tumour. Of these, 19 patients had further surgical resection of tumour, with nine patients achieving 'GTR' (an increase of 34.8% to 41.49% of patients achieving GTR). Further resection was not possible in 51.1% of patients due to the location of the residual tumour. In terms of morbidity, of those patients who underwent additional resection following iMRI, 4.4% had motor and 0.7% had language deficits respectively. Overall median survival was 12 months. Median survival in patients less than 65 years old with >98% resection was 14 months compared to 9 months in those with <98% resection ($P<0.001$). Gender and tumour localisation was not statistically significant.

Reviewer's opinion: This study highlights the use of novel planning and intraoperative MRI in order to optimise surgical resection in glioblastoma, particularly in patients under 65 years old. Furthermore it provides a comparison to current surgical planning methods. Further studies are required in order to validate the use of intraoperative imaging modalities and justify the expense of adaptations to current theatre suites. – SB

Correlation of the extent of tumour volume resection and patient survival in surgery of glioblastoma multiforme with high field intraoperative MRI.
Kuhnt D, Becker A, Ganslandt O, Butler M, Buchfelder, Nimsky C.
Neuro-Oncology
2011;13(12):1339-48.

Use of Flow cytometry in CSF analysis

Leptomeningeal carcinomatosis (LC) is an uncommon complication of cancer and is associated with an extremely poor prognosis (three to six months with treatment). Diagnosis currently relies on cytological examination of CSF fluid, however the diagnostic yield is usually low. Flow cytometry immunophenotyping (FCI) is used routinely in the assessment of haematological malignancies and is now being utilised for the identification of other neoplastic populations within fluids such as carcinoma and melanoma. In this study the authors assessed the use of FCI in a cohort of patients with known primary carcinoma and clinical suspicion of leptomeningeal spread. Ninety-nine patients were recruited of which full clinical and diagnostic results were available in 78. The majority of patients had a primary breast or lung adenocarcinoma (67 patients). In four patients, the primary location of the tumour was unknown. In addition to routine cytology, the CSF samples were stained for epithelial markers BER EP4 and EP-CAM and analysed using standard FACS analysis software. 49 of the 78 patients were confirmed to have LC (32 on cytology and 17 on radiology and biochemistry). FCI detected 37 cases of LC compared to 32 cases by cytology alone. The sensitivity of FCI was 75.5 (63.5-87.6) and the specificity 96.1 (88.8-100). Interestingly, 12 patients with a clinical and radiological diagnosis of LC had CSF samples which were negative for both cytology and FCI.

Reviewer's opinions: This study highlights the potential use of FCI as part of the routine assessment of CSF. There was good correlation between cytology (the current gold standard) and FCI. FCI may help to overcome diagnostic problems with small volumes of fluid received for cytological assessment. Further studies are required to optimise the markers used for detection of carcinoma cells. – SB

Role of flow cytometry immunophenotyping in the diagnosis of leptomeningeal carcinomatosis.
Subira D, Serrano C, Castanon S, Gonzalo R et al.
Neuro-Oncology 2012;14(1):43-52.

An IDH1 mutated in vivo model

IDH1/2 mutations are a feature of WHO Grade II/III gliomas and secondary glioblastomas and are associated with improved overall survival. The exact cellular function of these enzymatic mutations is unclear at present and efforts to investigate their function have been hindered by a lack of appropriate in vitro and in vivo models. In this study, the authors obtained fresh tissue from a 38 year old patient with a pathological diagnosis of anaplastic oligoastrocytoma (WHO Grade III) which showed IDH1 mutation (R132H antibody positive). Of note, FISH analysis of 1p/19q in this case was inconclusive. Neurospheres were cultured from the fresh samples using primary cell culture techniques with serum free media and growth factor supplements. Following 14 days culture the neurospheres retained the IDH1 mutation (R132H positive). Furthermore, the cells were also positive for stem cell markers, oligodendroglial and neuronal markers. SNP analysis showed loss of 1p and 19q in a subpopulation of the cell line. As in vivo growth was slow, 1x104 cells were injected into the brains of SCID mice. Median survival was 112 days after injection. Histology and immunocytochemistry revealed a largely undifferentiated tumour however the IDH1 mutation was retained. The mutation was also retained following serial intracranial passages which appeared to increase tumorigenicity and reduced the overall median survival of the mice (93 days); however this was not statistically significant. Both in vivo and invitro tumour cells harbouring the IDH1 mutation showed increased production of 2-HG when compared to 'wild type' tumour cells.

Reviewer's opinions: This interesting study highlights a potential model to investigate the metabolic function of IDH1 mutations in glioma cells. Further primary cell culture studies from a wider variety of histological glioma specimens are warranted. – SB

An in vivo patient derived model of endogenous IDH1-mutant glioma.
Luchman HA, Stechishin OD, Dang NH, Blough MD et al.
Neuro-Oncology
2012;14(2):184-9.1

Head & Neck

Oncologic outcomes in advanced laryngeal squamous cell carcinomas treated with different modalities in a single institution: a retrospective analysis of 65 cases

Treatment for laryngeal squamous cell carcinoma (SCC) has been predominantly surgical for decades, but in the last 20 years nonsurgical modalities (radiotherapy), with the aim of organ preservation, also became predominant among advanced stages. Retrospectively evaluating our series of stage III and stage IV laryngeal SCCs, we compared the two main therapeutic modalities.

Methods: Medical records of 65 consecutive patients with advanced laryngeal SCC, from November 2005 to January 2009, were reviewed.

Results: Among irradiated patients 2-year organ preservation was 86% for cT2, 43% for cT3, and 17% for cT4a ($p=.037$, Wilcoxon test). With respect to survival, the only significant differences between surgery and radiotherapy were detected among cT4a SCCs ($p=.03$, Wilcoxon test), in favor of surgery.

Conclusions: The present results confirm the surgical recommendation for cT4a laryngeal SCCs. On the other hand, for T<4, our results confirm that radiochemotherapy warrants a survival similar to that of total laryngectomy, thus allowing us to preserve the larynx in a relevant number of cases.

Comments: This paper shows us the importance of well designed retrospective studies. The study recommends the need for primary surgical treatment in case of bulky laryngeal tumours i.e. anything above T4 stage. – MD

Oncologic outcomes in advanced laryngeal squamous cell carcinomas treated with different modalities in a single institution: A retrospective analysis of 65 cases.
Bussu F, Miccichè F, Rigante M, et al.
Head & Neck
2012;34(4):573-9.

Meet the Editorial Team

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

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

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

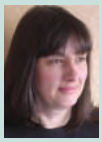
Dr Tom Lynch is Assistant Editor – Imaging, and is a Radiologist and Lead Nuclear Medicine Physician in the Northern Ireland Cancer Centre based at the Belfast City Hospital. Tom specialises in PET/CT scanning and nuclear medicine with a special interest in paediatric nuclear medicine.

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

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

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

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

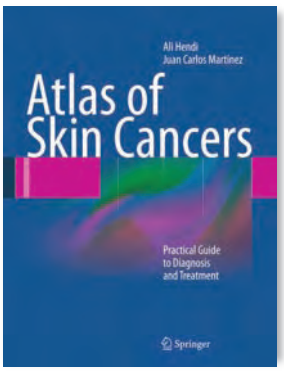


Ms Kathleen Mais is Assistant Editor – Nursing, and is a Nurse Clinician in Head & Neck Oncology at Christie Hospital, Manchester. Kathleen qualified as a nurse in Newcastle-upon-Tyne. Kathleen is a nurse-prescriber and runs a nurse-led chemotherapy clinic as well as continuing her work in clinical research.

Book Review

Atlas of skin cancers. Practical guide to diagnosis and treatment

Authors: Ali Hendi and Juan-Carlos Martinez. Published by: Springer. ISBN: 978-3-642-13398-5. Price: £62.99.



This atlas is written by two eminent dermatologists, practising in the USA. The aim of this atlas is to enable the non-dermatology trained physician to identify those skin lesions that warrant a biopsy. It is hoped that this book will help those interested parties to improve their clinical acumen. This is aided by the use of hundreds of good quality colour photographs. The atlas is well laid-out, makes good use of headings and is easy to read.

The text is well written, in a clear understandable style for the non-specialist. There are numerous photographs of the studied lesion as well as photographs of mimickers, or differential diagnoses. References are provided at the end of each chapter.

Chapter 3: Non-melanoma skin cancer. This chapter discusses the surgical treatment options in detail, in particular, electrodessication and curettage and excision. Moh's microangiographic surgery, a specialised technique of excision and margin examination is demonstrated in detail. The use of radiotherapy is just mentioned; its use is not described in any detail. This area could be expanded considerably. There are many photographs of clinical examples of variants of BCCs, as well as mimickers of BCC. This is followed by examples of SCC and mimickers of SCC.

Chapter 4: Melanoma. The introduction to melanoma is brief, as is the section on treatment of melanoma. I feel that this section could be expanded on; in particular, the size of margins of surgical excision. However the clinical photographs are good, displaying various variants.

Chapter 5: Miscellaneous cutaneous neoplasms, describes the uncommon skin malignancies. Photographic examples are provided for many lesions, though they are not discussed in any detail.

Chapter 6: Biopsy techniques, discusses how biopsies are to be taken for diagnostic purposes. It discusses several techniques, including the use of local anaesthesia, shave, punch, excisional and incisional biopsies. Photographs are provided, step by step, for the procedures.

Chapter 7: Complications of skin cancer treatment. This chapter discusses the "terrible tetrad" of infection, bleeding, dehiscence and necrosis. Again with the aid of the photographs, it explains how these complications develop, as well as their treatment.

In conclusion, I would recommend this book to those involved in the management of patients with skin malignancy. It use will help to increase one's diagnostic confidence and help to determine which patients may require a biopsy. ■

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

Diary of Events

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

May

4th IMPAKT Breast Cancer Conference
3-5 May 2012; Brussels, Belgium
W: www.impakt.org
E: impakt@esmo.org
T: +41 (0)91 973 19 94

ESTRO 31
9-13 May 2012; Barcelona, Spain
W: www.estro.org

Acute Cancer Care
10, 17, 24, 31 May & 7 June 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

World Congress Brachytherapy
10-12 May; 2012, Barcelona, Spain
W: www.estro.org

NEW
Challenges for the Radiographer in the Digital Age
11 May 2012; London, UK
British Institute of Radiology
E: admin@bir.org.uk

Children's Cancer and Leukaemia Friend's Day
14 May 2012; London, UK
Ruth Threadgold,
T: +44 (0)20 7290 3942
F: +44 (0)20 7290 2989
E: oncology@rsm.ac.uk

Exploring Cancer Practice
14, 28 May, 18, 25 June, 9, 23 July, 6, 20 August, 3 & 17 September 2012; London, UK
T: +44 (0)20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Clinical Leadership in Cancer Care
16, 30 May, 13, 27 June & 11 July 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Chemotherapy in Cancer Care
21, 22, 23, 31 May & 1 June 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Association Of Breast Surgery Conference & AGM
21-22 May 2012; Bournemouth, UK
Lucy Davies
T: +44(0)20 7869 6852
E: lucydavies@absgbi.org.uk

NEW
Paediatric Brain Tumours: Supporting Children and Their Families
22 May 2012; London, UK
W: www.royalmarsden.nhs.uk/studydays
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921/ 020 7808 2924

NEW
An Introduction to Acute Oncology
28 May 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

NEW
Developing Nurse Led Chemotherapy Clinics
30 May 2012; London, UK
W: www.royalmarsden.nhs.uk/studydays
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921/ 020 7808 2924

June

2012 ASCO Annual Meeting
1-5 June 2012; Chicago, Illinois, USA
W: www.asco.org

Casley-Smith Update (Unaccredited)
6-8 June 2012; Glasgow, UK
Mrs Margaret Sneddon,
Programme Director,
T: 0141 330 2071/2072,
E: lymph@glasgow.ac.uk
W: http://www.gla.ac.uk/departments/nursing/

10th European Congress of Neuropathology
6-9 June 2012; Edinburgh, Scotland
W: www.euro-cns.org

NEW
Oncoplastic Breast Surgery for Clinical Nurse Specialists and Nurse Practitioners
9 June 2012; London, UK
W: www.royalmarsden.nhs.uk/studydays
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921/ 020 7808 2924

22nd Meeting of the European Neurological Society
9-12 June 2012; Prague, Czech Republic
W: http://www.congrex.ch/ens2012

Breast Cancer Care
11, 12, 13, 14 & 15 June 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

NEW
Introduction to Cancer Care Day 2
12 June 2012; Middlesex, UK
E: anni.hall@nhs.net

World Conference on Interventional Oncology 2012
13-16 June, 2012; Chicago, IL, USA
W: www.wcio2012.com

NEW
2nd National Conference Independent Association of Nurses in Palliative Care
14 June 2012; Manchester, UK
W: www.ianpc.org

Connected – National Advanced Communication Skills Training
18, 19 & 20 June 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

ASCO update
20 June 2012; London, UK
Ruth Threadgold,
T: +44 (0)20 7290 3942
F:+44 (0)20 7290 2989
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Enhancing Communication Skills in Cancer Care – 2 day top up
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T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

19th International Brain Tumor Research and Therapy Conference (Asilomar Meeting)
21-24 June 2012; Niagara Falls, Canada
W: www.2012ibtrtc.ca/

15th International Symposium on Pediatric Neuro-Oncology
24-27 June 2012; Toronto, Canada
W: www.ispno2012.com/

7th Teenage Cancer Trust International Conference
25-26 June 2012; London, UK
E: info@tyac.org.uk,
W: www.tyac.org.uk or
T: +44 (0)116 249 4483

BNOS 2012
27-29 June 2012; Manchester, UK
E: secretary@bnos.org.uk
W: www.bnos.org.uk

ESMO 14th World Congress on Gastrointestinal Cancer
27-30 June 2012, Barcelona, Spain
W: www.esmo.org/events/gastrointestinal-2012-gi.html
E: registration@imedex.com
T: +1 855-276-6855

5th International Workshop on Advances in the Molecular Pharmacology and Therapeutics of Bone Disease
27-30 June 2012; Oxford, UK
E: janet@janet-crompton.com
W: www.oxfordbonepharm.org

Brain Tumour Epidemiology Consortium (BTEC) Annual Conference - Opportunities, Challenges and Future Directions
30 June-3 July 2012;
Montpellier, France
W: http://www.cbtrus.org/news/news.html

July

Leadership in Advanced Practice
2, 3, 4, 5 & 6 July 2012; London, UK
T: +44 (0)20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Radionuclide therapy and dosimetry
3 July 2012; London, UK
Ruth Threadgold,
T: +44 (0)20 7290 3942
F:+44 (0)20 7290 2989
E: oncology@rsm.ac.uk

BGCS 2012 annual conference / scientific meeting
5–6 July 2012; London, UK
W: www.bgcs.org.uk

NEW
First Annual Course in Advanced techniques in Neurosurgical Oncology
7-8 July 2012; London, UK
W: www.bnos.org.uk

EACR's Biennial Congress: EACR-22
7-10 July, 2012; Barcelona, Spain
Email: eacr22@ecco-org.eu
W: www.ecco-org.eu

NEW
EHNS Head & Neck Related Congress
8-11 July 2012; Prague,
Czech Republic
W: www.eurogin.com/2012

Foundations in Cancer Care
9, 10, 11, 12 & 13 July 2012;
London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Radiotherapy in Cancer Care
9, 10, 11, 12 & 13 July 2012;
London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Tracheostomy Care Study Day
10 July 2012; London, UK
W: www.royalmarsden.nhs.uk/studydays
E: conferencecentre@rmh.nhs.uk
T: 020 7808 2921/ 020 7808 2924

Palliative Care in Cancer
16, 17, 18, 19 & 20 July 2012;
London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

2012 NCRI Cancer Conference

BT Convention Centre, Liverpool, UK

4-7 November 2012

cancer conference ncri national cancer research institute

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

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

PLENARY SPEAKERS

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

ALSO FEATURING SYMPOSIA ON

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

Cancer evolution
Hosted by Gerard Evan (UK)

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

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

Cancer susceptibility
Hosted by Bruce Ponder (UK)

Palliative and supportive care
Hosted by Irene Higginson (UK)

Tumour immunology
Hosted by Adrian Hayday (UK)

The tumour microenvironment
Hosted by Margaret Frame (UK)

IMPORTANT DATES FOR THE 2012 NCRI CANCER CONFERENCE

Abstract submission opens
Monday 2 April

Abstract submission closes
Tuesday 5 June

Registration opens
Friday 1 June

Late breaking submission opens
Wednesday 1 August

Earlybird registration closes
Tuesday 31 July

Late breaking submission closes
Tuesday 28 August

Online registration closes
Sunday 30 September

Conference
Sunday 4 - Wednesday 7 November

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

www.ncri.org.uk/ncriconference

UNIVERSITY of DERBY

Derby Hospitals NHS
NHS Foundation Trust

Gynaecological Cancer Care:

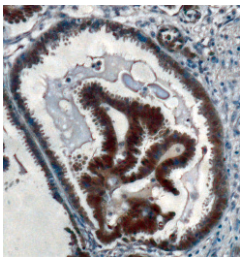
Translational research, clinical approaches and survivorship

11th and 12th October 2012
University of Derby Enterprise Centre
Sponsored by the BACR and Roche Pharmaceuticals

This meeting will bring together researchers and medics in order to address current issues facing gynaecological cancer patients. Particular focus will be given to translational science, screening, treatment improvement and survivorship. There will be a session focussing on collaborative grant writing.

Confirmed speakers include:
Prof. Simon Gayther (USC) Dr James Brenton (Cambridge) Dr Ian Spendlove (Nottingham) Dr Dawn-Marie Walker (Research Design Service)

We will be offering a poster prize and an opportunity for postdoctoral researchers and PhD students to give an oral presentation of their work. To submit an abstract, please follow the link below: The abstract submission deadline is 15th August 2012



Registration for abstracts and conference attendance opens on 1st May 2012

Early bird registration (before 31st August 2012)	**£150**
Registration after 31st August	**£175**

Price includes conference dinner (an exciting evening of Spanish cuisine and entertainment)
on 11th October
For registration and abstract submission please go to the following website: http://www.derby.ac.uk/gynaecologicalcancer

Organising committee:
Mr Anish Bali,
Senior Consultant Gynaecological Oncology Surgeon (Royal Derby Hospital),
Dr Heidi Sowter,
Senior Lecturer (University of Derby).

BNOS 2012

'Challenges and Controversies'

British Neuro-Oncology Society

Manchester 27th to 29th June 2012

ONLINE REGISTRATION NOW OPEN

BOOK NOW TO TAKE ADVANTAGE OF THE DISCOUNTED RATE*

Internationally renowned experts, who are leading the field in neuro-oncology research will deliver an informative and stimulating programme. The conference dinner will be held at Old Trafford, the home of Manchester United Football Club preceded by a tour of the stadium.

For full details and to register online please visit
www.bnos2012.co.uk

* Discounted rates applicable until 18th May 2012

News update

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

First Varian Educational Reference Center in Eastern Europe

The Maria Sklodowska-Curie Memorial Cancer Center in Gliwice, Poland, has become the first hospital in Eastern Europe to be designated a European Reference Center for Education by Varian Medical Systems. As part of this recognition, the hospital will conduct clinical training programs in advanced radiotherapy techniques with Varian equipment.

"This prestigious step can only improve the level of basic education in radiotherapy within Poland by proliferating courses and workshops for radiation oncologists, physicists and radiation technologists," says Professor Boguslaw Maciejewski, director of the center.

"Introducing advanced radiotherapy techniques such as intensity modulated radiotherapy, image-guided radiotherapy and RapidArc is challenging as these advances require well prepared educational courses and hands-on training programs," added Prof. Maciejewski. "As an educational reference center, we will be able to help implement new high tech radiotherapy treatment techniques so they can be introduced safely across many countries in Central and Eastern Europe".

Varian Medical Systems has established a new training center in Tokyo, Japan.

Michael Sandhu, head of Varian's international oncology business, added, "The experts at Gliwice have years of experience in advanced, high quality radiotherapy treatments and this will help them to make this knowledge more easily accessible to the regional community. This is a key step in the development and implementation of new treatment techniques in the region."

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

Elekta's new Agility MLC solution poised to revolutionize beam shaping of radiation therapy cancer treatments

Elekta has received clearance to CE mark Agility™*, a revolutionary beam-shaping device integrated into the head of a linear accelerator. Patients and clinics will benefit from the speed and reliability of this new MLC design.

Agility's leaf speeds are twice as fast as other MLCs commonly used within the industry. This means shorter treatment times for patients, while hospitals and clinics are able to treat patients more efficiently.

With twice as many leaves as a standard MLC, Agility will enable clinicians to sculpt delivered radiation doses to the unique contours of tumors with extreme precision. Clinicians can be confident that the leaves are producing the correct shape to deliver the prescribed treatment to the patient.

Reducing unwanted dose to healthy tissue or organs at risk is of primary importance. Consequently, Agility's leaf bank is designed for extraordinarily low transmission.

"For our patients, the use of Agility with VMAT delivery will allow us to administer Stereotactic Body Radiation Therapy (SBRT) more quickly and efficiently than our current fixed-field approach," says Vivian Cosgrove, Ph.D., head of radiotherapy physics at St. James's University Hospital, Leeds, UK.

Agility can be purchased as part of a new radiotherapy solution, as well as an upgrade option to a large part of Elekta's installed base of linear accelerators. Learn more: www.elekta.com/agility.

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

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

Wear A Hat Day

Brain Tumour Research has been overwhelmed by the support they have received for their Wear A Hat Day campaign this year.

Director Sue Farrington-Smith said "Our member charities and umbrella groups tell us they experienced their most successful Wear A Hat Day and as the money starts coming in the signs are that together we will have raised thousands of pounds to fund vital research into brain tumours."

Campaigners lobbied their MPs and the charity received a photo and letter of support from the Prime Minister, David Cameron.

A growing band of celebrities joined patrons such as celebrity milliner Philip Treacy and former Coronation Street star Bill Tarmey in working with the charity and were an important part of the social media campaign to raise awareness of brain tumours.

Once again actor and author Sheila Hancock CBE was at the forefront of the campaign.

Sheila is the patron of member charity Ali's Dream as well as being chancellor of The University of Portsmouth where Brain Tumour Research's dedicated research centre is based.

Sheila was photographed in a specially designed hat alongside her daughter Melanie Thaw and grandson Jack who was diagnosed with a brain tumour when four years old.

For more information please visit www.braintumourresearch.org

Fast and efficient RapidArc treatments spotlighted for doctors from across Africa

Fast RapidArc® radiotherapy treatments for cancer patients have captured the attention and interest of leading clinicians who have begun offering it in Africa. Clinicians from across Africa attended a week-long workshop sponsored here by Varian Medical Systems where image-guided RapidArc IMRT technology was the focus of discussion.

Doctors and decision makers from South Africa, Zimbabwe, Namibia, Kenya and Angola gathered at Addington Hospital in Durban, which has treated 250 patients with RapidArc since becoming the first public hospital in Africa to use this technique in 2010.

"Our experience has demonstrated the major benefits of RapidArc compared to conventional

radiation therapy in terms of patient satisfaction, treatment delivery and outcomes," says Professor Amo Jordaan, head of radiation oncology at Addington Hospital. "We were delighted to host this high-profile event which introduced RapidArc to many of our colleagues and shared our experiences."

"The oncology load and cancer disease burden here in the KwaZulu Natal province is a microcosm of the disease burden and oncology incidence across Southern Africa," adds Professor Jordaan. "By using RapidArc, our department is able to treat more patients in the specified time, while the treatment is more focused and therefore minimises the impact on healthy tissue."

For further information contact:
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AbD Serotec announces the availability of six new HuCAL® monoclonal antibodies targeting Herceptin®

AbD Serotec's new anti-idiotypic antibodies specifically recognise the humanised monoclonal antibody Herceptin (trastuzumab). The antibodies can be used to measure the Herceptin levels in serum from patients, with potential uses in patient monitoring and preclinical research. The anti-Herceptin antibodies are available in three formats to provide for a range of assay requirements; high affinity monovalent Fab antibodies, ultra-high affinity monovalent Fab antibodies, and fully human IgG1 antibodies for immunogenicity assays.

"In response to increasing demand for our antibodies recognising Rituximab, we produced six new antibodies targeting Herceptin to complement our product offering to CROs and researchers worldwide" said Market Segment Manager, Victoria Warltier.

The generation of novel anti-idiotypic antibodies using the strength of the HuCAL technology is an ongoing focus area for AbD Serotec, and in the pipeline are several further anti-idiotypic antibodies specific for marketed antibody drugs, to be launched within 2012. AbD Serotec also offers custom anti-idiotypic antibody generation services.

HuCAL® is registered trademark of MorphoSys AG. Herceptin® is a registered trademark of Genentech Inc.

For further information contact
Victoria Warltier
E: victoria.warltier@abdserotec.com
T: +44(0)1865 852 700
www.abdserotec.com

AbD serotec
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NEW for your chemo and radiotherapy patients

Dry, inflamed, red, itchy skin, brittle nails and a sore mouth are some of the painful problems patients can be faced with after chemo and radiotherapy.

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RaLife cream and RaLife milk – for use immediately after first radiotherapy treatment and with chemotherapy as required when the symptoms are irritation, redness, inflammation and pain.

DerLife cream and DerLife milk – can be used on skin 2 to 3 weeks before radiotherapy treatment begins and with chemotherapy as required when the symptoms are maceration (wetness), desquamation (peeling), dryness and reddening.

MOUTH

OraLife gel – for preventing and relieving pain, redness, swelling and dry mouth

OraLife mouthwash – to aid cleaning and hygiene of the oral cavity and mouth.

TraLife spray – for the treatment of the oropharynx.

NAILS

OnicoLife drops – for the treatment of tender and/or fragile nails, nail ridges, split nails, yellow or blackened nails.

OnicoLife gel – for the treatment of paronychia.

For further information visit www.mosaicpharma.com or T: +44 (0)0333 6000 166.

Announcing the first forum for Bladder Cancer Nurse Specialists

On October 12th 2012 in London, Nurses against Bladder Cancer (NaBC) will host the first meeting for Uro-oncology Nurse Specialists with a specific interest in bladder cancer. With the focus of urology activities often favouring renal and prostate cancer, this new forum will focus on improving the patient pathway for bladder cancer patients. The aims of the forum are to share expertise and experience, introduce new ideas and provide a networking platform for nurses who often work alone.

NaBC will encourage delegates to consider the whole patient pathway, to review, revise and share current working practices and structures; interactive sessions will include management of the MDT, the importance of patient power and advanced practice.

The meeting will be free to attend and is being chaired and organised by Uro-oncology Nurse Specialist, Paula Allchorne of Barts Health NHS.

NaBC
NURSES AGAINST BLADDER CANCER

To find out more or to reserve a place contact Pierre Fabre via email at contactus@pierre-fabre.co.uk

This meeting is being supported with an unrestricted medical grant from Pierre Fabre. For further information please contact nikki.roebuck@pierre-fabre.com

Wider use of stereotactic body radiotherapy corresponds with marked increase in survival rates

Widespread use of advanced radiotherapy techniques in the Netherlands has resulted in improved survival among elderly lung cancer patients, according to major new research conducted by one of the country's leading cancer centres. VU University Medical Center (VUMC) in Amsterdam, which has now treated more than a thousand patients for pulmonary tumours using stereotactic ablative radiotherapy (SABR) on treatment machines supplied by Varian Medical Systems, publishes its findings in the latest issue of the *journal Annals of Oncology**.

"The greater use of advanced radiotherapy techniques has led to large improvements in survival for Dutch lung cancer patients over the age of 75, many of whom are too frail to undergo surgery," says Dr. Niels Haasbeek from VUMC, who was the first author of the publication.

Lung cancer is the most common cause of cancer death worldwide[1] yet improvements in overall survival have been minimal in recent decades: five-year survival for non small-cell lung cancer (NSCLC) was 13% in 1975–1977 and had only increased to 16% by 1999–2005[2]. Using expertise gained by several years of advanced radiotherapy treatments for early-stage lung cancer patients, clinicians at VUMC embarked on a nationwide study to examine the impact of SABR on survival rates.

For further information contact:
Neil Madle, Varian Medical Systems,
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W: www.varian.com

* Early-stage lung cancer in elderly patients: A population-based study of changes in treatment patterns and survival in the Netherlands doi:10.1093/annonc/mds081

1. Ferlay J, Shin HR, Bray F et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127(12): 2893–2917.
2. Kris MG, Benowitz SI, Adams S et al. Clinical cancer advances 2010: annual report on progress against cancer from the American Society of Clinical Oncology. J Clin Oncol 2010; 28(36): 5327–5347.

Elekta announces first patients treated with major breakthrough in cancer therapy

Using Agility™*, Elekta's latest MLC innovation, patients at St. James's University Hospital were the first in the world to benefit from this modern advancement in the treatment of cancer. With twice the number of leaves typical of many standard MLCs, Agility precisely sculpts delivered radiation to the unique contours of the tumour while reducing the risk of exposure to surrounding healthy tissue.

A multileaf collimator, a device made up of numerous individual tungsten leaves, is commonly used to shape beams of radiation as therapeutic doses are delivered from different angles around the patient.

"This truly represents a radical improvement in the way we deliver radiotherapy, combining both speed and precision in tailoring the radiation beams to the exact shape of the patient's tumour," says Vivian Cosgrove, PhD, head of radiotherapy physics at St James's.

The product of an extensive R&D effort by Elekta to transform cancer care, the leaves of Agility are also capable of traveling at twice the speed of other MLCs commonly used in radiotherapy. This unique capability supports an added capacity for precision beam shaping as well as shorter treatment times, increasing both patient comfort and the clinic's delivery efficiency. Moreover, relying on a new and innovative design, Agility MLC has demonstrated extraordinarily low leaf transmission, to reduce the patient's non-therapeutic radiation exposure.

For further information visit:
www.elekta.com/agility.

**Agility is not available for sale or distribution in all markets. Please contact your local Elekta representative for details.*

Varian Medical Systems Establishes Office in Hungary

Varian Medical Systems is opening a local office in Hungary with the aim of helping the country's radiotherapy departments to offer advanced treatments for a growing cancer population. The headquarters, situated in Budapest and initially employing seven people, will serve Hungary's radiotherapy departments and act as a sales and support services support hub for customers across south-east Europe.

The majority of Hungary's 26 radiotherapy treatment machines are over ten years old and plans are in place to upgrade equipment at the country's 12 radiotherapy departments mainly using European Union grants. Very few clinical procedures using advanced radiotherapy techniques such as intensity modulated radiotherapy (IMRT) or kV-based image-guided radiotherapy (IGRT) currently take place in daily routine in Hungary.

"We are committed to helping the country's radiation oncologists implement advanced RapidArc® image-guided IMRT treatments at these radiotherapy centers within this upgrade program for the benefit of both patients and clinicians across the nation," says Szabolcs Fórizs, general manager of Varian Medical Systems Hungary. "A local office enables Varian to fulfil this commitment more effectively."

For further information contact:
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Paxman's Orbis system at ASCO 2012

Chemotherapy-induced hair loss is no longer inevitable and can be prevented using the Paxman hair loss prevention system.

Paxman Coolers Ltd, a UK based company, has developed an innovative technology for use by cancer patients which offers them the ability to minimise or eliminate the instant and complete loss of their hair while undergoing chemotherapy treatment.

Besides the initial diagnosis of cancer itself, hair loss continues to be the most traumatic and distressing psychological side effect that many cancer patients will experience and can result in a patient's reluctance, even refusal, to accept treatment.

The product has achieved regulatory approval in Brazil, Canada, South Korea, Russia and Saudi Arabia, with approval for the USA and Japan currently under way. Distributorships are in place throughout the Middle East and Gulf regions, across Europe, Russia, the Middle East, the Far East and the Americas.

Paxman will be showcasing the Orbis system at ASCO 2012 (American Society of Clinical Oncology) in Chicago from the 2nd to 4th June and invite you to view this innovative technology for yourself at booth number 5038.
For further information please visit www.paxman-coolers.com

The Oncotype DX® Breast Cancer Assay helps you find the answer

The Oncotype DX Breast Cancer Assay helps clarify one of the most difficult treatment questions by providing an individualised Recurrence Score® result that assesses the benefit of chemotherapy and the likelihood of breast cancer recurrence.[1,2]

Visit us at www.oncotypeDX.co.uk.

For information on how to order the Oncotype DX Breast Cancer Assay or to receive specimen transportation boxes, please contact Customer Service via email at: **international@genomichealth.com**

References: 1. Paik S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol.* 2006;24(23):3726-3734.
2. Paik S, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med.* 2004;351(27):2817-2826.

genomic health®

oncotype DX® Breast Cancer Assay

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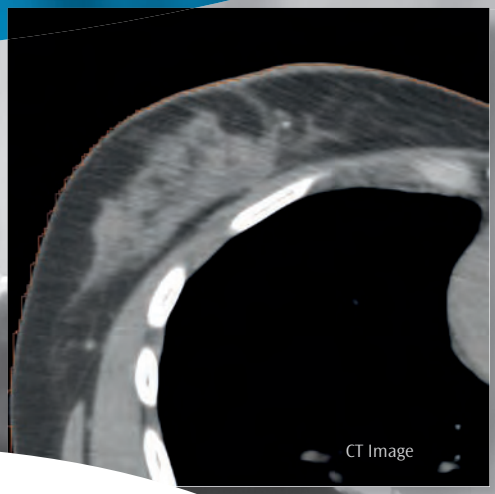

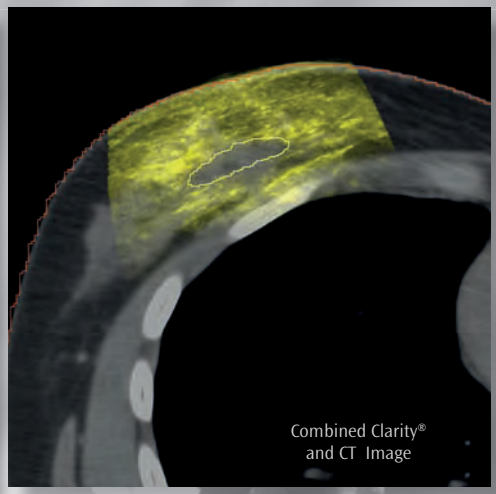

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