

comprehensive rehabilitation services. However, despite significant drivers in the UK, such as the NICE Guidance in Supportive and Palliative Care (NICE 2004) and the Cancer Reform Strategy (DOH 2007), rehabilitation is often still considered the 'icing on the cake' and is not properly planned or implemented.

This presentation will focus on the rehabilitation needs of breast cancer patients, with a particular focus on physiotherapy interventions. It is well known that patients can experience a wide range of physical problems following treatment; many of which can impact on quality of life and function. Some of these problems are due to surgical interventions e.g axillary web syndrome (post axillary dissection) and myofascial restrictions in the chest wall (post mastectomy). Others, such as cancer-related fatigue are consequences of chemotherapy and/or radiotherapy. Physiotherapy has an important role in the evidence-based management of problems such as upper limb dysfunction and physical deconditioning. These physical sequelae will be discussed in some detail, along with guidance for other healthcare professionals on how to identify and manage problems and when to refer on. Particular attention will be paid to Axillary web syndrome or 'cording', and some preliminary research involving ultrasonography will also be discussed.

The National Cancer Action Team have recently produced evidence-based rehabilitation pathways and these provide a 'gold-standard' comparator against which services can be measured. The challenge remains to deliver this high quality care wherever and whenever it is required. Improving the commissioning of rehabilitation services is a national priority and AHPs must work closely with commissioners to demonstrate the value of their interventions and the vital role they play in improving patient care.

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INVITED

Cancer as a Teachable Moment

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A "teachable moment" is often used to describe naturally occurring life transitions or health events thought to motivate individuals to adopt risk reducing health behaviours. When the timing is right the ability to learn is possible.

Cancer is still one of the most traumatic experiences that people have to face today. It can provoke a range of emotions including severe distress, feelings of anxiety, depression and uncertainty. For many it can trigger an existential crisis, challenging people's perception of themselves, their existence in the world and their sense of purpose and meaning in life. This impact goes beyond the person with cancer, to affect families, friends and carers.

Interestingly the Chinese character for 'crisis' combines the characters for danger and opportunity, a diagnosis of cancer and its subsequent impact on peoples lives certainly offers both. People who have successfully passed through the crisis phase of cancer have faced danger and decisions but also have the opportunity for change and growth. Changes catalyzed by a confrontation with death are described by Yalom (2008) as an "Awakening Experience", when you are faced with your own mortality and existence one is more anxious and 'primed to make significant changes', and prompted to reexamine who and where you are in the world, beginning to build an authentic life of engagement, connectivity, meaning and self-fulfillment. There are many points throughout the cancer journey from diagnosis to death which are opportunities for an awakening experience.

Since 1996 Maggie's (cancer charity) has been pioneering a new approach to cancer support in the UK utilising these moments of awakening as teaching opportunities. From our current ten centres (UK) and online centre we provide informational, practical, emotional and psychological support to all those people affected by cancer including family and friends, to enable them to manage the process of diagnosis as effectively as possible, experiencing a good quality of life throughout treatment and beyond. Maggie's centres are non institutionalised homely, uplifting buildings where people are welcomed by a team of qualified healthcare professionals including Cancer Support Specialists, Psychologists and Welfare Benefit Advisors. People can drop-in no appointment is necessary and an evidence based programme of support is available including individual or group support. The programme of support includes professionally facilitated support groups, psycho-educational courses/workshops such as nutrition stress management, supporting someone with cancer, and moving forward after cancer. It is a space where people can just "be" or meet others in a similar situation around our kitchen table.

Maggie's focus on psychological support and clear information links into the UK Governments Cancer Reform Strategy (2007) which points to the need to support and empower people through and beyond their cancer journey and recognises Maggie's as a leader in this area.

Scientific Symposium (Mon, 26 Sep, 09:00–11:00) Tailoring Personalised Medicine for The Future

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INVITED

Biomarkers in Early Phase Therapy Trials

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A biomarker is a characteristic that is objectively measured and evaluated as an indicator of pharmacologic responses to therapeutic intervention. With the advent of anticancer agents targeting specific proteins in cancer cells, it has become important to determine if a new drug is interacting with and modulating its target. In first-in-human studies, biomarkers are utilized as pharmacodynamic markers, which confirm that the drug is hitting its target. The most successful use of biomarkers have been as predictive markers, predicting tumour response if the biomarkers are present. Such biomarkers include EGFR mutations, EML4-ALK translocation, B-raf mutations, HER-2/neu expression and the oldest predictive marker of all, estrogen and progesterone receptors and response to tamoxifen and aromatase inhibitors. Prognostic biomarkers identify a patient population with a good (or bad) outcome (K-ras mutation in CRC with anti-EGFR antibodies). Unfortunately, a lot of prognostic markers are also predictive, creating complexities in study designs for validating biomarkers. Such examples will be highlighted. Finally, the challenges in using PD biomarkers incorrectly in predicting drug response in early stage trials will be highlighted. Also highlighted will be the pitfalls in using PD markers to guide dose selection, the so-called "optimal biologic dose".

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INVITED

Personalised Therapy in Breast Cancer

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Background: The inability of breast cancer (BC) cells deficient in homologous recombination to repair DNA double strand breaks (DSBs), such as *BRCA1/2*-mutated cells, offers a target for DNA crosslinking agents, e.g. bifunctional alkylating agents or platinum compounds. *In vitro* screens and studies in genetically engineered mouse models for *BRCA*-mutated breast cancer have shown that these tumours can only be eradicated with high doses of DSB-inducing agents.

Our group previously employed array Comparative Genomic Hybridization (aCGH) to assess the genomic patterns of human breast cancers with loss of *BRCA1*- or *BRCA2*. We hypothesized that these patterns might also be present in some sporadic BCs and might predict for improved outcome after treatment with high doses of DNA crosslinking agents.

Material & Methods: *BRCA*-like^{CGH} status, defined as positive when the previously published *BRCA1*-like^{CGH} and/or *BRCA2*-like^{CGH} pattern was present, was assessed in 249 stage-III, *HER2*-negative BC patients, who had participated in a randomized controlled trial studying adjuvant high-dose (HD) cyclophosphamide-thiotepa-carboplatin (CTC) versus conventional 5-fluorouracil-epirubicin-cyclophosphamide (FE₉₀C) chemotherapy. We evaluated whether the effect on recurrence-free and overall survival (RFS, OS) of HD-CTC compared to conventional FE₉₀C differed by *BRCA*-like^{CGH} status, stratified for 4–9 versus 10+ involved lymph nodes and triple negative status, and adjusted for tumour size and grade.

Results: 81 patients (81/249, 32%) appeared to have *BRCA*-like^{CGH} tumours and had a significant benefit of HD-CTC compared to conventional FE₉₀C regarding OS (adjusted HR 0.19, 95% CI: 0.08–0.48), while HD-CTC was not superior among patients with a Non-*BRCA*-like^{CGH} tumour (adjusted HR 0.90, 95% CI: 0.53–1.54). The difference was statistically significant (p-interaction: 0.004). Similar results were found for RFS. Sensitivity analyses showed that the aCGH test was robust and not dependent on small changes in tumour percentage or thresholds. Half of all *BRCA*-like tumours were ER-positive; 14% of *BRCA1*-like and 69% of *BRCA2*-like tumours. Twelve cases were both *BRCA1*- and *BRCA2*-like.

Conclusions: aCGH genomic patterns identify both ER-positive and triple negative BC patients who derive a marked survival benefit from high-dose DNA crosslinking chemotherapy.

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INVITED

Personalised Therapy in Lung Cancer

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A proposed model for DNA damage response to irradiation involves the formation of a *BRCA1* complex. In DNA damage response, ATM and ATR phosphorylate H2AX on Ser-139, which serves to recruit the MDC1 protein

to chromatin, where it is also phosphorylated. RNF8/UBC13 complexes go to sites of DNA damage through their forkhead domain and initiate the synthesis of K63 polyubiquitin chains on chromatin that recruit the BRCA1 complex through the ubiquitin-interacting motif domains (UIM) of RAP80. In addition, the SUMO pathways components (UBC9-protein inhibitor of activated STAT (PIAS) and UBC9-PIAS1) also accumulate at DSBs, where they catalyze the SUMOylation of BRCA1. SUMOylation stimulates BRCA1 E3 ubiquitin ligase activity, leading to ubiquitylation of target proteins at DSBs, including the H2AX. Depletion of PIAS1 and PIAS4 impaired recruitment of BRCA1 to DSBs, significantly impaired ubiquitylation at DSBs, and reduced ubiquitylation of H2AX. PIAS SUMO ligases are required for homologous recombination and non-homologous end-joining. PIAS1 and PIAS4 depletion resulted in ionizing radiation hypersensitivity. Therefore, these could be essential components – together with BRCA1 – for predicting response to radiotherapy and cisplatin-based chemotherapy. Based on the plethora of evidence for the central role of BRCA1 in conferring differential sensitivity to irradiation and DNA-damaging drugs (cisplatin, carboplatin) and to antimicrotubule drugs (paclitaxel, docetaxel, vinorelbine), we performed a study of customized treatment, mainly in adenocarcinoma, where stage IV NSCLC patients with EGFR mutations received erlotinib and those without EGFR mutations were assigned to chemotherapy based on BRCA1 mRNA levels. The multivariate analysis also showed that levels of RAP80 were an independent prognostic marker. We have examined multiple genes involved in DNA repair and outcome in EGFR mutant NSCLCs treated with erlotinib. Only BRCA1 was significantly relevant. The model shows that BRCA1 can independently repair the damage caused by EGFR TKI inhibitors in tumours with EGFR mutations. It could be cardinal for customizing PARP inhibitors to examine 53BP1 in conjunction with BRCA1. In wild-type cells, BRCA1 displaces 53BP1 from double strand breaks, enabling resection at the break site by factors such as CtIP, which promotes RPA loading onto single stranded regions of DNA. In contrast, in BRCA1 depleted cells, 53BP1 is not displaced and prevents resection. In the absence of resection the DNA breaks persist and are not repaired. However, in cells depleted by both BRCA1 and 53BP1, double strand breaks are repaired. It could be essential to interpret the benefit of PARP inhibitors according to the levels of BRCA1 and 53BP1. Recently important advances in squamous cell lung cancer have been found that constitute important new therapeutic targets which could be clinically exploited.

269 INVITED
Biomarkers: Differences Between Medical Oncology Versus Radiotherapy

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With the development of specific molecular targeted treatments and the establishment of new molecular methods, research into biomarkers that are able to predict treatment outcome is of increasing importance in oncology. It is perspicuous, that predictors for local tumour control after curatively intended radiotherapy will not be the same as those for chemotherapy alone. However, there may also be overlaps, like in the use of putative cancer stem cell markers. There are data showing a correlation of expression of the surface marker CD44 alone or in combination with other markers with tumour regression after chemotherapy. For radiotherapy, a recent publication has shown that expression of CD44 correlates with long-term local tumour control after primary radiotherapy in patients with early squamous cell carcinoma of the larynx. This correlation is in line with the observation of a preferential expression of CD44 in cancer stem cells, the knowledge that all cancer stem cells have to be inactivated to achieve permanent local tumour control and that a higher number of cancer stem cells needs a higher irradiation dose for local tumour control. However, in most cases biomarkers for Medical Oncology and Radiation Oncology will be different, not only because different treatments and different settings are used. Even for treatment effects of the same drug, used either as sole therapy or in combination with other systemic treatments versus in combination with radiotherapy, we have to expect different values of potential biomarkers. First, it is important which endpoint has to be predicted: In palliative schedules for patients with advanced tumours, biomarkers will be adequate that predict antiproliferative effects. For combination of different drugs, treatment interactions may be a relevant parameter. When combination schedules of drugs with radiotherapy are used in curative setting, a relevant biomarker has to predict cytotoxic effects that are either independent or due to radiosensitisation. A good example is the application of epidermal growth factor receptor (EGFR) inhibitors, where specific mutations of the EGFR-tyrosine kinase (TK) correlate with response to EGFR-TK inhibitors, whereas KRAS mutations appear to correlate with non-response to TK inhibitors or cetuximab.

In contrast, preclinical data suggest that KRAS mutated tumours may be radiosensitised by cetuximab and that for local tumour control after combined irradiation and cetuximab treatment the protein and gene expression of the receptor may be relevant. The talk will give an overview on potential biomarkers for radiotherapy and combined treatments.

Scientific Symposium (Mon, 26 Sep, 09:00–11:00)
Optimizing Treatment in Gliomas

270 INVITED
Molecular Biomarkers

Abstract not received

271 INVITED
Optimizing Treatment for Gliomas – Radiotherapy

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Optimal treatment of gliomas includes a judicious combination of observation, surgery, radiotherapy and chemotherapy, but because of the considerable biological heterogeneity of gliomas, the appropriate therapeutic combination can vary considerably. Key radiotherapy issues to be addressed from clinical trial results in this session will focus on the following questions:

1. For adult low grade glioma, does immediate post-operative radiotherapy alter survival for either the entire cohort, or for selected high-risk subsets of patients? Prior randomized trials have shown no dose-effect, and although a progression-free survival benefit is identified, there is no impact on overall survival. To these data, we will add a recent analysis from the US SEER database, showing a decrement in survival in low-risk patients, but possible improvement in high-risk cohorts.
2. For adult low grade glioma, does chemotherapy provide a survival benefit when combined with radiotherapy? Although the overall study results do not support, a subset analysis of RTOG 9802 is suggestive of a possible positive effect which needs to be explored further and will be presented.
3. For anaplastic oligodendroglioma, the addition of chemotherapy to radiotherapy provides an advantage in progression-free survival, and longer-term analysis of RTOG 9402 suggests an improving hazard ratio in terms of survival, and these data will be presented.
4. For anaplastic astrocytoma, the role of combining temozolomide with radiotherapy remains inadequately defined; results of RTOG 9813 suggest a superior toxicity profile with the use of temozolomide rather than procarbazine, lomustine and vincristine with radiotherapy.
5. For glioblastoma, the combination of 60 Gy radiotherapy with temozolomide has become "standard-of-care", and attempts at improving this through temozolomide dose-intensification were carried out in RTOG 0525, results of which will be presented. This trial also allowed two different radiotherapy techniques to be utilized, without a significant survival advantage from either. Earlier, non-temozolomide RTOG trials focusing on dose escalation with radiosurgery or 3D dose-escalation or fractionated stereotactic radiotherapy boost did not provide convincing evidence for a survival advantage.

These trials, and their results will be discussed.

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Optimising Treatment in Gliomas – Translational

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Numerous animal models have during the past 60 years been developed, to study brain tumour development. Although such models have made significant contributions to our understanding of the mechanisms related to tumour initiation and progression, it is now clear that this knowledge only to a limited extent has been translated into more effective treatment principles. Therapeutic efficacy has been demonstrated in different animal models, yet the same treatment modalities fail in Phase II/III clinical trials. We have developed human glioblastoma (GBM) animal xenograft models that display the clonal heterogeneity and the genotypic and phenotypic traits of the corresponding human GBMs. Since GBMs are highly hypoxic and angiogenic, they are considered as good candidates for anti-angiogenic therapy. Preclinical experiments targeting the Vascular Endothelial Growth Factor (VEGF) by the monoclonal antibody bevacizumab have shown anti-tumour effects that have led to clinical trials either as monotherapy or