decelerated protons, or with carbon ions mimicking the tumor treatment situation. RBE values were determined relative to x-rays.
For protons a sharp increase in RBE was found only for the stopping particles at the very distal (decreasing) end of the dose deposition profile. For low energy carbon ions, the RBE is increased over a broader range of energies corresponding to the peak of dose deposition. Therefore, after therapy like irradiation, for carbon ions in contrast to protons a considerable fraction of the dose deposited will correspond to ions with a high RBE.
At the molecular level, the enhanced effectiveness is believed to be based on the production of complex DNA double-strand breaks (DSBs) that are difficult to repair. To study the induction and repair of DSBs under conditions mimicking therapeutical ion irradiation, stacks of cells grown on glass plates were exposed to high energy carbon ions in a water phantom. Immunostaining of phosphorylated histone H2AX was used for DSB detection. After post irradiation incubation, despite efficient repair even of ion-induced DSBs, the level of residual DSBs was slightly but consistently increased after exposure to ions in the tumor region compared to the entrance channel.
In summary, based on their physical properties both protons and heavier ions are advantageous to treat deep seated tumors. For carbon ions an increase of the RBE towards the end of the particle range, together with the concomitant increase in dose potentiates the inactivation effect in the tumor region. The molecular basis is the localized production of complex damage and the impaired repair.

80 INVITED

Particle therapy: Physical potential amid clinical realities

T. Bortfeld. *Mass. General Hospital / Harvard Medical School, Department of Radiation Oncology, Boston, USA*

Background: Proton radiation therapy has moved mainstream. Many new proton centers have recently been completed, or are under construction or at planning stage. The main physical advantage of both proton and heavier charged particle therapy is the finite range of the beam in the patient, which may be utilized to reduce the overall integral dose to healthy tissues and to improve local dose conformality. However, the range of a particle beam in a patient on a given day is often not exactly known. The range is therefore not used for tight dose conformation. Instead, dose shaping with the lateral dose fall-off is preferred, just as in the case of conventional photon therapy.
Materials and Methods: We will review the state of the art in proton therapy and focus on sources of range uncertainties, such as motion, imaging artifacts, and dose calculation errors. We will discuss how the impact of range uncertainties is limited in current clinical practice using methods such as field patching and feathering. We will also discuss methods for in-vivo dose measurements, either directly or indirectly through PET/CT imaging of the positron emitters activated by the particle beam. We will then review the potential of intensity modulated proton therapy (IMPT) to improve dose conformality and the robustness of the treatment plan.
Results: In some cases, especially in lung cancer treatments, the range of a particle beam can vary by several centimeters during the treatment course. Even in cases where motion and anatomic variations are not an issue, the range can be off by 5mm, for example due to metal artifacts. In-vivo dosimetry and PET imaging are two methods to substantially reduce range uncertainties. Unavoidable residual uncertainties can be taken into account by carefully designing IMPT treatments using robust optimization techniques.
Conclusions: Particle beams can produce highly conformal dose distributions, but, primarily due to range uncertainties, the dose in the patient may differ substantially from the treatment plan. Image guided radiation therapy and motion management are therefore more critically important in particle therapy than in photon therapy. Without them, the physical advantage of particle beams cannot be fully utilized for the benefit of the patient.

81 INVITED

Critical review of the clinical evidence

D. De Ruysscher[1], M. Pijls-Johannesma[2], P. Lambin[3]. *[1]University Hospital Maastricht, Radiotherapy/GROW/MAASTRO Clinic, Maastricht, The Netherlands; [2]MAASTRO clinic, MAASTRO clinic, Maastricht, The Netherlands; [3]University Hospital Maastricht, Radiotherapy/GROW/MAASTRO clinic, Maastricht, The Netherlands*

Background: Protons and light ions (mainly Carbon), generate much excitement, for they exhibit a superior dose-distribution than the currently used photons. Light ions are on top of this biologically more active than photons and protons. We performed a systematic literature review of the clinical evidence.
Materials and Methods: Twelve databases were searched. No limit was applied to publication year, language or study design. Only studies with at least 20 patients and with a follow-up period of at least two years were included.
Results: *Prostate cancer*: Two phase III trials in locally advanced prostate cancer were identified (n=492). However, one used inadequate photon doses and techniques and the other used protons in both arms. From pro-and retrospective series, local tumor control, 5 year overall survival and late GI and GU toxicity were for protons 74%/89%/15%/7% and for C-ions 100%/89%/6%/<5%. The results with high dose photon therapy were similar
Ocular tumors: In the only phase III study, Helium ions were compared to brachytherapy. Tumor recurrences were more observed in the brachytherapy than in the He arm (13.3% vs. 0%, $p < 0.001$), with more side effects in the He group. From 9522 patients treated with protons, local tumor control and 5 year overall/cause specific survival were 97% and 85%/85% respectively. Eye retention was 90%, whereas neovascular glaucoma occurred in 12% of patients. Similar results were obtained with C-ions and in selected photon series. The latter were much smaller and with in general only short follow-up times.
Central nervous system: For common glioma's, no gain with protons or C-ions was observed. However, for chordomas of the skull base, the weighted local tumor control rate and 5 year overall survival treated with protons was 63% and 81% respectively and for C-ions 72% and 83%. With conventional photon therapy, local tumor control rates and 5 year survival were 25% and 44% respectively.
Head and neck cancer: For squamous cell carcinomas, the results of photon therapy were similar to protons or C-ions. However, for adenoid cystic carcinomas, local tumor control rates of over 75% as achieved with C-ions are much higher than reported with photons (approximately 25% local control).
Esophageal, hepatocellular, pancreatic, non-small cell lung, sarcomas, cervix and bladder cancer: no clear superiority of protons or C-ions was established, but all series were small.
Conclusions: Although most studies with protons and C-ions were performed in non-clinical research settings, the clinical results were superior to photons for tumors that are relatively radio-resistant (adenoid cystic carcinomas) or where normal tissues are critical (ocular tumors, base of skull chordoma's). For common malignancies, however, their superiority has not been established. The advent of multiple clinical facilities will enable to improve these new radiation qualities.

Special session (Tue, 25 Sep, 13:30−14:30)
Tumour responses – the contribute of targeting host cells versus tumour cells

82 INVITED

Radiation and endothelial cell damage

Z. Fuks. *USA*

Abstract not received.

83 INVITED

Pericytes and tumour cell metastases

H. Semb. *Lund University, Stem Cell CenterBMC B10, Lund, Sweden*

Tumour cells use two major routes to spread during metastasis, e.g. lymph vessels and blood vessels within or surrounding the primary tumour. The growth rate of the primary tumour often correlates with the quantity of new blood vessels that form within the tumour. However, recent studies directed our attention to the quality of tumour blood vessels, illustrating that the deficiency of the tumour environment to support or instruct a regular patterning and stabilization of blood vessels has profound effects on both perfusion of the primary tumour and escape of tumour cells into the circulation. Our recent evidence for a novel role of the supporting mural cells in limiting blood borne metastasis will be discussed.

84 INVITED

Gastrin – a pro-angiogenic factor and down stream target of HIF1a in gastro-intestinal malignancy

S. Watson, P.A. Clarke, R. Kumari, A.J. Tobias, E.L. Royal, A.M. Grabowska. *University of Nottingham, Academic Unit of Cancer StudiesD Floor West BlockQueen's Medical Centre, Nottingham, United Kingdom*

Background: The gut hormone gastrin is a transcriptional activator of a number of malignancy-associated genes including those involved in angiogenesis. The ability of gastrin to modulate endothelial cell activity via heparin-binding epidermal growth factor (HB-EGF) expression and shedding was assessed.

Methods: HUVEC cells tubule formation was measured in the presence of amidated gastrin-17 (G17) and glycine-extended gastrin-17 (GlyG17) peptides. HB-EGF gene and protein expressions were measured by qRT-PCR, immunocytochemistry, and Western blotting, and HB-EGF shedding by ELISA. Matrix metalloproteinases were assessed by Western blotting. Microvessel density (MVD) was assessed by immunohistochemistry and serum-amidated gastrin levels by RIA.
Results: HUVEC cells showed increased tubule and node formation in response to G17 which was blockaded by the cholecystokinin-2 receptor (CCK-2R) antagonist, JB95008 and by antiserum to gastrin and HB-EGF. Gastrin peptides increased HB-EGF gene expression/protein secretion in HUVEC and micro-vessel-derived endothelial cells and the levels of MMP-2, MMP-3, and MMP-9. G17 promoted angiogenesis in a chorioallantoic membrane assay, and MVD was significantly elevated in pre-malignant large intestinal tissue from hyper-gastrinaemic $APC^{Min+/-}$ mice. MVD in the normal mucosa surrounding colorectal adenocarcinomas correlated with patient serum gastrin levels and HB-EGF expression.
The extent to which H. pylori to up-regulation of HB-EGF can be attributed to its effect on gastrin was examined. Gastric cells, transfected with either gastrin small interfering RNA or antisense plasmid or the CCK-2R, were cultured for 24 hours with H. pylori(+/−), a CCK-2R antagonist.
H. pylori-induced significantly higher levels of HB-EGF gene expression and ectodomain shedding in the CCK-2R-transfected cells than the vector control which was reversed by the CCK-2R inhibitor. Gastrin down-regulation reduced the effect of the bacteria on HB-EGF gene and protein expression levels. Endogenous gastrin and CCK-2R expression were also found to be significantly up-regulated in all cell lines as a result of exposure to H. pylori. Finally gastrin has been shown along-with VEGF to be a target gene of HIF1a and be up-regulated under hypoxic conditions in vitro.
Conclusions: The above studies confirm the multi-factorial role of gastrin in gasto-intestinal malignancy confirming it as a target for both chemoprophylaxis and established cancers.

Symposium (Tue, 25 Sep, 14:45−16:45)
FECS/ASCO symposium – what have we learnt from pre-surgical medical therapy in breast cancer?

85 INVITED

The role of neoadjuvant therapy

G. Hortobagyi. *University of Texas, Department of Breast Medical Oncology, Houston, USA*

Experiments on preclinical models have suggested that preoperative introduction of chemotherapy (CT) of endocrine therapy can improve survival by abrogating a post surgical growth spurt and by addressing micrometastatic disease at an earlier stage than when given postoperatively. Clinical trials have not confirmed this hypothesis, although they have demonstrated that neoadjuvant systemic therapy (NST) reduced overall tumor burden, expanded the indications for breast-conserving surgery to patients (pts) with more advanced disease, and provided an in vivo assessment of response that facilitated the safe and effective administration of systemic treatment. NST also provides an improved investigational model, since sequential monitoring with the primary tumor in place offers the opportunity for multiple biopsies to monitor the biological effects of treatment. Large randomized trials have shown preoperative CT to be at least equivalent in disease-free and overall survival to the same CT administered postoperatively. Emerging data suggest, however, that the effects of systemic therapy in general, and NST in particular, vary with different subclasses of breast cancer (BC). The first such observations were based on estrogen receptor (ER). The magnitude of benefit from CT is proportionately more modest for pts with ER+ tumors than for ER− tumors. This is dramatically expressed in preoperative trials, where the pathological complete remission (pCR) rate is four to six-fold higher for ER− than for ER+ BC. Similar variation in pCR rate is observed by grade and histologic type (invasive lobular cancers vs. invasive ductal cancers). Paradoxically, although pCR identifies a group of patients with improved survival compared with patients who do not achieve pCR, patient groups with lower pCR rates (those with ER+ tumors, those with low grade or lobular cancer) have better overall survival than those that tend to have higher pCR rates. This observation emphasizes the importance of understanding the biological heterogeneity of BC. Studies based on gene expression profiling in BC have confirmed the existence of at least three distinct forms of BC: ER+/HER2-, HER2+, and “triple-negative”. These three groups differ by much more than the individual gene (ER or HER2) expression, and their clinical course and responsiveness to different treatments is quite different too. Thus, HER2+ and triple-negative tumors achieve a high pCR rate (40-50%) with standard combinations, while ER+/HER2− tumors do not (pCR rate <10%). Gene profiling also leads to the identification of potential new therapeutic targets. Validation of such novel targets and development of specific therapeutics might be the best legacy of NST.

86 INVITED

Biological lessons from adjuvant therapy

P.E. Lønning. *Institute of Medicine, Section of Oncology, University of Bergen, Haukeland University Hospital, Bergen, Norway*

Neoadjuvant therapy offers a convenient setting to test for predictive factors to drug response. Primary tumours in general are suitable for tissue sampling and tumour response evaluation. In addition, such studies allow us to draw important conclusion from a limited number of patients. However, while a complete response on primary chemotherapy has been found associated with long term outcome, patients achieving a complete response may still develop distant metastasis. Thus, micro-metastasis may harbour resistant cells not easily detectable in the primary tumour. Further, not every patients progressing locally on therapy are subject to subsequent relapse even in case they are treated with local salvage therapy only. These findings illustrate the complex issue of primary response versus risk of metastases and long-term outcome.
Despite these limitations, neoadjuvant therapy offers an important setting to test for chemoresistance. While success so far has been limited with respect to identify predictive factors validated for clinical use, this is likely to change. Following development of improved methodologies and, in particular, more knowledge about biological parameters to look for, it is likely that such studies may offer unique results in the not-to-far future. With more protocols becoming available and longer patient follow-up, the potential exist to obtain tissue from distant metastasis in patients who subsequently relapse following participation in neoadjuvant trials. Thus, comparing biological parameters of such metastatic deposits to primary tumour biopsies may offer a unique opportunity to identify key biological events involved in a transformation of cells towards resistance.

87 INVITED

Neoadjuvant antiHER2 therapy

E. Winer. *Dana Farber Cancer Center, Harvard Medical School, Boston, USA*

With the success of trastuzumab treatment of HER2 positive metastatic disease, a number of phase II trials were launched evaluating various trastuzumab-chemotherapy combinations in patients with HER2 positive stage II/III breast cancer. These combinations, which utilized trastuzumab in conjunction with agents including paclitaxel, docetaxel, carboplatin, cisplatin, and vinorelbine, demonstrated high response rates and relatively high pathologic complete response rates. A randomized phase II trial from MD Anderson Cancer Center demonstrated a pathologic compete response rate in excess of 50% with a combination of trastuzumab and paclitaxel followed by trastuzuamb with an epirubicin-based regimen. While there are multiple possible explanations for the extraordinarily high pathologic complete response rate in this study, the most intriguing explanation relates to the concurrent use of trastuzumab and an anthracycline. A phase III trial has been designed to evaluate this regimen further.
From a research perspective, preoperative studies represent an ideal opportunity to pose translational questions related to HER2 positive disease. To date, preoperative studies have suggested that neither ER status nor HER2 status change frequently in response to trastuzumab-based therapy. Furthermore, it appears that a brief exposure to trastuzumab does not change proliferation rate, but does induce apoptosis. Preliminary work also suggests that there may be a gene signature associated with trastuzumab resistance.
Three randomized trials will soon be open in BIG, the US Intergroup, and the NSABP to compare trastuzumab and lapatinib combinations in the preoperative setting. Not only will these studies compare pathologic complete responses rates, but more importantly, they will collect and interrogate tissue. In this way, it is hoped that the studies will lead to a more complete understanding of factors that predict and/or mediate sensitivity and resistance to HER2-directed therapy.
Recent results and planned trials will be reviewed.

88 INVITED

Biological lessons from pre-surgical endocrine therapy

M. Dowsett. *Royal Marsden Hospital, Academic Department of Biochemistry, London, United Kingdom*

Pre-surgical medical studies allow a unique opportunity to integrate clinical and biological observations as a result of the taking of sequential biopsies