similar to the concept developed in other solid tumours, e.g. breast cancer. The MVD (microvessel density) was calculated in the "hot spots" and expressed as the number of vessels/X250 field. The MVD of different hot spots within the same tumour section showed a very low variability whereas the intertumour variability was markedly higher. In an attempt to correlate areas of most intense vascularity with proliferation in tumour cells and endothelial cells, we developed a double staining technique with CD31 and Ki-67. These studies showed an impressive percentage of cycling endothelial cells within the tumour compared with the normal colon mucosa and the adjacent mucosa (21% vs 0.59% vs 1.5%). Within tumours the regional differences in MVD correlate with differences in tumour cell proliferation. The presence or absence of p53 expression was also found to be correlated to the MVD.

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PROGNOSTIC AND PREDICTIVE VALUE OF THE DETERMINATION OF TUMOUR ANGIOGENESIS IN PRIMARY SOLID TUMOURS

G. Gasparini
Department of Oncology, Vicenza-Hospital, Italy

Angiogenesis (AG) plays a key role in tumour progression and metastasis. The switch from the avascular to the vascular phase is regulated by multiple positive and negative mechanisms and is generally accompanied by rapid tumour growth. Two types of clinical applications of quantitation of AG seem to be promising: the definition of prognosis and of responsiveness to anticancer therapy. Our data as well as those from others demonstrated that assessment of intratumoral microvessel density (IMD) in primary breast cancer (BC) is a significant and independent prognostic marker (Gasparini and Harris, *JCO* 1995, **13**, 765,). Preliminary studies suggest a significant association between IMD and metastasis and/or prognosis also in other solid tumours. There is also evidence that AG may play a role to predict effectiveness of conventional anticancer treatments. For example, we have found in a series of 191 node-positive BC treated either with adjuvant hormone or chemotherapy with a median follow-up of 5 yrs, that IMD significantly predicts clinical outcome. In 73 patients with stage II–IV head & neck cancer, treated with concurrent chemoradiation-therapy, IMD significantly predicts objective response. The rationale, methods, and clinical results on the prognostic and predictive value of AG will be updated and reviewed.

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MOLECULAR MECHANISMS OF ANGIOGENESIS ASSOCIATED TO KAPOSI'S SARCOMA

F. Bussolino, R. Soldi, L. Primo, D. Giungiuglio[1], D. Ghigo, A. Albini[1]
Department of Genetics, Biology and Medical Chemistry, 10126 Torino
[1]IST, 16132 Genova, Italy

Imbalance in the network of soluble mediators may play a pivotal role in the pathogenesis of Kaposi's sarcoma (KS) a multifocal lesion characterized by a prominent angiogenesis. We demonstrated that KS cells grown *in vitro* produced and in part released platelet activating factor (PAF), a lipid mediator of inflammation and cell-to-cell communication. IL1, TNF and thrombin enhanced the synthesis of PAF. PAF receptor mRNA and specific, high affinity binding site for PAF were present in KS cells. Nanomolar concentration of PAF stimulated the chemotaxis and chemokinesis of KS cells, endothelial cells (EC) and vascular smooth muscle cells. The migration response to PAF was inhibited by WEB 2170, a PAF receptor antagonist. Since PAF activates EC we examined the potential role of PAF as an instrumental mediator of angiogenesis associated with KS. Conditioned medium (CM) from KS cells (KS-CM) or KS cells themselves induced angiogenesis and macrophage recruitment in Matrigel model. These effects were inhibited by treating mice with WEB 2170. The action of PAF was amplified by expression of other angiogenic factors and chemokines: these included basic and acidic FGF, PIGF, VEGF and its specific receptor *flk-1*, HGF, KC, and MIP2. Treatment with WEB 2170 abolished the expression of these transcripts within Matrigel containing KS-CM. These results indicate that PAF may cooperate with other angiogenic molecules and chemokines in inducing vascular development, in KS.

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OPTIMAL DOSE DELIVERY IN RADIOTHERAPY

A. Brahme
Department of Medical Radiation Physics, Karolinska Institutet and Stockholm University, P.O. Box 260, S-171 76 Stockholm, Sweden

The most efficient but also least developed area of treatment optimization is to use a few (≈3) non uniform radiation beams directed towards the tumor. Today patient individual collimation with beam blocks or multileaf collimators protect organs at risk laterally outside the tumor volume. Non uniform dose delivery also allows protection of normal tissues anterior, posterior and even inside the target volume by shaping the isodoses tightly around the tumor tissues and thereby also allowing longitudinal protection of normal tissues. Some of the most advanced new algorithms are even treating therapy optimization as an inverse problem where the optimal incident beam shapes are determined directly from the location of gross disease, presumed microscopic tumor spread and organs at risk. The optimization is then performed such that the probability, P_+, to eradicate all clonogenic tumor cells without severely damaging healthy normal tissues is as high as possible.

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TREATMENT ACCURACY: A CONSTRAINT ON CONFORMAL RADIOTHERAPY

D.P. Dearnaley
Department of Radiotherapy & Oncology, Royal Marsden NHS Trust & Institute of Cancer Research, Surrey, U.K.

Accuracy of the definition of gross, clinical, and planning radiotherapy target volumes varies for different tumour sites. It is a common experience that more detailed information from improved imaging techniques and methods for assessment of the accuracy of treatment planning and implementation lead to a greater appreciation of the uncertainties in the delivery of radiation therapy. This may translate into a perceived need for larger 'safety margins' to account for such variations. This approach certainly maximises the probability of comprehensive coverage of the tumour but at the expense of increasing the volumes of normal tissue treated. Conformal radiotherapy has been shown to reduce treatment volume and volumes of critical organs treated by approximately 50% for a variety of tumour sites. Provided a significant 'volume effect' exists for the relevant normal tissues dose escalation and improved tumour control becomes a realistic expectation. However, the size of 'margin' is critical: for example a 3 cm diameter tumour treated conformally with a 2 cm margin will include approximately the same volume of normal tissue as conventional treatment with a 1 cm margin. Data for a variety of tumour sites will be presented emphasising the importance of measuring departmental results to determine appropriate margins. The potential effects of accuracy and margins on TCP and NTCP will be discussed.

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THE USE OF MRI, CT AND SPECT REGISTRATION FOR TREATMENT PLANNING AND FOLLOW-UP

M. van Herk, A. Bruce, J. de Munck, S. Kwa, J.V. Lebesque, T. Shouman, A. Touw
Radiotherapy Department, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam

MRI for treatment planning: Due to geometric distortions, the use of MRI in radiotherapy planning has been limited. By accurate registration of CT and MRI (e.g., based on the skull) using the chamfer matching algorithm, the geometric accuracy of CT is combined with the diagnostic quality of MRI. This method is mainly in use for tumours in the head but applications for prostate cancer are under development. *Follow-up studies:* Tissue response after radiotherapy is sometimes visible on CT. For lung damage, ventilation and perfusion SPECT scans are the visualisation instrument of choice. By matching the planning CT with follow-up CT or SPECT a correlation of radiation dose and subsequent damage is possible. *Organ motion studies.* Matching of repeat scans of the same patient allows quantification of organ motion. Using this technique, motion of prostate and femurs relative to the pelvis has been measured accurately in 40 scans from 11 patients. Prostate motion was mostly be attributed to rectal volume variations, but femur motion has a small but significant influence on prostate rotation. *Conclusion.* Image registration is an essential tool for precision radiotherapy.