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INTERACTION RT-CT: RATIONALE AND CLINICAL EXPERIENCE IN HEAD AND NECK (HN) TUMOURS

M. Merlano, M. Benasso, F. Blengio, G. Numico
Div. di Oncologia Medica I, Istituto Naz. per la Ricerca sul Cancro, Genova, Italy

CT has been used in conjunction with RT in an attempt to increase locoregional control and survival of advanced squamous cell carcinoma (SCC) of HN. CT has been combined with RT according to one of the following modalities:

—adjuvant or neoadjuvant CT, which implies the sequential administration of CT and RT;

—concomitant or alternating CT and RT, which results in a close temporal integration of the two modalities.

While the results of the sequential use of CT and RT at best reflects the sum of the efficacies of the single modalities used, the integration of CT and RT has an impact on the biologic mechanisms by which each modality determines its cytotoxic effect with a possibly synergistic outcome. Inhibition of DNA-repair has been demonstrated in "*in vitro*" models after radiation exposition, adding cytotoxic drugs. This phenomenon may result in the conversion of "potentially lethal damage" or "sublethal DNA damage" to lethal damage increasing cell killing rate. Moreover, cyclospecific and phase specific drugs are effective on "S phase" of cyclating tumor cells, which are, generally, less sensitive to RT. Finally Split RT has been reported to be less effective than continous RT due to the repopulation occurring during the rests between courses. Filling-up these pauses with chemotherapy, gives the chance to administer drugs to a quickly proliferating tumor, with positive implications for cure. Simultaneous CT and RT using single agent 5-Fluorouracil (5-FU) i.v. bolus, Bleomycin (B), Mitomycin C or Cisplatin (CDDP) have been evaluated in phase II trials and in randomized trials against RT alone with controversial results, being the positive ones mainly observed when 5-FU was employed. Multiagent CT combined with simultaneous RT has been evaluated in many phase II trials using 5-FU continuous infusion (c.i.) with CDDP with or without Leucovorin and/or Hydroxiyurea; these combinations yield a large proportion of complete responses at the cost of substantial mucosal toxicity. Randomized trials against RT alone have not yet been reported. Alternating CT and RT utilizing Vinblastine, B, Methotrexate, 5-FU i.v. bolus or (c.i.) and CDDP has been evaluated in both phase II and III studies. The data suggest that alternating CT and RT promotes optimal tolerance of the host. Moreover alternating CT and RT correlates with significant better survival when compared to neoadjuvant CT followed by RT or to RT alone. These data definitively require further investigations.

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INTERACTIONS OF RADIOTHERAPY AND CHEMOTHERAPY IN THORACIC AND BREAST TUMORS

R. Arriagada
Institut Gustave-Roussy, Villejuif, France

In the last twenty years a worldwide effort has been done in the exploration of combined radio-chemotherapy approaches in locally advanced cancers. Main interest has been focused in the effects on normal and tumor tissues in an attempt to take advantage of spatial cooperation and radiosensitization. Many pilot studies and some randomized trials have allowed to increase the clinical knowledge concerning treatment effect on cure, acute and long-term toxicities. Because of the high incidence of lung and breast tumors a great amount of information has been accumulated. The knowledge on effects in locally advanced tumors can help in the understanding of new approaches in the adjuvant setting. Different parameters are critical in the occurrence of tumor control or normal tissue toxicity. They include total radiation dose, fractionation schedule, target volume, total drug dose and dose intensity, radio-chemotherapy timing and sequencing. The amount and quality of normal tissue included in the radiation fields are important in long-term sequelae, e.g. prophylactic brain irradiation in small cell lung cancer. A comprehensive knowledge of these multi parametric modalities may limit complications, improve quality of life and long-term survival rates, but also improve the design of studies evaluating new approaches with novel drug mechanisms or radiation schedules.

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RADIOTHERAPY WITH CONCOMITANT CHEMOTHERAPY PROVEN TO BE SUPERIOR TO RADIOTHERAPY ALONE IN THE TREATMENT OF ADVANCED ANAL CARCINOMA

F. Roelofsen, H. Bartelink, M. v. Glabbeke, M. Pierart, D. Peiffert, F. Eschwège, J.F. Bosset
EORTC-Cooperative Groups of Gastrointestinal Tract Cancer and of Radiotherapy
Ev. Bethesda Krankenhaus, Bocholderstr. 11–13, 45355 Essen, Germany

A randomized trial has been conducted from 1987 to 1994 to prove the benefit of concomitant chemotherapy to radiotherapy in advanced anal carcinoma. One hundred and three of 110 patients with T_3 and T_4 tumors or lymphnode metastases were evaluable. Radiotherapy consisted of 45 Gy in 5 weeks. After a rest period of 6 weeks patients with complete or partial remission received a boost of 15 resp. 20 Gy. Chemotherapy consisted of Mitomycin 15 mg/m^2 day 1 and 750 mg/m^2 5FU continuously day 1–5 and 29–33.

There was no significant increase of early and late toxicity. Complete remission rate of 81% vs. 55% was significantly better in the combinded arm, raising to 98% vs. 81% if results obtained with surgery were included ($P = 0.0008$). Local control after primary treatment remained different during follow up estimated to be 58% vs. 31% at 5 years. Colostomy free survival increased significantly, estimated at 5 years to be 41% vs. 22%. There was no difference in overall survival for both groups.

New concepts to optimize the effect of concomitant use of radiotherapy and chemotherapy will be presented.

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HOW INVASIVE TUMOURS ABUSE THEIR HOST

D. Stehelin
CNRS URA 1160, Institut Pasteur, I Rue Calmette, 59019 Lille Cédex, France

Invasive tumours surround themselves with a cocoon of stroma including endothelial, fibrocytic and inflammatory cells. This stroma, once protective and nourishing to the tumour, becomes an obstacle to expansion when tumours seek invasiveness, and must be destroyed.

The c-ets-1 proto-oncogene (1) encodes DNA binding proteins modulating transcription through specific ets-1 binding sequences (ETBS) (2) found essential in the gene promoters of ECM degradation pretenses like stromelysin-1 and collagenase-1, or of urokinase plasminogen activator (u-PA).

Using *in situ* hybridizations with labelled antisense ribo-probes (3), we examined human tumours and their surrounding fibrocytic stroma for the induction of *c-ets-1* and a possible correlation with the activation of matrix degrading proteases.

Our results are compatible with the following model: (i) tumours release factors that diffuse into the stroma, activate c-ets-1 expression in the stromal fibrocytes surrounding invasive carcinomas: (ii) In turn, c-ets-1 may activate the proteases. (iii) c-ets-1 expression is not seen in non invasive carcinomas, nor in the carcinoma cells themselves (4).

Experiments are underway to define the nature of the diffusible factors, and to examine if c-ets-1 down modulation has a hampering effect on tumour invasion.

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TUMOUR ANGIOGENESIS IN PRIMARY COLORECTAL CARCINOMA

L. Y. Dirix
Department of Medical Oncology, University Antwerp, Belgium

Angiogenesis is considered a key event in tumour growth and metastasis. Detailed information on tumour angiogenesis and its regulation, might predict clinical outcome and the sensitivity of radiotherapy. It might also lead to more efficient drug delivery and facilitate the development of angioinhibitors. We have investigated the microvascular supply in human primary and metastatic colorectal adenocarcinomas. Although overall vascular density between tumour tissue and surrounding colorectal mucosa differed only moderately, we could identify the presence of a collagen IV positive membrane as a demarcation for more intense angiogenic response in the stroma. We could also identify vascular hot spots,

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.