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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,