1007 ORAL

Interval between preoperative radiotherapy and surgery influences postoperative mortality in rectal cancer patients: the sooner the better

C.A.M. Marijnen[1], J.W.H. Leer[2], H. Putter[3], E. Kapiteijn[4], J.H.J.M. van Krieken[5], E.M. Noordijk[1], C.J.H. van de Velde[4]. *And the cooperative investigators of the DCRCG; [1] Leiden University Medical Center, Clinical Oncology, Leiden, The Netherlands; [2] University Hospital Nijmegen, Radiotherapy, Nijmegen, The Netherlands; [3] Leiden University Medical Center, Biomedical Statistics, Leiden, The Netherlands; [4] Leiden University Medical Center, Surgery, Leiden, The Netherlands; [5] University Hospital Nijmegen, Pathology, Nijmegen, The Netherlands*

Purpose: In a prospective randomized multicenter trial the value of preoperative radiotherapy (5x5 Gy) in combination with TME surgery was evaluated for rectal cancer patients. Treatment related toxicity is of major concern in such multimodality approaches. Anxiety for an increase of surgical complications after preoperative radiotherapy was the basis for the recommendation to keep the interval between radiotherapy and surgery as short as possible. This study was undertaken to assess the influence of the interval between radiotherapy and surgery on local recurrences and surgical complications.

Methods: We analyzed 690 preoperatively irradiated patients entered in a randomized trial and compared them with the patients treated with surgery alone. Patients were divided in two groups with either a very short interval between radiotherapy and surgery (< 3 days) or a longer interval (>3 days). Surgical complications, postoperative morbidity and mortality as well as local recurrence rate were compared.

Results: There was no difference in surgical complications or postoperative morbidity between patients with a short interval compared to patients with a long interval. A significant increase in the postoperative mortality rate at 180 days was observed in the patients operated after an interval of more than 3 days (4.1% vs. 8.4%, p=0.02). This difference was mainly observed in patients above 75 years of age. Patients with an short interval had similar mortality rates compared to patients that were treated with surgery alone (4.1% vs. 5.4%). There was no difference in local recurrence rate between the two interval groups.

Conclusion: Extension of the interval between preoperative radiotherapy and surgery leads to a significant increase of postoperative mortality. We suggest that this might be explained by a radiation-induced increase of systemic cytokines.

1008 ORAL

Phase II study of raltitrexed in combination with oxaliplatin as second line treatment in refractory advanced colorectal cancer

E. Van Cutsem[1], J. Van Laethem[2], L. Dirix[3], Y. Humblet[4], K. Van Eygen[5], J. Demol[6], H. Bleiberg[7], C. Verslype[1], R. Vermaut[8], K. Daems[8]. *[1] University Hospital Gasthuisberg, Internal Medicine, Leuven, Belgium; [2] Erasmus, Gastroenterology, Brussels, Belgium; [3] S-Augustinus, Medical Oncology, Antwerp, Belgium; [4] UCL, Medical Oncology, Brussels, Belgium; [5] AZ-Groeninghe, Medical Oncology, Kortrijk, Belgium; [6] H-Hart, Roeselare, [7] Bordet, Brussels, [8] AstraZeneca Belgium*

Raltitrexed ("Tomudex") is a specific thymidylate synthase inhibitor with comparable efficacy to 5-fluorouracil (5-FU)/folinic acid (FA) regimens in advanced colorectal cancer (aCRC). Recent phase II studies have demonstrated that the combination of raltitrexed and oxaliplatin is active in the first line treatment of aCRC. The aims of this multi-center phase II study were to determine the efficacy and tolerability of the combination of raltitrexed and oxaliplatin as second line therapy in patients with refractory aCRC. Patients received raltitrexed 3 mg/m² (15 min) followed 45 min later by oxaliplatin in 130 mg/m² (2h) every 3 weeks. Fifty patients (M/F: 26/24; mean age 61 years (38-75); performance status 0/1/2: 20/26/4) have been included. All patients had a documented progression while on 5-FU/FA ± irinotecan or within 3 months after stopping first line treatment. Nineteen patients received adjuvant chemotherapy prior to entering the study. Six patients had a relapse on adjuvant treatment and did not receive first line treatment prior to entering the study. In total 260 cycles were administered. The mean time on treatment was 97 days and the median number of cycles per patient was 5.0 (1-11). The objective response rate was 16% (n=8). The median duration of response was 6.4 months (mo) (range 2.1-8). In addition, disease stabilisation was observed in 26 patients (52%). The median TTP was 4.6 mo (0.7-8.5). The median survival amounted 7.1 mo. Hematologic toxicity was: neutropenia gr 3-4: 7.4% of courses; thrombopenia gr 3-4: 2.1%; febrile neutropenia: 0.8%: 45 patients (90%) had signs of polyneuropathy (gr 1-2-3: 48-36-6%); diarrhea gr 3-4 was present in 12% of patients; vomiting gr 3-4: 16%; severe fatigue 16%. One patient died due to neutropenic sepsis and diarrhea.

Conclusion: The combination of raltitrexed/oxaliplatin is active as second line treatment in refractory aCRC with acceptable toxicity.

Radiotherapy

1009a ORAL

Modelling the impact of two forms of hypoxia on novel radiotherapy approaches

A. Dasu. *Department of Radiation Sciences, Umeå University, 90 1 85 Umeå, Sweden*

Purpose: One of the aims of this project was to investigate the clinical implications of using two theoretical models for predicting the tissue response to radiation. The choice of the appropriate model is a very important issue in the theoretical estimation of the biological response to radiotherapy. The models investigated are the two most likely to be included in treatment planning algorithms: the linear quadratic model (LQ) and the linear quadratic model with inducible repair (LQ/IR). A second aim of the project was to make a realistic tumour model with respect to the micro-environmental conditions on which to investigate the clinical implications of different treatment strategies. The focus was on the availability of oxygen and other nutrients to cells in tissue.

Methods: Computer modelling was used throughout the whole project for calculating the tissue response to radiation. The most important aspect of the simulation was the inclusion in the tumour model of the relationship between cellular energy reserves and DNA repair ability. Low energy reserves usually determine a loss of repair capacity and thus a loss of radioresistance. This is a quite important fact, since it will affect the starved chronically hypoxic cells but not the acutely hypoxic ones that exibit only an increased radioresistance compared to the oxic cells. It is the first time that this aspect of tumour radiosensitivity has been incorporated into a theoretical model.

Results: The modelling performed in this project has shown that the LQ model cannot accurately predict the response of oxic and hypoxic cells for low doses and that the LQ/IR model should be used instead for predictive purposes in the clinically relevant dose range. It has also shown that the postulated radiobiological differences between acute and chronic hypoxia could explain why a curable treatment does not give irreparable damage to the normal tissue.

Conclusion: The results suggested that it is important to distinguish between the two types of hypoxia in predictive assays and other treatment simulations.

1009b ORAL

Intensity-modulated radiation therapy (IMRT) for tumours of the head and neck, pelvis and thorax: pre-clinical evaluation and implementation

C. Nutting, D. Convery, V. Cosgrove, C. Rowbottom, S. Webb, D. Dearnaley. *Institute of Cancer Research and Royal Marsden NHS Trust, Surrey, SM2 5PT*

Purpose: To evaluate the potential benefits of IMRT compared to current radiotherapy techniques, and to implement clinical trials of IMRT for appropriate tumour sites.

Methods: 30 patients with head and neck, pelvic and thoracic tumours underwent treatment planning for conventional radiotherapy (RT), 3-dimensional conformal RT (3DCRT) and inverse-planned IMRT. Dose distributions were compared using dose-volume histograms for tumour and normal tissues, and normal tissue complication probabilities were calculated. Methods were developed to optimise beam number and direction to determine the most efficient delivery techniques, and for pelvic tumours a clinical dose escalation trial protocol was designed.

Results: IMRT treatment plans for thyroid carcinoma and pelvic lymph nodes (tumours with a concave PTV) showed the greatest improvements compared to conventional and 3DCRT. There was 12% reduction in maximum spinal cord dose ($p<0.01$), and a 70% reduction in pelvic small bowel treated above 45 Gy ($p<0.01$) respectively. PTV dose homogeneity was improved, and other normal tissues also spared. Oesophageal, parotid, and para-nasal sinus tumours (with moderate or no concavities in the PTV), showed statistically significant but smaller improvements in normal tissue sparing of lungs, oral cavity and cochlea, and optic nerves respectively. 9,