3 cycles with standard co-medication (vitamin B_{12}, folic acid, and dexamethasone) on an outpatient base. If radiotherapy was used, minimum interval between start of radiotherapy and last dose of pemetrexed were 2 weeks. A LC-MS/MS method has been used for the determination of 5,10-methyleneTHF, THF, and 5-methylTHF levels. The folate extraction method involved homogenization, heat treatment and folate conjugate treatment to hydrolyze polyglutamyl folates to monoglutamyl folates. Biopsies of tumor and mucosa were taken before the patient received any vitamine supplementation.
Results: Mean methyleneTHF levels (1018±506 pmol/g) were significantly higher in tumor compared with mucosa (830±610 pmol/g), p = 0.013. Mean THF levels were also significantly higher in tumor (584±257 pmol/g) compared with mucosa (463±256 pmol/g), p = 0.013. Mean 5methylTHF levels were not significantly higher in tumor (436±316/g) compared with mucosa (352±199 pmol/g), p = 0.34.
Conclusions: These explorative data suggest that this unique method leads to understand intra- and inter-patient influence of folates during the course of the treatment and may help to identify patients who do profit from antifolate therapies.

6042 POSTER

Metastases prediction after preoperative radiochemotherapy in cT3M0 rectal cancer patients: an analysis of a large database

M.A. Gambacorta[1], R. van Stiphout[2], M.C. Barba[1], C. Coco[3], R. Persiani[3], G.B. Doglietto[3], R. D'Amico[1], M. Balducci[1], P. Lambin[2], V. Valentini[1].
[1]Pol. Univ."A. Gemelli"-Catholic University of the Sacred Heart, Radiation Oncology, Rome, Italy; [2]University Medical Centre, Radiation Oncology (MAASTRO) GROW, Maastricht, The Netherlands; [3]Pol. Univ."A. Gemelli"-Catholic University of the Sacred Heart, Surgery, Rome, Italy

Background: the last randomized trials showed that preoperative radiochemotherapy (CRT) has a local recurrence rate of 4−8% and distant metastases rate of 25−30%, in stage II-III rectal cancer patients.
Many of these studies focused on the subgroup analysis to identify risk factors correlated to local recurrence; few data are available to identify risk factors for distant metastases, and adjuvant postoperative chemotherapy after pre-operative chemoradiation is still far from consensus based on the available evidences.
At the Università Cattolica del Sacro Cuore of Rome a multidisciplinary rectal cancer database is available since 1980. We reviewed our clinical data to identify the metastases prediction risk factors in cT3M0 patients treated with preoperative radiochemotherapy.
Materials and Methods: from a large database containing 1420 patients, a group of 405 patients between 1985–2008 was collected retrospectively. The patients were diagnosed with rectal cancer with cT-stage 3 and cM-stage 0 and were treated with preoperative CRT (45−55 Gy, 1 or 2 drugs). Surgery was performed 6−10 weeks after treatment and metastasis presence (M^+) was evaluated at follow-up. Collected pre-treatment variables included sex, age, cN-stage, tumor distance from the anorectal ring, number of involved rectum quartiles (Qrt), tumor length, volume index (Qrt × tumor length), chemo type. Post-treatment were collected: the volume index and the relative difference between pre- and post treatment evaluations of tumor distance, Qrt, tumor length and volume index. Surgery variables included type of surgery, ypT-stage, ypN-stage, TRG score and adjuvant chemo. Multivariate analysis was performed with a 2-norm support vector machine (SVM). Performance of the model was expressed as the Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC) curves and assessed with leave-one-out (LOO) cross-validation. A nomogram was build based on the model output.
Results: CRT resulted in M^+ for 19% of the patients. Based on the AUCs (Mean ±SD) of the ROC-curves we found that the model performs with AUC 0.69±0.04. Predictive variables ranked to importance (i.e. weights): pN-stage (0.18), relative difference of volume index (−0.08), pT-stage (0.07), and type of surgery (0.06).
Conclusions: the analysis shows the presence of predictive risk factors of distant metastases mainly related to the different response to the treatment. A nomogram to tailor the adjuvant treatment in cT3M0 patients after radiochemotherapy will be proposed.

6043 POSTER

Late adverse effects of preoperative hyperfractionated radiation therapy (RT) for advanced rectal cancer

S. Bieri[1], A.D. Roth[2], A. Franzetti-Pellanda[3], M. Bonet[4], P. Gervaz[2], A.S. Allal[4]. *[1]Hospital Cantonal, Radiation Oncology, Sion, Switzerland; [2]University hospital of Geneva, Department of Surgery, Geneva, Switzerland; [3]Ospedale San Giovanni, Oncologic Institute of Southern Switzerland, Bellinzona, Switzerland; [4]University hospital of Geneva, Radiation Oncology, Geneva, Switzerland*

Background: To analyze the occurrence of late adverse effects in patients (pts) treated with preoperative hyperfractionated RT for LARC with or without gemcytabine or gefitinib (Iressa).
Materials and Methods: Between 1997 to 2006, 109 pts accepted to participate in the present study in three centers. All patients were enrolled in three successive phase I-II trials and treated preoperatively with 50 Gy in 40 fractions of 1.25 Gy over 4 weeks without (52 pts) or with concomitant gemcitabine (37 pts) or gefitinib (20 pts). Rectal surgery was scheduled 6 weeks after completion of RT. Fifty four pts received adjuvant chemotherapy (CT), according to local policy. Late adverse effects were defined as occurring at >3 months, according to RTOG criteria. Concomitant CT, age, sex, tumor location and field size were assessed for potential correlation with adverse late effects.
Results: The median age of the pts was 60 years (range: 30−88 years). One hundred and one patient had stages cT3−4 and cN+ in 56 pts. Surgery consisted in low anterior resection in 79 pts, abdominoperineal resection in 25 pts and other surgery in 5 pts. With a median follow-up of 55 months (range: 3–105 months), severe late complications (grade 3−4) occurred in 12 pts (11%). Erectile dysfunction was described by 14 pts. Neither CT, nor age or gender influenced the rate of late adverse effects. Field dimension (>15 cm) and distal location showed a trend (p = 0.07 and 0.13).
Conclusions: Although this small cohort size precludes detailed risk factor analysis, the rate of severe late complications was not influenced by the addition of gemcytabine or gefitinib to preoperative RT. Refinements in the RT (field size) and surgical techniques to reduce late sequela, particularly operative procedures allowing preservation of sexual function merit further investigation.

6044 POSTER

Multidisciplinary rectal cancer treatment: 'Looking for an European Consensus' (EURECA-CC2)

V. Valentini[1], C. Aristei[2], B. Glimelius[3], B.D. Minsky[4], K. Haustermans[5], H.J. Schmoll[6], D. Sebag-Montefiore[7], I. Taylor[8], E. van Cutsem[9], C. Van de Velde[10]. *[1]Università Cattolica S. Cuore, Cattedra di Radioterapia, Rome, Italy; [2]Università degli studi, Cattedra di Radioterapia, Perugia, Italy; [3]University Hospital Uppsala and Karolinska Institutet, Department of Oncology Radiology and Clinical Immunology, Stockholm, Sweden; [4]University of Chicago Medical Center, Department of Radiation Oncology, Chicago (Illinois), USA; [5]University Hospital Gasthuisberg, Department of Radiation Oncology, Leuven, Belgium; [6]Universitätsklinik Halle, Department für Innere Medizin Klinik für Innere Medizin II/Arbeitsbereich Rheumatologie, Halle, Germany; [7]St James's University Hospital, Department of Radiation Oncology, Leeds, United Kingdom; [8]Royal Free and University College Medical School University College, Department of Surgery, London, United Kingdom; [9]University Hospital Gasthuisberg, Department of Internal Medicine, Leuven, Belgium; [10]Leiden University Medical Center, Department of surgery, Leiden, The Netherlands*

Background: During the last two decades some important results from European randomized studies have been published. In order to conform the clinical practice to the best scientific evidence from the literature, the International Conference on 'Multidisciplinary Rectal Cancer Treatment: 'Looking for an European Consensus' (EURECA-CC2) was organized in Italy under the endorsement of European Society of Medical Oncology (ESMO), European Society of Surgical Oncology (ESSO), and European Society of Therapeutic Radiation Oncology (ESTRO).
Materials and Methods: The Delphi method was used to achieve the consesus. All Committee members had a document customized for the consensus process, available on the web. Eight chapters were identified: epidemiology, diagnostics, pathology, surgery, radiotherapy and chemotherapy, treatment toxicity and quality of life, follow-up, and research questions. Each chapter was subdivided by topic, and a series of statements were developed. Each sentence was voted and commented by all members three times. During the Consensus Conference held in Perugia (Italy) from 11 December through 13 December 2008, the sentences which did not reach agreement after voting round #2 were openly debated. After each debate the opinion of both the Committee members and the audience were collected by a hand-held televoting system. The Executive

Committee scored percentage consensus based on three categories: "large consensus", "moderate consensus", "minimum consensus".
Results: All chapters were voted on by at least 75% of the members, and the majority was voted on by more than 85%. The total number of the voted sentences was 207. Of the 207, 86% achieved "large consensus", 13% achieved "moderate consensus", and only 3 (1%) resulted in "minimum consensus". No statement was disagreed by more than 50% of members.
Conclusions: This Consensus Conference represents an expertise opinion process that may be useful to define guidelines for staging and treatment of rectal cancer and may help to draw future programs and investigational protocols throughout Europe.

6045 POSTER

Safety analysis of starpan (star-02) study with panitumumab, 5-fluorouracil, oxaliplatin and concurrent radiotherapy in locally advanced rectal cancer

F. Di Fabio[1], C. Pinto[1], E. Maiello[2], S. Pini[1], T. Latiano[2], C. Aschele[3], C. Garufi[4], A. Bochicchio[5], D. Tassinari[6], A. Martoni[1]. [1]*Medical Oncology Unit, S. Orsola-Malpighi Hospital, Bologna, Italy;* [2]*Medical Oncology Unit, IRCCS Casa Sollievo della Sofferenza, S. Giovanni Rotondo (FG), Italy;* [3]*Medical Oncology Unit, Galliera Hospital, Genoa, Italy;* [4]*Medical Oncology Unit, Regina Elena Institute, Rome, Italy;* [5]*Medical Oncology Unit, CROB, Rio Nero in Vulture (PZ), Italy;* [6]*Medical Oncology Unit, Degli Infermi Hospital, Rimini, Italy*

Background: The aim of this phase II study was to assess the activity of preoperative external radiotherapy combined with panitumumab, oxaliplatin and 5-fluorouracil in locally advanced rectal cancer patients (pts).
Materials and Methods: Pts entering the study had histologically-proven rectal adenocarcinoma, either cT3N+ or cT4N-/+ stage, with location <12 cm from the anal margin. Panitumumab was administered at a dose of 6 mg/kg IV, 2 weeks before the start of chemoradiotherapy, and then in combination with chemoradiotherapy, 3 times every 2 weeks. 5-fluorouracil and oxaliplatin were administered according to established schedule of STAR-01 Study (oxaliplatin 60 mg/m^2 IV weekly six times, 1 h after the panitumumab infusion, and 5-fluorouracil 225 mg/m^2/day continuous infusion IV days 1−38). Radiotherapy was delivered at a dose of 50.4 Gy in daily fractions of 1.8 Gy. Rectal surgery was performed 7−8 weeks after the end of neoadjuvant treatment. Eight courses of adjuvant chemotherapy with FOLFOX4 plus panitumumab at the dose of 6 mg/kg, every 2 weeks, were given post-surgery. The main study endpoint was complete pathological response rate.
Results: From February 2007 to April 2009 fifty-one pts were enrolled (9 too early pts). Characteristics of the 42 evaluated pts were: male 28 (66.7%), female 14 (33.3%); median age 60 (37−78); median Karnofsky PS 100 (70–100); stage: cT3N+ 31 (73.8%), cT4N− 3 (7.1%), cT4N+ 8 (19.1%). Thirty-three pts have completed neoadjuvant treatment and 30 have undergone surgery (12 pts ongoing). The most frequent grade 1−2 side effects were acneiform rash (56.7%), diarrhea (27%) and fatigue (8%). Grade 3−4 diarrhea was found in 32.4% of pts, and grade 3 cutaneous toxicity in 43.3%. No grade 3 hematological toxicity was found. The median cumulative dose of delivered radiotherapy was 50.4 Gy. The planned dose of panitumumab, 5-fluourouracil and oxaliplatin was administered in 78.8%, 63.6% and 69.6% of pts, respectively.
Conclusions: These early results demonstrate that panitumumab can be added to 5-fluorouracil/oxaliplatin-based chemoradiotherapy without compromising the concurrent radiotherapy dose. This combination treatment is associated with high incidence of grade 3−4 diarrhea.

6046 POSTER

Predictive role of 18f-fdg-pet in locally advanced rectal cancer patients treated with neoadjuvant chemo-radiotherapy (Bologna Project)

C. Pinto[1], F. Di Fabio[1], S. Pini[1], D. Cuicchi[2], B. Iacopino[3], P. Di Tullio[1], R. Lombardi[2], P. Castellucci[4], G. Compagnone[5], A. Martoni[1]. [1]*Medical Oncology Unit, S. Orsola-Malpighi Hospital, Bologna, Italy;* [2]*General Surgery Unit, S. Orsola-Malpighi Hospital, Bologna, Italy;* [3]*Radiotherapy Unit, S. Orsola-Malpighi Hospital, Bologna, Italy;* [4]*Nuclear Medicine Unit, S. Orsola-Malpighi Hospital, Bologna, Italy;* [5]*Medical Physics Unit, S. Orsola-Malpighi Hospital, Bologna, Italy*

Background: The identification of predictive response factors in locally advanced rectal cancer patients (pts) treated with neoadjuvant chemo-radiotherapy (CRT) can direct the choice of therapeutic strategy. The aim of the study was to evaluate the predictive value of basal and pre-surgical 18F-FDG-PET (PET).
Materials and Methods: Pts entering the study had cT3-T4 N-/+ rectal adenocarcinoma <12 cm from the anal margin. CT consisted in 5-fluorouracil with or without oxaliplatin; RT was delivered up to a dose of 50.4 Gy in daily fractions of 1.8 Gy; rectal surgery was performed 6−8 weeks after the end of CRT. PET was performed at initial diagnosis and before the surgery. Standard Uptake Value (SUV1 = basal PET, SUV2 = pre-surgery PET) was determined from the most active tumor site. The pathological examination of surgical specimens included the Tumor Regression Grade (TRG) evaluation according to the Dworak grading. Responder pts were defined as TRG4 = complete regression, TRG3 = good regression, TRG2 = moderate regression, and non-responder pts were defined as TRG1 = minor regression, TRG0 = no regression.
Results: Eighty pts were evaluated between June 2003 and February 2009. The pt characteristics were: 55 (68.7%) males, 25 (31.3%) females; median age 65 years (33−80); stage: 36 (45%) cT3N-M0, 33 (41.3%) cT3N+M0, 6 (7.5%) cT4N-M0, 5 (6.2%) cT4N+M0. The pathological responses were: TRG1 16 (20%) pts, TRG2 28 (35%), TRG3 20 (25%), TRG4 16 (20%). The SUV1 and SUV2 cut-off related to TRG are 19 and 4.9, respectively, was identified with ROC analysis. In 53 (66.3%) pts SUV1 was $\leqslant$19 (low) and in 27 (33.7%) it was >19 (high). The low SUV1 value was significantly correlated with TRG2−4 ($p = 0.002$). In 53 (66.3%) pts the SUV2 was $\leqslant$4.9 (low) and in 27 (33.7%) it was >4.9 (high). The low SUV2 value was significantly correlated with TRG2−4 ($p < 0.0001$). In multivariate analysis, TRG2−4 was statistically correlated with SUV1 ($p = 0.010$) and SUV2 ($p = 0.018$).
Conclusions: These results suggest that a low baseline SUV value and a low pre-surgical SUV value could predict the pathological response in locally advanced rectal cancer pts treated with neoadjuvant CRT. In this pt setting, the PET evaluation should be further investigated in order to establish the treatment strategy.

6047 POSTER

Development of nomograms for prediction of pathologic complete response in locally advanced rectum cancer: a multicentric study using PET before, during and after neoadjuvant chemoradiotherapy

R. van Stiphout[1], M. Janssen[1], J. van den Bogaard[1], L. Leccisotti[2], C. Coco[3], M. Lambrecht[4], G. Lammering[1], K. Haustermans[4], V. Valentini[5], P. Lambin[1]. [1]*Department of Radiation Oncology (MAASTRO) GROW University Medical Centre Maastricht, Maastricht, The Netherlands;* [2]*Università Cattolica del S. Cuore, Nuclear Medicine Department, Rome, Italy;* [3]*Università Cattolica del S. Cuore, Surgery Department, Rome, Italy;* [4]*University Hospital Leuven, Department of Radiation Oncology, Leuven, Belgium;* [5]*Università Cattolica del S. Cuore, Radiotherapy Department, Rome, Italy*

Purpose: The prediction of pathologic complete response (pCR) after preoperative chemoradiotherapy (CRT) might be helpful for selecting rectal cancer patients in which a less invasive surgery or a "wait and see policy" would be possible. A prediction of the pathological response already during CRT, as opposed to after CRT, would be more attractive, because it could enable response-guided modifications of the treatment protocol. In this study, data were prospectively collected at 3 different institutions. Three different imaging time points were analyzed for their predictive value: pre-CRT, during CRT and after CRT, just before surgery.
Methods: The datasets with both clinical and imaging variables from 3 different institutions were merged to have a statistical weight. A total of 64 patients were treated with long-term chemoradiotherapy (CRT). For all patients, three PET-CT scans were acquired (before CRT, during CRT, after CRT just before surgery). Clinical variables included age, sex, WHO performance status, BMI, cTNM stage. For PET-analyses, the tumors were semi-automatically contoured using standardized uptake-value (SUV) thresholding. Imaging variables consisted of tumor dimensions (GTV, maximal diameter, distance from anal verge) and metabolic activity of the tumor corrected by blood glucose (SUVmean, SUVmax). In addition, for the follow-up PET scans, all relative differences (response indices, RI) were also included in the evaluation. Multivariate analysis was performed with a 2-norm support vector machine (SVM). Performance of the model was expressed as the area-under-the-curve (AUC) of the receiver-operating-characteristic (ROC) curves and assessed with leave-one-out (LOO) cross-validation. Also, all output was converted to nomograms.
Results: For 23% of the patients, CRT resulted in a pCR. Based on the AUCs (Mean $\pm$SD) of the ROC-curves, the model containing PET variables during treatment reached the highest training performance (0.82 ± 0.07) when compared to pretreatment (0.75 ± 0.08) and pre-surgical (0.72 ± 0.10) models. For PET-imaging during treatment, these variables were predictive (ranked by their importance): response index of SUVmax during CRT (0.28), cT-stage (−0.22), cN-stage (−0.18).
Conclusion: The prediction of pCR based on both clinical variables and PET variables assessed early during treatment was found to be most accurate based on the multivariate analysis. Easy to use nomograms will be presented. A prospective validation of the model is underway and the