Conclusion: Our results suggest that postoperative adjuvant treatment with oral UFT (250 mg/m^2/day) significantly improves in survival in patients with pathological stage I adenocarcinoma of the lung, especially those with stage IB disease (T2N0M0).

1079 ORAL

A phase II trial of chemoradiotherapy followed by surgery in pancoast tumors: initial report of the Japan Clinical Oncology Group trial (JCOG 9806).

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Background: Although preoperative radiotherapy (Rx) has long been the standard treatment for Pancoast tumors, or superior sulcus tumors (SST), both the complete resection rate and long-term survival remain poor. SWOG reported favorable results when using preoperative chemoradiotherapy (CxRx) to treat SST (JTCS 2001). Objectives: To evaluate the safety and efficacy of a trimodality approach for the treatment of SST. The primary endpoint was the 3-year survival rate. Patients: Pathologically documented M0 NSCLC with at least invasion to the first rib. Patients with N2 disease were excluded, however, patients demonstrating involvement of the ipsilateral supraclavicular node (SCN) without any mediastinal node metastasis were included.

Methods: Two cycles of MVP chemotherapy (Cx) were given q 4weeks; mitomycin C 8mg/m2 on day 1, vindesine 3mg/m2 on days 1 and 8, and cisplatin 80mg/m2 on day 1. Rx for the tumor and ipsilateral SCN was started on day 2 of each Cx cycle. The total irradiated dose was 45Gy/25 fr comprising 27Gy/15fr with the first Cx and 18Gy/10fr with the second Cx. If the tumor was resectable, then the patients (pts) underwent a thoracotomy 2-4 weeks after the completion of the induction CxRx. Those with unresectable disease received an additional Rx booster.

Results: From May/99 to Nov./02, 76 pts were entered into the study. Median age; 57.5 (range 34-74), M/F; 67/9. Clinical stages were T3/T4 64/12, N0/1/3 64/9/3. PS 0/1 30/46, >5% weight loss in 17% of the pts. Histology; Ad/Sq/Others 34/27/15. As of Feb./03, 71 pts were reported to be off treatment. Induction CxRx was completed in 94% of the pts. Fifty-four pts (77%) underwent a surgical resection and 49 pts (69%) received a pathologically complete resection. A pathologic downstaging was achieved in 22 (31%), of whom 11 pathologically demonstrated CR (no residual viable tumor). Major postoperative morbidity was reported in 8 pts, which includes chylothorax, empyema (2), pneumonitis (2), hemorrhage and ARDS (2). There were 3 treatment-related deaths; 1 from post operative ARDS, 1 from postoperative hemorrhaging and 1 from septic shock during CxRx. The one-year survival rate was 77% (95%CI:66-87%), and the one-year progression-free survival rate was 65% (95%CI:54-77%).

Conclusions: These results reproduced those of the SWOG study in terms of resectability, safety and short-term survival. The effectiveness of this trimodality approach was thus suggested. All pts will have completed the therapeutic regimen by Aug./03.

1080 ORAL

Induction chemotherapy followed by concurrent RSR13 (Efaproxiral) and trt for patients with locally advanced NSCLC: mature results of a phase II study and comparison with the results from RTOG 94-10.

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Purpose: To compare survival results between RTOG 94-10 and Study RT-010, Phase 2 study of induction chemotherapy followed by concurrent RSR13 (efaproxiral) and thoracic radiation therapy (TRT).

Methods: RSR13 is a synthetic allosteric modifier of hemoglobin that reduces hemoglobin oxygen-binding affinity, facilitates oxygen release, and increases tissue pO_2. RSR13 has been studied as a radiation sensitizer for patients with locally advanced Stage IIIA-B NSCLC in a Phase 2 study (RT-010). Patients received induction chemotherapy [paclitaxel (225 mg/m^2) and carboplatin (AUC=6) on days 1 and 22 (2 cycles)] followed by TRT (64 Gy/32 fractions/starting on day 43-50) with concurrent daily infusion of RSR13 (50-100 mg/kg). RTOG 94-10 was a Phase 3 study in Stage II-III NSCLC patients. Here we compare survival results from RT-010 (N = 49 pts; minimum potential follow-up = 28 months) to both the RTOG 94-10 sequential chemoradiotherapy arm (S-CRT; N = 201 pts) and the concurrent chemoradiotherapy arm (C-CRT; N = 201 pts).

Results: Demographic characteristics were comparable among all groups; however, a higher percentage of RT-010 patients (85%) had KPS of 90-100 than S-CRT (77%) or C-CRT (75%) patients. Also, a higher percentage of RT-010 patients (53%) had Stage IIIA disease than S-CRT (41%) or C-CRT patients (43%). The median survival times (MST) for all patients in the RT-010 study and the S-CRT and C-CRT arms are 20.6, 14.6, and 17.0 months, respectively. A matched-case analysis was performed whereby patients in the 3 groups were matched by stage and KPS (exactly) and age (±5 yrs). MST for the matched-case patients in the RT-010 study and the S-CRT and C-CRT arms are 20.6, 15.1, and 17.9 months, respectively. A stratified Cox model indicated a slight improvement in survival favoring RT-010 over both the S-CRT (hazard ratio = 0.87) and C-CRT arms (hazard ratio = 0.76).

Conclusion: Although the sample size of the RSR13 study is too small to identify statistically significant differences in survival, these results suggest that RSR13 added to S-CRT may have a favorable impact on survival comparable to C-CRT. A randomized, Phase 3 trial of S-CRT±RSR13 for NSCLC is ongoing.

1081 ORAL

Stereotactic radiotherapy of primary lung cancer. Results of a phase II trial

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Background: Stereotactic radiotherapy is now used for treatment of tumours outside the brain. However, the evidence for this treatment is sparse.

Material and methods: Twenty-six patients with primary non-small-cell lung cancer were treated with stereotactic radiotherapy. All patients had stage T1-2,N0,M0 disease and were technically operable, but inoperable due to severe chronic obstructive lung disease or other co-morbidity. Patients were equally divided between between males and females. Median age was 69 (47-79) years. Patients were either immobilised by use of the Stereotactic Body Frame (Elekta) or by a custom made whole body fixation system. Stereotactic radiotherapy was given by use of 5-8 MLC-shaped fields with a central dose of 45 Gy in 3 fractions over 5-8 days. The CTV was encompassed by the 95% and the PTV by the 66% isodose curve. Margin between CTV and PTV was at least 5 mm in the transversal and 10 mm in the cranio-caudal plane. Evaluation of toxicity by the WHO toxicity scale was performed at baseline and 14 days, 56 days and every 3 months after treatment, and CT-scans were performed every 3 months after treatment. Median follow-up time was 12 (5-42) months.

Results: Local control was observed in more than 80% of the patients. Distant progression was observed in eight of the cases. Median time to progression was 10 months. Fifty percent of the patients were without progression and 65% were surviving at 18 months after treatment. Significant worsening of performance status and lung function was observed at 14 days and 6 months after treatment compared to baseline.

Conclusions: This study shows high local control probability and moderate toxicity after stereotactic radiotherapy of primary lung cancer.

1082 ORAL

Can we optimize timing of initial follow-up after radiotherapy from study of patterns of first failure? - Evidence from patients with NSCLC

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Increasing attention is being paid to evaluating the effectiveness of follow-up (FU) after cancer treatment. An important aim of regular surveillance is to detect events associated with treatment failure (recurrence, toxicity), which

is relevant to estimate the therapeutic ratio. Failure types occur at different times during FU. The exact occurrence of events is unknown and so the observed data are artificially clustered around the planned visits. If we knew the expected pattern of events, then it would be reasonable to schedule the visits at those times. Since events are related to prognostic factors, the FU visits should be adapted to individual patient characteristics. The aim of this study is to propose a method for defining optimal FU schedules for patients in a resource-efficient way. Data from the CHART bronchus trial are used to illustrate the methods.

Material and Methods: Patients alive without recurrence or serious side effects were scheduled to return at months 2-3, every 3 months to 2 years, every 6 months the next 3 years, then annually. Time to failure and its type (local(LR), distant(DM) or side effects(SE)) were recorded at each visit. Cox proportional hazards models were used to identify prognostic factors associated with each failure type. Competing risks methods were applied to estimate the cumulative incidence functions(CIF), adjusted on prognostic factors. Equally spaced quantiles of CIF were used to estimate the corresponding optimised FU times.

Results: 483 first events were recorded for 542 pts: 114 SE, 162 DM and 207 LR; 59 pts had no event at last FU. The 2-yr CIF rate=89%. Significantly higher risk of failure was observed for males (SE), stage III (DM) and conventional treatment (LR). At the 1st planned visit, the CIF rates were 15%, 13%, 11% and 9% in 4 groups (M-I-IIA, M-III, F-I-IIA, F-III) respectively. 10% failures are expected to occur at 6, 7, 8 and 9 weeks in these 4 groups, with earlier visits for males and later visits for females. Similar methods are used for each 10% CIF quantile. At the 2nd planned visit, 20% cumulative failures are expected to occur at 11, 12, 18 and 18 weeks respectively, etc. These methods allow an adaptation of the FU timing according to tumour site and prognostic factors. This optimisation should result in earlier scheduled visits for certain pts at high risk of failure, which may improve on overall survival. This work formed a part of the REACT programme of ESTRO funded by the EU.

1083 ORAL

Survival is better predicted with a new classification of stage III unresectable non-small cell lung carcinoma (NSCLC) treated by chemotherapy and radiotherapy.

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Background: The 1997 ISS classification separated stage III NSCLC patients into stages IIIA and IIIB. In a previous study including unresectable NSCLC initially treated with chemotherapy, we observed that survival was better predicted when patients were classified into stages IIIbeta (T3-4N3) and IIIalpha (other TN stage III) (Sculier et al, Crit Care Med 2000; 28: 2786). The aim of the study was to validate these results in a further set of patients.

Methods: Stage III unresectable NSCLC patients included in a phase III trial assessing the role of increased dose chemotherapy (SuperMIP: mitomycin 6 mg/m2, ifosfamide 4.5 g/m2, cisplatin 60 mg/m2, carboplatin 200 mg/m2) in comparison to standard chemotherapy MIP (mitomycin 6 mg/m2, ifosfamide 3g/m2, cisplatin 50 mg/m2), before thoracic irradiation (60 Gy in 30 fractions over 6 weeks) are the subject of this study. Survival distributions were assessed by the method of Kaplan-Meier. Survival comparisons were made by the log-rank test. Multivariate analysis using the Cox model, included all potential prognostic factors with a p value < 0.2 in univariate analysis.

Results: According to the 1997 ISS classification, 328 eligible patients were included in the study. There was no imbalance between the 2 arms. For the group as a whole, although a significantly better response rate was observed, there was no survival difference according to treatment arm. Five parameters were significantly associated ($p < 0.05$) with survival in univariate analysis: ELCWP staging (IIIalpha versus IIIbeta), Karnofsky index, weight loss, platelet and haemoglobin counts. These variables as well as the 1997 ISS staging, white blood cell count, LDH and sodium level were included in a multivariate analysis. Two models were constructed, including either the 1997 ISS (model 1) or the ELCWP (model 2) staging systems. In model 1, Karnofsky index (HR = 0.69; 95%CI 0.47-1.00; p=0.05) and haemoglobin (HR = 1.49; 95%CI 1.11-1.99; p=0.007)were significant. Model 2 included 3 covariates: ELCWP staging (HR = 1.68; 95%CI 1.20-2.35; p=0.002), haemoglobin (HR = 1.54; 95%CI 1.15-2.07; p=0.01) and Karnofsky index (HR = 0.72; 95%CI 0.49-1.05; p=0.08).

Conclusion: In unresectable stage III NSCLC treated by chemotherapy and radiotherapy, we validated the results of our previous study. The classification into stages IIIbeta (T3-4N3M0) and IIIalpha (other TN stage III) better discriminates the patients in term of survival than the 1997 ISS classification

Colorectal cancer

1084 ORAL

Only colon cancer patients with Dukes stage C benefit from adjuvant chemotherapy with 5-fluorouracil and levamisole among 425 patients with operable colorectal cancer in a Norwegian randomised study.

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Background: The introduction of adjuvant chemotehrapy for colon cancer with lymph node metastases by Laurie (1) and Moertel (2) was reluctantly accepted by Norwegian medical doctors. We wanted therefore to assess and confirm the role of adjuvant therapy with 5-fluorouracil (5-FU) combined with levamizole (Lev) in a confirmatory randomised study.

Materials and methods: 425 patients with operable colon and rectum cancer, Dukes stage B and C, were from January 1993 to October 1996, included in a randomised multicentre trial in Norway. The age limits were 18-75 years. The trial was approved by the Official Regional Ethics Committee. Therapy started with a loading course of bolus i.v. FU (450 mg/m2) daily for 5 days. From day 28 a weekly iv FU dose (50 mg/m2) were administered for 48 weeks. From day 28 a p.o dose of Lev (50 mg x 3) was sheduled for every 14 days. Totally 214 patients were randomised to 5FU/Lev and 211were included in the control group with surgery alone. Despite some did not met the inclusion criteria (one patient had prior cancer and one had an uterine carcinomars; and 9 actually had Dukes' stage A, one T1, 8 T2), all patients were included in the final analysis on an intention to treat basis. 70% had colon cancer, 30% rectal cancer, and 39% were Dukes' stage C, 59% B and 2% A.

Results: There were no significant difference in the two groups at 5 y: Overall survival was 68.2% in controls and 72.0.8% in the adjuvant group. There were no difference in the two groups when analysed for colon and rectum separately. However, in the subgroup of colon cancer Dukes' stage C the difference in cancer specific survival was significant (p=0.036): surgery alone 47.8%, adjuvant chemotherapy 65.4%.

Toxicity was acceptable: Haematological Gr. 3: 1, Gr 4: 3 and other Gr 3: 33 (mainly diarrhoea and nausea) and Gr. 4: 7 including one infection, among 190 patients where detailed scoring were recorded. No toxic death occurred.

Conclusions: Colon cancer patients with lymph node metastases benefit from adjuvant chemotherapy with FU/Lev and toxicity was acceptable and should continue to receive this therapy as standard therapy.

1085 ORAL

Multicenter international randomized study of oxaliplatin/5FU/LV (folfox) in stage II and III colon cancer (mosaic trial): final results

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FOLFOX4 regimen combining LV5FU2 (leucovorin 200mg/m^2 as a 2-hour infusion, 5-FU 400mg/m^2 bolus and 600mg/m^2 22-hour continuous infusion, d1-2) and oxaliplatin 85mg/m^2 d1, bimonthly, has demonstrated clinical activity in first line metastatic colorectal cancer (de Gramont, J Clin Oncol, 2000, Goldberg, ASCO 2003) as well as in second line (Rothenberg M, J Clin Oncol, 2003). In 1998, we initiated this large randomized phase III study in order to demonstrate efficacy of the FOLFOX4 regimen in earlier stages of the disease with the goal to achieve a 25% decrease in the risk of recurrence at 3 years for patients receiving FOLFOX4 compared to those receiving LV5FU2. From 10/98 to 01/01, 2248 patients with completely resected stage II (40%) or III (60%) colon cancer were