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EARLY TUMOUR CELL DISSEMINATION IN NON-SMALL CELL LUNG CANCER. Pantel, K., Passlick, B., Izbicki, J.R., Angstwurm, M., Kubuschok, B., Thetter, O. Nathrath, W. and Riethmüller, G. Inst. of Immunology, Inst. of Pathology & Dept. of Surgery, University of Munich, Germany.

Present diagnostic techniques do not allow the detection of early metastatic spread of tumour cells, although this spread largely determines the clinical course of patients with small primary cancers. We therefore developed sensitive immunocytochemical assays that allow the detection of single disseminated tumour cells in patients with completely (R_0) resected non-small cell lung cancer (stage M_0). Tumour cells in bone marrow or regional lymph nodes were identified with either monoclonal antibody (MAb) CK2 to cytokeratin component no. 18 or MAb Ber-Ep4 to two cell surface glycoproteins of 34 and 49 kD, respectively. Single aspirates of iliac bone marrow from 18 of 82 (21.9%) patients exhibited between 1 and 531 $CK2^+$ cells/4 x 10^5 nucleated marrow cells. In lymph nodes staged as negative (N_0) by conventional histopathological examination, individual $Ber\text{-}EP4^+$ cells were detected in 11 of 72 (15.2%) patients with no correlation to a positive bone marrow finding. The specificity of both assays was supported by negative staining of lymph nodes and bone marrow from non-carcinoma, control patients. Following a median observation period of 26 (15 - 39) months, the clinical relevance of single residual tumour cells was supported by univariate statistical analysis ($p \approx 0.005$) and the independency of this prognostic influence was further sustained by multivariate analysis ($p = 0.005$). In conclusion, the presence of single epithelial cells in lymph nodes or bone marrow indicates independent from each other the disseminatory capacity of an individual tumour. The immunohistochemical assessment of these cells is therefore recommended for tumor staging in operable non-small cell lung cancer as it might lead to a better stratification of patients for adjuvant therapy.

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HYPERFRACTIONATED ACCELERATED RADIOTHERAPY COMBINED WITH ALPHA-2 INTERFERON IN THE TREATMENT OF NON SMALL CELL LUNG CANCER

M.PARASKEVAIDES,N.KOLIARAKIS,I.STEFIS*TH.CHRISTODOULOU, P.KARAGEORGIS Dir.
METAXA CANCER HOSPITAL-PIRAEUS,2nd R/therapy Ongol. Dept. *401 GENERAL MILITARY HOSPITAL-ATHENS, R/therapy Dpt.

The aim of the Hyperfractionated accelerated radiotherapy regimen is to avoid the problem of repopulation during the treatment course and to complete the RT therapy minimising the acute reactions. Also taking into consideratior the radiosensitivity effect of Alpha interferon and its immunoregular properties, we have utillsed the product concomitant with the RT Treatment. 25 patients received RT to a large volume that encompassed the primary tumor andmediastinum, concomitant with a boost on a small volume that included the known tumor. At the same time they received s.c interferon three times a week at a dose of 5 mil I.U. The patients were evaluated at monthly intervals after the completion of the treatment. A Cobalt 60 unit was used and RT was given 3 times per day at a dose per fraction of 12 Gy. A complete radiological response has been achieved in 36% with 1 year survival of 46% and a 2 yaer survival of 24%. Acute and late effects are given in the study which is still under progress

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PLATINUM-ETOPOSIDE (PE) CHEMORADIATION FOR STAGE III INOPERABLE NON SMALL-CELL LUNG CANCER (NSCLC): TOWARD AN IMPROVED LOCAL CONTROL? Reboul F, Brewer Y, Vincent P, Chauvet B, Félix Faure C, Taulelle M. Thoracic Oncology Dept. Clinique Ste Catherine. BP 846. Avignon 84082 France.

In order to improve upon the results of standard thoracic radiotherapy (TRT) alone in stage III inoperable NSCLC, we have integrated early concurrent PE chemotherapy with standard fractionation continuous TRT (60 Gy over 6 weeks in 30 fractions). Chemotherapy began on day 1 of TRT with P (20 mg/sqm/d x 5 days) followed by E (50 mg/sqm/d x 5 days) on weeks 1, 5, 8 and 11. Response was assessed with CT-scan, fiberoptic bronchoscopy and biopsy at the initial tumor site 6 weeks following completion of therapy. From February 1992 to May 1993, 50 stage III patients (pts) with favorable CALGB criteria were enrolled in this study. Median age was 62 years with 28% WHO status 2, 74% squamous cell histology, 38% Stage IIIa, 62% Stage IIIb. Full dose TRT was delivered in 69% and a median of 3.5 courses of PE. Toxicity analysis showed mainly grade 3-4 esophagitis (10%), neutropenia (22%) and 2 treatment-related deaths due to infection. Complete clinical response rate was 66%, including normal endoscopy findings in 33 pts and negative biopsies in 26/31. Eight pts were resected after 45 Gy with a negative specimen in 3/8. With a median follow-up of 15 months (8-22), 25 pts are alive disease-free for an actuarial overall survival of 71% at 12 months and 57.4% at 18 months. Corresponding disease-free survival is 63.5% and 47%, respectively. Median survival was 18.2 months with a projected crude survival in excess of 40% at 2-year. Patterns of failure analysis showed 18 local recurrences (36%) with a remarkable 59% actuarial local control rate at 18 months. Distant failure occurred in 20 pts (38%) with brain metastasis in 9 pts. In a previous study, actuarial local control rate was only 37% at 18 months, among 73 comparable stage III pts treated with concurrent cisplatin alone at the same dose. This may be related to recently described radiosensitizing properties of etoposide, as well as its potential synergy with cisplatin. In conclusion, addition of etoposide to cisplatin in concurrent chemoradiation regimens may further enhance local control in stage III inoperable NSCLC and will hopefully result in a substantial survival benefit.

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HIGH-DOSE RATE BRACHYTHERAPY (HDR-BT) FOR ENDOBRONCHIAL LUNG CARCINOMA : RESULTS AND COMPLICATIONS IN 111 PATIENTS (PTS). Reboul F, Chauvet B, Vincent P, Brewer Y, Felix-Faure C, Taulelle M. Thoracic Oncology Dpt. Clinique Sainte Catherine. BP 846. Avignon. France.

From 9-1990 to 5-1993, we have treated 111 pts with HDR-BT (median age 68 years, squamous cell ca. 84.7%). Prior treatments included surgery (28%), chemotherapy (45%) and radiotherapy (64%). The majority of these pts had late endobronchial recurrence (38.8%) or persistent tumor (27.9%) following primary treatment. In some pts, HDR-BT was carried out upfront for massive obstructive tumor (20.7%) or small inoperable endobronchial tumor (12.6%). Main symptoms before treatment were cough (82.9%), dyspnea (71.2%) and hemoptysis (36%). Bronchial obstruction was > 50% in 80% of cases. Treatment protocol consisted of weekly Ir-192 implants at a dose of 10 Gy at 10 mm x 3 in the first 35 pts and 8 Gy x 4 in the following 76 pts for a total of 371 implants. Immediate tolerance was good in 95.4%. Response rate was assessed endoscopically at 1-month following completion of therapy with 72% major response including 57.7% complete response and 45 negative biopsies at the initial tumor site. A high CR rate (92.9%) was obtained in the small inoperable tumors group. Symptomatic improvement was systematically assessed in 79 pts with cessation of cough in 69.5% (41/59), dyspnea in 65.9% (29/44) and hemoptysis in 88.9% (16/18). Toxicity analysis showed 9 stenoses, 6 necroses, 1 pneumothorax, and 6 fatal hemoptyses for an overall rate of 18%, including 8 treatment-related deaths (7.2%). Multivariate analysis (treatment protocol, tumor location, dose characteristics) failed to show any significant predictive factor for these complications . With a median follow-up of 24.5 months, 16.2 % are alive and 63% are dead from disease (1- and 2-year survival rate 23.3 % and 3.6%, respectively). In the group treated with curative intent (small tumors n=14), 7 pts are alive disease-free with a median survival of 17 months. In conclusion, HDR-BT is a well tolerated treatement resulting in a significant improvement of distressing symptoms with an acceptable rate of late complications. Local control and survival in small inoperable tumors are specially encouraging while future studies should focus on the role of HDR-BT in the primary non-surgical treatment of lung cancer.

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FIVE-DAYS ADMINISTRATION OF CISPLATIN AND VEPESID IN INOPERABLE NON SMALL CELLS LUNG CANCER (NSCLC)

Sogno G., Addamo GF., Pastorino G., Martini MC., Moraglio L., Vallauri M. and Brema F.
Department of Medical Oncology, S. Paolo Hospital, Savona (Italy)

Between 12/87 and 8/93, 41 patients (pts) (34 males, 7 females) with metastatic, locally advanced or medically inoperable NSCLC were treated with cisplatin 20 mg/m^2 days 1-5 and vepesid 70 mg/m^2 days 1-5, every 21 days. The histotypes were 18 adenocarcinomas, 19 epidermoids, 1 large cells anaplastic, 3 untyped; AJCC-TNM stages: IIIA (8 pts), IIIB (9 pts), IV (22 pts), unstaged (2 pts); ECOG-P.S.: 0 (21 pts), 1 (19 pts), 2 (1 pt). 195 courses were administered, a median of 6 courses/pt (r=1-6). We achieved 12 ORs (34%) and 19 SD (54%); 6 pts progressed under treatment. Median overall survival was 11 months (r= 3-34) without a significant difference between responders and non responders. We didn't observe grade IV WHO toxicity, and the following grade III toxicities: alopecia 19.5%, nausea and vomiting 17.5%, leucopenia 17.5%, anemia 5%, neurotoxicity 2.5% and thrombocitopenia 2.5%. 10.7% of courses were delayed for leucopenia, 2.5% for anemia and 3% for nephrotoxicity. This scheduling appears equiactive with one-day cisplatin regimens and better tollerated.

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SURVIVAL IN NON SMALL CELL LUNG CANCER WITH MALIGNANT PLEURAL EFFUSION

Vietti-Ramus G. and Tonda L.
Medicina C, Ospedale Giovanni Bosco, Torino (Italy)

This study evaluated if survival (S) of pts with stage III b NSCLC was affected by the presence of malignant pleural effusion (PE) and by its response to intrapleural therapy. 53 consecutive pts (27 adenocarcinoma (A) and 26 large cell carcinoma (L)) were divided into two groups: with and without PE. The latter (18 A, 14L) was treated, after a complete thoracentesis, with 1 or 2 instillations of intrapleural Bleomycin (B1) (60UI). PE inversely affected S (4 ± 3 vs 9 ± 5 mo, $p< 0.001$) and performance status (PS) ($p<0.01$). In the PE group pts with A had a longer S than those with L (5 ± 3 vs 2 ± 1 mo, $p< 0.01$). In the group without PE S was not different between A and L. Pts with PE controlled by B1 survived longer than those who did not respond to therapy (4.5 ± 3 vs 2 ± 2 mo, $p<0.05$) and improved their PS ($p<0.001$). In stage IIIb of NSCLC (A and L) pts affected by PE had a reduced S if compared with pts without it. Definitive control of PE by B1 affected positively both S and PS.