

522 High dose-rate (HDR) endobronchial brachytherapy associated or not with previous Nd-YAG laser therapy for lung cancer: Results and complications of a prospective study

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Objective: To evaluate the effectiveness of HDR brachytherapy in curative treatment and palliation of symptoms due to endobronchial lung cancer.

Methods: From Jan. 91 to Oct. 96, 46 patients with malignant airway disease were treated with HDR brachytherapy. Only 36 cases, with histologic diagnostic of lung carcinoma and a minimum follow-up of 6 months, were included in this study. The patients were treated according to 3 categories: a) curative – 8 patients; b) palliative – 9 patients and c) recurrences after previous irradiation and/or surgery – 19 patients. The curative group received concomitant external irradiation (60 Gy as standard) and HDR brachytherapy. In the other two groups, external irradiation was used when indicated. Brachytherapy was delivered in three fractions of 7.5 Gy each, fortnightly or weekly, according to the association or not with concomitant external irradiation respectively. Dose was prescribed at 1 cm from the axis of the catheter, with variations until 0.5 cm when segmental bronchi were irradiated. Neodymium-YAG laser was used previously for desobstruction or hemostasis in 13 patients.

Results: In the curative category, mean survival was 30.1 months, with 3 patients alive at 6, 42 and 60 months. Of the group treated in the palliative category, one patient was alive at 6 months and the mean survival was 4 months. Patients treated for recurrent disease had a mean survival of 11.4 months with 1 patient alive at 60 months (salvage surgery after a second recurrence). Statistical analysis demonstrated a significant difference in survival among the 3 groups ($p = 0.01$). Symptom relief with improvement of the performance status was obtained in 85.2% of the cases. Complete or partial airway desobstruction occurred in 83.3%. Severe complication rate was 5.5%, represented by 2 patients not submitted to laser therapy (1 esophageal-mediastinal fistulae and 1 fatal hemoptysis associated with persistent tumor).

Conclusions: Our results indicate that HDR endobronchial brachytherapy may be useful in the curative treatment of well selected cases. Palliation of symptoms with improvement of the quality of life is obtained in the majority of the patients. In this study, association with laser therapy did not increase the complication rate.

523 Combined modality treatment using concurrent radiotherapy [RT] and pharmacologically guided carboplatin for non-small cell lung cancer [NSCLC]

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Background: In a previous randomized trial we observed a 50% increase in median survival in patients [pts] with inoperable NSCLC when carboplatin was given concurrently with RT [60 Gy in 30 fractions given over 6 weeks] compared with the same RT given alone. In that study, the dose of carboplatin was calculated according to the body surface area, but the safety and efficacy of the drug may be improved by pharmacologically guided dosing based on its renal excretion.

Patients and Methods: Patients were eligible if they had unresectable or incompletely resected NSCLC, good performance status [ECOG 0–1], weight loss < 10%, no evidence of distant metastases and adequate haematology and biochemistry. RT was given to the primary site and regional lymph nodes to a total dose of 60 Gy in 30 fractions over 6 weeks. Two cycles of carboplatin were given as daily one hour infusions before RT in weeks 1 and 6. A plasma area under the free platinum concentration versus time curve [AUC] of 7 mg/ml.min/cycle was targeted this being the known maximal single agent exposure. The total dose of carboplatin required was determined using the Calvert or Chatelut formula.

Results: Between 11/95 and 11/96 31 patients were enrolled. Patient characteristics: 77% male; median age 69 [range 46–78]; stage: I- 1 pt, II-2 pts, IIIA-13 pts, IIIB-11 pts, incomplete resection-3 pts, and 1 pt locally recurrent after surgery. Median dose of carboplatin per cycle was 840 mg [range 435–1350 mg]. 25 pts [81%] completed treatment as planned. Reasons for failure to complete treatment: 2 deaths [myocardial infarction]; 2 pts progressive disease; and 2 pts did not complete 2nd cycle carboplatin – 1 neutropenia, 1 oesophagitis. Neutropenia: grade 3 occurred in 4 pts

[13%], and 1 pt developed grade 4 and died of pulmonary sepsis after 2 cycles each of 850 mg. Grade 3 thrombocytopenia occurred in only 2 pts and 2 pts developed grade 3 oesophagitis.

Conclusions: Radical chest irradiation can be combined with 2 cycles of pharmacologically guided full dose carboplatin with acceptable toxicity in pts with NSCLC. The higher doses and the wide variation in total carboplatin dose indicates that this dosing method is preferable to a fixed mg/m² dosing.

524 Concurrent Paclitaxel/Cisplatin (PC) with thoracic radiation (TR) in patients with stage IIIa/b non-small cell lung cancer (NSCLC)

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Early concurrent use of chemotherapy and thoracic irradiation has shown improved survival in patients with limited small cell lung cancer compared with sequential therapy, and its use in NSCLC is reasonable. In this Phase I-II trial we have combined the active agents cisplatin and paclitaxel with concurrent TR to 64.8 Gy in patients with unresectable Stage IIIa and IIIb NSCLC to assess treatment tolerability, efficacy, and estimate survival. Between 1/24/94 and 3/20/96 20 patients with Stage III NSCLC were entered on this trial. One was withdrawn as ineligible, the remaining analysis is of all 19 eligible patients. All patients were required to be of ECOG PS 0–1, have adequate organ function to tolerate radiation and chemotherapy, and have no evidence of CNS metastases by enhanced CT or MRI. There were 14 men and five women, 2 IIIa (N2) and 17 IIIb, 7 Squamous, 6 Adenocarcinoma, and 6 Large Cell. Treatment was with Paclitaxel 135 mg/m² d1 and Cisplatin 75 mg/m² d2 four 4 cycles repeated every 28 days. Radiation was begun day 2 of cycle 1 and treated areas of gross disease to 64.8 Gy in 34 fractions over 7 weeks. Elective nodal regions in the mediastinum were treated to 50.4 Gy, and supraclavicular nodes were not electively treated. Four patients failed to complete protocol treatment due to objective progression (1 in SC node), declining PS (2), or refusal (1). Objective responses following all therapy were 2 CR, 6 PR, 3 SD, 5 PD, 3 inevaluable. Major toxicities were hematologic, with Grade 3/4 leukopenia in 16/19 patients and grade 4 esophagitis in 3, Grade 3 in 7. Median survival was 11 months for all patients entered. Two patients remain alive NED at more than two years from treatment. In this population of patients with advanced disease, this regimen was relatively toxic and not clearly more effective than sequential chemoradiation or radiotherapy alone, and cannot be recommended for routine use.

525 Pulmonary function changes in patients with lung cancer treated by combined radiation and chemotherapy

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Concomitant radiation and chemotherapy would improve outcome of patients with non metastatic advanced lung cancer. However, such combination might increase the rate of side effects. The present study was designed to assess the pulmonary function changes associated with such treatments administered with curative intent. So far 11 patients with primary lung cancer (stage III: A or B) have been recruited. Chemotherapy consisted of cisplatin, ifosfamide and vindesine. For radiation therapy, the target volume encompassed the tumor, the ipsilateral hilum, the mediastinum and both supraclavicular fossae. The total dose (40 to 60 Gy) was delivered in 2 Gy daily fractions, 5 days a week. Pulmonary function tests and dyspnea were assessed before any treatment, when 40 Gy had been delivered, during the 2nd, 3rd and 6th month following the completion of radiation therapy. Seven patients were afflicted with obstructive lung disease (FEV1 < 75%) at the time of inclusion. Three patients developed transient respiratory insufficiency. On average, there were small and transient changes in dyspnea and in FEV1. Diffusion capacity was worsened. This worsening was present at 40 Gy and persisted for at least 6 months after the end of radiation therapy. We conclude that combined radiation and chemotherapy induce moderate pulmonary function changes in most patients. This suggests that chemotherapy and external beam radiation

can be administered concomitantly without much damage to the lungs. Assessment of the value of predictive factors (e.g. pretreatment pulmonary function tests, irradiated lung volume, serial determination of TGF- β blood level) in determining which patients are at risk of developing pulmonary side effects during such treatments will be presented.

526 Local immunochemotherapy and systemic chemotherapy in early stage (I–II) malignant pleural mesothelioma

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Aim: To date surgery, radiotherapy and chemotherapy have been shown to be inadequate in the control of malignant pleural mesothelioma (MPM). This phase II study (4/90–10/95) evaluated the ability of a local immunochemotherapy (LICT) and systemic chemotherapy (CT) to prolong the time to progression and survival in stage I–II MPM (according to Butchard's criteria).

Methods: 26 eligible patients (pts) were entered into the study. All pts underwent thoracoscopy and, after histological diagnosis, ultrasound-guided thoracic drainage with 10F Percuflex pig-tail catheter (Medi-techa). Through it, an intrapleural therapy by epidoxorubicin 30 mg/sqm days 1, 3, 5 and by a biological response modifier (BRM) (19 pts by 14 mg lyophilized *Corynebacterium parvum* and 7 pts by 18×10^6 UI interleukin-2[r-IL2]) days 7, 9, 11 was administered. Cycles were repeated every 3 weeks until pleurodesis or for a max. of 3 courses. After catheter removal, all pts received ifosfamide (I) 3 g/m² days 1, 2, mesna (80–100% of the I dose), vincristine (V) 1.2 mg/m² day 1 and actinomycin D (A) 1.2 mg/m² day 1. Treatment was repeated, every 3 weeks, for a max. of 6 cycles. The pts, who received intrapleural r-IL2 and achieved an objective response (OR), underwent prosecution therapy with low dosage of r-IL2 for 6 mos (3×10^6 UI sc, 3 days per week).

Results: LICT achieved an OR in 24/26 pts with 15 complete responses (CRs) (according to Paladine's criteria). An average of 1.5 courses of LICT were necessary with a median drainage period of 29 days. A total of 126 courses of CT were given (average of 4.6, range 3–6). No treatment-related death occurred. The results of CT were 14 OR (4 CR), 10 stable disease (SD) and 2 progressive disease (PD). Overall median time to progression was 12 mos, 18 mos for ORs. Median survival time was 25 mos with actuarial 1-, 2-, 3-yrs survival rate of 92.0%, 56.1% and 12.4% respectively. Today 9 pts are alive and 3 pts are progression free.

Conclusions: We may conclude that the combination of LICT and CT is effective, with acceptable toxicity, in MPM. Further multicenter study with a large number of pts is necessary to confirm these high response rates in the treatment of MPM.

527 Neoadjuvant multimodal treatment approach for stage III non-small cell lung cancer (NSCLC): Results of a prospective phase II trial

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Evaluating a combined neoadjuvant treatment approach in NSCLC-patients with surgically proven stage III a multicenter phase II trial started in 1992: after completion of two cycles of chemotherapy [CT] (Carboplatin 300 mg/m²; d1/Ifosfamid 3×1.5 g/m²; d1, 3, 5/Etoposid 3×120 mg/m²; d1, 3, 5) a 3 week-period of hyperfractionated-accelerated radiotherapy [hFRT] (45 Gy; 2×1.5 Gy/d) with concurrent Carboplatin (100 mg/m²; d1, 8, 15)/Vindesin (3 mg; d1, 8, 15) followed.

Up to 9/95 54 patients (29 in stage IIIB), median age 57 (range 37–69), have been enrolled. Main toxicities turned out in esophagitis ($5 \times$ WHO III/IV^o) and pneumonitis ($5 \times$ WHO III/IV^o). 5 treatment related deaths occurred: 2 due to pneumonitis, 2 because of postoperative bronchopleural fistula and one due to postoperative pneumonia. For 37 of 54 (69%) a clinical response was achieved. 40/54 (74%) patients went on to surgery with a R0-resection – rate of 34/40 (85%). For 23 of 34 patients with R0-resection in the surgical specimens no evidence of tumor was found or tumor cells amounted less than 10% respectively. 20 of 29 patients in stage IIIB and 20 of 25 in stage IIIA were operated. Median survival time (MST) for all

patients is 20.4 mo. (IIa 24.9 mo.; IIIB 17.2 mo.) with a median follow up of 32 mo. Compared to inoperable or incomplete resected patients (MST: IIIA 11 mo.; IIIB 16.9 mo.) patients with R0-resection lived longer (MST: IIIa 35.9 mo.; IIIB 22.2 mo.). With acceptable toxicity this treatment approach results in good response- and resection rates, even in stage IIIB patients. Compared to conventional treatment MST ist doubled.

528 Phase I/II trial of paclitaxel (Taxol) and radical radiotherapy (XRT) in patients (PTS) with stage III non-small cell lung cancer (NSCLC)

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The addition of chemotherapy to XRT has been shown to improve survival in locally advanced NSCLC. Consequently different chemotherapeutic regimens in combination with XRT are being evaluated in the treatment of this disease. Taxol may be a valuable drug in this situation as, in addition to a demonstrated activity in NSCLC, it has been shown to enhance the effect of radiation on cell lines in vitro.

Seventeen patients with stage III NSCLC were enrolled onto a phase I/II trial, to initially determine the maximum tolerated dose (MTD) of paclitaxel given by a 3-hour infusion every 2 weeks throughout a 6 week course of XRT, 6000 cGy in 30 daily fractions, and then to assess the efficacy of this combination. Three patients were entered at each dose level (45, 90, 120 and 135 mg/m²), except for the 120/m² dose level which was expanded to 9 patients in the phase II part of the study. The dose limiting toxicity was neutropenia – 2/3 patients treated at the 135 mg/m² level experienced severe granulocytopenia on day 15 which precluded administration of scheduled chemotherapy. Esophagitis was only mild, and although profound lymphopenia was observed, there was no evidence of associated opportunistic infections previously described. The overall response rate was 58.8% (1 CR, 9 PR, 4 SD and 3 PD). Of the 9 patients treated at the MTD, there were 1 CR, PR, 1 SD and 1 PD (response rate = 78%).

XRT, 6000 cGy in 6 weeks and paclitaxel, 120 mg/m² q 2 weeks is a safe combination for patients with NSCLC. Although it demonstrates activity in this situation, further investigation is required to define its role in the treatment of this disease.

529 Ethical meta-analysis of randomised trials for lung cancer

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In order to promote a more productive debate on the ethics of randomised clinical trials (RCTs), I present a survey on the ethical aspects of published RCTs for lung cancer. From the Cancerlit 1993–1995 database, 92 published randomised trials for lung cancer with a total of 17803 patients were identified. The published data were supplemented by a questionnaire mailed to the authors of these publications. The analysis focused on respect of autonomy, non-maleficence, beneficence, and justice as the ethical principles applicable to society, patients in trials, patients not included in RCTs and physicians.

Results: Full information about the disease and prognosis was offered to 60.4% of patients; 55.8% of patients signed a consent form. The ratio between the recruitment period (mean, 36 months) and time to event (mean, 9 months) was greater than 5 in 28 trials; 4 of these trials reported a significant overall survival advantage. When innovative treatments were compared to the standard approach, only a marginal improvement in median overall survival (16.7 months vs. 15.7 months) and 2-year survival (27.1% vs. 24.2%) was seen, with an accompanying increase of the total number of treatment-related deaths (125 vs. 86).

Ethical Analysis and Conclusion: The benefits to society include an objective evaluation of new treatments; however, in view of only minimal therapeutic improvement the strategy of current research for lung cancer may need to be re-defined. The principle of autonomy was often violated for patients who were inadequately informed about the disease or about RCT. In some trials with prolonged recruitment, the principle of non-maleficence was not respected since patients continued to be randomised in spite of an obvious advantage of one of the treatments. When compared to those