Ctr., 1275 York Avenue, New York, NY 10021. World J Surg 1995;19:817-22.

Approximately 25%-30% of all patients with non-small cell lung cancer (NSCLC) present with stage III tumors. Except for specific subsets, these tumors are not usually amenable to complete surgical resection and are associated with a 5-year survival of 10% or less. Because patients with stage III NSCLC die of distant metastases, recent efforts to improve the prognosis of these tumors have focused on neoadjuvant therapy using chemotherapy or chemoradiotherapy as induction treatment and subsequent surgical resection for local control. Many trials have now shown the feasibility of neoadjuvant therapy and suggest that overall survival is approximately double that seen after surgical resection or radiation alone. Future clinical trials will define whether surgical resection after induction therapy provides better local control and survival than chemotherapy and high-dose radiation alone.

Induction chemotherapy followed by adjuvant surgery (IC-AS) in patients with stage I-II small cell lung cancer (SCLC)

Shibayama T, Hiyama J, Ueoka H, Tabata M, Segawa Y, Gemba K et al. *Second Dept. of Medicine, Okayama University Medical School, Okayama.* Jpn J Cancer Chemother 1995;22:1953-8.

Ten patients with stage I-II SCLC received IC-AS between 1984 and 1993. As induction chemotherapy, COMP-VAN alternating chemotherapy and CAV-PVP hybrid chemotherapy were administered. The former consisted of a 4 drug combination of cyclophosphamide(CPA), vincristine(VCR), methotrexate (MTX) and procarbazine alternated with a 3-drug combination of etoposide (ETP), adriamycin (ADM) and nimustine every 4 weeks. In the latter, a 3 drug combination of CPA, ADM and VCR given on day 1, and a 2 drug combination of ETP and cisplatin on day 8, were repeated every 4 weeks. All the patients had an objective response, including one complete response by induction chemotherapy. Post-operative pathology revealed SCLC in 4 patients, adenocarcinoma in 2 and no tumor (pathological CR) in 4. Four patients relapsed, and a intrathoracic relapse was experienced in only 2 patients. Six patients have died: 3 from relapsing SCLC, 2 from stomach cancer, and 1 from squamous lung cancer, who was salvaged from relapsing SCLC. The median survival time was 27.5 months, and the 3-year survival rate 37.5%. These results indicate that IC-AS is highly effective for stage I-II SCLC and warrant additional studies comparing IC-AS with chemo-radiotherapy.

Gemcitabine in the treatment of non-small-cell lung cancer

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Gemcitabine is a nucleoside analogue with activity in non-small-cell lung cancer (NSCLC). Phase I trials have determined the best tolerated dose of gemcitabine in chemotherapy-naive patients to be 1250 mg/m^2 given as a 30-minute infusion weekly x 3 every 4 weeks. The single-agent efficacy of gemcitabine has been assessed in 4 phase II trials (361 patients) at dose of 800-1250 mg/m^2/weekly x 3 every 4 weeks. Single-agent response rates (externally verified by Oncology Review Board) were >20%, with duration of response 7.6-12.7 months and median survival 8-9 months. Dose-limiting toxicity was neutropenia, but this was rare, even at the highest dose levels. In 3 Japanese studies, response rates of 16.3%, 26% and 20.9% were seen in untreated patients. Pooled data from all NSCLC studies shows that responses were seen in stages IIIA, IIIB and IV disease, and were similar in adeno and squamous cell types. Gemcitabine has also been studied in combination with other drugs active in NSCLC. In one study 50 patients were treated with gemcitabine and cisplatin given weekly x 3 every 4 weeks, cisplatin at a dosage of 25-30 mg/m^2 and gemcitabine at doses escalating from 1000 mg/m^2 in steps of 250 mg/m^2 per cycle. 38 of 50 patients have been evaluated to date, with an overall response rate of 31.6%. Dose Limiting toxicity was rare, but there was evidence of cumulative haematological toxicity with grade 4 granulocytopenia and thrombocytopenia becoming more frequent with repeated administration. Similar activity was seen when gemcitabine (1000 mg/m^2) was combined with monthly cisplatin (60, 75, 100 mg/m^2). Other studies have shown that gemcitabine can enhance radiosensitivity in NSCLC and other solid tumour types such as pancreas/breast and colorectal cancer cell lines.

Dealing with initial chemotherapy doses: A new basis for treatment optimisation in limited small-cell lung cancer

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Treatment of patients with small-cell lung cancer (SCLC) remains disappointing despite initially high complete response rates. The dramatic initial chemosensitivity of tumor cells is rapidly thwarted by the early emergence of chemo-resistant clonogenic cells, regardless of front line treatments. Although a dose-response relationship is well established its effect on survival is inconclusive. From 1980 to 1988, 202 patients with limited SCLC were included in four consecutive trials using an alternating schedule of thoracic radiotherapy and chemotherapy. Despite an increase in chemotherapy and/or the total radiation dose, no significant difference was observed between the four trials in terms of response, disease-free or overall survival. However, a retrospective analysis performed on a total of 131 consecutive patients led us to postulate that a moderate increase in the initial dose, i.e. first course, of cisplatin and cyclophosphamide, could improve overall survival. From 1988 to 1991, 105 consecutive patients were included in a large randomized trial to address this question. The difference in treatment options only concerned the initial doses of cisplatin (80 vs. 100 mg/m^2) and cyclophosphamide (900 vs. 1200 mg/m^2). According to the triangular test used in this study the trial was closed after inclusion of 105 patients, 32 months after the start of the study because, at that time, overall survival was significantly better in the higher-dose group ($p = 0.001$). This debatable concept of dose-intensity having an impact on survival offers new possibilities for the management of SCLC. The contribution of hematopoietic support may help to validate this concept.

Chemotherapy of stage IIIB and IV non-small-cell lung cancer

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Currently lung cancer is a leading cause of death in men with more than half million new cases diagnosed every year. Eighty percent of these tumors are non-small-cell carcinoma and 70% of these are unresectable or metastatic at the time of presentation, resulting in dramatically poor survival rates. The increasing number of drugs showing a significant activity against non-small-cell lung cancer and the widespread use of modern cisplatin based regimens offer some hope of progress and suggest that chemotherapy may have a role in treating this disease. A recent meta-analysis has confirmed the modest but significant survival benefit for patients treated with combined chemotherapy both in case of metastatic disease and in addition to radiotherapy, in locally advanced disease.

Induction or concomitant chemotherapy and radiotherapy for non-small-cell lung cancer: myth or reality

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If radiation therapy was often considered to be a classical treatment for locally advanced non-small-cell lung cancer, the overall results were

quite dismal. Failures were related both to local recurrences and distant metastases. During the last years, several studies have clearly suggested that combining radiation with chemotherapy given as an induction program or concurrently has led to some long term survival benefits. This paper reviews briefly the data available. Additional studies are required to better identify the optimal schedule.

The role of induction therapy and surgery for stage IIIA lung cancer

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In stage IIIA lung cancer, the role of induction chemotherapy or chemoradiotherapy prior to surgical resection has been studied extensively in patients identified preoperatively as having N2 disease. Both types of induction treatment have resulted in significant response and resection rates. Three trials have randomized patients to this form of treatment versus primary surgery. In all three trials the combined modality therapy has been significantly more effective, resulting in longer median survival times and estimated five year survival times. This new-found optimism for combine modality therapy including surgery is presently being compared to more standard therapy - chemoradiation for patients suffering from this stage of disease. In the future, this type of treatment will be investigated in earlier stage disease, classically treated by surgery, but often yielding less than satisfactory five year cancer free survival times.

Limited-stage small-cell lung cancer: Patient survival after combined chemotherapy and radiation therapy with and without treatment protocols

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Purpose: To compare survival of patients who undergo treatment in protocols versus survival of patients not in protocols. *Material and Methods*: Records of 81 adult patients with small-cell lung cancer who underwent chemotherapy and radiation therapy in 1987-1992 were reviewed retrospectively. Forty-one patients were in a protocol; 40 patients were not. Patient demographics and prognostic factors were not statistically significantly different. *Results*: Median overall survival was 16.7 months in the nonprotocol group versus 29.0 months in the protocol group (P = .0023). Median disease-specific survival was 18.3 months in the nonprotocol group versus 27.1 months in the protocol group (P = .0176). Survival was not statistically significantly influenced by Karnofsky performance status, weight loss, or thoracic radiation dose. *Conclusion*: There was a highly statistically significant difference in survival outcome in the nonprotocol group versus the protocol group (P = .0023). Differences in chemotherapy-radiation therapy timing and other treatment-related factors may have contributed substantially to the improved survival in the protocol group.

Treatment of Pancoast tumors: Combined irradiation and radical resection

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Eighteen patients underwent combined preoperative irradiation and radical resection for a Pancoast tumor at the Department of Thoracic Surgery, Chest Disease Research Institute, Kyoto University between 1977 and 1993. Four patients were applied a full radiation dose of 50-70 Gy and fourteen patients were applied a reduced dose of 33-40 Gy preoperatively. Eleven of these fourteen were applied a supplemental dose postoperatively up to a total dose of at least 50 Gy. Fourteen lobectomies, three partial resections, and one pneumonectomy were performed with combined resection of chest wall or adjacent structures: rib in 14, vertebra in 4, brachiocephalic vein in 3, subclavian artery in 2, spinal nerve in 3, sympathetic truncus in 2, phrenic nerve in 2 cases. Chest walls were reconstructed with marlex mesh in 5 patients, and two subclavian arteries and one brachiocephalic vein were repaired with artificial grafts. In 13 patients complete resections were achieved, but in the other 5 only incomplete resections leaving residual tumor were achieved. Incomplete resections consisted of 4 positive stumps at the brachial plexus of the apex and one aortic involvement by a metastatic lymph node. There was one operative death. Median survival was 21.6 months and the 5-year-survival rate was 38.5% for all 18 patients. In the complete resection group 5-year-survival was 56.4%, but in the incomplete resection group 0%, showing a significantly more favorable result for the complete resection group. It is considered that evidence of incomplete resection influences the prognosis and that particularly tumor invasion to the brachial plexus may serve as a limiting factor for surgery.

Neoadjuvant chemotherapy in non-small cell lung cancer for stages IIIa and IIIb

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The purpose of this study was to assess the ability of administering induction with chemo-radiotherapy in stage IIIa to reduce a tumoral mass. Therapeutic schedule: DDP 30 mg/m2 IV days 1, 8, 15, 22, VP 16 50 m/m2 days 1 to 26 HFX-RT 150 cGy x 2 days from day 8 up to 3600 cGy. We included 18 evaluable patients, 4 SIIIa and 14 SIIIb. Toxicity: 1 patient died because of pancytopenia GIV. Results: from 16 patients therapeutically evaluable 11 16 RP and 3/16 E, seven patients underwent gross tumoral resection and 6 with negative pathologic margins. This schedule is well tolerated and easy to be performed. The protocol will remain open until an adequate number of patients can be evaluated for a definitive measuration.

Neoadjuvant radio-chemotherapy in locally advanced non-small lung cancer. First results of a multicentric prospective study

Wagner W, Von Eiff M, Klinke F, Micke O, Rube C, Willich N. *Paracelsus-Strahlenklinik, Lurmannstrasse 38-40, 49076 Osnabruck.* Strahlenther Onkol 1995; 171:390-7.

Purpose: In the last years new encouraging methods in the therapy of bronchial carcinoma have been elaborated. The early stages of bronchial carcinoma are still a domain of operative treatment. The long-term results of surgical treatment for locally advanced disease are considered to be unfavourable. Multimodal treatment concepts with simultaneous or consecutive application of radio-chemotherapy followed by surgical resection seem to reveal improved possibilities of therapy. *Patients and Methods*: General treatment consists of 2 blocks of neoadjuvant chemotherapy with carboplatin, ifosfamide and etoposide, followed by a third course, consisting of carboplatin and vindesine. Simultaneously with the third course a hyperfractionated, accelerated radiotherapy with a single dose of 1.5 Gy 10 times per week is applied. The total dose is 45 Gy in 3 weeks, given at least to the 80% isodose. After restaging, tumor resection is carried out. Patients without tumor are randomized for prophylactic brain irradiation. *Results*: From January 1992 up to 1.10.1993 25 patients have been treated in accordance to the study. All tumors were locally advanced (stage IIIa and IIIb). Until 1.10.1993 4 patients died, 2 of them certainly related to the tumor. Thirteen patients have been resected after neoadjuvant treatment. In 11