the reporting of studies and results, testing the role of CT
in locally advanced NSCLC, testing postoperative RT, and
pursuing investigations in timing and dose of radiotherapy
and chemotherapy combined approaches.

REFERENCES
1 Arriagada R, Bertino JR, Bleehen NM, Brodin O, Feld R, Goldie
JH, Hansen HH, et al and the Workshop participants. Consensus
report on combined radiotherapy and chemotherapy modalities
2 Sørensen JB, Hansen HH. Review of methodological problems
in the interpretation of phase II trials in nonsmall-cell lung
in lung cancer. Basel: Karger, 1988; vol 41, 57-64
3 Bénichou J, Chastang C. Use of triangular test in the analysis
of randomized clinical trials when the response criterion is censored:
Application to two trials in lung cancer. In: Arriagada R, Le
Chevalier T, eds. Treatment modalities in lung cancer. Basel:
Karger, 1988; vol 41, 83-91
4 Payne DG, Feld R. Concurrent radiotherapy and chemotherapy in
lung cancer at the Princess Margaret Hospital. In: Arriagada
Basel: Karger, 1988; vol 41, 96-101
5 Kaasa S, Olsnes BT, Thorud E, Hast H. Reduced short-term
neuropsychological performance in patients with nonsmall-cell
lung cancer treated with cisplatin and etoposide. In: Arriagada
Basel: Karger, 1988; vol 41 226-31

Treatment of N2 Non-Small Cell Lung Cancer (NSCLC)
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SURGERY FOR NSCLC
WITH MEDIASTINAL ADENOPATHY

Complete resection is the treatment of choice for
NSCLC. Distant dissemination (M1) and local spread
with high likelihood of infraclinical distant metastases (pT4,
cN2, cN3) contraindicates surgery. Patients with incomplete
resection (marginal residual tumor or microscopic infiltra-
tion) do not survive over 2 years, even with 56 Gy postopera-
tive mediastinal irradiation. Optimal survival rates after
so-called complete resection (free margins, distant nodes
negative) range from 35% for pN1 to 27% for pN2 minimal-
disease (intranodal dissemination is ipsilateral nodes at only
1 level) to 18% for pN2 ipsilateral multi-level disease and to
less than 9% for pN2 bilateral disease. Prognosis is worse
for adenocarcinoma and poorly differentiated NSCLC.

The first site of recurrence is distant metastasis in ½ of
the patients with completely resected pN2 disease. Postopera-
tive mediastinal irradiation reduces the rate of local
recurrences (from 30% to 12%) without improvement of

survival rate.

For surgical decision-making and choice of adjuvant
therapies, the assessment of local spread of the tumor is
mandatory as the assessment of lack of distant metastasis.
Massive N2 disease is usually obvious on standard chest
x-ray examination. On the other hand, mediastinal nodes
over 10 mm in diameter on CT scans should be carefully
explored by preoperative mediastinoscopy in high risk
patients and/or to avoid unnecessary thoracotomy in N3 or
multi-level N2 disease, but also to avoid undue exclusion
from the benefit of surgery after a falsely positive CT scan.
Another approach is by extensive mediastinal exploration
at the time of thoracotomy with on-line frozen sections to
assess free margins. Whatever the policy adopted in
individual institutions may be, the final pathology report
should provide a clear-cut, detailed map of local extension of
the tumor (pT3T4) and lymph node dissemination (pN1, minimal
pN2, non-minimal pN2, pN3), and of free margins.

Postoperative adjuvant therapies are clearly needed if the
5-year survival rate is below 50% and if they may be
expected to delay the first relapse, decrease the number
of sites of recurrences and improve the survival rate. Medias-
tinal irradiation is thus only part of the optimal treatment.
Current trials investigate, after complete resection, the role
of irradiation in pN1 and minimal pN2 disease and the
possible role of radiation plus chemotherapy in non-minimal
pN2 disease. pN2 disease after complete resection also
deserves new trials to estimate the potential benefit of
systemic therapies.

Preoperative treatments are designed to reduce local
infiltration by the tumor (T3, superior sulcus tumor) and
improve resectability. There is no place for preoperative
irradiation in N2 disease. However, surgery after mediasti-
nal irradiation is feasible within 2-months after the end of
radiation, but may induce complications (healing delay,
bronchopleural fistula, infection, lung fibrosis).

The new approach of proadjuvant (neoadjuvant) chemo-
therapy should have, theoretically, the same effect on local
shrinkage of the tumor and, moreover, would select respon-
sive tumors for further chemotherapy after surgery, in order
to eradicate subclinical distant metastases.

Surgery after chemotherapy is feasible, but dissection
may be tedious, especially if performed more than 3 months
after the initial induction course.

RADIOThERAPY FOR INOPERABLE
NSCLC

The vast majority of patients with lung cancer of the
NSCLC varieties present with stage III disease that is
indeed unresectable. Chest radiotherapy, in selected pa-
ents, is beneficial in terms of local control, that can be
achieved in greater than 60% of the patients.

Curative radiation therapy for patients with regional
NSCLC is a controversial topic. While it is clear from most
major trials that only a small number of patients are cured
(approximately 5%), the occurrence of occasional long-term
cures cannot be casually dismissed in the absence of other
established alternatives for such patients.

Nevertheless, there is a high incidence of distant metas-
tases in patients with NSCLC treated with definitive radio-

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therapy (75-80%) and most patients die from disseminated disease.

**Chemotherapy in Inoperable NSCLC**

Chemotherapy is the logical therapeutic option in the case of neoplastic disease, such as NSCLC, which metastasizes early. Nevertheless, it has not been very helpful so far and, therefore, some authors have even questioned the value of routine chemotherapy in the management of NSCLC, stressing that clinical response does not translate into overall survival benefit and that chemotherapy-associated morbidity seriously impairs the quality of life of many patients. However, there are studies indicating that chemotherapy-induced response in NSCLC can lead to improved survival and probably the patients with a low tumor mass benefit the most.

Cisplatin-containing combinations have been extensively used in NSCLC patients during the past decade. The role of cisplatin itself is somewhat unclear; in our own early studies, the response rate of NSCLC to cisplatin (150 mg/m²) was in the range of 25%. More recently, our cooperative group (the EORTC Lung Cancer Working Party) completed a comparative study of cisplatin vs cisplatin plus etoposide; respectively, responses were seen in 14/70 (20%) and 19/68 (28%). In those patients with limited disease, the response rate was 4/28 (14%) with cisplatin and 10/27 (37%) with cisplatin plus etoposide.

Based on the present experience, it is probably fair to say that cisplatin plus etoposide is associated with a reproducible 30-40% objective response rate in NSCLC. Although symptomatic relief is not rare in responding patients, serious morbidity from chemotherapy may occur as well. Overall, the duration of the response is not very long (the median duration is approximately 6-8 months) and does influence only modestly the survival of responding patients (the median survival in responders is in the range of 12 months, while that of nonresponders is usually 4-5 months).

**"Neoadjuvant" Therapy for Treatment of NSCLC with N2 Disease**

Surgery, when possible, provides the highest likelihood of long-term survival in patients with non-small cell lung cancer. Unfortunately, surgery alone in patients with N2 disease provides very poor results. It therefore seems reasonable to try to make patients with limited but unresectable disease potentially resectable by giving them "neoadjuvant treatment" to shrink their tumor. This form of treatment can include combination chemotherapy, radiation therapy, biological response modifiers, or any possible combination of these treatments.

Such treatment at present is totally experimental and it is necessary to have very strict criteria for patients entered on trials attempting to test the hypothesis that this approach may be beneficial. Such patients should be medically fit for resection, willing to undergo thoracotomy, have stage IIIA disease, and have no contraindications to the specific neoadjuvant therapy being tested. Patients, of course, should not have other prior malignancies, and should have a performance status (ECOG) ≥2. They also should not have superior vena caval obstruction. Such patients should be thoroughly investigated to rule out evidence for metastatic disease using all available methods including history, physical examination, hematology, chemistry and appropriate scans. They must have biopsy proven N2 disease and not just x-ray film or CT evidence.

In most studies to date, patients have received 2 to 3 cycles of chemotherapy with or without thoracic radiotherapy and those who responded were then considered for surgery. Some studies stopped therapy at the time of thoracic radiotherapy, while others continued treatment with 3 to 4 additional courses of chemotherapy with or without radiotherapy. Patients who did not respond sufficiently for surgery to be considered were taken off study.

If chemotherapy is to be considered for this purpose, at least a 50% response rate in more advanced disease is required and the medication must be reasonably well tolerated by patients, as they may undergo surgery. The drugs used should not have major pulmonary toxicity or interact in a major way with radiotherapy.

Although many regimens have been considered, those that have been used most frequently for this purpose include cyclophosphamide, doxorubicin, (Adriamycin) and cisplatin (CAP), V/18 and cisplatin, vindesine and cisplatin plus or minus mitomycin-C (VCM), and 5FU and cisplatin. The 3-drug combination (VCM) at present seems to be among the most active, with up to 20% of patients found to be without evidence of tumor at the time of surgery. Initial data came from the group at Memorial Sloan-Kettering and have been confirmed in Toronto. More studies exploring this type of approach are necessary.

It may soon be appropriate to consider large randomized trials comparing neoadjuvant therapy to either postoperative radiation or chemotherapy alone in patients with N2 disease.

**Postoperative Radiation Therapy**

Today, there is no rigorous evidence that postoperative radiation therapy benefits patients' survival. However, the interpretation of the results of these studies is clouded by incomplete information concerning staging and failure to consider the influence of stage on performance status. The usual surgery performed in earlier studies was pneumonectomy, which may not be the treatment of choice. In addition, the details of radiotherapy in terms of equipment, treatment schedule and field size are highly variable in terms of technique and quality.

In a recent randomized study of 230 patients (Lung Cancer Study Group) with resected stage II or III epidermoid (squamous-cell) lung cancer between postoperative adjuvant radiotherapy or no adjuvant treatment, careful intraoperative staging had been performed in all patients. Before randomization, patients were stratified according to stage, weight loss, age and institution. Prognostic variables such as stage, weight loss, age nodal-disease status and tumor status, were equally distributed between the 2 groups. The mean time from randomization to analysis was 3.5 years among 210 eligible patients.

There was no evidence that radiotherapy improved survival, and although recurrence rates appeared to be somewhat reduced among patients assigned to radiotherapy, these
decreases were not statistically significant. However, radiotherapy did produce a striking and significant reduction in recurrences to the ipsilateral lung and mediastinum. Moreover, overall recurrence rates were reduced by radiotherapy in patients with N2 disease (p <0.05), although even this subgroup had no evidence of improved survival.

The conclusion is that radiotherapy can reduce local recurrences after resection, but that it does not increase survival rates. A prospectively randomized trial of radiation therapy, using state-of-the-art equipment and treatment planning techniques, in patients with resected N2 disease, is a critical need. However, the benefits of such modern radiotherapeutic techniques may be masked in this poor prognosis group because of the frequency of distant failure outside of the port. New staging technologies to accurately ascertain which patients have regionally advanced disease only might allow such a study to truly answer the question.

ADJUVANT CHEMOTHERAPY TO SURGERY IN NSCLC

Until now, there was no good evidence suggesting the benefit of adjuvant chemotherapy after surgical resection for NSCLC. Resected stage II and III patients have served as the major focus for these adjuvant trials, but the published results have been generally disappointing.

It is only recently that a reproducible response rate in the range of 30-40% has been obtained with chemotherapy in inoperable NSCLC. Adjuvant chemotherapy after surgical resection has been carried out by the Lung Cancer Group in stages II and III adenocarcinoma and large cell undifferentiated carcinoma. Patients were randomized after surgery and careful intraoperative staging to receive chemotherapy with CAP (48 patients), an immunotherapy with BCG and levamisole (46 patients). There was a significant prolongation in the disease-free survival among the patients who received adjuvant chemotherapy.

ADJUVANT IMMUNOTHERAPY TO SURGERY

Most studies using immunotherapy in NSCLC have failed to demonstrate any efficacy at the approach. BCG was the most employed immunostimulant after resection of the lung. All of the studies failed to demonstrate a significant increase in survival rates in patients with operable bronchogenic carcinoma when BCG immunotherapy was given. In all of these studies, the number of patients with N2 disease are very small. Other immunostimulating agents or drugs were studied and, once again, all these studies showed that no immunotherapy resulted in any significant improvement in survival.

Occasional responses have been claimed with adoptive immunotherapy using interleukin-2 and LAK cells in NSCLC; this approach, in spite of being a very demanding procedure, deserves further studies.

Radiotherapy in Non-small Cell Lung Cancer
An Overview

Maurice Tubiana, M.D.*

RT IN POTENTIALLY OPERABLE NSCLC

First, in NSCL, as in all other cancers, postoperative RT can have an impact on survival only in patients without occult metastases at the time of initial treatment and in whom residual tumor has been left by the surgeon. This subset of patients ought to be limited, because if the tumor is small, the surgeon will be able to resect it completely; if it is large and has spread along the lymphatic pathways, resection is difficult and there is a high likelihood of distant dissemination. The natural history of breast cancer is fairly well quantitated, and it was estimated that for breast cancer the subset of patients who can benefit from postoperative radiotherapy is not larger than approximately 20% of patients. This subset is probably smaller in patients with NSCL because postmortem examinations in patients who died shortly after an apparently satisfactory surgical resection of NSCL suggest that residual tumor is present in about one third and that occult metastases are already present at least half of these. Therefore, the maximum gain in survival which can be expected is about 15%. To demonstrate such a small increase in survival, a controlled clinical trial should include at least 650 patients. However, even this relatively large number is too small, because to identify the subset of patients in whom survival is increased, a proper stratification is mandatory at least by stage (TNM) and histology. Therefore, 1,200 patients is a good compromise both for the statisticians who wish to include a large number of patients to increase the reliability of the data and the clinicians whose intent is to shorten the duration of the trial. These considerations emphasize the fact that controlled trials which include only a few hundred patients cannot lead to significant results and can even be misleading. Trials with a small number of patients can contribute to the advancement of knowledge only if designed to be included in a meta-analysis; otherwise, they merely initiate discussions or controversies but fail to provide valid answers.

Amplified compared in a retrospective study the survival of 36 patients irradiated soon after surgery and 22 patients irradiated later for recurrent neoplasms. Contrary to expectations, there was no apparent advantage with early postoperative RT. However, it is difficult to draw any conclusion from this nonrandomized study performed on a small number of patients. In fact, the preliminary data of a randomized trial carried out by Alberti et al clearly conflict with these conclusions. They compared in a 3-arm trial immediate RT, CT + RT, and delayed RT. So far, the survival is higher in patients receiving immediate treatment (borderline significance).

One of the problems with RT studies is that the dose or the fractionation is often not optimal. Proper evaluation of the effectiveness of postoperative RT requires not only a large number of patients but also an adequate irradiation technique. The dose should be as high as 60 Gy and the

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