Role of Adjuvant Therapy in Resected Stage II/IIIA Non-Small-Cell Lung Cancer

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The role of adjuvant therapy following complete resection of node-positive (stage II/IIIA) non-small-cell lung cancer remains controversial. Five-year survival rates in pathologic stage II disease range from 30% to 50% and in resected stage IIIA disease from 10% to 30%. The majority of recurrences following surgery are distant metastases. This two-part review, which will conclude in the January 2002 issue, analyzes the role of adjuvant therapy in this setting, using an evidence-based approach and focusing primarily on randomized trials and meta-analyses. The key variables in evaluating these studies are elucidated, ranging from the extent of mediastinal, systemic, and "molecular" staging to the quality of the adjuvant treatments administered. Some of the potential flaws inherent in meta-analyses are reviewed. To date, there is no convincing evidence that any therapy consistently improves survival in the adjuvant setting. Postoperative radiotherapy has been associated with a significant improvement in local control, particularly in patients with pathologic N2 disease. Chemotherapy should be offered to patients in appropriate clinical trials, and active phase III trials are reviewed. Future strategies include novel chemotherapy, methods to reduce toxicity, the emerging role of neoadjuvant therapy, and the promise of new biologic agents. [ONCOLOGY 15:1549-1558, 2001]

For those who believe a role exists for adjuvant therapy following resection of stage II or IIIA non-small-cell lung cancer (NSCLC), the past few years have been disappointing. In 1998, the postoperative radiotherapy (PORT) meta-analysis published in the Lancet demonstrated a survival decrement with postoperative radiotherapy in patients with NSCLC. [1] The controversial results of this trial received widespread coverage in the media. In the Philadelphia area alone, headlines ranged from "Study Questions Radiation Therapy" in the Philadelphia Inquirer to the broad-based conclusion, "Radiation No Help in Lung Cancer," in the Philadelphia Daily News.

More recently, the Intergroup randomized trial (0115) published in the New England Journal of Medicine showed no survival advantage when adjuvant chemotherapy was added to radiotherapy. [2] Is it simply time to "give up" on adjuvant therapy in this setting? This two-part review, which will conclude in next month’s issue, evaluates the role of adjuvant therapy in completely resected (margin-negative) stage II/IIIA (node-positive) NSCLC, using an evidence-based approach and primarily focusing on randomized trials and meta-analyses.

Defining the Problem

Of all patients presenting with NSCLC, only about 30% are eligible for complete resections. [3] Mountain and others have shown that patients with pathologic stage I NSCLC (T1-2, N0) have 5-year survival rates ranging from 60% to 70%. [4-6] Patients with pathologic stage II (T1-2, N1; T3, N0) disease have lower 5-year survival rates of 30% to 50%, [7] and for those with resected stage IIIA (T1-3, N2; T3, N1) disease, 5-year survival rates range from 10% to 30%. [8, 9]

The majority of recurrences are distant metastases to bone, liver, or brain. Even in stage I NSCLC, Feld documented distant metastases as the first site of recurrence in 65% to 77% of patients. [10] Patients with resected stage II or IIIA tumors have a similar recurrence pattern, although with more locoregional recurrences. [11, 12] To decrease the incidence of recurrent disease following curative resections, a variety of adjuvant therapies, including radiation and/or chemotherapy, have been studied.

Key Variables

Surgical Staging
Detailed and consistent intraoperative surgical staging is essential for accurately assessing the efficacy of adjuvant therapy. In 1997, the tumor-node-metastasis (TNM) staging system was
modified (Table 1 and Table 2),[13] and stages I and II were divided into two subsets (IA: T1, N0 vs IB: T2, N0; IIA: T1, N1 vs IIB: T2, N1 or T3, N0). Any metastatic tumor deposits found in the ipsilateral lung (other than the primary tumor lobe) are now defined as M1 (rather than T4). The anatomic definitions of some of the intrathoracic lymph nodes were altered.[14] The minimum number of lymph node stations that should be resected or sampled during a right thoracotomy are levels 4, 7, and 10, and for a left thoracotomy, levels 5 or 6, and 7. It is unclear whether mediastinal lymph node sampling vs a complete lymphadenectomy affects survival. So far, only one randomized trial has compared mediastinal lymph node sampling with complete lymphadenectomy and found no difference in survival,[15] although this trial in 182 patients was underpowered to show a small improvement in survival. The American College of Surgeons Oncology Group (ACOSOG) has initiated a randomized trial of mediastinal lymph node sampling vs complete lymphadenectomy during pulmonary resection in patients with N0 or N1 (less than hilar) NSCLC (protocol Z0030). The accrual goal is 1,000 patients, and the primary end point is survival.

Patients with ipsilateral mediastinal lymph node involvement (N2) comprise a heterogeneous group of patients, with 5-year survival rates after surgery alone ranging from 6% to 35%.[16] Sawyer et al demonstrated that the number of N1 and N2 lymph nodes, as well as the number of N2 nodal stations involved are important prognostic variables.[17] In a recent analysis of over 700 patients who underwent surgical resection of N2 NSCLC, Andre et al detected four negative prognostic factors on multivariate analysis: clinical N2 status, involvement of multiple lymph nodes, pathologic T3/T4 stage, and no preoperative chemotherapy.[18]

Systemic Staging

Prior studies have demonstrated the value of positron-emission tomographic (PET) scanning in staging the mediastinum, as well as for systemic disease.[19] Van Tinteren et al [20] assessed the ability of PET to reduce futile thoracotomies in 188 clinically staged I to III NSCLC patients randomized (prior to mediastinoscopy or thoracotomy) to a conventional work-up vs conventional work-up plus PET. Thoracotomy was considered futile in benign disease, exploratory thoracotomy, pathologic stage IIIA (N2)/IIB/IV disease, or postoperative relapse within 12 months. After 1 year, there were 39 (41%) futile thoracotomies in the conventional work-up arm vs 19 (21%) in the conventional work-up plus PET arm—a relative reduction of 50%. Many of the studies to be reviewed span a period of more than 30 years. PET scans were unavailable at the beginning of that period, as were computed tomography (CT) scans of the chest or brain. The potential benefit of adjuvant therapy in the past may have been diluted by inadequate staging modalities.

Molecular Staging

A relative unknown in adjuvant therapy relates to underlying biologic or molecular genetic prognostic factors, which simply are not available for most patients. Molecular-clinical correlative studies in patients undergoing resection for NSCLC have identified various markers with differing prognostic significance, such as p53, K-ras, Bcl2, HER2, and Ki-67 among others.[21-23] These studies suggest that profiles of multiple markers may be necessary to obtain the greatest predictive value. Recently, Cox et al demonstrated the potential of such "molecular staging" in 168 patients with resected stage I-IIIA NSCLC.[24] Multivariate analysis identified independent poor prognostic factors, including high microvessel count (P = .002), matrix metalloproteinase (MMP)-9 (P = .009), a factor facilitating tumor invasion, nodal status (P = .01), and tumor grade (P = .05). The expression of both epidermal growth factor receptor (EGFR) and MMP-9 was associated with a poor prognosis (P = .0001). While prospective, well-designed, studies are necessary to confirm the value of potential markers, this type of "molecular fingerprinting" may pave the way for patients at high risk for recurrence to be candidates for molecular-based therapies targeting specific pathways.

Technical and Quality Variations

Many technical details of radiotherapy need to be evaluated, such as beam energy, volume of tissue irradiated, total dose, dose per fraction, overall treatment time, and timing of treatment in relation to surgery. Similarly, important issues must be considered regarding the administration of chemotherapy—the specific chemotherapy agents employed, their mechanisms of action, and potential interaction with radiotherapy and compliance with the planned regimen. The quality of each study itself must also be assessed.

Adjuvant Radiation

Unlike systemic therapy, the primary goal of radiotherapy is that of local control. Most radiation
oncologists consider a locoregional relapse rate of 15% high enough or more to warrant a recommendation for postoperative radiotherapy. The lack of a clear survival benefit does not necessarily negate the importance of enhancing local control. Locoregional failure in the mediastinum following surgery alone can have devastating quality-of-life consequences, leading to airway obstruction, hemoptysis, dysphagia, and/or chest pain. The potential benefit of postoperative radiotherapy in the enhancement of local control must be weighed against its side effects and possible complications. The main acute side effects include fatigue, skin irritation, and radiation esophagitis. Subacute and chronic complications primarily include radiation pneumonitis, lung fibrosis, and possible cardiac damage.

**Randomized Trials of Postoperative Radiotherapy**

Randomized trials of postoperative radiotherapy in NSCLC are summarized in Table 3.

**Lung Cancer Study Group Trial**

Perhaps the most well-known randomized trial in the United States is that of the Lung Cancer Study Group (LCSG) published in the *New England Journal of Medicine.*[25] In this study, 210 evaluable patients with completely resected stage II/IIIA squamous cell carcinoma received either radiotherapy (5,000 cGy at 180-200 cGy per fraction) or no further treatment. The majority of patients had pathologic N1 (pN1) disease, and 21% had pN2 disease. While there was no impact on survival, postoperative radiotherapy had "an undeniable effect on local recurrence."[25] Only 1% of first recurrences were local in the radiotherapy group, compared with 19% in the control group ($P < .001$). Based on subgroup analysis, the overall recurrence rate was significantly reduced with radiotherapy in pN2 patients ($P = .03$).

**MRC Lung Cancer Working Party Trial**

The Medical Research Council (MRC) Lung Cancer Working Party of the United Kingdom also conducted a randomized trial of the role of postoperative radiotherapy in patients with pathologically staged T1-2, N1-2, M0 NSCLC.[26] A mixture of histologies was permitted, and 37% had pN2 disease. Patients randomized to the radiotherapy arm received 4,000 cGy in 15 fractions (267 cGy per fraction). The spinal cord dose was limited to 3,500 cGy by the use of posterior lead blocks, a technique no longer considered standard because the radiation dose to the mediastinum under this block is reduced.

When "suspected" and "definite" local recurrences were analyzed together, there was no clear evidence that radiotherapy was beneficial. An analysis of the time to "definite" local recurrence did, however, show a significant advantage in the radiotherapy arm ($P = .04$). This discrepancy may reflect the difficulty in accurately defining the presence of a local failure, particularly in the context of evolving postradiotherapy fibrotic changes. Despite its limitations, this study essentially confirmed the local control benefit of postoperative radiotherapy reported by the LCSG. Another striking similarity is that in the pN2 subgroup (stratified from the start), 38 (70%) of the surgery-only patients had metastases, compared to 24 (46%) of those who also received radiotherapy ($P = .03$). As observed in the LCSG study, patients with pN2 disease were found to have a significant improvement in the overall recurrence rate with the use of a local-only modality.

**Austrian Trial**

The randomized trial by Mayer et al[27] was intentionally excluded from the PORT meta-analysis, presumably because randomization was performed intraoperatively based on frozen section information. While the policy of randomizing patients postoperatively (after the final pathologic review) appears preferable, the inclusion criteria of the PORT meta-analysis did not specify the timing of the randomization, and it is not clear that this study should have been excluded. Radiation was based on CT treatment planning, and standard fractionation was used, so the results may be more representative of modern radiotherapy treatment.

One flaw in this study (as in many of the other trials that were included in the PORT meta-analysis) is that patients with pathologic N0 disease were not excluded. Of note, there was no obvious imbalance of stage I patients in the radiotherapy arm (19%) vs the surgical arm (17%). As in the prior studies, postoperative radiotherapy was associated with a significant improvement in local control, with only 5 local failures (6%) vs 17 in the control group (24%). Moreover, the 5-year recurrence-free survival was almost twice as high in the radiotherapy group (27%) vs the control group (15.6%). The 5-year survival rates were 29.7% and 20.4%, respectively. Overall, toxicity from radiotherapy was minimal, and no serious late complications or toxicity-related deaths were encountered.[27]

**Chinese Trial**
In a large (N = 366), randomized trial from Beijing, China,[28] a critical flaw is that the results were analyzed only by the treatment delivered, rather than by intent to treat. No information regarding the surgical staging procedure is available. The patient characteristics appeared to favor the surgery-alone group significantly more patients were diagnosed with stage III vs stage II (ie, N2 vs N1) in the radiotherapy arm.

Radiotherapy was administered via a 6- or 8-MV photon beam, initially with opposed anterior-posterior fields to 4,000 cGy in 20 fractions. Oblique fields were then used to boost the midplane dose for an additional 2,000 cGy in 10 fractions. Once again, this study showed a significant reduction in thoracic relapse (including ipsilateral hilum, mediastinum, and primary site) with postoperative radiotherapy from 33% down to 13% (P < .01). The 5-year rates marginally (but not statistically) favored radiotherapy 43% vs 41% for survival and 43% vs 38% for disease-free survival. Patients with T3/4, N1, M0 tumors demonstrated a 20% improvement in overall survival (P = .09) and > 20% improvement in disease-free survival (P = .057).[28]

**French Study**

The largest randomized study to date (N = 728) was reported by Dautzenberg et al.[29] Unlike the other studies reviewed in Table 3, this one showed a dramatically inferior 5-year survival rate in the radiotherapy arm compared to the control arm (30% vs 43%, P = .002).

There are several possible explanations for this finding:

- Approximately 30% of patients had stage I (pN0) disease. These patients have a low risk of locoregional recurrence following surgery. Van Houtte et al previously demonstrated in a randomized trial that survival of patients with pN0 disease was inferior with postoperative radiotherapy compared to observation (24% vs 43% at 5 years).[30]
- There was no attempt to stratify patients by stage or nodal status. Rather, the results are combined for the entire group of patients, thus confounding the potential benefit of radiotherapy in those with positive nodes.
- All patients received a total radiation dose of 6,000 cGy. Each participating center, however, was allowed to use daily fraction sizes of either 200 or 250 cGy. Of note, the "noncancer-related deaths" were found to be related to the fractionation schema (16% to 18% in those who received 200 cGy/fraction or less vs 26% in those who received > 200 cGy/fraction). Both lung and cardiac toxicity have been associated with total radiation dose, as well as the dose per fraction.[31,32] The authors attempted to defend this practice by quoting the MRC study,[26] in which fraction sizes of 267 cGy were utilized. The key difference, however, was that the MRC study treated patients to a total dose of only 4,000 cGy, not 6,000 cGy.
- Intercurrent deaths unrelated to lung cancer varied significantly. The 5-year rate of intercurrent deaths, most from cardiorespiratory or infectious causes, was 8% in the control group and 31% in the radiotherapy group (P = .0001). In the words of the authors, "Any potential benefit from the use of adjuvant treatment may have been undetectable due to the fact that treatment appeared to result in a higher rate of cardiopulmonary toxicity."[29]
- An unknown variable relates to the radiation volume. According to the authors, "an additional dose of 2,000 cGy was delivered by lateral and/or oblique fields." Certainly, the use of lateral fields to 2,000 cGy (which approaches radiation lung tolerance), particularly in patients who have undergone a lung resection, could potentially be life-threatening. Figures 1 through 3 demonstrate the significant difference in the dose-volume histogram of the normal irradiated lung (Figure 1) between the use of lateral radiation fields (Figure 2) vs more traditional (eg, 30°) oblique fields (Figure 3) to protect the spinal cord.
- Variations in staging techniques, surgical resection, radiation techniques, and follow-up practices may have led to inconsistencies. While the study started with a "detailed" protocol collecting extensive information related to surgery, pathology, and radiotherapy, after the initial 189 patients, a "simplified protocol" was instituted to enhance accrual. The PORT meta-analysis[1] itself documents that the results from the "simplified protocol" showed a more detrimental and significant effect from the radiotherapy than the "detailed" protocol, which, by itself, did not show a significantly negative effect on survival or recurrence-free survival from radiation.

Despite these flaws, radiotherapy in this study[29] was still associated with a 22% decrease in the adjusted local recurrence risk (P = .09), although it was the only one of the randomized trials reviewed to demonstrate a survival decrement with radiotherapy. The other trials showed a
significant reduction in local recurrences with radiotherapy and some even suggested a benefit in
disease-free survival, especially in the pN2 subgroup.

PORT Meta-analysis
The PORT meta-analysis[1] obtained updated data on 2,128 patients from nine randomized trials
(published or unpublished). The results showed a significant adverse effect of postoperative
radiotherapy on survival (hazard ratio = 1.21). This was equivalent to a small but significant absolute
detriment of 7% (confidence interval = 3%-11%) at 2 years, reducing survival from 55% to 48%.

Subgroup Biases[] The problems noted above for the Dautzenberg trial[29] are even more applicable
to this meta-analysis. Indeed, the Dautzenberg trial made up approximately one-third of the patients
in the meta-analysis, and thus played a key role in determining its ultimate outcome.

A full 26% of the patients in this meta-analysis[1] had stage I (pN0) disease, a group for whom
postoperative radiotherapy is no longer offered in this country. The randomized trial that proved this
to be the case over 20 years ago[30] was included in this meta-analysis. Moreover, Lafitte et al[33]
subsequently published the results of a randomized trial for patients with T2, N0, M0 disease, to
determine if stage IB patients might, in fact, benefit from postoperative radiotherapy using more
modern techniques. This randomized trial (also included in the PORT meta-analysis) confirmed the
negative impact of postoperative radiotherapy in patients with stage IB disease, who also have a
relatively low incidence of locoregional failure.

A plot of the hazard ratio for survival shows that it is essentially these four trials (the two in stage I
patients and the two conducted by Dautzenberg) that bias the results against the radiotherapy arm.
The stage and nodal status subgroup analysis of the meta-analysis corroborated that the main group
to suffer a dramatic decrease in survival consisted of patients with stage I (or pN0) disease. For
patients with stage IIIA (or pN2) disease, the results actually slightly favored postoperative
radiotherapy.

Dose and Fractionation Variations[] There was wide heterogeneity in the doses and fractionation
schedules used in the trials included in the PORT radiotherapy meta-analysis.[1] The dose
fractionation schema in the meta-analysis ranged from a total of 3,000 cGy in 10 fractions (300 cGy
per fraction) to 6,000 cGy in 30 fractions. In his elegant commentary on the Lancet meta-analysis,
Dr. Munro demonstrated that the rate of adverse effects of radiotherapy in these randomized studies
appears to be directly related to the biologically equivalent dose.[34] This refutes the concluding
statement of the PORT meta-analysis that "although the meta-analysis was based on data from trials
that used different . . . doses and schedules carried out over a long period of time, there was no
evidence that the results were influenced by [radiation therapy] dose and therefore no indication
that any one of the individual schedules used was any less detrimental than the others." [1]

Equipment- and Technique-Related Problems[] Many have criticized the PORT meta-analysis because
seven of the nine randomized trials included patients treated with cobalt units. In a retrospective
study of postoperative radiotherapy for NSCLC, by Philips et al,[35] the 5-year survival for patients
treated on a cobalt unit was only 8%, compared with 30% for patients treated on a linear
accelerator. It appears, however, that the key difference in this study was the use of more accurate
CT scanning for treatment planning in the patients treated with the linear accelerator. Indeed, one of
the most precise applications of radiotherapy is the Gamma Knife, which has at its disposal 201
separate cobalt sources all pointing towards the same isocenter. It appears unlikely that the use of
coast radiation itself was the problem, but rather the less accurate treatment planning available in the
cobalt era that probably made the difference.

Drs. Marks and Prosnitz[36] point out that the detrimental effect of thoracic radiotherapy on survival
in the PORT meta-analysis[1] was not demonstrated in patients with stage IIIA (pN2) disease. They
hypothesize that the radiotherapy in higher-stage patients did improve lung cancer-specific survival.
This benefit, however, was likely offset by the detrimental effects of radiotherapy. Indeed, the rate of
treatment-related deaths was double in patients treated with radiotherapy (4% vs 2%). Moreover,
the rate of intercurrent deaths was 15% in the radiotherapy arm vs 9% with surgery alone, \( P =
.003.\) [1] Similarly, prior studies of postmastectomy radiotherapy had demonstrated an increased risk
of cardiac mortality that offset its potential benefit regarding cancer-specific survival.[37,38] With
more modern radiotherapy techniques, subsequent studies demonstrated that postmastectomy
radiotherapy does improve survival.[39,40]

Recent trials suggest that the potentially lethal effects of radiotherapy cited in the PORT
meta-analysis are rarely seen today with modern equipment and techniques. To more clearly define
the incidence of deaths from intercurrent disease, Lee et al[41] reviewed the records of 208
consecutive patients treated with postoperative radiotherapy at the University of Pennsylvania from 1981 to 1997. Radiotherapy was administered via linear accelerators with standard fractionation
Among the 18 intercurrent disease cases identified, only 3 were documented fatal radiation complications. The radiation therapy dose did not significantly affect the risk of intercurrent disease. The authors concluded that with the use of modern radiation therapy techniques, the rate of intercurrent disease is comparable to the expected death rate for age-matched noncancer patients.[41] Similarly, in the recently reported results of the randomized Intergroup trial (0115) comparing adjuvant radiation therapy to chemoradiation, the rates of treatment-related mortality were extremely low—1.2% in the radiation therapy arm and 1.6% in the chemoradiation arm.[2] General Criticisms of Meta-analysis: The validity of a meta-analysis rests on the assumption that the true treatment effect, if any, differs in magnitude, but not in direction, among different subgroups of patients.[42] Another criticism of meta-analyses is that they may include trials of different quality, combining reliable results with unreliable ones.[43] These criticisms certainly apply to the postoperative radiation therapy meta-analysis.[1]

LeLorier et al found that the outcomes of 12 large (> 1,000 patients) randomized trials were not predicted accurately 35% of the time by meta-analyses published previously on the same topic.[44] The authors suggested that simply summarizing all the information contained in several trials into "a single odds ratio may greatly oversimplify an extremely complex issue" and that "oversimplification may lead to inappropriate conclusions."[44]

Conclusions: The main message of the PORT meta-analysis[1] is this: Do not treat node-negative patients and do not use older radiation therapy techniques and fractionation schema that appear to be detrimental. The problem, however, is that some interpret the PORT meta-analysis to argue that postoperative radiation therapy should never be used. Perhaps the most important lesson to be relearned from the meta-analysis is that radiation therapy has the real potential to be harmful—even lethal—and must be administered with careful planning and attention to detail, including dose, fractionation, and volume. As indicated in my letter to the editor of the Philadelphia Inquirer, whereas in real estate, everything is "location, location, location," in radiotherapy, it is "technique, technique, technique." The editor appropriately entitled the letter, "Do some research before rejecting radiation."

Postoperative Chemotherapy

Early trials in the 1960s and 1970s examined the use of long-term alkylating agents, such as nitrogen mustard, cyclophosphamide (Cytoxan, Neosar), methotrexate, lomustine (CeeNu), hydroxyurea, and busulfan (Myleran) in patients with resected NSCLC.[45-49] None of these trials found an improvement in either disease-free or overall survival. Indeed, most of these agents have subsequently been shown to have minimal activity in NSCLC. The advent of cisplatin (Platinol)-based chemotherapy with activity in advanced NSCLC led to renewed interest in adjuvant chemotherapy in the 1980s.

Lung Cancer Study Group Trial

In a study conducted by the Lung Cancer Study Group (LCSG-772), patients with completely resected stage II/III adenocarcinoma or large-cell carcinoma of the lung were randomized to receive intrapleural bacillus Calmette-Guérin (BCG) plus levamisole (Ergamisol), 2.5 mg/kg orally daily × 3 days every other week for 18 months, vs six 1-month cycles of postoperative chemotherapy with CAP (cyclophosphamide, 400 mg/m²; doxorubicin [Adriamycin], 40 mg/m²; cisplatin, 40 mg/m²).[50] After complete resection, 141 patients were randomized, of whom 130 were evaluable. Approximately 45% had stage II disease, and 55% had stage III disease. Differences in disease outcome favored the CAP arm, which had a 7-month improvement in both median survival (15 vs 22 months) and disease-free interval. The majority of relapses (66%) occurred distantly, indicating the need for systemic therapy more effective than CAP. However, survival in the control arm was worse than expected, raising the question of a detrimental effect of levamisole.

Japanese Trials

In a study from Japan, 209 patients with completely resected stage IIIA NSCLC were randomized to either observation or three cycles of monthly vindesine (3 mg/m² on days 1 and 8) and cisplatin (80 mg/m² on day 1).[51] Of the 181 eligible patients, 119 had pN2 disease. The 5-year survival rates were 35% in the chemotherapy group and 41% in the control group. There was no difference in the pattern of the first site of recurrence (local vs systemic) between the two groups. This study failed to show any benefit for postoperative cisplatin and vindesine. An important caveat, however, is that only 41% of patients received all three planned chemotherapy cycles—a phenomenon that must be
considered in many of these studies. Indeed, a very similar randomized trial from Japan was recently reported, again showing no survival advantage to adjuvant chemotherapy with cisplatin plus vindesine in completely resected pathologic stage IIIA (pN2) NSCLC.[52] Several studies assessing the use of oral fluorouracil (5-FU) derivatives in the adjuvant setting have been conducted in Japan. Tegafur is an orally administered fluorouracil derivative that is converted in vivo to 5-FU. Degradation of the 5-FU is inhibited by the concomitant administration of uracil. Imaizumi et al randomized more than 300 patients to postoperative cisplatin, doxorubicin, and tegafur plus uracil (UFT) vs observation in completely resected stage I-III NSCLC.[53] Although the majority of patients had stage I disease (N = 118), 29 had stage II, and 78 had stage III disease. Chemotherapy in the treatment arm consisted of cisplatin (66 mg/m²) and doxorubicin (26 mg/m²) within 2 weeks of surgery, followed by oral UFT orally at a dose of 8 mg/kg daily for 6 months. Initially, the 5-year survival rate for surgery and chemotherapy vs surgery alone was not significant (62% vs 58%, respectively). Because a significant difference was observed between the two groups regarding pathologic lymph node involvement, the data were reanalyzed incorporating prognostic factors using the Cox proportional hazard model. While these results must be interpreted with caution, this reanalysis demonstrated a significant difference in overall and disease-free survival rates favoring the use of adjuvant chemotherapy (P = .044 and P = .036, respectively). This apparent advantage appeared to be limited to node-negative patients. In another trial from Japan, 323 patients with completely resected stage I-III NSCLC were randomly assigned to one of three treatment arms.[54] In the first arm, patients received cisplatin (50 mg/m²) and vindesine (2 to 3 mg/kg × 3) within 1 to 3 weeks of surgery, followed by oral UFT (400 mg/kg/d) for 1 year. In the second arm, patients received 1 year of daily oral UFT (400 mg/kg) only. The control group received no postoperative chemotherapy. Once again, the majority of patients (210) were stage I, 36 were stage II, and 62 were stage IIIA. Overall, UFT was well tolerated, and compliance with this agent was very good; 75% of the planned daily drug was actually received. Five-year survival rates were 61% for the cisplatin/vindesine/UFT group, 64% for the UFT-alone group, and 49% for the control group. On multivariate analysis, the hazards ratio for survival (vs control) was 0.64 in the cisplatin/vindesine/UFT group (P = .037) and 0.55 in the UFT group (P = .009). Based on these favorable results, the American College of Surgeons Oncology Group is planning to run a North American trial (ACOSOG Z0270) testing UFT and leucovorin vs placebo in the adjuvant setting in patients with early-stage NSCLC.

**NSCLC Cooperative Group Meta-analysis**

In 1995, the NSCLC Cooperative Group published a meta-analysis of 52 randomized chemotherapy trials conducted between 1965 and 1999.[55] Of these, 14 adjuvant trials were analyzed, containing 4,357 patients randomized to postoperative chemotherapy vs observation. Five trials used long-term alkylating agents (2,145 patients), mainly cyclophosphamide and nitrosourea; eight trials used cisplatin-based combination chemotherapy (1,394 patients). The intended dose of cisplatin in these studies ranged from 40 to 80 mg/m² per cycle and the total dose from 50 to 240 mg/m². An additional three trials used other drug regimens, all of which included tegafur or UFT. Some of these studies (containing more than one chemotherapy regimen) were counted twice.[55] The results showed that long-term alkylating agents were associated with a 15% increased risk of death (P = .005), which translated into an absolute detriment in survival of 5% at 5 years. In contrast, the cisplatin-containing regimen appeared beneficial, resulting in a 13% decrease in the risk of death, which translated into an absolute improvement in survival of 5% at 5 years. This improvement in survival approached, but did not reach, statistical significance (P = .08). The trials that contained "other" regimens were associated with a hazard ratio of 0.89 in favor of chemotherapy[although this was not statistically significant][which translated into a 4% improvement in survival at 5 years.

Overall, this meta-analysis suggested a small benefit with cisplatin-based chemotherapy regimens in the adjuvant setting over observation. The chemotherapy regimens included in this meta-analysis were extremely heterogeneous, but there was a concerted effort to separate out "older" regimens from "newer" regimens, rather than lumping them together. Indeed, if the alkylating agents had been combined with the cisplatin-based regimens, it is unlikely that any benefit to adjuvant chemotherapy would have been detected at all. The overall conclusions of this meta-analysis could have been quite different. Perhaps a similar strategy should have been applied to the PORT meta-analysis.

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