Combined Modality Therapy of Lung Cancer

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Abstract
Combined modality therapy for lung cancer was first demonstrated to be successful in limited-stage small cell lung cancer. Concurrent administration of chemotherapy with chest and elective brain irradiation appears to produce the best results, with cisplatin/etoposide as the core chemotherapy. Using such programs, 2-year survival in the 40% range and 5-year survivals in excess of 20% may be expected, based on the results of multiple studies. Attempts to improve on these results through the use of altered schemes of chest irradiation or the delivery of high-dose consolidation chemotherapy are ongoing but to date have not been shown to affect survival significantly. We remain at a plateau in the effectiveness of combined modality therapy for small cell lung cancer, with little evidence that it impacts survival in all in extensive-stage disease. The incorporation of new agents in combination chemotherapy regimens, more “specific” immunotherapy directed at tumor-associated antigens, and the potential adjunctive use of broad-spectrum neuropeptide antagonists offer promise for the future.

In non-small cell lung cancer, the sequential use of platinum-based chemotherapy and chest irradiation appears superior in survival to standard, daily fractionated radiation therapy used alone, with long-term survival increased from 5–10% to 15–20%. Concurrent administration of chemotherapy with cisplatin/etoposide and chest irradiation produces 2-year survival in the range of 30%, about twice that would be expected for radiation therapy alone, but has not been compared to it in the setting of a randomized trial.

Low-dose cisplatin on a daily basis has been combined as a “sensitizer” with chest irradiation, producing initial results that appeared encouraging. However, these have not been reproduced in subsequent, randomized trials.

Another approach to combined modalities has been to give chemotherapy or chemotherapy/radiation therapy as induction, followed by surgical resection, with or without subsequent additional treatment. Most patients (80–85%) can be resected, with encouraging survival at 2 and 3 years in the Southwest Oncology Group experience (37 and 26%, respectively). However, toxicity is greater, and such an approach is associated with an overall mortality risk in the range of 10%. A current intergroup study attempts to define the role of surgery in this setting.

The major recent development that is likely to influence the future of combined modality therapy for this disease is the advent of multiple new chemotherapeutic agents, such as the taxanes, gemcitabine, vinorelbine, and the topoisomerase-I inhibitors, which have activity in stage IV disease. The immediate challenge is how to combine these agents with platinum analogues, radiation, and surgery. Aiding this process may be the use of molecular biological “markers” that may predict the chance of success or failure with a given systemic agent. The next decade is likely to see substantial improvements in the outcome of treatment for patients with stages I–III non-small cell lung cancer, based on the systemic exploration of combined modalities.

SCLC
Sequential Approaches. When investigators began to use chemotherapy and RT together in the 1970s (1, 2), they chose the “sandwich” approach of chemotherapy → radiation therapy → chemotherapy, which had been pioneered with success in the treatment of pediatric cancers. Like these tumors, SCLC appeared to be “chemosensitive” as well as “radiosensitive.” The initial chemotherapy regimens involved agents that enhanced acute effects of RT on normal tissue via their systemic toxicities. Normal tissue damage could then be minimized by giving the modalities in sequence, rather than concurrently. This sequential combined approach appeared superior to RT used alone for patients with limited-stage disease but offered no apparent advantage over chemotherapy alone in extensive stage. In such programs for limited SCLC, the primary tumor was a common site of initial treatment failure. The reasons suggested were: inadequate field size; inadequate radiotherapy dose; and inherent tumor resistance. The SWOG addressed the issue of field size in a prospective, controlled trial (3). In that trial, patients with initial, partial response to combination chemotherapy were randomized to treatment with a large, “preinduction” field, which encompassed all of the tumor evident on X-ray before chemotherapy, or to the smaller “post-induction” treatment volume evident after chemotherapy. Although local failure was reduced by the use of the larger volume, there was no survival advantage. In fact, there were more 2-year disease-free

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1 The abbreviations used are: SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; RT, radiotherapy; SWOG, Southwest Oncology Group; CR, complete response; CALGB, Cancer and Leukemia Group B; NCI, National Cancer Institute; CAV, cyclophosphamide/doxorubicin/vincristine; PE, cisplatin/etoposide; PCI, prophylactic cranial irradiation; CNS, central nervous system; GM-CSF, granulocyte-macrophage colony-stimulating factor; CBP, cyclophosphamide/carmustine/cisplatin; PV, cisplatin/vinblastine; 5-FU, 5-fluorouracil; LCSG, Lung Cancer Study Group; RTOG, Radiation Therapy Oncology Group; RPSL, Rush-Presbyterian-St. Luke's.
survivors in the reduced-field group (17% versus 7%). Although a randomized trial of RT dose has not been conducted, a SWOG trial with an investigator’s option of 3000 cGy versus 4500 cGy total dose demonstrated better 2-year survival for the higher dose (4). The same conclusion was reached by Cox et al. (5) in a retrospective analysis. Using the sequential approach, four large randomized trials of chemotherapy alone versus combined modality treatment were reported in the 1980s. Three of these trials (3, 6, 7) found no advantage to RT plus chemotherapy over chemotherapy alone. Kies et al. (3) in the SWOG trial focused on patients who had achieved radiographic CR after induction chemotherapy; the failure to demonstrate an advantage in this favorable subgroup led our group to abandon the “sandwich” model. The fourth study, reported by Perry et al. (8) for the CALGB (8), demonstrated an advantage at 2 years for the sequential, combined modality approach versus chemotherapy alone (25% versus 15% at 2 years), but in that trial the “sequential” irradiation was delivered concurrently with the fourth cycle of chemotherapy. In addition, the local failure rate was still high in the combined modality arm (40%).

**Concurrent Approaches.** The NCI-Navy group and its predecessor at the NCI-VA pioneered the use of concurrent, combined modalities in limited SCLC. In their randomized trial of doxorubicin-based chemotherapy versus the same chemotherapy plus initial, concurrent RT (9), improved median survival was seen with the combined approach (15 months versus 11.6 months), and a reduced incidence of failure at the primary site was observed (13% versus 29% chest alone recurrence). There was, however, a clinically significant increase in myelosuppression, esophagitis, pulmonary dysfunction, and weight loss with the addition of RT. In a trial of the Southeastern Cancer Study Group, Johnson et al. (10) randomized patients to CAV versus CAV and RT, using a split-course regimen of RT (10). Median and 2-year survival rates favored the irradiated patients but were not statistically significantly different (14 months versus 13 months, 33% versus 24%, respectively). Again, the incidence of serious toxicities was higher in the combined modality group. A third randomized trial of initial concurrent chemotherapy with RT was that previously cited by CALGB (8), in which this approach was better than chemotherapy with cyclophosphamide, etoposide, and vincristine alone but slightly inferior to the concurrent, delayed approach (20% versus 25% at 2 years) for chemotherapy and RT. It should be noted that subsequent cycles of chemotherapy were markedly attenuated in the arm receiving initial chest RT, which may have impacted on the outcome.

The key to improved results with the concurrent model lay in the development of a chemotherapy program with minimal normal tissue interaction with RT. This involved the combination of PE. Cisplatin is an agent that produces no stomatitis or esophagitis at normal doses and little myelosuppression. Its dose-limiting toxicities of nephropathy and vomiting can be managed effectively by modern techniques of hydration and antiemetic therapy, with sensory neuropathy as a remaining serious side effect but one which is related to cumulative dose and can be largely avoided if the agent’s use is confined to the induction period. Used alone, cisplatin had modest activity in SCLC (11), but the PE combination was reported to produce CR rates of 50% or greater in limited disease (12), as well as having some non-cross-resistance with CAV and other “standard” regimens (13). Etoposide is a very active single-agent in SCLC (14), and at “standard” doses has myelosuppression as its only common major toxicity. Cisplatin has weak radiosensitizing properties (15, 16), but much less so than doxorubicin, and neither component of PE has been clinically implicated in “radiation recall” toxicity.

In a SWOG study, McCracken et al. (17) combined PE with vincristine and concurrent, initial RT to the chest at 180 cGy per fraction to a total dose of 4500 cGy (17). At the completion of combined modality induction, consolidation chemotherapy was administered with vincristine plus methotrexate/etoposide alternating with doxorubicin and cyclophosphamide. Among 154 patients in this group-wide Phase II trial, CR occurred in 56%, with a median survival of 18 months. The 5-year survival was 25%, in contrast to results in the 10% range in our previous experience with chemotherapy or chemotherapy → radiotherapy. This was followed by a randomized trial through NCI-Canada, reported by Murray et al. (18), in which two approaches to concurrent, combined chemoradiotherapy were tested: CAV/PE with “early” concurrent RT (first PE course); or CAV/PE with “delayed” concurrent RT (last PE course). The approach with “early” RT was superior with 5-year survival of 20% versus 11% (P = 0.008). Importantly, in this trial (as in SWOG), the early administration of chest RT did not compromise chemotherapy delivery; the dose intensity for each chemotherapy agent was nearly identical in the two arms.

Intrathoracic toxicity to normal organs was minimized by the use of concurrent PE and RT. In McCracken’s study, grade 3/4 esophagitis occurred in 4% and grade 3 pneumonitis in 1% versus respective incidences of 66 and 37% in the NCI-Navy trial with doxorubicin-containing therapy (9). Indeed, even with sequential use of CAV and RT, Livingston et al. (1) had observed respective incidences of 8 and 9%.

By the early 1990s, it was clear that concurrent, combined modality treatment of limited SCLC is superior to chemotherapy alone; that the intrathoracic toxicity of such treatment is reduced by coadministration of PE and RT, rather than earlier programs with more “interactive” drugs like doxorubicin and methotrexate; and that therapeutic efficacy is probably improved by early, concomitant administration of chest irradiation and chemotherapy.

**Improving Chest Radiotherapy.** An alternative approach to chest radiotherapy in the concurrent model was proposed by Turrisi et al. (19), based on the observation that some lines of SCLC, grown in cell culture, demonstrate markedly increased sensitivity to small individual doses of radiation (loss of the “shoulder” on the radiation cell-survival curve) compared to other epithelial cells grown in culture (20). Such a situation should favor the use of individual fractions less than 2 Gy, given at shorter intervals than 24 h, because the difference between tumor tissue with a smaller or absent shoulder and normal tissue with a greater ability to repair such damage should be amplified. In a pilot study from the University of Pennsylvania, 150 cGy twice daily to the chest were given in 30 fractions over 3 weeks to a total dose of 4500 cGy, combined with PE chemotherapy (19). To minimize esophagitis, oblique fields were used in weeks 2 and 3, using computerized tomography for treatment planning. Subsequently, alternating chemotherapy with CAV/PE for six cycles and brain RT were administered. The CR rate from this program was 87%, with 2-year disease-free survival in excess of 50%. This trial, and another

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encouraging pilot with similar design reported by Johnson et al. (21, 22) for the NCI-Navy group led to a prospective, randomized intergroup trial. In this study, such "hyperfractionated" chest RT was compared to standard, once-daily continuous fractionation, with initial concurrent PE induction chemotherapy. Preliminary analysis of this trial has been presented by Johnson et al. (23). Local control was improved by twice-daily RT, but the incidence of esophagitis greater than to equal to grade 3 was also significantly higher. No statistically significant difference in survival was seen, although more mature analysis may demonstrate an advantage for the twice-daily approach. What is clear from this very large study is that concurrent use of PE and chest radiotherapy will produce 2-year survivals in the 40% range quite reproducibly.

An even newer approach to optimization of chest radiotherapy in lung cancer involves three-dimensional, "conformal" treatment planning, which is made possible by modern techniques involving computerized tomography and exact simulation of target volume within the chest (24). Such treatment planning allows the delivery of unprecedented doses in the range of 70 Gy to the volume of interest, with a rapid falloff in the isodose plot such that surrounding normal structures do not receive substantially greater injury. Even with conformal therapy, however, the volume of normal tissue irradiated will depend on tumor size, and the tightness of margins will vary somewhat due to patient motion, breathing, and variation in the daily treatment setup. This is complex and labor intensive, and it remains to be seen whether conformal treatment planning will provide a practical advantage; no results have yet been reported in the combined modality setting.

**Elective PCI.** It was recognized early in the treatment of SCLC that the brain and CNS represent a common "pharmacological sanctuary," with resultant relapse at that site frequently identified. Following again the pediatric model of combined modality therapy as applied to acute lymphocytic leukemia, it became common practice to use PCI in an attempt to reduce the incidence of this devastating complication. It seems clear that PCI will reduce the likelihood of clinical relapse in the CNS, but it has little or no effect on the median survival in a disease where failure of control at other sites is the rule, nor does it affect the incidence of CNS metastases observed at autopsy (25, 26). Among 300 patients with SCLC who achieved CR, the cumulative risk of developing brain metastases was 19% for those not randomized to receive PCI versus 45% for those who received it (P < 10^{-6}), with an overall cumulative risk of "isolated" CNS relapse of 40% (27). The subgroup that may be particularly likely to benefit from PCI are those patients with limited disease who achieve a CR. All series reporting 5-year survivals of 20% or greater have made use of PCI, which suggests but does not prove this point. Follow-up on the NCI-Navy study reported recently by Johnson et al. (22), in which twice-daily chest RT was combined with PE induction, followed by CAV consolidation, makes a sobering point; although survival in this trial was 43% at 2 years, it had fallen to 19% at 5 years, and isolated CNS metastases caused more than 30% of the cancer deaths. About one-half of those with CNS relapse had received PCI.

It was also recognized early that the use of PCI may be associated with the development of serious, debilitating late neurotoxicity. The incidence of this complication varied greatly from one retrospective series to another (28–31). It does appear that the risk is a function of dose per fraction and is higher with the use of individual fractions in excess of 200 cGy. Our current practice in the SWOG is to use a total dose of 3000 cGy, delivered at 200 cGy per fraction, over 3 weeks. What has only been recognized relatively recently is that patients with SCLC have a higher incidence of definable abnormalities in CNS function at presentation than do other cancer patients (including those with lung cancer; Ref. 32). This may be related to the high incidence of paraneoplastic syndromes in this disease and to cross-reactivity of the neuroendocrine tumor antigendically with neural tissue. In the trial by Arriagada et al. (27), there were no significant differences in neuropsychological function or abnormalities detected on CT scan between those randomized to PCI and those who did not receive it.

**Improving Chemotherapy—Beyond PE.** In the SWOG, we attempted to reduce the hematological toxicity and morbidity of the PE/chest RT program by the concurrent use of a hematopoietic growth factor (GM-CSF). As reported by Bunn et al. (33), there was an unexpected and clinically significant increase in the frequency and duration of life-threatening thrombocytopenia in patients randomized to GM-CSF (P < 0.001). There were also significantly more toxic deaths (P < 0.01), more nonhematological toxicities, more days in hospital, a higher incidence of the need for i.v. antibiotics, and the need for more transfusions in the GM-CSF group. In retrospect, it is likely that the GM-CSF mobilized peripheral blood stem cells (34), and that megakaryocytic progenitors so mobilized were destroyed in increased numbers by the concurrently administered chest and brain radiotherapy. This trial effectively resulted in cessation of attempts to use growth factor support with concurrent chemo(radio)therapy programs. In turn, this has discouraged attempts at further dose escalation of chemotherapy during combined modality induction, because "standard" PE/RT produces a 24% incidence of grade 4 neutropenia, with 22% hospitalized for i.v. antibiotics (33). What has been attempted is high-dose consolidation chemotherapy after induction chemo(radio)therapy. In another SWOG trial, Goodman et al. (35) "intensified" patients with high-dose cyclophosphamide (150 mg/kg). Of 58 patients entered on the trial, only 21 (36%) actually received intensification, 7 of whom died of treatment-related causes. There was no evidence of an overall survival benefit. More recently, Elias et al. (36) from Dana-Farber Cancer Institute reported encouraging results from high-dose consolidation with the combination of CBP, combined with autologous bone marrow transplantation. Among 19 patients who underwent CBP consolidation in remission, 53% were 2-year disease-free survivors. When one analyzes the results of the recently completed SWOG trials with concurrent PE/RT induction, however, and includes only those patients who would have been eligible for the trial reported by Elias (CR or near CR, on study at 4 months), their survival appears to be comparable (51% 2-year disease-free). An intergroup Phase II pilot is now in progress, testing further the value of CBP with stem cell support after chemo(radio)-therapy induction.

In the past several years, a number of new drugs have been identified with single-agent activity in extensive SCLC, including the taxanes (37) (paclitaxel and docetaxel) and topoisomerase-

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ase-1 interactive drugs related to camptothecin (Refs. 38 and 39; CPT-11 and topotecan). None of these has yet been successfully incorporated into an induction program for limited SCLC.

**Other Approaches.** Although the initial trials with “nonspecific” immunotherapy using agents like BCG and thymosin were disappointing (40, 41), hope remains that it may be possible to exploit a mechanism of specific antitumor immunity. It is known that lines derived from SCLC are deficient in the expression of class I MHC-restricted antigens (42), and that IFNs can up-regulate their expression in model systems (43). Because class I antigen expression is necessary to T cell-specific cytotoxicity, it was hoped that the administration of IFN might augment the host response to SCLC. Clinical trials of α-IFN have been either equivocal or negative to date (44, 45). Recently, Grant et al. (46) reported preliminary results of another approach to the modification of biological response in which initial responders to combined modality induction were given “anti-idiotypic” therapy with BCG as an adjuvant plus a monoclonal antibody that mimics the GD3 ganglioside, a specific component of cells of neuroectodermal origin; four of six were alive at 3 years (three of six had extensive disease). A larger trial is necessary to confirm these findings.

A new approach involves “designer” molecules that can antagonize SCLC-related autocrine growth factors. A multiplicity of such factors, especially neuropeptides, have been identified in SCLC (47, 48). A group of “broad spectrum” neuropeptide antagonists, which are analogues of substance P, have been identified and are able to inhibit SCLC growth in preclinical systems induced by a wide range of neuropeptides (49). One such compound blocks the growth of a SCLC xenograft in nude mice (50).

**Summary.** Combined modality therapy with concurrent cisplatin-etoposide and chest radiotherapy has become the standard approach to the management of limited SCLC, with 2-year survival in the 40–45% range and 5-year survival in the 20–25% range. It is not yet clear whether twice daily RT will result in improved survival. PCI is widely applied today in the management of CR patients to prevent brain and CNS relapse and can reduce the incidence of this complication. It remains to be shown definitively that PCI improves survival, but this is suggested by its incorporation in the most successful programs. If it is to be used, PCI should be administered in low doses (≤200 cGy) per fraction, preferably separated in time from chemotherapy administration. We are presently at a plateau in the effectiveness of the combined modality approach to this disease, with little evidence that it impacts survival at all in extensive stage patients, who unfortunately constitute the majority. Promising approaches to move us off the plateau include conformal chest radiotherapy, high-dose consolidation chemotherapy; the incorporation of new agents in combination chemotherapy regimens; more “specific” immunotherapy; and the adjunctive use of broad-spectrum neuropeptide antagonists.

**NSCLC—Combined Modalities**

In 1990, Dillman et al. (51) for the CALGB reported a randomized trial of PV for two cycles followed by standard, continuous fractionated RT versus the same RT program without chemotherapy. Eligible patients had stage III disease by clinical or surgical staging, and patients were excluded with a history of weight loss more than 5%, positive supraclavicular nodes, or malignant pleural effusion. Induction chemotherapy with PV produced a 36% response rate, but overall response rates were not significantly different (56% versus 43%). However, survival was significantly improved in the combined arm (median of 14 months versus 10 months, P = 0.007) (Table 1). Dillman et al. (52) updated results of this study in 1996; the survival differences remained significant (24% versus 10% 3-year, 17% versus 6% 5-year survival). This study was closed earlier than initially planned, with a total of only 155 patients, and 14% of those entered were excluded from analysis as ineligible. These and other concerns prompted a second randomized trial, reported by Sause et al. (53). In that study, standard RT was compared to PV × 2 RT (“CALGB arm”) and to a third arm of hyperfractionated RT used alone (69.6 Gy at 1.2 Gy twice a day). Median survival was 11, 14, and 12 months for the three arms respectively, and 2-year survival was 19, 32, and 24% (P = 0.03). Staging in this trial was clinical, and patients with weight loss greater than 5% were again excluded. The power of this trial was greater (150 patients per arm). These two randomized studies led to the conclusion that combined modality therapy was superior to RT alone for the management of “good risk” patients with localized, but clinically inoperable NSCLC, and the use of PV × 2 RT remains an accepted community standard in such patients.

Other controlled trials of the sequential model have been less positive. Le Chevalier et al. (54) compared RT alone to the combination of vindesine, cyclophosphamide, cisplatin, and to a third arm of hyperfractionated RT used alone (69.6 Gy at 1.2 Gy twice a day). Median survival was 11, 14, and 12 months for the three arms respectively, and 2-year survival was 19, 32, and 24% (P = 0.03). Staging in this trial was clinical, and entry criteria were less rigid, and the difference in 2-year survival was of marginal significance (21% versus 14%, P = 0.08), although the incidence of distant metastasis was markedly reduced in the combined group. The response rate to initial chemotherapy was 27%. The SWOG compared RT alone to an alternating chemotherapy program followed by RT [5-FU, vincristine, mitomycin/cyclophosphamide, doxorubicin, and cisplatin], and found no evidence of a survival advantage for the combined modalities.5 Staging was clinical, and entry criteria were generous. Whether the positive results for the CALGB regimen are due to greater activity of PV than the other regimens or more strict selection criteria remain an open question, but these observations opened the door to rigorous exploration of combined modalities over the past decade.

A second sequential approach involves chemotherapy followed by surgery, rather than RT, as the local modality. Martini et al. (55) summarized the experience at Memorial Hospital with a regimen of mitomycin C, vindesine or vinblastine, and cisplatin given for two or three cycles to patients with clinical IIIA2 disease (ipsilateral involvement of mediastinal nodes). Among 136 treated, the response rate to induction chemotherapy was 77%; the resectability rate was 65%, with pathological CR in 14% of all patients (21% of those resected). Three- and 5-year survivals were 28 and 17%, respectively, with treatment-related deaths in 5%. Burkes et al. (56) reported a trial from Toronto in

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5 SWOG. unpublished data.
the confirmatory variable for this approach, using vinodesine as the Vinca alkaloid in all patients. These were surgically staged IIIAN2 by mediastinoscopic biopsy; all received two induction cycles; and two further cycles were attempted after resection. A high response rate of 64% was seen in these 39 patients, and 56% underwent resection. However, the pathological CR rate was lower (8%), and the incidence of treatment-related deaths was 18%, including two deaths from mitomycin pulmonary toxicity. The median survival was 19 months, with 26% alive at 3 years. Similar mortality risk (17%) was encountered in a trial of this regimen by the LCSG, with a median survival of only 12 months and 0 of 30 with pathological CR (57).

Sugarbaker et al. (58) for the CALGB deleted mitomycin C, giving two cycles of PV in 74 patients with surgically staged IIIAN2 disease prior to planned resection, with postoperative RT planned in those who underwent thoracotomy. Resection was accomplished in 73%, but no pathological CRs were observed. There was an 11% treatment-related death rate. The median survival was 15 months, with 3-year survival of 23%.

Two small, randomized trials compared surgery to chemotherapy followed by surgery in patients with stage III NSCLC who were deemed resectable. Rosell et al. (59) studied a total of 60 patients, one-half of whom received a preoperative regimen of mitomycin, ifosfamide, and cisplatin for three cycles (59). Response to chemotherapy was seen in 60%, with a higher frequency of aneuploidy and K-ras mutation in the surgery-alone group, which the authors attributed to chemotherapy effect. The median survivals were 26 months versus 8 months favoring the combined modality arm (P < 0.001). Roth et al. (60) also studied a total of 60 patients, randomized to surgery or to preoperative cyclophosphamide, etoposide, and cisplatin for six cycles. All patients were clinical stage IIIa, but postoperative staging revealed IIIb/IV disease in 41% of those randomized to surgery alone versus 11% of the combined modality group. The criteria used for resectability were very liberal, with N2 disease at two or more sites in 71% of the combined modality group and 48% of the surgery-alone group. Initial response to chemotherapy was seen in 35%. The median survival was 64 months for combined modality and 11 months for surgery alone (P < 0.008). These two trials are difficult to interpret. An optimist will attribute the lower incidence of K-ras mutation in one trial, and the lower incidence of IIIb/IV stage in the other, to chemotherapy effect in the combined modality group. A pessimist may conclude that there were chance imbalances in patient prognostic factors that influenced the outcome in these small studies. Favoring the latter point of view is the short median survival in the “control” group for both series.

**Concurrent Model.** One approach to concurrent use of modalities is to give the chemotherapy in low doses as a “radiosensitizer.” Schaeke-Koning et al. (61) compared a split course of 55 Gy alone to the same RT combined with weekly cisplatin (30 mg/m²) or daily cisplatin (6 mg/m²), with a significant survival advantage for combined treatment versus RT alone in the “daily” cisplatin group (3-year, 16% versus 2%); weekly cisplatin and RT yielded a 13% 3-year survival, but the difference was not significant (Table 2). Four randomized trials of this concept followed, reported by Trovo et al. (62), Ansari et al. (63), Soresi et al. (64), and Blanke et al. (65). All were negative, but none duplicated the exact design of the positive study. The Trovo trial used daily cisplatin at 6 mg/m² but gave only 45 Gy of continuous, fractionated RT. Ansari et al. (63) and Blanke et al. (65) gave a higher dose of cisplatin every 3 weeks (70 mg/m²), and Soresi et al. (64) gave a lower weekly dose (15 mg/m²). Hazuka et al. (66) for SWOG reported a Phase II trial of daily cisplatin at 5 mg/m² and concurrent, continuous RT to 61 Gy over 6.5 weeks, attempting to combine “optimal” cisplatin with “optimal” definitive RT by current North American standards (66). The median survival was 14 months, with 3-year survival approximating 15%. Although these results are similar to the “best arm” in the Schaeke-Koning study, they appear somewhat inferior to the 3-year survivals reported for other combined modality approaches.

A second approach is to attempt concurrent chemotherapy and RT at full doses of each. A study from SWOG (67) was performed in patients with surgically staged IIIb disease (ex-
The response rate was 55%. There was only one treatment-related death (2%), and serious toxicity was primarily transient grade 4 neutropenia (28%); only 10 patients (20%) had esophagitis of grade 3. The chemotherapy regimen in this trial was cisplatin on days 1 and 8 at 50 mg/m² and etoposide at 50 mg/m² per day, days 1 through 8, oral etoposide 37.5-50 mg twice a day on days 1-14, and concurrent chest RI at 180 cGy per fraction, starting on day 1 and given by continuous fractionation to 6100 cGy tumor dose. Others have attempted hyperfractionation of RT (twice-a-day dosing) and concurrent chemotherapy. Byhardt et al. (68) for RTOG gave vinblastine and cisplatin concurrent with such RT to 6960 cGy over 6 weeks. There were 42 patients, of whom 62% were clinically stage IIIb. The median survival was 12 months, with an estimated 2-year survival of 28%. The response rate was 57%. Toxicity of this program was significant, with a 45% incidence of grade 4 neutropenia and 7% with septic deaths while neutropenic. There was a 24% incidence of acute esophagitis ≥grade 3, and an additional four patients (9%) had delayed toxicities of grade ≥3. Lee et al. (69) for RTOG reported on a trial in 76 patients with cisplatin at 50 mg/m² on days 1 and 8, oral etoposide 37.5-50 mg twice a day on days 1-14, and hyperfractionated RT, daily and concurrent, to 6960 cGy (69). Response rate was 70%, median survival was 19 months, and 2-year survival was 35%. This program was also characterized by substantial toxicity: 57% grade 4 hematological, 53% grade ≥3 esophagitis, and 25% grade ≥3 pulmonary toxicity. There were three treatment-related deaths from nonhematological causes (4%), and although no septic deaths occurred, 17 (22%) were hospitalized for antibiotics while neutropenic. Building on the experience from these pilots, the current RTOG trial (9410) is a randomized comparison of the “control,” sequenced vinblastine-cisplatin → RT (“CALGB arm”) versus an arm identical to the study reported by Lee and a third arm of concurrent vinblastine-cisplatin and RT (24). The latter differs from the pilot reported by Byhardt in that the RT involves single daily “standard” fractionation, rather than twice-a-day dosing.

A third approach involves all three modalities, giving chemotherapy and RT as induction, followed by surgical resection when possible. Pioneering studies in this area came from the RPSL group in Chicago (70). They used cisplatin and 5-FU ± etoposide, given with concurrent RT during the week of chemotherapy (intermittent split course) to a total of four cycles, given every 2–3 weeks. Patients were clinically staged, and in these studies 21% had T3N0 disease, whereas only 6% were IIIb. Among 85 “good-risk” patients considered as medically operable, 71% were able to undergo resection; 27% of these had pathological CR; and there were 4% postoperative deaths. The median survival was 22 months, with a 3-year actuarial survival of 40%. Unfortunately, no breakdown of survival is available for this series with exclusion of the T3N0 patients; therefore, it is difficult to compare the RPSL series to others. Weiden et al. (71) for the LCSG reported another series in which cisplatin and 5-FU for two cycles were combined with concurrent RT. Important differences from the RPSL trials included: (a) surgical rather than clinical staging was mandated; (b) T3N0 disease was excluded; and (c) total doses of chemotherapy and RT were lower. This was primarily a study of IIIaN2 disease; only 13% had “minimal” IIIb at entry. Response was observed in 48 of 85 eligible patients to the induction treatment (56%), and 52% of all patients underwent resection. Pathological CR at surgery occurred in 8 (18% of those resected). There was a 7% postoperative mortality but no deaths and only one case of grade 4 toxicity due to induction chemo(radio)therapy. The median survival in this trial was 13 months, with 2-year survival of 22%.

The largest Phase II trial of this approach was a SWOG study (SWOG 8805) reported by Rusch et al. (72, 73) and Albain et al. (74). Like the LCSG trial, this study mandated surgical staging at the outset and excluded patients with T3N0 disease. Unlike the LCSG trial, it included 40% of all patients entered with IIIb disease (only those with IIIb and pleural effusion with positive cytology were excluded). There were 126 patients. Induction treatment involved cisplatin at 50 mg/m² on days 1 and 8 and etoposide at 50 mg/m² per day, days 1 through 5, repeated once at 4 weeks; and concurrent chest RT at 180

### Table 2 Concurrent model: Chemotherapy and RT in stage III NSCLC

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<tr>
<td>Ansari (63)</td>
<td>P + RT (I)</td>
<td>RT (std)</td>
<td>16</td>
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<tr>
<td>Soreni (64)</td>
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<td>24</td>
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<tr>
<td>Hazuka (66)</td>
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<td>55</td>
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<tr>
<td>Albain^a (67)</td>
<td>VeP + RT (H)</td>
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<td>57</td>
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<tr>
<td>Byhardt (68)</td>
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<td>PE + RT (H)</td>
<td>70</td>
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<td>Lee (69)</td>
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<td>PF ± E + RT (split) → S</td>
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<td>40</td>
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<td>PF + RT (split) → S</td>
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<td>Weiden (71)</td>
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<td>PE + RT (std) → S</td>
<td>59</td>
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<td>26</td>
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<tr>
<td>Albain (74)</td>
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<td>P + RT (D)</td>
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^a MST, median survival time; P, cisplatin; D, daily; S, surgery; I, intermittent (weekly); std, standard; VeP, vinblastine/cisplatin; H, hyperfractionated; PF, cisplatin/5-FU; E, etoposide.

^a IIIb only.

^a Included IIIaN2.
cGy/fraction to a total dose of 4500 cGy. Thoracotomy and resection were attempted 2–4 weeks later. The response rate to induction was 59%. Resection was possible in 85% of IIIaN2 and 80% of IIb patients. The median survival was 14 months, with 37% alive at 2 and 26% alive at 3 years. There was no survival difference between the IIIaN2 and IIb subgroups. In this series, the most powerful predictor of long-term survival was absence of tumor in the mediastinal nodes at the time of surgery; among 74 patients who had N2- or N3-positive disease initially, 39 (53%) had uninvolved nodes at resection, and these patients had a median survival of 30 months with 44% alive at 3 years. The remaining patients had a median survival of 10 months and 3-year survival of 18% \((P = 0.0005)\). In spite of the encouraging survival results, this program was also toxic, with 10% treatment-related deaths, the majority of which occurred in the postoperative period. An additional 13% of patients had reversible grade 4 toxicity primarily due to myelosuppression. Twenty-three of the 72 patients had grade \( \geq 3 \) esophagitis/mucositis (18%), but only 5 (4%) were grade 4. The results of this trial led to the current intergroup study (INT 0139) for IIIA\(n\) patients who are medically operable, which compares the “SWOG 8805” trimodality arm to the bimodality approach with more definitive chemotherapy and RT piloted in SWOG 9019. If brought to successful completion, this trial should define the role of surgical resection in the combined modality setting.

**Unanswered Questions—Future Directions.** Two important issues are presently under study in randomized trials. Does resection add to chemotherapy and RT (INT 0139), and is a simultaneous approach to chemotherapy and RT superior to a sequential one (RTOG 9410)? An important question that remains is that of how newer programs of chemotherapy can be successfully integrated into a combined modality approach. We now know that cisplatin/vinorelbine is superior to cisplatin alone (the previous SWOG standard) for patients with stage IV NSCLC (75). The combination of cisplatin/paclitaxel appears superior to cisplatin/etoposide (the previous ECOG standard; Ref. 76). In uncontrolled trials, the combination of carboplatin/paclitaxel appears to have activity equal or greater than those newer “standard” therapies (77, 78). Other families of drugs [topoisomerase I inhibitors like irinotecan (79, 80) and topotecan (81)] and antimitabolites like gemcitabine (82, 83) have encouraging activity in advanced NSCLC, both alone and combined with cisplatin. Docetaxel, a newer taxane compound, has shown exciting preliminary evidence of activity against “platinum-refractory” disease (84). Each of these newer agents may be expected to have normal tissue interactions with RT, and some may potentiate its antitumor effects to an even greater degree. The CALGB is currently involved in testing promising combinations of agents as induction therapy, followed by RT in the sequential mode, but there is a great need for additional Phase II studies in this area.

A question that can now begin to be posed is that of whether certain molecular biological characteristics can be used as “markers” to select the choice of systemic therapy. It has been suggested by Rusch et al. (85) that good pathological response to initial chemotherapy with DNA-damaging agents (cisplatin and mitomycin) is correlated with preservation of wild-type p53. This would fit the hypothesis that such agents are acting through p53-dependent signal transduction to produce apoptotic death (86). Because p53 mutation is extremely common in NSCLC (about 50% of cases), it is vital to determine whether these preliminary clinical correlations are reproducible. Agents in the antitubulin family, on the other hand, like the Vincus and taxanes, probably produce apoptotic death through p53-independent pathways, which may themselves be dependent on a series of events culminating in the activation of bax to produce apoptosis (87). Markers for the choice of such agents might be the presence of aberrant p53 expression and/or detectable bcl-2. It is well known that K-ras mutation is frequent in NSCLC, and its presence correlates with compromised prognosis in resectable patients (88) but may not predict for response to platinum-based chemotherapy (89). Another oncogene that is common in adenocarcinoma of the lung is her-2/neu (erb-B-2). This also imparts a worse prognosis when present in resectable patients (90). It is unknown what relevance its expression in lung cancer may have for chemotherapy response, but overexpression of her-2/neu in breast cancer may be associated with taxane responsiveness (91), and gemcitabine-containing regimens are differentially effective against NSCLC that overexpress her-2/neu (92). Hypotheses suggested by biomarker observations are potentially testable through well-designed clinical trials.

Finally, what of the role of combined modality therapy in earlier stage NSCLC? The initial, controlled trials of LCSG involved the regimen of cyclophosphamide/doxorubicin/cisplatin, now recognized to be an inferior program, yet results were suggestively positive (93, 94). An intergroup trial coordinated through ECOG has now been completed, comparing local treatment alone (surgery \( \rightarrow \) RT) versus local therapy and chemotherapy (surgery \( \rightarrow \) cisplatin/etoposide + RT). Results of this trial are not yet available. A successor study has just been activated, coordinated through NCI-Canada, which compares resection alone to resection followed by cisplatin/vinorelbine in resectable stage II and IIIa patients. Neoadjuvant chemotherapy alone (carboplatin/paclitaxel) is being explored in a Phase II trial by the Bimodality Lung Oncology Trial. Given the positive results for combined modality therapy in stage III inoperable patients, it may be reasonably anticipated that some or all of these trials in earlier stage, resectable disease will have favorable outcomes.

**References**


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Combined modality therapy of lung cancer.
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