The Role of Radiation, With or Without Chemotherapy, in the Management of NSCLC

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Lung cancer is the leading cause of cancer death in the United States. Surgery is the treatment of choice for early stage patients. Despite radical surgery, patients with early stage lung cancer remain at risk for recurrence. The

Introduction

Lung cancer is the leading cause of cancer death in the United States. In 1999, it is estimated that 171,600 people will be diagnosed with lung cancer, and 158,900 deaths will be attributed to this disease.[1] It is important first to distinguish small-cell lung cancer from non-small-cell cancer, because small-cell lung cancer is managed primarily with chemotherapy. Non-small-cell lung cancer, on the other hand, is managed primarily with local modalities, such as surgery in early stage disease, and radiation, with or without chemotherapy, in the locally advanced setting. Because treatment is based on the stage of disease at presentation, patients should be fully staged with a complete history, physical examination, computed tomography (CT) scan, and laboratory studies. Pathologic examinations by bronchoscopy, mediastinoscopy, or anterior mediastinotomy are important steps in determining resectability.[2] The American Joint Committee on Cancer and the Union Internationale Contre le Cancer have adopted the revised staging of lung cancer.[3] In the revised staging classification, T3, N0 has been moved from stage IIIA to stage IIB to reflect its better prognosis.[4]

Role of Surgery

Surgery is the treatment of choice for patients with early stage lung cancer (stages I and II). Some patients who are technically resectable are medically inoperable due to poor cardiac or pulmonary reserve; these patients should be treated with radiation alone with curative intent. Retrospective studies have shown that such patients can achieve a 5-year survival of 10% to 27%.[5,6] Controversy surrounds the need for patients with poor pulmonary function and small peripheral lesions to undergo elective mediastinal irradiation.[7] We currently use smaller target volumes to deliver higher doses to the primary tumor alone. Patients with early stage non-small-cell lung cancer (T1-T2, N0) who are resected generally do not require further adjuvant therapy. Randomized studies evaluating postoperative radiation in N0 patients have shown no benefit.[8] Randomized studies evaluating adjuvant chemotherapy in stage I patients have also not shown a consistent benefit. In a randomized study of 110 patients with T1-3, N0 non-small-cell lung cancer, the addition of adjuvant chemotherapy (cyclophosphamide, doxorubicin, and cisplatin) showed a slight benefit over surgery alone, with a 5-year survival of 67% vs 56% (P = .05). The randomization process, however, placed more patients with advanced disease in the surgery-only arm.[9] Despite radical surgery, patients with early stage non-small-cell lung cancer are at risk for both distant and local recurrence and may be considered for trials examining the role of adjuvant chemotherapy or biologic agents, but there is currently no established role for adjuvant therapy in this group. Even among patients with more advanced disease, surgery remains the treatment of choice for those who are resectable. The role of adjuvant therapy (radiation alone, chemotherapy alone, or radiation plus chemotherapy) in this group remains to be clearly defined. If combined, the best sequencing of these three modalities is still unclear.

Role of Radiation Alone
The role of adjuvant radiation alone was examined in a randomized study of 210 patients with stage II/III squamous cell carcinoma of the lung. Following surgery, patients received 50 Gy in 25 fractions or no further treatment. This study showed a significant decrease in local recurrence (3% vs 41%, P < .05) in node-positive patients but no difference in overall survival.[10] This lack of benefit may have been due to the fact that more than two thirds of first failures were systemic, not local, and therefore would not be expected to be changed by adding radiation. It is hard to extrapolate these data to the treatment of the average non-small-cell lung cancer patient, because all patients on this study had squamous cell histology and all were intraoperatively staged. Moreover, given the high incidence of distant metastasis, it seems logical that concurrent chemotherapy would be required to see a survival benefit. We are awaiting the final results of the recently closed intergroup trial, which randomized patients with resectable stage II/IIIA non-small-cell lung cancer to postoperative radiation alone or radiation combined with cisplatin and etoposide. Preliminary analysis does not show a statistically significant survival advantage for chemoradiotherapy over radiation alone.[11] Locally advanced lung cancer is disease that is too extensive for surgical resection, yet without any evidence of distant metastasis. Previously, these patients were treated with radiation alone. In an early study by the Radiation Therapy Oncology Group (RTOG), patients were randomized to 40-Gy split-course radiation, or 40-, 50-, or 60-Gy continuous-course radiation. Patients who received 60 Gy had a higher response rate, better local control, and improved 3-year survival.[12] This study provided the basis for our current standard of 60 Gy.

**Radiation Plus Chemotherapy**

Although radiation alone was previously considered the standard of care for unresectable non-small-cell lung cancer, several randomized studies[13-18] and meta-analyses[19-21] have provided the rationale for the current American Society of Clinical Oncology (ASCO) recommendations for combined-modality therapy using radiation with chemotherapy for patients with good performance status who have locally advanced disease.[22] The optimal sequencing of these modalities, however, remains to be determined. Chemotherapy, with or without radiation, may be used preoperatively (neoadjuvant) as a means of shrinking marginally resectable disease, postoperatively to decrease the risk of local and distant recurrence, or as primary therapy for unresectable disease. N2 disease can be divided into that which (1) is not visible by preoperative CT scans and found only at the time of mediastinoscopy or pathologic evaluation of resected specimens, (2) has multiple levels of nodal involvement easily seen on preoperative staging studies, or (3) has bulky mediastinal nodes. N2 disease not visible by preoperative evaluation is best suited for postoperative radiation, with or without chemotherapy, whereas nodal disease easily seen by preoperative staging evaluation is best treated with neoadjuvant, combined-modality therapy followed by surgery, when possible. Bulky mediastinal disease may be best suited for primary therapy with chemotherapy and radiation.

**Neoadjuvant Combined-Modality Therapy**

There have been several phase II studies suggesting the value of neoadjuvant therapy. Early randomized studies have established that radiation alone as neoadjuvant therapy is inadequate.[23] Radiation can be added to neoadjuvant chemotherapy either concurrently or sequentially. Advantages to concurrent chemotherapy and radiation include the potential for synergy between the two modalities. Sequential treatment, on the other hand, may be better tolerated, and both modalities can be given to their fullest extent. Southwest Oncology Group (SWOG) 8805 was a phase II trial that enrolled 126 patients to receive induction chemotherapy with two cycles of cisplatin and etoposide and concurrent radiation to 45 Gy, followed by resection if response occurred or disease stabilized. Objective response to induction therapy occurred in 59% of patients; 29% had stable disease. The 3-year survival rate was 26%.[24] Encouraging phase II studies led to the development of phase III studies examining the role of neoadjuvant chemotherapy (with or without radiation) in patients with potentially resectable non-small-cell lung cancer. Three randomized studies, summarized in Table 1, showed significant improvement in survival and distant recurrence favoring the induction chemotherapy arm.[25-27] In patients with unresectable non-small-cell lung cancer, radiation alone was previously considered the standard of care. Unfortunately, older series examining the role of radiation have not always found a survival advantage. In a multi-institutional trial randomizing patients with unresectable non-small-cell lung cancer to chemotherapy alone (vinodesine 3 mg/m²/week), standard radiation (60 Gy), or radiation and vinodesine, the median survival and overall survival were comparable in all three
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These poor results with radiation alone have led to the development of combined-modality treatments using chemotherapy and radiation with more effective systemic therapy, as well as agents that have the potential for radiosensitization. Randomized studies evaluating sequential chemotherapy and radiation in patients with unresectable non–small-cell lung cancer are summarized in Table 2. Cancer and Leukemia Group B (CALGB) 8433 randomized unresectable stage III patients to radiation alone or two cycles of cisplatin/vinblastine followed by radiation. The radiation consisted of 60 Gy in 2-Gy fractions. The response rate for the combined-modality arm was 56%, vs 43% for patients receiving radiation alone. The combined-modality arm had a significantly improved median survival (13.8 vs 9.7 months, \( P = .0066 \)) over radiation alone.[13] The long-term follow-up shows that 5-year survival remains superior for the combined-modality arm (17% vs 6%).[14] Although more toxicities were anticipated in the combined-modality arm, the incidence of esophagitis and pneumonitis was approximately the same in both arms. Severe infections, however, occurred more frequently in patients receiving combined-modality therapy (7% vs 3%).

A second randomized study of sequential chemotherapy and radiation, RTOG 8808/Eastern Cooperative Oncology Group (ECOG) 4588, also showed an improvement in median survival (13.8 vs 11.4 months, \( P = .03 \)) for combined-modality therapy over either standard fractionation radiation alone or hyperfractionated radiation alone. The radiation in the standard fractionation arm consisted of 60 Gy (2-Gy fractions, 5 days/week) over 6 weeks. The hyperfractionated regimen was 69.6 Gy (1.2 Gy/fraction, twice daily) over 4 weeks. The combined-modality arm received the same radiation as the standard fractionation arm but treatment was preceded by induction chemotherapy, consisting of cisplatin (100 mg/m²) on days 1 and 29 and 5 mg/m² vinblastine every week for 5 weeks. Radiation began on day 50. The 1-year survival was statistically better for the combined-modality arm (60%, \( P = .03 \)) over radiation alone given as standard fractionation (46%) or hyperfractionation (51%). The median survival was also improved on the combined-modality arm (13.8 months) over both arms receiving radiation alone.[15] In the 5-year update of this study, the 5-year survival remains significantly improved for induction chemotherapy followed by radiation (8%, \( P = .04 \)) over standard fractionation radiation (5%) or hyperfractionated radiation (6%).[29] The third large randomized study of sequential chemotherapy and radiation also showed an advantage to induction chemotherapy prior to radiation. The radiation was 65 Gy, and the induction chemotherapy included vindesine, cyclophosphamide, cisplatin, and lomustine. The 2-year survival was significantly improved on the combined-modality arm (21% vs 14%, \( P = .08 \)). There was also a significant improvement in the rate of distant metastases in the patients receiving chemotherapy.[16]

In locally advanced lung cancer, as in the neoadjuvant setting, concurrent chemotherapy and radiation has the added advantage of providing synergy between the two treatment modalities. Unfortunately, one can also anticipate an increase in toxicities. Table 3 summarizes randomized studies of concurrent chemotherapy and radiation for locally advanced non–small-cell lung cancer. The European Organization for Research and Treatment of Cancer (EORTC) trial evaluating cisplatin and radiation with weekly low-dose cisplatin (30 mg/m²/week) or radiotherapy with daily very-low-dose cisplatin (6 mg/m²/day) showed a significant improvement in 2-year survival (\( P = .009 \)) with daily low-dose cisplatin (26%) over radiation alone (13%). Patterns of failure showed that this was primarily due to an improvement in local control in patients who received combined-modality therapy.[17] A second randomized study examined the value of concurrent chemotherapy (carboplatin, etoposide) and hyperfractionated radiation to hyperfractionated radiation alone. The median survival was improved with combined-modality therapy (22 mo vs 14 mo, \( P = .021 \)). Interestingly, the two groups experienced similar incidence of acute and late high-grade toxicity.[18] Despite some controversy, several meta-analyses[20-21] have confirmed the value of chemotherapy plus radiation over radiation alone. In one meta-analysis using data from published reports, there was a 30% reduction in mortality at 2 years (odds ratio = .70) with platinum-based chemotherapy, compared to an 18% reduction in mortality at 2 years (odds ratio = .82) for non–platinum-based chemotherapy and radiation.[21] A separate meta-analysis using individual patient data from 52 randomized clinical studies showed an absolute survival benefit of 4% at 2 years with platinum-based chemotherapy over radiation alone.[19] These results have prompted ASCO, as well as the Ontario Lung Cancer Disease Site Group, to recommend combined-modality therapy as standard of care for good performance patients with locally advanced non–small-cell lung cancer.[22,30] Palliative radiation alone can be used for patients who cannot tolerate this aggressive approach.
A meta-analysis using data from 14 randomized trials and 2,589 patients found that the addition of chemotherapy to radiation reduced the risk of death at 2 years (relative risk 0.87, confidence interval 0.81 to 0.94). This corresponded to a mean gain in life expectancy of 2 months.[20] Although there is a small benefit with the addition of chemotherapy to radiation, this must be balanced against the increased toxicity of combined-modality treatment. Therefore, the use of combined-modality therapy remains under investigation for locally advanced non-small-cell lung cancer.

A retrospective analysis using data on 461 patients from five completed RTOG trials found that the overall response rate was significantly worse in patients who had received sequential chemotherapy and radiation over those who had received concurrent chemotherapy plus either standard or hyperfractionated radiation. The 3-year survival was better in the concurrent chemotherapy and hyperfractionated radiation arm compared to either sequential or concurrent chemotherapy with standard radiation. Nonhematologic toxicities were significantly worse in the concurrent chemotherapy with hyperfractionated radiation arm compared to either sequential or concurrent chemotherapy with standard radiation (Table 4).[31] A single study, reported thus far only in abstract form, has directly compared sequential to concurrent chemotherapy plus radiation and found concurrent therapy to be superior in terms of overall response rate (84% vs 66%, P < .05) and median survival (16.5 vs 13.3 months, P = .05, log-rank).[32] However, the optimal sequencing of radiation with chemotherapy for locally advanced non-small-cell lung cancer is still under investigation. The recently closed trial, RTOG 9410, which is summarized in Table 5, should answer some of these questions.[33]

**Newer Chemotherapy Agents Plus Radiation**

In addition to sequencing, the ideal chemotherapeutic agent to combine with radiation remains under investigation. Several newer chemotherapy agents are currently being combined with radiation in an attempt to improve both systemic and local control. Paclitaxel and carboplatin are two of these new agents that have shown not only activity as single agents in the treatment of non-small-cell lung cancer but are potent radiosensitizers.[34,35] Several other agents are currently being evaluated in the treatment of non-small-cell lung cancer, including gemcitabine, topoisomerase inhibitors (eg, topotecan), and vinorelbine.

**Paclitaxel**

Paclitaxel is derived from the bark of the Pacific yew tree, and is a potent chemotherapeutic agent in several cancers, including non-small-cell lung cancer,[36] that acts by interfering with the mitotic spindle function.[37] In addition to its direct cytotoxic effect, paclitaxel has been found to potentiate the effects of radiation in both in vitro and in vivo studies.[38] The exact mechanism of this interaction is unclear, but several have been postulated.

Paclitaxel arrests cells in the G2/M phase of the cell cycle. Flow cytometric analysis of HL-60 cells treated for 1 hour with paclitaxel resulted in 70% of cells being blocked in the G2/M phase.[34] This has long been established as the most sensitive phase of the cell cycle. A correlation has been found between the degree of G2/M block and the degree of radiosensitization among various cell lines in vitro. Preventing G2/M block with cycloheximide also stops paclitaxel's radiosensitizing ability.[39] Cell lines vary in the accumulation of G2/M cells and, therefore, their sensitivity to paclitaxel radiosensitization.[40]

A second mechanism of radiosensitization is that paclitaxel makes tumor cells more sensitive to radiation-induced apoptosis. In studies of mice bearing mammary tumors, paclitaxel enhanced radiation killing by a factor of 1.2 to 2.5. The greatest enhancement was not at times of greatest mitotic arrest, but 1 day after paclitaxel treatment, suggesting another mechanism of action. The efficacy of radiation-induced apoptosis in paclitaxel-treated tumors varies with the percentage of cells in mitosis. Radiation given 1 hour after paclitaxel administration was not as effective as radiation given 9 to 24 hours later, when many more cells are undergoing mitosis. A third radiosensitization mechanism is that paclitaxel results in reoxygenation of hypoxic tumor cells. Following paclitaxel administration, almost one third of the tumor cells undergo mitotic arrest, and most of these cells die. The remaining cells then regrow and a greater percentage are oxygenated. It has been well established that oxygen makes tumor cells 2 to 3 times more sensitive to radiation compared with hypoxic cells.[41] Direct measurements of tumor PO2 showed a median value in untreated tumors of 6.2 mmHg, which increased with time to 31.2 mmHg at 48 hours after paclitaxel administration.[42]

Numerous phase I studies have explored a variety of dosages and schedules for the delivery of...
radiation with paclitaxel, including continuous infusion and daily, weekly, and every-3-week cycles. The ideal dose and schedule is still under investigation. It is also not yet clear that the maximum tolerated dose is necessarily the most effective or whether sequential or concurrent treatment is superior.

An initial phase I trial evaluating paclitaxel with radiation used paclitaxel at a starting dose of 10 mg/m² as a 3-hour infusion. Doses were escalated by 10 mg/m² in successive cohorts of three patients. The radiation was administered in 2-Gy fractions to the primary and regional lymph nodes to a dose of 40 Gy, followed by a boost of 20 Gy to the tumor. Twenty-seven patients were treated, and the principal dose-limiting toxicity was esophagitis. At paclitaxel 70 mg/m²/week, one patient and two patients developed grade 3 and grade 4 esophagitis, respectively. At 60 mg/m²/week, one of six patients developed grade 3 esophagitis, and three of seven developed grade 2 esophagitis.[43] Other phase I studies currently in progress or reported are summarized in Table 6.[43-45] Various schedules, including continuous infusion, and daily, weekly, twice-weekly, and every-3-week administration have been tried.

On the basis of these phase I studies, phase II studies of paclitaxel and radiation have been performed. One of the earliest evaluated paclitaxel 60 mg/m² administered intravenously over 3 hours every week for 6 weeks during radiation. Radiation consisted of a total dose of 40 Gy (2 Gy/fraction) to the tumor and regional nodes, and an additional 20 Gy (2 Gy/fraction) to the boost volume, for a total dose of 60 Gy. The original volume consisted of the tumor, mediastinum, and the ipsilateral hilum with a 2-cm margin. The boost volume consisted of the tumor with a 2-cm margin. Twenty-nine of the 33 patients entered on study were evaluable for response. Overall, esophagitis was the most common grade 3 or 4 toxicity, occurring in 38% of patients. This usually occurred in the last 2 weeks of treatment. One patient died of non-neutropenic pneumonia, one patient had asymptomatic bilateral pneumonitis, and two patients developed shortness of breath, hypoxia, and interstitial infiltrates, which improved on corticosteroids. The median survival was 20 months, with a 2-year survival of 33%. The overall response rate of 86% was encouraging.[46]

**Platinum-Containing Compounds**

Other drugs with single-agent cytotoxic activity in many tumors and potent radiosensitization abilities are cisplatin and its many derivatives, including carboplatin. In vitro studies of Chinese hamster cells in culture have shown that cisplatin and its derivatives can produce enhancement ratios of 2 or greater and are more effective in hypoxic than oxygenated cells.[47] The mechanism of action for platinum-induced radiosensitization involves the inhibition of recovery from radiation-induced DNA damage. A second mechanism also involves reoxygenation. These compounds generate free radicals and thereby cause oxidation of hypoxic cells.[35]

Paclitaxel and carboplatin have been shown in phase II studies to be effective in the treatment of advanced non–small-cell lung cancer.[48-50] Both in vitro and in vivo data are available suggesting synergy between these agents and radiation; therefore, both drugs have been evaluated singularly and in combination in phase I and II studies in the treatment of locally advanced non–small-cell lung cancer. When used in combination without radiation, response rates of 27% to 62% have been reported.[48,49] The known radiosensitizing potential of each drug independently has also led to their study in combination with radiation in the treatment of locally advanced disease.

Phase II studies of paclitaxel and carboplatin with concurrent radiation have evaluated a variety of doses and schedules for both agents. Some of these are outlined in Table 7.[51-53] We have used paclitaxel 50 mg/m² (1-hour infusion) and carboplatin (area under the concentration-time curve of 2 [AUC in mg/mL • min]) weekly for 7 weeks plus radiation to a total dose of 66 Gy, followed by paclitaxel 200 mg/m² and carboplatin (AUC of 6) every 3 weeks for two cycles. The overall response rate to this regimen was 76%, with a 2-year survival of 38%. The major toxicity was esophagitis, with grade 3 or 4 toxicity occurring in 46% of patients. The onset of esophagitis was during the last few weeks of combination therapy, and patients had complete resolution of symptoms approximately 2 weeks following completion of therapy. Other significant toxicities included neutropenia (37%) and anemia (14%).[53]

**Other Agents**

The improvements in median survival with radiation and chemotherapy combinations have been modest at best. Many new agents are currently under evaluation alone or in combination. Some have also been shown to be potent radiosensitizers and will surely be used in combination with radiation. These include irinotecan (CPT-11), topotecan, and gemcitabine. In a phase II study, 146 patients received gemcitabine 1,000 mg/m²/week or cisplatin 100 mg/m² plus etoposide 100 mg/m² on days 1, 2, and 3. The single-agent activity of gemcitabine was equal to the more standard cisplatin/etoposide combination but with significantly less hematologic toxicity. Nausea and vomiting
were much more common in patients receiving cisplatin/etoposide (29%) than in those receiving gemcitabine (11%).[54]

A recently completed phase III study of cisplatin with or without gemcitabine has shown that the combination is better than cisplatin alone in terms of response, time to progression, and median survival.[55] Gemcitabine has been shown in vitro and in vivo to enhance radiation cell kill. The strongest radio-enhancement occurs when it precedes radiation by 24 to 72 hours.[56] Clinical trials are now in progress investigating gemcitabine plus radiation.

Although topotecan, a topoisomerase I inhibitor, has shown only modest activity as a single agent in the treatment of non-small-cell lung cancer, it is extremely well tolerated, with myelosuppression of short duration being its most common dose-limiting toxicity.[57] In vitro studies examining the effect of topotecan on radiation-induced cytotoxicity show that radiosensitization is related to the level of topoisomerase I in the individual cell line.[58]

Vinorelbine is a semisynthetic vinca alkaloid that is a potent inhibitor of mitotic microtubule polymerization. Four hundred thirty-two patients with advanced non-small-cell lung cancer were randomized to vinorelbine and cisplatin or cisplatin alone. The combination of vinorelbine plus cisplatin was superior in terms of 1-year survival (36% vs 20%), median survival (8 vs 6 months, P = .0018), and response rate (26% vs 12%, P = .0002). In vitro studies with non-small-cell lung cancer cell lines show that vinorelbine can potentiate the effects of radiation and that this potentiation is cell-cycle dependent, with maximal effect being when cells are in the G2 phase of the cell cycle.[59]

**Summary**

Although multimodality therapy using radiation, chemotherapy, and surgery has resulted in modest gains in the treatment of non-small-cell lung cancer, there is much that remains to be done. In the earliest stages of disease, surgery alone is curative. The large majority of patients, however, are diagnosed with more advanced stages of disease. Even for those with locally advanced disease that can be resected, the role for adjuvant therapy remains to be clearly defined. For the locally advanced setting, chemotherapy with radiation has been established as more effective than either modality alone. As the optimal chemotherapy is still not determined, future studies will continue to explore novel agents that are active in lung cancer and can also function as potential radiosensitizers, including the taxanes, platinum analogs, topoisomerase inhibitors, vinorelbine, and gemcitabine.

**References:**


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