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*Advances in radiation
plus other modalities
are improving results in
stage III non-small
cell lung cancer.*

Innovative Treatment Strategies in Locally Advanced and/or Unresectable Non-Small Cell Lung Cancer

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Background: While small improvements in outcome have occurred for patients with locally advanced non-small cell lung cancer (NSCLC), 5-year survival results remain low, ranging from 5% to 20%. Distant metastases and local-regional progression remain significant patterns of failure.

Methods: Trials investigating innovative treatment strategies for patients with locally advanced and/or unresectable NSCLC are reviewed, including altered radiation fractionation schema, conformal 3-dimensional radiotherapy, and combined chemoradiotherapy regimens.

Results: Whereas hyperfractionated radiation therapy (HFRT) alone does not appear to be beneficial, combined HFRT and chemotherapy appears promising in several trials. Patients treated with accelerated RT compared with standard RT have an improved survival. As higher radiation doses appear to enhance local tumor control, strategies involving 3-dimensional conformal radiotherapy merit further investigation. RT plus chemotherapy is superior to RT alone, albeit with greater toxicity. Amifostine is currently being investigated as a radioprotector. The optimal chemotherapy agents and their integration with radiotherapy are the subject of randomized trials.

Conclusions: Ongoing investigations are warranted to combat both local-regional and systemic failures for patients with locally advanced NSCLC. Treatment strategies need to consider not only the traditional endpoints of survival and local control, but also quality of life.

Introduction

Lung cancer is far and away the leading cause of cancer mortality in the United States for both men and women. The number of deaths secondary to lung cancer exceeds the combined total deaths from the second (colon), third (breast), and fourth (prostate)

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leading causes of cancer deaths combined.¹ Non-small cell lung cancer (NSCLC) comprises the vast majority (75% to 80%) of all lung cancers, with approximately 40% of patients presenting with locally advanced and/or unresectable disease. This group typically includes those with bulky stage IIIA and IIIB disease, excluding malignant pleural effusions.

Up until only a decade ago, the standard nonoperative management for this group of patients was conventional external beam thoracic radiotherapy (RT) alone — 60 Gy over 6 weeks, administered once per day. While this dose of radiation was shown in a randomized trial by the Radiation Therapy Oncology Group (RTOG trial 73-01)² to enhance short-term (3-year) survival compared to lower doses, the 5-year survival was disappointingly low (5%). In RTOG 73-01, the local control rate at 3 years appeared reasonable at approximately 70% for patients treated with 60 Gy. Yet, in a more recent study employing even higher radiation doses (up to 70 Gy), Hazuka et al³ reported local tumor progression as the first site of failure in 50% of patients. Part of this discrepancy in local control rates may reflect the difficulty in defining local failure; it is challenging to distinguish radiographically between fibrosis and local progression. While most studies have used clinical and radiographic criteria to define local control, Le Chevalier et al⁴ also employed serial bronchoscopic biopsies. They reported that less than 20% of patients achieved a “histologically” confirmed local control whether they received RT alone (65 Gy) or sequential chemotherapy and RT. Although nests of histologically viable cells may not necessarily translate into local progression, this study suggests that clinically and radiographically determined local control rates are substantially overestimated when strict criteria for local control are applied.

While local therapy will have no influence on survival if cells resistant to chemotherapy have escaped from the primary site, local control is still a prerequisite for cure. Indeed, failure pattern analyses in NSCLC demonstrate that both locally persistent (or recurrent) disease and distant metastases are significant problems.⁵ Even in small cell lung cancer (SCLC), in which the rate of distant metastases is higher than that in NSCLC, the addition of local therapy (thoracic radiation) to chemotherapy resulted in improved survival.⁶ A recent randomized study in SCLC demonstrates that the very type of local therapy employed (hyperfractionated vs standard radiation) can have a dramatic impact on survival.⁷ This article reviews several innovative treatment strategies to improve outcome in locally advanced NSCLC, with a particular focus on the “local issues.” These strategies include altered radiation fractionation schemes, radiation dose escalation via 3-dimensional conformal RT, and combined chemoradiotherapy regimens.

Altered Fractionation Schema

Conceptually, two distinct altered fractionation strategies can be utilized in the hope of improving local control or survival. Hyperfractionation involves smaller than conventional RT doses (eg, 1 to 1.2 Gy) administered multiple times daily (typically 2 to 3 times) to achieve a higher cumulative dose over the course of therapy. Radiobiologically, hyperfractionation yields differential sparing of late-reacting normal tissue compared with acute reacting malignant tissues.⁸ By contrast, with accelerated (hyperfractionated) RT, a more conventional radiation fraction size is utilized (eg, 1.5 to 2 Gy), but as multiple fractions are administered daily, the overall treatment time is significantly shorter. Unlike hyperfractionated radiotherapy (HFRT), the aim of accelerated RT is to reduce the tumor cell repopulation in rapidly proliferating neoplasms by shortening the overall treatment time. Indeed, tumor cell kinetic studies of human NSCLC cell lines have demonstrated short potential doubling times.⁹

Hyperfractionation

The RTOG trial 83-11¹⁰ was a multi-institutional, prospective, dose-seeking randomized phase II study of hyperfractionation in patients with NSCLC. Patients were randomized to receive total doses of 62 Gy, 64.8 Gy, 69.6 Gy, 74.4 Gy or 79.2 Gy in fractions of 1.2 Gy, administered twice daily. Among the 248 patients with favorable prognostic factors (ie, Karnofsky performance status of 70 or higher and weight loss of less than 5%), there was a survival benefit for the tumor dose level of 69.6 Gy compared with lower doses.

The 69.6 Gy arm of RTOG 83-11 was tested in a subsequent 3-arm phase III trial in patients with locally advanced NSCLC (RTOG 88-08/Eastern Cooperative Oncology Group [ECOG] 4588).¹¹ This study involved 490 patients who were randomized to standard RT (2 Gy once daily to 60 Gy for 6 weeks) vs HFRT (1.2 Gy twice daily to 69.6 Gy for 6 weeks) vs induction vinblastine plus cisplatin followed by standard RT. In the preliminary report, the median survival for the chemoradiotherapy arm (13.8 months) was found to be statistically significantly superior to the HFRT arm (12.3 months) or the standard RT arm (11.4 months). Based on these preliminary results, the chemoradiotherapy arm was widely viewed as the new standard against which future strategies should be compared. With longer follow-up, however, the curves for the chemoradiotherapy and hyperfractionation arms began to overlap, with 3-year survivals of 13% vs 14% and 5-year survivals of 8% vs 6%, respectively.¹² Overall, HFRT alone does not appear to be a beneficial strategy. However, several studies have demonstrated promising results

with a combination of HFRT and chemotherapy, as reviewed in the chemoradiation section.

Accelerated RT

A randomized trial of 563 patients compared accelerated RT with standard RT (66 Gy) in a strategy termed CHART — continuous hyperfractionated accelerated RT.¹³ CHART, designed to counteract tumor cell repopulation, involves 1.5 Gy administered 3 times per day for 12 consecutive days, to a total dose of 54 Gy. Patients treated with CHART had a significant improvement in 2-year survival (29%) vs those treated with standard RT (20%, $P=0.04$). While the rate of severe dysphagia was higher during the first 3 months in the CHART arm (19% vs 3%), this mostly occurred after completion of RT. A more “user-friendly” modification of this schema is now being developed in which patients (and physicians) are given the weekend off, nicknamed “CHART-WEL” (CHART weekend less).¹⁴ Using a novel accelerated radiation regimen with a concurrent boost technique to a total dose of 73.6 Gy, King et al¹⁵ reported a median survival in 49 patients of 15.3 months. Among 18 patients who underwent serial bronchoscopic evaluations, they documented an impressive “histologic” local control rate of 71% at 2 years. The ability to integrate chemotherapy with such intensive accelerated RT regimens is currently under investigation.

Radiation Dose Escalation/Conformal RT

Several studies have shown a relationship between higher radiation doses and improved local tumor control. In RTOG 73-01, patients treated with the highest dose (60 Gy) had an intrathoracic failure rate of 33% at 3 years compared with 42% of those treated with 50 Gy and 52% of those treated with 40 Gy in a continuous course.¹⁶ Patients treated with 50 to 60 Gy who manifested local tumor control had a 3-year survival of 22% compared with 10% if tumor control was not achieved ($P=0.05$).¹⁷ Similarly, Hazuka et al³ demonstrated a dose response relationship for local progression-free survival and survival for the stage III subgroup (favoring patients receiving doses of 67.6 Gy or higher compared to those who received a lower dose, $P=0.018$).

Three-Dimensional Conformal RT

Three-dimensional (3-D) conformal RT is external beam RT in which the prescribed dose volume (ie, treatment volume) is made to conform closely to the target volume, thereby facilitating dose escalation.

High-resolution computed tomography scans are used to acquire precise anatomical data from which a computerized 3-D image of the patient's normal structures and the tumor are constructed. The optimal radiation beam parameters and orientation can then be selected by comparing plans employing either multiple coplanar or non-coplanar fields. This approach enables dose escalation to the target volume by reducing the radiation exposure of normal tissues.

Radiation dose escalation can be achieved only by tailoring the treatment volume. Trials employing conformal RT typically do not attempt to treat the classic RT volumes, which encompass the regional lymph nodes. The long-term implications of this strategy are not yet known. In RTOG 73-01, approximately 8% of patients relapsed at a previously uninvolved supraclavicular region at 3 years if this region had not been treated, while 2% of patients relapsed if the region was treated by more than 45 Gy.¹⁸ Improved outcome was similarly reported when the tumor-negative contralateral hilar lymph nodes were treated according to protocol (ie, 1-cm margin) than for those treated with major variations ($P=0.017$). However, more recent studies have questioned the need to treat the traditional, larger thoracic RT volumes. When comparing large-volume treatment (ie, inclusion of the uninvolved contralateral hilar and supraclavicular lymph nodes) vs small-volume treatment (exclusion of these elective nodal sites), Hazuka et al³ found no difference in the local progression-free survival. Similarly, Robinow et al¹⁹ reported no failures in more than 100 patients in whom the radiographically uninvolved contralateral hilum was purposely not irradiated. These more recent trials may reflect more accurate tumor volume definition and targeting.

Investigators at the University of Michigan recently updated their experience with dose escalation using 3-D conformal RT in a phase I trial.²⁰ Doses were escalated based on the effective volume (V_{eff}) of both normal lungs irradiated and the risk of radiation pneumonitis (RP). Of 56 evaluable patients, grade 2 RP has occurred in 5 patients and grade 3 RP in only 1 patient. Currently, for a V_{eff} up to 12%, the level of dose escalation is 102.9 Gy. So far, no cases of isolated failures in clinically uninvolved nodal region (purposely not irradiated) have been found.²⁰ RTOG also has an ongoing study evaluating dose escalation using 3-D conformal RT (to the gross tumor volume only) in patients with inoperable NSCLC (RTOG 93-11). The dose escalation is stratified by risk groups and the percentage of total lung volume receiving more than 20 Gy. Future studies are being developed to integrate chemotherapy with maximally tolerated doses of 3-D conformal RT.

Combined Chemoradiotherapy Regimens

Of at least 11 large published randomized trials comparing RT alone to RT and chemotherapy, six studies have demonstrated superiority of combined treatment.^{11,21-25} It is important to note that most of these trials limited eligibility to patients with a favorable prognosis (eg, Karnofsky score of 70 or higher and maximum weight loss of 5%). In the Cancer and Leukemia Group B (CALGB) trial 84-33,²¹ patients were randomized to two cycles of induction chemotherapy (vinblastine and cisplatin) prior to RT vs RT alone. In addition to a significant improvement in the median survival time from 9.6 months to 13.7 months, a recent update²⁶ corroborated the 5-year survival benefit of 17% vs 7% and the 7-year survival benefit of 13% vs 6%, favoring the chemoradiotherapy arm ($P=0.01$). As previously discussed, RTOG 88-08 replicated CALGB 84-33, randomizing patients to RT alone (60 Gy) or to induction chemotherapy with cisplatin plus vinblastine followed by standard RT. A third randomized arm was also included: HFRT to a total dose of 69.6 Gy, which in phase II studies appeared promising. This study confirmed a statistically significant improvement in median survival for the induction chemotherapy arm (13.7 months) compared with RT alone (11.6 months), with HFRT demonstrating intermediate results.¹¹ Another trial, the French Multicenter Trial CEBI 138,²² used a "sandwich" regimen of induction and post-RT chemotherapy (vindesine, lomustine, cisplatin, and cyclophosphamide). In this study, a 2-year survival advantage of 20% vs 12% ($P=0.02$) favored the combined modality arm.

Rather than using induction chemotherapy, the trial by the European Organization Research in the Treatment of Cancer (EORTC 08844)²³ compared RT alone to RT plus concomitant (daily or weekly) cisplatin chemotherapy. This study demonstrated a significant survival advantage for low-dose daily cisplatin/RT compared with RT alone (3-year survival rates of 16% vs 2%, respectively). The weekly cisplatin/RT arm was intermediate (3-year survival of 13%). A study by Jeremic et al²⁴ randomized patients among three arms: HFRT alone (1.2 Gy twice daily to a total dose of 64.8 Gy) or two combinations of HFRT and carboplatin plus etoposide (administered weekly or every other week). Median survival times were 8 months, 18 months, and 13 months, respectively, and 3-year survivals were 6.6%, 23% and 16%, respectively ($P=0.027$). Similarly, in another phase III study by Jeremic et al,²⁵ the combination of HFRT and low-dose daily carboplatin plus VP-16 was superior to HFRT alone to 69.6 Gy (median survivals of 22 vs 14 months and 4-year survivals of 23% vs 9%, respectively, $P=.021$). While there have been nega-

tive trials with combined modality therapy compared to RT alone, several meta-analyses have demonstrated a small, but statistically significant, improvement in survival for the combination regimens.²⁷⁻²⁹

A close analysis of these positive randomized trials favoring chemoradiation over radiation alone suggests a difference in the patterns of failure that relates to the method used to combine chemotherapy with thoracic RT. In the three trials employing induction chemotherapy (RTOG 88-08,¹¹ CALGB 84-33,²¹ CEBI 138²²), the improvement in survival rates over RT alone appear to be linked to a decrease in detectable distant metastases. In the CEBI 138 study,²² there was a reduction in the distant metastasis rate from 65% to 45% with the addition of chemotherapy ($P<0.001$). Similarly, in RTOG 88-08,³⁰ the pattern of first failure showed that patients on the chemotherapy plus RT arm had significantly fewer distant metastases (other than brain) than patients on the RT alone arm ($P=0.04$). These differences were most marked in patients with squamous cell histology ($P=0.0015$). By contrast, in the three studies employing concurrent chemoradiation,²³⁻²⁵ the survival advantage was associated with an improvement in local-regional control. In the EORTC study,²³ which employed low-dose daily cisplatin and concomitant thoracic RT, survival without local recurrence at 2 years was 30% for the chemoradiotherapy groups vs 19% for the RT only group. Similarly, in the context of HFRT, concurrent chemotherapy improved local control rather than the rate of distant metastases. Jeremic et al²⁵ found that patients receiving HFRT and daily concurrent chemotherapy had a significant improvement in local recurrence-free survival (42% vs 19% at 4 years, $P=.015$) but not in distant metastasis-free survival ($P=.33$). One explanation is that while the use of high-dose induction chemotherapy combats systemic disease, the simultaneous delivery of low-dose chemotherapy (cisplatin or carboplatin) with RT might be necessary to yield improvement in local tumor control. Such a construct fits well with the prior observations that cisplatin-based chemotherapy can act as a radiosensitizer.³¹

Review of these positive randomized trials suggests several other important observations. In the trials involving concurrent chemotherapy and RT, it appears that, while not statistically significant, the optimal regimens integrated chemotherapy more often with the RT. For example, in the EORTC trial,²³ the use of low-dose daily cisplatin with RT appears to be superior to weekly concurrently cisplatin, in which the same cumulative doses of cisplatin were administered with RT (2-year survival rates of 26% vs 19%). Similarly, in the first randomized trial by Jeremic et al,²⁴ the best arm was weekly chemotherapy plus HFRT compared with chemotherapy administered every other week (3-year

survivals of 23% vs 16%). Indeed, in the subsequent randomized study by Jeremic et al,²⁵ low-dose daily chemotherapy (carboplatin plus VP-16) with HFRT led to an impressive median survival of 22 months and a 4-year survival rate of 23%. The optimal method of combining chemotherapy with thoracic RT needs to be further explored.

Another observation is that, except for the CALGB 84-33 trial, long-term results with sequential chemotherapy and RT appear disappointing. RTOG 88-08¹² (using the same regimen as the CALGB 84-33 trial) demonstrated a 5-year survival of only 8% for the induction chemotherapy/RT arm (vs 5% for the RT alone). In the French CEBI 138 trial,³² the 5-year survival rate was only 6% for the RT/chemotherapy arm (vs 3% for RT alone). These studies suggest that while the addition of sequential chemotherapy to RT enhances short-term survival by delaying distant failure, this strategy does not appear to dramatically alter the long-term results. By contrast, the 4-year survival in the patients treated with HFRT and low-dose carboplatin plus VP-16 was 23%.²⁴ In a phase II trial in which patients were treated with HFRT (69.6 Gy) with concurrent low-dose daily chemotherapy (carboplatin/VP-16) and high-dose chemotherapy on the weekends, Jeremic et al³³ reported a median survival of 25 months and a 5-year survival rate of 29%.

A recent phase III study reported, for the first time, an advantage of concurrent vs sequential chemoradiation. Furuse and colleagues³⁴ from Osaka, Japan, evaluated mitomycin, vindesine, and cisplatin (MVP) — either concurrent with or prior to thoracic radiation (RT) — in unresectable stage III NSCLC. In the sequential arm, after completion of MVP, RT was administered to a total dose of 56 Gy. In the concurrent arm, split-course RT 2 Gy/fraction for 14 days was followed by a 10-day rest, then additional RT (another 28 Gy) was administered. The overall response rate was superior for concurrent therapy (84% vs 66.4%) with a commensurate improvement in median survival (16.5 vs 13.3 months, respectively) and in the 3-year survival rates (27% vs 12.5%, respectively). Furuse et al³⁵ have recently reported their 5-year results, which continue to show a significant survival benefit for the concurrent arm of 15.8% vs 8.9% in the sequential arm. By contrast, in another randomized trial (in locally advanced NSCLC), CALGB/ECOG³⁶ found no benefit to adding weekly carboplatin (100 mg/m² per week) concurrently with thoracic RT when preceded by induction chemotherapy with vinblastine and cisplatin. Of note, the results in this trial (using the same strategy as CALGB 84-33, which reported a 5-year survival of 17% with induction chemotherapy followed by RT) demonstrated a 4-year survival of only 10%, closer to the 5-

year results (of 8%) seen in the RTOG 88-08 trial with this same regimen. Much still needs to be clarified regarding the underlying mechanisms, as well as the optimal agents and schedule, for radiation sensitization. Indeed, another recent randomized trial³⁷ of continuous infusion carboplatin (840 mg/m²) administered during 6 weeks of radiation vs radiation alone in stage III NSCLC showed that the addition of carboplatin alone as a radiosensitizer did not improve local control or median survival.

This important sequencing issue (of concurrent vs sequential therapy) will hopefully be answered by a large randomized trial, RTOG 94-10, which recently completed accrual in 1998 with more than 600 patients. In RTOG 94-10, the “gold standard” arm of induction chemotherapy (with cisplatin and vinblastine) followed by standard RT (as in CALGB 84-33) will be compared to the same chemotherapy and RT delivered concurrently starting on day 1. This study also included a third arm of HFRT and concomitant cisplatin and oral etoposide. This latter regimen was based on a prior promising phase II trial (RTOG 91-06)³⁸ in which preliminary results demonstrated a 1-year survival rate of 67% and a median survival of 20 months. Preliminary results from RTOG 94-10 should be available in the year 2000.

Novel Chemotherapy and RT

Beyond the sequencing issue, the optimal chemotherapy regimen to combine with RT in patients with locally advanced disease is also unknown at this time. In a 5-arm ECOG study³⁹ in advanced NSCLC of multiple cisplatin analogs in combinations, initial therapy with carboplatin produced the best long-term survival with a *P* value of <0.01 and the least grade 4 toxicity. With the exception of myelosuppression, carboplatin yields significantly less nonhematologic toxicity compared with cisplatin. Paclitaxel-based platinum combinations have proven superior to other regimens in advanced NSCLC. In an ECOG trial⁴⁰ for patients with advanced, previously untreated NSCLC, paclitaxel by 24-hour infusion was the most active single agent, with a response rate of 25% and a 1-year survival rate of 41%. A number of investigators have demonstrated comparable activity and survival for 3-hour paclitaxel infusion in advanced NSCLC.^{41,43} In a phase II study at Fox Chase Cancer Center (FCCC) and its network affiliates (FCCC 93024)⁴⁴ in 54 patients with metastatic and recurrent NSCLC, carboplatin and paclitaxel yielded a response rate of 62%, a 1-year survival rate of 54%, and a 2-year survival rate of 15%. Other investigators have generated similar results.^{45,46}

More recently, several institutions have accumulated considerable experience using carboplatin and paclitaxel with RT in patients with good-prognosis locally advanced NSCLC. At FCCC, induction therapy consisted of 2 cycles of paclitaxel (175 to 225 mg/m² every 3 hours) and carboplatin (targeted AUC of 7.5) on days 1 and 22 with granulocyte colony-stimulating factor (G-CSF) support.⁴⁷ Half of the patients were randomized to priming with G-CSF (q d × 5) prior to induction therapy. On day 43, thoracic RT (60 Gy/30 fractions/5 d q wk) was initiated with escalating doses of paclitaxel and carboplatin in the absence of hematopoietic growth factors. Initially, patients received carboplatin (targeted AUC 3.75) and paclitaxel (67.5 mg/m² every 3 hours) on days 43 and 64 during RT. In the absence of dose-limiting toxicity, a phase I escalation in 3-patient cohorts during RT proceeded to maximum doses (thus far) of carboplatin (AUC of 5.0) and paclitaxel (175 mg/m²). So far, 42 patients (81% stage IIIB) have received induction therapy; four are too early to evaluate for response. One patient developed a cerebrovascular accident 2 weeks after starting chemotherapy and was removed from the study. Another patient, who died secondary to neutropenic sepsis, was thought in retrospect to have an underlying myelodysplastic disorder. With these two exceptions, toxicity has been mild, thus prompting a paclitaxel dose increase during induction therapy to 225 mg/m² on days 1 and 22 after the first 7 patients were accrued. The phase III portion of the study evaluating G-CSF priming revealed no myeloprotective effect due to a lack of myelosuppressive toxicity with the conventionally dosed group.

Of 19 patients who received concurrent thoracic radiation and chemotherapy, 18 were evaluable for response and toxicity. There has been one episode each of grade 4 granulocytopenia and grade 3 anemia. The occurrence of grade 2 or higher esophagitis corresponded to the length (>16 cm) of the esophagus in the radiation treatment field ($P=0.006$). Grade 3 esophagitis occurred in 3 patients. Five episodes of grade 2 or higher corticosteroid-responsive pulmonary toxicity have occurred 2 to 6 months after conclusion of the thoracic radiation and chemotherapy. The major response rate to induction therapy was 41% and to combined modality was 55%. The 1-year survival rate for all 38 evaluable patients was 72% with a median survival of 15 months. For the 18 phase I patients, the 1-year survival rate was 85%, and the median survival was 17.5 months.⁴⁸

In another study by Belani et al⁴⁹ combining weekly paclitaxel (45 mg/m² in a 3-hour infusion) and carboplatin (100 mg/m²) with simultaneous thoracic RT (60 to 65 Gy) in locally advanced NSCLC, the 3-year

actuarial survival rate was 54% (95% confidence interval 35% to 70%). Similarly, Choy et al^{50,51} reported excellent response rates (approximately 70%) with regimens involving weekly paclitaxel and carboplatin with concurrent (daily or hyperfractionated) thoracic RT with a median survival in the range of 20 months. These studies indicate that chemoradiation with paclitaxel and carboplatin is active in locally advanced NSCLC.

Several cooperative groups are exploring these and other novel systemic agents in phase III randomized trials for patients with locally advanced NSCLC. The CALGB is conducting a phase III study of concurrent carboplatin, paclitaxel, and RT with or without prior induction carboplatin and paclitaxel in patients with medically inoperable/unresectable stage IIIA/B NSCLC. ECOG has a phase III study of induction paclitaxel and carboplatin followed by standard RT vs hyperfractionated accelerated RT for patients with unresectable stage IIIA/B NSCLC. The hyperfractionated accelerated RT is administered 3 times daily, 5 days per week over 13 days. The Hoosier Oncology Group plans to conduct a phase III study comparing two courses of either carboplatin plus paclitaxel or cisplatin plus vinblastine followed by standard RT.⁵² The EORTC has opened a phase III study (EORTC-08972) of induction chemotherapy (with gemcitabine and cisplatin) followed by RT vs daily low-dose cisplatin concurrent with RT. The RTOG has a phase III trial (RTOG 98-01) involving induction high-dose ("systemic") paclitaxel (225 mg/m² in a 3-hour IV) and carboplatin (AUC 7.5) every 3 weeks for 2 cycles followed by weekly concurrent "radiosensitizing" paclitaxel (50 mg/m² in a 1-hour IV) and carboplatin (AUC 2) with HFRT (1.2 Gy twice daily to 69.6 Gy) with or without randomization to the radioprotector amifostine.

Reducing the Toxic Effects of Therapy on Normal Tissue

While concomitant delivery of chemotherapy and thoracic RT appear to have a synergistic effect on tumor control, such a strategy has potential disadvantages. As treatment regimens become more and more aggressive, the risk of normal tissue injury also increases, potentially resulting in treatment breaks or dose reductions that may limit the success of therapy. Cox et al⁵³ reviewed data from three RTOG randomized trials to determine if prolonged treatment time adversely affected outcome for patients with inoperable NSCLC. The investigators found that for "favorable" patients (ie, high Karnofsky performance status, little weight loss, and less than N3 nodal disease), interruptions in the completion of the planned RT reduced survival.

The toxic effects of greatest concern from thoracic RT are acute esophageal toxicity and subacute or late lung toxicity. In RTOG 91-06, in which patients received HFRT and concomitant chemotherapy with cisplatin and oral etoposide, the risk of grade 3 or higher esophageal injury was 53% and late lung toxicity (grade 3) was 18% (3% grade 5).³⁸ Similarly, in the context of concurrent weekly paclitaxel (50 mg/m² in 1 hour) and carboplatin (AUC 2) and concomitant HFRT (1.2 Gy twice daily to 69.6 Gy), Choy et al⁵¹ found an RTOG grade 3-4 esophagitis rate of 26%. Of note, the corresponding rate of esophageal injury for induction cisplatin plus vinblastine followed by RT in RTOG 88-08 was less than 5%.¹¹

Scott et al⁵⁴ recently performed a quality-adjusted survival analysis of the RTOG chemoradiation lung studies. This analysis included almost 1,000 patients with locally advanced NSCLC who were treated on phase II or III RTOG studies employing various combinations of RT with or without sequential or concurrent chemotherapy. Quality-adjusted survival was calculated by weighting the time spent with a specific toxicity or local or distant tumor progression. Although patients receiving concomitant chemoradiation had the best overall survival, patients receiving induction chemotherapy followed by RT had nearly equivalent quality-adjusted time survival. This analysis suggests that while the concurrent chemoradiation may have increased overall survival, this apparent benefit came at the price of increased toxicity that adversely affected the quality of the survival increment. A subsequent analysis⁵⁵ found that reduction in esophageal, lung, and upper gastrointestinal toxicities led to the greatest improvement of quality-adjusted survival time. Thus, if one can reduce the toxicity of the more intense (concurrent) regimen, one may be able to improve not only the median survival time, but also the quality-adjusted survival time. This analysis underlies the rationale to employ a radioprotector, such as amifostine, to attempt to reduce the high rate of esophagitis encountered in the promising, yet toxic, concurrent chemoradiation regimens.

Amifostine

Amifostine (Ethyol, WR-2721) is an organic thiophosphate that was selected from more than 4,400 compounds screened by the US Army as the best radioprotective compound. It has been shown to protect experimental animals from lethal doses of radiation. Amifostine is dephosphorylated at the tissue site to its active metabolite (WR-1065) by alkaline phosphatase. Once inside the cell, WR-1065, the free thiol, acts as a potent scavenger of the oxygen free radicals induced by ionizing radiation and also provides an alternative

target to DNA and RNA for the reactive molecules of alkylating or platinum agents.⁵⁶ The normal tissues that are reported to be protected from radiation toxicity include salivary glands, bone marrow, skin, oral mucosa, esophagus, kidney, and testes.^{57,58} Thus, these preclinical data provide the rationale for the ability of amifostine to improve the therapeutic index for RT in the clinical setting.

Several studies of amifostine as a radioprotectant have been conducted.⁵⁹ A randomized trial for patients with inoperable or recurrent rectal cancer conducted in China⁶⁰ showed protection against the moderate or severe acute and late radiation toxicities ($P=0.026$) in the pelvis, with amifostine administered daily (340 mg/m²) prior to each radiation dose. At the same time, there was no evidence of tumor protection. In a study by Buntzel et al,⁶¹ 28 patients with squamous cell carcinomas of the head and neck were treated with a combination of RT (daily to 60 Gy) and concurrent carboplatin (70 mg/m² on days 1 through 5 and days 21 through 26) were randomized to receive either amifostine (500 mg prior to each carboplatin dose) or placebo. Toxicities graded by World Health Organization (WHO) score were significantly reduced with amifostine, including a significant decrease in dysphagia ($P=0.005$), as well as significant decreases in the hematologic toxicity ($P=0.002$) and mucositis ($P<0.001$). Brizel et al⁶² recently confirmed the radioprotective potential of amifostine in reducing xerostomia in a large randomized study of 315 patients with head and neck cancer. No difference in local-regional control was found.

Pilot data have recently become available regarding amifostine in patients with locally advanced NSCLC receiving chemotherapy/RT (Maria Werner-Wasik, MD, personal communication, 1999). In a phase II study, 22 patients with locally advanced NSCLC were treated with two cycles of induction chemotherapy with carboplatin (AUC 6) and paclitaxel (225 mg/m²) every 3 weeks, followed by concurrent standard thoracic irradiation with weekly paclitaxel (60 mg/m²). Since a high rate of grade 3 esophagitis was noted in the first 11 patients, amifostine at a dose of 500 mg IV twice weekly was added to the regimen. The incidence of grade 3 esophagitis was 18% in the initial 11 patients vs 0% in the amifostine-treated patients ($P=0.03$ for distribution of maximum grade). These results suggest that amifostine reduces severe esophagitis resulting from concurrent chemotherapy with weekly paclitaxel and thoracic irradiation.

While awaiting for the results of RTOG 94-10 to mature, RTOG 98-01 will build on the previous experience of the RTOG while incorporating novel chemo-

therapy (paclitaxel and carboplatin), both prior to HFRT (to combat systemic failure) and concurrent with HFRT (to combat local-regional failure), which has been shown to be promising in the experience of RTOG,³⁸ as well as others.²⁵ This regimen combines the underlying principles of prior investigational studies and does not, at this time, define a new "standard" treatment. However, as this strategy has been associated with increased toxicity (particularly grade 3/4 esophagitis), this study will randomize patients to the radioprotector amifostine to determine the ability of this agent to reduce the toxicity associated with concurrent HFRT and chemotherapy.

Future Strategies

Future trials currently in development are attempting to integrate the optimal local and systemic strategies reviewed above. Treatment strategies directed at enhancing local tumor control, such as altered fractionation or dose escalation via conformal RT, will need to be safely combined with systemic chemotherapy. In all of these novel strategies, investigators will need to consider not only the traditional endpoints of survival and local control, but also quality of life. As chemotherapy for lung cancer becomes more effective, the issue of local control will only gain in importance. In addition to paclitaxel and carboplatin, many other chemotherapeutic agents have emerged in the 1990s, including docetaxel, vinorelbine, gemcitabine, and irinotecan. Institutional data are beginning to emerge with these agents in combination with thoracic RT in the phase I/II setting.⁶³⁻⁶⁵ The CALGB has just reported the preliminary results of their randomized phase II study of gemcitabine or paclitaxel or vinorelbine with cisplatin as induction chemotherapy and concomitant chemoradiotherapy for unresectable stage III NSCLC (CALGB study 9431).⁶⁶ While the response rates in all arms appeared similar, the gemcitabine/cisplatin arm appeared to have the highest rate of grade 3/4 thrombocytopenia (53% vs 6% or 0% in the other arms) and esophagitis (49% vs 31% and 25% in the other arms). Vokes et al⁶⁶ found the median survival for all patients to be 18 months with a 1-year survival of 66%. The survival information for each arm has not yet been reported.

Newer therapies are on the horizon that may show promise in patients with locally advanced NSCLC. Tirapazamine, a hypoxic cytotoxin, has recently been shown to enhance survival in patients with advanced NSCLC when combined with chemotherapy compared to standard chemotherapy alone.⁶⁷ The RTOG is currently developing a trial to explore this agent in the context of thoracic RT for patients with locally advanced NSCLC. Studies are emerging in patients with



Computed tomography image revealing cigarettes in the pocket of a patient with locally advanced NSCLC (arrow).

metastatic NSCLC with monoclonal antibodies (eg, HER-2-neu antibody) and gene therapy. These strategies could potentially be integrated into therapy for locally advanced NSCLC. With the advent of antiangiogenesis therapies into clinical trials, it will be important to study the role of these agents in patients with NSCLC. Volm et al⁶⁸ found that the expression of vascular endothelial growth factor (VEGF), a pivotal mediator of tumor angiogenesis, was an independent prognostic factor for patients with squamous cell carcinoma of the lung. Fontanini et al⁶⁹ assessed the relationship between the expression of VEGF and the pattern of p53 expression in NSCLC. They found that p53-negative and lowly vascularized tumors showed a median VEGF expression significantly lower than the p53-positive and highly vascularized tumors ($P=0.02$). These findings support the hypothesis of a wild-type p53 regulation on the angiogenic process to VEGF upregulation. The above studies suggest that a more detailed analysis of angiogenic growth factor inhibitors in NSCLC will provide useful information that may be important in understanding the genetic regulation of angiogenesis and its potential impact on therapy.

With newer imaging techniques, such as spiral computed tomography, the issue of lung cancer screening needs to be re-evaluated.⁷⁰ Similarly, improved staging with newer functional-imaging techniques, such as photon emission tomography scans,⁷¹ may better select patients without metastatic disease who will benefit from a combined-modality approach. The Figure depicts cigarettes in the pocket of a patient with locally advanced NSCLC. This CT image poignantly reminds us that the best chance to fight this disease remains prevention.

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