Localized Non–Small Cell Lung Cancer: Adjuvant Radiotherapy in the Era of Effective Systemic Therapy

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Abstract Investigators in Europe, Canada, and the United States recently established a definitive role for adjuvant systemic chemotherapy following resection of early-stage non–small cell lung cancer (NSCLC). This was no small accomplishment, as upward of 20 randomized trials had previously been conducted. The role of postoperative radiotherapy (PORT) has been studied with far less vigor in the modern era. A 1998 meta-analysis of randomized trials suggesting that PORT was detrimental to survival included studies of doubtful quality. The value of PORT should be considered in the same context as recent chemotherapy trials. Advances in imaging have improved the accuracy of staging, patient selection, and target definition. Modern dosimetry and accelerator technologies have advanced the capacity to deliver radiation to the target with less tissue toxicity. Evolving philosophies in dosing and fractionation should improve the therapeutic ratio. Finally, it is reasonable to assume that the importance of local control will be enhanced in the setting of better systemic therapies. We will review the data on PORT and address critical issues in the design of trials to assess the role of modern radiotherapy in the integrated approach to management of early-stage NSCLC.

The disappointing prognosis following surgical resection of non–small cell lung cancer (NSCLC) has spurred a search for effective adjuvant therapy over the past several decades. Despite numerous prospective trials, convincing evidence of benefit from the administration of postoperative therapy appeared only recently. The results of three randomized prospective trials (from Europe, Canada, and the United States) have markedly impacted clinical practice (1–3). All three showed a significant absolute survival benefit for patients receiving adjuvant chemotherapy following resection of early-stage NSCLC. Whereas the European trial included a wide spectrum of patients with localized NSCLC, the North American trials restricted eligibility to patients with defined early-stage disease (i.e., stage IB and /or stage II). Although other contemporaneous studies did not show this benefit from adjuvant chemotherapy, a new standard of care has been established (4, 5). Factors contributing to the success of adjuvant chemotherapy in recent studies likely include the use of modern staging techniques, better defined patient populations, more effective agents, better patient support, and perhaps a change in the biology of this disease with a resultant shift in affected populations.

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In contrast to the growing consensus on adjuvant chemotherapy, the role of postoperative radiotherapy (PORT) remains nebulous. The PORT meta-analysis, despite questions regarding its relevance, has discouraged oncologists from including radiotherapy in multimodality regimens (6). Given the recent advances in adjuvant therapy, it may be appropriate to reexamine the potential synergy of local therapy in combination with effective systemic therapy. Potential misconceptions regarding PORT, as well as issues critical to finally determining the value of PORT in the treatment of early-stage NSCLC, will be discussed.

Patterns of Care

Formal collection and analysis of radiotherapy patterns of care data for lung cancer constitute a recent phenomenon. In the Survival, Epidemiology, and End Results (SEER) data collected between 1988 (the first year detailed nodal information was available in the SEER database) and 1995, PORT was administered in 58% of node-positive patients (7). PORT was more frequently used for N_2 than N_1 disease (72% versus 51%) and was independently associated with younger age, extent of nodal involvement, and less extensive surgery. Data reflecting changes in practice standards since the 1998 meta-analysis of randomized trials have not been published.

Opinions regarding the advisability of adjuvant therapy tend to reflect the respondent's specialty. A survey of nearly 1,000 oncologists in varied U.S. practice settings during the late 1990s illustrates the divide between medical oncologists and radiation oncologists (8). Only 16% of respondents recommended no further treatment for patients with completely resected N_1 and N_2 disease. The majority of radiation oncologists recommended radiotherapy alone and the majority of medical oncologists recommended including chemotherapy in the treatment plan.

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The inclusion of PORT in the standard arm of U.S. cooperative group trials of adjuvant therapy for node-positive NSCLC has, in part, been justified by the results of the Lung Cancer Study Group (LCSG) Trial 773 (9). This phase III trial assessed mediastinal radiotherapy (5,000 cGy in 5-5.5 weeks) following resection of stage II or stage III squamous cell carcinoma of the lung. A marked reduction in local relapse at the site of first failure, from 41% to 3% of all relapses, was observed for patients randomized to receive PORT. This local control advantage did not translate to a survival benefit. Although only 44 eligible patients with N_2 disease were actually included in the trial, subgroup analysis revealed significantly reduced overall recurrence for such patients with PORT ($P = 0.031$).

Relapse Patterns

The major impact of thoracic radiotherapy is reduction in the risk of locoregional relapse; thus, its potential benefit may be best assessed by analyzing failure patterns, with particular attention to the relative risk of systemic versus local failure. Not surprisingly, overall failure increases with both stage and extent of lymph node involvement. For example, method of staging (clinical versus pathologic), tumor bulk, and location of mediastinal adenopathy have prognostic importance for stage IIIA disease (10, 11). The incidence of locoregional relapse (as a proportion of total relapses) has generally been observed to increase with advancing stage and nodal involvement (Table 1; refs. 1, 2, 10, 12–19). Recent improvements in the ability to accurately stage NSCLC, as well as potential changes in the biology of the disease over time, must be accounted for in determining the risk of initial locoregional relapse. Moreover, the impact of effective systemic therapy may further shift the relative risk of local tumor failure. A recent update of the International Adjuvant Lung Cancer Trial (IALT) reported reduced rates of local and systemic relapse with the addition of chemotherapy to surgery for stage I to IIIA NSCLC. Whereas the 5-year local recurrence rate was reduced from 29% to 24% with chemotherapy, a breakdown of recurrence patterns according to stage was not reported (20). The publication of detailed patterns of relapse from other recent trials that have shown a survival benefit for patients receiving adjuvant chemotherapy are awaited.

Postoperative Radiotherapy Trials

The 1998 publication of the PORT Meta-Analysis Trialists Group was controversial (6). The study analyzed individual patient data from prospective trials of patients with resected

Table 1. Published trials of megavoltage adjuvant radiotherapy for resected NSCLC

Author	Year active	*n*	%NO	RT dose	RT Fx	CordPb	LatFld	CO-60	LR% (PORT/OBS)	OS% (PORT/OBS)	Comments
Israel (29)	1973-1976	230	62	45-55	2-3.33	NS	NS	NS	12/21 (0.095)	ND	Second randomization to chemotherapy/ immunotherapy
Van Houtte (14)*	1966-1975	175	100	60	2.0	Yes	Yes	All	4/19 (NS)	ND	Decreased survival for T_2 patients with PORT
LCSG 773 (9)*	1978-1985	210	0	50	1.8-2	Yes	Yes	Yes	1/19 (0.001)	ND	Overall recurrence reduced for N_2 with PORT
Debevic (21)*	1988-1992	74	0	30	2.5-3	No	Yes	No	16/28 (NS)	ND	
Lafitte (15)*	1985-1991	163	100	60	2.0	Yes	Yes	Yes	15/19 (NS)	ND	Trend to reduced survival (0.08) with PORT
MRC (16)*	1986-1993	308	0	40	2.6	Yes	Yes	Yes	18/29 (NS)	ND	Trend toward reduced local relapse with PORT (0.07) for N_2 patients. Reduced metastasis in N_2 patients with PORT
Dautzenberg (28)*	1986-1994	728	40	60	2-2.5	Yes	Yes	Yes	22/28 (NS)	30/43 (0.002; 5-y)	5-Y intercurrent death increased with PORT (31% versus 8%)
Feng (30)*	1982-1995	296	0	60	2.0	Yes	Yes	Yes	13/33 (0.01)	ND	
Mayer (31)	1985-1995	155	25	50-56	2.0	Yes	NS	No	6/24 (0.01)	ND	
Granone (32)	1989-1997	98	100	50.4	1.8	No	No	No	2/23 (0.039)	67/58 (0.048; 5-y)	CT-based planning with tissue heterogeneity corrections

Abbreviations: Fx, fraction size; OBS, observation; MRC, Medical Research Council; CordPb, spinal cord shielding; NS, not stated; *n*, number of eligible patients; LatFld, direct lateral field; ND, not different; RT, radiotherapy; CT, computed tomography; LR, local recurrence; OS, overall survival.
*Data included in PORT meta-analysis.

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early-stage NSCLC. Nine trials (involving >2,000 patients) were included in the analysis (9, 14–16, 21, 22). They had been initiated as early as 1965, and three had not been published in the peer-reviewed literature. The results strongly suggested that PORT had a detrimental effect on survival, presumably through the increased incidence of intercurrent death. Two-year overall survival was 48% in patients receiving PORT compared with 55% for patients treated with surgery alone. The detriment of PORT was inversely related to nodal status, with significantly reduced survival noted for N_0 and N_1 disease. The results for stage III and N_2 patients slightly favored PORT, although the difference was not significant.

Radiation oncologists were critical of the study for several reasons (23–26):

1. Staging: The initial staging evaluation and follow-up examinations utilized in many of the trials would be considered inadequate by modern standards. Moreover, the details of surgical resection and nodal staging were often not clearly defined, potentially leading to an imbalance between treatment arms.
2. Patient selection: Four trials allowed patients without nodal metastases, and approximately one quarter of all patients in the meta-analysis had N_0 disease, whereas fewer than one half of patients had N_2 disease. As patients without evidence of lymph node metastases generally have the lowest risk of local relapse, it would be expected that PORT could offer little benefit.
3. Technology: Treatment by Co-60 was allowed in seven of the nine trials. This outdated modality has been shown to produce less favorable outcomes than linear accelerators; in one PORT review, patients treated with Co-60 had a 5-year survival rate of only 8% compared with 30% for patients undergoing linear accelerator and computed tomography–based treatment planning (including correction for heterogeneity; ref. 27).
4. Technique: Most of the included trials used techniques that are now recognized as reducing the therapeutic ratio of radiotherapy. Lateral treatment beams, which greatly increase the lung volume exposed to moderate doses, were used in the majority of studies. Conversely, posterior spinal cord blocks, which reduce dose to the mediastinal nodes, were likewise commonplace.
5. Dose and fractionation: The cumulative nominal radiation doses utilized in the majority of trials would now be considered inappropriately high. Five trials used doses of 60 Gy, and two additional trials used large daily fractions (2.6-3.0 Gy), which have been linked to late pulmonary toxicity. The editorial accompanying the PORT meta-analysis showed that the risk of "intercurrent deaths" in PORT trials was directly correlated with the biological effective dose (23). Moreover, LCSG 773 showed that 50 Gy may be sufficient to minimize local relapse.
6. Trial size imbalance: The trial from the Groupe d'Etude et de Traitment des Cancers Bronchiques, formally published subsequent to the meta-analysis, had 728 subjects, accounting for more than one third of the meta-analysis population (28). Whereas significantly reduced survival was reported for patients receiving adjuvant radiotherapy, the trial contained all of the shortcomings enumerated above: It included patients with N_0 disease, administered 60 Gy in fractions of up to 2.5 Gy, and utilized Co-60 teletherapy. Five-year intercurrent deaths were 31% for the PORT arm compared with 8% for the surgery-only arm and the risk of intercurrent death directly correlated with fraction size in a retrospective analysis.

Published trials of megavoltage adjuvant radiotherapy for resected NSCLC are shown in Table 2, including trials excluded from the PORT meta-analysis and recently published trials (9, 14–16, 21, 28–32). If the trials included in the meta-analysis were analyzed in the context of modern therapy, not a single study would be considered acceptable. The suboptimal administration of PORT would be analogous to the use of alkylating agents as adjuvant chemotherapy of NSCLC (which were likewise associated with a detrimental effect on survival; ref. 33).

Are There Any Data to Support the Use of Modern Postoperative Radiotherapy?

1. Two moderately large single-institution experiences suggest a potential benefit from PORT when delivered to defined populations. A Mayo Clinic study of 224 patients, including 88 patients that received PORT to a median dose of 50.4 Gy, was limited to stage IIIA NSCLC (34). High-risk patients, based primarily on the number and location of involved nodes (N_1 and N_2), seemed to gain the greatest benefit from PORT, although a survival advantage was suggested for intermediate-risk patients as well. A report from the University of Pennsylvania of ~200 patients treated with PORT for pathologic stage II or III NSCLC showed the importance of using moderate radiation doses (35). All patients underwent simulation and were treated on a linear accelerator using energies of 6 MV or higher. Overall survival and local control were favorable (considering the patient population) and the risk of death from intercurrent disease for patients receiving <54 Gy was only 2%.
2. The SEER database (1988-1995), including >4,000 patients with resected T_{1-3}, $N_{1/2}$ NSCLC also suggests PORT may be beneficial in selected patients (7). In the N_2 population, PORT was associated with improved 5-year overall survival (22% versus 16%) and cause-specific survival (30% versus 25%). Patients with ≥4 positive nodes, whether N_1 or N_2, also seemed to benefit from PORT.

Table 2. Patterns of failure in selected series of resected NSCLC

Nodal status	Locoregional relapse	Distant relapse
N_0 (12–15)	6-17%	18-30%
N_1 (12, 13, 16)	9-28%	22-64%
pN_2 (10, 12, 13, 16, 17)	17-41%	70%
cN_2 (18, 19)	14-54%	38-55%

Abbreviations: p, pathologic; c, clinical.

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3. A recent randomized trial of 104 stage I patients from the Università Cattolica del Sacro Cuore provides provocative evidence supporting modern radiotherapy techniques—including computed tomography planning with heterogeneity correction (32). Radiation dose was limited to 5,040 cGy in 180 cGy fractions and restricted target volumes were utilized. Only one patient treated with PORT had a local recurrence (2.2%) compared with 12 patients in the surgery-only arm. Overall survival favored the PORT arm over surgery only, with 5-year survival rates of 67% and 58%, respectively (P = 0.048).

Adjuvant Trials Including Chemotherapy and Radiotherapy

There are few trials investigating the benefit of PORT when integrated with systemic therapy. Seven trials included in the chemotherapy for NSCLC meta-analysis compared surgery plus radiotherapy versus surgery plus radiotherapy plus chemotherapy (33). Radiotherapy schedules ranged from 40 Gy in 10 fractions to 65 Gy in 33 fractions and between two and six cycles of chemotherapy were given before PORT. Two trials were unpublished and three trials included patients with incompletely resected disease. Whereas this experience has limited applicability to modern practice, the feasibility of combined therapies was established. Moreover, the addition of cisplatin-based chemotherapy was associated with a (nonsignificant) 6% reduction in the risk of death (33).

The IALT allowed participating centers to determine PORT policy for patients with node-positive disease (1). PORT, when utilized, was given after the completion of chemotherapy (three to four cycles) to a dose of ≤60 Gy. Overall, PORT was planned for 30.6% of patients (of which two thirds were pN_2 and one-third pN_1). Among patients assigned to the PORT arm, only 70.4% in the chemotherapy group and 84.2% in the control group actually received it. Fewer patients in the chemotherapy arm received PORT because some developed disease progression (or expired) during the chemotherapy phase that preceded PORT. The authors concluded that it was *unlikely* that PORT would offset the beneficial effect of chemotherapy, and no interaction was observed between chemotherapy effect and PORT. Thus, the results of this large modern trial do not support the contention that PORT masks the benefit of adjuvant chemotherapy. Moreover, an analysis of both recent large European trials, IALT and the Adjuvant Lung Project Italy (ALPI), reveals that the largest benefit of adjuvant chemotherapy was observed in subgroups of patients where radiotherapy was readily administered (1, 4).

A recent trial from Cancer and Leukemia Group B (CALGB 9734) attempted to evaluate PORT following chemotherapy for resected N_2 disease (36). Following four cycles of carboplatin and paclitaxel chemotherapy, patients were randomized to mediastinal radiotherapy (50 Gy in 25 fractions or observation). Unfortunately, the trial failed to accrue adequately and closed prematurely in 2000 (perhaps in part because adjuvant chemotherapy was not the standard of care when the trial was undertaken). Forty patients were entered into the study, 20 in each arm. Median failure-free survival favored the PORT arm, 25.9 versus 15.6 months, although short-term (1 year) overall survival rates were similar.

The concurrent initiation of PORT and adjuvant chemotherapy allows both modalities to be given in a timely manner after surgery (37). This approach was evaluated in an intergroup trial headed by the Eastern Cooperative Oncology Group (ECOG 3590), which compared PORT only versus PORT plus concurrent etoposide and cisplatin, for patients with pathologic stage II or IIIA NSCLC. The PORT schedule was 50.4 Gy in 28 daily fractions, with a boost of 10.8 Gy to regions of extracapsular spread. Toxic side effects were more common in the chemotherapy arm, but treatment-related deaths were <2% overall. No differences in survival, in-field relapse, or locoregional relapse were observed between the arms. The late toxic effects of administering concurrent therapy in this population are not clear. Death from intercurrent disease at 4 years was 15.4% for patients who received PORT and 18.4% for patients treated with combined therapy (38). Although these figures are significantly different than the expected rate of intercurrent disease (based on mortality rates for age- and gender-matched controls derived from U.S. vital statistics and corrected for smoking status), the trial did not have an appropriate (no PORT) control arm.

A Radiation Therapy Oncology Group phase II trial, RTOG 9705, evaluating PORT concurrent with paclitaxel and carboplatin chemotherapy for pathologic stage II and stage IIIA NSCLC, has been reported in abstract form. In it, 50.4 Gy in 28 fractions was delivered during the first two (of four) cycles of chemotherapy (39, 40). The regimen was well tolerated; 86% of patients completed all chemotherapy. When initially reported in 2001, the median survival time was 35.7 months and appeared similar to the result from the phase III intergroup trial (ECOG 3590) previously discussed. However, with longer follow-up (reported in 2003), median survival improved to 56.3 months. Interestingly, median progression-free survival was 35.6 months in both reports.

Postoperative Radiotherapy for Patients Receiving Preoperative Chemotherapy

PORT was a major component of the landmark perioperative chemotherapy trials conducted by the Spanish Lung Cancer Group (SLCG; ref. 18) and MD Anderson Cancer Center (19) for IIIA NSCLC. The value of PORT was not assessed in these studies, however, and at this time important questions remain unanswered in this population:

- Does PORT improve outcomes for patients treated with neoadjuvant chemotherapy and surgery?
- Can PORT be substituted for preoperative radiotherapy for patients receiving trimodality therapy?

Preoperative radiotherapy may in fact be more attractive than PORT, as radiotherapy target volumes are more clearly defined, which may allow for better conformity of therapy with a resultant reduction in the treatment of normal tissues. Administering radiotherapy concurrent with chemotherapy may also allow for an enhanced biological effect. Alternatively, the perioperative morbidity associated with induction chemoradiotherapy might be reduced by delaying the administration of radiotherapy until after surgery. The current U.S. intergroup trial compares preoperative chemotherapy with preoperative

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chemoradiotherapy for clinical stage IIIA NSCLC and will begin to provide some answers to this issue, although PORT will only be administered under select circumstances. Carefully designed trials are necessary to fully address these questions.

The Rationale for Continued Postoperative Radiotherapy Research and Issues for Trial Design

There are several compelling reasons to reexamine the utility of PORT in the modern era, not the least of which is that effective adjuvant systemic therapy is now available for stage II and III NSCLC. As noted earlier, part of the reason for the improved survival may include changes in tumor biology and patient population, as well as improvements in staging and supportive care. For example, patients who either have never smoked or smoked in the remote past compose an increasing percentage of the population included in the modern North American trials for advanced lung cancer. As the toxic effects of radiotherapy seem to be linked to underlying pulmonary dysfunction and other comorbid illness, nonsmoking patients may be less likely to suffer from the toxic effects of PORT and, therefore, may derive a greater benefit from carefully delivered thoracic radiotherapy. Finally, marked advances in technologic sophistication developed during the past decade should allow for the safe administration of adjuvant radiotherapy.

The available evidence suggests the following elements would be required for a valid test of a survival benefit for NSCLC patients receiving PORT:

1. Meticulous clinical and surgical staging.
2. Restricting the study population to N_2 and/or multiple N_1 nodes (with appropriate stratification), perhaps with stratification by molecular/biological variables.
3. Limiting the cumulative radiotherapy dose to 5,000 to 5,040 cGy in 180 to 200 cGy fractions.
4. Computed tomography–based three-dimensional conformal treatment planning using tissue heterogeneity corrections.
5. Specified normal tissue constraints based on dose-volume relationships for lung (including V20), heart, and other normal structures.
6. Precisely defined radiotherapy target volumes with accompanying quality review.
7. Careful posttherapy monitoring with appropriate imaging studies, formal pulmonary function testing, and biological/molecular correlates.

Integration with chemotherapy will obviously be critical and the main considerations include the timing of PORT and the sequencing with chemotherapy. Given the suggested relationship between radiotherapy intensity and intercurrent deaths, coupled with the fact that in-field failures were not reduced with concurrent therapy in ECOG 3590, the judicious approach would call for radiotherapy to be administered without sensitizing chemotherapy. However, markedly delaying the initiation of radiotherapy may undermine the value of PORT. As was observed in the IALT trial, patients are less likely to receive assigned radiotherapy following administration of three to four cycles of chemotherapy. An acceptable approach might integrate PORT after the first or second cycle (of four total cycles) of chemotherapy. Prospective data suggest that chemotherapy can be successfully completed in the vast majority of patients even when radiotherapy is administered early (40). Moreover, a similar sequential study design was used in the landmark randomized trial of the Danish Breast Cancer Cooperative Group, which showed a significant survival advantage for patients with high-risk breast cancer receiving adjuvant radiotherapy plus chemotherapy versus chemotherapy alone (41).

In summary, there is finally reason to expect that advances in therapy can translate into improved outcomes for patients with resected NSCLC. The hypothesis that radiotherapy delivery has evolved such that it can be an effective partner with systemic therapy is well founded and merits investigation. Resolving this timely controversy would, moreover, have important ramifications for the optimal design of future studies assessing novel systemic and molecularly targeted agents that hold great promise for the population of patients with NSCLC.

Open Discussion

Dr. Thomas Lynch: You said that you don't believe it is reasonable to delay radiation until after the completion of adjuvant chemotherapy. I'm curious what the group thinks about that. We have experience in breast cancer that makes us comfortable giving chemotherapy to the breast after completing four cycles of radiotherapy.

Dr. Bogart: I would state it this way, if we get one chance to answer the question and I'm going to pick the optimal time to test the delivery of radiation, I would rather it not be after four cycles. Whether I feel comfortable delivering radiotherapy after four cycles is a slightly different question. In the breast cancer trial, chemotherapy was limited to 12 weeks and it is a different patient population. If you look at the IALT and other trials, the more chemotherapy given, the fewer patients who go on to get radiotherapy and that's going to be an issue.

Dr. Douglas Wood: You are the lone radiation oncologist here in a shark's nest of medical oncologists and thoracic surgeons. But one of your points is that locoregional failure is an important problem. I'm asking you to defend that statement because I don't see that locoregional failure from completely resected lung cancer is a problem. Patients die of systemic disease. Nodal disease is a surrogate for systemic disease from which they die. Patients who do fail locoregionally also fail systemically and die. So, what is the independent problem of locoregional disease that PORT is going to solve?

Dr. Bogart: You just espoused a philosophy that some people believe and some people—the entire radiation oncology community—do not. If you look at the data, locoregional control as the first site of failure goes up as nodal involvement goes up. Even in the IALT trial, the rate of distant metastases was ~40% to 43%, locoregional relapse, 25% to 29%. They're not so far apart, and the question then is, does a locoregional relapse mean that there is systemic disease already present or does it progress? Is there some subset of patients who are going to progress? It's the same argument as with breast cancer. There was a meta-analysis that showed a detriment or no improvement from radiotherapy for node-positive breast cancer [Lancet 2000;355:1757–70] and it wasn't until two well-designed trials, a Danish trial and a Canadian trial [N Engl J Med 1997; 337:949–55 and 956–62], were performed that we saw that,

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yes, not only is local-regional recurrence reduced, but this translates into an absolute survival benefit for these patients. So, I think we need to test your hypothesis and my hypothesis with modern techniques.

Dr. Thierry Le Chevalier: The major contributor to the PORT meta-analysis was the GETCB French study, which accounted for more than a third of the patients included in the report. In the GETCB, my institution was the largest contributor with close to 50% of the patients, more than 300, and approximately 70% were my patients. Unfortunately, for the patients who were correctly radiated using modern technique, there was a detrimental effect of radiation. In my opinion, the quality of the resection gives a lot of trouble in the interpretation of radiotherapy. Many of the patients we included were not operated on in our department. We see many patients who are staged pN_0 who in fact relapse within 6 months because they had N_2 disease, probably, which was not resected. We are presently trying to launch a big European study for N_2 disease comparing radiation to no radiation in patients with pN_2 resected NSCLC.

Dr. David Gandara: I just wanted to follow up on Dr. Wood's comments. To me, this issue is modified by a changing playing field and the fact that we now have shifted toward adenocarcinoma not only in the United States but really around the world. The local-regional issues are much more prominent for squamous cell carcinoma than they are for adenocarcinoma. When you say the radiation community is uniform on this, I don't think they are. As a medical oncologist, I can tell you that there are huge regional differences in whether postoperative radiation is given, and in most of our California affiliates it is not given except for cause.

Dr. Bogart: Let me just make a correction. I didn't say that they are uniform in saying the patient should get postoperative radiotherapy. I said they are uniform in believing that controlling local-regional disease can have an impact on survival, which we saw in breast cancer.

Dr. Glenwood Goss: I've always been interested in the biological question and that is, if you give a high enough radiation dose you will kill all the tumor. If you give a suboptimal dose every day for, say, 4 weeks, you are irradiating the thoracic duct with all the lymphocytes going through, which should be immunosuppressant. So, biologically, if you give a suboptimal dose, then it will likely be detrimental to the patient.

Dr. Bogart: That's exactly right. You need to define the right dose and—this is the challenge—to find the right area. The other issue is that the population is changing, as Dr. Gandara mentioned. It's now more adenocarcinoma, but it's also more nonsmokers, who may have better lung function and less underlying comorbidity and so may not have as much of a detrimental effect from postoperative radiotherapy. So, I don't think we can assume, because the population is changing, that radiotherapy has more or less a role.

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