

Early Stage Lung Cancer—New Approaches to Evaluation and Treatment: Conference Summary Statement

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“Early Stage Lung Cancer—New Approaches to Evaluation and Treatment,” held in Cambridge, MA, October 1 — 2, 2004, was convened to present and discuss recent study findings on the detection, staging, and treatment of stage I to III non-small cell lung cancer (NSCLC). This small multidisciplinary conference included participants from the United States, Canada, the United Kingdom, France, and Italy. Advances in medical oncology, radiation oncology, thoracic surgery, and basic science were presented from the perspective of how they affected early disease diagnosis and treatment. The conference format combined brief presentations with extended periods of open discussion. During the meeting, several themes emerged, which are summarized below and then presented at greater length in the individual articles and accompanying discussions that constitute the conference proceedings.

Screening and Early Detection

Although screening is an intuitively appealing and rational strategy for diagnosing early stage lung cancer, it is vital to show

that deaths from lung cancer are reduced. Additional significant issues include the cost-benefit ratios for different at-risk subgroups (i.e., current smokers versus ex-smokers with various histories) and the establishment of guidelines for diagnostic and surgical evaluation to minimize the risk of false-negative findings on the one hand and unnecessary surgery for benign lesions or overdiagnosis (i.e., unnecessary treatment of slow-growing tumors that are not life threatening) on the other. Conference participants expressed hope that the ongoing National Lung Screening Trial would be able to detect a meaningful mortality difference between the two arms, spiral computed tomography (CT) versus chest radiography, despite many concerns about its design, including the possibility that some participants in the chest radiograph arm may seek CT screening elsewhere. The National Lung Screening Trial, however, has closed its enrollment. While the National Lung Screening Trial matures, other potentially informative trials could be undertaken in the context of ongoing CT screening trials (e.g., International Early Lung Cancer Action Program). These would include exploring treatment options for suspicious or proven asymptomatic stage I lung cancer detected by CT screening. One possible design would be to randomize individuals with small noncalcified nonsolid or part-solid nodules to therapy or to follow-up. Moreover, as stage I cancer can be routinely and accurately diagnosed by screening, there will be a genuine need to develop, and to validate, less morbid interventions, whether pharmaceutical, radiotherapeutic, or improved surgical techniques that spare more of the normal lung.

The technology of CT screening is improving rapidly and resulting in a very large number of images. Computer-aided diagnosis (CAD) tools will be needed and they have potential for standardizing and increasing nodule detection. CAD tools also have potential for enabling more reliable disease monitoring and so may help resolve some of the issues of following part-solid nodules and other pulmonary lesions of uncertain significance. If validated, high-resolution CT scans and CAD analysis will increase the feasibility of designing observation and drug trials with a robust but noninvasive end point. Issues of CAD tool standardization and radiologist training, both for detection of nodules and for growth monitoring and appropriate follow-up, still need to be addressed. Conference participants noted the issues surrounding the interpretation of multiple small cancers, as these may be mistakenly assumed to represent metastatic disease when they may in fact be synchronous primary cancers in a patient with resectable early stage disease. Current efforts to build CT image and clinical outcomes databases will be important for understanding the

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behavior, prognosis, and appropriate management of screen-detected cancers.

Early diagnosis of lung cancer may also enhance a better understanding of lung cancer biology. Findings from the study of murine models of lung cancer were presented and discussed. There was particular interest in the *K-ras* murine models. On another front, research efforts are under way to identify biomarkers of early cancer using these models. Promising approaches include gene expression analysis and mass spectrometry-based proteomics studies of the serum and plasma that might reveal biomarkers that are involved in lung cancer progression.

Adjuvant Treatment of Early Stage Lung Cancer

Adjuvant treatment of resected lung cancer was a major point of discussion. The International Adjuvant Lung Trial was the first study that clearly showed a benefit to cisplatin-based treatment after curative surgery. Looking at a broad population of patients with stage I to III NSCLC, the International Adjuvant Lung Trial investigators reported that 5-year survival was increased by 4.1% with cisplatin-based adjuvant chemotherapy. Investigating a postsurgical regimen of mitomycin/vindesine/cisplatin versus no treatment, the Adjuvant Lung Cancer Project Italy trial did not find a survival benefit for chemotherapy in similar stages; however, toxicity was a significant issue, such that only 69% of patients in the treatment arm received a full three cycles. Another limitation of the International Adjuvant Lung Trial study was that the potential magnitude of benefit was modest.

In 2004, two important adjuvant studies reported more substantial differences in outcome. The Cancer and Leukemia Group B 9633 was the first randomized clinical trial to show improved survival in early stage (IB) lung cancer with a carboplatin-based regimen. In patients with stage IB NSCLC, four cycles of adjuvant chemotherapy with paclitaxel and carboplatin following resection were associated with a 12% reduction in lung cancer mortality with 4 years of follow-up. The National Cancer Institute of Canada JBR.10 study investigated the survival benefit of vinorelbine/cisplatin for resected stage IB/II patients and reported a 15% improvement in overall survival. The effect of these two trials has been to change the standard of care for patients with lung cancer after surgery. It was felt by the group, including medical oncologists, thoracic surgeons, and radiation oncologists, that these were meaningful advances in care for patients.

While validating the use of chemotherapy in early stage NSCLC, these trials have not clearly identified which subsets of patients are most likely to benefit from adjuvant chemotherapy. In subset analyses, stage II patients seemed to do better in JBR.10 and stage III patients in The International Adjuvant Lung Trial, whereas the Cancer and Leukemia Group B trial looked only at stage IB patients. These highly heterogeneous populations need to be carefully staged and further studies need to be done to determine which patients are more likely to achieve a meaningful improvement in survival versus those who should be spared the substantial morbidity potentially resulting from postoperative chemotherapy. Conference participants expressed reservations about extrapolating these trial findings to the treatment of stage IA disease. For stage IA NSCLC, there is no

convincing evidence from randomized clinical trials that adjuvant chemotherapy is effective. Nonetheless, a high proportion of stage I patients experience recurrence despite complete resection, and multimodality therapies for these patients merit further study.

In reviewing the trial data supporting adjuvant chemotherapy in early stage NSCLC, the conference participants noted that although four cycles are considered optimal many patients are unable to tolerate this much treatment without dose reductions or treatment delays. Both in the published trials and in clinical practice, patients frequently are able to receive only two or three of the planned cycles. Some preliminary data suggest that there may be an advantage to neoadjuvant chemotherapy compared with observation alone. A substantial number of patients may be better able to tolerate chemotherapy before, rather than after, thoracic surgery. There is a clinical rationale to compare preoperative versus postoperative chemotherapy in early stage NSCLC.

There was no consensus among conference participants regarding the role of radiotherapy in resected node-positive lung cancer, particularly those with hilar lymphadenopathy. Early negative trials of postoperative radiotherapy had significant design flaws; subsequent advances in dosimetry and target selection, as well as better patient selection through more accurate staging, may justify further investigation of the potential benefit of postoperative radiotherapy in carefully selected patients. As improved chemotherapy regimens reduce the rate of distant failure, local disease control may become a more important therapy component in extending patient survival.

Optimal Treatment of Locally Advanced Non – Small Cell Lung Cancer

All patients with locally advanced disease should receive a surgical evaluation before the initiation of chemotherapy and chest radiotherapy. The management approach that does the greatest disservice to these patients, in the opinion of conference participants, is the strategy of administering low doses of chemoradiation before a surgical consult has taken place. If it is then decided that the patient is not resectable, that individual has been denied the benefit of potentially curative doses of radiotherapy as well as potentially curative surgery. Patients who are judged to be unresectable before any treatment would retain the option of entering chemoradiotherapy trials for definitive therapy. Radiologic overstaging commonly occurs in this setting, with certain pathologically staged T₁ or T₂ tumors incorrectly staged by radiographic studies as T₃ or T₄. For this reason, clinically staged T₃ and T₄ tumors should not be judged inoperable without a consultation with an experienced thoracic surgeon.

For locally advanced disease, a multidisciplinary management and careful staging (i.e., by mediastinoscopy with or without CT and positron emission tomography scanning as well) provides the best opportunity for prolonged survival with good quality of life. Patients considered for extensive resection need a full preoperative assessment for comorbid disease or compromised pulmonary or cardiac function that would put them at an unacceptable risk for postoperative morbidity and mortality. The surgeon, radiation oncologist, medical oncologist, and pulmonologist need to be actively collaborating in

planning care for these complex cases. There is a role, as well, for the basic scientist, not in providing care but in analyzing treatment effects to help answer pertinent questions about the biology of the disease.

Participants expressed concern that others in the field have drawn a variety of conclusions about the management of N₂ disease from the initial report of the Intergroup 0139 trial, presented at the 2003 Annual Meeting of the American Society of Clinical Oncology. This study requires longer follow-up before it can be interpreted as establishing a standard for patients with stage IIIA disease. The participants considered that surgery may have benefit for a subset of patients. For patients with mediastinoscopy-staged N₂ disease, the participants felt that either chemoradiotherapy alone, induction chemotherapy followed by surgery, or even induction chemoradiotherapy followed by surgery could be a reasonable alternative depending on the clinical circumstances. The clinical circumstances could include the thoracic surgeon's level of expertise and comfort in operating after induction treatment. There is a clear need for better prognostic approaches for identifying the patients who would benefit from improved local control through surgery.

In unresectable stage III NSCLC, currently available evidence supports concurrent chemoradiation rather than sequential therapy and supports cisplatin-based chemotherapy (with etoposide or vinblastine) rather than carboplatin/paclitaxel. The data from the Cancer and Leukemia Group B 39801 and the LAMP study suggest that chemoradiotherapy with low-dose weekly carboplatin/paclitaxel may not be optimal and may be inferior to regimens using systemic doses of chemotherapy studied in the Intergroup 0139 trial, Radiation Therapy Oncology Group 92-04, and Southwest Oncology Group phase II study 9504.

However, the heterogeneity of stage III NSCLC presents a challenge in both clinical and research settings. Translating these findings from the clinical research environment, where only patients with good performance status were enrolled in trials, to community-based hospitals raises issues regarding the management of the toxicity. Many patients are in fact not eligible for concurrent therapy because of technical issues, comorbidity, or poor performance status. Induction chemotherapy is more effective than radiotherapy alone; thus, there is still a rationale for induction chemotherapy (two to three cycles of chemotherapy followed by radiation) in frail and/or elderly patients who would be unable to tolerate concurrent therapy. Studies aimed at defining more tolerable regimens for these groups of patients are needed.

Although current evidence points to concurrent cisplatin-based chemotherapy plus radiation as the most effective management strategy for unresectable stage III NSCLC, there are many issues and options that are still open to further study, including radiation dose, intensification of induction, or the use of novel agents in induction. More research is needed to determine the optimal dose and volume for radiation therapy in locally advanced NSCLC. Based on the Southwest Oncology Group concurrent chemoradiation

findings, the recommended dose would be 63 to 66 Gy using a standard fractionation scheme. However, trials to more accurately identify dose and schedule are clearly needed in this setting.

Future Research Directions

Although the novel molecularly targeted agents have been largely disappointing in trials when added to combination chemotherapy for metastatic lung cancer, there is great hope that these drugs can improve outcome in locally advanced disease. The novel agents may yet prove to have efficacy for subsets of NSCLC. In all likelihood, the role of these agents will be adjunctive, but it is far from clear how they will be incorporated, whether to enhance the efficacy of radiotherapy or provide additional control of distant metastases, such as in the brain. Given the many disappointing clinical trials of novel targeted agents in metastatic disease, it is essential that carefully planned correlative science accompany clinical trials to determine the biological effects of the agent and its contribution to both efficacy and toxicity. In discussing bevacizumab and other novel targeted therapies now being investigated in the advanced disease setting, participants expressed caution about assuming that targeted therapies showing efficacy in metastatic disease could be safely deployed in the treatment of early stage disease without more thorough investigation of their potential for toxicity and their mechanisms of action. The greatest concern was that agents judged to have an acceptable safety profile in the salvage setting may not be as tolerable for early stage patients with more treatment options and at least some possibility of cure.

Recent important trials that have limited accrual to specific disease stages, notably Cancer and Leukemia Group B 9633 and JBR.10, have taken as long as 7 years to accrue; other trials do not reach their planned accrual and as a result provide less robust data. There is a need for new study designs that will provide more rapid answers to clinically relevant questions. However, selection of study end points in early stage cancer is problematic, because the end points used in the advanced disease setting (time to progression and clinical response) are generally not applicable, and survival as an end point will likely be confounded by second-line and third-line therapies. Although enriching the population for studies of targeted therapies might seem a viable option, assuming the clinically relevant target has been correctly identified, if the subset is small, the studies may be very difficult to accrue. Phase II window-of-opportunity trials, looking at the biological and clinical effects of treatment given preoperatively, would be one option to provide data relatively rapidly that could then be used to plan larger trials.

Much promising research is now being done to identify genetic signatures associated with prognosis, progression, and metastasis. To further this research, greater efforts should be made to collect and analyze biological specimens from all disease stages but particularly in locally advanced NSCLC.