Adjuvant Treatment of Stage IB NSCLC: The Problem of Stage Subset Heterogeneity

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Stage IB non–small-cell lung carcinoma (NSCLC) represents a subset of early-stage, resectable NSCLC, usually treated with curative intent, but with historically modest 5-year survival rates ranging from 40% to 67% with surgical resection alone.[1,2] Disappointingly, modern adjuvant chemotherapy trials including stage IB patients have shown little evidence of chemotherapeutic benefit. In the Adjuvant Navelbine International Trialist Association (ANITA) trial, for example, the 5-year survival rate was 64% with surgery alone vs 62% with adjuvant chemotherapy.[3] Why is there such a wide range of results, and why does this subset of early-stage cancer patients have such a disappointing survival? As is often the case, the answer is likely multifactorial.

We hypothesize that considerable heterogeneity within the current stage IB category accounts for both the wide spectrum of results and relatively modest prognosis after therapy. With increased understanding of the molecular genetics of NSCLC, it has become more apparent that differences in the underlying cancer biology in individual patients account for a significant amount of the heterogeneity seen within any stage subset, especially one as broad as the IB category. As a distinct category within the tumor-node-metastasis (TNM) staging system for NSCLC, IB has long been under attack for being too broad, encompassing a wide range of tumor sizes (any tumor > 3 cm) and considerable variability in prognosis.[4-6]

Finally, it cannot be overemphasized that the stringency of preoperative and intraoperative staging greatly influences the accuracy of labeling NSCLC as stage IB, whether clinically or pathologically. Lack of positron-emission tomography/computed tomography (PET/CT) scan data, overinterpretation of increased standard uptake value (SUV) on PET/CT scan (false-positives), as well as lack of or incomplete nodal sampling/dissection at the time of surgery all result in inaccurate staging of some patients.

Herein, we review the available data regarding adjuvant chemotherapy following surgically resected stage IB NSCLC, framed within the context of present and future proposed definitions of this diagnosis. We discuss limitations of the current staging system and how this contributes to the mixed results seen with adjuvant treatment. Lastly, we present a perspective regarding current treatment options for stage IB NSCLC and review planned clinical trials for stage I disease designed to exploit new pharmacogenomic findings.

Staging Criteria

Current Criteria for Stage IB NSCLC

The most recent iteration of the staging system for NSCLC is the TNM International Staging System formulated in 1997.[2] As defined, stage IB represents T2, N0, M0 disease, indicating T2 for the tumor size/characteristic descriptor, N0 for negative nodes, and M0 for no evidence of metastasis. T2 denotes a primary tumor > 3 cm, any size tumor involving the visceral pleura, or any size tumor causing atelectasis extending to the hilum but not involving the whole lung. There is no upper limit on size. If the tumor is within the airway, it must not be within a lobar bronchus or more proximal, and > 2 cm from the carina.

The heterogeneity encompassed by this definition is demonstrated by the following comparative example: A 1-cm tumor detected on screening chest CT that involves the visceral pleura is designated stage IB, as is a 12-cm primary tumor with lobar collapse discovered on chest x-ray because of signs and symptoms of pneumonia. Both of these tumors are defined as IB, therein delineating one of the confounding issues with the current staging system, which influences the
range of prognoses associated with this stage.

**Proposal for Revised Criteria for Stage IB**

Recently, the International Association for the Study of Lung Cancer (IASLC) proposed a modification of the current staging system, and preliminary recommendations have been presented.[7] Analysis of over 18,000 patients in an international database revealed five distinct cutoff points in the absolute size of the primary tumor (in pathologically staged, node-negative patients) that correlated with survival (Figure 1).[8] Note the 58% 5-year survival rate in patients with a tumor > 3 cm but < 5 cm vs a 35% 5-year survival in patients with a tumor > 7 cm.

A summary of proposed T descriptor changes are shown in Table 1. Note the change in stage for tumors > 5 cm but ≤ 7 cm, from IB to IIA (the new T2b, N0, M0), and for tumors > 7 cm, from IB to IIB (the new T3, N0, M0). Adoption of the proposed changes in the T descriptor would appear to be a step forward in risk stratification for prognosis. Whether these changes would also assist in predicting potential benefit from adjuvant chemotherapy remains to be seen, although there is precedent for such a relationship, even within the currently defined T descriptor for stage IB, as discussed below.
Interestingly, the proposed changes to the IB stage subset do not address the clinical correlation of visceral pleural involvement independent of the size of the tumor or atelectasis, possibly because this detail has not been sufficiently delineated in the database. Relevant literature is divergent regarding the association between visceral pleural involvement and survival,[6] with some investigators reporting that outcomes are dictated more by the size of the primary tumor and other parameters.[9]

**Other Factors Related to Heterogeneity Within Stage IB**

As noted above, even within a given subset of T descriptors, individual cancers can differ greatly in regard to natural history, with divergent biologies conferring either an indolent course without distant metastases or an aggressive clinical course associated with early distant spread. It has become increasingly apparent that the TNM staging system reflects merely one component of a multifactorial process dictating the likelihood of survival in an individual patient. While it has long been known that specific features such as poor differentiation, presence of lymphovascular invasion,
and other variables\[6,10,11\] portend a worse prognosis in individual patients with NSCLC, it is understandable that clinicians have been reluctant to use this information to alter treatment recommendations outside of those specified by TNM status.

**Adjuvant Chemotherapy for Stage IB NSCLC**

Spurred by a 1995 meta-analysis demonstrating a statistically insignificant 5\% survival advantage in patients with stage I–III NSCLC who received adjuvant chemotherapy following surgical resection,\[12\] interest in adjuvant treatment for NSCLC was rekindled. Since then, six phase III studies evaluating the efficacy of cisplatin-based adjuvant therapy for NSCLC have been completed, three of which demonstrated a survival advantage, mostly restricted to patients with stage II or III disease (Table 2).\[3,13-19\] In a subgroup analysis, none of these trials demonstrated a survival benefit in patients with stage IB disease.

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<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjuvant Trials and Meta-analyses in NSCLC, 2003–2006</strong></td>
</tr>
<tr>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>IALT[18]</td>
</tr>
<tr>
<td>NCIC JBR.10[15]</td>
</tr>
<tr>
<td>ANITA[3]</td>
</tr>
<tr>
<td>CALGB 9633[16]</td>
</tr>
<tr>
<td>UFT Meta-analysis[17]</td>
</tr>
<tr>
<td>LACE Meta-analysis[14]</td>
</tr>
</tbody>
</table>

ANITA = Adjuvant Navelbine International Trialist Association; CALGB = Cancer and Leukemia Group B; IALT = International Adjuvant Lung Cancer Trial Collaborative Group; LACE = Lung Adjuvant Cisplatin Evaluation; NCIC = National Cancer Institute of Canada, NSCLC = non–small-cell lung cancer; UFT = uracil/tegafur.

Adapted from Wakelee H et al.[19]

In the Lung Adjuvant Cisplatin Evaluation (LACE), another meta-analysis incorporating data from more recent studies, an overall 5.5\% survival advantage at 5 years was conferred by adjuvant cisplatin-based chemotherapy (hazard ratio [HR] = 0.84, P < .001).\[14\] A trend toward benefit was seen in the stage IB subset, but it did not reach statistical significance. A recently reported updated Medical Research Council (MRC) meta-analysis did find a significant benefit of adjuvant therapy in stage I NSCLC. However, this may have been due to the inclusion of Asian trials, where differences in tumor biology and treatment protocols may have played a role in outcomes (see below).\[20\]

Two studies that have evaluated the role of adjuvant chemotherapy in stage IB NSCLC merit further discussion. Both excluded postoperative radiotherapy (PORT), a potentially confounding factor in some other adjuvant studies. The National Cancer Institute of Canada (NCIC) JBR.10 trial was a prospective, randomized trial evaluating observation vs four cycles of cisplatin/vinorelbine in completely resected NSCLC patients with stage IB–IIB disease.\[15\] This study demonstrated a 15\% survival advantage at 5 years in the chemotherapy group (HR = 0.7, P = .012). However, subset analysis revealed no significant survival advantage in stage IB patients (45\% of the study group)
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receiving adjuvant chemotherapy. The Cancer and Leukemia Group B (CALBG) 9633 trial is unique in specifically evaluating the role of adjuvant chemotherapy in surgically resected IB disease, and in using a regimen of carboplatin/paclitaxel vs observation.[16] This trial accrued 344 patients prior to early closure, when an interim analysis demonstrated a 12% survival advantage at 4 years (HR = 0.62) associated with adjuvant chemotherapy.

However, an update of CALBG 9633 reported at the annual meeting of the American Society of Clinical Oncology in 2006 revealed that the previously reported survival advantage was no longer statistically significant at 5-year follow-up. Failure-free survival still favored the chemotherapy arm (HR = 0.74, P = .03). Possible explanations for the lack of survival advantage of chemotherapy at 5 years include lack of power in the study (344 patients instead of the planned 500), lack of benefit with carboplatin as opposed to cisplatin, or true lack of effect in stage IB disease. An unplanned subset analysis of the CALBG 9633 data revealed that in patients with tumors ≥ 4 cm (approximately 100 patients in each arm), a survival advantage with adjuvant chemotherapy was still observed (HR = 0.66, P = .04).[21]

In contrast to the disappointing results of platinum-based chemotherapy for stage IB NSCLC, the novel oral agent uracil/tetrafluor (UFT), administered daily for 2 years, may produce a survival benefit in the adjuvant setting. A large randomized trial of adjuvant UFT in 978 patients with stage I NSCLC, conducted in Japan, demonstrated a survival advantage in the treatment group (HR = 0.71, P = .04).[22] Furthermore, a meta-analysis of six randomized trials of adjuvant UFT, consisting of more than 2,000 patients altogether, was also positive for survival (HR = 0.74, P = .001), and was limited to tumors > 2 cm in size.[17] It is possible that these results reflect the unique biology of NSCLC in Japanese patients, as emerging data increasingly suggest differences in the natural history and/or treatment outcome of NSCLC based on ethnicity and race.[23]

Future Directions

As discussed above, separating heterogeneous patient subsets—currently lumped together as stage IB NSCLC—into different stage subsets will assist in risk stratification. This change awaits adoption of the IASLC-sponsored revision of the TNM staging system, which should be ratified by 2009. The T descriptor has rightfully received the most attention, with five distinct size cutoffs that correlate with survival.[8] This new TNM system will undoubtedly be applied retrospectively to all of the recent adjuvant chemotherapy trials, providing a perspective not currently available.

In the interim, a newly activated Eastern Cooperative Oncology Group (ECOG)-led intergroup trial (E1505) is evaluating the role of adjuvant cisplatin-based chemotherapy, with or without the vascular endothelial growth factor inhibitor bevacizumab (Avastin), in early-stage NSCLC, including resected stage IB disease ≥ 4 cm. Based on the previous E4599 trial showing improved outcomes with bevacizumab plus chemotherapy in advanced-stage disease, this study offers the opportunity of revisiting adjuvant chemotherapy in a subset of stage IB (≥ 4 cm) as currently defined, where there is potentially the greatest likelihood of benefit.[24]

Lastly, emerging pharmacogenomic and gene-expression microarray data offer the opportunity to define a variety of biologically distinct patient subsets within stage I NSCLC—both those with an excellent prognosis, perhaps requiring no adjuvant therapy, and others with a relatively poor prognosis, but for whom biomarkers predict a benefit from platinum-based chemotherapy. Two cooperative group trials now in development are designed to test these concepts. The CALGB trial C30506 targets patients with resected stage I NSCLC 2 to 4 cm in size, who are not candidates for the ongoing E1505 Intergroup trial and who do not routinely receive adjuvant chemotherapy by current standards. This proposed study uses a genomics prognostic model known as the lung metagene score (LMS) to select patients for adjuvant chemotherapy based on recent preliminary data.[25] Patients with a low metagene score (who are felt to be at low risk for recurrence) are observed, whereas those with an unfavorable score are randomized to either adjuvant chemotherapy or standard observation. The two primary objectives of the trial are to validate the positive prognostic value for survival of a low LMS and to determine whether a survival advantage is associated with adjuvant chemotherapy in patients with a high LMS.

The concept of “personalized” chemotherapy in the adjuvant treatment of early-stage NSCLC is being investigated by the Southwest Oncology Group (SWOG) in a feasibility trial (S0720) building on the work of Zheng and Bepler as well as others demonstrating that ERCC1 and RRM1 share prognostic value and predictive value for platinum-based chemotherapy in NSCLC.[26,27] Using a recent innovation in methodology for quantitative protein expression (automated quantitative analysis, or AQUA, see Figure 2),[26] patients with high expression levels of both genes had better survival than other groups.
The S0720 trial is designed to test the feasibility of pharmacogenomic-directed adjuvant therapy by accruing patients with stage I NSCLC (≥ 2 cm in size) who have had a complete resection—a group for whom adjuvant chemotherapy is currently not the standard of care. Based on AQUA assessment of ERCC1 and RRM1 from the surgical specimen, patients will be assigned to either observation alone (because an excellent prognosis is suggested by high levels of ERCC1 or RRM1, and the tumor is unlikely to respond to platinum-based therapy) or cisplatin/gemcitabine (Gemzar) adjuvant chemotherapy (because they are predicted to be responsive due to low expression of both genes). The primary endpoint of S0720 is feasibility, defined by the percentage of patients who can be...
assigned treatment appropriately, reflecting the adequacy of tumor specimen collection and analysis.

**Conclusions**

In summary, stage IB NSCLC as currently defined represents a large and heterogeneous group of patients in whom prognosis and responsiveness to chemotherapy are likely highly variable. Revisions to the TNM staging criteria for stage IB disease should assist in risk stratification. As presently defined, platinum-based adjuvant chemotherapy cannot be considered standard of care for stage IB disease.[28] Future directions include refinement of prognostic subgroups, and clinical translation of emerging strategies for pharmacogenomics and gene-expression profiling in this important subset of NSCLC patients.

**References:**


13. Wakelee HA, Schiller JH, Gandara DA: Current status of adjuvant chemotherapy for stage IB


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