The role of surgery for N2-positive, stage IIIA non–small cell lung cancer (NSCLC) has evolved over the past three decades from primary therapy to its current role as an important component in a multimodality management strategy. In the era before the ubiquitous use of computed tomography, patients without symptoms, biochemical abnormalities, or mediastinal widening on plain chest radiography were offered resection as best therapy. Historical series from experienced centers document the dismal survival when patients with clinically obvious N2 NSCLC were treated with primary surgery (refs. 1–4; Table 1). The addition of adjuvant thoracic radiotherapy did not improve survival, suggesting that N2 disease was not merely a loco-regional problem; rather, it was a marker of systemic disease burden. Mediastinoscopy, although introduced by Harken (5) and Carlens (6) in the 1950s, gained favor only after Pearson et al. (4) showed the futility of proceeding to resection when clinical N2 disease was confirmed pathologically by this simple staging procedure (Table 1).

**Evolution of Multimodality Therapy Including Surgery**

Based on the common pattern of distant relapse and the availability of drugs with greater activity against NSCLC, strategies to incorporate chemotherapy into the treatment plan evolved through the late 1980s. The use of chemotherapy as an adjuvant treatment following surgery proved ineffective in enhancing survival. Moreover, this therapeutic sequence (surgery followed by multiple cycles of systemic therapy) was difficult to complete, with many patients requiring dose reductions and/or omitted cycles.

Two small (n = 120 combined) randomized trials published in early 1994 confirmed the superiority of induction chemotherapy followed by surgery over surgery alone for patients with stage IIIA disease (refs. 7, 8; Table 2). Unlike the previous experience with adjuvant chemotherapy, there were no alterations in the induction regimen in the Rosell et al. study, whereas 70% of patients in the Roth et al. study required dose reductions in subsequent cycles due to myelosuppression. Both trials employed three preoperative cycles of cisplatin-based combination chemotherapy but differed in how patients were managed postoperatively. In the Rosell trial, all patients received thoracic radiotherapy following resection. In contrast, radiotherapy was used in the Roth trial only for patients whose disease progressed or was unresectable. Patients in the Roth trial who experienced objective radiographic or pathologic responses received three additional cycles of cisplatin, etoposide, and cyclophosphamide. Both trials also included stage III patients by virtue of chest wall invasion (T3, N0-1). Patients with this discreet pattern of local invasion (usually of the chest wall) but without N2 disease have a documented survival superior to cohorts with stage IIIA disease by virtue of mediastinal nodal involvement. In 1997, this observation led to the revision of the NSCLC staging system creating new stage II NSCLC subsets including patients with T3, N0 tumors. Whereas mediastinoscopy was routinely used in the Roth trial, its use was unbalanced in the Rosell study. The majority of
patients (83%) in the chemotherapy followed by surgery and thoracic radiotherapy arm had N2 disease confirmed by mediastinoscopy, whereas mediastinoscopy was used in only 63% of patients having surgery and thoracic radiotherapy. Despite all of these criticisms and limitations, both trials were stopped early by their respective data monitoring boards because of the overwhelming survival benefit observed in the groups receiving chemotherapy. The durability of this approach was confirmed with 7 years of actual follow-up in both studies (9, 10).

Before these sentinel findings in patients with operable stage IIIA NSCLC, chemoradiotherapy was proven superior to chemotherapy alone in nonoperable stage III disease (11). Taken together, these trials served as the stimulus to investigate the safety and utility of preoperative chemoradiotherapy delivered sequentially (12, 13) or concurrently (14) for N2-positive patients (Table 2). The Southwest Oncology Group (SWOG) published the largest multi-institutional trial (n = 126) using this strategy (14). Compared with induction chemotherapy alone, concurrent chemoradiotherapy improved nodal downstaging (SWOG 8805 53% versus CALGB 8935 22%) and yielded a higher number of pathologic complete responses (21% versus 0%, respectively; Table 3). The sequential strategy employed by CALGB in a phase II trial (12) yielded similar 3-year survival rates (CALGB 23%, SWOG 26%; Table 2), although these patients experienced a pathologic response rate that was only one third that seen in SWOG 8805 (ref. 14; Table 3).

**Table 1.** Survival following primary surgery for N2 NSCLC

<table>
<thead>
<tr>
<th>Author/institution</th>
<th>Year</th>
<th>n</th>
<th>Disease burden</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paulsen and Urschel (1)</td>
<td>1971</td>
<td>193</td>
<td>N2 at thoracotomy</td>
<td>7%, 5 y</td>
</tr>
<tr>
<td>Martini/MSKCC (2)</td>
<td>1980</td>
<td>241</td>
<td>Clinical N2</td>
<td>20%, 3 y</td>
</tr>
<tr>
<td>Naruke/NCC-Japan (3)</td>
<td>1988</td>
<td>345</td>
<td>Clinical N2</td>
<td>16%, 5 y</td>
</tr>
<tr>
<td>Pearson/TGH (4)</td>
<td>1982</td>
<td>79</td>
<td>Mediastinoscopy, N2+</td>
<td>9%, 5 y</td>
</tr>
<tr>
<td>Pearson/TGH (4)</td>
<td>1982</td>
<td>62</td>
<td>Mediastinoscopy, N2</td>
<td>24%, 5 y</td>
</tr>
</tbody>
</table>

Abbreviations: MSKCC, Memorial Sloan Kettering Cancer Center; NCC-Japan, National Cancer Center, Tokyo, Japan; TGH, Toronto General Hospital.

**Table 2.** Important multimodality trials in N2 NSCLC

<table>
<thead>
<tr>
<th>Year</th>
<th>Author/affiliation</th>
<th>Design</th>
<th>n</th>
<th>Strategy</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>Roth/MDAC (8, 9)</td>
<td>Phase III</td>
<td>60</td>
<td>CTX-S-CTX/RT versus S-RT</td>
<td>43%, 3 y; 36%, 5 y versus 19%, 3 y; 15%, 5 y</td>
</tr>
<tr>
<td>1994</td>
<td>Rosell/Barcelona (7, 10)</td>
<td>Phase III</td>
<td>60</td>
<td>CTX-S-RT versus S-RT</td>
<td>20%, 3 y; 17%, 5 y versus 5%, 3 y; 0%, 0 y</td>
</tr>
<tr>
<td>1995</td>
<td>Sugarbaker/CALGB (12)</td>
<td>Phase II</td>
<td>74</td>
<td>CTX-S-RT</td>
<td>23%, 3 y</td>
</tr>
<tr>
<td>1995</td>
<td>Albain/SWOG (14)</td>
<td>Phase II</td>
<td>75</td>
<td>CTX/RT-R</td>
<td>26%, 3 y</td>
</tr>
<tr>
<td>2003</td>
<td>INT 0139 (23, 24)</td>
<td>Phase III</td>
<td>392</td>
<td>Chemo/RT versus Chemo/RT-S</td>
<td>33%, 3 y versus 38%, 3 y</td>
</tr>
</tbody>
</table>

Abbreviations: MDACC, M.D. Anderson Cancer Center; CALGB, Cancer and Leukemia Group B; INT, Intergroup; CTX, chemotherapy; RT, radiotherapy; S, surgery.

**Table 3.** Clinical versus histopathologic assessment of response to induction therapy

<table>
<thead>
<tr>
<th>Induction regimen</th>
<th>Clinical response (%)</th>
<th>Pathologic response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>cCR + cPR SD pCR pPR</td>
<td></td>
</tr>
<tr>
<td>CALGB 8935 (12)</td>
<td>0* 88†</td>
<td>0′ 22</td>
</tr>
<tr>
<td>Martini et al (15)</td>
<td>73 23</td>
<td>19 10</td>
</tr>
<tr>
<td>Chemoradiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faber et al (16)</td>
<td>65 23</td>
<td>20 26</td>
</tr>
<tr>
<td>SWOG 8805 (14)</td>
<td>59 29</td>
<td>15 57</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; c, clinical; p, pathologic; CALGB, Cancer and Leukemia Group B. *There were no CR’s in CALGB 8935. †cPR and SD were reported in aggregate.

**Assessment of Response**

Traditionally, response to chemotherapy was interpreted radiographically by reduction in the cross-sectional dimensions of areas of measurable disease. With computed tomography, clinical response could be assessed for both the primary tumor (T stage) and the mediastinal nodal disease (N stage). Of note, radiographic assessment soon after induction therapy was often inaccurate and correlated poorly with important outcomes such as resectability and/or survival. In different patients receiving an identical neoadjuvant regimen, the clinical assessment of response both underestimated and overestimated residual viable cancer with regard to both T and N (refs. 12, 14–16; Table 3). Patients with >50% reduction in radiographic tumor burden following induction therapy were often found to still have viable N2 disease at time of resection. Despite the objective partial response assessed clinically, these patients were not down-staged by the induction regimen. Conversely, other patients without dramatic clinical responses assessed by computed tomography following neoadjuvant therapy were found at resection to have only residual scar and/or necrosis at the primary tumor or nodal metastatic sites. Such clinical non-responders were actually effectively down-staged and enjoyed improved survival. Pathologic response became a more accurate predictor of outcome. Eradication of mediastinal...
nodal disease (N-status pathologic response, also called nodal downstaging) and completeness of resection became the best surrogates for survival (12, 14). Clinical, biological, or histologic predictors of pathologic response detectable at the time of diagnosis, during induction therapy, or before a planned resection remain elusive. In recent years, individual centers have tested variations in chemoradiotherapy schema including novel two to three drug combinations, dosing schedules, and intensity and radiation fractionation schemes to enhance downstaging, pathologic response, and hopefully survival (17). Whereas these trials show promise, no pretreatment factor has identified or predicted response. Moreover, the complexity of the regimens restricts access to highly selected patients at documented centers of excellence.

Restaging Strategies

If pathologic response cannot be predicted, perhaps patients who do not show a pathologic response are better targets of investigation. Multiple investigators have documented the negative effect of residual N2 disease following induction chemotherapy (12) or chemoradiotherapy (14, 18, 19). The aggregate 3-year survival from these series is ~18% for patients not down-staged by induction therapy and is similar to the survival reported in the 1970s and 1980s following primary surgery for N2 disease (Table 1). In the context of a multimodality treatment plan, major pulmonary resection for patients not experiencing pathologic response exposes them to operative risk without hope for benefit. Identification of the patients refractory to induction therapy would yield an important cohort of patients appropriate for alternative medical or radiation-based therapies.

Identifying the nonresponders has been the goal of a CALGB trial of thoracoscopic restaging following induction therapy initiated in 1999. Results of this feasibility study are expected at the American Society of Clinical Oncology in 2005. Other minimally invasive strategies with restaging potential include serial, quantitative positron emission tomography scanning (20); repeat mediastinoscopy (21); transbronchial needle aspiration; and endoscopic ultrasound-guided fine needle aspiration (22). By whatever means identified, nonresponders will be spared the morbidity of multiple futile and arduous therapies and will become an important cohort for investigations of novel therapeutics.

Response need not be all or nothing and should better be viewed as a continuum. It is affected by many treatment factors including sensitivity to, intensity of, and the interplay between drug(s) and/or radiation as well as the timing and technique of its assessment. As such, measurement of pathologic response earlier in treatment may not carry the same prognostic value as similar measurements done after multiple cycles of treatment. Investigators at the Cleveland Clinic employed an accelerated regimen of two-drug therapy with concurrent, hyperfractionated radiotherapy in which the induction therapy is completed in just 2 weeks (17). In this study, 35% of stage IIIA patients achieved nodal downstaging and nearly a 50% actuarial 5-year survival. Of interest, an additional 53% of the stage IIIA patients had some residual N2 disease but still experienced a 30% actuarial 5-year survival. Such results confound the paradigm of absolute nodal down-staging and create a new middle ground of “pathologic partial response” that warrants further evaluation.

Surgery as the Adjuvant Therapy

As induction therapy improved, the use of resection in stage IIA NSCLC was again called into question. The lung cancer Intergroup addressed this issue with a randomized trial evaluating 392 patients randomized to induction chemoradiotherapy followed by surgery versus definitive chemoradiotherapy (23). Surgery following induction chemoradiotherapy was associated with a significant improvement in progression-free survival and almost a 50% reduction in local failure (24). Overall survival was equivalent between the two treatments leading some to conclude that the addition of surgical resection provides no benefit. Proponents of surgery argue that the equivalence in overall survival is primarily because of early treatment-related mortality in the chemoradiotherapy followed by surgery cohort. They note that with 3 years of follow-up there is a trend in overall survival favoring the surgical arm. This controversy underscores the need for more mature outcome analysis before concluding that resection following induction chemoradiotherapy is standard of care.

Conclusions

This 30-year experience supports the ongoing and vital role of surgery in the management of operable patients presenting with N2-positive NSCLC. Resection following induction therapy provides for superior local control and is clearly the most accurate method to assess response to treatment and thus predict survival. The mediastinal dissection/sampling has been reported as more prognostic than therapeutic in this stage of disease (18); however, the recently completed ACOSOG trial Z0030 which randomized resected patients to mediastinal dissection versus sampling may provide more compelling evidence to support or refute this premise once mature results are available. Because distant relapse is so common, survival is most likely enhanced only in those patients who respond to the systemic arm of treatment. Refinement in analytic statistical methodology (e.g., propensity matching and hazard function analysis; ref. 25), chemosensitivity analyses, or identification of genetic or biochemical markers of response (26) will be necessary to enhance our ability to select patients who will benefit from resection.

Open Discussion

Dr. Thomas Lynch: You raised the issue of whether or not a patient with residual N2 disease should have surgery. I always struggled with the idea that the 18% 5-year survival for people with N2 was so bad that it justified not operating on those people. Clearly, we don’t want people who are destined to die of metastatic disease go through a morbid operation. On the other hand, 18% is not a terrible outcome in that setting.

Dr. DeCamp: The survival with combined chemoradiation in the Dillman study was 15%. If we had consistently effective therapy and I knew that surgery was futile, I wouldn’t offer it.
Right now, we don’t even know how to assess whether the patient has responded to therapy. Radiographic assessment doesn’t work. It’s wrong in both directions; it underestimates and overestimates.

Dr. David Gandara: Just to follow up on that last point. One of the striking things about the SWOG 8805 is that there were 26 patients who had only stable disease. There was no shrinkage of the tumor by CT scan, but in our study design, they all went to surgery if they were medically suitable. Of those 26 patients, 12 had a pathologic complete response, or what we called near CR, which meant only a few microscopic foci of tumor left behind. I think that just emphasizes the point that, at least by CT, it is very difficult to tell who to take to surgery unless they have obviously had progression.

Dr. DeCamp: The surgeons will agree that we like a narrow window between completion of therapy and getting them into surgery. The longer you wait for the biologic response, the more difficult and fibrotic the dissection is. In CALGB 8935 also there were stable patients who had good responses and patients with geometric shrinkage who still had residual N2 disease.

Dr. Joan Schiller: Can you summarize for me what you think the role of surgery is for patients who present with clinical N2 disease?

Dr. DeCamp: I think they need a mediastinoscopy. They need induction therapy, and then in the absence of a better way to assess response, I would still resect them.

Dr. Schiller: For patients with bulky N2 nodes that are mediastinoscopy positive, what do you think the standard of care is? Is it chemorads or is it some form of chemorad plus surgery?

Dr. DeCamp: Induction therapy implies surgery at least for some patients. I still think there’s a role for surgery because you can induce certain patients. If they have a clinical CR and you don’t resect them, I think you’re going to have a higher local failure rate.

Dr. Schiller: So the Intergroup 0139 study which looked at chemoradiation versus chemoradiation and surgery, in your interpretation that is a positive trial?

Dr. DeCamp: At least in failure-free survival it favored the surgery arm. The overall survival hasn’t yet. There is a trend and my prediction is that there will be an overall survival benefit.

Dr. Lynch: But what do you think the magnitude of benefit for surgery would be? I would argue it is going to be 5-7%, and that trial wasn’t powered to pick up a 5-7% survival benefit.

Dr. Douglas Wood: Many of our colleagues have extrapolated the Toronto data about mediastinoscopy and clinical N2 disease [J Thorac Cardiovasc Surg 1982; 83:1-11] into an argument that if N2 disease is not apparent clinically, then those patients should have an operation upfront and that N2 disease discovered then at thoracotomy is benefited by surgery. I’d say that is probably the most common thoracic surgical view in the United States, that clinically negative N2 nodes benefit from upfront surgery.

Dr. DeCamp: I think that group of patients is actually most likely to benefit from induction therapy and surgery. CT is a poor way to assess response—it has no ability to detect or predict microscopic disease. We know that 30% of patients with T2 tumors, especially if they are adenocarcinomas, have occult N2 disease. The harder you look, the more you find.

Dr. Bruce Johnson: You said that the surgery is a really good way to assess response; that particular way of assessing response, depending on the hands, carries with it between a 3% and 7% mortality, so I would argue that is a very poor way to assess response. In order to do a resection after treatment, it really has to carry with it some therapeutic benefit to the patient to subject them to that.

Dr. DeCamp: It’s the most accurate assessment of response. You give chemotherapy to a lot of patients who don’t benefit and we operate on patients who don’t benefit. Unfortunately, we treat a disease where we lose more often than we win.

Dr. Lynch: I never quite understood that idea of assessing response, particularly now in the era of PET scans and better CTs. I think surgery has a role still because it is the best local modality and, as Dr. Bogart said yesterday, that does impact on survival in this setting. I don’t think Intergroup 0139 rules out a substantial clinical benefit to surgery. It was underpowered to show the kind of benefit that a local modality would present.

Dr. James Jett: I take a different point of view. If there is positive N2 disease on mediastinoscopy, I don’t know of any good data to say that surgery adds to survival. I would treat those people with chemoradiotherapy. The problem here is giving the patient mixed messages. If the surgeon says, “You go back to the oncologist and I’ll give surgery another try after they do their induction therapy,” then I can’t put that patient on any trial with chemotherapy. So the thinking there has boxed us in and really dropped our accrual on trials in stage IIIA, IIIB unresectable disease.

Dr. Everett Vokes: Neck dissection clearly adds to local control and probably survival in some patients with head and neck cancer. It gives us a very accurate staging assessment, and it is not morbid by and large or at least with current modifications. So how does that concept apply to mediastinal lymph node dissection?

Dr. DeCamp: I hope we’ll have a systematic evaluation of that when ACOsog presents their randomized comparison of mediastinal lymph node dissection versus sampling. As Dr. Wood will agree, we have a hard time getting our rank and file to practice routine, effective mediastinoscopy. Formal mediastinal node dissection is going to be the next challenge if it is shown to be beneficial and we then try to disseminate it and change the standard of practice. The average thoracic surgeon or general surgeon doing thoracic surgery relies on a normal CT scan and operates on those patients.

Dr. Wood: We have been debating whether radiation or surgery or both provide the optimal means for local regional control and that we haven’t tested. We haven’t tested whether perhaps patients with nonbulky N2 disease should have chemotherapy and surgery without radiation. Nobody disagrees that all of these patients need systemic therapy, but we’re just not sure which combination provides the best local regional control.

Dr. Gandara: That will be tested in the RTOG trial for N2 disease. The postoperative radiation will only be for cause, for instance if there are positive margins.
References


Clinical Cancer Research

The Role of Surgery in N2 Non–Small Cell Lung Cancer
Malcolm M. DeCamp, Jr., Simon Ashiku and Robert Thurer


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