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The Role of Consolidation Therapy for Stage III Non-Small Cell Lung Cancer With Persistent N2 Disease After Induction Chemotherapy

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Abstract

Background—Persistent pathologic mediastinal nodal involvement after induction chemotherapy and surgical resection is a negative prognostic factor for stage III-N2 non-small cell lung cancer patients. This population has high rates of local-regional failure and distant failure, yet the effectiveness of additional therapies is not clear. We assessed the role of consolidative therapies (postoperative radiation therapy and chemotherapy) for such patients.

Methods—In all, 179 patients with stage III-N2 non-small cell lung cancer at MD Anderson Cancer Center were treated with induction chemotherapy followed by surgery from 1998 through 2008; 61 patients in this cohort had persistent, pathologically confirmed, mediastinal nodal disease, and were treated with postoperative radiation therapy. Local-regional failure was defined as recurrence at the surgical site or lymph nodes (levels 1 to 14, including supraclavicular), or both. Overall survival was calculated using the Kaplan-Meier method, and survival outcomes were assessed by log rank tests. Univariate and multivariate Cox proportional hazards models were used to identify factors influencing local-regional failure, distant failure, and overall survival.

Results—All patients received postoperative radiation therapy after surgery, but approximately 25% of the patients also received additional chemotherapy: 9 (15%) with concurrent chemotherapy, 4 (7%) received adjuvant sequential chemotherapy, and 2 (3%) received both. Multivariate analysis indicated that additional postoperative chemotherapy significantly reduced distant failure (hazard ratio 0.183, 95% confidence interval: 0.052 to 0.649, $p = 0.009$) and improved overall survival (hazard ratio 0.233, 95% confidence interval: 0.089 to 0.612, $p = 0.003$). However, additional postoperative chemotherapy had no effect on local-regional failure.

Conclusions—Aggressive consolidative therapies may improve outcomes for patients with persistent N2 disease after induction chemotherapy and surgery.

For patients with stage III non-small cell lung cancer (NSCLC), multimodality therapy remains the standard of care. Approximately 10% of all NSCLC cases present as stage IIIA-N2, and for these patients, disease control and overall survival continue to be poor, with 5-year survival rates of 23% [1]. Several randomized trials have demonstrated local recurrence rates of 11% to 34% among patients with stages I to III disease after surgery alone [2–4].

These recurrence rates are even higher for patients who have N2 disease at the time of surgery, as high as 60% at 5 years [5].

Based on randomized trials and meta-analysis demonstrating a survival benefit of induction chemotherapy plus surgery versus surgery alone [6–9], induction chemotherapy for stage IIIA-N2 NSCLC is a reasonable option for the management of potentially resectable stage IIIA-N2 NSCLC. Most of the benefit of induction chemotherapy is restricted to more locally advanced, stage II to III patients [10]. It is known that nodal response after induction chemotherapy is an important prognostic factor [8, 11–13]. In one trial [8], induction chemotherapy produced 3-year and 5-year survival rates of 67.7% and 51.6%, respectively, for patients with disease downstaged to pN0, compared with 38.5% and 17.6% for patients with pN1-3 disease. A study by the Swiss SAKK group [13] led to the conclusion that patients with nodal downstaging to N0-1 after induction therapy had better disease-free survival and overall survival than patients with mediastinal lymph node involvement. Despite the poorer outcomes, the importance of consolidative therapies for patients with persistent stage III-N2 disease after induction chemotherapy and surgery is largely unknown.

At our institution, postoperative radiotherapy (PORT) is standard practice for patients with persistent N2 disease after induction chemotherapy and surgery. However, additional consolidative chemotherapy is not commonly practiced and is only done according to the discretion of the treating physicians. In this study, we sought to determine the importance of consolidative chemotherapy with respect to disease-specific outcomes for patients with persistent nodal disease after induction chemotherapy, surgery, and PORT. We hypothesized that more aggressive treatment after surgery would be needed to improve outcomes for such patients.

Patients and Methods

Patient Selection

We identified 179 consecutive patients with stage III NSCLC (N2) who had been treated at MD Anderson Cancer Center with induction chemotherapy followed by surgery from 1998 through 2008. We excluded patients with tumors not of non-small cell origin, not having N2 disease at the time of surgery, and death within 1 month of surgery. We also excluded the 17 patients who did not receive PORT after surgery because that was a heterogeneous group of patients who did not receive PORT for various reasons (patient intolerance, prolonged postoperative recovery, progressive disease, prior radiation). After exclusions, 61 patients received PORT and were selected for this study. This post hoc analysis was approved by the Institutional Review Board of MD Anderson.

Treatment and Response Assessment

Patients who are deemed an inoperable candidate up front (multistation N2, medical or technical inoperability) usually receive definitive chemoradiation, with or without induction chemotherapy. However, all patients included in this study had clinically or pathologically proven N2 involvement before starting induction chemotherapy. The choice of neoadjuvant chemotherapy was at the discretion of the treating medical oncologist. All patients underwent surgical resection at MD Anderson. One patient had attempted resection of a T4 lesion that was deemed inoperable and was subsequently treated with chemoradiation. All patients received PORT after surgery. Additional treatments used after surgery and PORT include PORT with concurrent chemotherapy or adjuvant sequential chemotherapy, or both. The majority of patients ($n = 46$) received no additional chemotherapy after surgery. The PORT was conducted either at our institution or outside, with a median treatment dose of

50.4 Gy (range, 33 Gy to 64.8 Gy). Treatment fields included the whole mediastinum, hilum and stump, and the surgical site. The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was used to assess response to induction chemotherapy according to the change in the largest diameter of the tumor on positron emission tomography/computed tomography imaging.

Local-Regional and Distant Recurrence

Local-regional recurrences were defined as those at the surgical site, at the anastomotic or bronchial stump, or in the local-regional lymph nodes (levels 1–14, including supraclavicular). Cervical and abdominal lymph node disease was considered distant recurrence. Disease recurrence was verified by either imaging (positron emission tomography/computed tomography) or biopsy. Time to recurrence was based on the date of imaging-proven or biopsy-proven disease recurrence and the original date of surgery. Of the patients treated with PORT at MD Anderson, radiation treatment plans were overlaid by deformable registration onto the diagnostic scans documenting disease recurrence to determine the patterns of failure. Failure within the planning tumor volume was considered an in-field recurrence, outside the planning tumor volume was an out-field recurrence, and any failure that lies within the 50% isodose line was considered a marginal recurrence.

Follow-Up and Survival

The date of diagnosis was based on the date of biopsy-proven NSCLC. That was compared with the last contact date, which was the last known date of the patient's vital status and disease status, to calculate follow-up time. Overall survival was calculated based on the initial date of diagnosis. A total of 11 patients had missing data on disease recurrence (either local-regional or distant or both) owing to poor follow up. One patient had an unknown vital status.

Statistical Analysis

All statistical analyses were performed using SPSS version 17.0 (SPSS Inc, Chicago, IL). Pearson two-sided χ^2 tests were used to evaluate patient- and treatment-related differences between patients who did or did not receive PORT or chemotherapy. Univariate Cox regression analysis was performed using death, local-regional failure (LRF), or distant failure (DF) as outcomes, with a significance level of p less than 0.05. Covariates that were significant at p less than 0.25 were included in the multivariable Cox regression. Backward stepwise Wald elimination at $p = 0.10$ was used to establish the final model. Multivariate analysis were performed separately for overall survival, local, and distant metastasis. Patients with incomplete data were excluded from the multivariate analysis. Survival functions were calculated according to the Kaplan-Meier method, and differences were assessed with the log rank test.

Results

Patient and Treatment Characteristics

From May 1998 through December 2008, 61 patients had persistent pathologically proven N2 disease after induction chemotherapy and were treated with surgery followed by PORT. Median follow-up time for all patients was 28.1 months (range, 6.5 to 122.5). There were 29 cancer-related deaths and 13 noncancer-related deaths. Patient characteristics are listed in Table 1. The median age was 61 years (range, 40 to 74); a slight majority was female (56%), and most patients (92%) had good Karnofsky performance status (80%).

The median number of induction chemotherapy cycles was 3 (range, 1 to 6), with 89% of patients receiving a platinum-taxane doublet regimen. The majority of patients (80%)

received a lobectomy or bilobectomy. In this cohort, all patients received PORT after surgery. A subset of patients received concurrent chemotherapy ($n = 9$, 15%), adjuvant sequential chemotherapy ($n = 4$, 7%) or both concurrent followed by adjuvant chemotherapy ($n = 2$, 3%). The most common reasons for receipt of systemic dose concurrent or adjuvant chemotherapy were multilevel N2 disease, clinical T4 disease on initial presentation, or institutional protocols requiring additional adjuvant chemotherapy. Overall, 46 patients did not receive postoperative chemotherapy.

Table 2 summarizes the details of the chemotherapy used and the therapies delivered for this patient cohort. Of the 11 patients who received concurrent chemotherapy with PORT, 5 (45.5%) received the same therapy as their induction plan. For the 6 patients who received adjuvant systemic dose chemotherapy after PORT, only 1 patient received the same drug regimen as the induction course, with the majority of the patients receiving a different chemotherapy regimen ($n = 5$, 83.3%) several weeks after PORT.

Local-Regional Failure Patterns

Seven patients (11.4%) had LRF as the site of first failure, and overall, 10 patients (16.4%) had LRF at any time, with or without distant metastasis. On univariate analysis, no difference in LRF was observed with the receipt of postoperative chemotherapy (hazard ratio [HR] 0.864, 95% confidence interval [CI]: 0.223 to 3.354, $p = 0.833$; Fig 1A). Multivariate analysis demonstrated that only a lower treatment response following induction chemotherapy, measured by the change of tumor size as a continuous variable, was associated with higher LRF rates (HR 1.030, 95% CI: 1.001 to 1.060, $p = 0.044$).

Distant Failure Patterns

Under univariate analysis, the only predictor of lower DF rates was the addition of postoperative chemotherapy (HR 0.386, 95% CI: 0.149 to 1.002, $p = 0.05$; Fig 1B). In multivariate analyses, postoperative chemotherapy remained a significant independent predictor of lower distant failures (HR 0.183, 95% CI: 0.052 to 0.649, $p = 0.009$). In addition, a higher Karnofsky performance status, squamous cell histology, and clinical T1 or T2 at initial diagnosis also conferred a lower risk for DF (Table 3).

Overall Survival

Univariate analysis revealed that older age (HR 1.041, 95% CI: 1.006 to 1.077, $p = 0.020$), and clinical T4 disease, before surgery (HR 3.532, 95% CI: 1.207 to 10.339, $p = 0.033$), were associated with a worse overall survival, and postoperative chemotherapy was associated with improved overall survival (HR 0.425, 95% CI: 0.188 to 0.960, $p = 0.040$; Fig 1C). These same factors remained significant under multivariate analysis (Table 4).

Overall Recurrence Patterns

Distant failures were the most common sites of first failure in this group of patients (Table 5). Most local-regional recurrences appeared in the mediastinal and hilar lymph nodes. Of the 10 patients who had LRF at any time after PORT, 7 had radiation treatment plans available for review; of those 7 patients, 2 (29%) had failures within the treatment field, 4 (57%) outside the treatment field, and 1 (14%) was marginal. Most common site of distant metastasis is the lung (52%), followed by the brain (32%; Table 6).

Comment

According to the National Comprehensive Cancer Network version 2.2012 guidelines (NSCLC-7), induction chemotherapy, surgery, with or without additional PORT or chemotherapy is considered a reasonable choice for patients with N2 positive stage IIIA

disease, although the evidence to support the addition of either PORT or chemotherapy is rather scant. Our current study assessed the need for additional therapy after induction chemotherapy, surgery, and PORT for patients with persistent stage III-N2 NSCLC. We found that patients who underwent additional postoperative chemotherapy had significantly lower DF rates and improved overall survival. Although adjuvant chemotherapy is a standard of care for primarily resected stage II to III NSCLC without prior exposure to chemotherapy [14–16], the role for additional chemotherapy after induction chemotherapy, surgery, and PORT is not a standard therapy, and its benefit is currently unknown. We find that patients with persistent N2 disease are at the highest risk of having distant metastasis and, therefore, stand to benefit with additional courses of aggressive consolidative therapies with both radiotherapy and chemotherapy.

In a study conducted at the Dana-Farber Cancer Institute, patterns of failure were documented in patients with resectable stage III disease treated with neoadjuvant chemotherapy [17]. Patients with persistent N2 disease had worse outcomes, largely due to higher relapse rates at distant sites. The conclusion from this study, along with that of others [18, 19], was that more effective systemic therapies are needed. Our findings appear to support their conclusions that preventing DF with additional postoperative chemotherapy for these high-risk patients may cumulatively lead to better overall survival.

The survival benefit of adjuvant chemotherapy has been demonstrated in several trials evaluating primarily resected stage III-N2 NSCLC without induction chemotherapy. The Lung Adjuvant Cisplatin Evaluation meta-analysis [20], which summarizes these trials, showed a 5.4% improvement in overall survival with the addition of adjuvant chemotherapy, with the best outcomes seen among patients with stage III disease. The Adjuvant Navelbine International Trialist Association trial [15], a randomized study comparing the efficacy of adjuvant cisplatin and vinorelbine given sequentially with or without PORT for stage IB-IIIa NSCLC, found that survival was significantly improved in patients with pN2 disease who received multimodality treatment. This improvement was unique to the pN2 group, as the combined-modality treatment was found to have a detrimental effect on patients with pN1 disease. The combination of PORT and chemotherapy given concurrently has also been suggested to be beneficial in Radiation Therapy Oncology Group-9705 [21]. In contrast, Keller and coworkers [22], in a randomized trial comparing combination chemotherapy with PORT versus PORT alone for patients with stage II or IIIa NSCLC, found no difference in local recurrence or overall survival with the addition of chemotherapy to PORT.

Although these studies have established the role for adjuvant chemotherapy with or without sequential (but not concurrent) radiotherapy in primarily resected stage III patients, only a few studies have looked specifically at the role of consolidative therapy (PORT or chemotherapy) for patients with pathologically persistent N2 disease after induction chemotherapy. Taylor and associates [23] conducted a retrospective analysis of patients with stage IIB to IIIa NSCLC treated with induction chemotherapy and found 5-year actuarial local control rates to be 82% among patients with stage IIIa disease given PORT versus 35% for patients with stage IIIa disease without PORT. No difference was observed in overall survival. However, this study did not report LRF rates according to extent of nodal downstaging. In the Swiss SAKK (Swiss Group for Clinical Cancer Research) phase II trial [5], patients with stage III-N2 NSCLC received induction chemotherapy followed by surgery, but only patients with R1/R2 resections or upper mediastinal N2 disease received PORT. At 5 years, 60% of patients had LRF and 65% DF, again demonstrating high failure rates in such patients, thus emphasizing the need for chemotherapy and radiation to reduce both local and distant disease recurrence. From our results, it appears that combining chemotherapy with PORT may reduce disease recurrence and improve overall survival.

Our study is limited by its retrospective nature, small patient numbers, a relatively young patient cohort (median age 61 years), and mostly clinical assessment by radiographic imaging of disease recurrence, although patients were started on palliative/salvage treatments for these findings. Pathologic confirmation of disease recurrence was attempted occasionally by biopsy, but this was not consistent for the majority of the patients (58%). The main strength of this study is that it is one of the first attempts to address the importance of extending chemotherapy in the adjuvant setting for patients with persistent nodal disease after induction chemotherapy and surgery. This is an important issue that needs to be verified by prospective studies. We believe our results are hypothesis generating, and are the basis of a prospective phase II clinical trial being planned at MD Anderson that adds concurrent chemoradiation therapy in patients with persistent N2 disease after induction chemotherapy and surgery for stage III-N2 NSCLC.

In conclusion, while definitive chemoradiation remains a standard of care for stage III-N2 NSCLC, alternative approaches such as induction chemotherapy and surgery for a selective group of patients can be considered. For patients who have persistent N2 disease after induction chemotherapy, consolidative management with chemotherapy (adjuvant systemic dose) and radiation for patients with persistent N2 after induction chemotherapy may improve disease-specific and survival outcomes. The resistant nature of these tumors portends the worst prognosis, and therefore aggressive consolidative therapies should be considered for these patients. As more effective systemic therapies are made available, an even greater benefit could be foreseen. Future clinical trials are needed to compare a variety of consolidative treatment options to define the best approach.

Acknowledgments

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Fig 1. Kaplan-Meier curves illustrating (A) cumulative locoregional (LR)-free probability, (B) cumulative distant metastasis (DM)-free recurrence, and (C) cumulative overall survival (OS) with postoperative chemotherapy (chemo) versus without postoperative chemotherapy.

Table 1**Patient Characteristics**

Characteristic	No. of Patients (%)
Age, years	
Median (range)	61 (40–74)
Sex	
Male	27 (44.3)
Female	34 (55.7)
Smoking status	
Never	15 (24.6)
Former	20 (32.8)
Current	26 (42.6)
Karnofsky performance status	
90–100	27 (44.3)
80	29 (47.5)
<80	5 (8.2)
N2 status assessment method	
Mediastinoscopy	17 (27.9)
EBUS FNA	7 (11.5)
CT-guided FNA	2 (3.3)
PET/CT	35 (57.4)
Clinical T status	
T1	11 (18.0)
T2	33 (54.1)
T3	10 (16.4)
T4	7 (11.5)
Clinical N status	
N0	1 (1.6)
N1	5 (8.2)
N2	54 (88.5)
N3	1 (1.6)
Clinical M status	
M0	61 (100)
Level of N2 involvement at surgery	
Single station	45 (73.8)
Multiple station	16 (26.2)
Tumor histology	
Adenocarcinoma	33 (54.1)
Squamous cell carcinoma	13 (21.3)
Other	15 (24.6)
Tumor grade	
Well	0 (0)

Characteristic	No. of Patients (%)
Moderate	17 (27.9)
Poor	38 (62.3)
Unclear	6 (9.8)
RECIST response	
CR/PR	29 (47.5)
SD/PD	29 (47.5)
Unknown	3 (4.9)
Type of surgery	
Lobectomy/bilobectomy	49 (80.3)
Wedge/segmentectomy	4 (6.6)
Pneumonectomy	8 (13.1)
Pathologic T status	
T1	18 (29.5)
T2	34 (55.7)
T3	5 (8.2)
T4	4 (6.6)
Postoperative chemotherapy	
Concurrent	9 (14.8)
Adjuvant	4 (6.6)
Both	2 (3.3)
None	46 (75.4)

CR = complete response; CT = computed tomography; EBUS = endobronchial ultrasonography; FNA = fine-needle aspiration; PD = progressive disease; PET = positron emission tomography; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

Table 2**Treatment Details and Chemotherapies Used**

Treatment and Chemotherapy	Number
Types of therapy	
PORT alone	46
Concurrent chemotherapy+PORT	9
Concurrent chemotherapy+PORT+adjuvant chemotherapy	2
Sequential PORT+adjuvant chemotherapy	4
Induction chemotherapy	
Carboplatin+taxol	33
Cisplatin+taxotere	14
Carboplatin+taxotere	7
Cisplatin+gemcitabine	2
Carboplatin+pemetrexed	1
Carboplatin+gemcitabine	1
Unknown	2
Navelbine+taxotere	1
Concurrent chemotherapy	
Carboplatin+taxol	5
Cisplatin+taxotere	2
Taxotere	1
Cisplatin+VP16	1
Carboplatin+gemcitabine	1
Unknown	1
Adjuvant chemotherapy	
Erlotinib	2
Cisplatin+gemcitabine	1
Carboplatin+taxol	1
Pemetrexed	1
Erlotinib+pemetrexed	1

PORT = postoperative radiotherapy.

Table 3**Multivariate Analysis for Distant Failure**

Covariate	Frequency	Hazard Ratio (95% CI)	p Value
Karnofsky performance status			
70	4	1.000 (NA)	0.027
80	24	0.090 (0.015–0.525)	0.007
90	19	0.053 (0.007–0.402)	0.005
100	7	0.261 (0.043–1.564)	0.141
Tumor histology			
Adenocarcinoma	29	1.000 (NA)	0.008
Squamous cell	10	0.281 (0.084–0.937)	0.039
Other	15	0.141 (0.037–0.538)	0.004
Initial tumor status			
T1	10	1.000 (NA)	0.003
T2	30	0.294 (0.073–1.178)	0.084
T3	9	2.419 (0.436–13.420)	0.312
T4	5	2.536 (0.465–13.838)	0.282
Tumor status at surgery			
T1	18	1.000 (NA)	0.078
T2	33	4.333 (1.205–15.580)	0.025
T3	5	1.555 (0.184–13.177)	0.685
T4	3	7.667 (1.007–58.371)	0.049
Postoperative chemotherapy			
Yes	12	0.183 (0.052–0.649)	0.009
No	42	1.000 (NA)	

CI = confidence interval; NA = not applicable.

Table 4

Multivariate Analysis for Overall Survival

Covariate	Frequency	Hazard Ratio (95% CI)	p Value
Age	56	1.059 (1.015–1.105)	0.008
Initial tumor status			
T1	10	1.000 (NA)	0.001
T2	31	1.188 (0.450–3.140)	0.728
T3	9	3.400 (1.092–10.589)	0.035
T4	6	7.737 (2.144–27.295)	0.002
Postoperative chemotherapy			
Yes	14	0.233 (0.089–0.612)	0.003
No	42	1.000 (NA)	

CI = confidence interval; NA = not applicable.

Table 5

Sites of First Failure

Sites of Failure	n (%)
Locoregional	4 (6.8)
Distant	29 (49.2)
Locoregional + distant	3 (5.1)

Table 6

Sites of Any Failure

Sites of Failure	n (%)
No relapse	23 (39.0)
Locoregional	10 (17.2)
Surgical site	0
Mediastinal/hilar nodes	10
Same node involved preoperatively	3
Next echelon node	5
Other ^a	5
Distant	33 (55.9)
Lung	14
Brain	13
Liver	6
Distant lymph nodes	2

^aOther includes supraclavicular and contralateral lymph node involvement.