One size does not fit all: Nuances in postoperative N2 non–small cell lung cancer management

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Feature Editor's Note—N2 lung cancer is one of the most complex and controversial areas within thoracic oncology. To a large extent, this is because N2 disease is embodied by a spectrum of disease states that are often grouped together in clinical studies. The variability in the biologic outcomes of N2 disease states is highlighted by proposals for the American Joint Commission on Cancer 8th edition staging system, which included consideration, on the basis of differential survival outcomes, of N descriptor subsets such as single-station N2 disease in the absence of N1 disease (N2a1), single-station N2 disease in the presence of N1 disease (N2a2), and multistation N2 disease (N2b). This subgrouping was ultimately not included in the stage classification of non–small cell lung cancer because of the difficulties of accurate assessment during clinical staging. Such heterogeneity of N2 non–small cell lung cancer cohorts within clinical studies that inform management guidelines for these patients has often resulted in differences in opinions among the various disciplines of thoracic oncology regarding interpretation of these data and agreement on best available care. In this Feature Expert Opinion article, a multidisciplinary team of authors provides, with remarkable clarity, a balanced view of the common nuances of N2 disease. This piece is centered on a recently published randomized trial on the treatment of yet another subset of this disease, occult N2 disease discovered after surgical resection. The results of this trial are discussed in the context of the current landscape for treatment of patients with resectable N2 non–small cell lung cancer, and the reader is promised an enhanced understanding of the gradations of this heterogeneous disease.

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Despite more frequent use of computed tomographic screening in populations at high risk for lung cancer

Central Message

Choosing optimal therapy for patients with stage IIIA (N2) lung cancer depends on accurate clinical and pathologic assessment of N2 burden and relative risk of locoregional versus systemic recurrence.

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development, stage III lung cancer remains a commonly encountered scenario for the practicing thoracic oncologist. Whereas curable stage IIIB disease (7th American Joint Commission on Cancer system) is almost uniformly managed with definitive chemoradiotherapy, the management of stage IIIA disease is widely disparate and continues to be an area of active study and debate. Individual trials involving preselected patients with stage disease IIIA may achieve outcomes that appear promising; however supporting data for the 7th American Joint Commission on Cancer staging manual demonstrates that on a population level, outcomes in stage IIIA remain quite dismal, with 5-year overall survivals (OSs) of 24% for pathologic stage IIIA disease and 19% for clinical stage IIIA disease.¹ These observed prognostic differences between pathologic and clinical stage IIIA disease highlight the fact that stage IIIA disease encompasses a heterogeneous group of patients from both prognostic and therapeutic vantage points.

Although the value of systemic therapy in stage IIIA disease is well established and unquestioned, surgical resection and radiotherapy are both used as locoregional treatment modalities. The main debates in stage IIIA non–small cell lung cancer (NSCLC) management revolve around the use and timing of local options—surgery, radiation, or both?

A recent randomized study by Sun and colleagues² adds a layer of nuance regarding the use of both surgery and postoperative radiotherapy (PORT) in patients with occult stage

IIIA (N2) disease who have undergone upfront surgical management. Sun and colleagues² deserve credit for a well-conducted study examining adjuvant chemotherapy alone versus adjuvant concurrent chemoradiotherapy (CCRT) followed by chemotherapy in a subset of patients with stage IIIa (N2) NSCLC—those with “surprise” N2 disease burden. Patients (n = 101) were randomly assigned to receive either 4 cycles of adjuvant carboplatin and paclitaxel or CCRT with low-dose cisplatin and paclitaxel with 50 Gy of mediastinal radiotherapy followed by 2 additional cycles of cisplatin plus paclitaxel. The median disease-free survival (primary end point) in the CCRT arm was 24.7 months, not significantly different from the 21.9 months observed in the chemotherapy-alone arm (hazard ratio [HR], 0.94; $P = .40$). Likewise, the OS (74.3 months in the CCRT arm and 83.5 months in the chemotherapy arm; HR, 1.33; 95% confidence interval, 0.71-2.49) were not significantly different. These results suggest no benefit to PORT in this narrow subset of patients with stage IIIa (N2) disease. These results hold the potential to influence the approach to patients with pathologic stage IIIa disease; however, they deserve careful and thoughtful review before incorporation into daily clinical practice.

Nodal status has become one of the most important prognostic features in patients with lung cancer and serves as an integral factor in determining optimal treatment approach.³ Management of N2 disease remains an area of active debate, and often the therapeutic approach is guided by “how much” N2 disease is present. Currently, in the 7th and 8th editions of the American Joint Commission on Cancer staging manual, lymph node involvement in lung cancer remains categorized according to the location of the metastatic lymph nodes and not according to the number of lymph nodes involved.⁴ Studies suggest, however, that the amount of nodal disease burden (number, bulk, extracapsular extension, or multistation involvement) is a factor of prognostic significance, and it has become a method to subdivide stage III disease.⁴⁻⁶ Historically, management of patients with clinical stage IIIa (cN2) NSCLC disease depends on (1) the clinically apparent bulk of nodal disease, (2) the available institutional expertise, and (3) patient factors and preferences. Bulky or multistation cN2 disease is most commonly managed in a similar fashion to N3 disease, with surgery rarely used in lieu of definitive chemoradiotherapy. An intermediate risk category of “potentially resectable” cN2 disease exists, in which N2 disease is clinically apparent on staging workup, and either definitive chemoradiation or induction therapy after surgery (preferably a lobectomy) can reasonably be entertained. A further subcategory of patients with stage IIIa disease comprises those who have “surprise” N2 disease found on pathologic sampling of removed lymph nodes at the time of lobectomy after thorough preoperative staging of disease as stage I or II.

This clinical scenario is not rare, but it does depend on the rigor of preresectional invasive staging; a recent analysis demonstrated that 22.4% of patients with resectable NSCLC will have occult lymph node metastases with systematic lymph node inspection at the time of definitive resection.⁷

Despite published guidelines, practices vary in terms of preoperative imaging and mediastinal staging techniques and whether induction therapy is pursued before or after surgery.^{8,9} In the study by Sun and colleagues,² all patients had a positron-emission tomographic scan performed, but only 41% of patients had any invasive staging performed. This is even more surprising because 27% had clinical N1 disease and 65% had T2 or T3 tumors; both clinical factors are associated with occult N2 disease and recommended scenarios for invasive staging.^{10,11}

In the groups of patients with surprise N2 disease after surgery and those with resectable clinical N2 disease, PORT has often been recommended to decrease rates of mediastinal recurrence. This practice has not been without controversy, because an often-cited meta-analysis of PORT¹² examining 10 randomized studies (2232 patients) from 1966 through 1997 highlighted the pitfalls of overuse of PORT. Overall, PORT was associated with a *reduction* in 2-year survival (from 55% to 48%), with patients with N0 or N1 disease strongly demonstrating a negative survival impact with PORT. In patients with N2 disease, there was no OS benefit or detriment from PORT. An early Belgian study included in the meta-analysis is instructive. Van Houtte and associates¹³ randomized 224 patients with stage clinical I NSCLC to observation versus 60 Gy PORT delivered to the mediastinum through the (now outdated) cobalt technique. Although PORT decreased locoregional failure from 19% to 4%, there was an accompanying apparent OS detriment, from 43% to 24% at 5 years. Collectively, these studies suggest that the likelihood of mediastinal recurrence must be reasonably high if the benefit of disease control in the mediastinum is to outweigh the detrimental cardiopulmonary effects of PORT and that future investigations of PORT should be limited to the N2 population.

Subsequent studies examining modern radiation delivery in patients with N2 disease have had a more favorable response to PORT. Three nonrandomized examinations of the National Cancer Database examined PORT in patients with stage IIIa-pN2 disease, and all favored the use of PORT for patients with pN2 disease. Corso and coworkers¹⁴ examined 30,552 patients treated from 1998 to 2006 and found by multivariate analysis an association of PORT with improved OS in patients with pN2 disease (HR, 0.85), with a 5-year OS of 34.1% versus 27.8% without PORT. Only 23.8% of patients with pN2 disease received PORT during this time frame. Another group¹⁵ examined a smaller sample of patients from 2004 to 2006 and reached similar conclusions. Robinson and colleagues¹⁶ examined a

more recent cohort from 2006 to 2010. When restricting the analyses to those patients with pN2 disease who underwent complete resection and received adjuvant chemotherapy, the use of PORT (41.2% of patients) was associated with an improvement in the 5-year OS from 34.8% to 39.3% (HR, 0.886; $P = .014$).

Although these retrospective studies are prone to selection biases, their findings are supported by a Chinese randomized study by Shen and colleagues,¹⁷ in which 140 patients with stage IIIa-pN2 disease were randomly assigned to either postoperative chemotherapy alone versus postoperative chemoradiotherapy. Although the study closed early because of low accrual, 140 patients received either 4 cycles of adjuvant cisplatin and paclitaxel, or the same chemotherapy with 50.4 Gy of mediastinal radiotherapy given concurrently with the first 2 cycles of chemotherapy (CCRT arm). The CCRT arm had a median survival of 40 months, versus 28 months in the chemotherapy-alone arm; this difference favoring PORT approached statistical significance (HR, 0.69; $P = .07$). The 5-year disease-free survival (DFS) significantly favored the CCRT (30.3%) arm relative to the chemotherapy-alone arm (18.8%; $P = .041$).

How are we to reconcile the randomized study of Shen and colleagues,¹⁷ which is suggestive of an OS benefit and a significant 5-year DFS benefit to PORT in patients with stage IIIa-pN2 disease, with the randomized study of Sun and colleagues,² which suggested no utility of PORT in patients with stage IIIa-pN2 disease? (Table 1) An examination of the patterns of failures from these 2 studies demonstrates that preoperative staging effectively stratifies the risk of mediastinal recurrence after complete surgical resection. In the study of Sun and colleagues,² which examined patients with “surprise” pN2 disease that had been staged as cN0-N1 with thorough preoperative staging, the locoregional-only recurrence rate was 14.0% in the chemotherapy-alone arm. As such, most of the patients did not stand to benefit from PORT but were exposed to the associated toxicities. In contrast, the study of Shen and colleagues¹⁷ did not incorporate preoperative positron-emission tomographic and computed tomographic staging, and in the chemotherapy-alone arm, 49.2% of patients had locoregional failure after surgical resection.

PORT use reduced this to 27.3%, and this significant improvement in locoregional control translated into the smaller gains in OS and 5-year DFS.

Recent reports have investigated the morbidity and mortality associated with thoracic radiotherapy in a more robust fashion. Wang and associates¹⁸ reported symptomatic cardiac events in 23% of patients enrolled in prospective clinical trials delivering dose-escalated definitive thoracic radiotherapy for stage III NSCLC. These events occurred at a median of 26 months after radiotherapy, and significant correlation with cardiac dosimetric parameters was demonstrated. Similarly, a recent analysis of the Radiation Therapy Oncology Group 0617 study examining definitive CCRT showed that higher levels of radiation to the heart are associated with worse OS.¹⁹ Although these analyses suggest that advanced radiation techniques, such as intensity-modulated radiotherapy, may reduce some of these toxicities, it is vital to not expose patients at low risk of mediastinal recurrence to these potential detrimental effects.

The use of PORT in patients with stage IIIa-pN2 disease therefore deserves careful consideration according to the likelihood of residual mediastinal disease. One criticism of the study of Sun and colleagues² is that it delivered PORT with concurrent low-dose chemotherapy before adequate delivery of full-dose adjuvant chemotherapy. This resulted in 25% of patients in the CCRT arm not receiving the scheduled full-dose adjuvant chemotherapy cycles after CCRT, clearly a concern in a population in which distant recurrence (~40% in both arms) remains the dominant pattern of recurrence. Current National Comprehensive Cancer Network guidelines recommend that systemic therapy precede PORT¹⁰; the study of Sun and colleagues² does not fully address the utility of PORT after adequate systemic therapy has been delivered. Further, this study used a carboplatin-based adjuvant chemotherapy regimen, despite lack of evidence for survival benefit with carboplatin in the adjuvant setting.^{20,21} Multiple adjuvant chemotherapy trials in lung cancer have established cisplatin doublets as the optimal strategy for stage II-IIIa disease, and such regimens are endorsed by National Comprehensive Cancer Network, the American Society of Clinical Oncology, and Cancer Care Ontario.²² Finally,

TABLE 1. Summary of 2 randomized studies of mediastinal postoperative radiotherapy for stage IIIa-pN2 non-small cell lung cancer

Author, y	N	NSCLC patient population	Randomized arm	Local relapse*	Median OS (mo)	<i>P</i> value	Median DFS (mo)	<i>P</i> value
Shen et al, ¹⁷ 2014	135	All IIIa-pN2	Adjuvant chemotherapy	49.3%	28	.073	18	.041
			CCRT	27.3%	40		28	
Sun et al, ² 2017	101	Clinical stage I-II with “surprise” pN2 disease	Adjuvant chemotherapy	24%	83.5	.38	21.9	.40
			CCRT	15.7%	74.3		24.7	

NSCLC, Non-small cell lung cancer; OS, overall survival; DFS, disease-free survival; CCRT, concurrent chemoradiotherapy. *Includes both locoregional-only relapse and simultaneous distant and locoregional relapses.

the primary end point of DFS should not replace the objective of 5-year OS when pursuing curative intent therapy.

Nonetheless, some important takeaways can be gleaned. First, the predominant pattern of failure for pN2 disease remains distant. We should therefore redouble our efforts to use invasive staging appropriately at the time of original diagnosis. If N2 disease can be identified at the time of pre-resectional staging, then neoadjuvant chemotherapy can be delivered, with the expectation of even better control of systemic micrometastatic disease, while minimizing the risk that chemotherapy delivery is delayed, dose reduced, or compromised by surgical or radiotherapy complications. Patients with clinically apparent N2 disease before surgical resection will likely derive more benefit from PORT than will patients with “surprise” N2 disease. Adjuvant systemic therapy should be prioritized in these “surprise” patients, and it likely should precede if not supplant PORT, rather than be given concurrently. In addition, the ongoing European LUNG ART study²³ examining PORT in a randomized fashion will shed further light on patient subgroups that may derive benefit from PORT. In the meanwhile, balanced discussions of potential oncologic benefit versus the risk of cardiopulmonary detriment are needed to guide patient-centered decision making.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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