

# HOSPITAL PHYSICIAN®

## ONCOLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Oncology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in oncology. Each manual reviews a topic essential to the current practice of oncology.

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## Stage III Non–Small Cell Lung Cancer

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## Stage III Non–Small Cell Lung Cancer

*Curtis R. Chong, MD, PhD, MPhil, and Arthur T. Skarin, MD, FACP, FCCP*

### INTRODUCTION

Each year approximately 228,000 Americans will be diagnosed with lung cancer, and 159,000 will die of this disease.<sup>1</sup> An estimated 85% of lung cancer cases are non–small cell lung cancer (NSCLC), more than 50% of NSCLC is comprised of adenocarcinoma, the median age at diagnosis is 71 years, and 25% of patients with this diagnosis present with stage III disease.<sup>2,3</sup> In 2010 the seventh edition of the American Joint Committee on Cancer (AJCC) TNM staging system for lung cancer was released (**Figure 1**), and several changes were made which affect the patient population designated as having stage III disease:<sup>4,5</sup>

- Tumors larger than 7 cm (T3N1M0) were reclassified as stage IIIA rather than IIB. Tumors larger than 7 cm were previously classified as T2.
- Tumor nodules in the same lobe (T3N0M0) were reclassified to stage IIB rather than IIIB. Tumor nodules in the same lobe were classified as T4 in the 6th edition of the AJCC staging system, and were reclassified as T3.
- Tumor nodules in the same lobe with nodal in-

volvement (T3N1M0 or T3N2M0) were reclassified as IIIA, rather than IIIB.

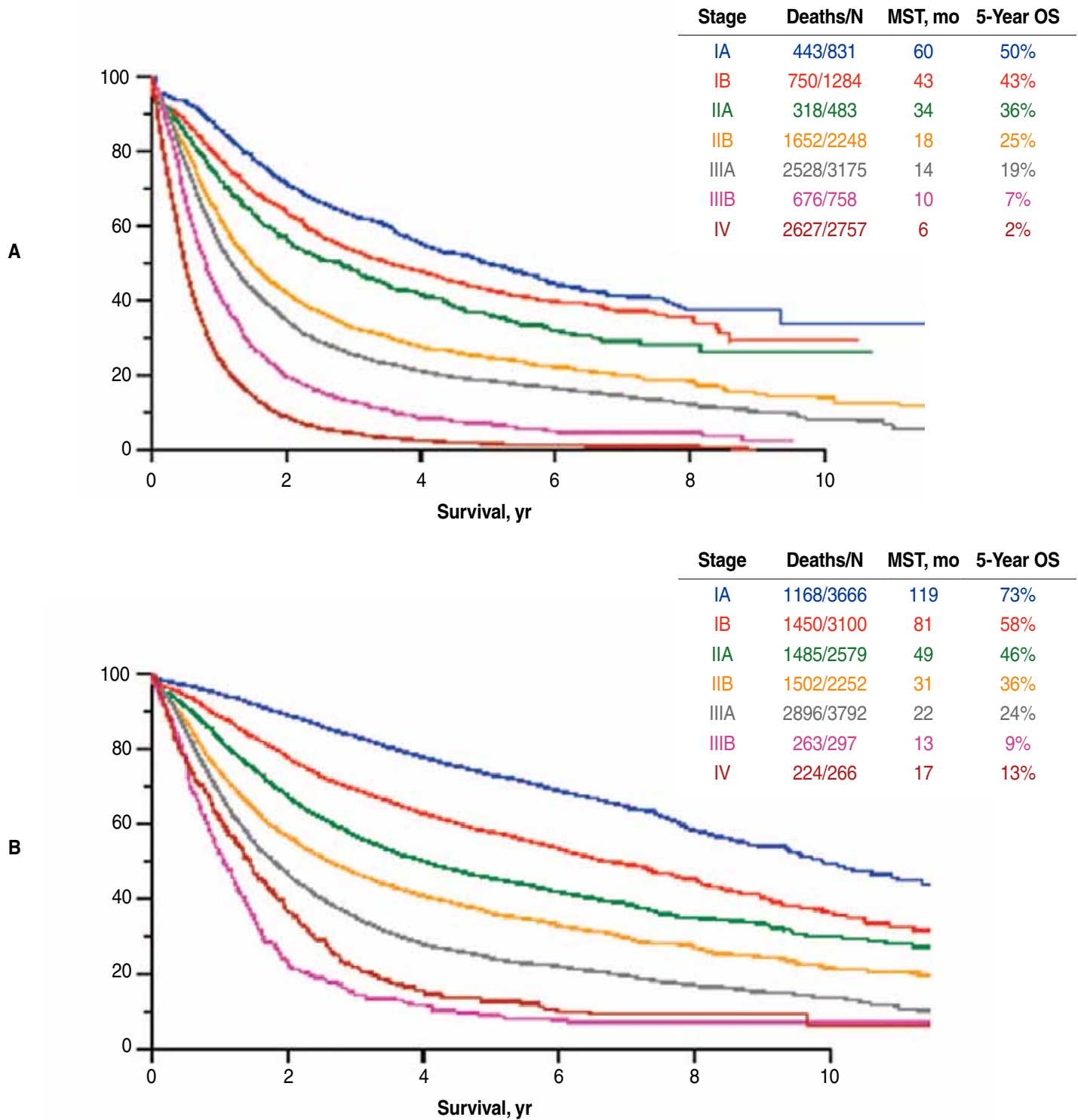
- Tumor nodules in ipsilateral lobes (T4M0) were reclassified as IIIA (N0/1) and IIIB (N2/3), rather than IV. Ipsilateral tumor nodules were reclassified as T4, rather than M1.
- Direct extension lesions (T4M0) were reclassified as IIIA (N0/1), rather than IIIB.
- Malignant pleural effusions (M1a) were reclassified as IV, rather than IIIB. Malignant pericardial or pleural effusions were reclassified as M1a, rather than T4.

The median and 5-year survival of patients is 14 months and 19% for patients with clinical stage IIIA disease, 10 months and 7% for clinical stage IIIB disease, 22 months and 24% for pathologic stage IIIA disease, and 13 months and 9% for pathologic stage IIIB disease (**Figure 2**).<sup>6</sup> Despite these grim statistics, stage III NSCLC is curable for some patients. Treatment typically involves combined-modality therapy, which may involve surgery, radiation, and/or chemotherapy. The optimal sequencing and combination has been the subject of some controversy and is tailored to individual patients, as discussed below. Using illustra-

## Stage III Non-Small Cell Lung Cancer

Primary tumor (T)			
T1	Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus		
T1a	Tumor ≤2 cm in diameter		
T1b	Tumor >2 cm but ≤3 cm in diameter		
T2	Tumor >3 cm but ≤7 cm, or tumor with any of the following features: Involves main bronchus, ≥2 cm distal to carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung		
T2a	Tumor >3 cm but ≤5 cm		
T2b	Tumor >5 cm but ≤7 cm		
T3	Tumor >7 cm or any of the following: Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina) Atelectasis or obstructive pneumonitis of the entire lung Separate tumor nodules in the same lobe		
T4	Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe		
Regional lymph nodes (N)			
N0	No regional lymph node metastases		
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension		
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)		
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion		
M1b	Distant metastasis (in extrathoracic organs)		
Stage groupings			
Stage IA	T1a-T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a, T1b, T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a, T1b, T2a, T2b	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1a or M1b

**Figure 1.** TNM staging for lung cancer. (Adapted with permission from Goldstraw P, Crowley J, Chansky K, et al; International Association for the Study of Lung Cancer International Staging Committee; Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2007;2:706–14.)



**Figure 2.** Survival for lung cancer (A) based on clinical stage and (B) pathologic stage. MST = median survival time; OS = overall survival. (Adapted with permission from Goldstraw P, Crowley J, Chansky K, et al; International Association for the Study of Lung Cancer International Staging Committee and Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming [seventh] edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007;2:706–14.)

tive cases, this manual will discuss the diagnostic workup and management of patients who present with stage IIIA disease discovered on resection, bulky stage IIIA (N2) disease, and stage IIIB disease.

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## DIAGNOSTIC APPROACH AND STAGING

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### CASE PRESENTATION 1



A 55-year-old woman with a 20-pack-year smoking history presents with a persistent cough that developed 3 months ago and did not respond to azithromycin treatment. Her past medical history is otherwise unremarkable; she has not smoked for the past 15 years. She has no other symptoms and no hemoptysis. A chest radiograph demonstrates a 2.5-cm left upper lobe pulmonary nodule. Her physical examination is unremarkable. Her Eastern Cooperative Oncology Group (ECOG) performance status score is 1, and she is able to run 4 miles several times per week.

- **What studies are needed to stage this patient appropriately?**

### Staging Modalities

**Positron emission tomography and computed tomography (PET-CT).**<sup>7</sup> PET-CT increases the sensitivity (74% versus 51%) for the detection of mediastinal lymph node disease, compared to CT alone, while maintaining similar specificity (85%).<sup>8</sup> Compared to CT-based staging, PET-CT–based staging reduces the number of thoracotomies and futile thoracotomies (stage IIIA [N2], IIIB, IV, benign lung lesion, or the patient died within 12 months of surgery or experienced disease recurrence) without an effect on overall mortality.<sup>9</sup> While PET-CT–based staging may be better than conventional staging at identifying patients with mediastinal

and extrathoracic disease, false-positive results may incorrectly upstage patients with early-stage disease.<sup>10</sup> It is therefore recommended that PET-positive lymph nodes or distant metastases be biopsied to rule-out false-positive results that may preclude surgical cure.<sup>8</sup>

**Mediastinal lymph node evaluation.** Biopsy to establish a diagnosis of lung cancer is typically performed at the site that would result in the highest stage of disease, if accessible. In the absence of extrathoracic disease on PET-CT and brain imaging, mediastinal lymph node evaluation is indicated for patients with enlarged (>1 cm) or PET-active mediastinal lymph nodes, central tumors, T2–T4 tumors, hilar lymphadenopathy, or FDG-avid N1 lymph nodes.<sup>11</sup> The prevalence of pathologically confirmed N2 disease from mediastinoscopy/resection in patients with clinical T1 or T2 disease was 6.5% and 8.7%, respectively.<sup>12</sup> Cervical mediastinoscopy allows access to station 2R/L, 4R/L, 7, and 10R/L lymph nodes and has a reported sensitivity of 72% to 89% with a 91% negative predictive value.<sup>13</sup> An anterior mediastinoscopy (Chamberlain procedure) may sample station 4L, 5, 6, and 7 lymph nodes. Thoracoscopy may sample station 4R, 5, 6, 8, and 9 lymph nodes, assess for chest wall/pleural invasion, and detect pleural effusions.<sup>14</sup> Other approaches include biopsy of palpable supraclavicular lymph nodes, and ultrasound-guided endobronchial or transesophageal biopsies.

### Other Diagnostic Studies

Patients who will undergo surgery or thoracic radiation should be evaluated with pulmonary function tests, including spirometry and diffusion capacity. A bone scan is not necessary if a PET study is performed; it may be performed if PET is unavailable. A brain magnetic resonance imaging (MRI) exam is indicated for patients with neurologic




symptoms and clinical stage II–IV disease; it may be considered for patients with stage IB tumors. Patients who are unable to undergo brain MRI may have a head CT with intravenous contrast.

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## STAGE IIIA DISEASE

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### CASE 1 CONTINUED

 The patient's PET-CT exam confirms an FDG-avid 2.5-cm left upper lobe mass; there is no mediastinal lymphadenopathy or FDG-avidity, and a brain MRI exam is normal. A CT-guided fine-needle aspiration reveals adenocarcinoma. The patient is classified as having clinical stage IA disease (cT1bN0M0). She then undergoes a video-assisted left upper lobectomy and mediastinal lymph node dissection. The pathology report confirms a 2.5-cm adenocarcinoma in the lobectomy specimen and also notes metastatic disease in a single, left anteroposterior window lymph node.

#### • How should the patient be managed?

The patient is now stage IIIA (pT1bN2M0) due to the presence of tumor in the ipsilateral anteroposterior window lymph node. The risk of N2 disease increases with tumor size in early clinical stage lung cancer, from 4.8% (0–2 cm) to 6.5% (2.1–4 cm), 6.3% (4.1–6 cm), and 57% (>6 cm).<sup>12</sup> The presence of micrometastatic disease detected by immunohistochemistry or genetic analysis is classified as N0 disease under the 2010 TNM staging system.

#### Adjuvant Chemotherapy for Resected Stage III Disease

The effect of adjuvant cisplatin-based chemotherapy on survival in patients with resected

NSCLC was studied in the LACE meta-analysis, which showed a 5-year absolute survival benefit of 5.4%.<sup>15</sup> This survival benefit was seen for patients with resected stage III disease (hazard ratio [HR] for death = 0.83; 95% confidence interval [CI], 0.72 to 0.94). Both the American Society of Clinical Oncology and the National Comprehensive Cancer Network recommend adjuvant chemotherapy for resected stage IIIA NSCLC.<sup>16</sup> The optimal cisplatin-based regimen has not been determined. Patients with squamous histology should not receive cisplatin + pemetrexed based on the inferior overall survival seen in the metastatic setting compared to cisplatin + gemcitabine.<sup>17</sup> The results of studies that investigated the impact of adjuvant chemotherapy on resected stage III disease demonstrate the benefit of adjuvant cisplatin-based regimens, with a reported hazard ratio for death (compared to observation) of 0.69 to 0.85 (**Table 1**).<sup>15,18–20</sup>

The use of epidermal growth factor receptor (EGFR) inhibitors as adjuvant therapy in the treatment of resected stage IIIA disease has been examined in 2 studies, but these agents cannot currently be recommended outside of a clinical trial. The NCIC CTG BR19 study randomly assigned resected stage IB–IIIA patients unselected for EGFR status to adjuvant gefitinib or placebo, and did not demonstrate an overall or disease-free survival benefit at 4 years.<sup>21</sup> In a retrospective series of patients with *EGFR* mutation–positive resected stage I–III lung cancer, adjuvant erlotinib or gefitinib was associated with a lower risk of recurrence (HR = 0.43; 95% CI, 0.26 to 0.72).<sup>22</sup> A phase II study of 2 years of adjuvant erlotinib enrolled 10 patients with stage III disease (SELECT). At a median follow-up of 2.5 years, the 2-year disease-free survival was 94%; however, 90% of patients who experienced recurrence did so after discontinuing erlotinib.<sup>23</sup>

**Table 1.** Impact of Adjuvant Chemotherapy on Resected Stage III Disease


Study	Regimen	Outcome
Pignon et al (LACE Collaborative Group) <sup>15</sup>	Meta-analysis of cisplatin-based trials from the mid 1990s to 2001	HR for death at 5 years = 0.83 (95% CI, 0.72 to 0.94)
Arriagada et al (IALT Collaborative Group) <sup>19,20</sup>	Cisplatin-based regimens versus observation	HR for death at 5 years = 0.79 (95% CI, 0.66 to 0.95); HR for death at 7.5 years = 0.85 (95% CI, 0.72 to 1.01)
Douillard et al (ANITA) <sup>18</sup>	Cisplatin + vinorelbine × 4 cycles versus observation	5-year survival was 42% with adjuvant treatment versus 26% with observation; HR for death at 5 years = 0.69 (95% CI, 0.53 to 0.9)

ANITA = Adjuvant Navelbine International Trialist Association; CI = confidence interval; HR = hazard ratio; IALT = International Adjuvant Lung Cancer Trial; LACE = Lung Adjuvant Cisplatin Evaluation.

### Adjuvant Radiotherapy


Adjuvant radiotherapy is beneficial for patients with positive resection margins, insufficient lymph node sampling, and N2 disease, and is detrimental in combination with chemotherapy for patients with N1 disease. Patients treated with postoperative radiotherapy with N2 disease had an increased survival (HR = 0.855; 95% CI, 0.75 to 0.96), while patients with N0 or N1 disease experienced a significant decrease in survival (HR = 1.18; 95% CI, 1.0 to 1.38; HR = 1.1; 95% CI, 1.02 to 1.19, respectively); this study did not assess the impact of chemotherapy.<sup>24</sup> In a retrospective analysis of patients treated with adjuvant cisplatin + vinorelbine (ANITA trial), postoperative radiation was associated with a survival benefit both in patients who received chemotherapy (47.4 months versus 23.8 months) and those who did not receive chemotherapy (22.7 months versus 12.7 months).<sup>25</sup>

### CASE 1 CONCLUSION

 The patient underwent 4 cycles of adjuvant cisplatin + pemetrexed treatment followed by adjuvant radiotherapy and has remained disease-free 5 years after completing treatment.

## BULKY STAGE IIIA (N2) DISEASE

### CASE PRESENTATION 2

 A 59-year-old woman with a 40-pack-year smoking history (now abstinent) presents with back pain and a cough. A chest radiograph reveals a right upper lung lesion. Chest CT shows a 1-cm right upper lobe nodule and a 3 x 3-cm hilar mass, both of which on PET-CT are FDG-avid; a brain MRI is normal. Mediastinoscopy reveals adenocarcinoma in a right paratracheal lymph node. The patient is seen by thoracic surgery, and is felt to be an excellent preoperative candidate.

- **Would neoadjuvant chemotherapy or chemoradiotherapy benefit this patient?**

Proposed criteria for unresectability in stage IIIA NSCLC includes bulky mediastinal disease (ie, a lymph node or group of lymph nodes greater than 2 to 3 cm on CT or more than 2 involved lymph node stations), although this criterion has been subjectively determined.<sup>26</sup> T3N1, T4N0, or T4N1 disease may also potentially be resectable. In making a determination regarding resectability, the

judgment of the surgeon and the patient's overall condition and preferences are key. Considerable controversy exists regarding patients with stage IIIA (N2) disease.<sup>27</sup>

### Neoadjuvant Therapy

Initial studies comparing surgery or radiotherapy after induction chemotherapy with a cisplatin-based regimen in patients with stage III-N2 disease confirmed by mediastinoscopy showed no difference in overall survival (EORTC 08941, RTOG 89-01).<sup>28,29</sup> In the Intergroup 0139 trial, neoadjuvant chemoradiotherapy (cisplatin/etoposide 50:50 x 2 cycles + 45 Gy) followed by lobectomy and 2 cycles of consolidation cisplatin/etoposide improved median (33.6 months versus 21.7) and 5-year overall survival (36% versus 18%) compared to definitive chemoradiotherapy (cisplatin/etoposide 50:50 x 4 cycles + 61 Gy).<sup>30</sup> Patients in this study treated with neoadjuvant chemoradiotherapy followed by pneumonectomy had a decreased median survival (18.9 months versus 29.4) and decreased 3-year overall survival (36% versus 45%) compared to patients who received definitive chemoradiotherapy. The lower efficacy of neoadjuvant chemoradiotherapy followed by pneumonectomy was likely due to a high rate of postoperative mortality (26%), which may be overcome in centers with lower mortality rates (3%–10%).<sup>31,32</sup>

A retrospective study of patients with stage IIIA-N2 disease showed neoadjuvant chemoradiation plus lobectomy improved 5-year overall survival compared to lobectomy plus adjuvant therapy (33.5% versus 20.3%).<sup>33</sup> No significant difference in event-free survival (12.8 months versus 11.8 months), local failure rate (22% versus 24%), or median overall survival (27.1 months versus 26.2 months) was noted between 3 cycles of neoadjuvant docetaxel + cisplatin (TC) followed by 44 Gy of boost radiotherapy followed

by surgery compared to 3 cycles of neoadjuvant TC in patients with stage III-N2 disease (SAKK 16/00).<sup>34</sup>

### Adjuvant Therapy

While adjuvant radiotherapy has a harmful effect in patients with completely resected N0 or N1 disease, the PORT meta-analysis found no clear evidence for an adverse effect in patients with N2 disease.<sup>35,36</sup> In the ANITA trial, postoperative radiotherapy was associated with superior survival compared to no postoperative radiotherapy in patients with resected N2 disease who were treated with chemotherapy (47% versus 34% 5-year survival) or no chemotherapy (21% versus 17%).<sup>18</sup> Similarly, a retrospective study of data from the SEER database found improved survival in patients with N2 disease treated with postoperative radiotherapy (HR = 0.855; 95% CI, 0.762 to 0.959).<sup>24</sup> A retrospective series has suggested that consolidation chemotherapy may improve survival due to decreased rates of distant failure in patients with persistent N2 disease treated with induction chemotherapy and surgery.<sup>37</sup>

### SUPERIOR SULCUS TUMORS

The SWOG Intergroup 0160 trial tested concurrent etoposide + cisplatin + 45 Gy radiation followed by resection and 2 more cycles of chemotherapy in patients with superior sulcus (Pancoast) tumors (T3/4N0/1). This trial showed a pathologic complete response in 56% of patients and a 44% 5-year survival with disease progression seen most frequently at distant sites, typically the brain (41% of cases).<sup>38</sup>

### CASE 2 CONCLUSION



The case patient was initially felt to be unresectable after surgical evaluation. She underwent 2 cycles of neoadjuvant cisplatin + etoposide + radiation with a partial tumor response



and underwent lobectomy followed by 2 cycles of consolidation cisplatin + etoposide. She remains tumor-free 2 years after surgery.

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## STAGE IIIB DISEASE

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### CASE PRESENTATION 3



A 62-year-old woman with a 60-pack-year smoking history (now abstinent) presents with hoarseness. Chest CT shows 2 left upper lobe nodules (1.1 × 0.8 and 2.0 × 1.5 cm) and left supraclavicular and paratracheal lymphadenopathy; on PET-CT these lesions are FDG-avid without any other lesions noted. A brain MRI exam and mutational analysis are negative. Biopsy of the left supraclavicular lymph node shows metastatic adenocarcinoma.

#### • How should this patient be managed?

#### Definitive, Concurrent Chemoradiotherapy in Unresectable Stage III Disease

This patient has stage IIIB disease (cT3N3M0), which is best treated with combined chemoradiotherapy. Two chemotherapy regimens are commonly administered with radiation in patients with unresectable disease: etoposide + cisplatin and carboplatin + paclitaxel (**Table 2**).<sup>39–41</sup> Patients who received carboplatin + etoposide + 61 Gy of radiotherapy followed by 2 more cycles of consolidation chemotherapy had a median survival of 15 months and a 17% and 15% 3-year and 5-year survival, respectively (SWOG 9019).<sup>42</sup> Weekly carboplatin + paclitaxel + 63 Gy radiotherapy followed by 2 cycles of consolidation chemotherapy resulted in a 16.3-month median survival (LAMP).<sup>43</sup> These 2 regimens were compared in a phase II trial that showed a superior 3-year overall survival in the cisplatin + etoposide arm (33% versus 13%,

$P = 0.04$ ).<sup>44</sup> The greater efficacy of cisplatin/etoposide versus weekly carboplatin/paclitaxel was thought to be related to the increased efficacy of cisplatin as a radiosensitizer and higher doses of systemic chemotherapy.

The superiority of concurrent chemoradiation over sequential treatment was demonstrated in the RTOG9410 trial in which patients treated with cisplatin + vinblastine with 60 Gy concurrently experienced longer median survival times (17 months versus 14.6 months, HR for death = 0.81; 95% confidence interval, 0.66 to 0.996) compared to patients treated with this regimen sequentially.<sup>45</sup> Two meta-analyses confirmed the superiority of concurrent over sequential treatment in locally advanced NSCLC. The NSCLC Collaborative Group performed a meta-analysis of 6 trials with a median follow-up of 6 years and found concomitant treatment resulted in an overall survival benefit of 5.7% at 3 years (HR = 0.84; CI, 0.74 to 0.95,  $P = 0.004$ ), compared to sequential treatment.<sup>46</sup> This was likely due to decreased locoregional progression (HR = 0.77; CI, 0.62 to 0.95), as there was no difference in distant progression. Concomitant treatment was associated with greater esophageal toxicity (18% versus 4%). A Cochrane meta-analysis that likewise included 6 trials of concurrent versus sequential chemoradiotherapy found a 10% absolute survival benefit at 2 years, with an increase in esophagitis.<sup>47</sup>

Induction chemotherapy prior to chemoradiotherapy increased toxicity without a survival benefit in the CALGB39801 study. This phase III trial compared 2 cycles of upfront carboplatin + paclitaxel followed by weekly carboplatin + paclitaxel + radiotherapy to immediate chemoradiotherapy and found no statistically significant survival differences (29% versus 31% at 2 years).<sup>48</sup>

Various approaches to improve survival after definitive chemoradiotherapy have been tried unsuc-

**Table 2.** Etoposide + Platinum versus Taxane + Platinum Regimens

Study	Regimen	Response Rate, %	Median Survival, mo	Overall Survival	Toxicity
Wang et al <sup>44</sup>	Etoposide 50 mg/m <sup>2</sup> + cisplatin 50 mg/m <sup>2</sup> + 60 Gy XRT	63.7	20.2 (10.8–29.6)	65.6% 1 yr 36.4% 2 yr 33.1% 3 yr	78% grade 3/4 neutropenia
	Weekly carboplatin (AUC = 2) + paclitaxel 45 mg/m <sup>2</sup> + 60 Gy <i>versus</i>	81.3 ( <i>P</i> = 0.11)	13.5 (8.3–18.7)	54.5% 1 yr 16.2% 2 yr 13% 3 yr	51.5% grade 3/4 neutropenia ( <i>P</i> = 0.05)
Note: Consolidation therapy determined locally.					
Albain et al (SWOG 9019) <sup>42</sup>	Etoposide 50 mg/m <sup>2</sup> + cisplatin 50 mg/m <sup>2</sup> + 61 Gy XRT → 2 cycles etoposide + cisplatin	NR	15	58% 1 yr 33% 2 yr 17% 3 yr 15% 5 yr	20% grade 3/4 esophagitis
Jalal et al (HOG LUN 01-24) <sup>39</sup>	Etoposide 50 mg/m <sup>2</sup> + cisplatin 50 mg/m <sup>2</sup> + 59.4 Gy XRT	NR	26.1	36.7% 3 yr 23.8% 4 yr 23.8% 5 yr	27% grade 3/4 esophagitis, 11% febrile neutropenia
Vokes et al (CALGB 39801) <sup>48</sup>	Weekly carboplatin (AUC = 2) + paclitaxel 50 mg/m <sup>2</sup> x 7 cycles + 66 Gy XRT	67	12	29% 2 yr 19% 3 yr	32% grade 3/4 esophagitis
Belani et al (ACR 427) <sup>43</sup>	Weekly carboplatin (AUC = 2) + paclitaxel 45 mg/m <sup>2</sup> x 7 cycles + 63 Gy XRT → 2 cycles consolidation carboplatin + paclitaxel x 2 cycles	NR	16.3	63% 1 yr 31% 2 yr 17% 3 yr	28% grade 3/4 esophagitis
Yamamoto et al (WJTOG 0105) <sup>40</sup>	Weekly carboplatin (AUC = 2) + paclitaxel 40 mg/m <sup>2</sup> x 6 cycles + 60 Gy XRT → carboplatin (AUC = 5) + paclitaxel 200 mg/m <sup>2</sup> x 6 cycles	63	22	26.4% 3 yr 19.5% 5 yr	8% grade 3/4 esophagitis, 66% grade 3/4 leucopenia
Segawa et al (OLCSG 0007) <sup>41</sup>	Weekly docetaxel 40 mg/m <sup>2</sup> + cisplatin 40 mg/m <sup>2</sup> x 4 cycles + 60 Gy	78.8	26.8	60.3% 2 yr	22% > grade 3 febrile neutropenia, 14% > grade 3 esophagitis

AUC = area under the curve; CALGB = Cancer and Leukemia Group B; HOG LUN = Hoosier Oncology Group; NR = not reported; OLCSG = Okayama Lung Cancer Study Group; SWOG = Southwest Oncology Group; West Japan Thoracic Oncology Group; XRT = radiotherapy.

cessfully. Three cycles of consolidation docetaxel or paclitaxel after etoposide + cisplatin + radiotherapy was associated with increased toxicity with no survival benefit (HOG LUN 01-24, SWOG S9712, respectively).<sup>49,50</sup> Gefitinib maintenance for up to 5 years after concurrent etoposide + cisplatin + 61

Gy radiotherapy followed by 3 cycles of docetaxel failed to improve survival in patients unselected for *EGFR* mutation status.<sup>51</sup> Increasing the radiation dose to 74 Gy/37 daily fractions resulted in worse median overall survival (19.5 months versus 28.7 months) and an increased rate of locore-

**Table 3.** Initial Results of New Regimens to Improve Combined Chemoradiotherapy

Reference	Regimen	Outcome
Blumenschein et al (RTOG 0324) <sup>54</sup>	Cetuximab induction (400 mg/m <sup>2</sup> week 1) → cetuximab (250 mg/m <sup>2</sup> ) + carboplatin (AUC = 2) + paclitaxel (45 mg/m <sup>2</sup> ) + 63 Gy (weeks 2-8) → cetuximab consolidation (250 mg/m <sup>2</sup> ) (× 3 wks) → cetuximab + carboplatin (AUC = 6) + paclitaxel (200 mg/m <sup>2</sup> ) (every 3 wks × 2 cycles) consolidation	62% response rate, 22.7-month median survival, 49% 2-year OS
Govindan et al (CALGB 30407) <sup>55</sup>	Carboplatin (AUC = 5) + pemetrexed 500 mg/m <sup>2</sup> × 4 cycles + 70 Gy XRT	77% response rate, 21.2-month median OS, 58% 18-month OS, 12.6-month failure-free survival
	<i>versus</i> Carboplatin (AUC = 5) + pemetrexed 500 mg/m <sup>2</sup> × 4 cycles + cetuximab (w/ XRT) + 70 Gy XRT	72% response rate, 25.2-month median OS, 54% 18-month OS, 12.3-month failure-free survival

AUC = area under the curve; CALGB = Cancer and Leukemia Group B; OS = overall survival; RTOG = Radiation Therapy Oncology Group; XRT = radiotherapy.

gional recurrence (44% versus 35%) compared to 60 Gy/30 daily fractions (RTOG 0617).<sup>52</sup> Use of bevacizumab and erlotinib along with carboplatin/paclitaxel + radiotherapy increased the risk of toxicity without any increased efficacy.<sup>53</sup>

A phase II study of cetuximab in combination with chemoradiotherapy demonstrated an impressive 62% response rate, 22.7-month median survival, and 49% 2-year overall survival.<sup>54</sup> Cetuximab induction was followed by concurrent cetuximab + carboplatin + paclitaxel and 63 Gy radiotherapy followed by 3 cycles of weekly consolidation cetuximab and then cetuximab + paclitaxel + carboplatin for 6 weeks (**Table 3**). The study was notable for a toxic death rate of 6.5% and 20% grade 4 hematologic toxicity. The combination of carboplatin, pemetrexed, and radiotherapy in a phase II trial resulted in a 77% overall response rate, 21.2-month median overall survival, and 58% 18-month overall survival.<sup>55</sup> Interestingly, patients with squamous histology had a similar overall survival compared to patients with nonsquamous histology. The combination of radiation plus either pemetrexed or cisplatin is being compared to etoposide/cisplatin in patients with nonsquamous histology in an international phase III trial.<sup>56</sup>

In summary, for unresectable disease the most commonly used regimens are a platinum agent + etoposide or a taxane administered concurrently with radiotherapy. No benefit has been found for sequential chemotherapy followed by radiotherapy, induction chemotherapy, or consolidation chemotherapy with a taxane. The use of biologic agents and newer generation chemotherapy regimens is an area of ongoing study.

### TREATMENT OF ELDERLY OR POOR PERFORMANCE STATUS PATIENTS

For elderly patients with an adequate performance status and physiologic reserve, combined modality treatment may be used with curative intent. There was no difference in 2- and 5-year survival rates for patients over or under 70 years of age with stage IIIA-B NSCLC treated with etoposide + cisplatin + radiotherapy, although older patients had increased grade 4 hematologic toxicity (81% versus 62%) and increased grade 4 pneumonitis (6% versus 1%).<sup>57</sup> The JCOG0301 trial demonstrated a survival benefit (median survival 22.4 months versus 16.9 months) for patients older than 70 years (96% ECOG ≤1) treated with low-dose carboplatin (30 mg/m<sup>2</sup>) with 60

Gy radiotherapy compared to radiotherapy alone.<sup>58</sup> The study was notable for increased grade 3-4 hematologic toxicity (57% neutropenia versus none) and increased grade 3 infection (12.5% versus 4%) in the combined modality group compared to radiotherapy alone, with no statistically significant difference in the toxic death rate (3%–4%). A retrospective analysis of patients treated with curative-intent surgical or nonsurgical approaches found no difference in survival for patients younger than 65 years versus patients aged 65 to 80 years.<sup>59</sup> Patients who are not candidates for a combined approach may benefit from sequential chemotherapy followed by definitive radiotherapy, and patients unable to tolerate chemotherapy may benefit from radiotherapy alone.<sup>3</sup>

### PROPHYLACTIC CRANIAL IRRADIATION AND ZOLEDRONIC ACID

In treated stage III patients with disease progression, 26% to 55% have brain metastases, 83% of which occur within 1 year of initial treatment.<sup>60,61</sup> Prophylactic cranial irradiation decreases the incidence of brain metastases by 2- to 10-fold but confers no survival benefit, and is associated with decreased memory 1 year after treatment (RTOG 0214).<sup>62–64</sup> Treatment with zoledronic acid to prevent or delay bone metastases in patients with treated stage IIIA/B disease did not significantly affect progression-free or overall survival.<sup>65</sup>

### SURVEILLANCE

Following curative-intent treatment of stage III NSCLC, distant relapses account for approximately 40% of progression.<sup>66</sup> NCCN guidelines recommend a history and physical exam every 6 to 12 months with a chest CT ± IV contrast for 2 years and then an annual history and physical exam with a noncontrast chest CT.<sup>67</sup> The American College of Chest Physicians provides similar recommen-

dations for follow-up and recommends against routine surveillance PET imaging.<sup>68</sup>

### CASE 3 CONCLUSION



The patient in this case was treated with 2 cycles of etoposide + cisplatin + radiotherapy followed by 2 cycles of consolidation etoposide + cisplatin. Five months after completing treatment, she had a recurrence causing hemoptysis and airway obstruction. She subsequently enrolled in a clinical trial, developed postobstructive pneumonia due to progressive disease after 1 month of treatment, declined further care, and died at home with hospice support.

### CONCLUSION

The care of patients with stage III NSCLC remains challenging because of the heterogeneity of disease presentation and the high risk for relapse and death. Fortunately, a number of tools are available to treat patients with NSCLC, including chemotherapy, radiation, and surgery. The best approach to the care of patients with stage III NSCLC involves a multidisciplinary team comprised of the medical oncologist, surgeon, and radiation oncologist. Patients should be encouraged to participate in well-designed clinical trials so that further progress can be made in the management of stage III NSCLC.

### BOARD REVIEW QUESTIONS

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