

**American College of Radiology  
ACR Appropriateness Criteria®**

**INDUCTION AND ADJUVANT THERAPY FOR  
N2 NON-SMALL-CELL LUNG CANCER**

Expert Panel on Radiation Oncology–Lung: Henning Willers, MD<sup>1</sup>; Thomas E. Stinchcombe, MD<sup>2</sup>; Joe Yujiao Chang, MD, PhD<sup>3</sup>; R. Bryan Barriger, MD<sup>4</sup>; Indrin J. Chetty, PhD<sup>5</sup>; Mark E. Ginsburg, MD<sup>6</sup>; Larry L. Kestin, MD<sup>7</sup>; Sanath Kumar, MD<sup>8</sup>; Billy W. Loo, Jr., MD, PhD<sup>9</sup>; Benjamin Movsas, MD<sup>10</sup>; Andreas Rimner, MD<sup>11</sup>; Kenneth E. Rosenzweig, MD<sup>12</sup>; Gregory M. M. Videtic, MD, CM.<sup>13</sup>

**Summary of Literature Review**

**Introduction**

Only ~20% of patients with non-small-cell lung cancer (NSCLC) present with early-stage disease (American Joint Committee on Cancer [AJCC] clinical stage I and II), which has been traditionally treated with surgical resection alone [1]. In patients with stage IIIA disease (~15% of patients with NSCLC), the role of surgery is much more complicated. Stage III is a heterogeneous disease group, and several distinct subgroups of patients are identifiable and may be classified as below [2]. However, this classification is not reflected in the AJCC staging system.

- Stage IIIA without N2 involvement, ie, T3N1 or T4N0/1 (IIIA-0).
- Incidental pN2 metastasis, found either intra-operatively in a single station (IIIA-1) or in the final pathological examination of the surgical specimen (IIIA-2).
- Clinical N2 node(s) involvement documented by computed tomography (CT) or/and positron emission tomography/computed tomography (PET/CT) imaging (IIIA-3): single station or multistation N2 disease.
- Bulky cN2 disease (IIIA-4), often defined as N2 nodes  $\geq 2$  cm.
- Stage IIIB due to N3.

The greater the mediastinal nodal involvement, the worse is the outcome with surgery alone. In a French series [3], the 5-year overall survival (OS) rates following primary surgery for microscopic single-station, microscopic multiple-station, macroscopic single-station, and macroscopic multiple-station mediastinal N2 involvement were 34%, 11%, 8%, and 3%, respectively. These data highlight the heterogeneity of stage III disease and the poor long-term survival for patients with macroscopic or multistation N2 involvement. Patients with stage III disease are at higher risk for occult metastatic disease and local disease progression, and treatment paradigms must include therapies that provide both local and distant disease control.

In some clinical trials, patients from different subgroups are included, the definitions of “unresectable” or “marginally resectable” are vague or absent, and methods of documentation of N2 status (radiographic versus pathologic) have varied. In trials that include surgical resection, patients undergoing surgery (those with stable disease or those with responding tumors), and in the definition of a complete resection (removal of gross disease versus complete resection with negative microscopic margins) has varied. The definition of “bulky” N2 disease has also varied. In the more recent trials, it has often been used to describe multiple nodes and/or nodes that measure  $>2$ – $3$  cm. Finally, in some of the surgical trials, resection and survival rates were stated only for those patients undergoing thoracotomy and did not include patients who received preoperative treatment and were unable to undergo surgery. The clinical criteria for enrollment (eg, pulmonary function, performance status, and

---

<sup>1</sup>Principal Author, Massachusetts General Hospital, Boston, Massachusetts. <sup>2</sup>Co-author, University of North Carolina Health Care System, Chapel Hill, North Carolina, American Society of Clinical Oncology. <sup>3</sup>Panel Chair, University of Texas MD Anderson Cancer Center, Houston, Texas. <sup>4</sup>Indiana University School of Medicine, Indianapolis, Indiana. <sup>5</sup>Henry Ford Health System, Detroit, Michigan. <sup>6</sup>Columbia University, New York, New York, Society of Thoracic Surgeons. <sup>7</sup>21<sup>st</sup> Century Oncology/Michigan Healthcare Professionals, Farmington Hills, Michigan. <sup>8</sup>Henry Ford Hospital, Detroit, Michigan. <sup>9</sup>Stanford University and Stanford Cancer Institute, Stanford, California. <sup>10</sup>Henry Ford Health System, Detroit, Michigan. <sup>11</sup>Memorial Sloan Kettering Cancer Center, New York, New York. <sup>12</sup>Mount Sinai School of Medicine, New York, New York. <sup>13</sup>Cleveland Clinic Foundation, Cleveland, Ohio.

The American College of Radiology seeks and encourages collaboration with other organizations on the development of the ACR Appropriateness Criteria through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply individual or society endorsement of the final document.

Reprint requests to: Department of Quality & Safety, American College of Radiology, 1891 Preston White Drive, Reston, VA 20191-4397.

the presence and degree of weight loss) have varied within trials as well. The heterogeneity of the patient population and different treatment approaches has also been compounded by the small size of many of the trials.

Here, we will evaluate the roles of surgery, radiation therapy (RT), and chemotherapy in the setting of surgically resectable N2 disease in NSCLC. In patients who are not surgical candidates, the roles of induction and adjuvant chemotherapy with regard to chemoradiation as the primary treatment modality will be reviewed elsewhere.

### **Upfront Surgery**

The general argument in favor of surgery is based on the assumption that surgery results in better local control of primary disease than conventional RT. Although this may be true for early stage NSCLC, it is unproven for patients with N2 disease. As discussed above, there are uncertainties about the total population from which the surgical patients were drawn compared to the RT population with regard to smaller primary tumors, better performance status, less pretreatment weight loss, etc. [4]. Also, most studies in the literature have used postoperative RT (PORT) when indicated in selected patients, which further complicates the interpretation of the role of surgery. The collective 5-year survival rates for surgery alone in stage III (N2) disease are typically reported to be in the range of 14%–30% [5-7], but these are usually highly selected patients often with incidental, microscopic N2 disease discovered at the time of resection. Despite negative preoperative staging, including mediastinoscopy, approximately one-fourth of patients felt to be cT1-3N0-1 may have occult N2 disease [8]. The increased use of fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scanning has improved preoperative staging. FDG-PET compared to CT is more sensitive and specific at mediastinal nodal staging [9], and more sensitive in the detection of distant metastatic disease. Several factors predict a poor prognosis: preoperatively identified N2 disease, multiple involved lymph nodes or sites, bulky extracapsular disease, T3 tumors, and nonsquamous histology [1,3,5]. The benefit of surgery in these patients is not defined. Preoperative staging that identifies these features suggests a marginally resectable situation. Surgery as upfront treatment should no longer be considered a standard option for most patients with known pathologic N2 disease [10]. This extends even to patients with single-station aortopulmonary window nodal involvement (station 5), who have long been considered candidates for upfront surgery, as their prognosis is no better than other N2 patients [11].

### **Adjuvant (Postoperative) Chemotherapy**

Adjuvant chemotherapy is the standard of care in patients with completely resected stage II and III NSCLC based on multiple randomized phase III trials and meta-analyses [12-19]. (See [Variant 1.](#)) Generally, the absolute OS benefit with chemotherapy at 5 years has been ~4%–15% with the most recent meta-analyses showing a 4%–5% benefit across all stages [12,17]. This includes stage IIIA patients for whom the 5-year absolute survival benefit was also only 5% (95% confidence interval [CI], 3%–8%) [12]. Therefore, for incidental pN2 disease (IIIA-1, -2), adjuvant cisplatin-based chemotherapy is the standard of care, whereas the management of preoperatively identified N2 disease (IIIA-3) is more controversial. In pN2 patients, even after complete resection and adjuvant chemotherapy, the risk of locoregional relapse is still in the order of 20%–40% [20,21], highlighting the need for additional therapy to improve locoregional control.

### **Postoperative Radiation Therapy**

Despite evidence of improved local control from Phase II and III trials of PORT compared to surgery alone, no consistent OS benefit has been documented for patients with stage IIIA disease [22]. A phase III trial of PORT conducted by the Lung Cancer Study Group (LCSG) restricted to squamous histology showed a significant reduction in local recurrences (and disease-free survival rate benefit for N2 patients) but no OS benefit [23]. The so-called PORT meta-analysis, which compared PORT to observation, revealed improved local control without an improvement in OS for patients with stage III disease. This meta-analysis included many older studies that used antiquated radiation and staging techniques, which may have impacted the results. The role of PORT in N2 patients was not clarified by this study [24].

In a retrospective single-institution study of 173 postoperatively irradiated patients, locoregional control for stage IIIA was 85%, and the 5-year actuarial survival rate was 20% [25]. In a regression-tree analysis of recurrence risks, patients with N2 nodes who underwent gross resection were at a high risk for local recurrence and were thought to be likely to benefit from PORT [26]. In 1997, the Canadian Lung Cancer Disease Site Group (CLCDSG) published a practice guideline for PORT for stage IIIA NSCLC, stating that the evidence available suggests PORT reduces the local recurrence rate by 18% in completely resected stage IIIA NSCLC [27]. For this reason, the CLCDSG recommended PORT but also concluded that there was no evidence of a survival benefit

from PORT alone. The survival benefit from PORT, if it exists, is likely small, estimated to be in the order of 5%–10% [28].

This issue has been further analyzed in the Surveillance, Epidemiology and End Results (SEER) database among patients who underwent either observation or PORT [29]. After excluding patients who survived <4 months to account for perioperative mortality, 7,465 patients were identified, with a median follow-up time of 3.5 years for patients still alive. For the whole group, PORT did not have a significant impact on survival. For patients with N2 nodal disease, there was a significant increase in survival (hazard ratio [HR] 0.855; P=0.0077). However, there was a significant decrease in survival for patients with N0 (HR 1.176; P=0.0435) and N1 (HR 1.097; P=0.0196) nodal disease. Similarly, a subset analysis of the Adjuvant Navelbine International Trialist Association (ANITA) study [14,30] demonstrated that the use of PORT was associated with improved 5-year survival in pN2 patients, both in the adjuvant chemotherapy arms (47.4% versus 34%) and in the observation arms (21.3% versus 16.6%). In the chemotherapy arms, PORT decreased crude local failure from 18.6% to 6.3%. Of note, in this study, the use of PORT was not randomly assigned but rather decided by each institution.

An ongoing multicenter randomized study in Europe, the Lung Adjuvant Radiotherapy Trial (LungART), randomizes completely resected pN2 patients, with or without adjuvant chemotherapy, to PORT versus observation [20]. In the meantime, the relative benefits versus risks of PORT (after completion of chemotherapy) in resected pN2 patients should be discussed with patients.

PORT in NSCLC patients with pN0/1 disease can lead to worse outcomes [24,29,30]. However, especially in patients with pN1 disease, actuarial rates of locoregional failure as high as ~40% have been reported in retrospective analyses [31,32], suggesting that the use of highly conformal PORT at least in subsets of pN1 patients may need to be explored [31].

### **PORT Toxicity, Fields, and Dose**

The 1995 PORT meta-analysis has been criticized for old, suboptimal radiation techniques leading to morbidity and mortality [20,24]. For example, many studies used Co<sup>60</sup> radiation, and treatment fields were typically large to include the entire mediastinum and sometimes supraclavicular areas (ie, elective nodal irradiation [ENI]). PORT in the more modern era of 1988–2000 was also associated with worse outcome in pN0/1 patients in a SEER analysis [29]. It is likely that treatment toxicity can be reduced further by the use of CT-based conformal planning techniques and incorporation of the likely patterns of locoregional failure [21,33]. Likely sites of failure include the bronchial stump, ipsilateral hilum, and ipsilateral mediastinum [33]. In the European LungART trial for pN2 patients, PORT targets the following mediastinal stations: irrespective of nodal involvement, PORT always targets ipsilateral paratracheal nodal (4R or 4L) and subcarinal (7) stations as well as prevascular and aortopulmonary stations (5,6) for left lung tumors; all lymph nodes that lie between 2 involved nodal stations; and one additional station superior and inferior to the most superiorly and inferiorly involved stations, respectively [20]. Further study is required to define the optimum size of PORT fields and balancing the inclusion of all possible microscopic disease spread against toxicity associated with large volume irradiation.

The optimal dose of PORT in NSCLC is unclear. A range of radiation doses are acceptable for the treatment of microscopic tumor, with doses of 45–50 Gy perhaps most commonly employed [21]. Higher doses of 54–60 Gy may be considered for areas suspected to contain a large volume of microscopic disease or positive margins [21]. Highly conformal techniques and a shrinking field technique may be needed to minimize toxicity. The tolerance of the bronchial stump to doses of >50–54 Gy is not established. The use of fraction sizes of >1.8–2.0 Gy should be avoided [21,28]. The utility of intensity-modulated radiation therapy (IMRT) or protons to potentially further reduce normal tissue toxicity remains to be explored.

PORT is generally administered in a sequential fashion following completion of adjuvant chemotherapy. The occasional presence of positive resection margins may dictate the use of PORT earlier after surgery (ie, concurrently with chemotherapy). However, the toxicity of concurrent chemoradiotherapy compared to sequential chemotherapy and radiation has to be considered, and thus selection of therapy needs to be highly individualized.

### **Homogeneity Correction**

Tissue heterogeneity in the vicinity of the lung has implications on the accuracy of the dose distributions for postoperative as well as preoperative and definitive thoracic radiation therapy. Dose that would have normally been deposited in the tumor is carried away into the surrounding lung tissue, resulting in potential underdosage of the tumor. The literature is replete with articles demonstrating the need for accurate, “heterogeneity-corrected,” dose algorithms in lung cancer planning [34,35]. Consequently, the Radiation Therapy Oncology Group<sup>®</sup>

(RTOG<sup>®</sup>) has adopted the requirement that algorithms employing heterogeneity corrections be used for treatment planning for both early and locally advanced stage lung cancer [36-38]. To mitigate inaccuracies with dose calculations, it is strongly recommended that algorithms employing accurate heterogeneity correction techniques be utilized for lung cancer treatment planning. Pencil-beam-type algorithms should be avoided [39].

### **Surgery After Induction Chemotherapy**

Numerous phase I/II and retrospective studies have addressed the use of induction chemotherapy before surgery in patients with stage IIIA/B disease [40-53]. These studies established the safety of performing surgery after induction chemotherapy. In a few of these studies PORT was given to some patients, and some lower stage patients were also included. Response rates to induction chemotherapy were 40%–74%, however with only a few complete responders. Good responses correlated with favorable outcomes. Median survival times ranged from 15 to 33 months, and long-term survival rates were 15%–40%. In responding patients, median survival times were in the 26-month range, and long-term survival rates were as high as 55%.

The existing phase III randomized data for induction chemotherapy are contradictory; patients with stage I-III disease were enrolled, and a variety of chemotherapy combinations have been investigated. A French study randomized 355 resectable stage I (except T1N0), II, and IIIA patients to either preoperative chemotherapy (cisplatin, mitomycin, and ifosfamide for 2 cycles; 2 additional cycles were assigned postoperatively for responders) or surgery alone [54]. PORT was given to patients with pT3 or pN2 disease. (See [Variant 2.](#)) A statistically significant difference in OS was not observed [54]. On the other hand, in a randomized study reported by Rosell et al [55], 60 patients were randomized to similar preoperative chemotherapy with cisplatin, ifosfamide, and mitomycin, given for 3 cycles every 3 weeks preoperatively, or to surgery alone. Median survival time was 26 months in the chemotherapy group compared to 8 months in the surgery-alone group ( $P<0.001$ ). Similarly, in the study reported by Roth et al [56] patients were randomized to 6 cycles of perioperative cisplatin, etoposide, and cyclophosphamide or to surgery-alone. The median survival time in the chemotherapy arm was 64 months compared to 11 months in the surgery alone arm ( $P<0.008$ ). The Roth and Rosell trials have been much discussed, and the results have been somewhat controversial because they were strongly positive, favoring neoadjuvant chemotherapy, and because of the small number of patients ( $n=60$ ) in both trials. Additionally, N2 involvement was not required, and mediastinoscopy was not mandated if the mediastinum was negative by CT. In the surgery-only arm of the Roth trial, 40% of participants had stage IIIB disease, leading to speculation that an imbalance in the stage distribution between the 2 arms was skewed in favor of the chemotherapy arm. In contrast, the Rosell trial had unexpectedly low survival rates (0% at 3 years) in the surgery-alone arm, even though 37% had only N0 or N1 disease. Other factors, such as potential imbalances in one or several prognostic factors between study arms for the 2 trials, may also explain the observed differences.

In the S9900 trial, patients with stage IB-III A lung cancer were randomized to induction therapy with carboplatin/paclitaxel followed by surgery or to surgery alone. A statistically significant difference in progression-free survival rates (PFS) or OS was not observed. [57]. The European Organisation for Research and Treatment of Cancer (EORTC) 08012 trial is the largest neoadjuvant trial of 519 patients with clinical stage IA-III A disease who were randomized to either neoadjuvant platinum-based chemotherapy or surgery alone [58]. Results did not reveal a benefit in PFS or OS, and neoadjuvant chemotherapy did not change the type of surgery performed. In the Ch.E.S.T. study [59] cisplatin with gemcitabine was chosen as induction chemotherapy. The 3-year PFS rates were 48% in the surgery-alone arm and 53% in the induction chemotherapy arms ( $P=0.11$ ). The common result in these studies has been the inability to demonstrate a robust and significant improvement in survival with the addition of neoadjuvant chemotherapy to surgery alone. Several studies have had to close prematurely with incomplete accrual. Concurrent with the conduct of these studies, the positive results of adjuvant chemotherapy trials were announced. Hence it was no longer accepted to randomize patients to a surgery-alone arm, leading to early closure of neoadjuvant studies. The Berghmans et al [60] meta-analysis on 25 trials published between 1986 and 2004 showed that the 6 neoadjuvant trials demonstrated a HR of 0.66 (95% CI, 0.48–0.93) in favor of addition of induction chemotherapy. The Burdett et al [61] meta-analysis included 7 randomized neoadjuvant clinical trials, which resulted in a HR of 0.82 (95% CI, 0.69-0.97) again in favor of neoadjuvant chemotherapy. Patients enrolled in neoadjuvant studies are frequently clinically staged, whereas patients enrolled in adjuvant trials are pathologically staged, which makes comparisons between the 2 trials difficult. The current clinical question is whether neoadjuvant therapy offers any advantages over adjuvant therapy. At this time, induction therapy with chemotherapy alone for stage IIIA disease should be considered investigational.

The EORTC 08941 study [62] compared radical surgery versus 3 cycles of platinum-based induction chemotherapy followed by RT in selected patients with stage IIIA(N2) NSCLC. Only responding patients were randomized between radical resection with lymph node dissection and optional PORT versus thoracic RT (at least 40 Gy in 2 Gy daily fractions to the mediastinum with a boost to at least 60 Gy). Three hundred thirty-three patients were randomized. One hundred fifty-four patients actually had surgery, and 155 had radiation. Operative mortality was 4%, and 39% received PORT. With a median follow-up of 72 months, median survival times and 5-year OS rates for patients randomized to surgery compared to RT were 16.4 months versus 17.5 months and 16% versus 13%, respectively (HR: 0.95, 95% CI, 0.75–1.19). Median survival times and 2-year PFS rates for patients randomized to surgery and radiation were 9.0 months versus 11.4 months and 27% versus 24%, respectively (P=0.6). In conclusion, even in patients with a response to induction chemotherapy surgery does not improve either OS nor PFS compared to thoracic RT in stage IIIA (N2) patients.

There exist limited prospective data on comparing induction chemotherapy alone (with/without PORT) versus induction concurrent chemotherapy and radiation [63]. A German Phase III study of stage III NSCLC randomized 558 patients to preoperative cisplatin/etoposide for 3 cycles followed by concurrent twice-a-day RT (45 Gy at 1.5 Gy per fraction) with carboplatin and vindesine or to preoperative cisplatin/etoposide followed by PORT to 54 Gy [64]. Only 54% and 59% of patients underwent surgery following induction chemotherapy and chemoradiation therapy, respectively. The addition of chemoradiation increased mediastinal downstaging and pathological response rates compared to induction chemotherapy alone but did not significantly improve PFS (5-year rates of 30% versus 25%) or OS (39% versus 31%) in those patients who underwent resection. The surgical mortality rate doubled with the addition of chemoradiation, especially in pneumonectomy patients. The rates of complete pathological response in the mediastinum were not reported. However, the rate of clinical complete response was only 5% in the radiation arm.

This study does not adequately address the question of induction chemotherapy versus induction chemoradiation or whether radiation should be used preoperatively or postoperatively in stage IIIA(N2) patients. First, the use of induction chemotherapy prior to chemoradiation may not improve outcomes [65,66]. Second, the study enrolled a large fraction of advanced IIIB (T4 or N3) patients, which comprised approximately two-thirds of all patients. These patients are rarely considered for trimodality therapy in the United States. In a subset analysis of 125 N2 patients from this trial, 3-year OS for patients on the induction chemoradiation arm compared to the induction chemotherapy alone arm was 31% versus 18%, respectively (P=0.21) [63].

The therapeutic benefits of PORT in cN2 patients undergoing induction chemotherapy and surgery have not been well studied in prospective trials. In a retrospective 2-center experience of 153 patients with N2 disease who did not receive PORT, there was a high incidence of locoregional failure, particularly in patients with pN1 disease (5-year local failure rate of 62%) [67]. There is also a paucity of adequate level 1 evidence data comparing preoperative radiation to PORT for stage IIIA(N2) patients who are similarly staged. Retrospective data showing superior survival for preoperative radiation are subject to selection bias [68].

### **Surgery After Induction Concurrent Chemotherapy and Radiation**

The survival benefit of reducing distant failure by adding chemotherapy to RT as demonstrated in randomized phase III trials for inoperable NSCLC [60,61,69,70] stimulated interest in preoperative treatment with RT and chemotherapy instead of either RT or chemotherapy alone. The objectives of these trials were to use RT to shrink the primary tumor and nodal disease, use the chemotherapy to provide radiosensitization and sterilize distant micrometastases, and perform surgery to optimize the outcome by removal of residual tumor and enhance local control.

Phase II studies demonstrated the feasibility of induction chemoradiation and demonstrated promising OS results [71-82]. The phase III Intergroup 0139 (RTOG<sup>®</sup> 93-09) study was designed to address the role of surgery in combined-modality therapy [83]. (See [Variant 3.](#)) Patients with T1-3pN2M0 tumors were eligible if the resection was technically feasible at registration. On pretreatment mediastinoscopy, the majority of patients had only one nodal station involved (76%), whereas 22% of patients had 2–3 positive stations. A total of 429 randomized patients received induction with cisplatin and etoposide for 2 cycles and daily RT to 45 Gy starting on day 1. Patients on arm 1 then had a resection if there was no progression, followed by 2 more chemotherapy cycles. Subjects on arm 2 had uninterrupted RT to 61.2 Gy with 2 more cycles of chemotherapy. With a median follow-up time of 69.3 months and 396 analyzable patients, the trial did not meet its primary endpoint of 10% absolute survival improvement in the surgical arm. For arms 1 and 2, the median survival times and 5-year OS rates were 23.6 versus 22.2 months and 27% versus 20%, respectively (P=0.24). PFS rates were superior in the trimodality

arm, 22% versus 11% at 5 years ( $P=0.017$ ), respectively. When analyzing the site of first relapse, there were fewer local failures in arm 1 compared to arm 2, 10% versus 22%, respectively. In the trimodality arm, patients with mediastinal sterilization (pN0) experienced improved 5-year OS of 41%, whereas survival in patients with residual nodal disease (pN1/2) was 24%.

Importantly, in the Intergroup 0139 trial [83], the OS curves crossed at about 1 year of follow-up, owing to a high surgical mortality of 26% (14/54) in patients undergoing pneumonectomy (comprising approximately one-third of all resections) primarily due to respiratory causes, which the authors suggested offset any survival gain achieved with surgery. In an unplanned subset analysis of lobectomy-only patients, the surgical group was compared to a matched control group, revealing a statistically significantly improved 5-year OS rate of 36% versus 18% ( $P=0.002$ ). The authors noted that a prospective trial is unlikely to be completed to validate the hypothesis that a trimodality approach with lobectomy is better than nonsurgical therapy (based on 2-D planned radiation to 61.2 Gy). Various interpretations of this trial are possible, ranging from considering nonsurgical therapy as the standard in stage IIIA(N2) patients to selecting patients for lobectomy following induction therapy, particularly at experienced centers [84,85]. Furthermore, the use of pneumonectomy in the trimodality setting remains controversial. Institutional reports from large academic centers suggest that induction with chemotherapy and radiation does not necessarily increase mortality rates associated with pneumonectomy in carefully selected patients [86,87]. (See [Variant 4](#).)

### **Preoperative Radiation Dose and Toxicity**

Preoperative RT doses have historically been limited to 45 Gy, primarily due to concerns of excess postoperative morbidity and mortality. In the Intergroup 0139 trial, grade 3–4 esophagitis and pulmonary complications in the trimodality arm using 45 Gy versus the nonsurgical arm were 10% versus 23% and 9% versus 14%, respectively [83]. A higher incidence of grade 5 events in the trimodality arm was thought to be mainly driven by the pneumonectomy cases as discussed above. Of note, radiation planning involved historical 2-D planning and large fields by modern standards (including ENI). There was mediastinal nodal clearance (pN0) in 47% of patients, which was associated with improved OS. There have been multiple institutional attempts to increase the preoperative dose, ranging from 54 Gy to 60 Gy, in an attempt to increase nodal complete response rates and improve locoregional control and, ultimately, survival [88–92]. These retrospective data illustrate the potential benefit of the approach but also the possibility of increased morbidity and mortality when radiation is intensified [89,90].

Subsequently, the RTOG<sup>®</sup> designed a phase II study of preoperative RT to a total dose of 61.2 Gy at 1.8 Gy per fraction with concurrent weekly carboplatin and paclitaxel in stage III NSCLC followed by lobectomy or pneumonectomy with complete nodal dissection followed by consolidation chemotherapy (RTOG<sup>®</sup> 0229). In order to limit toxicity, the trial required certification of surgical excellence. The frequency of grade 3–5 pulmonary side effects associated with chemoradiation was 24.5%, whereas the incidence of grade 3 postoperative pulmonary complications was 14%, and there was one 30-day death after pneumonectomy [93]. The rate of mediastinal nodal sterilization (pN0) was 63%. Two-year OS for patients with or without nodal sterilization were 75% and 52%, respectively ( $P=0.002$ ). This study demonstrated that surgical resection can be performed safely after full-dose radiation with concurrent chemotherapy and can support the concept that intensification of preoperative therapy can improve mediastinal sterilization rates and potentially survival outcomes.

Similar to the technology considerations for PORT, the use of IMRT or proton beam therapy has the potential to further reduce toxicity in a trimodality setting, but little published data exist to date in support of this concept. Of note, RTOG<sup>®</sup> 0839, which is a trial of induction high-dose RT with chemotherapy and epidermal growth factor receptor (EGFR)-directed therapy, does allow IMRT usage while proton beam radiation is being tested in prospective clinical trials [94,95].

### **Integration of Molecular Targeted Agents**

There is increasing evidence for the presence of targetable driver mutations in both lung adenocarcinoma and squamous cell carcinoma. To date, most clinical trials with molecular targeted agents have been conducted in stage IV disease, but their utility in earlier stage patients is being studied. Institutional experiences suggest that such mutations can also be found at clinically meaningful frequencies in nonmetastatic patients [96]. In a multicenter phase II study of 36 patients with resected stage I-III NSCLC harboring mutations in the EGFR treated with adjuvant erlotinib, disease-free survival at 2 years was 94% [97]. However, in the Canadian BR.19 trial of postoperative gefitinib versus placebo in resected stage I-III NSCLC, there was inferior survival with the

use of EGFR inhibitor (HR 1.23, P=0.136) [98]. The benefit, if any, of gefitinib in the EGFR mutant subset is as of yet unclear. The use of targeted therapies as neoadjuvant or adjuvant therapy for patients with stage IIIA disease should be considered investigational.

## Conclusions

The optimal treatment of stage IIIA(N2) NSCLC patients remains controversial with limited level I evidence to guide patient selection for preoperative, postoperative, or definitive RT. Interpretation of literature data is complicated by inconsistent diagnostic procedures for N2 disease (pretreatment pathological confirmation versus imaging studies only), heterogeneity of N2 disease (ranging from single-station microscopic tumor to bulky, multistation disease), and pooled analysis of N2 patients with other stage III patients.

The patients with the best results after surgery are those with no evidence of mediastinal disease on preoperative studies, including mediastinoscopy, who are found to have incidental N2 involvement at time of resection or in the final pathological report (IIIA-1,-2; see Introduction). In surgically resected patients such as these, adjuvant cisplatin-based chemotherapy is the standard of care and improves OS. PORT remains a reasonable treatment option, but it is unknown whether it improves OS. PORT is the subject of an ongoing randomized phase III study in Europe. In the interim, the pros and cons of PORT (after completion of chemotherapy) should be discussed with these patients.

Options for patients presenting with clinical, nonbulky N2 disease (IIIA-3) diagnosed preoperatively include 1) definitive chemoradiation +/- adjuvant chemotherapy; 2) induction chemoradiation followed by surgery +/- adjuvant chemotherapy; and 3) induction chemotherapy followed by surgery +/- PORT. Based on the overall negative results of the Intergroup 0139 trial, level 1 evidence exists for the approach of chemoradiation alone. However, for selected patients and in expert hands, trimodality therapy, especially if restricted to lobectomy, remains a reasonable option. Further research is needed to define the best treatment approach based on the number and bulk of involved nodal stations and the presence of microscopic versus gross disease on preoperative studies. Induction chemoradiation is associated with better downstaging than induction chemotherapy, but whether this translates into improved survival remains to be established. Patients considered surgically unresectable (IIIA-4, IIIB[N3]) or medically inoperable should be treated with concurrent chemotherapy and RT.

Historically, neoadjuvant RT or PORT has employed large fields and 2-D planning techniques, which are potentially associated with poor outcomes. This limits the interpretation of the results of older randomized trials. Commonly employed modern 3-D conformal RT techniques that avoid large volume ENI will need to be tested in prospective trials. IMRT and particle therapy such as protons have the potential to further reduce toxicity and thus have potential to translate improved locoregional control into true survival gains.

## Summary

- PORT with a dose of 45–54 Gy is an appropriate therapy following completion of adjuvant chemotherapy in patients with incidental pN2 disease (IIIA-1, -2).
- The therapeutic benefits of PORT in patients undergoing induction chemotherapy and surgery for clinical N2 disease remain to be fully defined.
- In patients with clinical N2 disease (IIIA-3) who are potential candidates for a lobectomy, both definitive concurrent chemotherapy and radiation therapy (60–70 Gy) and induction concurrent chemotherapy and radiation therapy (45–50 Gy) are usually appropriate treatment options while induction chemotherapy alone followed by surgery +/- PORT may also be appropriate.
- In patients with clinical N2 disease (IIIA-3) who would require a pneumonectomy, definitive concurrent chemotherapy and radiation therapy (60–70 Gy) is most appropriate, whereas induction chemotherapy and radiation therapy may be appropriate in expert hands.
- For postoperative, preoperative, and definitive radiation therapy, 3-D conformal techniques and IMRT are most appropriate.

## Supporting Documents

- [ACR Appropriateness Criteria® Overview](#)
- [Evidence Table](#)

## References

1. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest*. 1997;111(6):1710-1717.
2. van Meerbeeck JP, Surmont VF. Stage IIIA-N2 NSCLC: a review of its treatment approaches and future developments. *Lung Cancer*. 2009;65(3):257-267.
3. Andre F, Grunenwald D, Pignon JP, et al. Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. *J Clin Oncol*. 2000;18(16):2981-2989.
4. Lilenbaum RC, Green MR. Multimodality therapy for non-small-cell lung cancer. *Oncology (Huntingt)*. 1994;8(5):25-31; discussion 32, 35-26.
5. Ginsberg RJ. Multimodality therapy for stage IIIA (N2) lung cancer. An overview. *Chest*. 1993;103(4 Suppl):356S-359S.
6. van Klaveren RJ, Festen J, Otten HJ, Cox AL, de Graaf R, Lacquet LK. Prognosis of unsuspected but completely resectable N2 non-small cell lung cancer. *Ann Thorac Surg*. 1993;56(2):300-304.
7. Watanabe Y, Shimizu J, Oda M, Hayashi Y, Watanabe S, Iwa T. Results of surgical treatment in patients with stage IIIA non-small-cell lung cancer. *Thorac Cardiovasc Surg*. 1991;39(1):44-49.
8. Goldstraw P, Mannam GC, Kaplan DK, Michail P. Surgical management of non-small-cell lung cancer with ipsilateral mediastinal node metastasis (N2 disease). *J Thorac Cardiovasc Surg*. 1994;107(1):19-27; discussion 27-18.
9. Toloza EM, Harpole L, McCrory DC. Noninvasive staging of non-small cell lung cancer: a review of the current evidence. *Chest*. 2003;123(1 Suppl):137S-146S.
10. Vansteenkiste JF, De Leyn PR, Deneffe GJ, Lerut TE, Demedts MG. Clinical prognostic factors in surgically treated stage IIIA-N2 non-small cell lung cancer: analysis of the literature. *Lung Cancer*. 1998;19(1):3-13.
11. Tanoue LT, Detterbeck FC. New TNM classification for non-small-cell lung cancer. *Expert Rev Anticancer Ther*. 2009;9(4):413-423.
12. Arriagada R, Auperin A, Burdett S, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. *Lancet*. 2010;375(9722):1267-1277.
13. Butts CA, Ding K, Seymour L, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. *J Clin Oncol*. 2010;28(1):29-34.
14. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIa non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol*. 2006;7(9):719-727.
15. Le Chevalier T. Results of the Randomized International Adjuvant Lung Cancer Trial (IALT): cisplatin-based chemotherapy (CT) vs no CT in 1867 patients (pts) with resected non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol*. 2003;22:(abstr 6)
16. Le Chevalier T, Dunant A, Arriagada R, et al. Long-term results of the International Adjuvant Lung Cancer Trial (IALT) evaluating adjuvant cisplatin-based chemotherapy in resected non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2008;26:suppl; abstr 7507.
17. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26(21):3552-3559.
18. Scagliotti GV, Fossati R, Torri V, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIa non-small-cell Lung cancer. *J Natl Cancer Inst*. 2003;95(19):1453-1461.
19. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med*. 2005;352(25):2589-2597.
20. Le Pechoux C. Role of postoperative radiotherapy in resected non-small cell lung cancer: a reassessment based on new data. *Oncologist*. 2011;16(5):672-681.
21. Saynak M, Higginson DS, Morris DE, Marks LB. Current status of postoperative radiation for non-small-cell lung cancer. *Semin Radiat Oncol*. 2010;20(3):192-200.
22. Wagner H, Jr., Lad T, Piantadosi S, Ruckdeschel JC. Randomized phase 2 evaluation of preoperative radiation therapy and preoperative chemotherapy with mitomycin, vinblastine, and cisplatin in patients with technically unresectable stage IIIA and IIIB non-small cell cancer of the lung. LCSG 881. *Chest*. 1994;106(6 Suppl):348S-354S.
23. Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. The Lung Cancer Study Group. *N Engl J Med*. 1986;315(22):1377-1381.



24. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. *Lancet*. 1998;352(9124):257-263.
25. Emami B, Kaiser L, Simpson J, Shapiro S, Roper C, Lockett MA. Postoperative radiation therapy in non-small cell lung cancer. *Am J Clin Oncol*. 1997;20(5):441-448.
26. Sawyer TE, Bonner JA, Gould PM, et al. Effectiveness of postoperative irradiation in stage IIIA non-small cell lung cancer according to regression tree analyses of recurrence risks. *Ann Thorac Surg*. 1997;64(5):1402-1407; discussion 1407-1408.
27. Logan DM, Lochrin CA, Darling G, Eady A, Newman TE, Evans WK. Adjuvant radiotherapy and chemotherapy for stage II or IIIA non-small-cell lung cancer after complete resection. Provincial Lung Cancer Disease Site Group. *Cancer Prev Control*. 1997;1(5):366-378.
28. Wagner H, Jr. Postoperative radiation therapy for patients who have resected non-small cell lung cancer. *Hematol Oncol Clin North Am*. 2005;19(2):283-302, vi.
29. Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol*. 2006;24(19):2998-3006.
30. Douillard JY, Rosell R, De Lena M, Riggi M, Hurlteloup P, Mahe MA. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. *Int J Radiat Oncol Biol Phys*. 2008;72(3):695-701.
31. Higgins KA, Chino JP, Berry M, et al. Local failure in resected N1 lung cancer: implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys*. 2012;83(2):727-733.
32. Varlotto JM, Medford-Davis LN, Recht A, Flickinger JC, Schaefer E, DeCamp MM. Failure rates and patterns of recurrence in patients with resected N1 non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2011;81(2):353-359.
33. Kelsey CR, Light KL, Marks LB. Patterns of failure after resection of non-small-cell lung cancer: implications for postoperative radiation therapy volumes. *Int J Radiat Oncol Biol Phys*. 2006;65(4):1097-1105.
34. Chetty IJ, Curran B, Cygler JE, et al. Report of the AAPM Task Group No. 105: Issues associated with clinical implementation of Monte Carlo-based photon and electron external beam treatment planning. *Med Phys*. 2007;34(12):4818-4853.
35. Xiao Y, Papiez L, Paulus R, et al. Dosimetric evaluation of heterogeneity corrections for RTOG 0236: stereotactic body radiotherapy of inoperable stage I-II non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2009;73(4):1235-1242.
36. Bradley J. A Randomized Phase III Comparison of Standard- Dose (60 Gy) Versus Highdose (74 Gy) Conformal Radiotherapy with Concurrent and Consolidation Carboplatin/Paclitaxel +/- Cetuximab (IND #103444) in Patients with Stage IIIA/IIIB Non-Small Cell Lung Cancer. Available at: <http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0617>. Accessed 9 May 2013.
37. Bezjak A. Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients Available at: <http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0813>. Accessed 9 May 2013.
38. Videtic GMM. A Randomized Phase II Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients with Stage I Peripheral Non-Small Cell Lung Cancer. Available at: <http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0915>. Accessed 9 May 2013.
39. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. *Med Phys*. 2010;37(8):4078-4101.
40. Altorki NK, Keresztes RS, Port JL, et al. Celecoxib, a selective cyclo-oxygenase-2 inhibitor, enhances the response to preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer. *J Clin Oncol*. 2003;21(14):2645-2650.
41. Andre F, Grunenwald D, Pujol JL, et al. Patterns of relapse of N2 nonsmall-cell lung carcinoma patients treated with preoperative chemotherapy: should prophylactic cranial irradiation be reconsidered? *Cancer*. 2001;91(12):2394-2400.
42. Betticher DC, Hsu Schmitz SF, Totsch M, et al. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial. *J Clin Oncol*. 2003;21(9):1752-1759.

43. Cappuzzo F, De Marinis F, Nelli F, et al. Phase II study of gemcitabine-cisplatin-paclitaxel triplet as induction chemotherapy in inoperable, locally-advanced non-small cell lung cancer. *Lung Cancer*. 2003;42(3):355-361.
44. Cappuzzo F, Selvaggi G, Gregorc V, et al. Gemcitabine and cisplatin as induction chemotherapy for patients with unresectable Stage IIIA-bulky N2 and Stage IIIB nonsmall cell lung carcinoma: an Italian Lung Cancer Project Observational Study. *Cancer*. 2003;98(1):128-134.
45. Date H, Kiura K, Ueoka H, et al. Preoperative induction chemotherapy with cisplatin and irinotecan for pathological N(2) non-small cell lung cancer. *Br J Cancer*. 2002;86(4):530-533.
46. De Candis D, Stani SC, Bidoli P, et al. Induction chemotherapy with carboplatin/paclitaxel followed by surgery or standard radiotherapy and concurrent daily low-dose cisplatin for locally advanced non-small cell lung cancer (NSCLC). *Am J Clin Oncol*. 2003;26(3):265-269.
47. Maurel J, Martinez-Trufero J, Artal A, et al. Prognostic impact of bulky mediastinal lymph nodes (N2>2.5 cm) in patients with locally advanced non-small-cell lung cancer (LA-NSCLC) treated with platinum-based induction chemotherapy. *Lung Cancer*. 2000;30(2):107-116.
48. Santo A, Pedersini R, Pasini F, et al. A phase II study of induction chemotherapy with gemcitabine (G) and cisplatin (P) in locally advanced non-small cell lung cancer: interim analysis. *Lung Cancer*. 2001;34 Suppl 4:S15-20.
49. Scinto AF, Ferraresi V, Milella M, et al. Ifosfamide, cisplatin and etoposide combination in locally advanced inoperable non-small-cell lung cancer: a phase II study. *Br J Cancer*. 1999;81(6):1031-1036.
50. Takita H, Pitoniak RF. Induction chemotherapy for locoregional lung cancer using paclitaxel combination. A preliminary report. *J Exp Clin Cancer Res*. 2000;19(3):291-293.
51. Torre W, Sierra A. Postoperative complications of lung resection after induction chemotherapy using Paclitaxel (and radiotherapy) for advanced non-small lung cancer. *J Cardiovasc Surg (Torino)*. 2002;43(4):539-544.
52. Yang CH, Tsai CM, Wang LS, et al. Gemcitabine and cisplatin in a multimodality treatment for locally advanced non-small cell lung cancer. *Br J Cancer*. 2002;86(2):190-195.
53. Sugarbaker DJ, Herndon J, Kohman LJ, Krasna MJ, Green MR. Results of cancer and leukemia group B protocol 8935. A multiinstitutional phase II trimodality trial for stage IIIA (N2) non-small-cell lung cancer. Cancer and Leukemia Group B Thoracic Surgery Group. *J Thorac Cardiovasc Surg*. 1995;109(3):473-483; discussion 483-475.
54. Depierre A, Milleron B, Moro-Sibilot D, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. *J Clin Oncol*. 2002;20(1):247-253.
55. Rosell R, Gomez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med*. 1994;330(3):153-158.
56. Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J Natl Cancer Inst*. 1994;86(9):673-680.
57. Pisters K, Vallieres E, Bunn PA, et al. S9900: Surgery alone or surgery plus induction (ind) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): Follow-up on a phase III trial. *J Clin Oncol, 2007 ASCO Annual Meeting Proceedings Part I*. 2007;25(18s):7520.
58. Gilligan D, Nicolson M, Smith I, et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. *Lancet*. 2007;369(9577):1929-1937.
59. Scagliotti GV, Pastorino U, Vansteenkiste J, et al. A phase III randomized study of surgery alone or surgery plus preoperative gemcitabine-cisplatin in early-stage non-small cell lung cancer (NSCLC): Follow-up data of Ch.E.S.T. *J Clin Oncol*. 2008;26:suppl; abstr 7508.
60. Berghmans T, Paesmans M, Meert AP, et al. Survival improvement in resectable non-small cell lung cancer with (neo)adjuvant chemotherapy: results of a meta-analysis of the literature. *Lung Cancer*. 2005;49(1):13-23.
61. Burdett S, Stewart LA, Rydzewska L. A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. *J Thorac Oncol*. 2006;1(7):611-621.
62. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst*. 2007;99(6):442-450.

63. Shah AA, Berry MF, Tzao C, et al. Induction chemoradiation is not superior to induction chemotherapy alone in stage IIIA lung cancer. *Ann Thorac Surg.* 2012;93(6):1807-1812.
64. Thomas M, Rube C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol.* 2008;9(7):636-648.
65. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol.* 2005;23(25):5883-5891.
66. Vokes EE, Herndon JE, 2nd, Kelley MJ, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol.* 2007;25(13):1698-1704.
67. Amini A, Lou F, Correa AM, et al. Predictors for locoregional recurrence for clinical stage III-N2 non-small cell lung cancer with nodal downstaging after induction chemotherapy and surgery. *Ann Surg Oncol.* 2013;20(6):1934-1940.
68. Koshy M, Goloubeva O, Suntharalingam M. Impact of neoadjuvant radiation on survival in stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2011;79(5):1388-1394.
69. Dillman RO, Herndon J, Seagren SL, Eaton WL, Jr., Green MR. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst.* 1996;88(17):1210-1215.
70. Sause WT, Scott C, Taylor S, et al. Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst.* 1995;87(3):198-205.
71. Cesario A, Margaritora S, Trodella L, et al. Incidental surgical findings of a phase I trial of weekly gemcitabine and concurrent radiotherapy in patients with unresectable non-small cell lung cancer. *Lung Cancer.* 2002;37(2):207-212.
72. Granetzny A, Striehn E, Bosse U, et al. A phase II single-institution study of neoadjuvant stage IIIA/B chemotherapy and radiochemotherapy in non-small cell lung cancer. *Ann Thorac Surg.* 2003;75(4):1107-1112.
73. Ichinose Y, Fukuyama Y, Asoh H, et al. Induction chemoradiotherapy and surgical resection for selected stage IIIB non-small-cell lung cancer. *Ann Thorac Surg.* 2003;76(6):1810-1814; discussion 1815.
74. Junker K, Langner K, Klinker F, Bosse U, Thomas M. Grading of tumor regression in non-small cell lung cancer : morphology and prognosis. *Chest.* 2001;120(5):1584-1591.
75. Kuten A, Anacak Y, Abdah-Bortnyak R, et al. Neoadjuvant radiotherapy concurrent with weekly paclitaxel and carboplatin and followed by surgery in locally advanced non-small-cell lung cancer. *Am J Clin Oncol.* 2003;26(2):184-187.
76. Law A, Karp DD, Dipetrillo T, Daly BT. Emergence of increased cerebral metastasis after high-dose preoperative radiotherapy with chemotherapy in patients with locally advanced nonsmall cell lung carcinoma. *Cancer.* 2001;92(1):160-164.
77. Machtay M, Lee JH, Stevenson JP, et al. Two commonly used neoadjuvant chemoradiotherapy regimens for locally advanced stage III non-small cell lung carcinoma: long-term results and associations with pathologic response. *J Thorac Cardiovasc Surg.* 2004;127(1):108-113.
78. Sawabata N, Keller SM, Matsumura A, et al. The impact of residual multi-level N2 disease after induction therapy for non-small cell lung cancer. *Lung Cancer.* 2003;42(1):69-77.
79. Stamatis G, Djuric D, Eberhardt W, et al. Postoperative morbidity and mortality after induction chemoradiotherapy for locally advanced lung cancer: an analysis of 350 operated patients. *Eur J Cardiothorac Surg.* 2002;22(2):292-297.
80. Takita H, Shin KH. Radiation induced chemotherapy sensitization in trimodality therapy of stage III non small cell lung cancer. A preliminary report. *J Exp Clin Cancer Res.* 2000;19(4):413-416.
81. Veronesi G, Solli PG, Leo F, et al. Low morbidity of bronchoplastic procedures after chemotherapy for lung cancer. *Lung Cancer.* 2002;36(1):91-97.
82. Martin J, Ginsberg RJ, Abolhoda A, et al. Morbidity and mortality after neoadjuvant therapy for lung cancer: the risks of right pneumonectomy. *Ann Thorac Surg.* 2001;72(4):1149-1154.
83. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet.* 2009;374(9687):379-386.

84. Daly BD, Cerfolio RJ, Krasna MJ. Role of surgery following induction therapy for stage III non-small cell lung cancer. *Surg Oncol Clin N Am.* 2011;20(4):721-732.
85. De Craene S, Surmont V, van Meerbeeck JP. Adjuvant or neoadjuvant chemotherapy in minimal N2 stage IIIA nonsmall cell lung cancer. *Curr Opin Oncol.* 2010;22(2):102-111.
86. Daly BD, Fernando HC, Ketchedjian A, et al. Pneumonectomy after high-dose radiation and concurrent chemotherapy for nonsmall cell lung cancer. *Ann Thorac Surg.* 2006;82(1):227-231.
87. Gaissert HA, Keum DY, Wright CD, et al. POINT: Operative risk of pneumonectomy--influence of preoperative induction therapy. *J Thorac Cardiovasc Surg.* 2009;138(2):289-294.
88. Caglar HB, Baldini EH, Othus M, et al. Outcomes of patients with stage III nonsmall cell lung cancer treated with chemotherapy and radiation with and without surgery. *Cancer.* 2009;115(18):4156-4166.
89. Deutsch M, Crawford J, Leopold K, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy with thoracotomy in the treatment of clinically staged IIIA non-small cell lung cancer. *Cancer.* 1994;74(4):1243-1252.
90. Fowler WC, Langer CJ, Curran WJ, Jr., Keller SM. Postoperative complications after combined neoadjuvant treatment of lung cancer. *Ann Thorac Surg.* 1993;55(4):986-989.
91. Sonett JR, Suntharalingam M, Edelman MJ, et al. Pulmonary resection after curative intent radiotherapy (>59 Gy) and concurrent chemotherapy in non-small-cell lung cancer. *Ann Thorac Surg.* 2004;78(4):1200-1205; discussion 1206.
92. Vora SA, Daly BD, Blaszkowsky L, et al. High dose radiation therapy and chemotherapy as induction treatment for stage III nonsmall cell lung carcinoma. *Cancer.* 2000;89(9):1946-1952.
93. Suntharalingam M, Paulus R, Edelman MJ, et al. Radiation therapy oncology group protocol 02-29: a phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys.* 2012;84(2):456-463.
94. Abramson Cancer Center of the University of Pennsylvania. Proton Beam Radiation Therapy and Chemotherapy in Treating Patients With Stage III Non-Small Cell Lung Cancer That Can Be Removed By Surgery. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). 2013 April 3. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01076231?term=NCT01076231&rank=1>. NLM Identifier: NCT01076231.
95. Massachusetts General Hospital. Proton Radiation Therapy With Cisplatin and Etoposide Followed by Surgery in Stage III Non-Small Cell Lung Cancer. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). 2013 April 3. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01565772?term=NCT01565772&rank=1>. NLM Identifier: NCT01565772.
96. Mak RH, Doran E, Muzikansky A, et al. Outcomes after combined modality therapy for EGFR-mutant and wild-type locally advanced NSCLC. *Oncologist.* 2011;16(6):886-895.
97. Neal JW, Pennell NA, Govindan R, et al. The SELECT study: A multicenter phase II trial of adjuvant erlotinib in resected epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC). *ASCO Meeting Abstracts.* 2012;30(15\_suppl):7010.
98. Goss GD, Lorimer I, Tsao MS, et al. A phase III randomized, double-blind, placebo-controlled trial of the epidermal growth factor receptor inhibitor gefitinib in completely resected stage IB-IIIa non-small cell lung cancer (NSCLC): NCIC CTG BR.19. *ASCO Meeting Abstracts.* 2010;28(18\_suppl):LBA7005.

The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

**Clinical Condition:** Induction and Adjuvant Therapy for N2 Non–small-cell Lung Cancer

**Variant 1:** 65-year-old man with a good performance status presents with cT2N1M0 non–small-cell lung cancer of the left lower lobe. Preoperative mediastinoscopy demonstrates absence of nodal disease in stations 7, 4L, and 4R. Following lobectomy and mediastinal nodal sampling, pathology shows a 3.5 cm-adenocarcinoma in left lower lobe and a positive left hilar and a subcarinal node (pT2N2, IIIA). Other sampled hilar and mediastinal nodes are negative. Surgical margins are negative.

| Treatment   | Rating | Comments  |
|---|--------|---|
| Postoperative radiation therapy (PORT) alone  | 3      |   |
| Adjuvant chemotherapy alone   | 7      | Chemotherapy alone, without PORT, is acceptable because of single lymph node involvement and no adverse features. |
| Adjuvant concurrent chemoradiation  | 3      |   |
| Adjuvant sequential chemotherapy followed by PORT   | 8      |   |
| Adjuvant sequential PORT therapy followed by chemotherapy   | 3      |   |
| <b>Local Irradiation Doses</b>  |        |   |
| 45–54 Gy/5 weeks (1.8 or 2 Gy fraction)   | 8      | Areas at risk for high-burden microscopic disease may receive higher doses (54 Gy).                               |
| 60–70 Gy/6–7 weeks (1.8 or 2 Gy fraction)   | 3      |   |
| 74 Gy/7.5 weeks (2 Gy fraction)   | 1      |   |
| <b>Radiotherapy Technique</b>   |        |   |
| 2-D radiation (AP/PA and/or off-cord obliques)  | 3      |   |
| 3-D conformal RT  | 8      |   |
| <a href="#">IMRT</a>  | 7      |   |
| <b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate |        |   |

**Clinical Condition:** Induction and Adjuvant Therapy for N2 Non-small-cell Lung Cancer

**Variant 2:** 65-year-old man with a good performance status presents with low-volume cT2pN2M0 non-small-cell lung cancer of the left lower lobe. After 4 cycles of platinum-based induction chemotherapy he has a left lower lobectomy. Pathology shows a 2.5-cm adenocarcinoma in left lower lobe with treatment effect and 2 positive left hilar nodes (pT1N1). Other sampled hilar and mediastinal nodes are negative. Surgical margins are negative.

| Treatment  | Rating | Comments |
|--|--------|----------|
| Postoperative radiation therapy (PORT) alone   | 5      |          |
| Adjuvant chemotherapy alone  | 3      |          |
| Adjuvant sequential PORT therapy followed by chemotherapy  | 2      |          |
| Adjuvant concurrent chemoradiation   | 2      |          |
| Adjuvant sequential chemotherapy followed by PORT  | 2      |          |
| <b>Local Irradiation Doses</b>   |        |          |
| 45–54 Gy/5 weeks (1.8 or 2 Gy fraction)  | 8      |          |
| 60–70 Gy/6–7 weeks (1.8 or 2 Gy fraction)  | 2      |          |
| 74 Gy/7.5 weeks (2 Gy fraction)  | 1      |          |
| <b>Radiotherapy Technique</b>  |        |          |
| 2-D radiation (AP/PA and/or off-cord obliques)   | 2      |          |
| 3-D conformal RT   | 8      |          |
| <a href="#">IMRT</a>   | 7      |          |
| <b><u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate</b> |        |          |

**Clinical Condition:** Induction and Adjuvant Therapy for N2 Non–small-cell Lung Cancer

**Variant 3:** 62-year-old man with a good performance status with cT2pN2M0 non–small-cell left lung cancer. Candidate for lobectomy.

| Treatment  | Rating | Comments  |
|--|--------|---|
| Radiation therapy alone  | 2      |   |
| Surgery alone  | 2      |   |
| Concurrent chemoradiation therapy alone  | 7      |   |
| Induction concurrent chemoradiation therapy followed by surgery  | 7      |   |
| Induction chemotherapy, followed by surgery with or without postoperative radiation therapy (PORT)             | 6      |   |
| Upfront surgery, followed by adjuvant chemotherapy alone   | 3      |   |
| Upfront surgery, followed by adjuvant sequential chemotherapy and PORT   | 3      |   |
| <b>Local Irradiation Doses</b>   |        |   |
| 45–50 Gy/5 weeks (1.8 or 2 Gy fraction)  | 8      | This treatment is given as a neoadjuvant and adjuvant dose. |
| 54–60 Gy/5.5–6 weeks (1.8 or 2 Gy fraction)  | 6      | This treatment is given as adjuvant dose                    |
| 60–70 Gy/6–7 weeks (1.8 or 2 Gy fraction)  | 8      | This treatment is given as a definitive dose.               |
| 74 Gy/7.5 weeks (2 Gy fraction)  | 2      |   |
| <b>Radiotherapy Technique</b>  |        |   |
| 2-D radiation (AP/PA and/or off-cord obliques)   | 2      |   |
| 3-D conformal RT   | 8      |   |
| <a href="#">IMRT</a>   | 7      |   |
| <b><u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate</b> |        |   |

**Clinical Condition:** Induction and Adjuvant Therapy for N2 Non–small-cell Lung Cancer**Variant 4:** 62-year-old man with a good performance status with cT2pN2M0 non–small-cell right lung cancer. Right pneumonectomy planned.

| Treatment   | Rating | Comments  |
|---|--------|---|
| Radiation therapy alone   | 2      |   |
| Surgery alone   | 2      |   |
| Concurrent chemoradiation therapy alone   | 8      |   |
| Induction concurrent chemoradiation therapy followed by surgery   | 4      | This treatment should only be done in highly expert centers.                                  |
| Induction chemotherapy, followed by surgery with or without postoperative radiation therapy (PORT)      | 5      |   |
| Upfront surgery, followed by adjuvant chemotherapy alone  | 3      |   |
| Upfront surgery, followed by adjuvant sequential chemotherapy and PORT                                  | 3      |   |
| <b>Local Irradiation Doses</b>  |        |   |
| 45–50 Gy/5 weeks (1.8 or 2 Gy fraction)   | 8      | This treatment is given as a neoadjuvant dose.  |
| 54–60 Gy/5.5–6 weeks (1.8 or 2 Gy fraction)   | 4      | This treatment is given as a neoadjuvant dose.  |
| 60–70 Gy/6–7 weeks (1.8 or 2 Gy fraction)   | 8      | This treatment is given as a definitive dose.   |
| 74 Gy/7.5 weeks (2 Gy fraction)   | 2      |   |
| <b>Radiotherapy Technique</b>   |        |   |
| 2-D radiation (AP/PA and/or off-cord obliques)  | 2      |   |
| 3-D conformal RT  | 8      |   |
| <a href="#">IMRT</a>  | 7      | In a pneumonectomy setting, care should be taken to minimize low-dose bath of remaining lung. |
| <b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate |        |   |