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

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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 ≥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

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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^{60} 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®

(RTOG®) 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-IIIA lung cancer were randomized to induction therapy with carboplatin/paclitaxel followed by surgery or to surgery alone. A statistically significantly 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-IIIA 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-analyses 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® 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® 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® 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® 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-IIIA 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-IIIA 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

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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	
Local Irradiation Doses		
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	
Radiotherapy Technique		
2-D radiation (AP/PA and/or off-cord obliques)	3	
3-D conformal RT	8	
IMRT	7	
Rating Scale: **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	
Local Irradiation Doses		
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	
Radiotherapy Technique		
2-D radiation (AP/PA and/or off-cord obliques)	2	
3-D conformal RT	8	
IMRT	7	
Rating Scale: 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 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	
Local Irradiation Doses		
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	
Radiotherapy Technique		
2-D radiation (AP/PA and/or off-cord obliques)	2	
3-D conformal RT	8	
IMRT	7	
Rating Scale: **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 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	
Local Irradiation Doses		
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	
Radiotherapy Technique		
2-D radiation (AP/PA and/or off-cord obliques)	2	
3-D conformal RT	8	
IMRT	7	In a pneumonectomy setting, care should be taken to minimize low-dose bath of remaining lung.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		