Surgical Resection Following Neoadjuvant Concurrent Chemotherapy and High Dose Radiotherapy for Stage III NSCLC: Results of NRG Oncology RTOG 0229

Running Head: Surgery after chemoradiation: RTOG 0229

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Data Availability Statement

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Abstract

Background: This study assessed the ability of chemotherapy and high dose radiation to increase mediastinal nodal sterilization in patients with N2/ N3 non-small cell lung cancer (NSCLC).

Methods: All patients underwent pathologic lymph node (LN) staging utilizing bronchoscopy, transbronchial needle aspiration (TBNA)/mediastinoscopy or thoracoscopy pretreatment. Induction chemoradiation consisted of carboplatin, paclitaxel every week for 6 weeks with 61.2 Gy to the mediastinum and primary tumor. The LN were then reassessed prior to, or at the time of resection. Surgical quality assurance (QA) was performed of all operative notes from staging and resection. The primary endpoint of the study was improving mediastinal clearance rate by 20%.

Results: 57 of 60 patients were eligible. N2 disease was present in 98%; N3 in 2%. 51% were adenocarcinoma. 88% received radiation therapy (RT) and 91% received induction chemotherapy per protocol. 43 (75%) were evaluable for analysis of the primary endpoint of LN clearance. 37 patients underwent surgical resection (76% R0/24% R1). Six patients had pathologic residual LN involvement; 5 were unresectable, 5 had medical contraindications, 2 had progression of disease, 1 patient died preoperatively, and 1 physician refused. 27/43 (63%) achieved mediastinal nodal clearance. There were 34 lobectomies and 3 pneumonectomies. 23/37 underwent surgery per protocol. 16% (6/37) had grade 3 postoperative pulmonary complications with one death (3%). 27/37(75%) had an intercostal muscle flap (and 1 serratus) at surgery. 36 of 37 had adequate LN sampling.

Conclusions: Tri-modality therapy remains a viable option for carefully selected stage III NSCLC patients.

Introduction

Treatment of locally advanced non-small cell lung cancer (AJCC 7th edition stage IIIa/IIIb mediastinal lymph node (LN) positive (N2/N3)) remains a significant challenge. Given the success of concurrent chemotherapy and radiation therapy (chemoradiation) in non-operative disease, the use of tri-modality has been the focus of many studies trying to offer a curative approach.

The objective of NRG Oncology RTOG 0229 was to determine the ability of induction concurrent chemotherapy and high dose radiation to increase the rate of mediastinal nodal sterilization in patients presenting with N2/N3 NSCLC, and assess surgical outcomes in this setting. Mediastinal sterilization has been demonstrated to be a surrogate marker for overall survival and cure in this setting. In addition, this study aimed to evaluate the pathologic response rate and the overall and disease free survival (OS and DFS) of patients treated with this regimen. This report will focus on issues related to the consideration of surgical resection for this patient cohort.

Methods

Patients with stage III NSCLC were evaluated by surgical, medical and radiation oncology physicians. This was generally done in the context of a prospective multidisciplinary case conference or multidisciplinary cancer care clinic. Eligibility criteria included: pulmonary function tests (PFTs) as per the prior Intergroup study 0139, including residual post-bronchodilator forced expiratory volume in one second (FEV1) greater than 800 cc. Exclusion criteria included malignant pleural effusion or T4 disease. In addition, patients were excluded if the primary tumor location prevented delivery of 60 Gy (such as posterior superior sulcus), and simultaneous limiting total cord dose to 50 Gy. Finally, weight loss greater than 5% or ECOG

performance status greater than 2 were exclusion criteria as well. All institutions were required to have institutional review board approval prior to enrollment of any patient and all patients provided written informed consent.

Surgeons were required to demonstrate expertise in surgery after induction chemoradiation. This was due to older reports stating the high incidence of perioperative complications including bronchopleural fistula after preoperative chemoradiation. Before the study could be opened at a given institution, submission of a minimum of five operative reports of resections which included placement of a muscle flap after chemotherapy and/or radiation was required. A formal surgical quality assurance (QA) program was put in place to allow the surgical principle investigator (MJK) to evaluate cases on an ongoing basis for compliance with surgical staging, preoperative testing, decision making to proceed to surgery and perioperative surgical techniques. Surgical QA was performed using all operative notes from staging and resection procedures at the midpoint of the study and at its completion. As a result, this study was limited to 22 RTOG member and affiliate institutions (Appendix 1). Minor deviations included performing surgery less than 4 weeks or greater than 8 weeks (but less than 10 weeks) after completion of chemoradiation. Major deviations included resection of patients with an FEV1 less than 800 cc, inadequate LN sampling, lack of muscle flap, performing surgery greater than 10 weeks after chemoradiation and surgery not performed other than for medical reasons.

Pretreatment evaluation for all patients consisted of chest X-ray (CXR), computed tomography (CT) scan, pulmonary function testing (PFTs), routine laboratory serum tests (including BUN, Cr, LFTs) and positron emission tomography (PET). Pathologic LN staging utilizing bronchoscopy with TBNA, mediastinoscopy or thoracoscopy (VATS) pretreatment was completed in all patients.

Induction chemoradiation consisted of carboplatin (CBDCA) AUC=2.0 and paclitaxel 50 mg/m2 weekly x 6 with concurrent radiation to a dose of 61.2 Gy to the mediastinum and primary tumor. Radiation was generally delivered using 3-D conformal radiation in fractions of 1.8 Gy/d. The planned dose to the primary tumor and the mediastinum was 50.4 Gy and included a boost of 10.8 Gy.

Pre-surgical reevaluation testing, after the completion of neoadjuvant chemoradiation, included a repeat PFT, restaging CT and mediastinal LN restaging either by minimally invasive approach or at the time of surgical exploration. The goal was to determine possible systemic progression of disease or to identify patients with changes in their functional status that would preclude resection. In patients in whom there was a marginal ability to tolerate surgery based on PFTs (such as an FEV1 < 800 cc), ventilation perfusion scans with split function or cardiopulmonary exercise tests were recommended but not required.

Resection was performed if, indicated, 4-8 weeks following neoadjuvant chemoradiation. Suitable patients were those who did not show evidence of local disease progression or systemic metastasis, and demonstrated mediastinal clearance as verified by surgical lymph node re-staging after reevaluation underwent thoracotomy. The protocol specified that procedures could include lobectomy, bilobectomy or pneumonectomy; wedge resections and VATS lobectomy were not allowed in this study. All l resections were preceded by full mediastinal LN restaging which was defined as dissection of the ipsilateral levels 2, 4, 7, 8, and 9 LN stations together with levels 5 and 6 on the left side. If LNs were found to be persistently positive at restaging or thoracotomy, the decision whether to resect was left up to the surgeon's discretion, as this result already satisfied the study's primary endpoint. All resections were to be performed in an en bloc fashion. Following resection, buttressing of the bronchial stump, was required using a vascularized

pedicle of either intercostal or serratus anterior muscle (the bulkier serratus muscle flap was preferred for pneumonectomy operations). A pathologic complete response (CR) was demonstrated when the surgical specimen contained no histological evidence of viable cancer either in the primary or the lymph nodes. In an attempt to reduce postoperative pulmonary barotrauma, all patients were preferably extubated in the operating room and postoperative fluids were kept to a minimum.

After recovery from successful surgical resection, the patient subsequently received adjuvant chemotherapy consisting of full dose carboplatin (AUC =6) and paclitaxel (200mg/m2) for two cycles 21 days apart. Alternatively, the same chemotherapy was administered as soon as possible if a patient failed to demonstrate mediastinal lymph node clearance following chemoradiation, if progression of disease occurred, or if the patient was determined to be anatomically unresectable or medically inoperable.

The primary endpoint of this study was to improve the rate of mediastinal nodal clearance (MNC) from 50%, achieved in SWOG-8805, to 70%. The hypotheses were: H_o: r=0.50 versus H_a: r=0.70, where r equals the MNC rate. A Simon two-stage design [1] with α=0.10 and 90% statistical power was used; the first stage required 21 patients and the second 24 patients for a total of 45 evaluable patients. Based on INT-0139, a phase III study comparing concurrent chemoradiation with or without surgery, it was anticipated that 80% of the patients accrued would undergo surgery [2]. Accounting for 20% of the patients not having surgery and a 5% ineligible/ unevaluable rate, the final sample size of the study was 60 patients. Secondary endpoints included complete pathological response after surgery, surgical morbidities, rate of resectability, rates of R0/R1/R2 resections, overall (OS) and progression-free survival (PFS), and overall toxicity rates. The survival results have been presented previously [3].

Results

The study opened to enrollment in September, 2004, and met targeted accrual goals in November, 2008. 60 patients were accrued from 22 institutions. 57 patients were eligible; two were excluded due to weight loss greater than 5% and one did not start protocol treatment. The median age was 59 with a range of 41-79 years. There were 35 males (61%) and 22 females (39%). Pretreatment LN stage was N2 in 56 (98%), and N3 in 1 (2%). 29 (51%) were adenocarcinomas, 11(19%) were squamous cell carcinomas and 17 (30%) "other" NSCLC. Pretreatment clinical staging is shown in Table 1.

88% of patients received their radiation therapy (RT) per protocol. 91% of patients received induction chemotherapy per protocol; 49% required dose modifications. There were few significant grade 3 toxicities from neoadjuvant therapy including: hematological (12%), GI (8%), and pulmonary (19%).

43 patients (75%) were evaluable for analysis of the primary endpoint of LN clearance. Reasons for unevaluable cases included 13 who did not undergo resection (or remediastinoscopy) and one who did not have adequate LN sampling at resection. The posttreatment pathological stage was N0 in 21 patients, N1 in 5 and N2 in 14 patients (Table 2).

37 patients underwent surgical resection (75% R0/ 25% R1). Of 20 patients not undergoing resection, 6 had residual mediastinal LN at the time of repeat mediastinoscopy/thoracoscopy and were thus evaluable for the primary endpoint. Five patients were considered unresectable, 5 were medically inoperable, and 2 had metastatic disease, in one case the surgeon refused resection and one patient died preoperatively.

27 of 43 (63%) patients achieved mediastinal nodal clearance (MNC); therefore, the primary endpoint of the study was met (increase rate by 20%) (p=0.05). The change in TN stage for those patients undergoing resection is shown in Table 3.

There were 34 lobectomies and 3 pneumonectomies, including 2 right pneumonectomies. Procedures performed based on location of the tumor are shown in Table 4.

Postoperative complications included: atelectasis, persistent chest tube drainage, infection, pleural effusion, pneumonitis, pneumothorax, arrhythmias and thromboembolism (see table 5). There were 7 patients with significant (grade 3/4) postoperative complications. Two patients had three complications each. Although pulmonary complications were common postoperatively, there was only one death (3%) caused by ARDS.

Of 37 surgeries, 23 were done per protocol with 11 (30%) major deviations. The most frequent major deviations included no muscle flap/muscle flap substitution in 11, one of which also had inadequate LN sampling. 26 of 37 (70%) surgical patients had a muscle flap (26 intercostal and 1 serratus) at the time of surgery. There were 2 minor deviations including one patient who underwent VATS resection and one patient who was done outside the 4-8 week window.

The most common site of distant occurrence was the brain which was noted in 6 patients.

Discussion

Treatment of stage IIIA/IIIB NSCLC remains controversial. Chemoradiation has long been the standard, replacing radiation alone with the results of CALGB 8433 reported by Dillman in 1988 with a doubling in the survival at 7 years of follow up [4]. Concurrent, rather than sequential, chemoradiation therapy has been accepted since the study by Furuse et al in

1990 [5]. CALGB 9734 showed no difference when surgical resection and chemotherapy were compared with or without adjuvant radiation therapy for stage III NSCLC [6].

Use of neoadjuvant therapy was first reported in two small prospective, randomized trials in the early 1990's. Survival in patients receiving perioperative chemotherapy and surgery was 26-64 months compared with 8-11 months for patients who had surgery alone [7,8]. Both of these studies suffered from limitations in sample size. In addition, their chemotherapy regimen was considered out-of-date. A recent report described 75 of 90 mediastinoscopy- proven, stage IIIA (N2) NSCLC patients treated with neoadjuvant chemotherapy with docetaxel–cisplatin followed by resection. Positive margins were found in 16%; the response rate was 66% and pathologic CR was 19% patients. 33 (44%) received XRT for a positive margin and/or involved upper mediastinal LN [9].

Since then, the value of adding surgery after chemoradiation was evaluated in several clinical trials. SWOG 8605 used cisplatin/ etoposide together with 45 Gy of XRT. The pathologic CR rate in this study was 21% with a 23% five year survival and 6% perioperative mortality [10]. Following this, a similar regimen in mediastinal LN negative patients with superior sulcus tumors was reported with a clinical/pathological CR rate of 22% and 2.4 % mortality [11]. Intergroup 0139 were performed to study the difference between definitive chemoradiation versus tri-modality therapy. The pathologic CR rate was 18% in the tri-modality group, and perioperative mortality was 8%. Overall survival in this study was not different between the two arms, but progression-free survival was significantly better after tri-modality therapy with a median of 12.8 months versus 10.5 months. The main limitation in this study was the excessive high mortality after pneumonectomy (26%) versus lobectomy procedures. Modern series have reported pneumonectomies after chemoradiation with an expected mortality 3-8%

[12,13]. If these patients were excluded, the survival analysis was significant for both overall and progression free survival [2].

The use of full dose radiation was avoided in these prior studies due to the alleged high risk of bronchopleural fistula from bronchial stump disruption [14]. Several single institution studies, using full dose RT preoperatively in doses ranging from 59-69.6 Gy have been reported with better pathological CR rates ranging from 29% -53% and survival of 43-48%. Surgical procedures included pneumonectomy. These results were achieved by utilizing routine use of muscle flaps, minimizing perioperative barotrauma and judicious use of perioperative fluids [15-18].

Other institutions have reported similar findings with a different strategy to minimize post-pneumonectomy pulmonary edema, including fluid restriction and 48 hours of mechanical ventilation [19,20].

These studies were the impetus to undertake the current trial, NRG Oncology RTOG 0229. In a limited number of selected centers, with rigorous surgical quality assurance, this trial investigated the impact of full dose neoadjuvant chemoradiation on MNC. This trial employed the low dose carboplatin/paclitaxel regimen with concurrent radiotherapy. In RTOG 0617 this regimen was the control arm and resulted in excellent overall survival [21]. A recent comparison of this regimen with cisplatin/etoposide and concurrent radiotherapy, employing the VA database demonstrated that the low dose carboplatin/paclitaxel regimen was associated with similar efficacy and superior patient tolerance. Therefore, the low dose carboplatin/paclitaxel regimen seems uniquely suited for the tri-modality approach. This was felt justified as the delivery of full dose XRT led to a higher pathological CR rate, with the ability to still administer “full dose” chemotherapy in the adjuvant “consolidation” setting. Although performed at fewer institutional

settings than the previous Intergroup trial, the results seem to justify the use of rigorous institutional and surgeon selection criteria and validate the recent reports demonstrating the ability to perform safe major lung resection following chemoradiation including pneumonectomy following high dose chemoradiation.

NRG Oncology RTOG 0229 achieved excellent surgical results as demonstrated by impressively low mortality and perioperative morbidity. Although there may be several reasons for this, we propose that the surgical QA process, which included rigorous review of participating surgeons, was part of the success. Although detailed data on use of fluids and barotraumas was not able to be collected prospectively, the general behavior of the participating surgeons, as well as the use of muscle flaps probably helped. In addition, the ability to tolerate weekly paclitaxel and carboplatin with concurrent radiation meant fewer grade 3 and higher toxicities in the preoperative setting. Finally, the delivery of high dose radiation therapy by groups with this expertise, together with centralized radiation QA, resulted in safer radiation delivery despite these doses being higher than any other tri-modality trial to date.

One major concern relates to the low number of patients who underwent surgery overall. All but one of these patients was excluded due to progression or medical condition. Only one was excluded by surgical option. Had the additional 14 patients who were not evaluable for the primary endpoint at least undergone repeat surgical staging, the endpoint may have been more robust. The key criticism of the surgical aspects of the trial, therefore, is the lack of adherence to a protocol that mandated “proof of unresectability”. Clinical judgment no doubt weighed into each surgeon’s decision; however, participation in a clinical trial should drive to greater adherence in the future.

Similar to other trials in stage III disease, the brain was a major site of relapse. Though closed early, the results of RTOG 0214, evaluating prophylactic cranial irradiation (PCI) in this setting indicate that prophylactic cranial irradiation while reducing the risk of CNS relapse did not change overall mortality and was associated with significant toxicity [22,23].

At the current time, most surgeons seem to believe that perioperative morbidity and mortality can be managed and minimized using careful perioperative techniques allowing full dose therapy to be delivered. The choice of using neoadjuvant chemotherapy versus chemoradiation has been studied in a few studies from the US and Europe. Unfortunately, the definitive study randomizing patients to one approach or the other will likely not be done anytime soon.

In conclusion, tri-modality therapy remains a viable option for carefully selected NSCLC patients presenting with stage III disease with the ability to sterilize known mediastinal LN disease. In addition, we have demonstrated the ability of multiple surgeons and institutions to successfully manage these patients safely in the context of a clinical trial.

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Table 1. Nodal Station Status Clinical Status at Time of Registration (n=37)

Location	Unknown	Not evaluated	Positive	Negative
Highest mediastinal (1)	4 (11%)	11 (30%)	2 (5%)	20 (54%)
Right upper paratracheal (2R)	8 (22%)	6 (16%)	5 (14%)	18 (49%)
Left upper paratracheal (2L)	6 (16%)	10 (27%)	1 (3%)	20 (54%)
Pre and retro paratracheal (3)	5 (14%)	8 (22%)	5 (14%)	19 (51%)
Right lower paratracheal (4R)	7 (19%)	5 (14%)	7 (19%)	18 (49%)
Left lower paratracheal (4L)	8 (22%)	5 (14%)	1 (3%)	23 (62%)
Subaortic (5)	6 (16%)	9 (24%)	3 (8%)	19 (51%)
Para-aortic (6)	6 (16%)	9 (24%)	3 (8%)	19 (51%)
Subcarinal (7)	7 (19%)	3 (8%)	14 (38%)	13 (35%)
Paraesophageal (8)	6 (16%)	10 (27%)	0 (0%)	21 (57%)
Pulmonary ligament (9)	6 (16%)	10 (27%)	0 (0%)	21 (57%)
Right hilar (10R)	5 (14%)	8 (22%)	12 (32%)	12 (32%)
Left hilar (10L)	5 (14%)	9 (24%)	5 (14%)	18 (49%)
Interlobar (11)	6 (16%)	10 (27%)	1 (3%)	20 (54%)
Right lobar (12R)	5 (14%)	11 (30%)	0 (0%)	21 (57%)
Left lobar (12L)	5 (14%)	10 (27%)	0 (0%)	22 (59%)
Right segmental (13R)	6 (16%)	11 (30%)	0 (0%)	20 (54%)
Left segmental (13L)	5 (14%)	11 (30%)	0 (0%)	21 (57%)
Right subsegmental (14R)	6 (16%)	11 (30%)	0 (0%)	20 (54%)
Left subsegmental (14L)	5 (14%)	11 (30%)	0 (0%)	21 (57%)
Supraclavicular (R)	5 (14%)	10 (27%)	0 (0%)	22 (59%)
Supraclavicular (L)	5 (14%)	10 (27%)	0 (0%)	22 (59%)

Table 2. Nodal Station Status Pathologic Status at Time of Registration (n=37)

Location	Unknown	Not Evaluated	Positive	Negative
Highest mediastinal (1)	3 (8%)	29 (78%)	1 (3%)	4 (11%)
Right upper paratracheal (2R)	3 (8%)	18 (49%)	6 (16%)	10 (27%)
Left upper paratracheal (2L)	4 (11%)	29 (78%)	0 (0%)	4 (11%)
Pre and retro paratracheal (3)	3 (8%)	25 (68%)	4 (11%)	5 (14%)
Right lower paratracheal (4R)	3 (8%)	11 (30%)	12 (32%)	11 (30%)
Left lower paratracheal (4L)	4 (11%)	23 (62%)	1 (3%)	9 (24%)
Subaortic (5)	3 (8%)	27 (73%)	4 (11%)	3 (8%)
Para-aortic (6)	4 (11%)	29 (78%)	2 (5%)	2 (5%)
Subcarinal (7)	2 (5%)	15 (41%)	10 (27%)	10 (27%)
Paraesophageal (8)	4 (11%)	30 (81%)	0 (0%)	3 (8%)
Pulmonary ligament (9)	5 (14%)	29 (78%)	0 (0%)	3 (8%)
Right hilar (10R)	2 (5%)	29 (78%)	2 (5%)	4 (11%)
Left hilar (10L)	4 (11%)	31 (84%)	0 (0%)	2 (5%)
Interlobar (11)	4 (11%)	30 (81%)	0 (0%)	3 (8%)
Right lobar (12R)	4 (11%)	31 (84%)	0 (0%)	2 (5%)
Left lobar (12L)	4 (11%)	32 (86%)	0 (0%)	1 (3%)
Right segmental (13R)	4 (11%)	31 (84%)	0 (0%)	2 (5%)
Left segmental (13L)	4 (11%)	32 (86%)	0 (0%)	1 (3%)
Right subsegmental (14R)	4 (11%)	31 (84%)	0 (0%)	2 (5%)
Left subsegmental (14L)	4 (11%)	32 (86%)	0 (0%)	1 (3%)
Supraclavicular (R)	4 (11%)	31 (84%)	0 (0%)	2 (5%)
Supraclavicular (L)	4 (11%)	32 (86%)	0 (0%)	1 (3%)

Table 3. Change in T/N Stage (n=37) Baseline

At Surgery	T1/N2	T2/N2	T3/N2
T0/N0	2 (5%)	1 (3%)	0 (0%)
T02/N2	0 (0%)	0 (0%)	1 (3%)
T1/N0	4 (11%)	4 (11%)	4 (11%)
T1/N1	2 (5%)	2 (5%)	0 (0%)
T1/N2	1 (3%)	0 (0%)	0 (0%)
T2/N0	0 (0%)	4 (11%)	0 (0%)
T2/N1	0 (0%)	1 (3%)	0 (0%)
T2/N2	2 (5%)	6 (16%)	1 (3%)
Unknown/No	1 (3%)	1 (3%)	0 (0%)

Table 4. Surgical Method by Tumor Location (n=37)

Tumor Location	Lobectomy	(n=34) Pneumonectomy
Lower Lobe (left)	4 (12%)	0 (0%)
Lower Lobe (right)	7 (21%)	0 (0%)
Upper Lobe (left)	4 (12%)	1 (33%)
Upper Lobe (right)	16 (47%)	1 (33%)
Middle Lobe (right)	3 (9%)	1 (33%)
Left	8 (24%)	1 (33%)
Right	26 (76%)	2 (67%)

Table 5. Surgical Series Using High Dose Neoadjuvant Chemoradiation

Author	# Patients	RT Dose	Path CR	Survival	Postop Mortality
Sonett	40	59.6	40%		2.5%
Krasna	25	61	53%	48%	3%
Edelman	47	69.6	29%	29.6 mos	0%
Daly	30	59.4		33	13.3
Cerfolio	216	60	34%		2.3%

Appendix 1. Approved Institutions And Surgeons For Participation In NRG Oncology RTOG 0229 A Limited Access Study (Surgical PI Named)

Site	**Participating Surgeon(s)**
Arizona Oncology Services Foundation	John Maurice
Boston Medical Center	Benedict Daly
East Carolina University	Jon Moran
Lehigh Valley Hospital	Gary Szydlowski
Mayo Clinic	Francis Nichols, Claude Deschamps
MD Anderson Cancer Center at Cooper-Voorhees	Vincent Lotano
Medical College of Wisconsin/Zablocki VA Medical Center	Mario Gasparri, George Haassler
Medical University of South Carolina	Carolyn Reed, John Derosimo
Nebraska Methodist Hospital	Tracy Dorheim
Norton Suburban Hospital and Medical Campus	George Mikos
Saint Vincent Hospital	Edward Coleman
St. Luke's Hospital	James McCaughan
University of Alabama at Birmingham Medical Center	Robert Cerfolio
University of Maryland/Greenbaum Cancer Center	Mark Krasna, Ziv Gamliel, Whitney Burrows, Richard Battafarano
USC / Norris Comprehensive Cancer Center	Jeffrey Hagen
Washington University School of Medicine	Alex Patterson
Wheeling Hospital/Schiffler Cancer Center	Gary Parenteau
Yale University	Frank Detterbeck