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Resection following Concurrent Chemotherapy and High Dose Radiation for Stage IIIA NSCLC

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Abstract

Objective: Concern exists regarding surgery after thoracic radiation (RT). We aim to assess early results of anatomic resection following induction therapy with platinum-based chemotherapy (C) and full dose RT for resectable N2 + stage IIIA NSCLC.

Methods: Two prospective trials were recently conducted by NRG Oncology in patients with resectable N2 + IIIA NSCLC with primary end point of mediastinal node sterilization following concurrent full-dose CRT (RTOG 0229 and 0839). All surgeons demonstrated post-induction resection expertise. Induction consisted of weekly carboplatin (AUC =2.0) and paclitaxel (50 mg/m^2) and concurrent RT 60 Gy (0839)/ 61.2 Gy (0229) in 30 fractions. Patients in 0839 were randomized 2:1 to weekly panitumumab + CRT or CRT alone during induction. Primary results were similar in all treatment arms and reported previously. Short-term surgical outcomes are reported here.

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Results: 126 patients enrolled; 93 (74%) had anatomic resection, 77 lobectomies and 16 extended resections. R0 resections occurred in 85 (91%). Fourteen (15%) resections were attempted minimally invasively including 2 converted without event. Grade 3/4 surgical adverse events (AEs) were reported in 26 (28%), 30-day mortality in 4 (4%) and 90-day mortality in 5 (5%). Patients undergoing extended resections suffered similar rates of Grade 3/4 AEs [OR 0.95, CI: 0.42-3.8] but higher 30-day (1.3% vs. 18.8%) [OR 17.54 95%CI: 1.75-181.8] and 90-day mortality (2.6% vs. 18.8%) [OR8.65, 95%CI: 1.3-56.9].

Conclusion: Lobectomy was performed safely following full-dose concurrent CRT in these multi-institutional prospective trials, increased mortality was noted with extended resections.

Background

Stage III non-small cell lung cancer (NSCLC) presents a treatment challenge. Patients are treated for cure, but only 20-30% achieve that goal, and acceptable treatment plans vary dramatically.[1] Chemotherapy-based multimodality therapy is standard of care, but ideal local therapy is unclear. Concurrent chemoradiotherapy (CRT) without surgery is commonly accepted as the standard of care,[2] but local relapse is the first site of failure in >30%.[3] Therefore, adding surgery to improve outcomes is attractive. Lung resection following induction CRT to 45 Gy was shown to be safe in Southwest Oncology Group 8805[4] and the Pancoast Intergroup study 0160.[5] The Intergroup trial 0139 evaluated adding surgery to CRT for the treatment for N2+ IIIA NSCLC.[6] The primary endpoint was improved overall survival (OS), but was not met despite a significant improvement in progression-free survival (PFS). Some of this discrepancy was due to an unacceptably high number of patients undergoing pneumonectomy and excessive mortality following pneumonectomy.[6] Preoperative radiotherapy (RT) was limited to 45 Gy in these trials, but multiple single institution series report the safety of lung resection following CRT to 60Gy.[7,8] NRG Oncology RTOG 0229 trial (0229) and RTOG 0839 trial (0839) evaluated the feasibility of a multicenter trial of trimodality therapy in which surgical resection followed CRT with full dose (60 Gy) RT. Surgical certification was required in both trials to ensure expertise in post-induction lung resections. (Figure 1) Mediastinal lymph node (LN) sterilization was the primary endpoint of both trials; as a potential surrogate for long-term benefit because of its strong association with OS following induction therapy.[6] RTOG 0839 (0839) also tested the hypothesis that adding an epidermal growth factor receptor (EGFR) antibody to concurrent induction CRT could improve mediastinal LN sterilization and outcomes in operable N2+IIIA NSCLC. EGFR antibodies potentiate radiation effects in head and neck cancers,[9] and RTOG trial 0324 combined cetuximab with CRT in inoperable stage III NSCLC patients and demonstrated excellent 2-year OS with minimal toxicity increase.[10,11] Panitumumab is a fully human monoclonal EGFR antibody.

Primary endpoints for each trial were previously reported and similar in all treatment arms, mediastinal LN sterilization rate was 63% in 0229,[12] 68% in the control arm of 0839 and 50% in experimental arm.[13] Since inclusion criteria, induction strategies, and surgical requirements were similar in the trials, short-term surgical results are combined to increase power and reported here. The primary goal of this analysis examination of short-term

surgical outcome following full-dose concurrent CRT induction and determine factors associated with Grade 3/4 adverse events (Gr3/4AEs), and 30-day and 90-day mortality.

Materials and Methods

Patients

Patients with histologically documented NSCLC, stage III N2+, ECOG performance status of 0-1 and normal organ function (creatinine < 1.5, normal liver function tests) were potentially eligible. Mediastinal LN involvement had to be proven pathologically, and with the goal of reducing extended resections LN had to be < 3cm in greatest diameter, and could not be in direct continuation with the primary tumor. Multimodality evaluation with the operating surgeon was required prior to enrollment to determine suitability for tri-modality therapy and resectability. Each institution was required to have local Institutional Review Board approval, and patients to provide written informed consent. This analysis is limited to those patients who completed CRT and anatomic resection.

Induction and Consolidative Therapy

In both trials, chemotherapy consisted of weekly carboplatin (AUC =2.0), paclitaxel (50 mg/m^2) for 6 weeks. Weekly panitumumab at 2.5 mg/kg was added during CRT in the experimental arm of 0839. Concurrent thoracic RT in 0229 was 61.2 Gy in 1.8-Gy daily fractions (50.4 Gy to the gross disease, ipsilateral hilar and mediastinal nodes, and 10.8 Gy boost to gross disease and involved nodes). In 0839 a total 60 Gy was delivered in 2 Gy daily fractions to gross disease only without irradiation of clinically uninvolved LNs. Consolidation chemotherapy in both trials consisted of carboplatin (AUC =6) and paclitaxel (200 mg/m^2) every 21 days for two courses.

Surgery

All surgeons required authorization from RTOG. Surgeons were all board certified in thoracic surgery, and needed to 1) be familiar with the American Thoracic Society LN map, 2) adhere to intra-operative requirements for mediastinal staging and bronchial buttressing, and 3) perform a minimal of 10 lobectomies or pneumonectomies per year, with 5 after induction therapy. Required pre-surgical evaluation following CRT included repeat history and physical, pulmonary function tests, and restaging PET/CT to identify changes in functional status and rule out disease progression. The mediastinum was pathologically reassessed pre-operatively in a separate procedure or at the time of resection at each institution’s discretion. Resections were performed 4-8 weeks following CRT by lobectomy or greater to achieve complete resection. Minimally invasive resections were permitted in 0839. Systematic mediastinal LN evaluation was required at resection including stations 2R, 4R, 7, 9R, and 10R for right sided tumors and stations 5, 6, 7, 9L, and 10L for the left side. If persistently positive mediastinal LNs were found at pre-operative staging or thoracotomy, resection of the primary was at the surgeon’s discretion. Bronchial stump buttressing with autologous vascularized soft-tissue was required. Patients were preferentially extubated in the operating room and postoperative fluids kept to a minimum. Major surgical deviations included resection of patients with FEV1 < 800 cc, inadequate LN sampling, lack of bronchial stump coverage, surgery > 10 weeks after CRT, and surgery deferred for other than

medical reasons. Surgical Quality Assurance was performed using operative notes and pathology reports at the midpoint of 0229 and continuously during 0839. Adverse events were recorded by each institution per the NCI Common Terminology Criteria for Adverse Events (CTCAE) v3 in 0229 and v4 in 0839. No significant differences exist between versions for AEs reported here.

Dosimetric Assessment

Correlations between induction RT dose to specific cardiothoracic structures and short-term surgical outcomes was evaluated in the 0839 cohort (0229 radiation plans were not accessible). The lungs were delineated using automatic thresholding and excluding gross tumor volume (GTV). The heart was contoured from base to apex beginning at the origin of the ascending aorta. Dose volume histograms were generated for heart, combined lungs, ipsilateral and contralateral lungs, and esophagus.

Statistical Considerations

Univariate logistic regression methods were used to differentiate between grade 3-5 and less serious morbidity. When logistic regression modeling was not possible due to insufficient events (< 10 events), Fisher's exact testing was used to compare categorical outcomes and Wilcoxon rank sum was used for continuous data comparisons.. For multiplicity adjustment, the Benjamini-Hochberg method was used to control the false discovery rate less than 0.25 for univariate analysis of morbidity.

Role of the funding source

The sponsors were not involved in the data interpretation.

Results

The trials were open sequentially, 0229 from 9/04-11/08 and enrolled 60 patients from 22 institutions. 0839 was open 11/10- 8/15; it accrued 71 patients from 33 institutions prior to closure by the Data Monitoring Committee after a planned interim analysis. A total of 93 (74.4%) patients underwent anatomic resection. Reasons for not undergoing resection were similar between trials and are outlined in CONSORT diagram (Figure 2).

The distribution of patient and tumor characteristics is presented in Table 1. The median age is 60, 57% of the patients were male, and the majority were white (85%). Most patients had T1 (37%) or T2 (51%) tumors. All patients had at least one N2+ node either clinically or pathologically. More tumors were situated in the right upper lobe (47%) and were adenocarcinomas (58%). The median FEV1 at enrollment was 2.34 L. Only 25% of patients undergoing resection had a pathologic complete response (pCR) to CRT, but 72% achieved mediastinal LN clearance.

Distribution of surgical data is presented in Table 2. The median time from the end of CRT to surgery was 42 days. Most patients had lobectomies (83%), but lobectomy rate was higher in 0839 (87%) than in 0229 (77%). In 0839, 14 resections were attempted minimally invasively, two converted to open. RO resections occurred in 91% of surgical patients and

68% of all eligible patients. Median duration of surgery was 240 minutes. The number of mediastinal and hilar LN stations sampled was similar in both studies, with a median of 3 mediastinal and 2 hilar. Bronchial stump coverage was used in 84% of surgeries, most frequently with an intercostal muscle (71%). Estimated blood loss was also lower in 0839, and fewer patients required a transfusion than in 0229 (4% vs. 21%). The median length of stay was 7 days for 0229, 5 days for 0839.

The distribution of dosimetric data obtained from 0839 is in Supplemental Table 1. The median lung V_5 was 56.5%, indicating that over half of the lung excluding GTV received at least 5 Gy in half of the patients. The median mean dose to the lungs excluding GTV was 16.1 Gy. Ipsilateral lung V_5 was 68.2% and contralateral lung V_5 44.3 %. The ipsilateral and contralateral mean lung doses were 24.5Gy and 6.15 Gy respectively. Heart V_{10} was 25.3%, but the median heart V_{60} was low at 0.7%. The mean and maximum esophageal doses were 23.3 Gy, and 63.1 Gy.

Non-fatal post-operative AEs were reported in 50 (53%) patients and rates were similar between trials. Most common AEs were Grade 1-2 atrial fibrillation (20), atelectasis (18) and pneumothorax (17). All AEs are outlined in Table 3. Grade 3/4AEs occurred 21(23.6%). Post-operative 30-day mortality occurred in 4 (4%) and 90-day mortality in 5 (5%). For all resections the rates for any AE, Gr 3/4AE, 30-day mortality, and 90-day mortality were 59%, 28%, 4%, and 5%; for the 77 lobectomy patients the rates were 57%, 26%, 1.3% and 2.6%. In a comparison of outcomes between patients who received panitumumab or not, rates of any AE (40% vs. 71%, p=0.003) and Gr 3/4AE (9% vs. 31%, p=0.02) were lower with the EGFR antibody, but there was trend to higher 30-day (9% vs. 2%, p=0.15) and 90-day mortality (11% vs. 2%, p=0.06). The only death in the cohort that did not receive panitumumab, was a patient with post-operative pulmonary edema following pneumonectomy.

The distribution and univariate analysis for morbidity are outlined in Table 4. Panitumumab and higher T-stage were associated with decreased risk of morbidity in the full cohort, while extended resections were associated with an increased risk of fatal morbidity. No RT dose to heart or lung was associated with Gr3/4 AEs in these models, but there was a trend toward increased risk of fatal AEs with higher lung V_5, ipsilateral lung V_{10}, and contralateral lung V_5. Details for each of mortality are outline in Table 3 and distribution for 90-day mortality is outlined in Table 5. Use of panitumumab and extended resections were associated with an increased risk for operative mortality. While there was a trend toward increased 90-day mortality with higher ipsilateral and contralateral lung V_5 and higher total lung V_{10}, that effect was lost after taking into account panitumumab and extent of resection. These models should be viewed with caution given the low number of events.

Discussion

The major finding of this analysis is that lobectomy following full-dose concurrent CRT to 60 Gy was performed safely in a multidisciplinary setting. The addition of induction therapy for patients with N2+ IIIA NSCLC who undergo resection has been standard of care since the early 1990s when a series of small phase III trials showed dramatic survival

improvements compared with surgery alone.[14,15] Controversy has existed ever since as to the best induction strategy, with considerable debate of safety and efficacy of pre-operative RT. Full-dose concurrent CRT appears to provide the highest rates of mediastinal LN sterilization,[16–18] but many are hesitant to use it due to high rates of operative complications reported in early series.[4,19] Several single institution studies have reported the feasibility of full-dose concurrent CRT and resection,[7,8,20,21] but these two RTOG trials are the first to prospectively evaluate this approach in a multi-institutional setting. These findings provide an important and timely baseline as the field moves into an era where immunotherapy is being added to induction regimes.

Two recent randomized trials from Europe attempted to define the role of induction CRT in resectable N2+ NSCLC. The Clinical Trial Group for the German Cancer Society compared CRT plus resection to CRT alone, similar to the Intergroup 0139 trial, but used a more complex induction protocol, and limited enrollment to high volume thoracic centers.[22] RT in the surgery group was limited to 45 Gy, 2/3 of patients had IIIB disease and extended resections were used in 43%. Similar to the surgical arm of the Intergroup, 90-day operative mortality was 7%.

The second trial from the Swiss Cancer Research Group randomized 232 patients to 3 cycles of cisplatin-based chemotherapy alone or with the addition of RT to 44 Gy in a sequential fashion followed by resection in both arms.[23] The low RT dose and sequential approach limit the ability to evaluate the trimodality approach. Overall operative morbidity was 23% and mortality was 1.5%, and neither were increased in the RT arm. This trial had more extended resections (34%) and fewer R0 resections (86%) suggesting some difference in inclusion criteria or treatment response to the data presented here. Overall, the 23% Gr3/4AEs and 4% 30-day mortality from the RTOG trials compares favorably to these European prospective trials.

The short-term outcomes for lobectomy in this trial also compare favorably with contemporary outcomes for NSCLC resections from the Society for Thoracic Surgery General Thoracic Surgery Database (STS-GTSDB) and resections following chemotherapy alone in IIIA disease. Morbidity and mortality following NSCLC resection reported in the STS-GTSDB from 2002-2008 were 18.5% and 2.2% respectively,[24] and lower between 2012-2014, where 30-day mortality was only 1.4% for all NSCLC resections and 1.3% for lobectomy.[25] 30-day mortality following lobectomy in this series are the same despite higher stage, fewer minimally invasive procedures, and full-dose induction CRT. Similar to outcomes in the STS –GTSDB, thoracic surgical expertise may explain the short-term outcomes of this analysis compared to previous prospective analysis of tri-modality therapy, most specifically, the Intergroup trial 0139. Participating surgeons in these trials were required to be board certified in thoracic surgery, demonstrate experience with resections following induction therapy, and pre-treatment surgical evaluation was required prior to enrollment.

An equally important finding of this analysis is that extended resections were associated with increased mortality, 19% at 30 and 90 days. Excessive mortality following pneumonectomy[6,19] and bilobectomy[26] as part of tri-modality therapy is previously

reported. Extended resections did not portend an increased rate of Gr3/4AEs, but when an AE occurred patients were significantly more likely to die as a result compared to those with AEs following lobectomy. “Failure to rescue” is an important concept in systems related to peri-operative care; induction therapy[27] and extended resections[28] have independently identified as risks factors for mortality following lung resection, and the combination may expose weaknesses in the biological system. The decreased tolerance of complications increases the importance of appropriate patient selection and intraoperative skill to avoid extended resections in this setting. Excluding patients with central tumors and bulky nodes, decreased, but did not eliminate use of extended resections in these trials.

The complications related to the panitumumab in 0839 limit some of the applicability of this work, but are also a meaningful finding. The addition of an EGFR antibody did not improve the primary outcome and was associated with increased mortality following resection. The etiology of this toxicity is unclear, as similar toxicity is not reported with use of EGFR antibodies prior to resections for other histologies.[9,29] It is significant to note the toxicity of EGFR antibodies with RT is related to local inflammation,[30] suggesting pneumonitis as a potential cause. This increased toxicity is in line with the results from RTOG 0617, the large 4-arm phase III trial in unresectable stage III NSCLC, where neither the addition of can EGFR antibody nor the increase in RT to 74 Gy improved survival over standard concurrent CRT to 60 Gy.[1] More severe toxicity and treatment-related deaths occured in the cetuximab arms of this trial. The results of RTOG 0617 were not yet known when 0839 was designed and implemented, but had been identified in 2015 at the time of the interim analysis which resulted in the trial’s early closure. This represents the second NSCLC trial to report increased toxicity with an EGFR antibody and full dose RT.

A rarely discussed benefit of high dose concurrent CRT over other induction strategies is that concurrent CRT to 60 Gy is standard of care for unresectable IIIA NSCLC,[31] and a significant proportion of patients (20.8% in this trial) who start a tri-modality treatment plan, do not undergo resection due to progression or medical decline. This group is not included retrospective series. The reasons for not undergoing surgery in this analysis were progression outside of RT field, persistent N2 on pre-resection biopsy, and medical decline. In this approach, these patients are provided definitive therapy without delays, gaps or sequential RT, and now have the potential for consolidative immunotherapy. The response induction treatment serves as an important in-vivo test of tumor biology. These results also provide evidence for resection of patients referred with residual or persistent disease after definitive CRT, although the majority of resections in these series were all performed within 8 weeks of CRT completion and may not be applicable for resections performed after a prolonged interval.

Recent data on definitive CRT in unresectable stage III NSCLC patients indicate heart dose may be responsible to increased toxicity and poor OS.[32,33] Correlations between induction RT dose to specific cardiothoracic structures (heart, esophagus, ipsilateral and contralateral lung) and short-term surgical outcomes has not been previously investigated, but was queried here in the 0839 cohort. While there was a trend toward increased severe toxicity and 90-day mortality with increasing ipsilateral and contralateral V_5 and lung V_{10}, the

number of events was small and the effect was not seen after controlling for panitumumab and extent of resection.

This analysis has several limitations. First, its small size, despite being a combined cohort from two prospective RTOG trials, only 93 patients were evaluable. The subsequent limited number of events (4 deaths within 30 days and 5 at 90 days) makes the toxicity models for mortality exploratory. This was further hindered by the lack of RT planning data from 0229. While a trend toward increased toxicity was noted with increase ipsilateral and contralateral lung V5, and total lung V_{10}, events were too few for definitive conclusions. This topic deserves greater investigation, and could provide RT planning guidance to reduce surgical morbidity without decreasing the benefit of mediastinal LN sterilization. Second, the trials permitted surgeons to defer resection in patients with persistent nodal disease on post-induction invasive staging. This design allowed for evaluation of the primary outcome of mediastinal nodal clearance, but may have skewed the population in this analysis. A third limitation is the lacks of diffusion data from pulmonary function tests, which has strong correlation with short-term lobectomy outcomes.

Additionally, these trials employed the low dose carboplatin/paclitaxel regimen with concurrent RT. Some argue this approach results in lower chemotherapy doses and decreased efficacy outside of the RT field. The same regime was used in the control arm of RTOG 0617, and resulted in 58% OS at 2 years, the best results for unresectable stage III reported prior to use of immune therapies.[1] Two recent meta-analyses also demonstrate comparable outcomes with less toxicity for this approach compared with a “full dose” cisplatin based regimen.[34,35] Therefore, the low dose carboplatin/paclitaxel regimen seems uniquely suited for the tri-modality approach. It allows for delivery of full dose induction RT, and chemotherapy in the consolidation setting.

Finally, this analysis examines only short-term surgical outcomes and does not look at survival or toxicity past 90 days. While it is recognized that full-dose induction CRT increases rates of pCR and mediastinal LN sterilization, it is less clear if that translates to improved OS survival compared to lower doses or bimodality approaches. A major question regarding aggressive CRT induction strategies is the potential for increased long-term non-cancer mortality.[18] Others hypothesize that the response to systemic therapy is the driver of primary long-term survival and local control is secondary and should be achieved by which ever therapy can provide it with the least toxicity.[17] Unfortunately data from retrospective analyses are affected by inherent treatment bias and of limited value when comparing such divergent treatments. Some of these issues could be addressed in longer-term follow up of this cohort.

In conclusion, tri-modality therapy with concurrent high dose CRT remains a viable option for well-selected stage IIIA NSCLC patients, but was associated with excessive mortality when combined with extended resections. This approach is known to increase sterilize mediastinal LN disease, which is strongly associated with OS benefit. We have demonstrated the ability of thoracic surgeons at multiple institutions, including community and VA hospitals to perform these resections safely in the context of a clinical trial. Additional follow-up is required to determine long-term benefit of the tri-modality approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biographies

Glossary of Abbreviations

AE	adverse events
AUC	area under the curve
C	chemotherapy
CI	confidence interval
CRT	chemoradiotherapy
CTCAE	NCI common terminology criteria for adverse events
Dmax	Maximum dose
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
FEV1	forced expiratory volume in one second
GTV	gross tumor volume
LN	lymph nodes
NSCLC	non-small cell lung cancer

OR	odds ratio
OS	overall survival
pCR	pathologic complete response
PET/CT	Positron emission tomography–computed tomography
PFS	progression free survival
PTV	primary tumor volume
RT	radiation therapy
R0	microscopically margin-negative (resection)
RTOG	Radiation Therapy Oncology Group
STS	Society for Thoracic Surgery
STS-GTSDB	Society for Thoracic Surgery General Thoracic Surgery Database

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Central Message

Lobectomy was performed safely following full-dose concurrent chemoradiotherapy in these multi-institutional prospective trials.

Perspective Statement

Controversy exists over ideal induction strategy for resectable N2+ IIIA NSCLC. Full-dose concurrent chemoradiotherapy results in high rates of mediastinal lymph node sterilization, but there is fear of operating after full-dose radiation. This multi-institutional prospective analysis suggests no excess in morbidity or mortality for lobectomy following full-dose concurrent chemoradiotherapy.

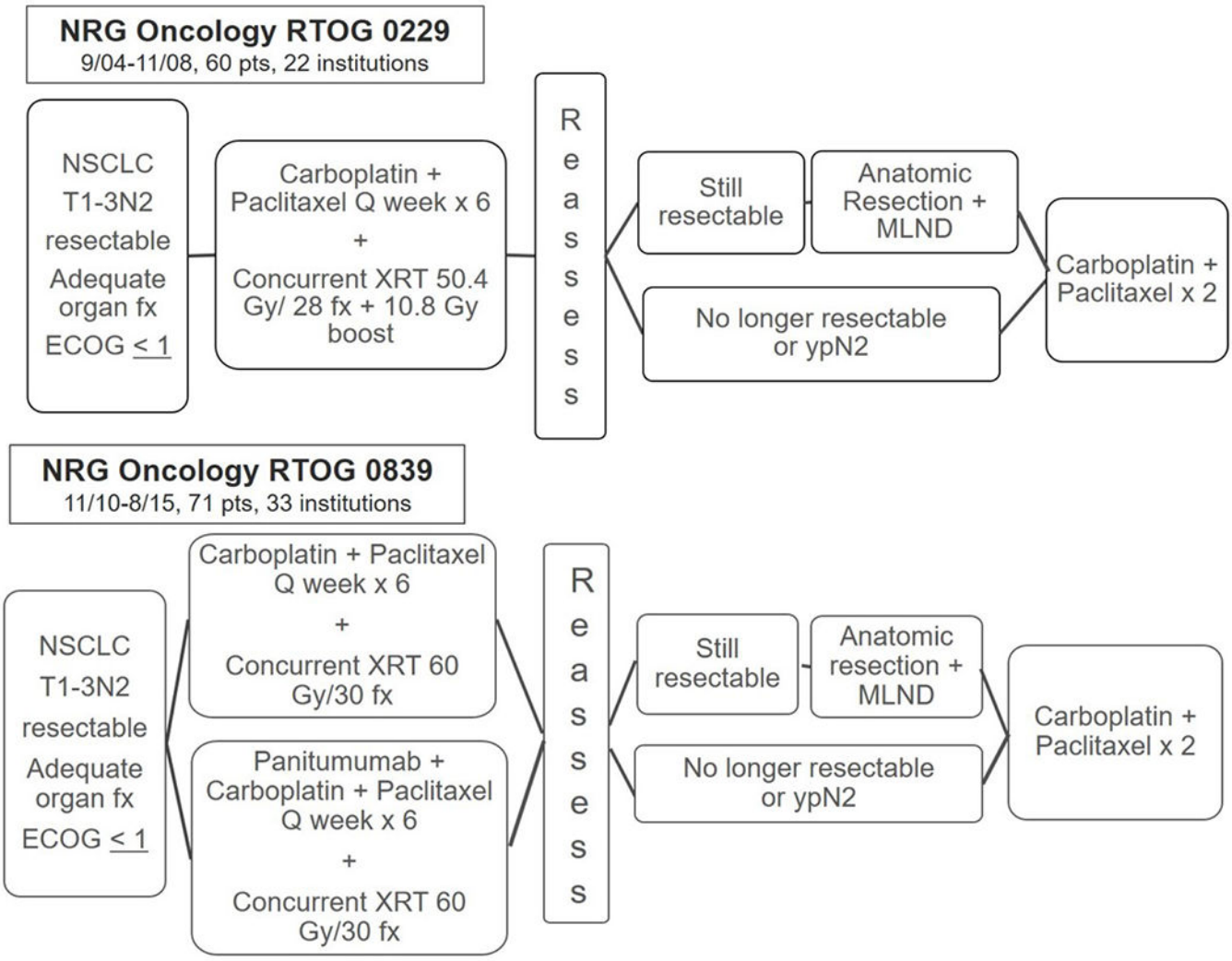


Figure 1.

Schema for NRG Oncology trial 0229 (A) and NRG Oncology trial 0839 (B): both were prospective, multi-institutional phase II trials evaluating the efficacy of concurrent neoadjuvant chemotherapy and high-dose chest radiation prior to resection for stage III non-small cell lung cancer, with the primary endpoint of mediastinal nodal clearance. Randomization in NRG Oncology 0839 was 2:1 in favor of research arm.

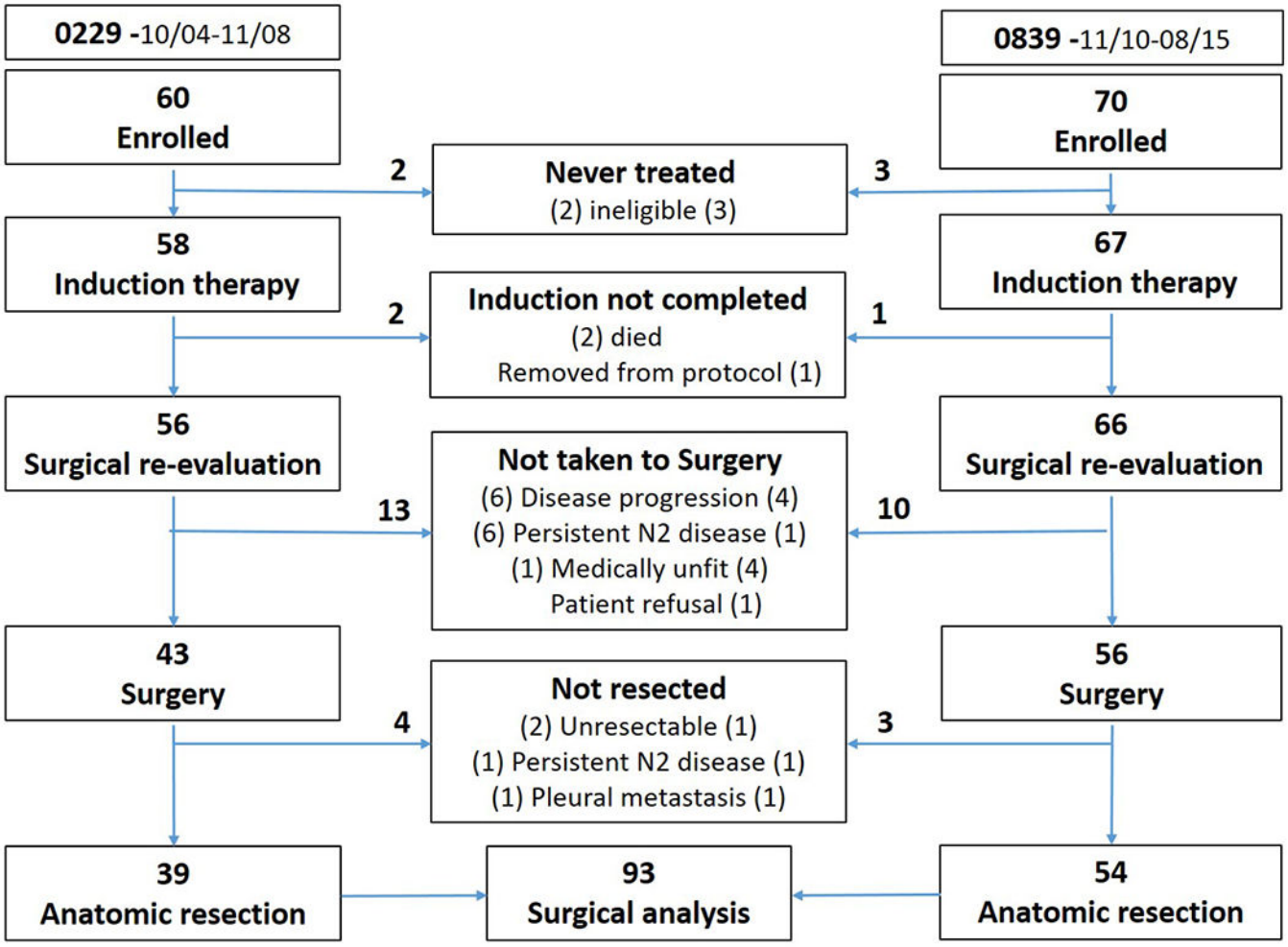
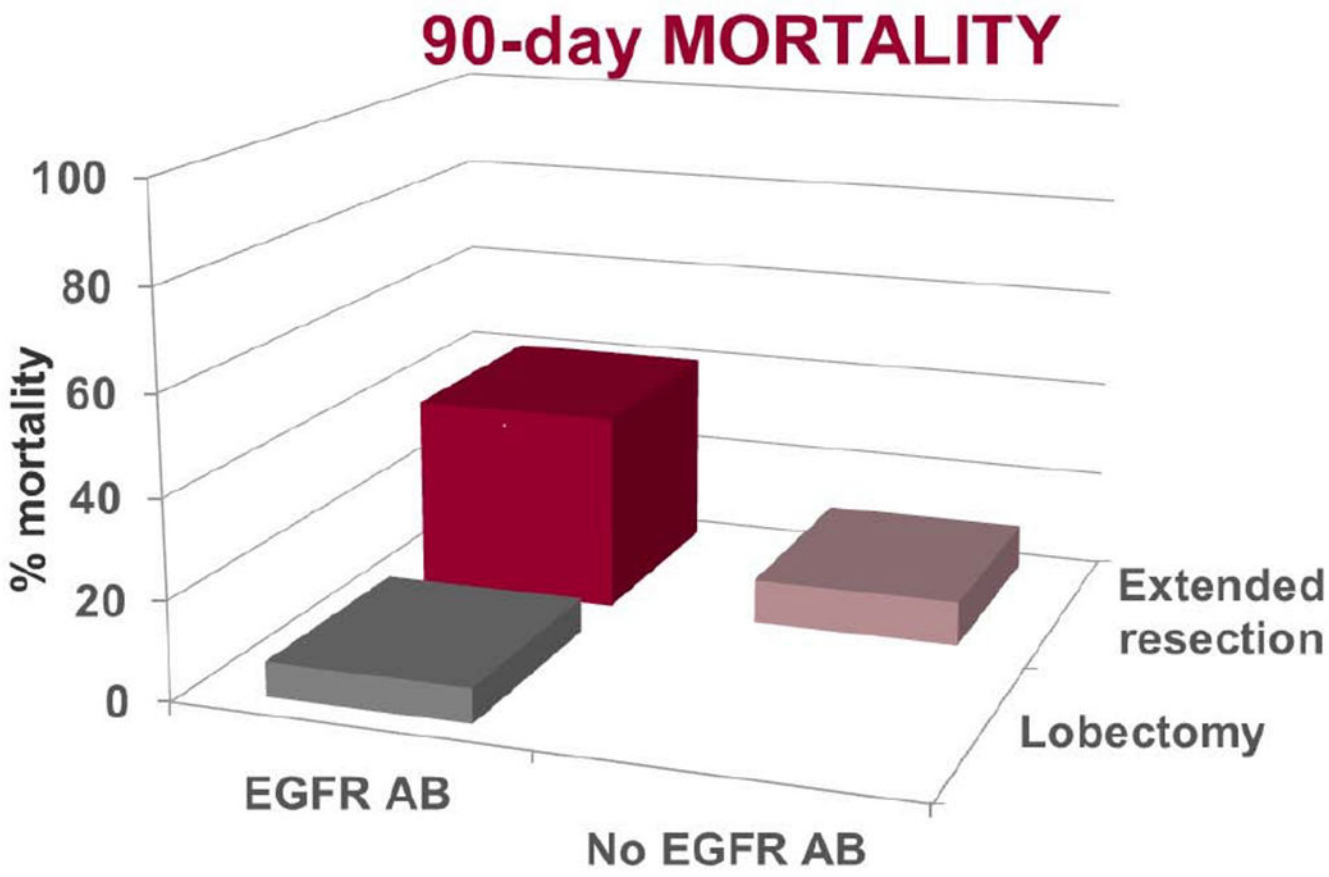


Figure 2.

CONSORT (CONsolidated Standards of Reporting Trials) Diagram for the inclusion of patients in the pooled analysis of short-term surgical outcomes form NRG Oncology trial 0229 and NRG NRG Oncology trial 0839. Surgical outcomes analysis was limited to the 93 patients that underwent anatomic resection.



Central Picture.

NRG Oncology 0229 and 0839 trials assessed full dose concurrent chemoradiotherapy and resection.

Table 1.

Patient and Tumor Characteristics

	0229 (n=39)	0839 (n=54)	Total (n=93)
Age			
Median	58	60.5	60
Min - Max	41 - 75	32 - 78	32 - 78
Q1 - Q3	53 - 64	54 - 67	53 - 65
Gender			
Male	23 (59.%)	30 (56%)	53 (57%)
Female	16 (41.%)	24 (44%)	40 (43%)
Race			
White	30 (77%)	49 (91%)	79 (85%)
Non-white	9 (23%)	5 (9%)	14 (15%)
T-stage at enrollment			
T1	14 (36%)	20 (37%)	34 (37%)
T2	19 (49%)	28 (52%)	47 (50%)
T3	6 (15%)	6 (11%)	12 (13%)
Smoking History			
Never	2 (5%)	4 (7%)	6 (6%)
Former	25 (64%)	39 (72%)	64 (69%)
Current	8 (21%)	8 (15%)	16 (17%)
Unknown	4 (10%)	3 (6%)	7 (8%)
Pack Years (including non-smokers as 0)			
Median	39	34	35
Min - Max	0 - 110	0 - 136	0 - 136
Q1 - Q3	30 - 60	8.5 - 53	15 - 54
ECOG performance status			
0	31 (84%)	42 (78%)	73 (80%)
1	6 (16%)	12 (22%)	18 (20%)
# Clinically or Pathologically + N2 Nodes @ Diagnosis			
Median	1	1	1
Min - Max	1 - 4	1 - 4	1 - 4
Q1 - Q3	1 - 2	1 - 2	1 - 2
Tumor Location			
RUL	18 (46%)	26 (48%)	44 (47%)
RML	4 (10%)	4 (7%)	8 (9%)
RLL	6 (15%)	11 (20%)	17 (18%)
LUL	7 (18%)	11 (20%)	18 (19%)
LLL	4 (10%)	2 (4%)	6 (6%)
Histology			
Adenocarcinoma	19 (49%)	35 (65%)	54 (58%)
Squamous	7 (18%)	13 (24%)	20 (21%)

	0229 (n=39)	0839 (n=54)	Total (n=93)
Other	13 (33%)	6 (11%)	19 (20%)
FEV1 at Baseline			
Median	2.3	2.385	2.34
Min - Max	1.28 - 4.13	1.09 - 3.82	1.09 - 4.13
Q1 - Q3	1.98 - 2.93	2.06 - 2.91	2.06 - 2.92
Institution Type			
Community	12 (31%)	15 (28%)	27 (29%)
Academic	25 (64%)	34 (63%)	59 (63%)
VA	2 (5%)	5 (9%)	7 (8%)
Panitumumab			
No	39 (100.0%)	19 (35%)	58 (62%)
Yes	0 (0.0%)	35 (65%)	35 (38%)
pCR			
No	29 (74%)	41 (76%)	70 (75%)
Yes	10 (26%)	13 (24%)	23 (25%)
Mediastinal Nodal Clearance			
No	9 (23%)	17 (31%)	26 (28%)
Yes	30 (77%)	37 (69%)	67 (72%)

Q1 = first quartile; Q3 = third quartile; ECOG PS, Eastern Cooperative Group performance status; pCR, Complete Response to Chemoradiation

Table 2.

Surgical Information

	0229 (n=39)	0839 (n=54)	Total (n=93)
Days from End of RT to Surgery			
Median	47	41.5	42
Min - Max	30 - 78	27 - 119	27 - 119
Q1 - Q3	42 - 52	38 - 48	38 - 50
Extent of Resection			
Lobectomy	30 (77%)	47 (87%)	77 (83%)
Pneumonectomy	5 (13%)	3 (6%)	8 (9%)
Bilobectomy	3 (8%)	3 (6%)	6 (6%)
Sleeve	1 (3%)	1 (2%)	2 (2%)
Approach			
Open	38 (97%)	41 (76%)	79 (85%)
Minimally invasive	1 (3%)	13 (24%)	14 (15%)
RO			
No	5 (13%)	3 (6%)	8 (9%)
Yes	34 (87%)	51 (94%)	85 (91%)
Surgery Duration (minutes)			
Median	236.5	246	240
Min - Max	69 - 570	120 - 2503	69 - 2503
Q1 - Q3	199 - 292	184 - 321	189 - 318
Number of Mediastinal Node Stations Sampled			
Median	3	3	3
Min - Max	0 - 7	1 - 7	0 - 7
Q1 - Q3	2 - 5	3 - 4	2 - 4
Number of Hilar Node Stations Sampled			
Median	2	2	2
Min - Max	0 - 5	0 - 5	0 - 5
Q1 - Q3	1 - 3	1 - 3	1 - 3
Bronchial Coverage			
No	7 (18%)	8 (15%)	15 (16%)
Intercostal	26 (67%)	40 (74%)	66 (71%)
Other	6 (15%)	4 (7%)	10 (11%)
Intraoperative Transfusion			
No	31 (79%)	52 (96%)	83 (89%)
Yes	8 (21%)	2 (4%)	10 (11%)
Estimated Blood Loss (cc)			
Median	200	150	175
Min - Max	100 - 1400	0 - 2000	0 - 2000
Q1 - Q3	150 - 350	62.5 - 259.5	100 - 300
Length of Stay (days)			

	0229 (n=39)	0839 (n=54)	Total (n=93)
Median	7	5	5
Min - Max	2 - 60	2 - 29	2 - 60
Q1 - Q3	5 - 9	4 - 7	4 - 8

Q1 = first quartile; Q3 = third quartile.

Table 3.

Adverse events entire cohort (N=93)

Grade 1/2 AEs	Grade 3/4 AEs
Atrial fibrillation (20) Atelectasis (18) Pneumothorax (17) Effusion (16) Pain (5) Pneumonia (4) Chylothorax (3) Hypotension (3) Hypocalcemia (3) Rash (2) Constipation (2) Anemia (2) ACS, arterial injury, atrial flutter, confusion, diarrhea, esophagitis, hypoglycemia, ileus, narcotic OD (1)	Pneumonitis (5) Pneumonia (4) Respiratory failure (3) RLN injury (3) Dyspnea (3) Pulmonary edema (3) Atelectasis (2) Pulmonary embolus (2) AKI, anemia, aspiration, bronchial obstruction, chylothorax, DTs, effusion, empyema, esophagitis, hemorrhage, hypocalcemia, hyponatremia, hypotension, hypoxia, lymphopenia, necrotic muscle flap, sepsis, ventricular arrhythmia, UTI, wound infection (1)

Grade 5 AEs				
Demographic	**Resection**	**EGFR AB**	**Gr 5AE**	**POD**
43 M	R pneumonectomy	No	PPE	6
52 M	Bilobectomy	Yes	Hemorrhage	23
61 M	Lobectomy	Yes	BPF	28
63 F	L pneumonectomy	Yes	Aspiration	29
71 F	Lobectomy	Yes	Pneumonitis	45

AE, adverse event; CT, cardiothoracic; ACS, acute coronary syndrome, OD, overdose; AKI, acute kidney injury; DTs, delirium tremors; UTI, urinary tract infection; M male: F, female: EGFR AB, panitumab; R, right; L, left; PPE, post-pneumonectomy pulmonary edema; BPF, broncho-pleural fistula; POD, post-opertative day. Events were reported by each institution per the NCI common terminology criteria for adverse events (CTCAE) v3 in 0229 and v4 in 0839.

Table 4.

Distribution of Surgical Morbidity and Univariate Models of Grade 3+ Morbidity

Variable	Grade 3-4 (n=21)	Grade 5 (n=5)	< Grade 3 Morbidity (n=67)	Grade 3+ Morbidity (n=26)	OR (95% CI)	FDR-adjusted p-value*
Study						
0229 (RL)	10 (26%)	1 (2%)	28 (72%)	11 (28%)		
0839	11 (20%)	4 (7%)	39 (72%)	15 (28%)	0.98 (0.39, 2.45)	0.96
Age						
Median	62	61	60	61.5	1.01 (0.96, 1.07)	0.64
Min-Max	41-72	44-71	32-78	41-72		
Q1-Q3	56-65	52-69	53-65	54-66		
Gender						
Male (RL)	9 (17%)	3 (6%)	41 (77%)	12 (23%)		
Female	12 (30%)	2 (5%)	26 (65%)	14 (35%)	1.84 (0.74, 4.59)	0.33
Race						
White (RL)	19 (24%)	5 (6%)	55 (70%)	24 (30%)		
Non-white	2 (14%)	0 (0%)	12 (86%)	2 (14%)	0.38 (0.08, 1.84)	0.33
T-Stage						
T1 (RL)	12 (35%)	3 (9%)	19 (56%)	15 (44%)		
T2/T3	9 (15%)	2 (3%)	48 (81%)	11 (19%)	0.29 (0.11, 0.74)	0.17
cN2 positive stations						
1 (RL)	16 (26%)	4 (7%)	41 (67%)	20 (33%)		
2-4	5 (16%)	1 (3%)	26 (81%)	6 (19%)	0.47 (0.17, 1.33)	0.33
Tumor location - right vs left						
Right-sided (RL)	17 (25%)	4 (6%)	48 (70%)	21 (30%)		
Left-sided	4 (17%)	1 (4 %)	19 (79%)	5 (21%)	0.60 (0.20, 1.83)	0.48
Tumor location - upper vs lower						
Upper lobe (RL)	13 (21%)	3 (5%)	45 (74%)	16 (26%)		
Lower/Middle lobe	8 (25%)	2 (6%)	22 (69%)	10 (31%)	1.28 (0.50, 3.27)	0.61
Histology						
Adenocarcinoma/other (RL)	14 (19%)	4 (6%)	55 (75%)	18 (25%)		
Squamous	7 (35%)	1 (5%)	12 (60%)	8 (40%)	2.04 (0.72, 5.77)	0.33
FEV1						
Median	2.16	2.24	2.41	2.20	0.75 (0.36, 1.53)	0.49
Min-Max	1.28-3.82	1.65-3.36	1.09-4.13	1.28-3.82		
Q1-Q3	1.97-2.85	2.16-2.39	2.09-2.93	1.97-2.85		

Variable	Grade 3-4 (n=21)	Grade 5 (n=5)	< Grade 3 Morbidity (n=67)	Grade 3+ Morbidity (n=26)	OR (95% CI)	FDR-adjusted p-value*
Institution type						
Community/VA (RL)	9 (26%)	2 (6%)	23 (68%)	11 (32%)		
Academic	12 (20%)	3 (5%)	44 (75%)	15 (25%)	0.71 (0.28, 1.80)	0.52
Received Panitumumab						
No (RL)	18 (31%)	1 (2%)	39 (67%)	19 (33%)		
Yes	3 (9%)	4 (11%)	28 (80%)	7 (20%)	0.51 (0.19, 1.39)	0.33
pCR						
No (RL)	15 (21%)	3 (4%)	52 (74%)	18 (26%)		
Yes	6 (26%)	2 (9%)	15 (65%)	8 (35%)	1.54 (0.56, 4.24)	0.49
Mediastinal LN clearance						
No (RL)	6 (23%)	2 (8%)	18 (69%)	8 (31%)		
Yes	15 (22%)	3 (5%)	49 (73%)	18 (27%)	0.83 (0.31, 2.23)	0.71
Days from end of RT to surgery						
Median	48	38	42	44	1.02 (0.99, 1.05)	0.44
Min-Max	33-119	38-47	27-106	33-119		
Q1-Q3	42-54	38-39	38-49	39-51		
Extended resection						
Lobectomy (RL)	18 (23%)	2 (3%)	57 (74%)	20 (26%)		
Extended resection	3 (19%)	3 (19%)	10 (62%)	6 (38%)	1.71 (0.55, 5.31)	0.48
Surgical approach						
Open (RL)	18 (23%)	4 (5%)	57 (72%)	22 (28%)		
Minimally invasive	3 (21%)	1 (7%)	10 (71%)	4 (29%)	1.04 (0.29, 3.65)	0.96
RO resection						
No (RL)	0 (0%)	0 (0%)	8 (100%)	0 (0%)	N/A	0.10†
Yes	21 (25%)	5 (6%)	59 (69%)	26 (31%)		
Surgery duration						
Median	243	305	233	248	1.00 (1.00, 1.00)	0.94
Min-Max	180-561	180-397	69-2503	180-5641		
Q1-Q3	218-297	248-362	184-312	218-326		
# mediastinal LN sampled						
Median	3	4	3	3.5	1.09 (0.82, 1.44)	0.58
Min-Max	1-7	1-7	0-7	1-7		
# hilar LN sampled						
Median	2	2	2	2	0.66 (0.42, 1.03)	0.25
Min-Max	0-4	1-3	0-5	0-4		

Variable	Grade 3-4 (n=21)	Grade 5 (n=5)	< Grade 3 Morbidity (n=67)	Grade 3+ Morbidity (n=26)	OR (95% CI)	FDR-adjusted p-value*
Bronchial coverage						
No (RL)	4 (24%)	0 (0%)	13 (76%)	4 (24%)		
Yes	17 (22%)	5 (6%)	54 (71%)	22 (29%)	1.32 (0.39, 4.51)	0.65
Intraoperative transfusion						
No (RL)	18 (22%)	5 (6%)	60 (72%)	23 (28%)		
Yes	3 (30%)	0 (0%)	7 (70%)	3 (30%)	1.12 (0.27, 4.70)	0.88
Estimated blood loss						
Median	175	88	200	150	1.00 (1.00, 1.00)	0.33
Min-Max	0-500	50-300	10-2000	0-500		
Q1-Q3	100-300	50-213	100-300	87.5-275		
RTOG 0839 RT Data	**Grade 3-4 (n=11)**	**Grade 5 (n=4)**	**< Grade 3 Morbidity (n=39)**	**Grade 3+ Morbidity (n=15)**	**OR (95% CI)**	**p-value**
Lung V5						
Median	55.9	75.0	52.9	57.7	1.03 (1.00, 1.07)	0.25
Min-Max	44.0-86.0	57.7-88.2	19.0-85.1	44.0-63.8		
Q1-Q3	49.0-72.9	60.8-87.1	41.2-67.4	34.4-50.6		
Ipsilateral Lung V10						
Median	60.9	76.2	61.1	62.9	1.03 (1.00, 1.07)	0.25
Min-Max	46.1-79.6	56.3-95.5	26.5-87.0	46.1-95.5		
Q1-Q3	50.7-72.2	61.1-91.0	44.2-72.0	51.7-77.5		
Contralateral Lung V5						
Median	45.1	64.5	42.4	55.6	1.03 (1.00, 1.06)	0.25
Min-Max	29.8-85.6	49.6-83.0	0.5-83.4	29.8-85.6		
Q1-Q3	37.4-64.0	52.6-78.2	24.2-58.2	39.8-67.7		

OR, Odds Ratio modeling the risk of developing Grade 3 + Morbidity; RL, Reference level; Q1, first quartile; Q3, third quartile; pCR, pathologic complete response, LN, lymph nodes;

*FDR, false discovery rate; p<0.25 considered significantly different

†Fisher's exact test

Table 5.

Surgical Mortality

	30 Day Mortality		90 Day Mortality	
	No	**Yes**	**No**	**Yes**
Received Panitumumab				
No	57 (98%)	1 (2%)	57 (98%)	1 (2%)
Yes	32 (91%)	3 (9%)	31 (89%)	4 (11%)
p-value†	0.15		0.06	
Extended Resection				
Lobectomy	76 (99%)	1 (1%)	75 (97%)	2 (3%)
Extended resection	13 (81%)	3 (19%)	13 (81%)	3 (19%)
p-value†	0.02		0.03	
RTOG 0839 RT Data	n=51	n=3*	n=50	n=4
Lung V5				
Median	55.9	57.7, 64.0, 86.0*	55.0	75.0
Min-Max	19.0-88.2		19.0-86.0	57.7-88.2
Q1-Q3	46.0-69.2		46.0-68.3	60.8-87.1
p-value‡	0.17		0.04	
Ipsilateral Lung V10				
Median	61.1	56.3, 65.9, 95.9*	61.0	76.2
Min-Max	26.5-87.0		26.5-87.0	56.3-95.5
Q1-Q3	48.0-72.2		48.0-72.0	61.1-91.0
p-value†	0.30		0.09	
Contralateral Lung V5				
Median	43.4	49.6, 55.6, 73.4*	42.9	64.5
Min-Max	0.5-85.6		0.5-85.6	49.6-83.0
Q1-Q3	26.7-64.0		26.7-62.9	52.6-78.2
p-value‡	0.25		0.07	

*All three values reported, due to small number of events

†Fisher's exact test

‡Wilcoxon rank sum test