Redefining the Risk of Surgery for Clinical Stage IIIA (N2) Non-Small Cell Lung Cancer: A Pooled Analysis of the STS GTSD and ESTS Registry

Andrew T. Arndt8 · Alessandro Brunelli2 · Silvia Cicconi3 · Pierre-Emmanuel Falcoz4 · Michele Salati5 · Benjamin Kozower6 · Michael J. Liptay1 · Gaetano Rocco7 · Justin M. Karush1 · Nicole Geissen1 · Sanjib Basu1 · Christopher W. Seder1

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Abstract

Background Management of clinical stage IIIA-N2 (cIIIA-N2) non-small cell lung cancer (NSCLC) remains controversial. We evaluated treatment strategies and outcomes in cIIIA-N2 NSCLC patients who underwent pulmonary resection in The Society of Thoracic Surgeons General Thoracic Surgery Database (STS GTSD) and the European Society of Thoracic Surgeons (ESTS) Registry.

Methods The STS GTSD and ESTS Registry were queried for patients who underwent pulmonary resection for cIIIA-N2 NSCLC between 2012 and 2016. Demographic variables, treatment strategies, and outcome measures were collected and analyzed. Significance of differences was determined using the \( \chi^2 \) test for categorical variables and the Wilcoxon rank sum test for continuous variables.

Results Pulmonary resection was performed in 4279 cIIIA-N2 NSCLC patients (2928 STS GTSD; 1351 ESTS). Induction therapy was administered to 49%. Lobectomy was performed in 67.1% and pneumonectomy in 13%. Lobectomy was associated with 19.2% major morbidity and 1.6% operative mortality, while pneumonectomy was associated with 34.1% and 5%, respectively. Induction therapy was associated with a higher rate of major morbidity or mortality than upfront surgery (23.2% vs 19.5%, \( p = 0.004 \)), driven by pneumonectomy (40.7% vs 30.3%, \( p = 0.012 \)) rather than lobectomy (20.3% vs 18.8%, \( p = 0.31 \)).

Conclusions Pulmonary resection for cIIIA-N2 NSCLC is associated with low rates of operative morbidity and mortality, with lobectomy having lower morbidity and mortality than pneumonectomy. Induction therapy, particularly chemoradiotherapy, is associated with a higher rate of composite morbidity or mortality than upfront surgery in pneumonectomy patients but not lobectomy patients.

Introduction

Lung cancer is the leading cause of cancer death worldwide [1]. Approximately 1 in 4 patients diagnosed with non-small cell lung cancer (NSCLC) in the USA will present with...
locally advanced disease, with an overall 5-year survival of 29.7% [2, 3]. Significant variation in the treatment of stage IIIA-N2 NSCLC exists, both on a national [4] and international level [5]. Furthermore, there is no standard of care based on best medical evidence, as a number of multicenter, randomized controlled trials have demonstrated the efficacy of different multimodality strategies [6–9].

The INT-0139, a phase III prospective, randomized controlled trial, demonstrated no difference in overall survival between definitive chemoradiotherapy and induction chemoradiotherapy followed by resection for patients with stage IIIA-N2 NSCLC [6]. The lack of survival benefit in the surgical arm was partially driven by a 26% mortality rate following pneumonectomy [4]. However, a recent report from the Society of Thoracic Surgeons General Thoracic Surgery Database (STS GTSD) that examined management of stage IIIA-N2 NSCLC in North America reported excellent results with surgical resection [10].

The STS GTSD and the European Society of Thoracic Surgeons (ESTS) Registry Taskforces have worked over the past number of years to standardize definitions and terminology for efficient and accurate database collaborations [11]. Building upon this, the current study analyzed pooled STS GTSD and ESTS Registry data to produce contemporary intercontinental outcome data and allow comparison of stage-specific practice patterns for clinical stage IIIA-N2 (cIIIA-N2) NSCLC, with the hypothesis that surgical resection, when performed as part of a multi-modality regimen, is associated with low rates of perioperative morbidity and mortality.

Methods

This study was granted exemption from full review and was therefore approved by the Rush University Medical Center Institutional Review Board.

Data Sources

The STS GTSD is the largest thoracic database in North America and includes demographic, operative, perioperative, and short-term outcome data. Similarly, the ESTS Registry is a comprehensive European database that maintains data including demographic information, operative details, and perioperative outcomes for thoracic surgical patients. To abide by international data transfer regulations, only aggregate data were obtained from the ESTS Registry.

Patients

Patients who underwent pulmonary resection for clinical stage IIIA (T1-3N2M0) NSCLC between 2012 and 2016 were identified from the STS GTSD and the ESTS Registry. Demographic variables, disease characteristics, treatment strategies, and outcome measures were defined by STS GTSD or ESTS Registry guidelines [12, 13]. Staging was according to the seventh edition of the American Joint Committee on Cancer NSCLC staging system [14]. Pulmonary resection was defined as either thoracoscopic or open: wedge resection, segmentectomy, lobectomy, bilobectomy, or pneumonectomy. Patients younger than 18 years of age and those who underwent non-elective procedures were excluded from analysis.

Variables

Demographic variables examined from the STS GTSD and ESTS Registry included: age, gender, height, weight, coronary artery disease, diabetes mellitus, dialysis, congestive heart failure, prior cardiothoracic surgery, chronic obstructive pulmonary disease, cigarette smoking (never, past, or current), Zubrod score, clinical staging modality [computed tomography (CT) scan, positron emission tomography-computed tomography (PET-CT), or invasive staging (endobronchial ultrasound (EBUS), endoscopic ultrasound (EUS), or mediastinoscopy)], pathologic stage, and lung cancer histology. Treatment details collected included type of pulmonary resection performed, laterality, and the administration of preoperative chemotherapy and radiotherapy. Perioperative outcome data collected included date of surgery, date of discharge, major morbidity, and 30-day mortality. Major morbidity was defined in accordance with postoperative measures tracked in the STS GTSD and synchronized with measures in the ESTS Registry. Major morbidity in this study included variables that are tracked as major morbidity in the STS Database (tracheostomy, reintubation, initial ventilator support > 48 h, adult respiratory distress syndrome, bronchopleural fistula, pulmonary embolism, pneumonia, unexpected return to the operating room for bleeding, myocardial infarction) as well as additionally compiled post-operative complications [deep vein thrombosis requiring treatment, atrial arrhythmia requiring treatment, renal failure (RIFLE criteria), chylothorax, and recurrent laryngeal nerve paralysis] [15]. Data related to patient baseline characteristics, treatment strategy, and frequency of complications (Tables 1, 2, 3) are presented as from the STS, the ESTS, and the combined cohort, allowing for both direct comparison of the societies and for analysis of aggregate data over the exact same time period.

Statistical Methods

Descriptive analyses were performed across the populations with patients stratified by upfront surgery, induction chemotherapy followed by surgery, and induction
chemoradiotherapy followed by surgery. The groups were compared using the $\chi^2$ test for categorical variables and the Wilcoxon rank sum test for continuous variables. A $p$ value of <0.05 was considered statistically significant.

Patients who underwent lobectomy and pneumonectomy were the primary focus of this study and were specifically analyzed. These patients were categorized as having had upfront surgery versus any induction therapy; the “any induction” category was then further classified into chemoradiotherapy and chemotherapy subgroups, excluding those that received induction radiation alone.

### Results

### Patients

Between 2012 and 2016, pulmonary resection was performed on a total of 4279 cIIIA-N2 NSCLC patients: 2928 in the STS GTSD and 1351 ESTS Registry. STS patients were older (mean 65.2 vs 63.3 years, $p<0.001$), were less likely to be male (51.8 vs 70%, $p<0.001$), had a higher body mass index (27.5 vs 26.1, $p<0.001$), and...
were more likely to have coronary artery disease (18.1 vs 13.8%, \(p = 0.001\)), diabetes mellitus (15.8 vs 5.1%, \(p < 0.001\)), prior cardiothoracic surgery (14.2 vs 5.6%, \(p < 0.001\)), and COPD (35 vs 24.7%, \(p < 0.001\)). ESTS patients had a higher rate of baseline renal failure (1.9 vs 0.4%, \(p < 0.001\)) and a lower mean DLCO (69.7 vs 71.7% predicted, \(p = 0.002\)) (Table 1).

### Staging

Most patients in the combined cohort had a PET-CT (83.9%) rather than a CT alone (7%) for radiographic staging. ESTS patients were more likely to be staged by CT alone (13 vs 4.2%, \(p < 0.001\)), whereas STS patients were more likely to have a PET-CT (89.9 vs 71.1%, \(p < 0.001\)). Overall, 45.3% of patients underwent invasive mediastinal staging, with STS patients more likely to undergo invasive mediastinal staging than ESTS patients (57.1 vs 19.7%, \(p < 0.001\)). STS patients were more likely to present with T1a, T1b, T2a, or T2b than ESTS patients, whereas ESTS patients had a higher rate of clinical T3 lesions (28.5 vs 11.1%, \(p < 0.001\)).

### Treatment Strategy

In the combined cohort, 48.9% of patients underwent induction treatment, with STS patients being more likely to have received induction therapy than ESTS patients (52.5 vs 41.2%, \(p < 0.001\)) (Table 2). STS patients were more likely to have chemoradiotherapy than chemotherapy alone (32.6 vs 19.9%, \(p < 0.001\)), whereas ESTS patients were more likely to have chemotherapy alone (29.4 vs 11.8%, \(p < 0.001\)).

Minimally invasive surgical techniques were employed 31% of the time, with the STS cohort being more likely than the ESTS cohort to have undergone minimally invasive surgery (37.8 vs 16.4%, \(p < 0.001\)). Among upfront surgery patients, 57.5% of STS and 18% of ESTS patients had minimally invasive surgery. The most commonly performed procedure was lobectomy at 67.1%. Pneumonectomy was performed in 13% of patients overall and was the second most common operation in each database.

### Pathology

While histopathology was unknown in 60.3% of patients (60.9 and 58.8% in STS and ESTS patients, respectively), the most common reported histopathology was adenocarcinoma, accounting for 24.9% of overall diagnoses and 65.7% of patients with a documented histopathology. The most common pathologic stage was IIIA, found in 42.3% of patients in the combined group. Among upfront surgery patients in the combined group, nodal overstaging (clinical N2, pathologic N0/1) occurred in 47.8% (998/2088).

### Major Morbidity

The major morbidity rate in the combined cohort was 20.8%, with no difference between the STS and ESTS cohorts (21.4 vs 19.4%, \(p = 0.185\)) (Table 3). The 30-day mortality was 2% overall, with no difference between the STS and ESTS cohorts (2.1 vs 1.9%, \(p = 0.735\)). The STS group had a significantly higher rate of tracheostomy (1.2 vs 0.3%, \(p = 0.042\)), reintubation (2.1 vs 1.2%, \(p = 0.036\)), unexpected return to OR for bleeding (4.6 vs 1.3%, \(p < 0.001\)), DVT requiring treatment (1 vs 0.1%, \(p = 0.001\)), and atrial arrhythmia requiring treatment (12.6 vs 8.3%, \(p < 0.001\)). The ESTS cohort had a higher rate of pneumonia (7.8 vs 5.2%, \(p = 0.002\)) and a greater length of stay (7.6 vs 6.3 days, \(p < 0.001\)).

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**Table 2** Treatment strategy

|                      | STS-ESTS | STS     | ESTS    |
|----------------------|---------|---------|---------|
| Induction therapy    | 48.9 (2093) | 52.5 (1537) | 41.2 (556) |
| Induction chemotherapy| 22.9 (980)  | 19.9 (583)  | 29.4 (397)  |
| Induction chemoradiotherapy | 26.0 (1113) | 32.6 (954)  | 11.8 (159)  |
| Minimally invasive   | 31.0 (1328) | 37.8 (1106) | 16.4 (222)  |
| Thoracotomy          | 68.4 (2927) | 62.1 (1818) | 82.1 (1109) |

**Primary procedure**

- Wedge resection: 7.2 (310) vs 8.3 (242) vs 5.0 (68)
- Segmentectomy: 2.2 (96) vs 2.3 (68) vs 2.1 (28)
- Lobectomy: 67.1 (2871) vs 69.2 (2027) vs 62.5 (844)
- Sleeve lobectomy: 3.8 (164) vs 2.7 (78) vs 6.4 (86)
- Bilobectomy: 6.5 (280) vs 6.2 (181) vs 7.3 (99)
- Pneumonectomy: 13.0 (558) vs 11.3 (332) vs 16.7 (226)

**Histopathology**

- Adenocarcinoma: 24.9 (1065) vs 24.8 (725) vs 25.2 (340)
- Squamous cell carcinoma: 12.0 (512) vs 11.1 (326) vs 13.8 (186)
- Neuroendocrine: 1.9 (80) vs 2.3 (66) vs 1.0 (14)
- Mixed histology: 1.0 (43) vs 0.9 (27) vs 1.2 (16)
- Unknown: 60.3 (2579) vs 60.9 (1784) vs 58.8 (795)

**Pathologic stage**

- pCR: 5.4 (229) vs 6.6 (193) vs 2.7 (36)
- IA: 12.6 (538) vs 12.3 (360) vs 13.2 (178)
- IB: 6.8 (290) vs 8.2 (239) vs 3.8 (51)
- IIA: 8.7 (373) vs 10.1 (295) vs 5.8 (78)
- IIB: 7.6 (324) vs 7.6 (223) vs 7.5 (101)
- IIIA: 42.3 (1835) vs 46.3 (1357) vs 35.4 (478)
- IIIB: 2.5 (107) vs 2.2 (65) vs 3.1 (42)
- IV: 1.5 (65) vs 1.6 (47) vs 1.3 (18)
- TX or NX or unknown: 12.1 (518) vs 5.1 (149) vs 27.3 (369)

All data presented as % (n)

STS Society of Thoracic Surgeons, ESTS European Society of Thoracic Surgeons
Major Morbidity or Mortality for Lobectomy and Pneumonectomy by Treatment Strategy

Overall, lobectomy was associated with 19.2% major morbidity and 1.6% operative mortality, while pneumonectomy was associated with 34.1% major morbidity and 5% operative mortality. (Table 4) Among patients who underwent lobectomy or pneumonectomy, induction therapy was associated with a higher rate of composite major morbidity or mortality than upfront surgery (23.2 vs 19.5%, \( p = 0.004 \)). The increased risk of morbidity or mortality with induction therapy was driven by patients who underwent pneumonectomy (40.7 vs 30.3% complication rate in induction vs upfront surgery, \( p = 0.012 \)) rather than lobectomy (20.3 vs 18.8% complication rate in induction vs upfront surgery, \( p = 0.31 \)). Induction chemoradiotherapy was associated with a higher rate of composite morbidity or mortality than induction chemotherapy (25.2 vs 20.9%, \( p = 0.025 \)) in patients who underwent lobectomy or pneumonectomy. Similarly, the increased risk of morbidity or mortality with induction chemoradiotherapy vs induction chemotherapy alone was driven by patients who underwent pneumonectomy (46.2 vs 34.6%, \( p = 0.05 \)) rather than lobectomy (22.1 vs 18.2%, \( p = 0.06 \)).

Examining mortality, patients who underwent any induction therapy had a 1.6% and 6.2% mortality rate with lobectomy and pneumonectomy, respectively. Mortality in the post-induction right pneumonectomy group was similar to the post-induction left pneumonectomy group (5.6% vs 6.9%, \( p = 0.661 \)).

Discussion

This study pooled 4279 cIIIA-N2 NSCLC patients from the STS GTSD and ESTS Registry, allowing for a robust analysis of a heterogeneous patient population. The results suggest pulmonary resection, as part of a multi-modality approach, is associated with low rates of perioperative morbidity and mortality, with lobectomy having lower morbidity and mortality than pneumonectomy. In addition, induction therapy, particularly chemoradiotherapy, is associated with a higher rate of composite morbidity or mortality than pneumonectomy. In addition, induction therapy, particularly chemoradiotherapy, is associated with a higher rate of composite morbidity or mortality than pneumonectomy. In addition, induction therapy, particularly chemoradiotherapy, is associated with a higher rate of composite morbidity or mortality than pneumonectomy. In addition, induction therapy, particularly chemoradiotherapy, is associated with a higher rate of composite morbidity or mortality than pneumonectomy. In addition, induction therapy, particularly chemoradiotherapy, is associated with a higher rate of composite morbidity or mortality than pneumonectomy.

These data highlight that radiographic and invasive mediastinal staging practices vary widely for cIIIA-N2 NSCLC. Despite being recommended for all cIIIA-N2 NSCLC patients by the American College of Chest Physicians [16] and the ESTS, [16] only 89.9% of STS and 71.1% of ESTS patients underwent PET-CT. Similarly, invasive mediastinal staging is recommended for cIIIA-N2 NSCLC patients [16, 17] but was performed only 45.3% of patients in the combined cohort. Invasive mediastinal staging was more frequently performed in the STS group than in the ESTS group (57.1 vs 19.7%). Perhaps the lower rate of invasive
mediastinal staging in the ESTS group is explained by the higher rate of clinical T3 presentation (28.5 vs 11.1%, \(p < 0.001\)), and a radiographic T3N2 was more likely to be accepted as accurate and less likely to prompt invasive mediastinal staging than a radiographic T1-2N2 patient. A more likely explanation may be that surgeons and treatment teams in both the STS and ESTS used clinical judgment in determining which patients would benefit from invasive mediastinal staging. Examples could include a surgeon not judging lymph nodes that were “barely” over 1 cm or nodes that were faintly FDG avid to be high yield for biopsy despite a strict radiographic designation of N2 and a recommendation for invasive mediastinal staging [16, 17].

Nevertheless, the infrequent use of invasive mediastinal staging certainly drove the 47.8% nodal overstaging in the upfront surgery group of patients.

An equally surprising finding was the low rate of induction therapy use for cIIIA-N2 NSCLC patients. In the combined STS and ESTS cohort, only 48.9% of patients underwent induction chemotherapy or chemoradiotherapy (52.5% in STS; 41.2% in ESTS). This number is particularly noteworthy given that the cohort included only pretreatment, clinically N2 patients and is not reflective of nodal upstaging or “surprise” N2 disease in a group of clinical N0-1 patients; therefore, this group would be advised to undergo induction therapy by most current guidelines [18]. As with the possibility that some surgeons omitted invasive mediastinal staging in patients for whom they felt it was low yield, it is possible that this same subset of patients with mediastinal adenopathy that was deemed “borderline” would have at times undergone upfront surgery rather than induction treatment. However, clinical leeway in such “borderline” situations seems unlikely to account for such a disparity between recommendation and actual practice. In line with previous literature [5], STS patients who underwent induction therapy were more likely to have chemoradiotherapy than chemotherapy alone, while ESTS patients were more likely to receive chemotherapy alone rather than chemoradiotherapy.

Surgical management of cIIIA-N2 NSCLC was predominantly with an open lobectomy. Pneumonectomy

### Table 4
Major morbidity and mortality stratified by treatment strategy

| Treatment Strategy                        | n   | Major Morbidity | Mortality | Major Morbidity or Mortality |
|-------------------------------------------|-----|-----------------|-----------|-----------------------------|
| All lobectomy or pneumonectomy\(^a\)     | 3428| 21.6 (739)      | 2.2 (74)  | 22.1 (758)                  |
| Lobectomy\(^b\)                           | 2886| 19.2 (554)      | 1.6 (47)  | 19.6 (565)                  |
| Pneumonectomy                             | 542 | 34.1 (185)      | 5.0 (27)  | 35.6 (193)                  |
| Right pneumonectomy                       | 237 | 31.2 (74)       | 5.5 (13)  | 33.8 (80)                   |
| Left pneumonectomy                        | 275 | 36.7 (101)      | 4.7 (13)  | 37.5 (103)                  |
| Upfront surgery                           | 1929| 18.9 (365)      | 1.9 (37)  | 19.5 (376)                  |
| Lobectomy                                 | 1372| 18.4 (253)      | 1.7 (23)  | 18.8 (258)                  |
| Pneumonectomy                             | 267 | 28.5 (76)       | 3.7 (10)  | 30.3 (81)                   |
| Right pneumonectomy                       | 111 | 27.9 (31)       | 5.4 (6)   | 31.5 (35)                   |
| Left pneumonectomy                        | 131 | 28.2 (37)       | 2.3 (3)   | 29.0 (38)                   |
| Any induction \(\rightarrow\) surgery     | 1978| 22.8 (451)      | 2.3 (45)  | 23.2 (460)                  |
| Lobectomy                                 | 1514| 19.9 (301)      | 1.6 (24)  | 20.3 (307)                  |
| Pneumonectomy                             | 275 | 39.6 (109)      | 6.2 (17)  | 40.7 (112)                  |
| Right pneumonectomy                       | 126 | 33.3 (43)       | 5.6 (7)   | 35.7 (45)                   |
| Left pneumonectomy                        | 144 | 44.4 (64)       | 6.9 (10)  | 45.1 (65)                   |
| Chemoradiotherapy \(\rightarrow\) surgery | 1075| 24.8 (267)      | 2.5 (27)  | 25.2 (271)                  |
| Lobectomy                                 | 816 | 21.6 (176)      | 1.6 (13)  | 22.1 (180)                  |
| Pneumonectomy                             | 145 | 46.2 (67)       | 6.9 (10)  | 46.2 (67)                   |
| Right pneumonectomy                       | 63  | 36.5 (23)       | 6.3 (4)   | 36.5 (23)                   |
| Left pneumonectomy                        | 79  | 53.2 (42)       | 7.6 (6)   | 53.2 (42)                   |
| Chemotherapy \(\rightarrow\) surgery      | 903 | 20.4 (184)      | 2.0 (18)  | 20.9 (189)                  |
| Lobectomy                                 | 698 | 17.9 (125)      | 1.6 (11)  | 18.2 (127)                  |
| Pneumonectomy                             | 130 | 32.3 (42)       | 5.4 (7)   | 34.6 (45)                   |
| Right pneumonectomy                       | 63  | 31.7 (20)       | 4.8 (3)   | 34.9 (22)                   |
| Left pneumonectomy                        | 65  | 33.8 (22)       | 6.2 (4)   | 35.4 (23)                   |

All data presented as % (n)

\(^a\)Data include patients who underwent radiation alone followed by surgery

\(^b\)Sleeve lobectomy patients included
was more common in the ESTS Registry than in the STS GTSD. The frequencies of lobectomy and pneumonectomy in the current study are consistent with other recently published reports [10]. Additionally, the rate of nodal over-staging noted in the upfront surgery group was in line with previous reports [10]. The overall mortality for lobectomy in the combined cohort was 1.6%, which did not differ for the upfront surgery, induction chemoradiotherapy, or induction chemotherapy groups. Overall mortality for the pneumonectomy group was 5% with similar rates between the induction chemotherapy only and chemoradiotherapy patients. This finding is in line with a recent report from the ESTS Database Committee that post-induction pneumonectomy, in a largely chemotherapy-only cohort, was not associated with a higher mortality than pneumonectomy without induction therapy [19]. Additionally, in contradiction to some prior reports [20], post-induction right pneumonectomy in this study did not carry a higher rate of mortality than post-induction left pneumonectomy. However, this finding is consistent with other reports that demonstrated no difference in post-induction mortality between right and left pneumonectomy [10].

This study has certain limitations. The STS GTSD and the ESTS Registry are voluntary databases that do not capture all surgically managed NSCLC patients and likely reflect trends at busy major centers that desire participation in the databases. Therefore, while this study’s 5% operative mortality for pneumonectomy after induction therapy is in line with other recent published reports of STS and ESTS data [10, 19], this outcome may not be generalizable to every hospital. In addition, the inability to compare patient-level data between the STS GTSD and the ESTS Registry limits the conclusions that can be drawn. Without the ability to risk adjust, comparing outcomes become difficult; this report is purely descriptive, and caution should be used when interpreting the findings in this unadjusted dataset. Additional limitations include lack of information on number of lymph node stations involved, which would improve granularity of the dataset given the heterogeneous nature of the disease, and high rate of unknown pathology.

In conclusion, this study suggests that pulmonary resection for cIIIA-N2 NSCLC is associated with low rates of operative morbidity and mortality, with lobectomy having lower morbidity and mortality rates than pneumonectomy. Induction therapy, particularly chemoradiotherapy, is associated with a higher rate of composite morbidity or mortality than upfront surgery in pneumonectomy patients but not lobectomy patients. In addition, this report highlights that there is room for improvement in both radiographic and invasive staging in patients with cIIIA-N2 NSCLC.

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Declarations

Conflict of interest The authors have no conflicts of interest.

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