Major Pulmonary Resection After Neoadjuvant Therapy in Potentially Resectable Stage IIIA/B Non-Small Cell Lung Carcinoma: R0 or No R0

Michael Peer (michaelpe@tlvmc.gov.il)
Tel Aviv university

Sharbel Azzam
Tel Aviv university

Arnold Cyjon
Tel Aviv university

Rivka Katsnelson
Ben Gurion university

Henri Hayat
Tel Aviv university

Ilan Bar
Ben Gurion university

Ofer Merimsky
Tel Aviv university

Research Article

Keywords: Pneumonectomy, Lobectomy, Non-Small Cell Lung Carcinoma, Neoadjuvant Chemoradiation, Neoadjuvant Chemotherapy

Posted Date: May 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-534014/v1

Abstract

Objective The aim of this study was to identify predictors of postoperative outcome and survival of locally advanced non-small cell lung carcinoma (NSCLC) resections after neoadjuvant chemotherapy or chemoradiation.

Methods Medical records of all patients with clinical stage III potentially resectable NSCLC initially treated by neoadjuvant chemotherapy or chemoradiation followed by major pulmonary resections between 1999 to 2019 were retrieved from the databases of four Israeli Medical Centers.

Results: The 124 suitable patients included, 86 males (69.4%) and 38 females (30.6%), mean age of 64.2 years (range 37-82) and mean hospital stay of 12.6 days (range 5-123).

Complete resection was achieved in 92.7% of the patients, while complete pathologic response was achieved in 35.5%. Overall readmission rate was 16.1%. The overall 5-year survival rate was 47.9%. One patient (0.8%) had local recurrence. Postoperative complications were reported in 49.2% of the patients, mainly atrial fibrillation (15.9%) and pneumonia (13.7%), empyema (10.3%), and early bronchopleural fistula (7.3%). Early in-hospital mortality rate was 6.5% and the six-month mortality rate was 5.6%. Pre-neoadjuvant bulky mediastinal disease (lymph nodes >20 mm) (p=0.034), persistent postoperative N2 disease (p=0.016), R1 resection (p=0.027) and postoperative stage IIIA (p=0.001), emerged as negative predictive factors for survival.

Conclusions: Our findings demonstrate that neoadjuvant chemotherapy or chemoradiation in locally advanced potentially resectable NSCLC followed by major pulmonary resection is a beneficial approach in selected cases.

Introduction

Stage III non-small cell lung carcinoma (NSCLC) is a very heterogeneous disease that depends upon the tumor size (T1-4), tumor local extension and extension of nodal involvement. N2 disease is heterogeneous by itself, as it may include several options depending on site, number of stations, and nature of nodes: bulky or separate. Stage IIIA disease is usually approached by preoperative induction therapy followed by surgical resection. Postoperative anti-EGFR osimertinib has shown to improve disease-free survival in patients with EGFR-mutated tumors [1]. On the other hand, IIIB disease may be approached by chemoradiation followed by immunotherapy (PACIFIC trial) [2]. Selected cases of IIIB disease may be treated by induction therapy followed by a curative surgery only. Post-operative immunotherapy in these cases has not yet been defined. The goals of induction therapy are downstaging and downsizing the primary disease, in order to improve resectability, and eradicate systemic micrometastatic disease. Patients whose disease is downstaged may be good candidates for surgery.

Surgery, however, is still associated with an increased incidence of postoperative morbidity and mortality, with pneumonectomy being associated with high complication rates [3, 4].

Skilled surgeons, modern surgical techniques and perioperative care in highly specialized thoracic intensive care units are key words for improving the postoperative outcome. We have analyzed our results in treating stage IIIA/B potentially resectable NSCLC, and investigated the factors that have affected the patient's outcome.

Patients And Methods

Patients

We retrospectively reviewed the data of 124 patients, with a confirmed diagnosis of stage IIIA/B NSCLC. All the patients were oncologically treated and followed in one of four Israeli centers: Tel Aviv Medical Center, Tel Aviv, Shamir Medical Center, Zerifin, Kaplan Medical Center, Rehovot, and Wolfson Medical Center, Holon, from May 1999 and through December 2019. Follow up data were available for 121 patients.

There were 86 (69.4%) males and 38 females (30.6%) with mean age of 64.2 years (range, 37-82). One-hundred and ten patients (88.7%) were smokers. The retrieved baseline data were comprised of patient demographics, comorbidities, induction therapy, primary tumor size, location, and histology, side and type of surgery, stages at diagnosis (clinical) and postoperative stages (pathologic), postoperative outcome, including complications, morbidity, mortality, length of hospital stay, readmission, and local recurrence rates. Patient demographics, comorbidities, histological type of tumor, type and kind of surgery, induction treatment, and other characteristics were summarized in Table 1.

Methods

The initial treatment plan, medical treatment results and options for surgery or immunotherapy were discussed and approved by a multidisciplinary team at a tumor board meetings in each case.

In all the patirnts, an induction chemotherapy by platinum-based chemotherapy regimen was administered, together with a second agent such as paclitaxel, etoposide, vinorelbine or pemetrexed, depending on tumor histology, (checkpoint inhibitors were not registered for induction therapy, and were not available).

Radiation therapy (RT) was given concurrently (60 Gy/30 courses, 5 days weekly) in 85 patients [68.5%], starting from cycle one or 2 or 3, depending on availability of RT service. The radiation dose of 60Gy is used in our centers as for induction as for definitive therapy. Thirty-nine patients (31.5%) got only chemotherapy. Time elapsed between the end of the induction therapy to the date of surgery was 4-6 weeks.

All the patients underwent resection by permanent thoracic-oncology surgical team.

Preoperative workup and tumor classification

The diagnostic workup/staging included a complete medical history and a physical examination, chest radiography, bronchoscopy, contrast-enhanced computed tomography (CT) of the chest, electrocardiography, and complete blood counts, chemistry profiles, and coagulation tests. All patients underwent pre-treatment (neo-adjuvant therapy) and post-treatment (preoperative) restaging by positron-emission tomography-CT (PET-CT) or contrast-enhanced CT of the chest, as well as contrast-enhanced CT of the brain.

Congestive heart failure was defined as a reduced ejection fraction of less than 45%. Cardiac comorbidity was defined as the presence of coronary artery disease, or any previous cardiac surgery or catheterization, current cardiac failure, or arrhythmia. Chronic renal failure (CRF) was defined as an elevated creatinine level of >1.5 mg/dl. Chronic obstructive pulmonary disease (COPD) was defined as a forced expiratory volume in 1 second/forced vital capacity ratio less than 70%.

Tumors were classified and staged preoperatively and postoperatively according to the 1997 International System for Staging Lung Cancer [5]. Most of the patients had either squamous cell carcinoma or adenocarcinoma (37.9% and 41.1%, respectively). Pretreatment mediastinal staging was performed by cervical mediastinoscopy (27 patients, 21.8%), or endobronchial ultrasound (EBUS) (16 patients, 12.9%, when enlarged (>1.0 cm) mediastinal lymph nodes were seen on CT, or when high fluorodeoxyglucose (FDG) uptake was seen in mediastinal lymph nodes on PET-CT (performed in 92 patients (74.2%). Chest wall involvement was classified as invasion of the diaphragm, chest wall muscles, or ribs. Involvement of mediastinal structures was classified as invasion of mediastinal pleura (or pericardium), the great vessels (aorta), esophageal wall, vertebral bodies, trachea, carina, or recurrent laryngeal nerve. Fifteen patients had been diagnosed preoperatively as having superior sulcus (Pancoast) tumors (SST) (12.1%).

Single-station N2 disease was classified according to PET-CT results when only one mediastinal station lymph node was positive (generally, R4, 7 or L5), and as multi-station N2 disease when at least one mediastinal and one or more hilar and mediastinal station lymph nodes were positive on PET-CT; or >10 mm on the CT of the chest in pre-PET-CT era. The data on the clinical staging of the 124 patients before admission to induction therapy are summarized in Table 2. Hilar/mediastinal lymph nodes were dissected or sampled within anatomical landmarks during surgery; at least three mediastinal/hilar nodal stations were routinely revised. The data on the pathologic staging of the 124 patients without radiologic disease progression by pre-surgical staging are summarized in Table 3.

Surgical technique

All of the study patients underwent standard anesthesia with a double-lumen endotracheal tube; perioperative low thoracic epidural analgesia, and surgery by means of a similar technique consisting of a standard serratus muscle-sparing posterolateral thoracotomy in the fifth or sixth intercostal space [6] with lung surgery performed according to the European Society of Thoracic Surgeons Guidelines [7]. Mechanical staples were used for the closing of pulmonary veins and arteries, and bronchi. The bronchial stumps were reinforced with viable intercostal, serratus or latissimus muscle flaps in selected cases (5 patients, 4.0%). Additional thoracic structures, and/or the mediastinal pleura including the pericardium

were resected in cases of local invasion. The pericardium reconstruction was done by bovine pericardium (Gore-tex soft tissue patch, Delaware Corp, Newark) in cases of intrapericardial resections. One 36 French chest tube was placed in the empty chest cavity, and it was generally removed within 24 hours after the surgery in cases of pneumonectomy. One curved and one straight 36 French chest tubes were used in cases of bilobectomy or lobectomy.

Patients were generally extubated in the recovery room and initially monitored in the high-dependency unit for 24-48 hours and transferred to the thoracic surgery department intensive care ward thereafter. Early hospital mortality was defined as death occurring during the postoperative hospitalization period. Late mortality was defined as death occurring within six months from surgery. The data relating to all types of postoperative complications are summarized in Table 4.

The patients were followed postoperatively for cancer recurrence and survival every three months for the first year and every six months thereafter (mean follow up duration was 43.6 months); the final data on survival were recorded on January 1, 2020.

Statistical analysis

Due to the heterogeneity of stage III NSCLC, we evaluated different parameters of locally advanced potentially resectable disease separately and together in order to analyze the factors that potentially influence on postoperative outcome or survival. They included:

- postoperative complications: atelectasis, mechanical ventilation, atrial fibrillation, acute renal failure, empyema, tracheostomy, pneumonia, early and late bronchopleural fistula, acute respiratory distress syndrome (ARDS), air leak, intraoperative hemorrhage and recurrent laryngeal nerve palsy (Table 5);

- comorbidities: coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), chronic renal failure (CRF), hypothyroidism, obesity, non-insulin dependent diabetes mellitus (NIDDM), hypertension (HTN), pulmonary edema (PE), cerebrovascular accident (CVA) and smoking (Table 5);

- sex, side of surgery, kind of surgery (pneumonectomy, lobectomy, bilobectomy), extent of surgery (extrapleural, intrapericardial & completion resections), location of the tumors (endobronchial, Pancoast tumors, subcarinal & paraesophageal tumors) (Table 5);

- histologic type of the tumors, preoperative treatment (chemotherapy & chemoradiation), pre-neoadjuvant PET-CT, surgical margins (R0 & R1), pre-neoadjuvant mediastinal staging (N2 negative or N2 single & N2 multiple lymph nodes), pre-neoadjuvant size of mediastinal lymph nodes (<20 mm and >20 mm), pretreatment staging (IIIA & IIIB), pathologic staging (IA-IV & complete pathologic response), persistent N2 disease, visceral & parietal pleural invasion, vascular invasion and local recurrence (Table 5).

Patients preoperative, surgical and postoperative characteristics were compared between the groups, continuous variables with normal distribution were summarized with means & standard deviation and

compared using independent t-test, for variables that deviate from normal distribution were summarized with medians and IQR (interquartile range) and compared using Mann Whitney test. Categorical variables were summarized with counts and percentages and compared using chi square test. The primary endpoint was death.

The cumulative rates of death were compared using the Kaplan-Meier curves and the cox regression model was applied to evaluate the adjusted effect of surgery and patient characteristics on patient survival (Figures 1-4). The p value < 0.05 was considered to define statistical significance (Table 5). Analyses were carried out using IBM Corp. Released 2020 IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.

Results

All the patients underwent major pulmonary resections due to locally advanced potentially resectable stage IIIA/B NSCLC. Pneumonectomy was performed in 61 patients (49.2%, completion pneumonectomy in 8 patients (6.5%), extrapleural pneumonectomy in 8 patients (6.5%), and intrapericardial pneumonectomy in 7 patients (5.6%), bilobectomy in 5 patients (4.0%), and lobectomy in 58 patients (56.8%), including extrapleural lobectomy in 14 patients (11.3%). Thirteen patients underwent chest wall resection (10.5%), two patients underwent vertebral body resection (1.6%), and seven patients (5.6%) underwent pericardium resection and reconstruction.

The mean hospital stay for the operated patients was 12.6 days (range, 5-123). Postoperative complications were sustained by 61 patients (49.2%), including seven patients with intraoperative hemorrhage (5.6%). Atrial fibrillation and pneumonia were the most common postoperative complications: 19 (15.9%) and 17 (13.7%) patients, respectively. Lobar atelectasis confirmed by chest radiography and treated by immediate bronchoscopy was recorded for 11 patients (8.9%). A prolonged air leak defined as an air leak documented one week after lobectomy or bilobectomy was recorded for six patients (4.8%). Empyema occurred in 13 patients (10.5%), with early broncho-pleural fistulas (BPF), during the first 3 postoperative months, occurred in nine patients (7.3%), and a late BPF (between 3–6 months postoperatively) in two patients (1.6%). BPF was treated by an Amplatzer device implantation (Amplatzer PFO Occluder Corp, USA) through the post-pneumonectomy and post-bilobectomy stumps [6] in two patients (1.6%). Empyema in post-pneumonectomy patients was treated by video-assisted thoracoscopic surgery (VATS) in five patients (4.9%), by three-rib open window thoracoplasty in seven patients (5.5%), and by sternotomy with trans-pericardial BPF repair in one patient (0.8%). Prolonged mechanical ventilation was required postoperatively in 10 patients (8.1%), of whom three developed acute respiratory distress syndrome (ARDS) (2.4%), two developed pulmonary edema (PE) (1.6%), and five required a tracheostomy (4.0%). The overall readmission rate was 16.1% (20 patients).

Early (in-hospital) mortality was recorded for eight patients (6.5%), five after pneumonectomy (three right-sided and two left-sided), one after bilobectomy (RML/RLL), and two after lobectomy (RUL). The causes of death were ARDS in three patients, pneumonia in two, complicated BPF with empyema in two, and

empyema without BPF in one. Late (six months) mortality was recorded for seven patients (5.6%), four after pneumonectomy (three right-sided and one left-sided), one after bilobectomy (RML/RLL), and two after lobectomy (RUL/LUL). The causes of death were empyema without BPF in one patient, complicated BPF with empyema in two, metastatic disease in three, and pneumonia in one.

A complete pathologic response (i.e., no residual tumor with free lymph nodes) was recorded in 44 patients (35.5%), and microscopic residual tumor (< 10 mm) was identified in 13 patients (10.5%). R0 resection (i.e., complete resection of tumor with free margins and negative highest mediastinal lymph nodes) was achieved in 115 patients (92.7%), and local recurrence was seen in one patient (0.8%).

The factors that found had a negative influence on survival were: postoperative stage IIIA (p = 0.001), pre-neoadjuvant bulky mediastinal disease (lymph nodes > 20 mm) (p = 0.034), persistent postoperative N2 disease (p = 0.016) and R1 resection (p = 0.027). The factors that found had a positive influence on survival were: PET-CT (p = 0.001), complete pathologic response ($p = 0.001$), R0 margins ($p = 0.027$), pre-neoadjuvant N2 free disease ($p = 0.026$), and intrapericardial resections ($p = 0.048$). The Kaplan-Meier survival curves for postoperative stage IIIA, pre-neoadjuvant PET-CT, complete pathologic response, and bulky mediastinal disease (lymph nodes > 20mm) are demonstrated in Figs. 1–4.

Follow-up was complete for 121 patients (97.6%) (Mean 43.6 months), the 5-year survival rate was 47.9% (58 patients), and survival to date (January 1, 2020) was 34.7% (43 patients).

Discussion

Management of patients with locally advanced NSCLC remains one of the major challenges of thoracic oncology [8]. The treatment strategy is influenced by disease stage, the patient's functional status, and the decisions reached by the interdisciplinary discussions at the institutional tumor board meetings. Resectable patients benefit from surgery when a radical resection is achieved without major morbidity and mortality. Patients with locally advanced NSCLC undergoing surgery without preoperative oncologic treatment, chemotherapy, or chemoradiation, however, are at a greater risk to develop distant metastases or locally recurrent disease. There is a statistically confirmed survival benefit of neoadjuvant chemotherapy followed by surgery compared with surgery alone [9–13], but the main concern with regard to surgery is the increased risk of postoperative morbidity and mortality [3, 4, 14, 15].

Pneumonectomy remains associated with high and possibly unacceptable rates of perioperative morbidity and mortality, especially after induction therapy [16–19]. The recommendation of the American College of Chest Physicians (ACCP) is to avoid performing pneumonectomy after neoadjuvant chemoradiotherapy [20]. For example, Thomas et al. [16] found that independent predictors of mortality on multivariate analysis in patients that received induction therapy followed by pneumonectomy were age more than 65 years, male sex, ASA score of three or greater, and right laterality of the procedure. Contrarily, Mansour et al. [21] and Refai et al. [22] did not find any significant differences in terms of early or late morbidity and mortality when comparing patients undergoing pneumonectomy after induction chemoradiotherapy with those who had no form of induction treatment. We had also concluded in our

study that pneumonectomy could safely be performed after neoadjuvant chemoradiation or chemotherapy with low early and late mortality rates [23].

Detterbeck FC et al.[24] reported the 5-year survival rates was 19%/24%for clinical/pathological stage IIIA NSCLC (TNM 7), respectively, and 7%/9% for clinical/pathologic stage IIIB NSCLC (TNM 7), respectively. Andre F et al. [25] reported the 5-years survival rates was 35% versus 5%, if the ipsilateral single mediastinal station lymph node versus multiple mediastinal station lymph node involvement was detected. The PACIFIC was the first randomized study which demonstrated a benefit in progression-free survival after simultaneous chemoradiotherapy with immunotherapy by durvalumab (PDL-1 inhibitor), with significantly prolonged overall survival compared to placebo ($p = 0.0025$) in patients with unresectable stage III NSCLC (2), but limitations of this study were in the exact staging and re-staging methods and high local recurrence rate [26].

Five-year survival rates after neoadjuvant chemotherapy or chemoradiation have been reported to range from 21–41% [11–13, 27]. Van Meerbeck et al. [27] reported that only complete resection has a positive impact on survival, and that the results of an incomplete resection are compatible with the results of patients treated solely with radiotherapy (a 5-year survival of 15.7%). Koshy et al. [11] and Kim et al. [28] reported a 40% and 61% 5-year survival rate, respectively, in patients achieving a pathologic complete nodal response.

Martin et al. [29] concluded that pulmonary resection after neoadjuvant chemotherapy is associated with acceptable morbidity and mortality, with right pneumonectomy ($p < 0.002$), blood loss ($p < 0.001$), and forced expiratory volume in one second ($p < 0.001$) being predictive risk factors for postoperative complications. Weder et al. [30] demonstrated that pneumonectomy after chemotherapy or chemoradiotherapy can be performed with low perioperative mortality (3%) and acceptable major morbidity (13%) rates, and Kim et al. [28] demonstrated a 3% rate of early 30-day mortality and an 8% rate of 90-day mortality for patients that underwent pulmonary resection after neoadjuvant chemoradiation.

Mc Elnay et al. [31] posed the key question of whether surgery should be considered as part of multimodality treatment for patients with resectable lung cancer and ipsilateral mediastinal nodal disease. Those authors concluded that there were no significant differences in overall survival in patients randomized to surgery as part of bimodality (chemotherapy + surgery) or trimodality (chemoradiation + surgery) treatment. Other studies that reviewed randomized evidence of radiochemotherapy *versus* surgery within multimodality treatment in stage III NSCLC found no significantly different overall survival in patients with locally advanced NSCLC after induction treatment and surgery compared with those receiving definitive radiochemotherapy [32, 33]. Arguments in favor of surgery in patients with resectable disease were referring to large residual necrotic tumors, which are difficult to control with radiotherapy and which may lead to the formation of a lung abscess, or to multiple nodules in the same lobe. The combination of preoperative concurrent chemotherapy and radiotherapy followed by surgery should be considered also where local control is especially important for quality of life, such as with invasion of the

brachial plexus in superior sulcus tumors (the Pancoast tumors) or central tumors without mediastinal nodal disease.

Looking back upon more than 20 years of performing major pulmonary resections after neoadjuvant chemoradiation or chemotherapy, we must admit that not all of our results were good and that some were inarguably bad. We statistically found that positive surgical margins, persistent mediastinal disease & pathologic IIIA stage, pre-neoadjuvant bulky mediastinal disease & central extension of the tumors to the proximal airways negatively influenced on our patients' postoperative outcome and survival. At the same time, we found that our results are compatible with those of other authors [34]. Our study has several potential limitations. This is a retrospective nonrandomized study, which is subject to selection bias; others are a need for more scrupulous preoperative mediastinal staging after neoadjuvant chemoradiation or chemotherapy and a need for lung sparing surgeries instead to pneumonectomies.

It is our impression that by selection of good surgical candidates, by achieving complete pathologic response, negative surgical margins & R0 radical resections, we can continue to perform major pulmonary resections that may be considered an acceptable treatment option in selected patients with stage III potentially resectable NSCLC after neoadjuvant chemoradiation or chemotherapy.

Conclusions

Based upon the results of our 20 years' experience operating post-neoadjuvant major pulmonary resections, we recommend to avoid operate patients with bulky mediastinal disease; and to avoid pneumonectomies' in patients with tumors involving central airways before neoadjuvant chemotherapy or chemoradiation, but we strongly recommend operate the selected patients that are free of those contraindications, including the performance of pneumonectomies'. Finally, we recommend performing more aggressive surgical staging before induction therapy, and restaging to reduce the incidence of postoperative N2 disease. We suppose that development of lung-sparing resection techniques will avoid part of pneumonectomies in the future, strongly dedicated to achieve R0 resections.

Declarations

Compliance with Ethical Standards

The Institutional Review Board of Shamir Medical Center (formerly Assaf Harofeh), a referral Center of thoracic surgery until 2019, approved this retrospective study and waived informed Consent.

Funding

This research received no specific grant from any funding agency, commercial or others.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding Author on reasonable request.

Conflict of Interest

The authors declare that they have no competing interests.

Acknowledgements

I express my appreciation to Dr. Ilan Bar for being my mentor in thoracic surgery and to Mrs Esther Eshkol for reviewing this manuscript.

References

1. Wu YL, Tsuboi M, He J. Osimertinib in resected EGFR mutated non-small cell lung cancer. N Engl J Med 2020 Oct 29; 383 (18): 1711-1723.
2. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiaotherapy in stage III non-small-cell lung cancer. N Engl J Med 2017 Nov 16; 377 (20): 1919-1929.
3. Licker M, Spiliopoulos A, Frey JG, Robert J, Höhn L, de Perrot M, et al. Risk factors for early mortality and major complications following pneumonectomy for non-small cell carcinoma of the lung. Chest 2002; 121:1890-7.
4. Van Schil P, van Meerbeeck J, Kramer G, Splinter R, Legrand C, Giaccone G, et al. Morbidity and mortality in the surgery arm of EORTC 08941 trial. Eur Respir J 2005; 26:192-7.
5. Bramilla E, Travis WD, Colby TV, Corrin B, Shimasato Y. The new World Heart Organization classification of lung tumors. Eur Respir J 2001; 18:1059-68.
6. Anraku M, Keshavjee S. Lung cancer: surgical treatment. In: Selke FW, del Nido PJ, Swanson SJ editors. Sabiston & Spencer Surgery of the Chest. Eighth ed. Philadelphia, PA: Elsevier; 2009. p. 254-5.
7. Lardinois D, De Leyn P, Van Schil P, Porta RR, Waller D, Passlick B, et al. ESTS guidelines for intraoperative lymph node staging in Non-small cell lung cancer. Eur J Cardiothorac Surg 2006; 30:787-92.
8. Fruchter O, Kramer MR, Dagan T, Raviv Y, Abdel-Rahman N, Saute M, et al. Endobronchial closure of bronchopleural fistulae using amplatzer devices: our experience and literature review. Chest 2011; 139:682-7.
9. Rigas JR, Kelly K. Current treatment paradigms for locally advanced Non-small cell lung cancer. J Thorac Oncol 2007; 2:S77-85.
10. Sonett JR, Suntharalingam M, Edelman MJ, Patel AB, Gamliel Z, Doyle A, et al. Pulmonary resection after curative intent radiotherapy (>59 Gy) and concurrent chemotherapy in non-small-cell lung cancer. Ann Thorac Surg 2004; 78:1200-5.

11. Koshy M, Federa SA, Malik R, Ferguson MK, Vigneswaran WT, Feldman L, et al. Improved survival associated with neo-adjuvant chemoradiation in patients with clinical stage IIIA(N2) non-small-cell lung cancer. J Thorac Oncol 2013; 8:915-22.
12. Ripley RT, Rusch VW. Role of induction therapy: surgical resection of non-small-cell lung cancer after induction therapy. Thorac Surg Clin. 2013; 23:273-285.
13. Cerfolio RJ, Maniscalco L, Bryant AS. The treatment of patients with stage IIIA non-small-cell lung cancer from N2 disease: who returns to the surgical arena and who survives? Ann Thorac Surg. 2008; 86: 912-920.
14. Kim AW, Boffa DJ, Wang Z, Detterbeck FC. An analysis, systematic review, a meta-analysis of the perioperative mortality after neoadjuvant therapy and pneumonectomy for non-small-cell lung cancer. J Thorac Cardiovasc Surg. 2012; 143:55-63.
15. d'Amato TA, Ashrafi AS, Schuchert MJ, Alshehab DS, Seely AJ, Shamji FM, et al. Risk of pneumonectomy after induction therapy for locally advanced non-small cell lung cancer. Ann Thorac Surg 2009; 88:1079-85.
16. Thomas PA, Berbis J, Baste JM, Le Pimpec-Barthes F, Tronc F, Falcoz PE, et al. Pneumonectomy for lung cancer: contemporary national early morbidity and mortality outcomes. J Thorac Cardiovasc Surg 2015; 149; 73-82.
17. Gudbjartsson T, Gyllstedt E, Pikwer A, Jönsson P. Early surgical results after pneumonectomy for Non-small cell lung cancer are not affected by preoperative radiotherapy and chemotherapy. Ann Thorac Surg 2008; 86:376-82.
18. Albain KS, Swann RS, Rusch VW, Turrisi AT 3rd, Shepherd FA, Smith C, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomized controlled trial. Lancet 2009; 374:379-86.
19. Kappers I, van Sandick JW, Burgers SA, Belderbos JS, van Zandwijk N, Klomp HM. Surgery after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer: why pneumonectomy should be avoided. Lung Cancer 2010; 68:222-7.
20. Robinson LA, Ruckdeschel JC, Wagner H, Stevens CW, American College of Chest Physicians. Treatment of Non-small cell lung cancer-stage IIIA: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007; 132:243S-65S.
21. Monsour Z, Kochetkova EA, Ducrocq X, Vazilescu MD, Maxant G, Buggenhout A, et al. Induction chemotherapy does not increase the operative risk of pneumonectomy! Eur J Cardiothor Surg 2007; 31:181-5.
22. Refai M, Brunelly A, Rocco G, Ferguson MK, Fortiparri SN, Salati M, et al. Does induction treatment increase the risk of morbidity and mortality after pneumonectomy? A multicenter case-matched analysis. Eur J Cardiothorac Surg 2010; 37:535-9.
23. Peer M, Stav D, Cyjon A, Sandbank J, Vasserman M, Haitov Z, et al. Morbidity and mortality after major pulmonary resection in patients with locally advanced stage IIIA non-small cell lung carcinoma who underwent induction therapy. Heart Lung Circ 2015; 24:69-76.

24. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. Chest 2009; 136: 260–271.
25. Andre F, Grunenwald D, Pignon JP, et al. Survival of patients with resected N2 Non-small- cell-lung cancer: evidence for a sub classification and implications. J Clin Oncol 2000; 18: 2981–2989.
26. Huber RM, Ruysscher DD, Hoffmann H, et al. Interdisciplinary multimodality management of stage III non-small cell lung cancer. European Respiratory Review 2019 28: 190024.
27. van Meerbeck JP, Kramer GW, Van Schil PE, Legrand C, Smit EF, Schramel F, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer. J Natl Cancer Inst 2007; 99:442–50.
28. Kim HK, Cho JH, Choi YS Zo JI, Shim YM, Park K, et al. Outcomes of neoadjuvant concurrent chemoradiotherapy followed by surgery for non-small-cell lung cancer with N2 disease. Lung Cancer 2016; 96: 56-62.
29. Martin J, Ginsberg RJ, Abolhoda A, Bains MS, Downey RJ, Korst RJ, et al. Morbidity and mortality after neoadjuvant therapy for lung cancer: the risk of right pneumonectomy. Ann Thorac Surg 2001; 72:1149-54.
30. Weder W, Collaud S, Eberhardt WE, Hillinger S, Welter S, Stahel R, et al. Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non-small-cell lung cancer. J Thorac Cardiovasc Surg 2010; 139:1424-30.
31. Mc Elnay PJ, Choong A, Jordan E, et al. Outcome of surgery versus radiotherapy after induction treatment in patients with N2 disease: systematic review and meta-analysis of randomized trials. Thorax 2015; 70: 764–768.
32. Pöttgen C, Eberhardt W, Stamatis G, et al. Definitive radiochemotherapy versus surgery within multimodality treatment in stage III non-small cell lung cancer (NSCLC) – a cumulative meta-analysis of the randomized evidence. Oncotarget 2017; 8: 41670–41678.
33. Pless M, Stupp R, Ris HB, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomized trial. Lancet 2015; 386: 1049–1056.
34. Brunelli A, Rocco G, Szanto Z, Thomas P, Falcoz PE. Morbidity and mortality of lobectomy or pneumonectomy after neoadjuvant treatment: an analysis from the ESTS database. Eur J Cardiothorac Surg. 2020 Apr 1; 57(4):740-746. 35.

Tables

Table 1 Demographic, comorbidity, radiologic, histologic, and surgical characteristics of the 124 patients

Variable	Number	%%
Male	86	69.4
Female	38	30.6
Surgical procedures	74	59.7
Right-sided	50	40.3
Left-sided – 50 (40.3%)		
Pneumonectomy	61 (right=31, left=30)	49.2
Intrapericardial	7	5.6
Extrapleural	8	6.5
Completion	8	6.5
Bilobectomy	5 (RUL/RML=1, RML/RLL=4)	4.0
Lobectomy	58 (RUL=32, LUL=18, RLL=6, LLL=2)	46.8
Histologic type of tumors		
Adenocarcinoma	51	41.1
Squamous cell carcinoma	47	37.9
Large cell carcinoma	10	8.1
Poorly differentiated carcinoma	11	8.9
Other carcinoma	5	4.0
Comorbidities		
Chronic obstruction pulmonary disease	54	43.5
Peripheral vascular disease	15	12.1
Non-insulin-dependent diabetes mellitus	22	17.7
Obesity	23	18.5
Other malignancy	29 (7=secondary primary lung carcinoma)	23.4
Coronary artery disease	30	24.2
Hypertension	17	13.7

Peptic disease	4	3.2
Chronic renal failure	3	2.4
Cerebrovascular accident	6	4.8
Hypothyroidism	3	2.4
Liver disease	2	1.6
Drug/alcohol abuse	3	2.4
Chronic heart failure	5	4.0
Pulmonary edema	3	2.4
Chronic atrial fibrillation	3	2.4
Pre-treatment staging		
IIIA	91	73.4
IIIB	33	26.6
Smokers	110	88.7
Type of induction treatment		
Chemoradiation	85	68.5
Chemotherapy	39	31.5
PET-CT	92	74.2
R1 resection	9	7.3

Table 2 Clinical staging of 124 patients with locally advanced stage IIIA/B NSCLC before admission to neoadjuvant chemotherapy or chemoradiation

cTNM	Involvement of different thoracic structures	Total
Stage IIIA		91 (73.4%)
T1N2	N2 single - 3, N2 multiple - 7	10
T2N2	N2 single – 10, N2 multiple - 27	37
T3N2	Main bronchus involvement - 2 (N2 single – 1, N2 multiple - 1) Chest wall involvement - 5 (N2 single – 2, N2 multiple – 3)	7
T4N0	(SST, Pancoast tumor) - 10, mediastinal structure involvement (mediastinal pleural & pericardium & recurrent laryngeal nerve) & aorta & carina & vertebral body[a] – 17, 4, 4, and 2 patients, respectively	37
Stage IIIB		33 (26.6%)
T4N2	Two satellite lesions - 4 (N2 single – 1, N2 multiple – 3); mediastinal structures involvement (mediastinal pleural & pericardium & recurrent laryngeal nerve) – 10 (N2 single – 3, N2 multiple – 7); superior sulcus tumors (SST, Pancoast tumor) – 4 (N2 single – 2, N2 multiple -2); aorta & esophagus & carina involvement – 9: 6 (N2 single – 3, N2 multiple -3) & 2 (N2 single – 1, N2 multiple – 1) & 1 (N2 single), respectively	27
T1-2N3	N3 single – 2	2
T3N3	Main bronchus involvement -1 (N3 single – 1)	1
T4N3	Mediastinal structures involvement (mediastinal pleural & pericardium) – 2 (N3 – single) & aorta – 1 (N3 single)	3
Total[b]		124

cTNM - recommendations for clinical stage groups.

[a]Superior sulcus tumor (SST) – 1 patient

[b]Intra-bronchial tumors – 7 patients

Table 3 Surgical staging of 124 patients with locally advanced stage IIIA/B NSCLC after neoadjuvant chemotherapy or chemoradiation

	No residual disease	IA	IB	IIA	IIB	IIIA	IIIB	IV	Total
Total	44 (35.5%)	24 (19.4%)	17 (13.7%)	8 (6.5%)	10 (8.1%)	18 (14.5%)	1 (0.8%)	2 (1.6%)	124

Table 4 Overall complications, mortality, and hospital stay of 124 locally advanced NSCLC patients that underwent major pulmonary resection after induction therapy

Complications	No. patients	%
Overall complications	61	49.2
Atelectasis lobar radiologically confirmed	11	8.9
Tracheostomy	5	4.0
Prolonged (>48 hours) mechanical ventilation	10	8.1
Atrial fibrillation	19	15.3
Pneumonia	17	13.7
Hospital/30-day mortality	8	6.5
Late/6-month mortality	7	5.6
Intraoperative hemorrhage	7	5.6
Early (<3 months) bronchopleural fistula	9	7.3
Late (>3 months) bronchopleural fistula	2	1.6
Empyema	13	10.5
Readmission	20	16.1
Prolonged >1 week air leak post-lobectomy	6	4.8
Acute respiratory distress syndrome	3	2.4
Chylothorax	1	0.8
Mediastinal shift	2	1.6
Vocal cord palsy	3	2.4
Ischemic central & peripheral event	2	1.6
Pulmonary thromboembolism	2	1.6
Pulmonary edema	2	1.6
Acute renal failure	2	1.6
Delirium	1	0.8

Table 5 Statistical analysis of surgical, pathologic and clinical parameters of 124 patients with locally advanced stage IIIA/B NSCLC underwent neoadjuvant chemotherapy or chemoradiation and adjuvant surgery

		No. patients	%	P-value
Comorbidities	NIDDM	22	17.7%	0.194
	COPD	54	43.5%	0.511
	CAD	30	24.2%	0.290
	PVD	15	12.1%	0.907
	Hypothyroidism	3	2.4%	0.543
	CRF	3	2.4%	0.999
	HTN	17	13.3%	0.954
	Obesity	23	18.5	0.991
	CVA	6	4.8%	0.417
	PE	3	2.4%	0.543
	Smoke	110	88.7%	0.556
Surgery side	Right	74	59.7%	0.368
	Left	50	40.3%	0.368
PET-CT	PET-CT	92	74.2%	**0.001**
Complications	Mechanical Ventilation	10	8.1%	0.999
	Recurrent laryngeal nerve palsy	5	4.0%	0.658
	Early BPF	9	7.3%	0.999
	Atelectasis	11	8.9%	0.229
	Tracheostomy	5	4.0%	0.162
	Pneumonia	17	13.7	0.163
	Atrial fibrillation	19	15.3%	0.175
	Intraoperative hemorrhage	7	5.6%	0.420
	Air leak	6	4.8%	0.664
	Acute renal failure	2	1.6%	0.543
	ARDS	3	2.4%	0.551
	Empyema	13	10.5%	0.371
	Late BPF	1	0.8%	0.347
Pathology postoperative	Vascular invasion	9	7.3%	0.161

	Visceral pleura invasion	6	4.8%	0.664
	R1 positive margins	9	7.3%	**0.027**
	IA Stage	24	19.4%	0.423
	IB Stage	17	13.7%	0.299
	IIA Stage	8	6.5%	0.260
	IIB Stage	10	8.1%	1.000
	IIIA Stage	18	14.5%	**0.001**
	IIIB Stage	1	0.8%	0.999
	IV Stage	2	1.6%	0.999
	No residual tumor	44	35.5%	**0.001**
	Persistent N2	19	15.3%	**0.016**
	Local recurrence	1	0.8%	1.000
	Parietal pleura invasion	6	4.8%	0.417
Preoperative characteristics	Preoperative IIIA	91	73.4%	0.812
	Preoperative IIIB	33	26.6%	0.812
	N2 <10mm on CT or PET-CT negative	39	31.5%	**0.026**
	Mediastinal lymph nodes >20mm on CT	22	22.6%	**0.034**
	Mediastinal lymph nodes <20mm on CT	69	55.6%	0.061
	N2 single station on PET-CT	28	22.6%	0.749
	N2 multiple station on PET-CT	58	46.8	0.053
Gender	Mail	86	69.4%	0.118
	Female	38	30.6%	0.118
Induction therapy	Chemotherapy	39	31.5%	0.066
	Chemoradiation	85	68.5%	0.066
Histology	Squamous cell carcinoma	48	37.7%	0.673
	Adenocarcinoma	51	41.1%	0.673
	Other	25	20.2%	0.673
Surgery group	Lobectomy	58	46.8%	0.142

	Bilobectomy	5	4.0%	0.142
	Pneumonectomy	61	49.2%	0.142
	Completion pneumonectomy	8	6.5%	0.999
	Intrapericardial pneumonectomy	7	5.6%	**0.048**
	Extrapleural pneumonectomy	8	6.5%	0.242
	Extrapleural lobectomy	14	11.3%	0.999
	Endobronchial tumor	7	5.6%	0.751
	Subcarinal & paraesophageal central tumor	7	5.6%	0.751
	Pancoast tumor	15	12.1%	0.751

Figures

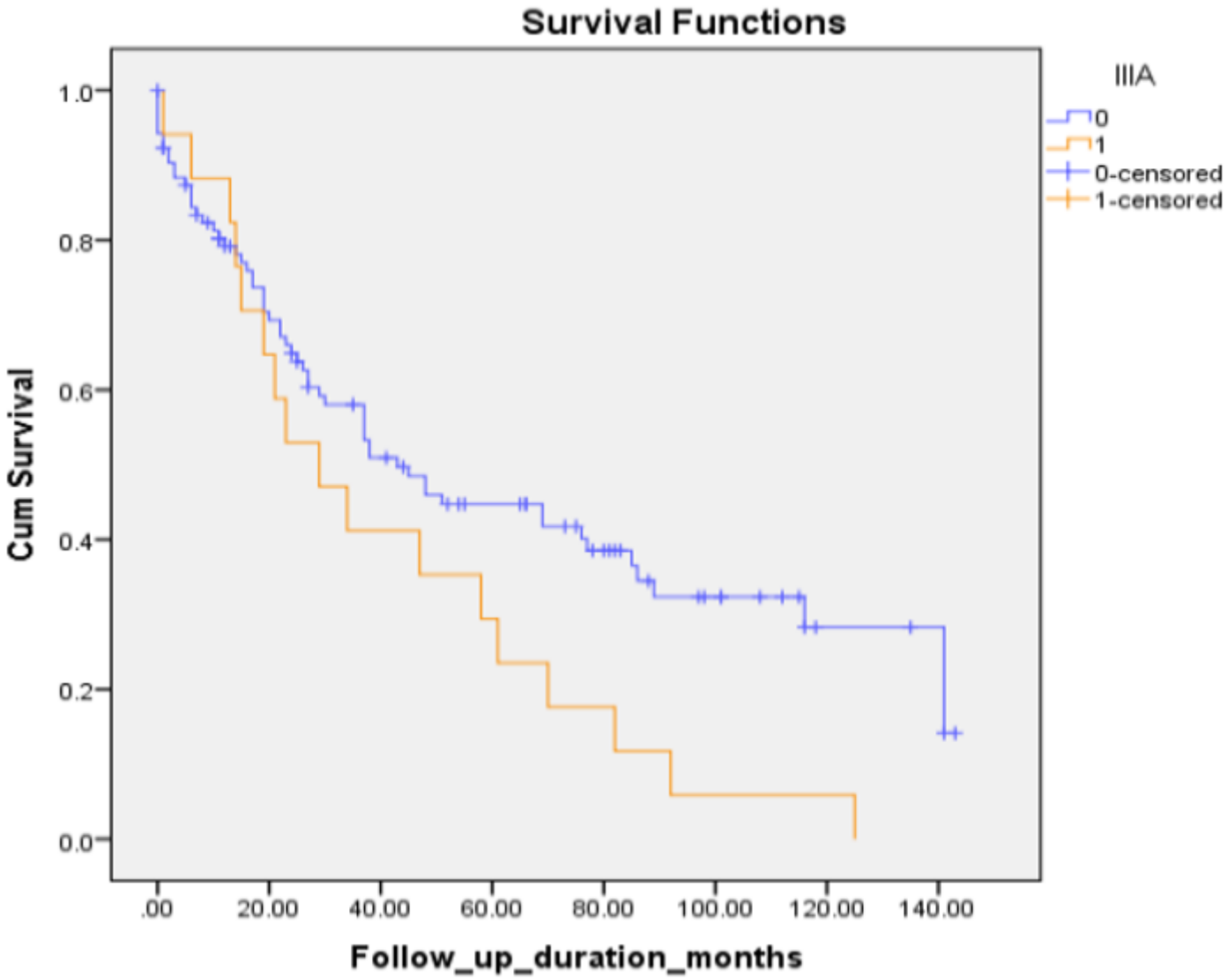

Figure 1

Survival for patients after induction therapy diagnosed with stage IIIA postoperatively

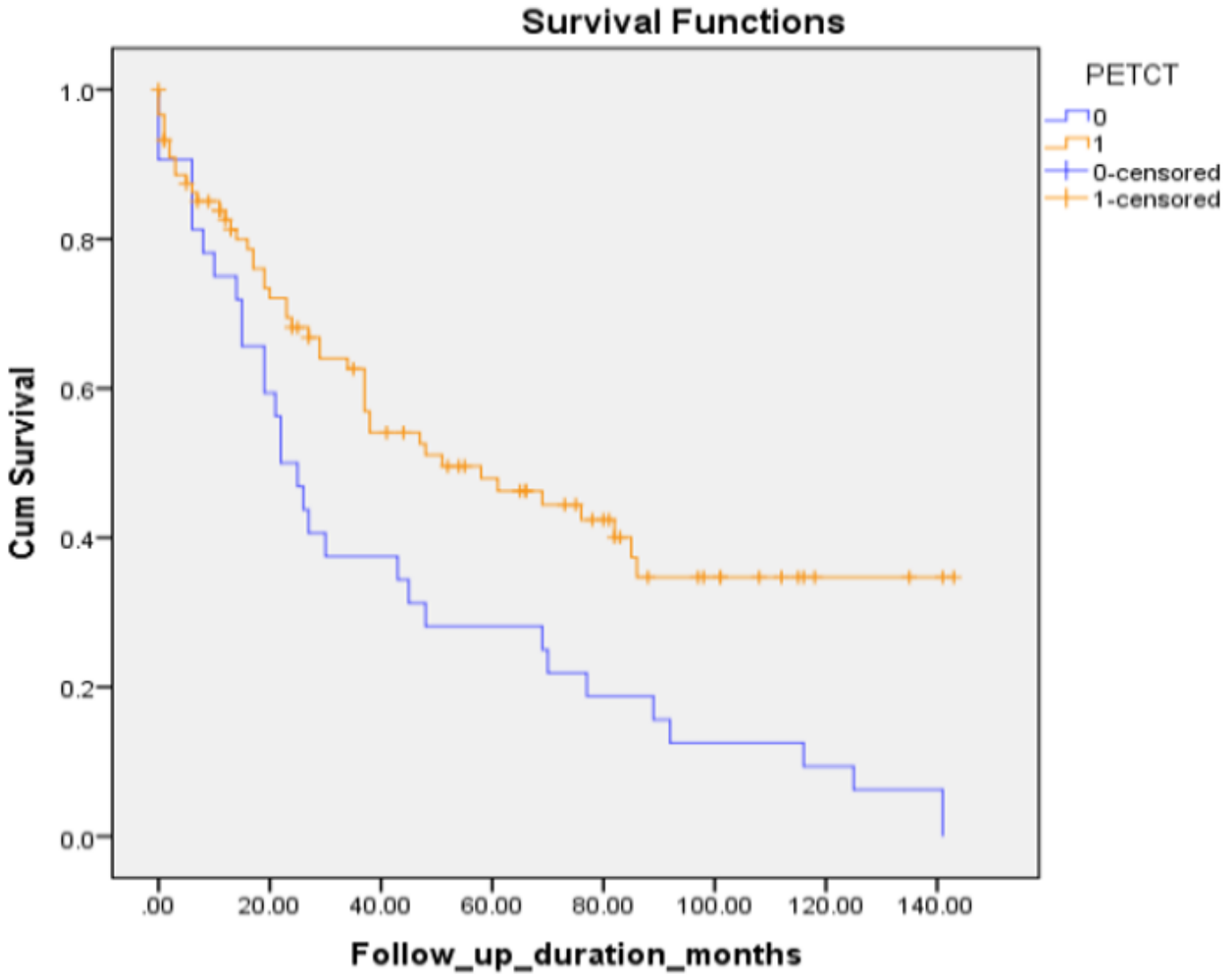

Figure 2

Survival for patients underwent PET-CT before induction therapy

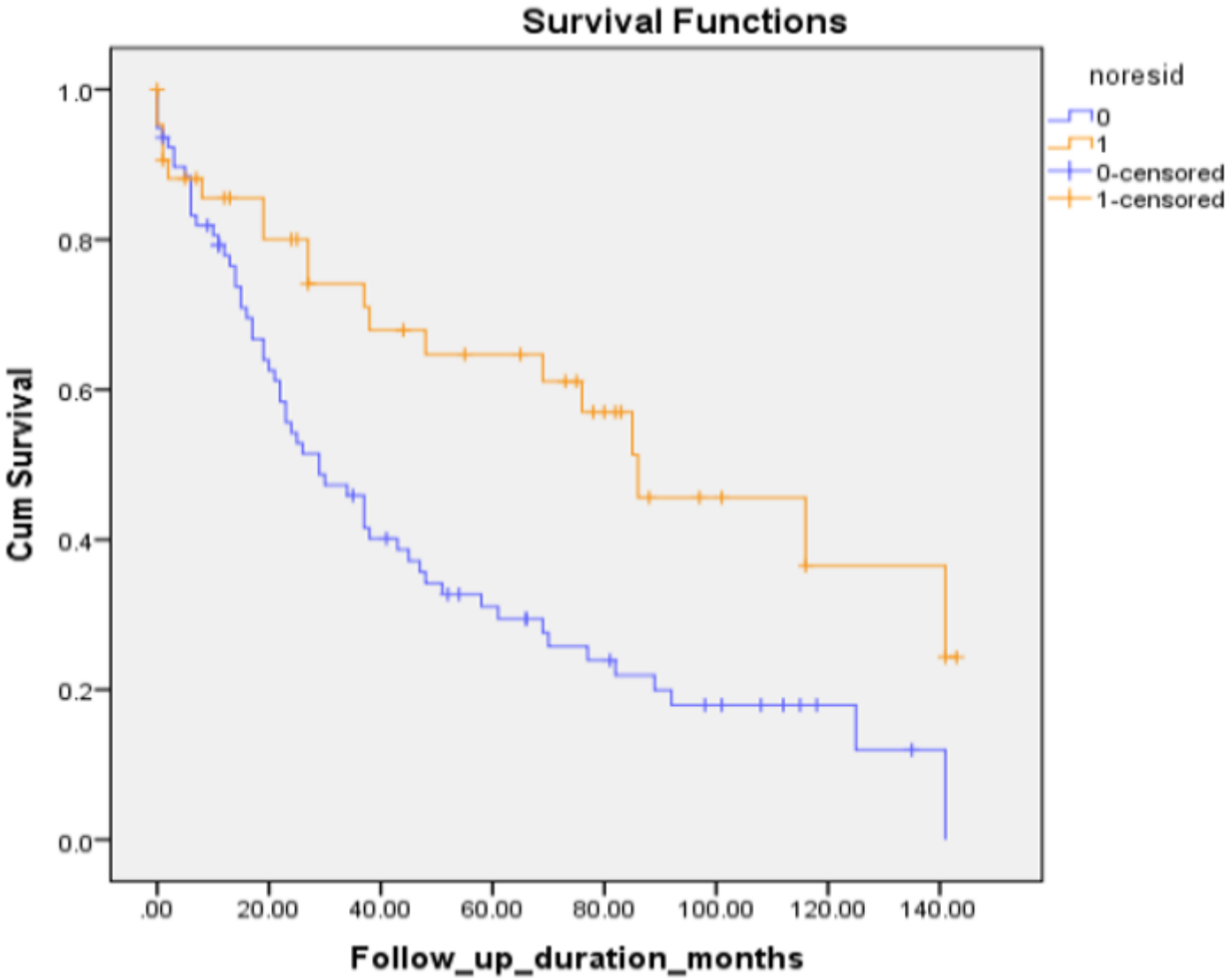

Figure 3

Survival for patients after induction therapy diagnosed with complete pathologic response

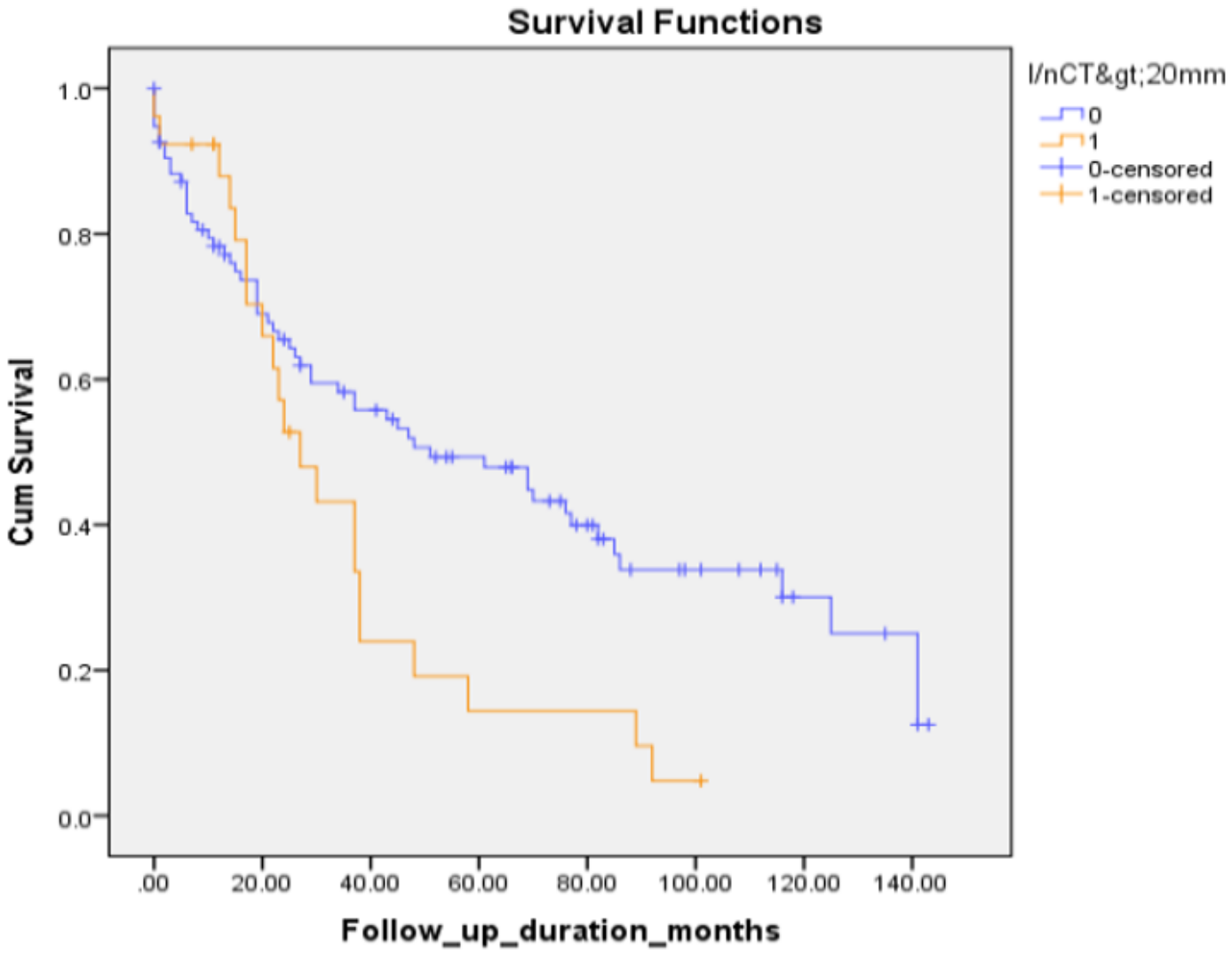

Figure 4

Survival for patients with bulky mediastinal disease (lymph nodes >20mm) before induction therapy