Lung resections in the lung screening of International Early Lung Cancer Action Program (IELCAP): 6 years of experience

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Abstract

Screening programs (SP) with low-dose computed tomography (LDCT) have proven useful for early detection of and reducing mortality from lung cancer (LC). However, there are numerous publications on SP in LC, but aspects of surgery and its implications in this program are poorly reported. The aim of this paper is to present our experience in the surgical treatment of the LC patients in the SP study of the International Early Lung Cancer Action Program (IELCAP). **Materials and Methods:** The study was conducted with patients diagnosed with LC who underwent pulmonary resection in our hospital according to the IELCAP protocol. The study period covered September 2008 to December 2014, with a follow-up until November 2015. From each patient, the demographic, clinical and histology variables were collected prospectively. **Results:** Since the SP started in September 2008 and lasted until December 2014, 6,489 individuals were recruited. A hundred and four patients were diagnosed with LC. Eighty-three (79.8%) underwent surgery for lung resection. Fifty-three patients (63.8%) were classified as pathological stage IA. Twenty-one (25.3%) patients suffered 26 postoperative complications. The postoperative mortality of our series was 1.2%. The overall survival rate of specific cancer in the surgical series was 90.6% for stage I and 82% in general. **Conclusion**: Screening Program for LC with LDCT has allowed a change in staging LC diagnosis from advanced stages to earlier stages, and therefore surgical stage. This program reduces the rate of pneumonectomy and permits surgical treatment in early stages; these advantages can imply the reduction in mortality and morbidity of these patients.

Keywords: lung cancer, screening program, lung resection

1. Introduction

Lung cancer (LC) is currently the most important cause of death from male and female cancer. The overall cancer survival rate at 5 years is estimated at 12-18%, usually diagnosed in advanced stages (Siegel, Ma, Zou, & Jemal, 2014).

Screening programs (SP) with low-dose computed tomography (LDCT) have proven useful for early detection of and reducing mortality from this disease (The National Lung Screening Trial Research Team, 2011). The tumors diagnosed in this program, are small, and therefore, resectable. In early stages, surgery remains the treatment of choice. However, there are numerous publications on SP in LC, but aspects of surgery and its implications in this program are poorly reported (Infante et al., 2011). Van't Westeinde et al's review of perioperative morbidity and mortality in LC, showed that perioperative mortality in patients enrolled in the NELSON program was lower than the published patient series not undergoing screening (van't Westeinde et al., 2012). Flores and Infante groups (Flores et al., 2014; Infante et al., 2011) reported the importance of reducing surgery in benign processes in SP.

The aim of this paper was to present our experience in the surgical treatment of the LC patients in the SP study of the International Early Lung Cancer Action Program (IELCAP), and to describe the morbidity, mortality, days hospitalized and survival of these surgical patients.

2. Materials and Methods

This descriptive study focused exclusively on surgical treatment outcome, which was conducted in patients diagnosed with LC, who underwent pulmonary resection in our hospital according to the IELCAP protocol. The study period covered September 2008 to December 2014, with a follow-up until November 2015, and a minimum of a year of follow-up period. The common protocol specifies the basal and control LDCT and defines the positive, semi-positive or negative nodules detected. The inclusion criteria, workup and treatment of each patient were determined by the institution (C. Henschke, 2011). The inclusion criteria at our institution were: individuals aged > 50 years; history of smoking beyond 15 years / pack; former smokers in the previous 15 years; no previous neoplasia. Participation was voluntary and informed consent was obtained in all cases.

Non-calcified nodules solid or partially solid of between 5-14 mm, or solid nodules of between 8-14 mm, and nodes ≥15 mm were classified as positive according to the IELCAP protocol (Figure 1).

Non-calcified nodules nodules solid and part-solid of < 5 mm as well as, non-solid nodules of < 8 mm were considered

semi-positive. In consequence, annual controls were performed to LDCT with all semi-positive nodules (C. Henschke, 2011).

Each patient, with a positive pulmonary nodule was studied by: computed tomography (CT) with a contrast and perfusion study; positron emission tomography (PET); pulmonary function tests (PFTs); histological examination with non-surgical methods with a transthoracic needle biopsy (TTNB) or by endobronchial biopsy, depending on lesion location. If possible, pneumonectomy or securities PFR limits, lung perfusion quantified scintigraphy. A surgical biopsy was performed whenever histology for non-surgical methods was not possible, due to inaccessible location of nodule or discordance between continuous growth of nodule and biopsy negative.

All the patients eligible for surgery were operated by the same group of surgeons at the Thoracic Surgery Unit of our institution, according to a previously published fast-track program. This program consists of a multidisciplinary approach that combines patient education before surgery to reduce postoperative stress by anesthetic, analgesic and pharmacological techniques, and aggressive postoperative rehabilitation, to promote fast patient recovery and to, consequently, cut hospitalization length (Padilla Alarcón & Peñalver Cuesta, 2013). All the patients were undergoing lung resection for LC by thoracotomy.

From each patient, the following variables were collected prospectively: sex, age, Smoking status, comorbidity, forced vital capacity (FVC), expiratory volume in one second (FEV1), FEV1 / FVC, alveolar diffusion capacity of carbon monoxide (DLCO), amplitude of pulmonary resection, number of analyzed nodes, histology, tumor size, TNM classification, perioperative morbidity and mortality according to the classification published by Seely et al. (Table 1) (Seely et al., 2010), hospitalization length in days, readmission and follow-up.

Initially we did a descriptive analysis of the study series. Quantitative mean variables, standard deviation and range were calculated. For the categorical variables, absolute frequency and percentage were calculated. Subsequently, we constructed a Kaplan-Meier curve for LC-specific survival at 2 and 5 years of the all cases who underwent resection. We used SPSS program version 20.

3. Results

Since the SP started in September 2008 and lasted until December 2014, 6,489 individuals were recruited, and 111 patients presented lung nodules suggestive of malignancy (Figure 2). Lesions were detected in the baseline LDCT in 46 patients (41.4%), in the annual controls of the first 3 years in 48 (43.2%), and in the other controls between 4 and 5 years. Twenty-one

patients were inoperable (18.9%), 20 were in an advanced clinical stage of LC and one presented bad cardiorespiratory function.

Ninety patients (81.1%) underwent surgery. Intraoperatory biopsies were performed in 43.3% of patients (39/90) for technical difficulty for histology by non-surgical methods, and for suspicious growth of malignity. The percentage change was consistent with malignancy = (diameter at time 2 - diameter at time 1)/ diameter at time 1; a) if nodule was < 5 mm in diameter, % change > 50% growth, b) nodules 5-9 mm, % change > 30% growth, c) nodules > 10 mm, % change > 20% growth, according to the IELCAP criteria (Henschke, 2011). Of these patients, 32 (35.5%) were diagnosed with LC and surgery was completed in the act. Seven patients (7.8%) were diagnosed as benign, one patient underwent lobectomy for filing a central lesion, and the others underwent non-anatomic wedge resections.

A hundred and four patients were diagnosed with LC. Eighty-three (79.8%) underwent surgery for lung resection with lymph node sampling by thoracotomy, and the following were performed: 65 (78.3%) lobectomies, 3 (3.6%) bilobectomies, 12 (14.5%) anatomic segmentectomies and 3 (3.6%) pneumonectomies. The patients were undergoing to anatomic segmentectomies due to limited cardiorespiratory function and negative margins for malignancy as reported in all the cases.

Table 2 shows the clinical and demographic characteristics of our sample. Fifty-nine patients (71.1%) were men. Mean age was estimated at 59.8±5.5 years. Hypertension and COPD were the most widely found comorbidities. The commonest histological type was adenocarcinoma, and it was diagnosed in 66 (79.5%) tumors.

Fifty-three patients (63.8%) were classified as pathological stage IA, whereas 14 (16.8%) were classified as stage IIIA (Figure 3). Three patients underwent neoadjuvant chemotherapy by nodal affectation N2. No exploratory thoracotomies were performed in this series.

Twenty-one patients suffered 26 postoperative complications (25.3%). Five patients presented air leakage > 5 days. Two patients presented pneumothorax after removing chest tubes and required new drainage placement. Endobronchial aspiration by bronchoscopy was necessary for two patients to retain secretions / atelectasis. Three patients had a hemothorax, and one underwent thoracotomy review. Finally, two patients were diagnosed with pneumonia and respiratory failure, while three required non-invasive ventilation (NIV). As for the non-respiratory complications, five patients had atrial fibrillation and were controlled exclusively by medical treatment. One patient died of heart failure. In accordance with Seely's paper, Table 3 shows the surgical

complications, where minor complications (grade I and II) were more frequent.

Hospitalization length in days was 4.9±4 days (range, 3-23), with a median of 3 days. It was 3.3 ± 0.6 days if there were no complications (range, 3-6), and 9.9 ± 5.7 (range, 4-23) if there were complications. No patient was readmitted to hospital. The LC-specific survival of the series, both overall and by stage at 2 and 5 years, is represented in Figure 4.

4. Discussion

Real evidence of the benefits of the SP for LC has been reported (Aberle, Abtin, & Brown, 2013). However, these benefits are described less for lung resection surgery. We herein describe our experience in lung resection surgery in patients assigned to this program.

The number of nodules diagnosed by LDCT is very large, so protocols and management are important for studying these patients, as is the usefulness of a multidisciplinary team in which thoracic surgeons were involved (Rocco et al., 2013). In their 2011 publication, Infante et al., report the highest probability of surgical procedures in patients with benign lesions in centers where patients are referred to surgical teams not involved in the program. The same article not only reports the largest number of benign lesions operated in the DANTE group (22%), but reviews these data in different studies with various benign lesions that vary between 5 and 45% of patients according to surgical procedures. The IELCAP group reported a figure of 11% (Flores et al., 2014). Our 7.8% rate of surgery in benign nodules was comparable with other centers like the IELCAP program and the ITALUNG study, and we obtained a lower rate than that obtained by the National Lung Screening Trial Research Team (NLST), which reported 21% of surgeries that did not result in cancer diagnosis (Flores et al., 2014; The National Lung Screening Trial Research Team, 2011). Of the seven patients who had surgery, six underwent wedge resection and only one lobectomy was performed by anatomic nodule location. No morbidity or mortality from surgery occurred in any patient.

Many patients who undergo surgery have not been previously diagnosed. In the study of Flores et al., more than half of the patients operated on had no preoperative diagnosis (209/402) (Flores et al., 2014). In our series, 43.3% of the patients underwent surgical biopsy. A small diameter of pulmonary nodules is a limiting factor for prior diagnosis, which decreases yields in imaging tests, such as PET, and when obtaining histological samples by non-surgical methods. Doubtlessly, it would be ideal for all patients who undergo surgery to have had a previous histological diagnosis obtained by non-surgical methods. However,

this is not always possible in practice, and the drawbacks of an untreated malignant pulmonary nodule usually lead to a high mortality rate (Crestanello et al., 2004; Flores et al., 2014). Hence appropriately managing pulmonary nodules and their ongoing reviews are important.

Small-size diagnosed lung nodules offer a good advantage for the early detection of LC (Crestanello et al., 2004; Infante et al., 2011). Unlike what typically occurs in LC, the resectability rate in our series was 79.8%, which is consistent with the results reported by other authors in patients who enter SP (Crestanello et al., 2004; Infante et al., 2011; The National Lung Screening Trial Research Team, 2011; Veronesi et al., 2008).

The lung resection type in sublobar or lobar in nodules < 2 cm is controversial; although sublobar resections preserve more lung parenchyma, benefits in recurrence and survival are still a matter of debate. Therefore, a standard resection is still a lobectomy (Crestanello et al., 2004; Zhang et al., 2015), and this surgery type was performed in 78.3% of the cases in our series. The pneumonectomy rate was 3.6%, which is slightly higher than the SP series described by Flores (1%), but is lower than those described by others in general populations (7-14%) (Flores et al., 2014; Ginsberg & Rubinstein, 1995; Safi et al., 2015). These results imply reduced mortality, especially in association with pneumonectomy, which has been described to be between 0-15% (Allen et al., 2006; Flores et al., 2014; Ginsberg et al., 1983; Powell et al., 2013; Thorsteinsson et al., 2012) (Table 4). In our series, postoperative mortality by pneumonectomy was not evident and the overall mortality of our series was 1.2%, which is similar to that reported by Crestanello et al (Crestanello et al., 2004). Infante et al., reported a mortality rate of 4%, probably due to the high pneumonectomy rate found in their study (Infante et al., 2011). IELCAP (International Early Lung Cancer Action Program, 2006) indicated a mortality of 0.5% in 411 stage I tumors, and NLST (The National Lung Screening Trial Research Team, 2011) reported mortality to be 1% in the group that underwent LDCT and 2.1% in the chest-rx group. However, both series included patients who had undergone thoracotomy, thoracoscopy or mediastinoscopy.

The incidence of postoperative complications in the population in SP has been reported to be between 25% and 57%. Major complications were 6-10% (Crestanello et al., 2004; Infante et al., 2011; The National Lung Screening Trial Research Team, 2011; Veronesi et al., 2008). According to our experience, 21 patients (25.3%) presented morbidity associated with surgery, of whom 8 (9.6%) were considered major complications. Allen et al. described

the rate of postoperative complications in a general population to be between 32% and 38% (Allen et al., 2006; Boffa et al., 2008) (Table 4). Our reoperation rate was 1.2%, which is similar to that reported by Veronesi et al (Veronesi et al., 2008).

Our experience indicates that hospitalization length in days was shorter than the average published by other authors for thoracotomy (Boffa et al., 2008; van't Westeinde et al., 2012; Veronesi et al., 2008), and we had no readmissions.

The overall survival rate of specific cancer in the surgical series was 90.6% for stage I and 82% in general at 5 years (Figure 4), which is consistent with the IELCAP that recently reported a survival rate of 92% at 5 years for stage I and 80% in general (C. I. Henschke, 2015). However, still these data imply a clear limitation, which is the small size of the series, therefore, it is not possible compare survival rates between stage IA vs IB, and IIA vs IIB.

In conclusion, SP for LC with LDCT has allowed a change in staging LC diagnosis from advanced stages to earlier stages, and therefore surgical stage. Even though it's true that surgical morbidity and mortality were reported within the pulmonary resection standards, this program reduces the rate of pneumonectomy and permits surgical treatment in early stages; these advantages can imply indirectly reduction in the mortality and morbidity in these patients, as well as largest lung parenchyma preservation and a higher cure rate. Although further and extensive studies are required, we believe that these results are a substantially verifiable and relevant element to support SP in LC.

5. Conflicts of interest

No further conflicts of interest.

Table 1: Classification of complications according to Clavien-Dindo, published by Seely (Seely et al., 2010)

Complications	Any deviation from the normal postoperative course
Minor	
Grade I	Any complication without a need for pharmacological treatment or other intervention
Grade II	Any complications that need treatment or minor intervention
Major	
Grade III	Any complication that requires surgical, endoscopic, radiologic intervention or multitherapy
Grade IIIa	Intervention that does not require general anesthesia
Grade IIIb	Procedure requiring general anesthesia
Grade IV	Any complication that requires treatment in the intensive care unit and life support
Grade IVa	Single organ dysfunction
Grade IVb	Multiorgan dysfunction
Mortality	
Grade V	Complication that determines the patient's death

Table 2: Clinical and demographic characteristic of the series

Gender	
Men	59 (71.1%)
Women	24 (28.9%)
Years	59.8±5.5 (range 50-73)
Packs / year	44.3±16.8 (range 20-90)
Active smokers	51 (61.4%)
Comorbidity	
Hypertension	26 (31.3%)
Mellitus diabetes	13 (15.7%)
COPD	23 (27.7%)
Heart disease	9 (10.8 %)
Peripheral vascular disease	6 (7.2%)
Liver disease	2 (2.4%)
Neoadjuvant therapy	3 (3.6%)
Lymph nodes examined	12.5±6 (range 1-33)
Tumor size (mm)	18.4±12.5 (range 4-55)
Histology	
Adenocarcinoma	66 (79.5%)
Squamous	5 (6%)
Adenosquamous	3 (3.6%)
Large cell	1 (1.2%)
Small cell	3 (3.6%)
Carcinosarcoma	1 (1.2%)
Carcinoid	4 (4.9%)

Table 3: Complications and treatment degree according to Seely (8)

Degree of complication	**n**	**Treatment**
Minor	18 (21.7%)	
Grade I		
Grade II		
Air leak > 5 days	5 (6%)	*Observation*
Pneumonia	2 (2.4%)	*Medical treatment*
Retained secretions / atelectasis	2 (2.4%)	*Physiotherapy*
Hemothorax	2 (2.4%)	*Blood transfusion*
Atrial fibrillation	5 (6%)	*Medical treatment*
Wound infection	2 (2.4%)	*Medical treatment*
Major	*8 (9.6%)*	
Grade IIIa		
Pneumothorax	2 (%)	*Thoracic drainage*
Retained secretions / atelectasis	2 (2.4%)	*Endobronchial aspiration*
Grade IIIb		
Hemothorax	1 (1.2%)	*Thoracotomy*
Grade IVa		
Respiratory insufficiency	3 (3.6%)	NIV
Grade IVb		
Mortality		
Grade V		
Heart failure	1(1.2%)	*Exitus*

Table 4: Morbidity and mortality in lung resection for LC in population outside SP

Study	Mortality	Mortality in lobectomy	Mortality in pneumonectomy	Complication rate
Ginsberg 1983 (Ginsberg et al., 1983)	3.7%	2.9%	6.2%	ND
Allen 2006 (Allen et al., 2006)	1.4%	1.3%	0	38%
Boffa 2008 (Boffa et al., 2008)	2.5%	2%	6.2%	32%
Thorsteinsson 2012 (Thorsteinsson et al., 2012)	1%	0.7%	3.3%	37.4%/8.7%*
Powel 2013 (Powell et al., 2013)	2.9%	4.6%	11.5%	ND

ND: No data. * Minor complications / major complications

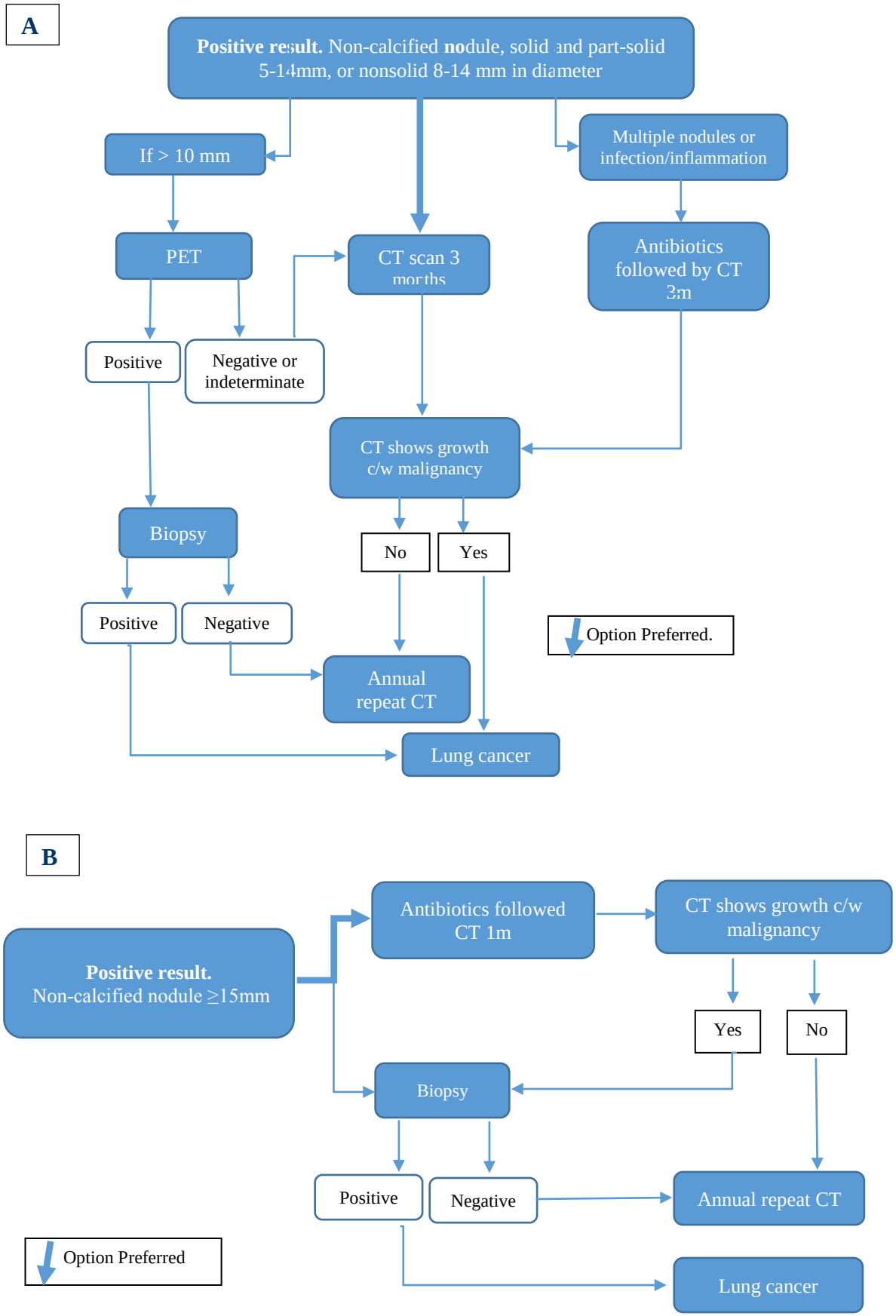


Figure 1: Protocol positive pulmonary nodules, modified program IELCAP. A) Nodule < 15 mm. B) Nodule ≥ 15 mm (C. Henschke, 2011)

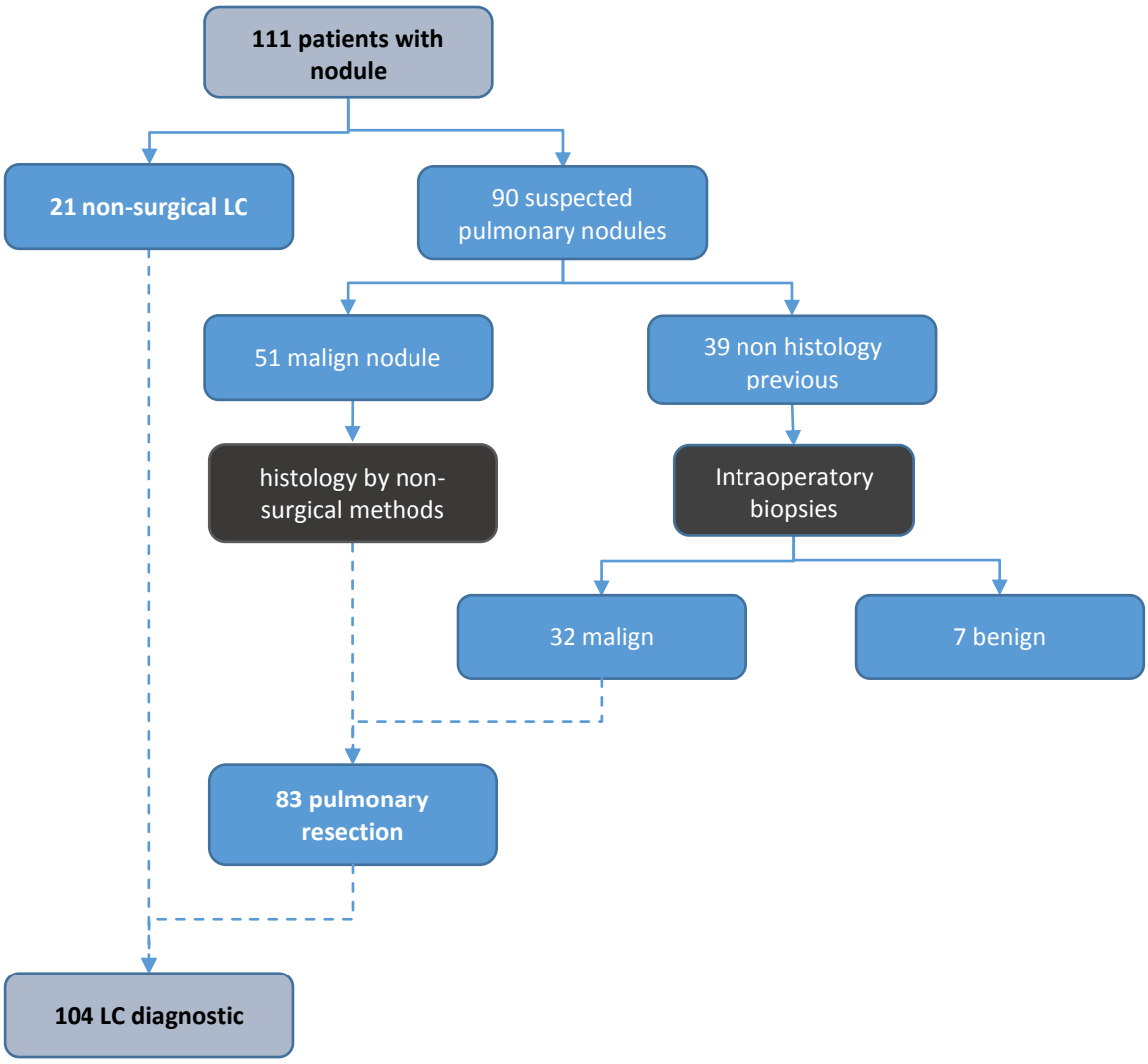


Figure 2: Flow chart of patients with pulmonary nodule according to IELCAP program diagnosis

FIGURE 3: PATHOLOGICAL STAGE TNM OF THE SERIE

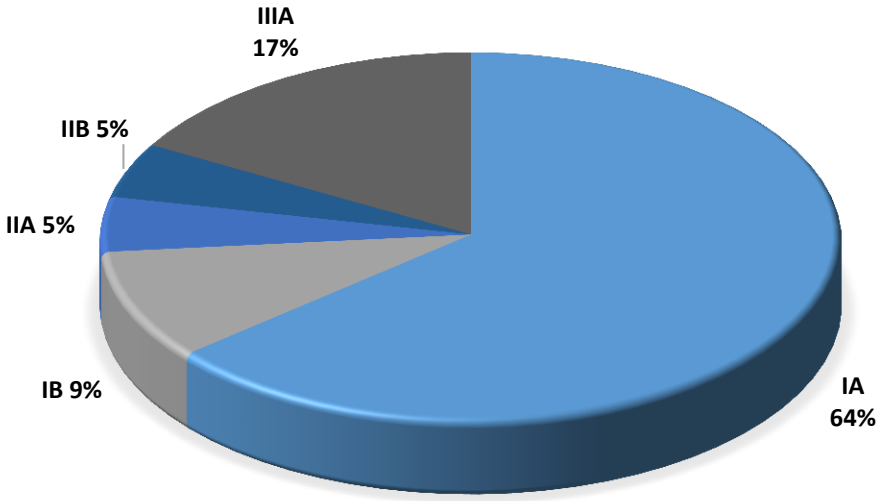
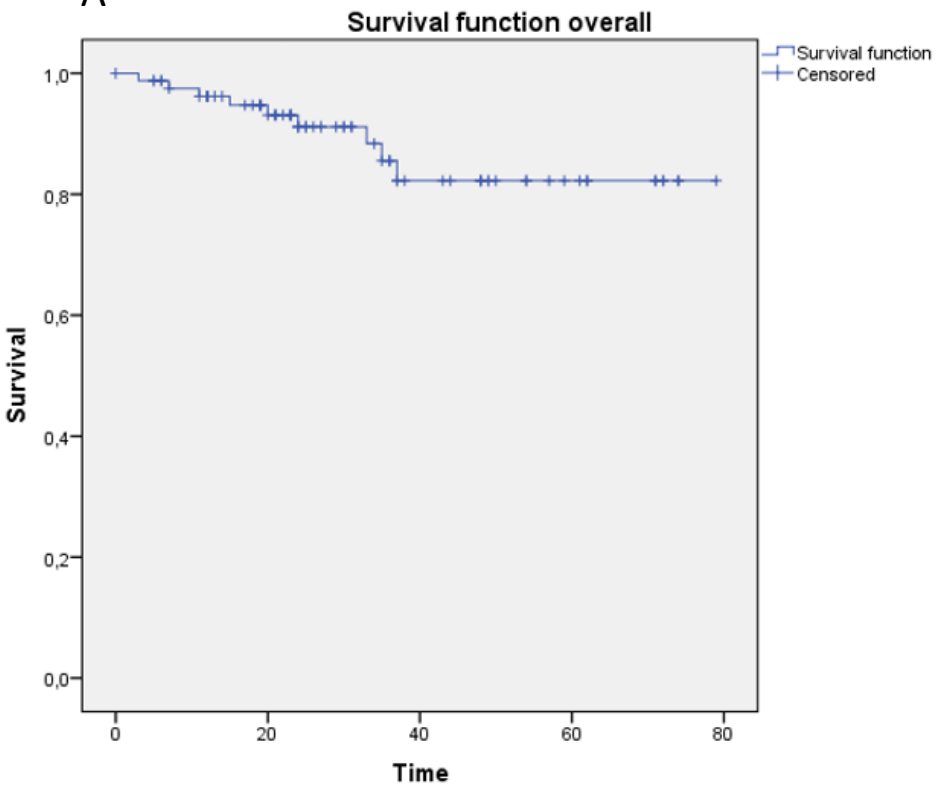


Figure 4: LC-specific survival. A: overall survival. B: by stage survival. C: table of LC-specific survival both overall and by stage.

A



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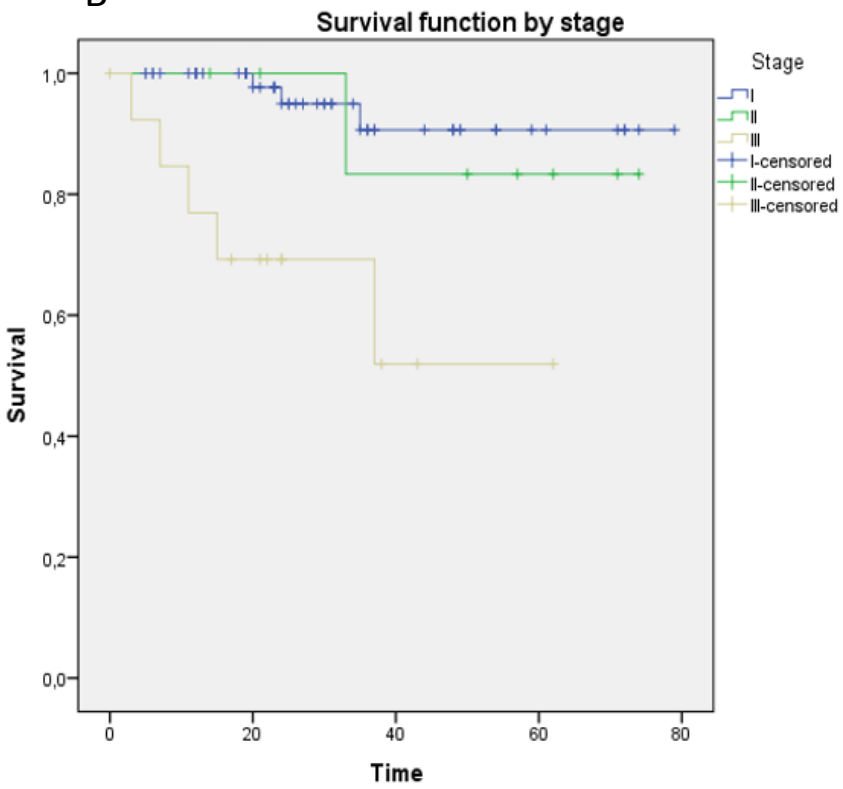

C

	Survival	
	24 months	60 months
Overall	94,7%	82,2%
I Stage	97,7%	90,6%
II Stage	100%	83%
III Stage	69,2%	51,9%

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