Surgical Oncology 28 (2019) 223–227

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Long-term oncologic results for robotic major lung resection in non-small cell lung cancer (NSCLC) patients

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ARTICLE INFO

Keywords:
Robotic lobectomy
Outcomes
NSCLC

ABSTRACT

Objective(s): Robotic lobectomy is becoming a widespread surgical procedure in NSCLC treatment, but data on oncologic outcomes is still lacking. The aim of this study was to analyze long term oncologic results of robotic lobectomy for non small lung cancer.

Methods: Clinical records of consecutive NSCLC patients underwent robotic major surgery, between January 2010 and December 2015, were collected and analyzed.

Results: We analyzed data of 212 patients (127 male and 85 female), with a median age of 66.3 years. The median follow-up time was 40.3 months (range 4–83).

The median disease free survival was 66.3 months. Free disease survival stage-correlated was 75.6 months for stage I, 42.3 months for stage II, 51.2 months for stage III and 10.3 months for stage IV. The median overall survival was 78.6 months. Overall survival stage-correlated was 82 months for stage I, 73.5 months for stage II, 61.4 months for stage III and 41.3 months for stage IV.

Conclusions: This study suggests high safety level, positive post-operative and oncologic outcomes for patients NSCLC underwent robotic major surgery, also in advanced stages.

1. Introduction

Robotic surgery has been developed to overcome the restrictions of Minimally Invasive Surgery maintaining the advantages related to low invasiveness. The high definition three-dimensional vision, the greater flexibility of the arms, the downscaling and the tremor filtration implies clinical advantages such as less trauma, less pain, safer surgery especially for complex thoracic procedures. In addition, thanks to the technologic developments in parallel with the refinement of the technique, robotic thoracic surgery is widely considered a significant evolution over the more established VATS procedures [1,2].

Several Authors have analyzed perioperative results in patients who underwent robotic lung resection for NSCLC showing a significant reduction of length of stay, postoperative pain, complications (atrial fibrillation, air leak and bleeding) and mortality compared with conventional approaches [3,4]. To date, little data has been published on long term oncological results in NSCLC patients undergoing robotic approach; furthermore the above said studies contain results only for early stage NSCLC [5].

The aim of this paper is to analyze surgical results and long-term oncological outcomes in patients who underwent robot-assisted major lung resection for NSCLC.

2. Materials and methods

Between January 2010 and December 2015, the data of 212 consecutive patients who underwent robotic major lung resection for NSCLC with Da Vinci Surgical System (Sunnyvale, CA, USA), was collected and retrospectively analyzed.

Age, comorbidities, diagnosis, gender, type and duration of surgery, conversion rate, length of stay, early and late complications were reviewed retrospectively and analyzed descriptively. All patients were studied with standard staging that included chest/abdomen computer tomography scan (CTscan) and positron emission tomography scan (PET scan) [6,7]. The histopathologic diagnosis was obtained by endoscopic exams (brushing, biopsy or endoalveolar wash) or by CT-

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https://doi.org/10.1016/j.suronc.2019.02.003
Received 26 October 2018; Received in revised form 23 January 2019; Accepted 3 February 2019

guided needle biopsy [8]. Only NSCLC patients without mediastinal nodes involvement (cN0-N1) were recruited for this study. The patients with a suspected mediastinal lymph node involvement (cN2) or treated with induction therapies were excluded, instead the single treated brain metastasis has not been considered exclusion criteria.

The pre-operative evaluation included: general blood test, chest X-ray, respiratory function evaluation, cardiac function evaluation.

The patients underwent a major anatomic lung resection (lobectomy, bilobectomy) with extended lymphadenectomy and the disease was staged according to the 7th edition of International Association for the Study of Lung Cancer (IASLC) TNM classification and pathologically define according to 2015 Word Health Organization (WHO) classification [9,10].

2.1. Surgical technique

A single lung ventilation and general anesthesia is required to perform robotic lung resection and patients were positioned in a lateral decubitus and draped as in posterolateral thoracotomy.

A standardized port mapping was applied using four arms "totally endoscopic" approach for both sides: the camera port positioned in the 7th/8th intercostal space on the posterior axillary line; the posterior ports positioned along the same intercostal space, in the auscultatory area; the anterior port positioned in the 5th-6th intercostal space on the anterior axillary line, just over the diaphragm. The CO2 insufflation was applied (5–8 mmHg) to obtain the complete collapse of the lung, ensuring an adequate maneuvering space in chest cavity.

During the follow-up (at 3-6-12 months), the patients underwent chest CT scan, general blood test and tumor markers (CEA, TPA, Cyfra21.1,NSE), abdomen ultrasound or abdomen CT scan, while total body PET-CT scan, bronchoscopy and head CT scan were performed when considered necessary.

2.2. Data analysis

Statistical analysis was performed using the software SPSS version 23.0 for Windows (SPSS, Chicago, USA).

Continuous variables were expressed in terms of median and range.

Overall survival (OS) and disease free survival (DFS) were estimated with Kaplan-Meier method and were compared across groups using univariate and multivariate Cox proportional-hazards models.

Survival was calculated from the date of surgery to last follow up (December 2016) or death.

The data was considered statistically significant when $p \leq 0.05$.

3. Results

From January 2010 to December 2015, 212 patients underwent robotic major lung resection. They were 127 male (59.9%) and 85 female (40.1%), with a median age of 66.3 years (range 30–82). 57 patients (26.9%) underwent right upper lobectomy (RUL), 17 (8%) medium lobectomy (ML), 74 (34.9%) right lower lobectomy (RLL), 34 (16%) left upper lobectomy (LUL), 29 (13.7%) left lower lobectomy (LLL) and 1 (0.5%) upper bilobectomy. The median number of removed lymph nodes was 17.4 nodes (range 7–37).

The median operative time was 215 min (range 65–460), the median chest drainage duration was 3.6 days (range 2–13) and the median postoperative hospital stay was 3.6 days (range 4–29). We observed a rate of 4.2% conversions to open surgery, due to calcified nodes tenaciously adherent to hilum vessels (1 case) and to severe pleural adhesions (8 cases). 54 (25.5%) patients presented post-operative complications: 39 (18.3%) cases of prolonged air leak (not requiring re-intervention); 2 (0.9%) chylothorax, treated by conservative approach and 13 (6.1%) atrial fibrillation resolved by medical therapy. There were no intraoperative deaths and the postoperative mortality at 30 and 90 days was 0.4% (1 patient died on the 4th postoperative day for myocardial infarction).

Table 1
Histopathological evaluation and pathological stage.

Histology	Adenocarcinoma	193 (91%)
	Squamous cell carcinoma	14 (6,6%)
	Others	5 (2,4%)
	Large cell neuroendocrine carcinoma	2
	Adenosquamous carcinoma	2
	Large cell carcinoma	1
Staging	IA	80 (37,7%)
	IB	68 (32,1%)
	IIA	20 (9,4%)
	IIB	17 (8%)
	IIIA	23 (10,8%)
	IIIB	1 (0,5%)
	IV	3 (1,4%)

Histopathological analysis showed 193 (91%) adenocarcinomas, 14 (6.6%) squamous cell carcinomas and 5 (2.4%) other types of carcinoma (large cell neuroendocrine carcinoma, adenosquamous carcinoma, large cell carcinoma). According to the 7th Edition of TNM classification, 80 pIA (37.7%), 68 pIB (32.1%), 20 pIIA (9.4%), 17 pIIB (8%), 23 pIIIA (10.8%), 1 pIIIB (0.5%) and 3 pIV (1.4%), were observed. All IV patients presented single brain metastasis, pre-operatively treated by radiotherapy (Table 1).

After surgical treatment 57 (26.9%) patients underwent adjuvant chemotherapy, based on pathological stage and performance status, while the other 155 patients underwent follow up. The median time to start adjuvant therapy was 35 days (range 28–51) after surgical treatment. In 49 patients (86%) the planned adjuvant treatment was completed, in the other cases it was interrupted for toxicity in 7 cases and for poor patient compliance in 1 case.

The median follow-up time was 40.3 months (range 4–83). During the follow-up period, a loco-regional relapse was observed (lung or mediastinal nodes) in 27 patients (12.7%) and in 23 patients (10.9%) a distant metastasis was observed and the related lung cancer mortality was 5.2%.

The DFS of the entire cohort was 66.3 months (range 1–83) (Fig. 1). In particular the disease free cancer-related survival was 66.4 months for adenocarcinoma patients; 64.4 months for squamous cell carcinoma and 47.6 months for patients with other lung cancer histotypes (Fig. 2).

When a subset analysis was performed by stage, the DFS was 75.6 months for stage I; 42.3 months for stage II; 51.2 months for stage III

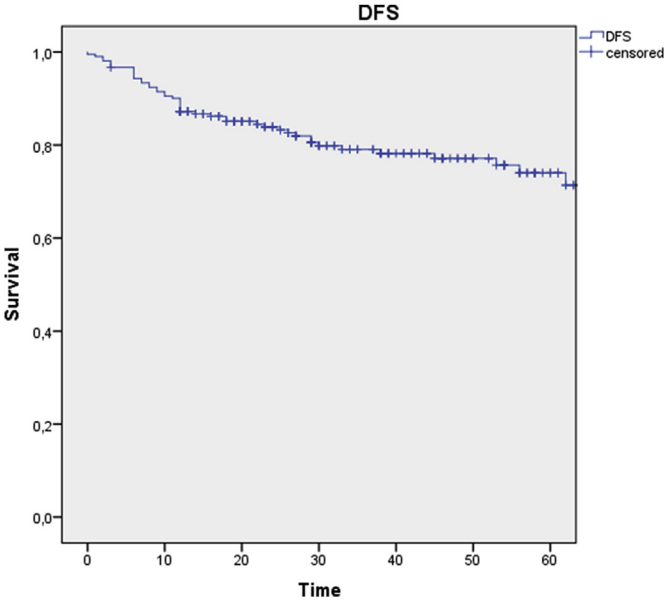

Fig. 1. Disease free survival.

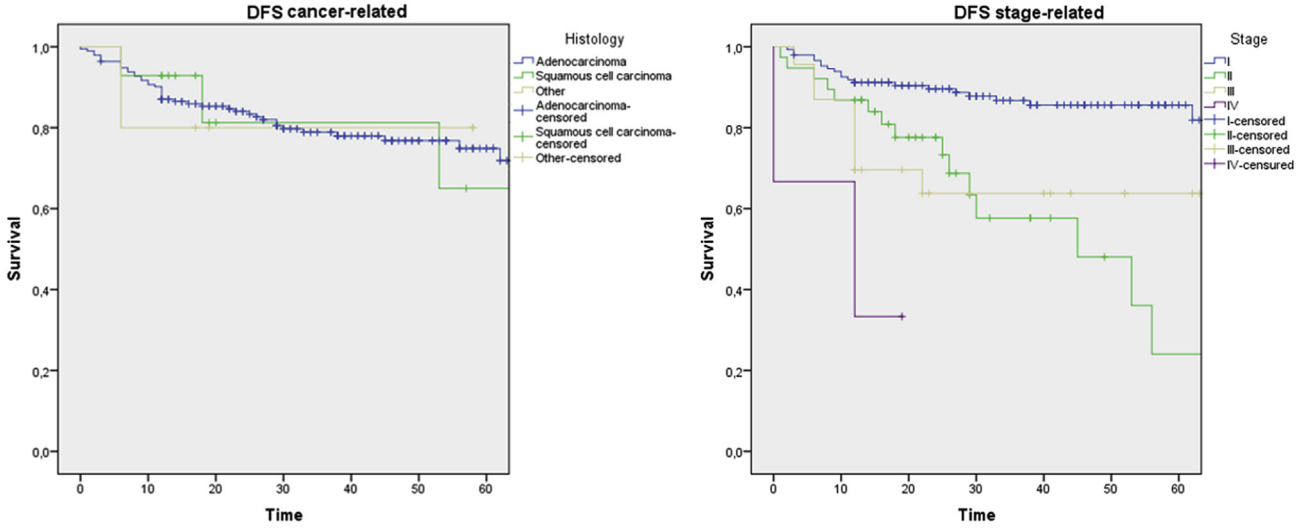

Fig. 2. Cancer-related and stage-related DFS.

and 10.3 months for stage IV (Fig. 2). Patients with diagnosis of advanced lung cancer, except Stage IV, underwent adjuvant chemotherapy and they had a DFS of 61 months.

The actuarial DFS related to the stage at 12, 24, 36 and 60 months was analyzed. The actuarial DFS at 12 months was 92.5%, 91.2%, 69.6% and 3.33% for stage I, II, III and IV respectively; at 24 months was 90% for stage I, 73.3% for stage II, 63.8% for stage III and 0% for stage IV; at 36 months was 89.6% for stage I, 48.1% for stage II, 54.6% for stage III and 0% for stage IV; at 60 months was 81.9%, 28.4%, 25.4% and 0% for stage I, II, III and IV respectively (Table 2).

The OS of the entire court was 78.6 months (Fig. 3). The overall cancer related survival was 79.2 months for patients with adenocarcinoma; 79 months for patients with squamous cell carcinoma and 48.8 months for patient with other histotypes (Fig. 4).

According to the Stage, the OS was 82 months for stage I; 73.5 months for stage II; 61.4 months for stage III and 41.3 months for stage IV (Fig. 4).

The actuarial OS according to the Stage at 12, 24, 36 and 60 months showed: at 12 month 99.3%, 97.4%, 91.3% and 84.7% for stage I, II, III and IV respectively; at 24 months 98.5% for stage I, 93.8% for stage II, 81.5% for stage III and 66.7% for stage IV; at 36 months 98.5% for stage I, 93.7% for stage II, 73.1% for stage III and 0% for stage IV; at 60 month 98.5%, 93.7%, 73.1% and 0% for stage I, II, III and IV respectively (Table 3).

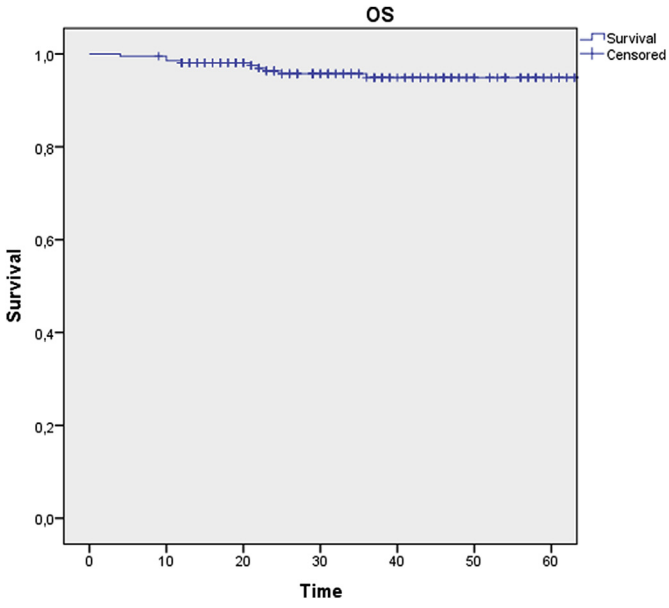

Fig. 3. Overall survival.

4. Discussion

Since 2001, when the first robotic lung lobectomy was performed [11], several studies have been conducted on the feasibility, safety and results of robotic lung resections, inasmuch the use of robotic surgery for NSCLC disease has significantly increased.

Thanks to the robotic system features (high-definition 3D vision, tremor filtration, a 7-degree articulation of the instruments), this approach is considered the latest evolution in surgery, overstepping the technical limits of VATS approach. Several studies have reported less postoperative pain, shorter hospitalization and better aesthetic results in robotic surgery when compared to open surgery and, in line with literature, our experience confirms that the robotic technique is safe and feasible with a low rate of postoperative mortality and a low incidence of complications [12–14].

However, to date few papers have analyzed long-terms oncological outcomes and only for early stage NSCLC patients treated with robotic surgery. According to Park et al., robotic approach guarantees appropriate oncological results for early stage NSCLC showing a 10% rate of recurrence and an overall 5-year survival of 80% [15]. Moreover, Yang et al., analyzing 184 pI stage patients, with a follow-up period of 39.8 months, found a recurrence in 25 patients (13.6%) and a 5-year OS of 77.6% [16]. Currently, significant studies with long term survival data for NSCLC advanced stage patients, are lacking. Recently, Toosi et al. analyzed the oncological outcomes of 247 NSCLC patients, not only in early stages (134 pI, 44 pII, 59 pIII, 10 pIV), who underwent robotic surgery and reported a 3-year OS of 75%, 73%, 44% and 0% for pI, pII, pIII and pIV respectively [17].

The latest NCCN guidelines, considering the effectiveness of procedure, suggest that minimally-invasive approach should be proposed

Table 2
Actuarial DFS stage-related.

	Stage I	Stage II	Stage III	Stage IV
12 months	92,5%	91,2%	69,6%	3,33%
24 months	90%	73,3%	63,8%	0%
36 months	89,6%	48,1%	54,6%	0%
60 months	81,9%	28,4%	25,4%	0%

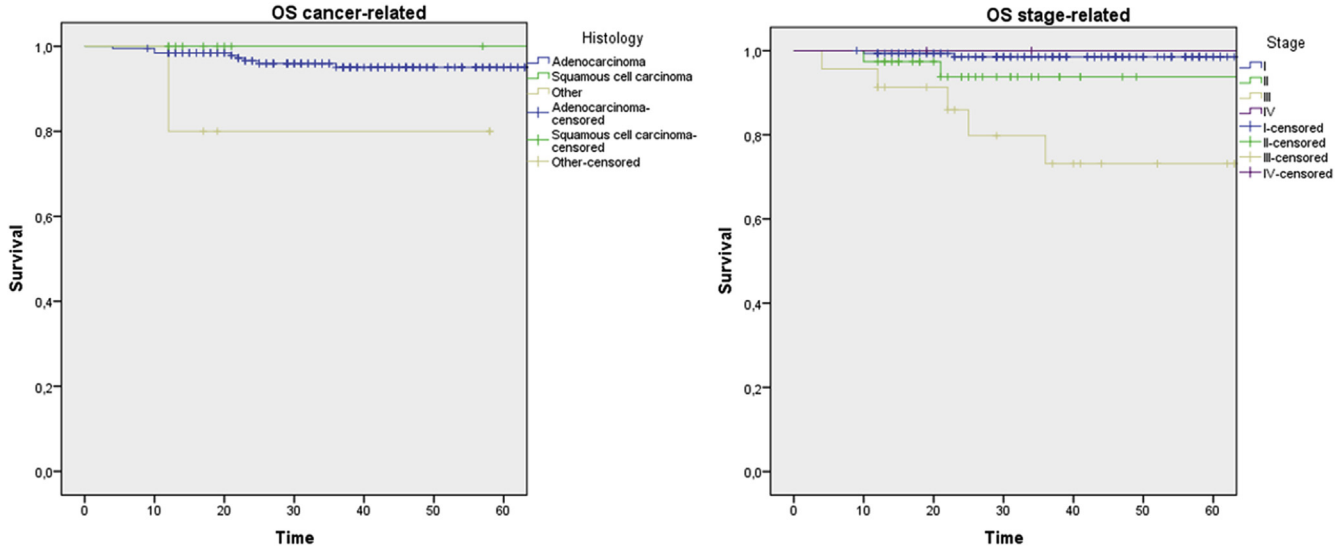

Fig. 4. Cancer-related and stage-related OS.

Table 3
Actuarial OS stage-related.

	Stage I	Stage II	Stage III	Stage IV
12 months	99,3%	97,4%	91,3%	84,7%
24 months	98,5%	93,8%	85,1%	66,7%
36 months	98,5%	93,7%	73,1%	0%
60 months	98,5%	93,7%	73,1%	0%

to all patients whenever possible [18]; for this reason, thanks to the advanced robotic technology and the standardization of surgical procedure, is considerable to extend the indications of robotic surgery also to advanced stage NSCLC patients. Indeed our oncological results are in line with the most consistent open surgery data, confirming that robotic technique has good perioperative and long-term oncologic outcomes.

In the data analysis, we observed a correlation between histology and DFS. Patients with adenocarcinoma and squamous cell carcinoma showed a similar DFS with no statistical significance (66.4 months and 64.4 months respectively, $p > 0.05$), but a worse DFS for other histotypes. In the same way our series showed a similar correlation for OS with no significant difference in adenocarcinoma and squamous cell carcinoma patients (79.2 months versus 79 months respectively, $p > 0.05$), but a remarkably worse OS for other histotypes such as adenosquamous and large cells (48.8 months).

We evaluated actuarial DFS stage-related and actuarial OS stage-related at 12, 24,36 and 60 moths. Our results are in accordance with oncological outcomes reported for conventional approach, confirming that there is no difference in terms of oncological results between patients underwent different surgical approaches.

In conclusion we can affirm that major lung robotic surgery for lung cancer is safe and feasible, with a low rate of postoperative morbidity and mortality giving satisfactory oncologic long-term results, also in advanced stages. However more large series are mandatory to support these conclusions, and undoubtedly long-term follow-up analyses on NSCLC patients treated by robotic surgery are required.

Conflicts of interest

Prof F. Melfi is an official proctor for Intuitive Surgical. The other authors have no conflicts of interest to declare.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgement

To Teresa Hung Key for linguistic accuracy checking.

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