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Nodal upstaging evaluation in NSCLC patients treated by robotic lobectomy

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Abstract

Background Open pulmonary resection is considered the gold standard treatment of early-stage non-small cell lung cancer (NSCLC). However, in the last decades, the use of minimal-invasive techniques has given promising results. Survival in lung cancer, after surgery, depends on the number of pathological nodes (pN), thus lymph nodal upstaging can be considered a surrogate for surgical quality of the procedure. Several studies have demonstrated a lower rate of upstaging in video-assisted thoracic surgery than in open surgery, suggesting an approach-related difference in lymphadenectomy. Features of robotic technique could consent a lymph nodal dissection similar to open surgery. The aim of the study is to compare nodal upstaging between thoracotomy and robotic approaches to evaluate the oncologic radicality.

Methods Between January 2013 and December 2016, 212 consecutive cN0 NSCLC patients underwent lobectomy and lymphadenectomy (N1 + N2 stations) by either thoracotomy (Open Group) or robotic surgery (Robotic Group).

Results Lobectomy and lymphadenectomy were performed in 106 cN0–cN1 NSCLC patients by robotic surgery and in 106 cN0–cN1 NSCLC patients by open surgery. A mean of 14.42 ± 6.99 lymph nodes was removed in the Robotic Group (RG) and a mean of 14.32 ± 7.34 nodes in the Open Group (OG). Nodal upstaging was observed in 22 (20.75%) RG patients and in 19 OG (17.92%) patients.

Conclusions Robotic lobectomy for clinical N0–N1 NSCLC appears to be equivalent to thoracotomy in terms of efficacy of lymph node dissection and nodal upstaging. Given that the nodal upstaging is a surrogate of quality of surgery, we can consider robotic lobectomy an appropriate procedure which ensures similar result to the open approach.

Keywords Robotic surgery · Lobectomy · Lymph nodes · Nodal upstaging · NSCLC

According to the TNM classification system for non-small cell lung cancer (NSCLC), an accurate staging is mandatory to evaluate prognosis and to plan a multimodality treatment, when it is required. Lymphadenectomy is an important step of the surgical treatment for lung cancer [1].

Currently, open surgery is considered the gold standard for major lung cancer surgery. However, several studies have compared the surgical outcomes of video-assisted thoracic surgery (VATS) versus open surgery, confirming that the minimally invasive technique represents an advantageous approach, particularly in early lung cancer stages, in terms of less post-operative pain, shorter hospitalization, lower incidence of complications, and reduction in peri-operative mortality compared with thoracotomy [2–4]. In robotic surgery, additional advantages are related to a better vision thanks to the 3D vision and magnification of the image, greater range of tools motion, and tremor filtration. All these features enable to perform complex procedures, safely and easily [5, 6].

Despite these advantages, the oncologic outcomes in minimally invasive surgery are still considered a controversial issue. Theoretically, the decreased invasive of mini-invasive technique should have an influence on the radicality of the

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procedure. Several studies analyzed lymphadenectomy during lobectomy to evaluate radicality of surgery in VATS and thoracotomy. Frequently after VATS lobectomy, we observe a lower median number of dissected lymph nodes compared to open surgery, as fewer nodal upstaging, in particular for the N2 group [7–9]. In NSCLC, an adequate lymphadenectomy is essential to prevent understaging, with consequent lack of adjuvant treatment and worsening of prognosis. The most important parameter of positive results in surgery remains the long-term survival outcome. Despite these data, in NSCLC patients treated by VATS, the overall survival and disease-free survival rates are similar to the ones found in open surgery, confirming the effectiveness of the mini-invasive procedure [10–13]. Experience for oncologic results in the robotic treatment of lung cancer is more recent than VATS. Not many large studies on long-term outcomes have been reported, but preliminary data confirm that robotic lobectomy in the treatment of early-stage NSCLC guarantees similar long-term results when compared to VATS and open surgery [14, 15].

In the surgical treatment of lung cancer, the execution of appropriate oncologic resection is necessary, including hilar–mediastinal lymphadenectomy. In fact, lymph nodes upstaging, which is the capacity to histopathologically identify metastatic lymph nodes, otherwise clinically staged as negative, is considered one of the elements of the oncologic radicality of surgical technique. Clinical non-invasive lymph nodes staging, based on pre-operative CT scan and PET, is characterized by limited sensitivity and specificity, which is the reason why after surgical treatment up to 20% of patients can present metastatic lymph nodes [16, 17].

Considering the features of the robotic system, we expect an adequate radicality during robotic lobectomy, thus we analyzed lymphadenectomy and in particular the rate of upstaging in NSCLC patients treated by robotic surgery compared with open surgery.

Materials and methods

We retrospectively analyzed the data of 212 consecutive patients who underwent lobectomy and hilar–mediastinal lymphadenectomy. Between January 2013 and December 2016, 106 of these patients underwent open surgery procedures, whereas the other 106 were operated with robotic technique. All patients had a cN0 NSCLC diagnosis, based on computed tomography (CT) and positron emission tomography (PET) imaging. At the pre-operative staging lymph nodes were considered negative when CT scan showed short-axis < 1 cm and/or when in PET the standardized uptake value was < 3, according to the guidelines of nuclear medicine physicians. In the event of nodes > 1 cm and SUV in PET scan < 3, transbronchial fine needle aspiration, mediastinoscopy, or both were performed to exclude malignancy.

The surgical approach to be used, robot or thoracotomy, was chosen by the individual surgeon. Generally, in our institution, we favor the open lobectomy approach in patients with central lesions, with suspected pleural adhesion or in the absence of interlobar fissure. All robotic lobectomies were performed according to our standard totally endoscopic technique, through four centimetric intercostal incisions, without utility incision in order to optimize CO_2 insufflation (5–8 mmHg). Standard postero-lateral or lateral thoracotomy was performed in all patients who underwent open lobectomy procedure. In all cases, the surgeon explored all the lymph node stations in order to perform a systematic lymphadenectomy.

Information on sex, age, comorbidities, tobacco use (never, past/current smoker), date of surgical procedure, surgical approach, clinical stage, pathological stage, removed lobe, number and station of resected lymph nodes, and histology was collected. The patients were staged according to the guidelines of the 7th Editions of the TNM Staging System for Lung Cancer.

Statistical analysis was performed with SPSS 20 (IBM SPSS Statistics, IBM Corporation, Chicago, IL). Descriptive statistics were calculated and expressed as mean and standard deviation or median and range. Groups were compared using χ^2 for categorical data and t test for continuous variables.

Results

From January 2013 to December 2016, the data of 212 consecutive cN0 NSCLC patients undergoing lobectomy and lymphadenectomy were analyzed. The patients were divided into two groups: 106 patients treated by robotic surgery and 106 patients submitted to open surgery. The two groups having a similar median age, whereas for gender distribution, we observed a smaller number of women in the open technique group (Table 1).

At pre-operative staging, 61 Ia, 37 Ib, 7 IIa, and 1 IIb lung cancers were included to the robotic group, while the neoplasm staging in thoracotomy group was of 43 Ia, 39 Ib, 13 IIa, and 11 IIb.

In the robotic group, 35 left lobectomies and 71 right lobectomies were performed; in thoracotomy group, 42 left lobectomies and 64 right lobectomies were performed by open surgery (Table 1). There were no conversions in robotic group. Post-operative complication was observed in 22 (20.7%) patients of the robotic group (16 cases of prolonged air leaks grade II, 5 atrial fibrillation grade II, 1 chylothorax grade IIIb) and in 24 (22.4%) patients of open group (14 prolonged air leaks grade II, 8 atrial fibrillation

Table 1 Patient characteristics

	All patients (212)	Open (106)	Robot (106)	*p* Value
Median age (range)	70 years (48–85)	71 years (51–85)	70 years (48–84)	0.171*
Gender (%)	139 M (65.6), 73 F (34.4)	77 M (72.6), 29 F (27.4)	62 M (58.5), 44 F (41.5)	0.030[a]
Lobe (%)				0.483[a]
RUL	88 (41.5)	42 (29.6)	46 (43.4)	
ML	18 (8.5)	9 (8.5)	9 (8.5)	
RLL	29 (13.7)	13 (12.3)	16 (15.1)	
LUL	43 (20.3)	20 (18.9)	23 (21.7)	
LLL	34 (16)	22 (20.8)	12 (11.3)	
Side (%)	R 135 (63.7), L 77 (36.3)	R 64 (60.4), L 42 (39.6)	R 71 (67), L 35 (33)	0.317[a]
Median dimension (range)	3 cm (0.6–12.5)	3.45 cm (1–12)	2.8 cm (0.6–7.50)	0.001*
Dimension > 3 cm (%)	103 (48.6)	60 (56.6)	43 (40.6)	0.019[a]

*Chi-square test

[a]ANOVA test

Table 2 Histopathological characteristics

	All patients	Open	Robot	*p* Value
Histology (%)				0.001[a]
Adeno	146 (68.9)	58 (54.7)	88 (83)	
Squamous	55 (25.9)	38 (35.8)	17 (16)	
Adeno/squamous	5 (2.4)	5 (4.7)	0 (0)	
Other	6 (2.8)	5 (4.7)	1 (0.5)	
pT (%)				0.007[a]
1a	43 (20.3)	15 (14.2)	28 (26.4)	
1b	24 (11.3)	13 (12.3)	11 (10.4)	
2a	99 (46.7)	46 (43.4)	53 (50)	
2b	15 (7.1)	8 (7.5)	7 (6.6)	
3	31 (14.6)	24 (22.6)	7 (6.6)	
pN (%)				0.111[a]
N0	171 (80.7)	87 (82.1)	84 (79.2)	
N1	28 (13.2)	16 (15.1)	12 (11.3)	
N2	13 (6.1)	3 (2.8)	10 (9.4)	

[a]Chi-square test

Table 3 Clinical and pathological staging

	All patients	Open	Robot	*p* Value
cStage (%)				0.019[a]
1a	106 (50)	44 (41.5)	62 (58.5)	
1b	71 (33.5)	36 (34)	35 (33)	
2a	20 (9.4)	13 (12.3)	7 (6.6)	
2b	14 (6.6)	12 (11.3)	2 (1.8)	
3a	1 (0.5)	1 (0.9)	0 (0)	
pStage (%)				0.062[a]
1a	60 (28.3)	27 (25.5)	33 (31.1)	
1b	73 (34.4)	33 (31.1)	40 (37.7)	
2a	36 (17)	20 (18.9)	16 (15.1)	
2b	27 (12.7)	20 (18.9)	7 (6.6)	
3a	16 (7.5)	6 (5.7)	10 (4.7)	

[a]Chi-square test

grade II, 4 anemia grade II). No complication occurred during surgical procedures in neither group.

We observed a higher number of adenocarcinoma in the robotic group than in the thoracotomy group. Specifically, in the robotic group, the histological diagnosis was of 88 (83%) cases of adenocarcinoma, 17 (16%) cases of squamous carcinoma, and 1 (0.5%) case of large cell carcinoma. In the open group, adenocarcinoma was diagnosed in 58 (54.7%) cases, squamous carcinoma in 38 (35.8%) cases, and in 10 (9.4%) patients other histotypes (4 large cell carcinomas, 5 adenosquamous, 1 adenoid cystic carcinoma) were found. (Table 2).

The median size of the pulmonary lesions was 2.8 cm (range 0.6–7.5) in the robotic group and 3.45 cm (range 1–12) in the open group.

The pathological stages found in patients who underwent robotic lobectomy were 33 Ia (31.1%), 40 Ib (37.7%), 16 IIa (15.1%), 7 IIb (6.6), and 10 IIIa (4.7%), while in the thoracotomy approach group, we observed 27 Ia (25.5%), 33 Ib (31.1%), 20 IIa (18.9%), 20 IIb (18.9%), and 6 IIIa (5.7%) (Table 3).

In all cases, the lymph nodes located in the proximity of the hilum and in the mediastinum were checked and, when present, removed. The number of lymph nodes removed during lobectomy was similar, independently of the surgical approach used. In particular, in the robotic lobectomy, the mean number of removed lymph nodes was 14.42 (±6.99), while during open surgery was 14.32 (±7.34). The number

of nodal stations according to Naruke map in robotic procedure was higher than in open procedures (4.95 vs. 4.22), as well as the mediastinal stations (3.13 vs. 2.27). The analysis of the mean number of removed nodal stations and particularly of the mediastinal stations shows a statistically significant difference (Table 4).

The percentage of nodal upstaging in patients from the two group was similar, although in the robotic group, a higher percentage of patients presented an upstaging from N0 to N2, with a statistically significant difference. Nodal upstaging was observed in 22 cases of robotic approach group, in detail in 12 (11.3%) patients to N1 and in 10 (9.4%) patients to N2. In the open group, the upstaging was reported in 19 patients, in 16 (15.1%) cases to N1, and in 3 (2.8%) to N2 (Table 5).

Table 5 Nodal upstaging

	All patients	Open	Robot	*p* Value
Pathological upstage (%)	52 (24.5)	24 (22.6)	28 (26.4)	0.523[a]
Nodal upstage (%)	41 (19.3)	19 (17.9)	22 (20.8)	0.602[a]
Hilar upstage (%)	28 (13.2)	16 (15.1)	12 (11.3)	0.417[a]
Mediastinal upstage (%)	13 (6.1)	3 (2.8)	10 (9.4)	0.045[a]

[a]Chi-square test

Discussion

Robotic surgery is being affirmed as a feasible and reliable surgical approach for the treatment of lung cancer. The robotic system** thanks to its features, 3D vision associated with the capacity of magnifying images 10–15 times normal and a greater range of movements and tremor filtration, allows the surgeon to perform anatomical lung resection with exceptional precision and safety. From 2002, several studies have shown the benefits of robotic technology in the surgical treatment of lung cancer. Robotic major lung resections are associated with short duration of chest tube application, minimal post-operative pain with good quality of life, reduction of hospitalization, low percentage of perioperative complication, and mortality [6, 18]. Data on oncologic follow-up in patients with NSCLC treated by robotic surgery show that the results on local, systemic recurrence, and overall 5 years of survival are concordant with outcomes of NSCLC treated by traditional open surgery. However, utilization of robotic system in thoracic surgery is recent and only a few studies have analyzed recurrences and long-term survival of patients with lung cancer who underwent robotic pulmonary surgery [19, 20].

Usually, the quality of lymphadenectomy, consisting in the number of lymph nodes removed, is considered an indirect indicator of the oncologic radicality of the lung cancer surgical resection. In 2011, Cerfolio et al. compared the number of nodes removed during robotic lobectomy and open lobectomy, achieving a similar number of dissected lymph nodes from the hilum and mediastinal stations [21]. Robotic lymphadenectomy, differently from VATS, appears to guarantee greater radicality during the exeresis of regional lymph nodes, thanks to the better vision and maneuverability of instruments. A specific element of the radicality of oncologic surgery is represented by the lymph nodal upstaging, consisting in the possibility of detecting unknown metastasis in nodes. Several authors reported their experience on the analysis of lymph nodal upstaging in VATS procedures and thoracotomic resections, which is the gold standard approach in lung cancer. In most cases, the studies reported a lower rate of upstaging in VATS group. D'Amico et al. evaluated 199 patients who underwent VATS lobectomy and 189 open lobectomy patients observing upstaging to N1/N2 in 8.8% of the patients in the VATS group and in 14.5% of cases [22] in the open group. Moreover, Licht in the evaluation of 1513 lobectomies for clinical stage I NSCLC performed by VATS or open surgery, confirms lower upstaging in VATS group when compared to the thoracotomy group (11.9 vs. 24.6%), albeit the similar mean number of dissected lymph node stations no difference in survival was observed between two groups [23]. Conversely, some authors report a different experience, Boffa et al. in a report of 11,500 anatomic lung cancer resection from the Society of Thoracic Surgeon database revealed a similar lymph nodal upstaging after VATS and open surgery (11.6 vs. 14.3%) [24]. An important aspect of comparison of lymph nodal dissection by VATS and open surgery is the evidence of superior number of mediastinal nodes removed during thoracotomic procedures, probably due to the greater difficulty encountered to

Table 4 Nodal dissection details

	All patients	Open	Robot	*p* Value
Mean of lymph nodes removed (±SD)	14.37 (±7.36)	14.32 (±7.34)	14.42 (±6.99)	0.926[a]
Mean of removed nodal station (±SD)	4.58 (±1.44)	4.22 (±1.58)	4.95 (±1.2)	0.001*
Mean of mediastinal station (±SD)	2.7 (±1.24)	2.27 (±1.21)	3.13 (±1.11)	0.001*

*Chi-square test

[a]ANOVA test

reach comfortably all mediastinal areas with thoracoscopic instruments [25]. Dissimilar results in comparative studies about VATS and thoracotomic lymphadenectomy could be directly correlated with different levels of skills and expertise of the surgeon.

The first experience of analysis of upstaging, in patients with clinical stage I NSCLC, which underwent robotic segmentectomies or lobectomies was reported by Wilson. In his multiple institutions study, upstaging was observed in 10.9% of cases, especially in those patients with larger lung tumor [26]. These data were consistent with that reported by Lazar et al., that observed in 100 patients an upstaging rate of 10% [27]. A higher percentage of nodal upstaging (26.9%) was described by Toosi et al. analyzing 249 stage pI–pIV patients. The mean number of resected lymph node was 13.9 (±0.4) and the checked nodal stations were 5.5 (±0.1) [28] .

We compared the rate of nodal upstaging after robotic and thoracotomic surgery, with a greater rate of upstaged cases in the robotic group, this was due, in particular, to the detection of metastatic mediastinal lymph nodes. Furthermore, we observed a high number of dissected lymph nodes during robotic lobectomy, confirming the feasibility to perform complete lymph nodal dissection by this approach. Thanks to the robotic technology, the surgeon can reach all mediastinal stations comfortably. The large range of instruments' maneuverability and optimal 3D vision, characterized by zoom ×10 of image is useful to visualize and remove even the smaller nodes located in deeper areas. Furthermore, by using robotic system, it is possible to perform also more complex cases, surgeon can perform the procedure in a safe manner also in the case of node without a clear cleavage plane or in the event of neo-adjuvant treatment resulting in a scared tissue.

Despite the consecutive enrolment of patients in this study, we observed differences in patient demographics, tumor staging, and histopathology between the two groups, representing a limitation for this study. But when we analyzed lymph node dissection, we observed similar data in the two groups (robot vs. open) in terms of total number of nodes, confirming the accuracy in nodal dissection in both groups. We observed similar data in the two groups (robot vs. open) concerning lymph node dissection, in terms of total number of nodes, confirming the accuracy in nodal dissection in both groups. Moreover, we noticed a statistically significant higher number of total harvested stations and of mediastinal stations assessed during robotic procedures when compared to open surgery, probably linked to the greater complexity to perform nodal dissection in the uncomfortable mediastinal area through the open access, due to more limited vision. Robotic technology allows to perform lobectomy following similar steps to open surgery, whereas in VATS there are several different techniques adopted to reach the hilum and mediastinum and this could explain the differences found in nodal dissection and upstaging. The opportunity to have an accurate lymph nodal dissection, also in case of pathological nodes, permits to enlarge the indications for robotic lobectomy for more advanced stages of lung cancer, even after neo-adjuvant chemotherapy or radiotherapy, not limiting its application only to early-stage NSCLC.

To confirm our promising experience, further studies are necessary to evaluate the feasibility, safety, and radicality of anatomical robot-assisted resections in NSCLC.

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Compliance with ethical standards

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