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ROBOTIC APPROACH IN THE TREATMENT OF LOCALLY ADVANCED (STAGE IIIA-pN2) NON SMALL CELL LUNG CANCER AFTER INDUCTION THERAPY

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Summary

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Abbreviations

- NSCLC - Non Small Cell Lung Cancer
- SCLC - Small Cell Lung Cancer
- PET - Positron Emission Tomography
- VATS - Video-Assisted Thoracoscopic Surgery
- TBNA - Transbronchial Needle Aspiration
- BAL - Bronchoalveolar lavage
- EBUS - Endobronchial Ultrasound
- EUS - Endoscopic Ultra Sound
- ROSE - Rapid On-Site Evaluation
- PS - Performance Status
- GGO - Ground Glass Opacities
- CT - Chemotherapy
- RT – Radiotherapy

ABSTRACT

Introduction: Despite there are already many studies on robotic surgery as minimally invasive approach for non-small cell lung cancer (NSCLC) patients, the use of this technique for stage III disease is still poorly described. These are the preliminary results of our prospective study on safety and effectiveness of robotic approach in patients with locally advanced NSCLC, in terms of postoperative complications and oncological outcome.

Methods: Since 2016, we prospectively investigated, using standardized questionnaire and protocol, 21 consecutive patients with NSCLC stage IIIA-pN2 (diagnosed by EBUS-TBNA) who underwent lobectomy and radical lymph node dissection with robotic approach after induction treatment. Then, we performed a matched case-control study with 54 patients treated with open surgery during the same period of time, with similar age, clinical and pathological tumor stage.

Results: The individual matched population was composed of 14 robot-assisted thoracic surgery and 14 patients who underwent open surgery. The median time range of resection was inferior in the open group compared to robotic lobectomy (148 vs 229 minutes; P=0.002). Lymph nodes resection and positivity were not statistically significantly different (p=0.66 and p=0.73 respectively). No difference was observed also for PFS (P=0.99) or OS (P=0.94).

Conclusions: Our preliminary results demonstrated that the early outcomes and oncological results of N2-patients after robotic lobectomy were similar to open surgery. Considering the advantages of minimally invasive surgery, robotic assisted lobectomy should be a safe approach also to patients with local advanced disease.

INTRODUCTION

I. The Minimally Invasive Surgery: A New Era

The minimally invasive approach in thoracic surgery has proven advantages in terms of reduced postoperative pain, shorter immune response, quicker resumption of daily activities, and better aesthetic and functional result [1–5]. The minimally invasive surgery despite it is recognized, as the majority of thoracic surgeons has, not embraced an effective procedure for the treatment of initial localized non-small-cell lung cancer (NSCLC). This slowness in the diffusion of the technique could be attributed to some reasons, such as the technical difficulty of the method, the long-lasting learning curve and, probably, the difficulties involved in the implementation of the radical mediastinal lymphadenectomy, which is the standard procedure in the treatment of lung cancer [6–11]. The result of this situation is that a large part of thoracic surgeons still prefers an open traditional approach to perform a lung anatomical resection (lobectomy or segmentectomy).

Despite minimally invasive approach in thoracic surgery has already proven advantages in terms of reduced postoperative pain, shorter immune response, quicker resumption of daily activities, and better aesthetic and functional result [12], video-assisted thoracic surgery (VATS) lobectomy is slowly becoming the standard approach to early-stage lung cancer treatment. This was probably related to technical limitations, such as two-dimensional vision, lack of instrument flexibility with difficult hand-eye coordination and long-lasting learning curve, in particular performing radical mediastinal lymphadenectomy, which is the standard treatment for lung cancer [2–4] and highly related to the long –term outcome. To address the limitations of conventional VATS, a tele surgical system was developed offering surgeons the benefits of three-dimensional high-definition imaging, greater hand movements using wristed instruments, and a computer-assisted scaling down of motion with reduction of hand-related tremors (da

Vinci system, Intuitive Surgical, Sunnyvale, CA, USA): an innovative approach to lung cancer resection and staging, with a more precise dissection and theoretically better oncological results. Among the advantages of minimally invasive approach over tradition thoracotomy, we know that traditional open techniques have significant effects on the immune system. In particular, the surgical trauma causes an inflammatory condition characterized by the release of pro-inflammatory cytokines and acute phase proteins. Surgical manipulation also exerts a depressing cell-mediated immunity, which is manifested through the alteration in the cell, activation and function of lymphocytes and monocytes. The magnitude of these effects is proportional to the extent of the surgical procedure [13].

Although it is still controversial in literature, a reasonable number of experimental and basic studies support the notion that the minimally invasive surgery is associated with a lower immunosuppressive effect. One possible clinical consequence of the observed immunological changes can be the significant improved cancer specific survival of patients treated with VATS lobectomies compared to thoracotomies [13].

II. Robotic-Assisted Surgery

Robot-assisted thoracic surgery (RATS) has been introduced in the operating room for pulmonary resection only in 2002, and it could be considered a new minimally invasive approach for lung lobectomy. The first preliminary reports on pulmonary resection performed by RATS were published by Melfi in 2002 and Giulianotti in 2003, showing the clinical feasibility of the technique with encouraging results [14,15]. Then, feasibility and safety of the robotic technique were confirmed by other early publications including that published in 2006 by Park [6] on 34 lung cancer lobectomies and another study published in 2010 by Giulianotti [16] regarding 38 lung resections. Afterwards, Melfi [9] was the first to describe a series of 107 robotic lung lobectomies with lymphadenectomy performed in oncologic patients, with acceptable results in terms of complications, conversions and length of surgery.

Since then, robotic resection started gaining popularity and to be accepted in the thoracic community as one of the possible minimally invasive techniques. Indeed, according to the Nationwide Inpatient Sample (NIS) database [17] published by Paul in 2014, the number of centers performing RATS lobectomy and the rate of RATS compare to all lobectomies per center increased dramatically in the last ten years. The percentage of robotic lobectomies performed per year in US went from 1% in 2008 to 48.8% in 2011, compare to a stable proportion of VATS lobectomy which have been maintained around 20-30% over the years.

III. Robotic Technology

So far, the Da Vinci Surgical System is the only robotic system approved and available on market for RATS. Da Vinci Surgical System is composed by a surgeon console, patient-side cart, EndoWrist instruments, and vision system. The surgeon operates seated comfortably at a console which is positioned in close proximity to the robotic unit. The surgeon controls the da Vinci System using his or her hands, via “master” instruments at the console, and the system seamlessly translates the surgeon's hand, wrist and finger movements into precise, real-time movements of surgical instruments inserted into the patient’s body via small incisions. The EndoWrist instruments attached to the arms of the patient-side cart bend and rotate with wide range of high-precision movements (seven degrees of motion), which is even greater than the human wrist, and with the hand tremor filter. The robotic arms move around fixed pivot points to minimize stress on the thoracic wall during manipulations. The stereo-endoscope positioned in one of the robot arms allowed the surgeon to have a magnified, high-definition and three-dimensional view of the operating field via a console binoculars. The console also has foot pedals that allow the surgeon to engage and disengage the robotic arms, to guide the camera, and to activate electric cautery.

With the introduction in 2014 of the last generation system (da Vinci XI), some technical issues have been improved. First of all, a simpler docking due to a better maneuverability of the cart, improved by "port placement" menu and laser guidance in addition to the improved design of the arms, allows placement of the ports relatively close together reducing the risk of arm collision. Another important improvement is the possibility to use the EndoWrist Vessel Sealer as well as the EndoWrist Stapler (30 mm and 45 mm) entirely controlled by surgeon's hands through the da Vinci Xi System. Lastly, the thoracoscope has a lighter and digital end-mounted camera with autofocus for an improved crystal clear vision, and it could be placed on any robotic arms.

Figure 1. Robotic positioning. From [18].

IV. Robotic Assisted Lobectomy and Lymphadenectomy: Different Approaches

Lobectomy associated to a radical lymphadenectomy is considered the gold standard therapy for patients with early stage NSCLC [12]. With the ever-expanding screening programs as well as the greater attention of patients to their health, the number of lung cancer in the early stage is gradually increased, and associated to the development of new surgical techniques has progressively led pulmonary surgery to become less and less invasive.

During the last decade, different robotic approaches have been described on performing a lung resection ranging from the use of 3 or 4 robotic arms, utility incision or CO_2 insufflation, and different port placement. To describe these approaches without being confusing, we decided to group them based on the use of utility incision (not completely portal lobectomy) or not (completely portal robotic lobectomy-CPRL), highlighting the evolution and the changes of the robotic technique based on the surgeon's experience over the years, as well as their short and long term results.

a. *Not completely portal robotic lobectomy (with utility incision)*

In 2006, Park [6] was the first to describe a 3-arm robotic approach with a non-rib-spreading utility incision, usually of 3–4 cm in the 4th or 5th intercostal space on the mid axillary line, and the use of two other trocars for the camera port (7th or 8th intercostal space at the posterior axillary line) and for the second instrument (above the diaphragm behind the tip of the scapula), respectively (Figure 2).

Figure 2. Port placement and patient position for the 3-arm not completely portal robotic approach. From [12].

This robotic approach mimed their VATS lobectomy technique in term of patient and trocars position, other than anterior to posterior hilar vessels and bronchi dissection with the completion of the fissure as the last step, just before the removal of the specimen; CO_2 insufflation was not needed, the robot was positioned at the head of the patient (45° angle respecting the long axis of the patient) and 30° camera was used. The results of Park preliminary study demonstrated that RATS was feasible and safe with 12% of conversion rate, higher than those reported in the contemporary largest series of VATS lobectomy but acceptable considering the early experience, with 4.5 days post-operatively length of stay, and no in-hospital or 30-day mortalities; besides, all patients had a R0 resection, with a median of 4 lymph node stations resected.

In 2010, Veronesi and Melfi [7] modified the 3-arm robotic approach described by Park introducing the use of a fourth robotic arm, positioned posteriorly in 7th intercostal space (auscultator triangle), to held the lung parenchyma in a fixed position, posteriorly, and have a better vision of the surgical field; 3 cm utility incision was performed at the 4th or 5th intercostal space, anteriorly, the camera port was positioned in 7th or 8th intercostal space on the mid-axillary line, and another port at the 7th or 8th intercostal space in the posterior axillary line (Figure 3).

Figure 3. Port placement and patient position for the 4-arm not completely portal robotic approach. The red circle indicates the 3-cm utility incision. From [12].

This 4-arm robotic lobectomy approach, always using 3 cm utility incision, was investigated by Veronesi on 54 patients between 2006 and 2008, and compare to the same number of patients having open lobectomy, using a propensity scores match showing a 13% of conversion rate, 4.5 days of post-operatively length of stay for RATS vs. 6 days for open surgery, and no difference in term of post-operative morbidity and mortality, and lymph nodes removed.

Since then, we always used the same 4-arm non-completely portal robotic approach performing 339 robotic anatomical lung resection (307 lobectomies, 29, segmentectomies and 3 pneumonectomies) with 6.5% of conversion rate, 5 days of postoperatively length of stay, no in-hospital or 30-day mortalities, and a median of 5 lymph node stations removed [data presented at 31th EACTS meeting, Vienna 2017]. The portal placement did not change with the type of resection or the side, and with the different robotic system (S, SI and XI).

However, with the introduction of the new da Vinci XI robotic system in 2015, some technical changes were made: 1) the surgical cart was docked from the left side of the patient either for right or left thoracic procedures thanks to the technical innovation of the new robotic system which displaced the robotic arms correctly despite its side position; 2) the new system allowed us to work with a minimum distance of 4 cm between the ports, without respecting a particular distance between the ports; 3) the camera could be moved between two different ports allowing a better view; 4) the use of the EndoWrist stapler (30 vascular and 30 or 45 parenchyma) which could be placed through a 12-mm port, as previously reported [19].

In this group of not completely portal lobectomy we included also the hybrid technique described by Gharagozloo in 2008 [20]. This approach involved the use of the Robot for the hilar and mediastinal dissection (vessels, bronchi and lymph nodes) and the use of VATS technique (when the robot is removed, and the surgeon is back to the operating table) for the vascular, parenchymal, and bronchial division; usually three 2-cm incisions were performed using a non-trocar technique, other than an additional 1- to 2-cm incision anteriorly for the endoscopic retractor and the chest tube at the end of the surgery [18]. The author published 100 consecutive cases in 2009 showing no conversion rate, a median hospitalization of 4 days, 21% of post-operative morbidity with 3 post-operative death (3%) during the first 20 cases, (not due to the robotic technique but to a poor lung function of the patients), and concluded that robot assistance may facilitated nodal and vascular dissection during VATS lobectomy, even if increasing the complexity and the length of the procedure [20].

→ WHY UTILITY INCISION?

a) To extract the specimens such as lymph nodes during the lymphadenectomy or the lung at the end of the surgery

b) To introduce small gauzes and suction instrument in case of bleeding

c) To palpate the nodule in case of wedge resection performed before lobectomy

b. Completely portal robotic lobectomy

Ninan and Dylewski in 2010 [21] reported the effectiveness of a completely portal robotic lobectomy using 3 arms (CPRL-3) without the need of utility incision. Robotic camera port for a 0° camera was placed in the 5th or 6th intercostal space along the major pulmonary fissure and two other ports were then placed in the same intercostal space anteriorly and posteriorly, to reduce intercostal neurovascular injuries. An utility 7-mm port was inserted anteriorly at the tip of the 11th rib on the anterior abdominal wall, and tunneled over the top of the 10th rib to place a 5-mm camera for the initial exploration of the thoracic cavity and for guiding the port placement; during surgery the utility access was used for suctioning and passages of staplers, and at the end of the surgery for removing the specimen, enlarging it to 3-4 cm (Figure 4).

Figure 4. Port placement and patient position for CPRL-3. From [12].

CO_2 insufflation was used to move the diaphragm inferiorly facilitating the use of the utility access. In 2011, Dylewsky [21] described 200 consecutive patients underwent anatomical lung resection using this completely portal robotic approach showing the safeness and feasibility of this technique: only 3 (1.5%) conversion to thoracotomy, a median length of stay of 3 days, a 60-day mortality and morbidity of 2% and 26%, respectively; though, the number of lymph node or the lymph node station removed was not reported.

In 2011, Cerfolio [11] described a new CPRL with 4 robotic arms technique (CPRL-4). In this new approach, all the 4 ports were placed along the 7th intercostal space between mid-axillary line, or as anteriorly as possible, and 2-3 cm lateral to the spinous process of the vertebral bodies always keeping 9-10 cm of distance between the ports; an access port was then place 2-3 ribs lower to give more working space to the assistant surgeon (Figure 5).

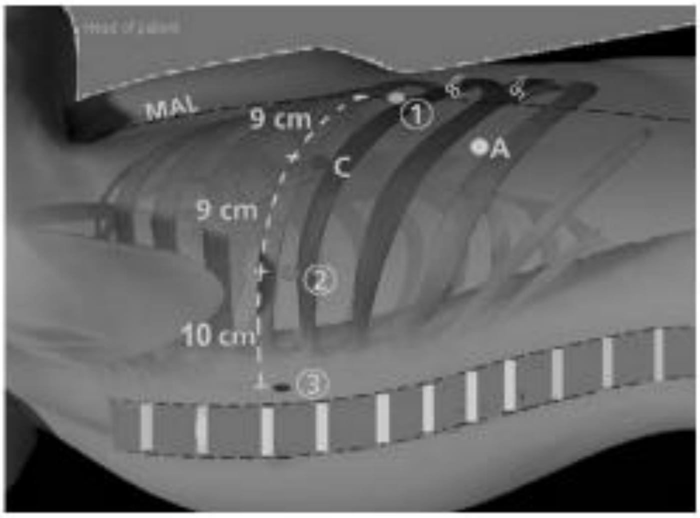

Figure 5. Port placement and patient position for CPRL-4. C, the camera port; the circled number 1, 2, 3 are the robotic arms; A, access port (the camera, the access port, and the site for robotic arm 1 always form an isosceles triangle to have a greatest working area for the assistant). From [12].

Even in this CPRL-4, CO_2 insufflation and 0° camera were used. Cerfolio demonstrated that the new CPRL-4 was safe and allowed R0 resection with complete lymph node removal (median of 5 N2, 3 N1 nodal stations, 17 lymph nodes removed). CPRL-4 was associated with lower post-operative morbidity and mortality, shorter length of stay, and a better quality of life than thoracotomy, with a conversion rate of 12% (13/106).

→ WHY CO_2 INSUFFLATION?

a) to move the diaphragm inferiorly, creating more working space for the assistant through utility port

b) to facilitate the hilar dissection unsticking the tissue with the CO_2 pressure

c) to squeeze the lung in case of incomplete pulmonary exclusion

V. Robotic Surgery in Locally Advanced NSCLC

The commonly accepted indications for minimally invasive approach in lung cancers with either VATS or RATS, are localized stage I or II disease [22]. Despite in literature there are only few studies on the use of robotic surgery in patients with both initial and locally advanced NSCLC [19,23–26], the results of this kind approach specifically for stage III disease after induction treatment (IT) is still poorly described.

Cerfolio in 2011 [11], using a propensity score matched 106 consecutive patients who received robotic lobectomy to 318 patients who received open rib and nerve-sparing lobectomy. The robotic group had numerically lower morbidity and mortality (0% vs. 3.1%), significantly better mental QOL and significantly shorter hospital stay (2.0 vs. 4.0 days). However, operating time was significantly longer with the robotic approach (2.2 vs. 1.5 hours). In this study, cases with larger tumors, hilar node involvement, or previous chemo radiation for nodal involvement were not excluded, amounting to enlarged indications for minimally invasive lung cancer resection, and the authors commented that the robot made it possible to perform an “outstanding” node dissection.

Veronesi et al. recently published a retrospective multicenter study describing one of the largest series of patients (n=223) with pN2 NSCLC and carcinoid undergoing RATS [13]. In this retrospective study the author showed acceptable perioperative outcomes with only 2.7% of converted cases to open surgery due to bleeding demonstrating the safety and feasibility of the procedure, even in patients underwent induction chemotherapy. One of the major difficulty related to RATS is the lack of perception that can make surgery particularly challenging especially in the case of chemotherapy or radiotherapy, with higher risk of intra operative complications. However, in this series they highlighted that large tumor size and >2 positive lymph nodes were associated with higher risk of conversion to open surgery despite unexpected mediastinal nodal invasion as well as pre-operative treatments were not the major cause of thoracotomy conversion. In this important series, the estimated 3-year survival in NSCLC patients was 61.2%, showing an excellent oncological result even if it could be related by the fact that most of the patients (n=142/223; 63%) had occult N2 disease and only 34 (15%) patients underwent induction therapy.

Also in our recent series of 339 patients who underwent RATS for clinical stages I-II NSCLC, we showed an excellent overall lymph node upstaging (17.6%) and 58% of 5-year stage specific survival for occult pN2 patients (n=28) confirming that mediastinal lymph node dissection during RATS adequately assesses lymph node stations leading to excellent oncologic results [12].

A potential advantage of the use of this approach over traditional VATS is the increased “radicality” obtained with RATS while the benefit over open thoracotomy are related to the improved “tolerability” of surgical trauma in fragile patients when surgery is delivered after induction treatment. In addition, a potential oncological benefit can be obtained with the reduced immune system activation.

AIM OF THE STUDY

This is a prospective multicenter study in which consecutive patients with NSCLC stage IIIA-pN2 (diagnosed by EBUS-TBNA) undergoing lobectomy and radical lymph node dissection with robotic approach with radical intent after IT will be investigated using standardized questionnaire and protocol. The aim of this prospective study is to assess the safety and effectiveness of robotic approach in patients with locally advanced NSCLC in terms of postoperative complications and oncological outcome.

MATERIAL AND METHODS

I. Study design

This study is a prospective study in which consecutive patients with NSCLC stage IIIA-pN2 (diagnosed by EBUS-TBNA) undergoing lobectomy and radical lymph node dissection with robotic approach after IT will be investigated using standardized questionnaire and protocol. IEO Ethical Committee has approved and deliberated the study on February 2017 (IEO 560).

On September 2019, the study became multicenter including the Division of Thoracic Surgery of Pisa (Azienda Ospedaliera Universitaria Pisana, responsible Prof. Franca Melfi).

II. Timing

The primary end point of the study will include the evaluation of in-hospital morbidity (minor and major complication) and mortality, and peri- and post-operative outcomes, including operating time, amount of bleeding, duration of thoracic drainage, and the days of hospitalization.

The secondary endpoints will be overall and disease specific survival at 12, 24 and 36 months and the percentage of patients with local and distant recurrence.

All the outcomes will be compare to the European Institute of Oncology and the literature results of alternative procedures such as open surgery and other minimal invasive approaches (e.g. VATS).

III. Enrollment criteria

Inclusion criteria:

- Patients with diagnosis of NSCLC stage IIIA for mediastinal ipsilateral lymph node involvement (N2) with pathological confirmation of nodal involvement by EBUS-TBNA
- Patients underwent platinum-based induction chemotherapy (at least 2-3 cycles) or molecular therapy in patients with EGFR mutation (exon 19-20)
- All patients have to be staged by total body CT scan and PET-FDG
- No distant metastasis clinically evident
- No severe cardiopathy or other severe co-morbidity
- FEV1 >60%, FVC>60%
- Age between 18 and 75 years old

Exclusion criteria:

- Patients with progression after IT (bulky N2 or infiltration of surrounding mediastinal structures, N3 disease or distant metastasis)
- Patients unfit for surgery
- Previous thoracic surgery on the same side.
- Pneumonectomy as primary aim.

IV. Clinical Evaluation and Procedures

a. *Pre-operative evaluation*

Preoperative evaluation will include staging exams such as chest CT scan and PET scan. Standard functional evaluation will include ECG, cardiological evaluation, PFT and anesthesia evaluation. When required by the physician additional tests can be introduced as stress test, heart ultrasound, and pulmonary scintigraphy. Staging and functional exam should be done after induction chemotherapy and within 5 weeks from surgery.

b. Surgery

All patients underwent anatomical lung resection and radical lymphadenectomy. Systematic lymph node dissection according to the classification of the American Thoracic Society was performed in all patients removing all lymphatic tissue from stations 2R, 4R, 7 and 10R for right-sided tumors and from stations 5, 6, 7 and 10L for left-sided tumors.

c. Operative technique of RATS lobectomy

The patient is positioned in a lateral decubitus. The patient is prepared and draped with the arm down but if conversion to open surgery is necessary, the arm is moved up and a lateral muscle-sparing thoracotomy performed. The robot is positioned at the head of the patient. The approach includes three port incisions and a 3 cm utility thoracotomy in the IV intercostal space anteriorly, with no rib spreading. The camera is introduced in the VII intercostal space on the mid axillary line. The robotic instruments are introduced through the utility incision anteriorly and through the two posterior ports in the VIII and VII intercostal spaces, respectively. The robot is driven over the patient's shoulder on a 15° angle and attached to the 4 ports. The ports are standard for all lobectomies except that, on the right side, the camera port through the seventh intercostal space is in the mid-axillary line, whereas on the left side this port is moved 2 cm posteriorly (compared with the right) to avoid the heart obscuring vision of hilar structures. Pulmonary arterial branches, vein and bronchus were separated using a mechanical robotic stapler (EndoGIA 30 or 45 vascular and 30 or 45 parenchyma).

d. Post-intervention and follow-up period

Patients were admitted to a high dependency unit for 1 days following surgery only if required by the anesthesiologist based on ASA score. Post-operative pain control during the hospital stay was managed with patient-controlled morphine administration supplemented with intra venous analgesia. Oral analgesia was subsequently used when patient is discharged.

Patients will be followed with a physical exam, chest X-ray and blood tests at 1 month after surgery and with a physical exams plus CT scan of the chest and upper abdomen every 4 months for 3 years, then every 6 months until the fifth year, and annually after 5 year.

Recurrence in the site of surgery, in the thorax region (omo- and contralateral) and metastasis outside the region were recorded and classified as follow: local, regional and distant respectively.

V. Ethical consideration

This study is conducted in agreement with the Declaration of Helsinki. The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (ref: http.//www.ifpma.org/pdfifpma/e6.pdf).

A sequential identification number will be automatically attributed to each patients enrolled in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patients initials (maximum of 4 letters), and year of birth will also be reported on the case report forms.

All patients will be informed of the aims of the study, the procedures and possible hazards to which they will be exposed, and the study procedures. They will be informed as to the strict confidentiality of their patient data, but that authorized individuals other than their treating physician may review their medical records for trial purposes. The patient's informed consent statement is given at the end of the protocol. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are enrolled. The informed consent procedure must conform to the ICH guidelines on Good Clinical Practice.

This implies that “the written informed consent form should be signed and personally dated by the patient or by the patient’s legally acceptable representative”.

VI. Statistical analysis

The evaluation of primary end points (in-hospital morbidity and mortality, and peri and post-operative outcomes, including operating time, amount of bleeding, duration of thoracic drainage, and the days of hospitalization) will be made using descriptive statistics (i.e. percentage with 95% confidence intervals for categorical variables, mean +/- standard deviation, median and range for continuous variables).

Survival analysis using Kaplan-Meier curve and cumulative incidence analysis will evaluate the secondary endpoints (overall and disease specific survival, development of local and distant relapses).

In order to evaluate the outcome, we performed a matched case-control study: patients who had RATS lobectomy were individually matched with patients treated with open surgery. Due to heterogeneity in thoracotomy patients and considering that, in the last years we have increased our experience in RATS for advanced staged, we have matched the patients who had the same similar clinical stage, age and pathological tumor stage to avoid any bias. The McNemar test of symmetry and the non-parametric sign rank test were used to assess differences in the distribution of categorical and continuous characteristics between the 2 paired groups. The log-rank test and Gray’s test, respectively, were used to assess differences in overall survival (OS) and the progression-free survival (PFS) between the 2 groups. All analyses were 2-tailed; P-values vas considered significant when p> 0.05.

RESULTS

Since February 2017, at our Division of Thoracic Surgery 1225 patients underwent anatomical lung resection (960 lobectomies, 38 bilobectomies, 94 pneumonectomies, and 33 segmentectomies) for NSCLC. Two hundred patients out of 1225 (16.3%) underwent anatomical lung resection after IT.

Since 2006, when the Robotic Program started at our Institute, we performed 24 anatomical surgical resection using RATS. Among these patients 18 were enrolled into the study (since February 2017). Then, one patient was excluded from the study because he did not have a complete mediastinal invasive staging before chemotherapy. Since September 2019, the external center (Azienda Ospedaliera Universitaria Pisana) enrolled 4 patients.

Thus, the analysis was performed on 21 patients, who matched the inclusion criteria.

I. Demographic-clinical characteristics

Clinical-demographic characteristics of the 21 patients enrolled are shown in Table 1. The median age was 66 years (range 45-78 years), and a total of 10 males (47.6%). Nine (42.8%) patients were smoker, one (4.7%) non-smoker, and 11 (52.3%) former smokers.

Ten (47.6%) patients did not have any comorbidity, whereas eight (38.0%) patients had cardiovascular disease (i.e. atrial fibrillation, hypertensions), one (4.7%) pulmonary conditions (i.e. BPCO), and two diabetes (9.5%).

Based on clinical staging with CT scan and PET, all patients underwent EBUS-TBNA mediastinal staging in case of suspected mediastinal lymph node involvement. At least one lymph nodes station resulted positive in all patients, with station #7 and #4R the most represented. The final clinical stage was IIIA in 17 (81.0%) patients, IIIB in 4 (19.0%) cases.

The histology was mostly adenocarcinoma (n=19; 90.5%), whereas two (9.5%) patients had squamous cellular carcinoma.

After multidisciplinary discussion, patients were candidate to IT: 17 (81.0%) underwent to chemotherapy treatment: cisplatin based chemotherapy in 14 patients and carboplatin based chemotherapy in 3. Two (9.5%) patients underwent combined treatment, with chemotherapy platinum-based, Pemetrexed and Atelizumab. Two (9.5%) patients underwent to target therapy with Afatinib, considering Epidermal growth factor receptor mutation.

All patients were re-staged before the surgical procedure to confirm the feasibility of surgical resection. Twelve (57.1%) patients showed a stable disease, 3 (14.2%) patients had a complete response, and 6 (28.5%) patients had a partial response.

At the pulmonary pre-operative tests, median percentage forced expiratory volume in the 1st second (FEV1%) was 96.6% (range 67.1-118.0%), the diffusing capacity (DLCO/VA) was 76.1% (40.0 - 116.0%). The ASA score was 2 in the 73% of patients, and 3 in the remaining 27%.

	N = 21 (100%)
Age, years (range)	66 (45-78)
Male	10 (47.6)
Smoking status	
Yes	9 (42.8)
No	1 (4.7)
Former smoker	11 (52.3)
Histology	
Adenocarcinoma	19 (90.5)

Squamous cell carcinoma	2 (9.5)
Clinical stage (after mediastinal staging)	
cIIIA	17 (81.0)
cIIIB	4 (19.0)
Induction treatment	
Chemotherapy	17 (80.0)
Target therapy	2 (9.5)
Combined treatment	2 (9.5)
Reponses to induction therapy	
Stable disease	12 (57.1)
Complete response	3 (14.2)
Partial response	6 (28.5)
Cardiopulmonary test	
FEV 1 % (range)	96.6 (67.1 – 118.0)
DLCO/VA (range)	76.1 (40.0 -116.0)

Table 1. Clinical-demographic characteristics of the patients enrolled

II. Robotic surgery results

Two patients (9.5%) were converted to thoracotomy: one for oncological reason (suspected bronchial infiltration), and one for pleural adhesions.

Thus, the further analysis was done only on 19 patients undergoing RATS lobectomy with radical lymphadenectomy without conversion to thoracotomy. The majority of the patients underwent right upper lobectomy (36.8%), followed by middle lobe resection (26.3%). The median size of the tumor was 23 mm (range 3-60 mm).

The median time of skin-to-skin RATS surgery was 264 minutes (153-540). All patients had a complete resection (R0).

The final pathological stage was listed in Table 2. The median number of lymph node harvested was 21 (range 6-52): 12 (range 1-27) N2, and 9 (0-26) N1. Besides, the median number of total lymph node station was 6 (range 3-13).

Minor post-operative complications occurred in 5 patients (21.1%): 3 prolonged air leaked, and 1 fever treated with antibiotics. Major complications were not recorded.

The median time of chest tube was 4 days (range 2-15). The median length of hospital stay was 6 days (range 4-22), and only 1 patient went to ICU after surgery due to comorbidities.

Post-operative treatment was indicated in 10 patients (52.6%): mediastinal radiotherapy was indicated in 7 patients (36.8%) for N2 persistent disease whereas one patient underwent post-operative chemotherapy plus radiotherapy (5.3%). Instead 2 patients continued their immunotherapy (10.5%).

	N = 19 (100%)
Site	
Right superior lobe	7 (36.8)
Right inferior lobe	3 (15.8)
Middle lobe	5 (26.3)
Left superior lobe	3 (15.8)
Left inferior lobe	1 (5.3)
Size mm (range)	23 (3-60)

Duration of surgery min (range)	264 (153 - 540)
ICU stay, days (range)	0 (0-1)
Post-operative stay, days (range)	6 (4-22)
Number lymph nodes (N1+N2) (range)	21 (6-52)
Number lymph nodes (N1+N2) station (range)	6 (3-13)
Pathological stage	
y0	2 (10.5)
yIA1	4 (21.1)
yIA3	2 (10.5)
yIB	1 (5.3)
yIIB	1 (5.3)
yIIIA	8 (42.1)
yIIIB	1 (5.3)
Post-operative complication	
None	15 (78.9%)
Minor	4 (21.1%)
Drainage removal, median days (range)	4 (2 - 15)
Post-operative stays, median days (range)	6 (4-22)

Adjuvant treatment	
No	9 (47.4)
Yes	10 (52.6)
Mediastinal radiotherapy	7 (36.8)
Chemotherapy plus radiotherapy	1 (5.3)
Immunotherapy	2 (10.5)

Table 2: Surgical and post-operative information.

III. Follow-up

The median follow-up was 14 months (range 1-32 months, Table 3).

Recurrences were detected in 4 patients (21.1%): 2 lymph node relapses (N2 relapses) and 2 distant metastasis (i.e. brain or liver metastasis). These patients were treated with radiotherapy and immunotherapy in case of N2 relapses, and chemo-radiotherapy for the distant metastasis. At the last follow-up, 16 (76.2%) patients were alive without any evidence of the disease, 2 (9.5%) were alive with disease under treatment and 1 died do to the progression of the disease (4.8%).

	N = 19 (100%)
Median follow-up (range)	14 (1-32)
Recurrence	
No	16 (84.2)

Yes	3 (15.8)
Local	2 (10.5)
Distant	1 (5.3)
Status follow-up	
Alive with the disease	2 (9.5%)
Not evidence of the disease	16 (76.2%)
Dead of the disease	1 (4.8%)

Table 3: Patients' follow-up

IV. Comparison between RATS and open lobectomy

We performed a match case-control analysis between our 19 RATS patients and 54 patients undergoing open lobectomy for stage N2-IIIA NSCLC in the same period of time, with similar clinical, pathological and demographical characteristics.

Thus, the individual matched population was composed of 14 RATS lobectomies and 14 patients who underwent open surgery, matched for age, clinical and pathological TNM.

The demographic and clinical characteristics of patients in the two matched groups are shown in Table 4.

Twelve patients were cIIIA (85.7%) and 2 cIIIB (14.3%) in both groups (p=1.00). The N2 disease was pre-operatively diagnosed with EBUS-TBNA in all patients, with #4R and carinal station #7 involvement in the majority of cases.

The median time of resection was inferior in the open group compared to RATS (148 vs 229 minutes; p=0.002). No RATS lobectomy was converted during the surgery.

The median number of N1+N2 lymph nodes dissected was 24 (range 15-52) in the RATS group and 27 (range 11-55) in the open surgery patients (p=0.42), whereas the overall lymph node stations removed were 7 (range 4-9) for the RATS group and 7 (range 5-10) for the open thoracotomy (p=1.00).

The mean duration of ICU and hospital stay was comparable (p=0.56 and p=0.61 respectively), and also the post-operative complication rate (p=1.00).

The pathological exam revealed 16 patients with persistence of ypN2 (57.1%), 2 down staging to ypN1 (7.1%) and 10 ypN0 (35.7%), without differences in the RATS and open groups (p=1.00).

Post-operative mediastinal radiotherapy was administered in 15 patients still pN2 persistent after induction therapy, 1 patients refused the treatment (3.6%).

MATCHED			
	Robot	**Open**	**P-value**
Total	14	14	
Age			
<60	3	4	
60-69	8	4	
70+	3	6	0.32
Sex			
Male	8	10	
Female	6	4	0.69

Size, mm			
mean ± SD	23 ± 15	28 ± 15	0.32
ASA			
2	10	13	
3	4	1	0.33
Lymph nodes resected			
mean ± SD	24 ± 10	27 ± 12	0.42
Lymph nodes positive			
mean ± SD	3 ± 5	4 ± 4	0.82
Intevention, hours			
mean ± SD	229 ± 56	148 ± 156	**0.002**
ICU, days			
mean ± SD	0.1 ± 0.3	0.1 ± 0.4	0.56
Hospital stay, days			
mean ± SD	6.9 ± 5.4	6.1 ± 1.7	0.61
Complications			
No	11	11	
Yes - Pulmonary	3	3	1.00

Table 4: Clinical-demographic information of the matched patients (n=28). Matching information is not reported. For statistical analysis, differences were considered significant for p<0.05 (bold text).

A total of 4 (14.3%) patients in the RATS group developed recurrence of the disease: 2 local and 2 distant metastasis. Regarding the 2 local recurrences, both patients had mediastinal lymph node relapse (1 station #4R and 1 station #7).

In the thoracotomy group, 9 patient had recurrence (32.1%): 1 local relapses (#ST7, 4%), 1 contralateral nodule and 5 distant metastasis (18%; 3 brain metastasis, 1 kidney and 1 abdominal lymph nodes recurrence).

The median follow-up of RATS groups was 19.4 months instead in the open group was 27.3 months. The majority of the patients are alive without any evidence of the disease (17 patients, 60.7%). Three (10.7%) patients are alive with the disease, and 8 (28.6%) are dead due to the progression of the disease.

No difference was observed between the groups both in terms of recurrence-free survival (P=0.83, Figure 6), and in term of OS (P=0.92, Figure 7).

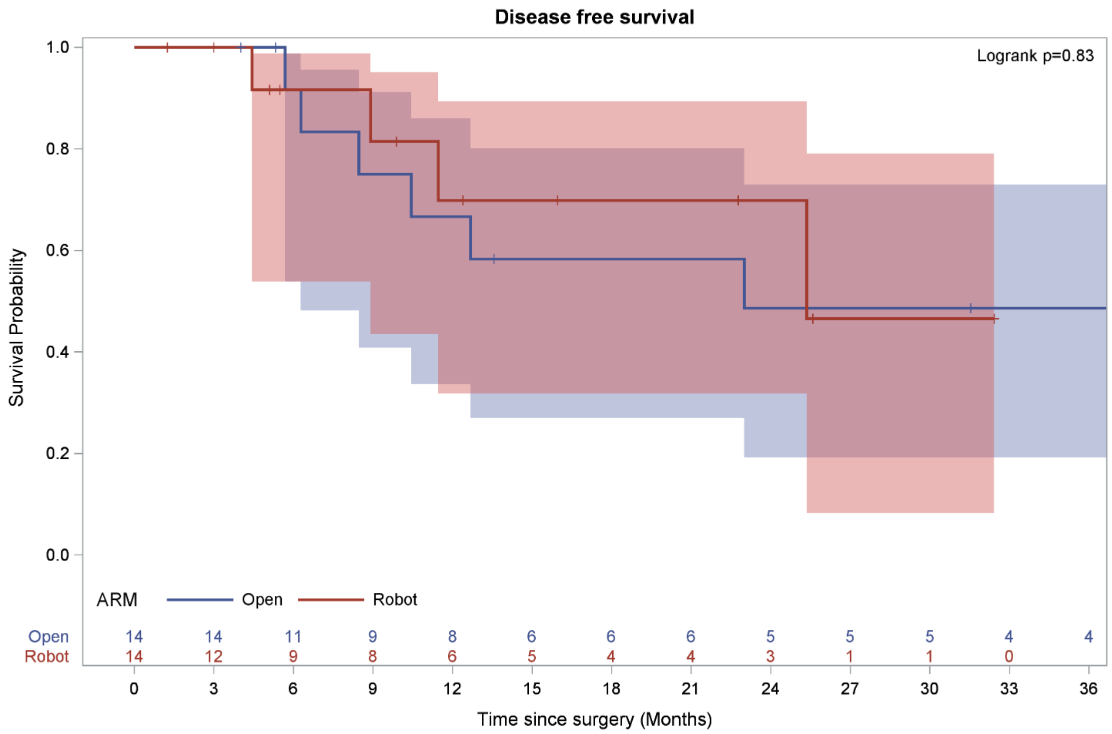

Figure 6. Progression free survival of the matched group.

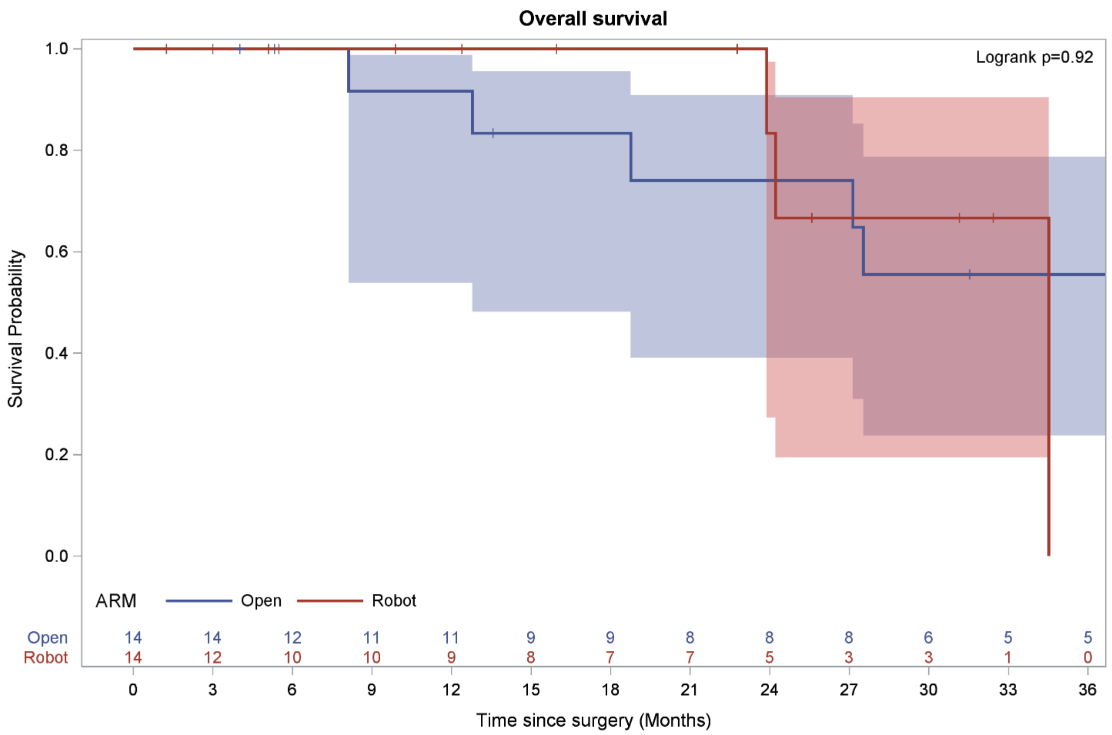

Figure 7. Overall survival of the matched group.

DISCUSSION

The minimally invasive approach in thoracic surgery has proven advantages in terms of reduced postoperative pain, shorter immune response, quicker resumption of daily activities, and better aesthetic and functional result [27]. The minimally invasive surgery despite it is recognized by the majority of thoracic surgeons still has a slow diffusion due to the technical difficulty and the long-lasting learning curve [2–4]. The result of this situation is that a large part of thoracic surgeons still prefers an open traditional approach to perform a lung anatomical resection.

One of the major criticisms of minimally invasive surgery is the inadequate mediastinal lymph node dissection compared to open surgery. Concern over inferior oncologic outcomes has contributed to the slow adoption of minimally invasive surgery techniques. However, robotic approach using the da Vinci system represented a technological evolution of the video-thoracoscopic procedure leading to a better view of the operative field (3D instead of 2D), a simpler use of the instruments, and more precise movements, even superior to the human hand [7–9,13]. These improvements become particularly useful in case of advanced disease with lymph nodes involvement allowing an easier and safer N1 and N2 lymph node dissection [11,28,29].

Although different studies have demonstrated that RATS is associated with reduced mortality, shorter hospital stay, and fewer overall complications compare to open surgery, only few studies have evaluated oncological outcomes [11,25,30].

In literature, the median number of lymph nodes harvested by RATS range between 13.9 to 18 [11,31], compare to a median of 16 harvested by VATS [31] and 14.7 resected in open surgery [32].

Park et al. in 2012 [29] published a robotic multicenter experience showing an overall pathologic lymph node upstaging of 24% (18% N1 upstaging and 6% N2 upstaging), with similar results compare to the larger open series (14.3%-24.6%) and better than conventional VATS (10.6%-11.9%) [23,26,32]. More recently, Toosi et al. [25] confirmed that RATS allowed an adequate lymphadenectomy with detection of occult lymph node metastatic disease, with significant upstaging (14.8%) and equal oncologic outcomes compare to open radical lymphadenectomy. In a multicenter study published in 2017, Cerfolio [31] showed a median number of lymph nodes resected of 13 (5 N2 stations and 1 N1), with a cumulative incidence of local recurrence in the ipsilateral operated chest of 3% only.

In our previous experience, the overall median number of lymph node stations removed was five, with a median number of 15 lymph nodes harvested and an overall pathological lymph node upstaging of 17.6% [19] as well as in this study where the median number of lymph node harvested in RATS was 24, showing the oncological safety of RATS also for advanced NSCLC. Even when after the individual match of RATS with open surgery, we did not find any difference between the two groups highlighting that the excellent lymphadenectomy performed by robotic approach, could be comparable to open surgery.

Indeed, Toosi highlighted as patients pathologically staged with robotic surgery had a better stage-specific survival at the earlier stages compared with clinical stage suggesting that staging was significantly improved with robotic lymphadenectomy [25].

However, the most common indication for minimally invasive approach in lung cancers with either VATS or RATS, are early stage NSCLC (stage I and II) [19]. Despite some series report already showed the use of robotic surgery in patients with both initial and locally advanced NSCLC [7–11], the results of this approach specifically for stage III disease have been described only in very limited retrospective studies [10,33–36], showing anyhow similar oncological outcomes between open and minimally invasive groups, in term of post-operative outcome and survival even after chemotherapy.

Veronesi et al. recently published a retrospective multicenter study describing one of the largest series of patients (n=223) with pN2 NSCLC and carcinoid undergoing RATS [13]. In this study the author showed acceptable perioperative outcomes with only 2.7% of converted cases to open surgery due to bleeding demonstrating the safety and feasibility of the procedure, even in patients underwent induction chemotherapy. One of the major difficulty related to RATS is the lack of perception that can make surgery particularly challenging especially in the case of chemotherapy or radiotherapy, with higher risk of intra operative complications. However, in this series they highlighted that large tumor size and >2 positive lymph nodes were associated with higher risk of conversion to open surgery despite unexpected mediastinal nodal invasion as well as pre-operative treatments were not the major cause of thoracotomy conversion.

In our study, even if our conversion rate was 9.5% (2 cases out of 21), we did not have any case due to bleeding, but only one case for a bronchial infiltration of a pathological lymph node, and another one for massive pleural adherences.

Regarding the long-term outcome, Cerfolio [31] showed excellent 5-year stage-specific survival (83% for stage IA NSCLC, 77% for the stage IB, 68% for stage IIA, 70% for IIB, 62% for stage IIIA (N2 disease, 73%), and 31% for stage IIIB) in particular for N2 stage IIIA, which was up to 73%. In Veronesi series, the estimated 3-year survival in NSCLC patients was 61.2%, showing an excellent oncological result even if it could be related by the fact that most of the patients (n=142/223; 63%) had occult N2 disease and only 34 (15%) patients underwent induction therapy. However, even in our previous study of 339 patients who underwent RATS for clinical stages I-II NSCLC had an excellent overall lymph node upstaging (17.6%), and a 58% of 5-year stage-specific survival for occult pN2 patients (n=28). This confirmed that mediastinal lymph node dissection during RATS adequately assesses lymph node stations leading to excellent oncologic results [19].

In this study, our median follow up was 19.4 months and 27.3 months, respectively for the RATS group and comparable to the open surgery one (p=0.92). Also the recurrence-free survival was comparable in the two groups (p=0.83). Unfortunately our median follow up is still too short, considering preliminary nature of our results, to make any oncological or long term considerations.

The major biases of this study are the small number of patients evaluated, and the short follow up, which probably limit and influence all of the variables included into the analysis, in particular the long term results.

In conclusion, considering the advantages of minimally invasive surgery, our data suggests that RATS lobectomy should be a valid alternative after induction treatment, with comparable favorable prognosis to open surgery. The post-operative morbidity and oncological results are in agreement with retrospective study [13, 36] and underline the importance of patient's selection, even if a longer follow up period is needed.

CONCLUSION

RATS lung resection for advanced NSCLC is safe and feasible both in term of post-operative outcome and oncological results. However, these results require prospective studies (ongoing our multicenter prospective study for stage IIIApN2 NSCLC) and further testing on a larger population to be validated.

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