Original Article

Uniportal video-assisted thoracoscopy major lung resections after neoadjuvant chemotherapy

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Background: The combination of neoadjuvant chemotherapy and surgery in lung cancer therapy is well established. The role of uniportal video assisted thoracoscopy (VATS) is still not described in literature. This study presents the preliminary short-term results of uniportal VATS after neoadjuvant therapy in our series.

Methods: The prospectively collected data of 154 patients after uniportal VATS anatomical lung resection (18 patients after neoadjuvant chemotherapy and 136 surgeries alone) were retrospectively reviewed. The perioperative results and follow-up of patients after neoadjuvant therapy were analyzed and compared to those after surgery alone.

Results: The mean age of population was 67.51±10.63 years. The mean operative time was overlapping in both groups: 248.97±118.17 min in surgery group and 287.17±94.13 min in chemotherapy + surgery group (P=0.190), with no difference in terms of types of anatomical lung resections performed and number of lymph nodes retrieved. The intraoperative mortality was null in both groups. The incidence of all complications was the same in both groups and no correlations was found with any possible risk factor evaluated (age, gender, comorbidities, type of resection, histology, etc.). Among minor complications, the incidence of parenchymal fistula was significantly higher in the 18 patients underwent chemotherapy (22.2% *vs.* 5.1% respectively, P=0.013). The overall survival of the series was 93% at 1 year follow-up and 88% at 5-year. The 1- and 2-year survival in only surgery group was 94% and 89% respectively *vs.* 85% and 85% in Chemotherapy + surgery, without any significant difference (P=0.324).

Conclusions: According to our experience, uniportal VATS after neoadjuvant therapy is feasible and quite safe. The oncological results and postoperative complications are comparable to those of other techniques. Uniportal VATS can be performed even for complicated cases in experienced centers.

Keywords: Uniportal video assisted thoracoscopy (uniportal VATS); induction therapy; lung cancer; lung major resections

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Introduction

Neoadjuvant therapy in the treatment of advanced stages non-small-cell lung cancer (NSCLC) is well established and part of the guidelines (1-3). This enables a better survival rate (4,5). However, surgery after the application of induction therapy is associated with higher complication rates compared to surgery alone (6). Several complications are also due to the surgical approach itself. The optimal surgical approach for these cases is still under investigation. Due to just few studies, the evidence for a long-term survival for patients with video assisted thoracoscopy (VATS) *vs.* patients with an open approach after chemotherapy is still outstanding (7,8).

The uniportal VATS is now well developed in several experienced thoracic centers worldwide. This technique is used not only for minor but also for major resections in thoracic surgery. Several case reports describing advanced complicated cases operated in a uniportal VATS technique were published recently in the literature (9). Few non-randomized studies showed that uniportal VATS can be superior to multiportal VATS and conventional surgery in terms of postoperative complications (10). However, the role of uniportal VATS for cases after neoadjuvant therapy is still scientifically not well-defined (11). The already described benefits of uniportal VATS like direct vision and reach of the target tissue as well as less complication rates could play a significant role in cases after induction therapy (7,12).

This single center study elucidates the preliminary short-term results for uniportal VATS in terms of safety of the technique, survival and complications, investigating any possible risk factor influencing outcomes.

Methods

Between June 2012 and September 2017, 642 Uniportal VATS procedures were performed at Thoracic Surgery Department, Charité-Universitätsmedizin Berlin (Germany). Among these, 154 patients underwent a uniportal VATS anatomical lung resection for primary lung cancer: 136 without a preoperative neoadjuvant treatment and 18 after induction chemotherapy. The prospectively collected clinical data of all these patients were retrospectively reviewed and analyzed.

The clinical evaluation of the patients before the neoadjuvant therapy included: routine blood tests, electrocardiography, radiological and diagnostic examinations [chest/total body computed tomography (CT), positron emission tomography (PET)-CT, endobronchial ultrasound (EBUS) and preoperative biopsies] and pulmonary function test. Each case was discussed in a multidisciplinary tumor board, where—according to the stage of disease and patient's comorbidities—the indication to a possible preoperative treatment was given. The patients underwent 3 cycles of platinum-based chemotherapy and then revaluated for surgery. The re-staging for patients after neoadjuvant chemotherapy was carried out mainly by PET-CT scan and when necessary also preoperative biopsies with EBUS.

Intraoperative results and short-term postoperative outcomes in terms of complications, duration of chest tube, intensive care unit (ICU) admission, hospital stay, mortality and overall survival were recorded and evaluated.

Surgical technique

The same surgical team performed all procedures. The surgery was performed under general anesthesia and single-lung ventilation. The patients were placed in lateral decubitus with their arms flexed and stretched towards their head (13). A single 3–4 cm muscle-sparing incision was made on the midaxillary line in the IV or V intercostal space according to which lobe to be operated on. A wound protector was placed in all cases. A 10 mm 30° thoracoscope and special thoracoscopic instruments were used. All specimens were removed after putting in an endobag. The pain management was started with an extrapleural paravertebral intercostal nerve block as described previously (13). Only one chest drain (24 Fr) was placed at the end of the operation.

Postoperative management

All patients were treated according to our fast track protocol (14). The postoperative management was started with forced mobilization and respiratory physiotherapy in the immediate postoperative period.

The first chest X-ray was performed 2 hours after the operation and on the first postoperative day as well as before the expected chest tube removal, that was done when there was no air leak sign and the secretion was below 200–300 mL within 24 h.

Statistical analysis

Categorical variables are reported as n (%). Continuous variables are expressed as mean ± standard deviation (SD). Categorical variables were compared by Fischer's exact test

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Table 1 Demographic and preoperative clinical characteristics of the two groups: surgery and chemotherapy + surgery

Preoperative characteristics	Surgery alone (#136)	Chemotherapy + surgery (#18)	P value
Gender (Male)	90 (66.2%)	11 (61.1%)	0.671
Age (years)	67.42±10.64	68.27±10.82	0.749
Smoker	120 (88.2%)	15 (83.3%)	0.681
ASA score	2.56±0.62	2.56±0.61	1.000
Cardiovascular diseases	42 (30.9%)	7 (38.9%)	0.749
Respiratory diseases	41 (30.1%)	8 (44.4%)	0.452
Kidney diseases	18 (13.2%)	2 (11.1%)	0.904
DM II	31 (22.8%)	5 (27.8%)	0.844
Preop FEV1%	79.27±19.36	87.15±16.57	0.162
Side (right)	81 (59.6%)	13 (72.2%)	0.317

ASA, American Society of Anaesthesiologists; DM, diabetes mellitus.

and continuous variables by independent sample Student's *t*-test. Any possible correlations between outcome variables were explored by Pearson's sample correlation r. Kaplan-Meier method was used for evaluating overall survival of the series; the comparison of two survival curves was done using the log-rank test. A P value less than 0.05 was considered statistically significant.

Statistical analysis was performed using IBM SPSS Statistics for Macintosh, Version 25.00 (Armonk, NY, USA).

Results

The mean age of 154 patients was 67.51±10.63 years and the 65.6% (101 patients) of the series were males.

The main demographic and preoperative clinical characteristics of the two groups (the 136 patients underwent surgery and the 18 patients underwent neoadjuvant chemotherapy (ChT + surgery) are reported in *Table 1*. The two groups resulted comparable in terms of age, gender, comorbidities and preoperative lung functionality.

The group of patients underwent neoadjuvant therapy presented in the 33% (6 patients) of cases a clinical stage IIIA, in 17% (3 patients) a cIIIb stage and in 50% (9 patients) a cIV stage (oligo metastatic patients). In the 72% of cases (13 patients) the diagnosis was an adenocarcinoma, in 28% (5 patients) a squamous cell carcinoma.

The mean operative time was overlapping in both groups: 248.97±118.17 min in surgery group and 287.17±94.13 min in ChT + surgery group, P=0.190.

No difference was also recorded between the main types of major lung resections performed in the two groups (P=0.487) and in the number of lymph nodes retrieved during lymphadenectomy (20.14±10.73 in surgery group *vs.* 21.61±7.37 in ChT + surgery, P=0.133, see *Table 2*).

There was no conversion in ChT + surgery group, while there was 8 cases (5.6%) in the surgery group (P=0.291). The intraoperative mortality was null in both groups.

The rate of ICU admission was the same in both groups (P=0.764, see *Table 3*).

A trend toward statistical significance was found in hospital stay, that was longer in ChT + surgery group compared to the other (P=0.061, see *Table 3*).

The 30-day mortality was null for ChT + surgery group and 1.5% for surgery group (2 patients dead for ARDS, P=0.605).

The incidence of complications was the same in both groups (*Table 3*) and no correlation was found with any possible risk factor evaluated (age, gender, comorbidities, type of resection, histology, etc.). The types of complications in ChT + surgery group were parenchymal fistula in 4 cases, pneumonia in 1 case and lung torsion in another one.

Among minor complications, the incidence of parenchymal fistula (causing a prolonged air-leakage) was significantly higher in the 18 patients underwent chemotherapy [4 (22.2%) *vs.* 7 (5.1%) cases, respectively, P=0.013). Consequently, in the same group, a higher incidence of reoperation rate (3 cases for re-checking aerostasis and 1 case for lung torsion) was also found (22.2%

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Table 2 Intraoperative characteristics and results of the two groups: surgery and chemotherapy + surgery

Intraoperative characteristics	Surgery alone (#136)	Chemotherapy + surgery (#18)	P value
Type of resection			0.487
Segmentectomy	18 (13.2%)	1 (5.6%)	
Lobectomy	114 (83.8%)	16 (88.8%)	
Bilobectomy	2 (1.5%)	1 (5.5%)	
Pneumonectomy	2 (1.5%)	0	
Operative time (min)	248.97±118.17	287.17±94.13	0.190
Pleuro-pulmonary adhesions	28 (20.6%)	5 (27.8%)	0.552
Tumor size (mm)	27.05±17.35	35.06±18.92	0.781
Total N lymph nodes retrieved	20.14±10.73	21.61±7.37	0.133
Conversion rate	8 (5.9%)	0	0.291
Intraoperative mortality	0	0	1.00

Table 3 Postoperative results of the two groups: surgery and chemotherapy + surgery

Postoperative characteristics	Surgery alone (#136)	Chemotherapy + surgery (#18)	P value
ICU admission	80 (58.8%)	10 (55.6%)	0.764
Postop drainage time (days)	7.06±7.44	7.59±6.31	0.780
Postop hospital stay (days)	10.76±9.60	15.83±16.59	0.061*
30-day mortality	2 (1.5%)	0	0.605
Overall survival (months)	15.00±12.95	13.15±7.96	0.590
Complications	25 (18.4%)	6 (33.3%)	0.137
Parenchymal fistula	7 (5.1%)	4 (22.2%)	0.013*
Reoperation rate	5 (3.7%)	4 (22.2%)	0.007*

*, P value <0.005.

vs. 3.7%, P=0.007).

The overall survival of the whole series was 93% at 1 year follow-up and 88% at 5-year (*Figure 1*).

Comparing the survival between the two groups (*Figure 2*), the 1- and 2-year survival in only surgery group was 94% and 89% respectively *vs.* 85% and 85% in ChT + surgery, without any significant difference (P=0.324).

Discussion

In the last 20 years the role of the VATS has been more and more established for patients with early-stage NSCLC (15,16). The advantages of VATS towards thoracotomy have been proven by many studies as it allows faster recovery by reducing post-operative pain, preserving lung function allowing a reduction in the length of hospitalization time and a faster access to adjuvant treatments (17,18). Although the advantages of the minimally-invasive approach were recognized, it was initially considered contraindicated to treat advanced stage patients (stage IIIA) who had received neoadjuvant chemotherapy through VATS surgery (19). Neoadjuvant therapy causes the onset of pleural adhesions making the determination of the cleavage plans more complicated, favors vascular fragility increasing the difficulty of hilar and mediastinal dissection and making surgery a challenge even for an experienced surgeon (20,21). In the last years, due to the improvement of the surgical techniques and to the technological progress in the

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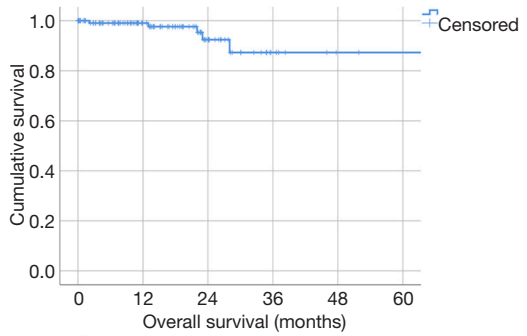
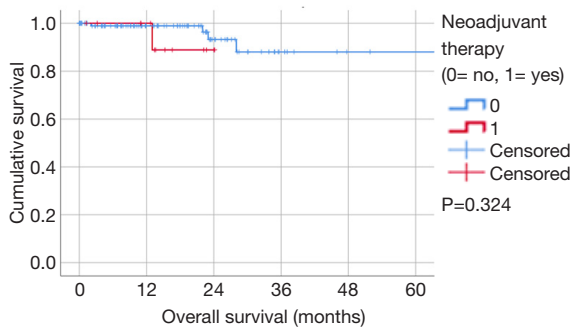


1-year survival	5-year survival
93%	88%

Figure 1 Overall survival of the whole series. Kaplan-Meier survival curve.



	1-year survival	2-year survival	5-year survival
Neoadjuvant =1	85%	85%	/
Neoadjuvant =0	94%	89%	89%

Figure 2 Survival of the two groups (surgery and Chemotherapy + surgery). Kaplan-Meier survival curves.

thoracoscopic field, this indication has changed (9). Several studies have shown that VATS lobectomy in patients with locally advanced NSCLC is safe and feasible and does not appear to compromise the oncologic outcomes confirming also the advantages against open thoracotomy (11,12,21,22). Few studies have shown how the VATS approach, when technically possible, was always preferable to open surgery but no comparative studies have been carried out between neoadjuvant- and non-neoadjuvant-treated patients who then underwent the same minimally-invasive technique.

In the best of our knowledge, this is the first work in literature, describing the short-term results of Uniportal VATS for anatomical lung resection for NSCLC performed with or without induction chemotherapy. In particular from June 2012 to September 2017, 18 patients in the ChT + surgery group (stage IIIA, IIIB, and IV) were evaluated and compared to 136 only surgery group.

According to the literature, patients undergoing neoadjuvant therapy face more complications after surgery than others. The rate of specific complications like cardiovascular diseases (38.8% *vs.* 30.9%) and respiratory diseases (44.4% *vs.* 30.1%) are higher in patients who have undergone induction therapy (11).

In our study, the length of operation was similar in the induction therapy group and surgery group (287.17±94.13 *vs.* 248.97±118.17 min, P=0.190). Probably the longer operative times and the prolonged duration of pleural drainage were due to the radical lymphadenectomy performed on different stations according to our standard, with a number of lymph nodes removed higher than this reported by others. In our series, the average number of lymph nodes removed was 21.61±7.37, compared to other studies (12,21,23).

Tissue edema and tissue inflammation induced by the neoadjuvant treatment caused a greater production of pleural effusion which resulted in the positioning of a pleural drainage for a longer period in ChT + surgery group (7.59±6.31 days). The chest tube duration in our group was more prolonged than others reported for pure VATS procedures in literature (12,21,23).

In concordance with other studies (24) we registered a greater risk of prolonged air leakage (4/18, 22.2% *vs.* 7/136, 5.1%) in ChT + surgery group, probably caused by inflammatory fibrosis, similar to those reported by other groups (12,21).

In 3 cases, it was necessary to revise the aerostasis surgically. We registered only one major complication (1/18, 5.55%, lung torsion) that required a reoperation and this was less than what reported in other studies following neoadjuvant therapy (12,21,25) or in multiportal VATS without induction therapy (16,26).

In the ChT + surgery group we did not register conversion to open thoracotomy [0% *vs.* 8/136 (5.9%) in the surgery group] and this was less than data reported in other series following neoadjuvant therapy (12,21,25).

The 30-day mortality rate in the ChT + surgery group was 0% (0/18) and 1.5% (2/136) in surgery group. This result was similar to those reported by other studies (21,25).

However, our study had some limitations: it was a monocentric and a retrospective one, involving a quite small sample of patients after neoadjuvant therapy. Furthermore, there was no comparison group of open surgery. Large and randomized studies would be needed for evaluating results

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on Uniportal VATS treatment of locally advanced NSCLC following neoadjuvant therapy and for validating the long-term oncologic outcomes.

In conclusion, from our preliminary results, uniportal VATS seems to be a quite safe and feasible technique for the treatment of locally advanced NSCLC following neoadjuvant therapy. Further corroborations are claimed.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was evaluated by the Institutional Review Board (IRB) of Charité-Universitätsmedizin in Berlin and, as this was a retrospective review for service evaluation and there was no modification in patients' care (no prospective randomized study), we did not need the final ethical approval of our IRB. All patients provided an informed consent for the treatment of their clinical data.

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