Original Article

Postoperative morphine consumption and anaesthetic management of patients undergoing video-assisted or robotic-assisted lung resection: a prospective, propensity score-matched study

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Background: Robotic assistance is increasingly being used for treatment of early stage of non-small cell lung cancer. Our objectives were to compare the morphine consumption during the postoperative 48 hours after robotic-assisted thoracic surgery and that after video-assisted thoracic surgery as well as compare the patient's haemodynamic and respiratory function during the procedures.

Methods: This observational, prospective study was conducted in a single referral centre for thoracic surgery from January 2016 to March 2017. Patients who were scheduled to undergo surgical lung resection were included. A propensity score based on age, sex, American society of Anesthesiology score was used between groups. Linear regression analyses were used to determine the mean difference in the postoperative morphine consumption. We also compared the haemodynamic and respiratory function during the two procedures.

Results: Among the 194 patients included, 105 (54%) and 89 (46%) underwent video and robotic surgery, respectively. Total 75 of each group were matched using the propensity score. The consumption of morphine was 23.0 (16.5–39.0) mg and 33.0 (19.3–46.5) mg (P=0.05) in the video and robotic groups, respectively. Linear regression revealed an average difference β (95% CI) of 6.76 mg (0.32–13.26) (P=0.04) in the morphine consumption after adjusting for the body mass index and local anaesthetic use. Robotic surgery was associated with worse haemodynamic and respiratory function than video surgery.

Conclusions: As compared with video, robotic surgery was associated with increased use of morphine and greater alteration in the haemodynamic and respiratory functions.

Keywords: Robotic-assisted thoracic surgery (RATS); video-assisted thoracic surgery (VATS); lung resection; morphine consumption

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Introduction

Surgery is the gold standard treatment for early stage non-small cell lung cancer (NSCLC). Thoracotomy use is decreasing worldwide due to the emergence of minimally invasive approaches, such as video-assisted (VATS) and robot-assisted (RATS) thoracic surgeries. VATS is associated with lower postoperative pain and better quality of life compared to anterolateral muscle-sparing thoracotomy (1). Furthermore, several retrospective cohort studies and meta-analyses of non-randomised studies have shown significant reduction in the morbidity, especially due to respiratory complications (2-6). Despite these advantages of VATS, certain limitations of this technique, such as the steep learning curve, challenging hand-eye coordination, lack of instrument flexibility, two-dimensional vision, and some uncertainty regarding the quality of lymph node dissection that can be achieved using VATS, may still hinder its development (7).

RATS is an emerging option for managing patients requiring lung resection. Compared to VATS, RATS exhibited better procedure ergonomy and surgeon comfort. As RATS mimics open surgery, the learning curve for surgeons is possibly less steep than that for VATS. Moreover, the computer-assisted interface palliates hand tremor, thereby enhancing surgeon dexterity, and the magnified three-dimensional view improves visualisation of the operative field with the help of carbon-dioxide insufflation, potentially assisting more extensive dissection of the lymph nodes. Finally, articulated instruments allow seven degrees of motion as well as precise dissection and suturing in a confined operating space (8). However, whether this technologically expensive innovation provides superior outcomes remains unclear. The available literature suggests that RATS lobectomy is a feasible and safe technique that can achieve a short-term surgical efficacy equivalent to that achieved using VATS (9).

To our knowledge, no prospective study has evaluated the perioperative anaesthetic outcomes in patients undergoing VATS and RATS for lung resection. Thus, we conducted a study that aimed to compare the anaesthetic management and post-operative morphine consumption in patients undergoing lung cancer resection either with VATS or with RATS. Our primary objective was to compare the cumulative morphine use during the first two postoperative days. The secondary objective of our study was to compare the haemodynamic and respiratory changes during these two procedures.

Methods

This prospective, observational, comparative, single-centre study was conducted by the departments of anaesthesiology and thoracic surgery of the North University Hospital, Marseille, France. This research trial was approved by our Liberty and Informatics Committee (2016-18) and by the SFAR IRB (CERAR 00010254-2016-049). The study period ranged from January 2016 to March 2017. Written and oral information regarding the study purpose and procedures was given to all the patients before enrolling them, and written consents were collected. Consecutive patients undergoing lung resection for NSCLC suspicion were screened. Patients who required a thoracotomy or pre-resection mediastinoscopy, those who had previously undergone an ipsilateral thoracic surgery, those who reported chronic use of narcotics, and those with an altered mental status were excluded.

Surgical procedure

In accordance with the national and international guidelines, all operable patients referred to our high-volume academic institution with suspected clinical stage I NSCLC were offered a minimally invasive approach, either VATS or RATS (10,11). This study also included few patients who presented with benign conditions that necessitated lung resection. Two board-certified academic staff surgeons performed all the RATS procedures and performed or supervised all the VATS procedures. Patients were thus allocated either to the VATS or to the RATS group depending on the surgeon's recruitment.

Our VATS program was initiated in the early 90's (12). In 2010, we adopted the so-called totally thoracoscopic technique described by Gossot *et al.* (13). Accordingly, VATS pulmonary resections were performed using a 3-port technique, and no utility incision was used. The RATS procedures were performed with a da Vinci Surgical System Si (Intuitive Surgical Inc., Sunnyvale, CA, USA) available at our institution since Spring 2015. Among the four staff surgeons of the surgical team, two were previously identified to follow the step-by-step dedicated training. Both the RATS surgeons completed their clinical learning by 2015. The number of operations required was estimated to be 20, according to the literature (14). The 3-arm technique was used as routine, with an additional incision through which staplers were inserted and used by the assistant surgeon. Intrathoracic CO_2 insufflation was used only in the RATS

group.

On completion of the VATS or RATS pulmonary resection, the specimen was retrieved through a port site that was slightly enlarged, depending on the specimen size. The use of a rib spreader was not required for this task. In all cases, only one chest tube was placed through one of the port sites and was connected to a portable suction drainage system. Its removal was decided based on the standard guidelines, that is, no air leakage and output of <200 mL/day.

Full perioperative anaesthetic protocol and post-operative management is available on *Figure S1*.

Data management

All perioperative data were collected as shown in *Figure S1* and *File 1*.

Data collection for pain evaluation

As per our primary objective, postoperative morphine consumption data were collected on day 1 and day 2, including the morphine used in the recovery room and surgical unit as well as the oral oxycodone (converted to intravenous morphine equivalent). Data collection was performed by a single investigator blinded to the surgical procedure. The visual analogue scale for pain (VAS) score was evaluated every 4 hours and reported by the nurse in charge of the patient. Nurses were not blinded to the surgical technique; however, they were not informed of the primary study objective. Minimal, mean, and maximal VAS scores on day 1 and day 2 were reported. The VAS score on coughing was evaluated once daily on days 1 and 2 after physiotherapist consultation by the same investigator.

Postoperative data collection

Postoperative complications were reported according to the modified Clavien-Dindo scale adapted to thoracic surgery during hospital stay and 28-day follow-up in cases of re-admission (15,16). Only the higher-grade complications were recorded. Postoperative complications were classified as minor according to the severity [grade I and II (including atrial fibrillation)] or major (grade III, IV, and V). Specific morphine consumption complications, such as nausea, vomiting, and urinary retention, were specifically reported. Durations of chest tube and hospital stay were recorded. Data regarding tumour grade, tumour histology, and lymph nodes were recorded from the definitive histological report after the surgery.

Sample size calculation

We hypothesised that the morphine consumption was lower after VATS than after RATS and aimed to detect a difference of 25% with a power of 0.9 and a 5% level significance. Under the assumption of a cumulated mean consumption of 30 (±14) mg morphine at day 2 for VATS, our calculation showed that 74 patients needed to be enrolled in each group for our primary end-point.

Considering the cardiac index (CI) comparison between the groups, we hypothesised a decrease in the RATS group compared to that in the VATS group and aimed to detect a difference of 15% with a power of 0.9 and a 5% level significance. Based on a local audit, we observed a mean CI of 2.5 (±0.6) L/min/m² during VATS. We calculated that 46 patients were needed in each group for this secondary end-point.

Statistical analysis

The initial clinical characteristics were first described and compared according to the two groups of interest (VATS *vs.* RATS). Quantitative variables are presented as means (± SD) or medians (IQR) and compared using Student *t*-test when appropriate (Mann-Whitney test otherwise). Categorical variables are presented as numbers (percentages) and compared using Chi-Squared test when appropriate (Fisher test otherwise). Global outcomes (length of hospital stay, chest tubes duration, and incidence of complications) were analysed as per the intention to treat. Perioperative and post-operative data were described and compared for the two groups using the same indicators and statistical tests.

The statistical analyses of the primary outcome (morphine consumption at 48 hours) required a transformation of the dependent variable as the normality assumption could not be verified. The square root transformation method was chosen because of the existence of 0 in the morphine consumption, and this transformation allowed for non-rejection of the normality assumption. Univariate comparisons were performed between the transformed dependent variable and the characteristics potentially associated with morphine consumption (Student *t*-test was used for binary characteristics and Pearson correlation test was used for quantitative characteristics). Thereafter, a multivariate linear regression model was built, including

the potential confounders of morphine consumption (use of continuous infusion of naropeine through the PVB and BMI); no data selection procedure based on statistical criteria was performed. To facilitate result interpretation by expressing the differences in milligrams of morphine, we presented a β coefficient using the square of the predicted values from the model using the transformed variable. To reduce the confounding by indication, we performed the same analyses using propensity score method (17), including baseline clinical variables (age, sex, and ASA score. Nearest neighbour matching without replacement was performed using a 1:1 ratio and a calliper equal to 0.3 of the standard deviation of logit of the propensity score.

The analysis of the evolution over time of secondary outcomes (perioperative data) was performed using multivariate linear mixed regression models. Multivariate models were proposed that included RATS (versus VATS), time, and basal value (T0 value) of the considered parameter. These final models incorporated β coefficients that represent a change in the dependent variable (I) when being exposed to RATS (reference: VATS), (II) when time increases (one additional measure), and (III) in reference to the basal value.

All analyses were performed using R software version 3.0.3 [R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: http://www.R-project.org/].

Results

From January 2016 to March 2017, 332 patients who underwent lung resection were screened for study inclusion: three patients were unwilling to participate, and 125 did not meet the inclusion criteria. Finally, 194 patients were enrolled in the study, including 105 patients undergoing VATS and 89 patients undergoing RATS (*Figure S2*). The patients' demographic data are presented in *Table 1*. No difference was found between the two groups with respect to preoperative characteristics (*Table 1*). We noted a difference in the mean comorbidity index of the VATS [5.7 (±4.0)] and the RATS [4.2 (±3.6)] groups (P=0.006); however, the mean thoracoscore of the VATS group [1.8 (±1.4)] was not significantly different from that of the RATS group [1.7 (±1.1)] (P=0.39). The use of continuous infusion from PVB was higher in the RATS group than in the VATS group (13.7% *vs.* 27.4%; P=0.02).

With respect to the intention-to-treat analysis, 10 (9.5%) and 5 (5.6%) patients required an open-procedure conversion in the VATS group and the RATS group (P=0.31), respectively (*Table 1*). No significant differences were noted in the mean duration of chest intubation in the VATS group [3.5 (3.0–5.0)] and the RATS group [3.5 (3.0–4.0)] days (P=0.25) and the average hospital stay duration of the two groups [VATS: 5.0 (4.0–7.0) *vs.* RATS 5.5 (3.5–8.0) days (P=0.07)]. There was no significant difference in the rate of minor complications between the groups. However, the rate of major complications was higher in the VATS group than in the RATS group (17.1% *vs.* 5.6%, P=0.01) (*Table 1*).

With respect to our primary outcome, after excluding the patients requiring open surgery conversion, 75 patients in each group were propensity score-matched for age, sex, and ASA status (*Table 2*). Using univariate analyses, the RATS group had higher morphine consumption during postoperative 48 hours than the VATS group [33.0 (19.3–46.5) *vs.* 23.0 (16.5–39.0) mg, P=0.05] (*Figure 1*). Linear regression revealed a mean difference β of [6.76 (0.32–13.26) mg; P=0.04] in morphine consumption, adjusted for BMI and on continuous infusion through the PVB, used in 13.7% and 27.4% of patients in the VATS and RATS groups, respectively (P=0.02). The use of continuous infusion was associated with reduced cumulated morphine use on day 2 [mean difference β of –9.65 (–17.8 to –1.6) mg; P=0.02].

The surgical and anaesthetic durations were 142 (±51) *vs.* 161 (±45) min (P=0.01) and 215 (±44) *vs.* 244 (±45) min (P<0.01) in the VATS group and the RATS group, respectively. Sufentanil use was higher in the RATS group than in the VATS group [44.5 (±15) *vs.* 50.6 (±12) µg, P=0.02]. Urinary retention was higher in the RATS group (16.7% *vs.* 6.3%, P=0.03). Reported incidence rates of nausea and vomiting were similar in the two groups (*Table 2*). Graded complications analysis found a higher rate for grade 2 complications in the RATS group and a higher rate of major complications in the VATS group (P=0.01). Detailed distribution of the complications is presented in *Table 2*.

Perioperative haemodynamic and respiratory data were fully assessed for 103 patients (51 VATS and 52 RATS) (in total online: http://jtd.amegroups.com/public/system/jtd/supp-jtd.2018.05.179-1.pdf) (*Table S1*). No differences were found in the demographic features of the two groups (*Table S1*). Respiratory and haemodynamic data were similar at T0, except for PEP [6 (±1) *vs.* 5 (±1) cmH_2O in the VATS and the RATS group, respectively, P=0.02]. Anaesthetic management was similar for the groups (*Table S1*). No significant differences were reported between BIS, TOF

Table 1 Comparison of preoperative and postoperative variables between patients undergoing VATS or RATS. Analysis in intention to treat

Variable	VATS (n=105)	RATS (n=89)	P
Age (years)	64 [57–70]	66.5 [59–73]	0.43
BMI (kg/m²)	25.9 [22.4–28]	25.2 [22–28]	0.47
Male (%)	57 (54.3)	50 (56.2)	0.94
Active smokers (%)	43 (41.0)	36 (40.4)	0.74
FEV1 ratio of predicted value (%)	94 [82–106]	91 [77–104]	0.14
DLCO ratio of predicted value (%)	64 [60–77]	67 [54–75]	0.74
ASA score (%)			0.69
2	73 (69.5)	60 (67.4)	
3	32 (30.5)	29 (32.6)	
Lee score (%)			0.56
0	63 (60.0)	57 (64.0)	
1	30 (28.6)	27 (30.3)	
2	10 (9.5)	5 (5.6)	
3	2 (1.9)	0 (0)	
Apfel score (%)			0.18
0	42 (40.0)	40 (44.9)	
1	45 (42.9)	28 (31.5)	
2	15 (14.3)	17 (19.1)	
3	1 (0.9)	4 (4.5)	
4	2 (1.9)	0 (0)	
Tumor type (%)			0.57
No cancer	12 (11.4)	10 (11.2)	
Primary cancer	81 (77.2)	73 (82.0)	
Metastasis	12 (11.4)	6 (6.7)	
Tumor histology [%]			0.67
Adenocarcinoma	67 [82]	61 [83]	
Squamous cell carcinoma	11 [14]	11 [15]	
Others	3 [4]	2 [3]	
T stage [%]			0.9
1	49 [60]	46 [62]	
2	25 [31]	24 [33]	
3	6 [8]	3 [4]	
4	1 [1]	0 [0]	
N stage [%]			1.0
0	69 [85]	62 [85]	
1	8 [10]	7 [9]	
2	4 [5]	4 [6]	

Table 1 *(continued)*

Table 1 *(continued)*

Variable	VATS (n=105)	RATS (n=89)	P
R stage [%]			0.61
0	80 [99]	71 [97]	
1	1 [1]	2 [3]	
Right side (%)	73 (69.5)	56 (63.0)	0.29
Surgery duration (min)	143 (±50)	160 (±45)	<0.01
Conversion (%)	10 (9.5)	5 (5.6)	0.31
Minor complication rate (%)	26 (24.8)	30 (33.7)	0.20
Major complication rate (%)	18 (17.1)	5 (5.6)	0.01
Death (%)	2 (1.9)	1 (1.1)	0.65
Chest tube duration (days)	3.0 [3.0–5.0]	3.5 [3.0–4.0]	0.25
Length of hospitalisation (days)	5.0 [4.0–7.0]	5.5 [3.5–8.0]	0.64

BMI, body mass index; FEV1, forced expiratory volume in the first second; DLCO, diffusion lung capacity of carbon monoxide; ASA, American society of Anesthesiologists.

count, and central temperature between the two groups over time.

The influence of time and robotic procedure, adjusted on baseline (T0), on the evolution of the haemodynamic and respiratory variables is shown in *Table S1*. The kinetics of the measured and predicted haemodynamic and respiratory variables are represented in *Figures 2,3*.

With respect to haemodynamics, the use of vasopressors was similar in both the groups. Total volume of crystalloid was higher in the RATS group than in the VATS group [1,470 (±570) *vs.* 1,740 (±540) mL; P=0.01]; however, it was comparable when adjusted to the anaesthesia duration and patient weight [5.6 (±2.2) *vs.* 5.9 (±1.8) mL/kg/h; P=0.72]. The CI did not differ between the groups; no influence of time or RATS was determined. The heart rate increased with an effect of RATS [β =3.95 (0.32 to 7.57); P=0.03], while a decrease in the indexed stroke volume was affected by RATS [β = –0.28 (–0.46 to –0.10); P<0.01] (*Table S1*).

With respect to respiratory assessment, we found an effect of RATS on plateau pressure increase [β =4.82 (3.58 to 6.05); P<0.01] and on end-tidal expiratory CO_2 increase [β =2.18 (1.04 to 3.31); P=0.001] despite a significant increase in the respiratory rate [β =0.23 (0.14 to 0.32); P<0.01] (*Table S1*).

Discussion

To our knowledge, our study is the first prospective comparison of RATS and VATS. RATS was associated with an increased cumulated consumption of morphine on day 2. We also found haemodynamic and respiratory differences, suggesting significant effects of RATS.

The choice of the morphine consumption as a primary outcome seemed relevant because it is an indicator of postoperative pain, is an independent factor for postoperative complications, and is a quality marker of ERAS procedure (18,19). The increased use of morphine in the RATS group could be explained by the forced rib traction exerted during RATS without force-return to the surgeon, creating potential intercostal nerves lesions, and the addition of one utility incision in RATS compared to that in VATS. In a retrospective study, Kwon *et al.* found no differences in the morphine consumption and pain between patient undergoing RATS or VATS as compared to those undergoing open thoracotomy (20). Their study showed pain risk factors, such as age, sex, and pre-operative morphine use. In our study, we used age and sex for elaborating a propensity score matching. The patients with preoperative morphine use were excluded from our study.

Regarding the haemodynamic and respiratory assessment, our analyses suggests a significant role of CO_2 insufflation during RATS with a mean pressure of 8 mmHg. The heart rate increased during the RATS procedure, associated with decreased stroke volume; however, the cardiac index remained unchanged. This may indicate that the venous return was more impaired in patients undergoing RATS

Table 2 Comparison of morphine consumption and pain evaluation between patients undergoing VATS or RATS before and after propensity score-matching

Variable	Full cohort			Matched cohort		
	VATS (n=95)	RATS (n=84)	P	VATS (n=75)	RATS (n=75)	P
Continuous infusion PVB (%)	13 (13.7)	23 (27.4)	0.02	8 (10.7)	19 (25.3)	0.02
VAS on day 1	2.3 [1.3–3.0]	2.5 [1.5–3.7]	0.14	2.3 [1.3–3.1]	2.6 [1.5–3.8]	0.15
Coughing VAS on day 1	4.0 [3.0–5.0]	5 [3.8–6.0]	0.01	4.0 [3.0–5.0]	5 [3.5–6.0]	0.05
Morphine consumption on day 1 (mg)	20 [12–35]	21 [12–34]	0.7	20 [12–29]	23 [12–35]	0.51
VAS on day 2	1.8 [1.0–2.8]	2.0 [1.0–3.3]	0.16	1.8 [1.0–3.0]	2.0 [1.0–3.0]	0.22
Coughing VAS on day 2	3.0 [2.0–4.5]	4.0 [2.0–5.3]	0.06	3.0 [2.0–4.5]	4.0 [2.0–5.0]	0.25
Morphine consumption on day 2 (mg)	23 [16–42]	32 [19–47]	0.12	23 [17–39]	33 [19–47]	0.05
Surgery duration (min)	140 [105–173]	155 [130–180]	<0.01	140 [110–168]	155 [130–180]	<0.01
Anaesthesia duration (min)	215 [190–235]	243 [215–261]	<0.001	215 [190–235]	243 [214–260]	<0.001
Sufentanil use during surgery (μg)	44.8 (±14)	50.3 (±12)	0.02	44.5 (±15)	50.6 (±12)	0.02
Treated urinary retention (%)	6 (6.3)	14 (16.7)	0.03	5 (6.7)	11 (14.7)	0.11
Treated vomiting or nausea (%)	9 (9.5)	6 (7.1)	0.57	8 (10.7)	5 (6.7)	0.38
Any postoperative complications (%)	35 (36.8)	34 (40.5)	0.61	30 (40.0)	31 (41.3)	0.86
Post-operative complication, grade [%]						
1	8 [23]	7 [21]	0.12	6 [20]	6 [19]	<0.01
2	11 [31]	21 [62]		8 [27]	21 [68]	
3a	9 [25]	4 [12]		9 [30]	3 [10]	
3b	3 [9]	1 [3]		3 [10]	0 [0]	
4	3 [9]	1[3]		3 [10]	1 [3]	
5	1 [3]	0 [0]		1 [3]	0 [0]	
Chest tube duration (days)	2.0 [2.0–4.0]	3.0 [2.0–4.0]	0.15	2.0 [2.0–3.5]	3.0 [2.0–4.5]	0.44
Hospitalisation duration (days)	4.0 [3.0–6.0]	4.5 [3.0–7.0]	0.92	4.0 [3.0–6.0]	4.0 [3.0–7.0]	0.64

PVB, Paravertebral block; VAS, visual analogic pain score.

than in those undergoing VATS. It is noteworthy that stroke volume variations increased during RATS. This could be attributable to inadequate fluid resuscitation, impaired right ventricular function, or a non-relevant measurement technique. The elevation of plateau pressure associated with insufflation pressure of CO_2 suggests increased heart-lung interaction in RATS. However, we cannot rule out the usefulness of pulse contour analysis in these patients. Effect of CO_2 insufflation has been widely described during abdominal celioscopic surgery on haemodynamic and respiratory impairment and increased pain (21). Even if the effect of CO_2 reabsorption may be comparable, effects of CO_2 reabsorption during RATS need to be confirmed in future studies.

Regarding the rate of major complications and open-surgery conversion, RATS appears to be a safer procedure. The number of minor complications was higher in the RATS group. However, there was an increase in the post-operative atrial fibrillation in the RATS group, if the open-procedure conversions were excluded. This could be secondary to pericardial irritation with CO_2. Velez-Cubian *et al.* described atrial fibrillation as a frequent complication following RATS. An association between postoperative atrial fibrillation and impaired outcome was reported (22).

Our study has certain limitations. First, although this was a prospective study, our subjects were not randomised. We attempted to minimise this bias by using propensity score-matched analyses. However, undetermined variables may have influenced the differences determined between the RATS and VATS groups. For instance, in our institution, RATS is a recent procedure, while VATS is a standard treatment. However, our findings underline the need for a randomised clinical trial that assesses the relevance of RATS compared to VATS. Another issue is that the use of PVB with or without continuous infusion of an anaesthetic solution differed between the two groups. This is attributable to the gradual arrival of the "one shot" PVB technique in our centre that aims to decrease catheter use promoted by our fast recovery protocol. However, our statistical analyses considered this difference by means of multivariate regression models. In fact, we showed that continuous infusion was associated with lower morphine use. Thus, this reinforces our result, underlining the higher morphine consumption associated with the RATS group. VATS and RATS were performed by different surgeons, leading to potential bias. This is explained by the shared robotic material with other surgery units and the minimal learning curve for RATS (20 to 30 procedures) that explained the need of concentrate the use other 2 of the 4 broad-certified surgeons of our center (14). Finally, the use of clearsight™ for haemodynamic measurement is questionable. Though this device has been validated in cardiac surgery against thermodilution, it has not been validated during one-lung ventilation (23). However, the use of this volume clamp monitoring technique on the ipsilateral side of surgery is believed not to interfere with any arterial compression or intrathoracic manipulation (24).

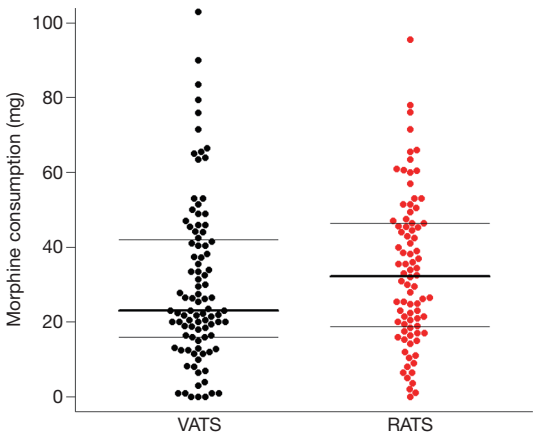

Figure 1 Box plot of morphine consumption on day 2. Lines represent median [interquartile range (IQR)]. VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery.

In conclusion, our results show that RATS is associated with a higher postoperative morphine consumption. In addition, it highlights the haemodynamic and respiratory effects associated with RATS. Finally, in our cohort, the RATS procedure appeared safer than VATS.

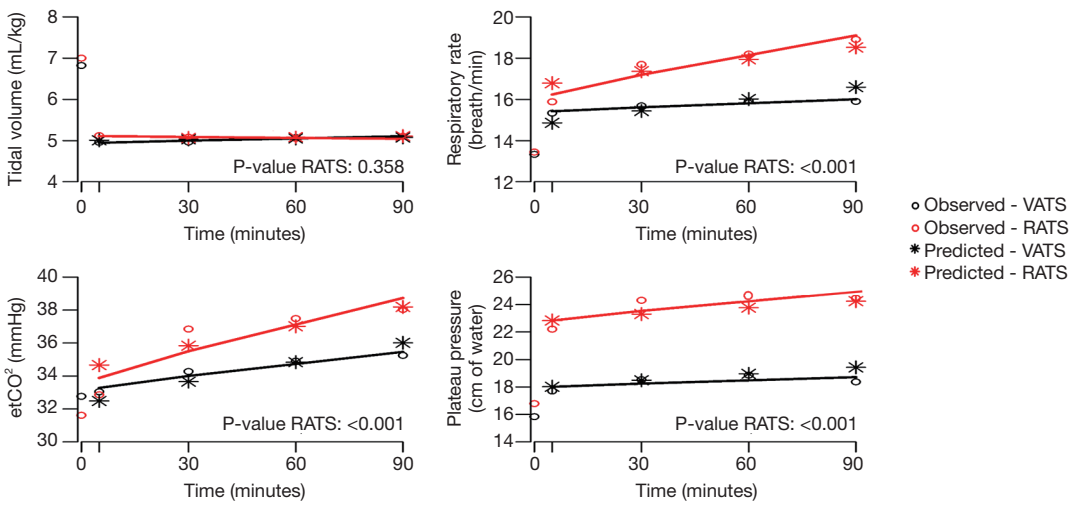

Figure 2 Evolution over time of the haemodynamic data from a multivariate linear regression model. Circles represent the measured data. Stars represent modelised predicted data. VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery.

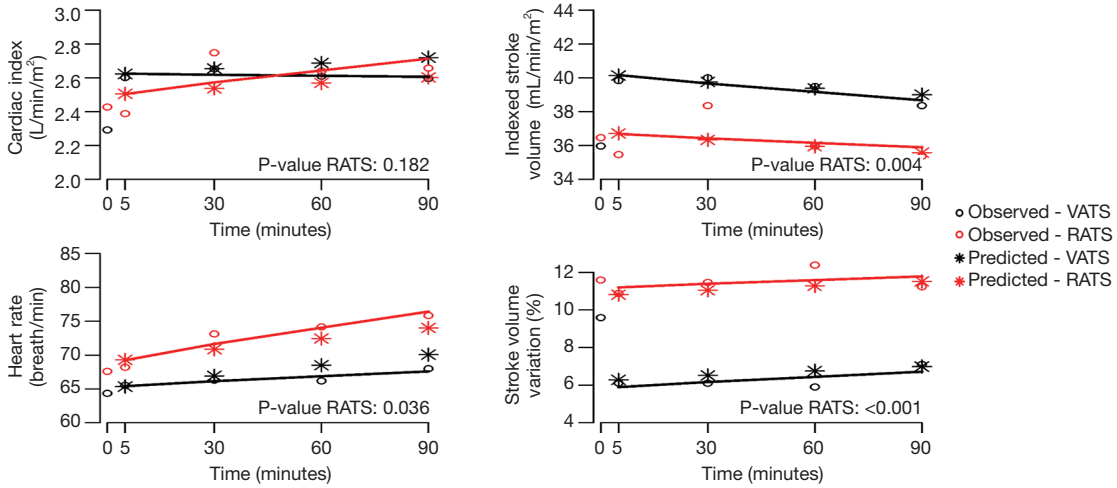

Figure 3 Evolution over time of the respiratory data from a multivariate linear regression model. Circles represent the measured data. Stars represent modelised predicted data. VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery.

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Footnote

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

Ethical Statement: This research trial was approved by our Liberty and Informatics Committee (2016-18) and by the SFAR IRB (CERAR 00010254-2016-049). The study period ranged from January 2016 to March 2017. Written and oral information regarding the study purpose and procedures was given to all the patients before enrolling them, and written consents were collected.

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Supplementary

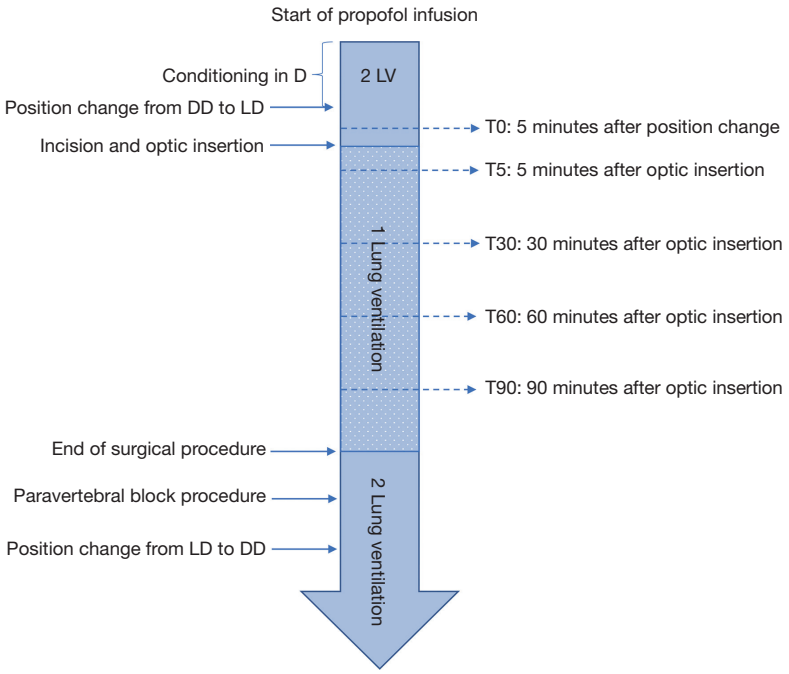

Figure S1 Intraoperative protocol of data collection. LV, lung ventilation; DD, dorsal decubitus; LD, lateral decubitus.

File 1 Intraoperative anaesthesia protocol

Surgical procedure

In accordance with the national and international guidelines, all operable patients referred to our high-volume academic institution with suspected clinical stage I NSCLC were offered a minimally invasive approach, either VATS or RATS (10,11) This study also included few patients who presented with benign conditions that necessitated lung resection. Two board-certified academic staff surgeons performed all the RATS procedures and performed or supervised all the VATS procedures. Patients were thus allocated either to the VATS or to the RATS group depending on the surgeon's recruitment.

Our VATS program was initiated in the early 90's (12). In 2010, we adopted the so-called totally thoracoscopic technique described by Gossot *et al.* (13). Accordingly, VATS pulmonary resections were performed using a 3-port technique, and no utility incision was used. The RATS procedures were performed with a da Vinci Surgical System Si (Intuitive Surgical Inc., Sunnyvale, CA, USA) available at our institution since Spring 2015. Among the four staff surgeons of the surgical team, two were previously identified to follow the step-by-step dedicated training. Both the RATS surgeons completed their clinical learning by 2015. The number of operations required was estimated to be 20, according to the literature (14). The 3-arm technique was used as routine, with an additional incision through which staplers were inserted and used by the assistant surgeon. Intrathoracic CO_2 insufflation was used only in the RATS group.

On completion of the VATS or RATS pulmonary resection, the specimen was retrieved through a port site that was slightly enlarged, depending on the specimen size. The use of a rib spreader was not required for this task. In all cases, only one chest tube was placed through one of the port sites and was connected to a portable suction drainage system. Its removal was decided based on the standard guidelines, that is, no air leakage and output of <200 mL/day.

Specific anaesthetic procedures

Perioperative anaesthetic protocol

Anaesthesia management was performed according to our protocol. For induction, propofol was used at an initial effect-site target concentration between 4 and 6 µg/mL using a target-controlled infusion device with a built-in modified Schneider model (Orchestra™ Base Primea; Fresenius Vial, Brézins, France). Sufentanil was administered as a single bolus (0.1 to 0.3 µg/kg). Cisatracurium was administered as the initial bolus (0.15 to 0.2 mg/kg). The trachea was intubated with a double lumen

tube of Carlens™ type.

For anaesthesia maintenance, a continuous infusion of propofol with site effect target concentration between 3 and 5 µg/mL was used. The anaesthesia depth was measured using the BIS (BIS™, Philips M1034A, Eindhoven, The Netherlands) with a target between 40 and 60. The muscle relaxant effect was measured using TOF monitoring with a target at 0–1 count on the ulnar nerve. All patients were monitored using an intranasal thermic probe.

Surgery was performed with the patient in the lateral decubitus position, depending on the surgery side. After incision, one-lung ventilation was initiated. Mechanical ventilation during one lung ventilation was set for a tidal volume of 5 mL/kg of the ideal weight, positive end-expiratory pressure of 5 cmH_2O, and oxygen fraction of 0.6 to 1 for an oxygen saturation of ≥95%.

Paravertebral block protocol

All patients received a unilateral paravertebral block (PVB) established by the in-charge anaesthesiologist at the end of the procedure using either anatomic, using the loss-of-resistance technique, or ultrasound-guided, using the in-plane approach, aiming the 5th thoracic vertebral level. For improving rehabilitation, our protocol recommends a single shot; however, the use of continuous infusion was at the anaesthesiologist's discretion. A 10-mL bolus of 10 mg/mL xylocaine with 0.005 mg/mL adrenaline was used to check for the absence of intravasculaire infusion. Thereafter, a 20-mL bolus of 5% ropivacaine was administered as a single shot (in the operative room) or before the onset of continuous infusion of 2% ropivacaine (in the postoperative room) in case of catheter use after its placement was evaluated using chest radiography with opacification. Patients were monitored for at least 30 minutes for signs of local anaesthetic toxicity and efficiency of PVB using cold tests. When catheters were used, the infusion protocol involved the use of ropivacaine 2% with degressive infusion posology other time (24 mg/hour on day 1 to 12 mg/hour on day 5). Catheters were removed at the team's discretion between day 3 and day 5.

Postoperative analgesic protocol

Thirty minutes before sedation interruption, all the patients received intravenous paracetamol and ketoprofen; for prevention of nausea and vomiting, 2.5 mg droperidol was administered. Pain was evaluated in the post-operative recovery room using a visual analogic scale (VAS) pain score. Titrated morphine was infused, if required, to achieve a VAS score <30. In the surgical unit, all the patients received a combination of intravenous paracetamol and ketoprofen as well as a patient-controlled analgesia pump (PCA) that was initiated in the recovery room. The morphine dilution was 1 mg/mL with the addition of 0.05 mg/mL droperidol. Boli were administered by patient: 1 mg every 7 minutes or 1.5 mg every 7 minutes for patients weighing >80 kg. Oral analgesics and narcotics were used if the venous lines were removed. Oral narcotics included oxycodone medication. VAS was evaluated every 4 to 6 hours and recorded. Oral narcotics were prescribed to patients whenever the VAS was >30 mm. An investigator collected data regarding narcotic consumption and VAS score during coughing for 48 h after the surgery.

Post-operative management

Post-operative management was performed according to our local protocol. All the patients underwent a standardised fast rehabilitation protocol, including early post-operative oral nutrition and armchair positioning (within 6 hours). ERAS protocol included a systematic daily respiratory rehabilitation, early ambulation with physiotherapist and oral transition of medication at day 1 if possible (adequate pain evaluation and absence of refractory vomiting). Chest tubes were removed as soon as possible after the post-operative chest radiography excluded exhaustive pneumothorax or pleural effusion.

Data collection

Pre-operative data collection

Demographic characteristics were extracted from the electronic medical chart. Age, sex, height, weight, side of surgery, and type of lung reduction were recorded. The ASA, Lee, and Apfel scores were computed. Respiratory function was assessed using pulmonary function testing, including forced expiratory volume in 1 second and the carbon monoxide diffusion capacity adjusted for the alveolar volume. The Thoracoscore and associated morbidity index were extracted from the EPITHOR database (15).

Smoking status was recorded, including the total tobacco use calculation and weaning. Patients were considered as weaned if they had stopped smoking for more than 4 weeks, as defined in the French guidelines for maximal clinical benefit (16).

Perioperative data collection

Patients were gradually included for perioperative data collection, depending on availability of the haemodynamic monitoring system that was shared with others surgical units. Patients included in the haemodynamic evaluation were monitored using a Clearsight™ system with adapted

EV 1000 monitoring station (Edwards Lifesciences, Irvine, California, USA). An appropriately sized sensor was placed around the second phalange of the second finger of the ipsilateral hand of the surgery to prevent arterial compression due to lateral decubitus. The anaesthesiologist in charge of the patient was blinded from the EV 1000 monitoring station that was placed on a parametric screen instead of on a monitoring screen, and data were collected using USB Key after the surgical procedure. Systolic, mean, and diastolic blood pressure, heart rate and cardiac index were assessed. Respiratory data were recorded from the ventilator readings (Primus, Dragër Medical, Lübeck, Germany), including the tidal volume, respiratory rate, positive expiratory pressure, oxygen fraction, oxygen arterial saturation, end-tidal CO_2, and tele-inspiratory plateau pressure. Data of train-of-four (TOF), bi-spectral index (BIS), and body temperature were collected. The insufflation pressure of carbon dioxide used during RATS and incidence of per-operative cardiac rhythm abnormalities were also recorded.

At the end of the procedure, the time from skin incision to skin closure (including the time taken for chest tubes fixation) was calculated. After PVB was established the time of anaesthesia and total consumption of propofol, sufentanil, cisatracurium, and fluid infusion were reported. In cases where a vasopressor was used, the type and dosage administered were noted.

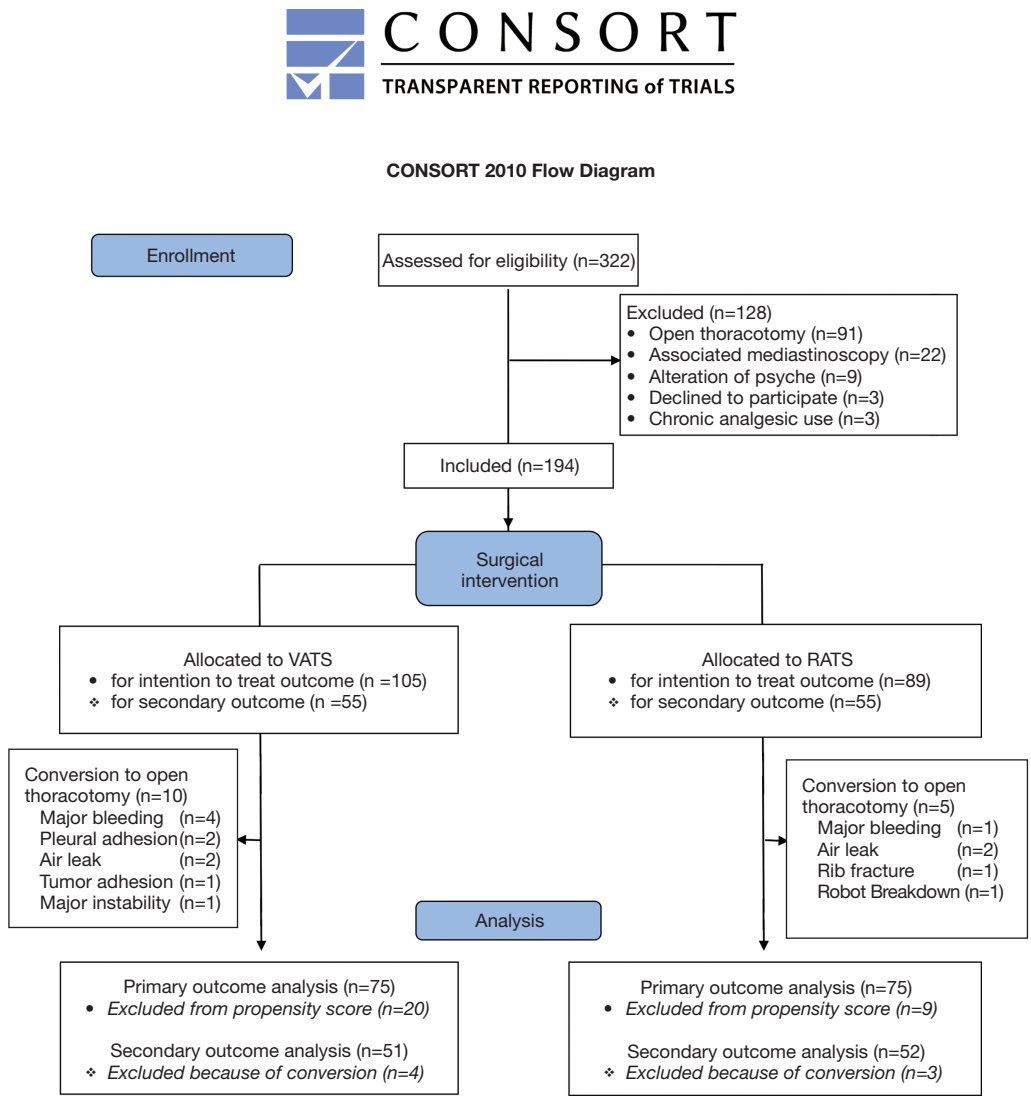

Figure S2 Consort flowchart. VATS, video assisted thoracic surgery; RATS, robotic assisted thoracic surgery.

Table S1 Intraoperative effect of time and of robotic surgery from linear regression

Variable	β (95% CI)	P
Hemodynamic assessment		
Evolution of cardiac index (L/min/m²)		
Effect of RATS (β)	0.12 (–0.29 to 0.05)	0.18
Effect of time (β)	0.03 (0.00–0.07)	0.06
Effect of T0 (β)	0.82 (0.69–0.96)	<0.001
Evolution of stroke volume (mL/m²)		
Effect of RATS (β)	–0.28 (–0.46 to –0.10)	<0.01
Effect of time (β)	–0.03 (0.06–0.01)	0.17
Effect of T0 (β)	0.61 (0.49–0.73)	<0.001
Evolution of heart rate (beat/min)		
Effect of RATS (β)	3.95 (0.32–7.57)	0.03
Effect of time (β)	1.57 (0.99–2.16)	<0.001
Effect of T0 (β)	0.74 (0.59–0.89)	<0.001
Evolution of stroke volume variation (%)		
Effect of RATS (β)	4.53 (3.40–5.66)	<0.001
Effect of time (β)	0.23 (–0.03 to 0.50)	0.07
Effect of T0 (β)	0.33 (0.08–0.47)	<0.001
Evolution of systolic arterial pressure (mmHg)		
Effect of RATS (β)	–2.53 (–7.83 to 2.77)	0.35
Effect of time	–1.96 (–3.32 to –0.61)	<0.01
Effect of T0	0.82 (0.16–0.44)	<0.001
Evolution of mean arterial pressure (mmHg)		
Effect of RATS (β)	0.10 (–3.75 to 3.95)	0.95
Effect of time (β)	–0.46 (–1.40 to 0.49)	0.34
Effect of T0 (β)	0.39 (0.24–0.54)	<0.001
Evolution of diastolic arterial pressure (mmHg)		
Effect of RATS (β)	1.82 (–1.48 to 5.12)	0.28
Effect of time (β)	–0.09 (–0.79 to 0.61)	0.80
Effect of T0 (β)	0.39 (0.24–0.54)	<0.001
Any use of vasopressor [%]*	17 [33]/25 [48]	0.12
Total fluid infusion (mL)*	1,470 (±570)/1,740 (±540)	0.01
Fluid infusion over time (mL/kg/min)*	5.6 (±2.2)/5.9 (±1.8)	0.72
Atrial fibrillation issue (%)*	0 (0)/4 (8%)	0.04
Respiratory assessment		
Evolution of tidal volume (mL/kg)		
Effect of RATS (β)	0.01 (–0.04 to 0.06)	0.69
Effect of time (β)	0.01 (0.00–0.01)	0.85
Effect of T0 (β)	0.2 (0.03–0.38)	0.02
Evolution of respiratory rate (breath/min)		
Effect of RATS (β)	0.23 (0.14–0.32)	<0.001
Effect of time (β)	0.07 (0.06–0.08)	<0.001
Effect of T0 (β)	0.27 (0.08–0.47)	<0.01
Evolution of end tidal capnography (mmHg)		
Effect of RATS (β)	2.18 (1.04–3.31)	<0.001
Effect of time (β)	1.18 (0.95–1.40)	<0.001
Effect of T0 (β)	0.20 (0.05–0.36)	<0.01
Evolution of plateau pressure (cmH_2O)		
Effect of RATS (β)	4.82 (3.58–6.05)	<0.001
Effect of time (β)	0.47 (0.26–0.68)	<0.001
Effect of T0 (β)	0.75 (0.54–0.96)	<0.001
Evolution of end to expiratory pressure (cmH_2O)		
Effect of RATS (β)	0.03 (–0.49 to 0.55)	0.91
Effect of time (β)	0.12 (0.06–0.17)	<0.001
Effect of T0 (β)	0.62 (0.35–0.89)	<0.001
Evolution of arterial oximetry (%)		
Effect of RATS (β)	–0.37 (–0.91 to 0.18)	0.19
Effect of time (β)	0.27 (0.12–0.42)	<0.001
Effect of T0 (β)	0.42 (–0.02 to 0.83)	0.06
Evolution of FIO_2 (%)		
Effect of RATS (β)	6.78 (2.46–11.10)	<0.01
Effect of time (β)	1.45 (0.65–2.26)	<0.01
Effect of T0 (β)	0.22 (0.02–0.42)	0.03

*, data were presented in RATS group/VATS group. BMI, body mass index; ASA; American society of Anesthesiologists.