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► To cite this version:

Elodie Berg, Leslie Madelaine, Jean-Marc Baste, Marcel Dahan, Pascal Thomas, et al.. Interest of anatomical segmentectomy over lobectomy for lung cancer: a nationwide study. *Journal of Thoracic Disease*, 2021, 13 (6), 10.21037/jtd-20-2203 . hal-03944267

HAL Id: hal-03944267

<https://hal.science/hal-03944267v1>

Submitted on 17 Jan 2023

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Interest of anatomical segmentectomy over lobectomy for lung cancer: a nationwide study

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Background: Anatomical segmentectomy is an alternative to lobectomy for early-stage lung cancer (LC) or in patients at high risk. The main objective of this study was to compare the morbidity and mortality associated with these two types of pulmonary resection using data from the French National Epithor database.

Methods: All patients who underwent lobectomy or segmentectomy for early-stage LC from January 1st 2014 to December 31st 2016 were identified in the Epithor database. The primary endpoint was morbidity; the secondary endpoint was postoperative mortality. Propensity score matching was implemented and used to balance groups. The results were reported as odds ratios (OR) and 95% confidence intervals (CI).

Results: During the study period, 1,604 segmentectomies (9.78%) and 14,786 lobectomies (90.22%) were performed. After matching, the segmentectomy group experienced significantly less atelectasis (OR 0.54; 95% CI: 0.4–0.75, $P<0.0001$), pneumonia (OR 0.72; 95% CI: 0.55–0.95, $P=0.02$), prolonged air leaks (OR 0.75; 95% CI: 0.64–0.89, $P=0.001$) or bronchopleural fistula (OR 0.35; 95% CI: 0.14–0.83, $P=0.017$), and fewer patients had at least one complication (OR 0.7; 95% CI: 0.62–0.78, $P<0.0001$). According to the Clavien-Dindo classification, postoperative complications were significantly less severe in the segmentectomy group (OR 0.52; 95% CI: 0.37–0.74, $P<0.0001$). There was no significant difference in postoperative mortality at 30 days (OR 0.67; 95% CI: 0.38–1.20, $P=0.18$), 60 days (OR 0.78; 95% CI: 0.42–1.47, $P=0.4$), or 90 days (OR 0.77; 95% CI: 0.45–1.34, $P=0.36$).

Conclusions: Anatomical segmentectomy is an alternative surgical approach that could reduce postoperative morbidity, but it does not appear to affect mortality.

Keywords: Segmentectomy; lobectomy; postoperative complications; mortality; early-stage lung cancer (early-stage LC)

Submitted Jun 13, 2020. Accepted for publication Mar 25, 2021.

doi: 10.21037/jtd-20-2203

View this article at: <http://dx.doi.org/10.21037/jtd-20-2203>

Introduction

Lung cancer (LC) remains the leading cause of mortality worldwide, and was responsible for 1,761,007 deaths in Europe in 2018 (1). In patients with localized LC, surgical

management remains the best curative treatment as indicated by the 2013 American College of Chest Physicians (ACCP) guidelines, which recommend lobar resection (2). In these guidelines, segmentectomy was described as an alternative to lobectomy in "compromised" patients if

margins greater than 2 cm could be achieved (2).

These guidelines are partly based on the results of the Lung Cancer Study Group which led a prospective, multi-institutional randomized trial comparing lobectomy to sublobar resection in 1995 (3). This trial showed that lobectomy was superior to sublobar resection. Therefore, and despite the limits of this trial including wedge resection, lobectomy was accepted as the standard resection for early LC. Since then, numerous papers comparing lobectomy and segmentectomy have been published regarding overall survival, but this topic remains controversial.

In recent years, the practice of segmentectomy has expanded. Several reasons could explain this trend: firstly, the increased incidence of early stage LC managed by surgery, secondly, the ageing of patients with localized LC, and, thirdly, the development of multimodal surgical navigation systems and minimally invasive surgery (4-9).

In 2019, the results of the first randomized control trial comparing anatomical pulmonary segmentectomy to lobectomy was published from data recorded in highly specialized Japanese centers (10). It did not highlight any differences in postoperative mortality, but revealed that, compared to lobectomy, segmentectomy was a predictor of severe pulmonary complications including air leaks and empyema (10). Data regarding overall survival were not yet available.

The main objective of our study was to compare morbidity for the two types of pulmonary resection using data from the Epithor National database. The secondary endpoint was postoperative mortality at 30, 60 or 90 days. The Epithor database collects data from more than 100 hospitals and is thus more representative of real-life thoracic surgery practices than databases that collect data from highly specialized centres alone. A Kernel matching analysis was used to yield a more powerful and comprehensive comparison of postoperative complications and mortality.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/jtd-20-2203>).

Methods

Data collection

Epithor is a government-recognized clinical database that is financed by the French National Cancer Institute (*Institute National du Cancer*) for data-quality monitoring. Epithor has been accredited as a methodologically

appropriate tool for assessing professional surgical practices by the French Health Authorities (*Haute Autorité de Santé*), a governmental agency dedicated to improving the quality of patient care and to guaranteeing equality within the health care system. French hospitals are now required to participate in Epithor in order to obtain their medical accreditation and thoracic surgery unit certification (11,12). Data accuracy has been checked in regular external on-site audits since 2010 (11).

Study population

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). From January 1st, 2014 to December 31st, 2016, 16,390 patients underwent segmentectomy or lobectomy for LC in France. Baseline demographic and clinical characteristics include age, gender, medical history (chronic bronchitis, tobacco use, chronic heart failure, alcoholism, neurological disease, haematological disease, cancer history, thoracotomy history, chronic respiratory failure), American Society of Anaesthesiologist (ASA) score, World Health Organization (WHO) performance status, body mass index (BMI), and forced expiratory volume (FEV1). The surgical technique was the video assisted thoracic surgery (VATS) or thoracotomy. For all patients, LC was diagnosed with pathology analyses according to the 2004 World Health Organization classification of LC (13).

Outcome measurements

The primary endpoint was postoperative complications, including atelectasis, prolonged air leaks (>5 days), bronchopleural fistula, pneumonia, haemorrhage, empyema or at least one complication (14). The Clavien-Dindo classification was used in order to assess the severity of the postoperative complications (14).

The secondary endpoints were postoperative mortality at 30, 60 and 90 days, defined as any patient who died within the first 90 days following surgery, or the initial hospitalization if longer.

Missing data

The proportion of missing information regarding tumour stage, lymph node involvement and quality of resection for this study were respectively 18%, 20.5% and 20%. We applied a multiple imputation framework to compensate for

missing FEV data. For the variable TNM stage, we created a variable category to include in the analysis. We assumed that the missing data were missing at random.

Statistical analysis

We used kernel matching algorithms that were developed from a nonparametric regression method for curve smoothing (15,16). A mirrored histogram was used to measure the discriminatory ability of the Kernel matching. Kernel matching used a search algorithm to find a set of weights for each covariate so that the version of optimal balance is achieved after matching (16). We evaluated the ability of Kernel matching to balance the measured covariates between segmentectomy and lobectomy by reducing the standardized difference (17). The standardized difference is the difference between sample means in the segmentectomy and lobectomy group divided by the standard deviation in the treatment group overall (18).

Finally, odds ratios (OR) were used for dichotomous variables: postoperative mortality and postoperative complications. For this study, we used Stata, version 14 (StataCorp, college station, TX, USA).

Results

Study cohort

Over the study period, 1,604 segmentectomies and 14,786 lobectomies were performed and recorded in the Epithor database.

Unmatched patient demographics, surgical management, tumour and hospital characteristics are presented in *Table 1*. In the segmentectomy group, the proportion of women and older patients was significantly higher. They were more likely to have a history of pulmonary disease, heart disease, cancer, or previous thoracotomy, and there was a higher proportion of ASA score ≥ 3 , performance status score ≥ 2 , BMI ≥ 28 kg/m² and lower FEV1 (*Table 1*). Segmentectomies were more often performed by VATS in higher volume non-teaching hospitals. The diagnoses was more often for stage I, without lymph node involvement, but segmentectomies resulted in more incomplete R1 or R2 resection (*Table 1*).

The characteristics of the matched groups are outlined in *Table 2*. In the matched samples, 1,594 patients in the

segmentectomy group were balanced with 14,477 patients in the lobectomy group. None of the patient characteristics were significantly different for the 2 groups (*Table 2*).

Kernel matching estimation

The mirrored histogram shows a well-balanced distribution of covariates after kernel matching (*Figure 1*). The median distribution of the standardized biases was of 0.045 for the kernel matching approach (*Table 2*). The standardized difference never reached the value of 10% (*Table 2*), indicating that the covariates were well balanced for the 2 groups.

Postoperative complications

After matching, we found that the segmentectomy group had significantly less atelectasis (OR 0.54; 95% CI: 0.4–0.75, $P < 0.0001$), pneumonia (OR 0.72, 95% CI: 0.55–0.95, $P = 0.02$), prolonged air leaks (OR 0.75, 95% CI: 0.64–0.89, $P = 0.001$), bronchopleural fistula (OR 0.35, 95% CI: 0.14–0.83), $p = 0.17$) or at least one complication (OR 0.7, 95% CI: 0.62–0.78, $P < 0.0001$). According to the Clavien-Dindo classification, the postoperative complications were significantly less severe in the segmentectomy group (OR 0.52, 95% CI: 0.37–0.74, $P < 0.0001$) (*Table 3*).

Postoperative mortality

There were no significant differences in postoperative mortality at 30 days (OR 0.67; 95% CI: 0.38–1.2, $P = 0.18$), 60 days (OR 0.78; 95% CI: 0.42–1.47, $P = 0.4$), or 90 days (OR 0.77; 95% CI: 0.45–1.34, $P = 0.36$).

Discussion

Almost 50 years ago, Jensik *et al.* was the first to suggest that segmentectomy could be equivalent to lobectomy in terms of overall survival and recurrence for early LC (19). However, in 1995, data from the LC Study Group indicated that lobectomy should be the standard procedure for early primary LC (3). Since then, considerable amounts of data have been published, including from large databases, yet no large randomized controlled trials (excluding wedge resection) have definitely settled the interest of segmentectomy over lobectomy for early primary LC, especially regarding overall survival and recurrence (20–25).

Table 1 Unmatched patient baseline characteristics

Patient characteristics	Segmentectomy (n=1,604)	Lobectomy (n=14,786)	P Value
Gender			
Male	972 (61%)	9,595 (65%)	0.001
Female	632 (39%)	5,191 (35%)	
Age (Years)	66±9	64±10	0.00001
Medical History			
Chronic bronchitis	466 (29%)	3,139 (21%)	0.0001
Smoker	365 (23%)	3,760 (25%)	0.02
Chronic heart failure	45 (3%)	301 (2%)	0.04
Alcoholism	99 (6%)	740 (5%)	0.04
Neurological disease	16 (1%)	204 (1.4%)	0.2
Anemia	1 (0.6%)	35 (0.24%)	0.15
Hematological disease	42 (2.6%)	255 (1.7%)	0.01
Cancer history	613 (38%)	4,225 (28%)	0.0001
Thoracotomy history	244 (15%)	988 (6.7%)	0.0001
Chronic respiratory failure	142 (9%)	856 (5.8%)	0.0001
ASA score			
1	308 (19%)	2,370 (16%)	0.0001
2	739 (46%)	7,699 (52%)	
≥3	557 (35%)	4717 (32%)	
Performance status			
0	827 (51.5%)	7,337 (50%)	0.002
1	611 (38%)	6,202 (42%)	
≥2	166 (10.5%)	1,247 (8%)	
Body mass index			
<24 Kg/m ²	695 (43%)	6,634 (45%)	0.16
24 to 28 Kg/m ²	435 (27%)	4,114 (28%)	
>28 Kg/m ²	474 (30%)	4,038 (27%)	
Forced expiratory volume (%)	82±20	85±20	0.00001
Surgical Management			
VATS	942 (59%)	6,121 (41%)	0.0001
Hospital characteristics			
Hospital volume	226±236	208±197	0.0005
Type			
Non-teaching hospital	171 (11%)	1,325 (9%)	0.04
Private hospital	551 (34%)	5,006 (34%)	
Teaching hospital	876 (55%)	8,441 (57%)	

Table 1 (continued)

Table 1 (continued)

Patient characteristics	Segmentectomy (n=1,604)	Lobectomy (n=14,786)	P Value
Postoperative pathological tumour characteristics			
Stage			
I	906 (56%)	5,850 (40%)	0.0001
II	278 (17%)	4,465 (30%)	
III	82 (5%)	1,842 (12%)	
IV	47 (3%)	448 (3%)	
Missing	291 (18%)	2,181 (15%)	
Lymph node involvement			
N0	1,139 (71%)	9,393 (63.5%)	0.0001
N1	72 (4.5%)	1,470 (10%)	
N2	65 (4%)	1,671 (11%)	
Missing	328 (20.5%)	2,252 (15%)	
Quality of resection			
R0	1,273 (79.4%)	12,289 (83%)	0.0001
R1	18 (1%)	291 (2%)	
R2	9 (0.6%)	57 (0.4%)	
Missing	304 (20%)	2,149 (14.6%)	

Table 2 Patients' baseline characteristics after kernel matching with their standardized difference

Patient characteristics	Segmentectomy (n=1,594)	Lobectomy (n=14,477)	P value	Standardized difference
Gender				
Female	39%	39%	0.9	0.002
Age (minus mean) (years)	1.11	1.08	0.9	0.003
Medical history				
Chronic bronchitis	29%	29%	0.9	0.003
Smoker	23%	23%	0.9	0.002
Chronic Heart failure	3%	2%	0.9	0.003
Alcoholism	6%	6%	0.9	0.003
Neurological disease	1%	1%	0.9	-0.005
Hematological disease	2.6%	2.7%	0.9	-0.004
Cancer history	38%	38%	0.8	0.009
Thoracotomy history	15%	15%	0.7	0.015
Chronic respiratory failure	9%	9%	0.9	0

Table 2 (continued)

Table 2 (continued)

Patient characteristics	Segmentectomy (n=1,594)	Lobectomy (n=14,477)	P value	Standardized difference
ASA score				
2	46%	47%	0.7	-0.012
≥3	35%	34%	0.9	0.006
Performance status				
1	38%	38%	0.9	-0.001
≥2	166 (10.5%)	1247 (8%)	0.9	0.002
Body mass index				
24 to 28 Kg/m ²	27%	27%	0.9	0.004
>28 kg/m ²	29%	29%	0.9	0
Forced expiratory volume (%) [§]	0.045	0.045	0.9	0
Surgical management				
VATS	58.5%	59%	0.6	-0.017
Hospital characteristics				
Hospital volume (minus mean)	16	14.7	0.8	0.008
Type				
Teaching hospital	55%	55%	0.9	-0.003
Postoperative pathological tumour characteristics				
Stage				
II	17%	17%	0.7	0.012
III	5%	5%	0.7	0.008
IV	3%	3%	0.7	0.011
Missing	18%	19%	0.7	-0.012
Lymph node involvement				
N1	4.5%	4%	0.8	0.006
N2	4%	4%	0.8	0.006
Missing	20%	20%	0.9	-0.002
Quality of resection				
R1	1%	1%	0.8	0.005
R2	0.5%	0.5%	0.9	0.004
Missing	19%	19.6%	0.7	-0.013

A standardized difference greater than 0.1 (10%) represents meaningful imbalance in a given variable between treatment groups.

[§], polynomial transformation: $X = FEV/100 \cdot X^{-0.5} - 1.08$

Nowadays, the ACCP recommends segmentectomy over lobectomy in patients with a major risk of perioperative mortality or competing causes of death such as age or other co-morbidities (2). However, the outcomes of

segmentectomy and lobectomy have rarely been compared. In their recent randomized controlled trial, Suzuki *et al.* (10) reported finding no difference in postoperative outcomes between the two approaches.

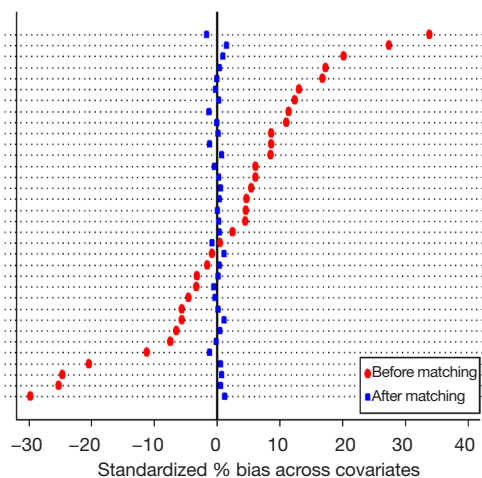


Figure 1 Standardized differences of covariates before and after matching.

Postoperative mortality

After matching, our analysis found no difference in mortality rates between the two types of pulmonary resection, even after 90 days. Other single centre studies have highlighted comparable results: there was no decrease in postoperative mortality even though it could have been expected after a more limited resection (26-28). Only Zhang *et al.*, who reported data from ten different centres including 106 segmentectomies with 1,164 lobectomies, showed a trend towards decreased postoperative mortality after segmentectomy compared with lobectomy (0.9% *vs.* 5%, $P=0.0894$). As mentioned above, Suzuki *et al.* found similar postoperative mortality after comparing 552 segmentectomies with 554 lobectomies. Their randomized trial was conducted in almost 10 centres with surgeons highly-skilled in the practice of complex segmentectomy, which could explain the lack of difference. Furthermore, the ongoing increase in quality of care has led to a dramatic decrease in postoperative mortality after lobectomy. In recent studies, hospital mortality after lung resection ranges from 0.9% to 2.3% in clinical databases and from 1.8% to 3% in administrative databases (29-31). The progressive improvement in quality of care has likely reduced the difference in outcomes between segmentectomy and lobectomy.

Postoperative complications

Though postoperative mortality was similar in the two

groups, postoperative complications appeared to be significantly more frequent in the lobectomy group. We found that patients were more likely to have at least one complication after lobectomy, with an OR of 0.7 in favour of segmentectomy. Deng *et al.*, reporting data from the Mayo Clinic, showed that after matching of 177 segmentectomies to 531 lobectomies operated by open thoracotomy, there were fewer complications in the segmentectomy group (32.2% *vs.* 41.6%, $P=0.02$). However, this difference disappeared when they used a matching analysis to compare patients who were operated with a VATS approach (28).

Ohtsuka *et al.*, whose study compared 61 segmentectomies to 61 lobectomies after propensity score matching, highlighted a higher rate of postoperative complications after segmentectomy, mostly due to pulmonary air leaks (32). Air leaks may occur more often after segmentectomy because a longer section of pulmonary parenchyma is stapled or because the intersegmental plane is divided using electrocautery and then covered with a fibrin sealant. Others studies have reported similar rates of air leaks in both segmentectomy and lobectomy (26,27,33). Our study showed comparatively fewer pulmonary air leaks after segmentectomy. In our opinion, because the remaining segment is placed against the remaining lobes after segmentectomy, the duration of air leaks should be shorter.

Moreover, we found fewer postoperative pulmonary complications after segmentectomy, whether it was atelectasis or pneumonia. These complications are rarely mentioned in the literature, and the mechanisms are uncertain. Suzuki *et al.* highlighted more pulmonary air leaks or fistula after segmentectomy (6.5% *vs.* 3.8%), but they did not distinguish between pulmonary air leaks and bronchial fistula. Two additional studies found similar levels or less pneumonia after lobectomy. These varying results are difficult to explain. Our study includes a large number of lobectomies for which we were not able to specify the location of the resected lobe. So, as previously described, patients who undergo lobectomy have a higher risk of developing air leaks, especially after upper lobectomy (34). Regarding atelectasis or pneumonia, we did not find any explanation in the literature. We believe that these differences may be linked to the fact that segmentectomy preserves more lung function than lobectomy, resulting in earlier rehabilitation and a decrease in postoperative pulmonary complications; the differences may also be associated with the quality of patient outcomes data entered in the database (35).

Table 3 Comparison of outcome variables in segmentectomy vs. lobectomy in kernel matched sample

	Segmentectomy (n=1,594)	Lobectomy (n=14,477)	OR (95% CI)	P value
Postoperative complications				
Atelectasis	2.5%	4.4%	0.54 (0.4–0.75)	0.0001
Prolonged air leak (>5 days)	7.8%	9.8%	0.75 (0.64–0.89)	0.001
Broncho-pleural fistula	0.19%	0.5%	0.35 (0.14–0.83)	0.017
Pneumonia	4.7%	6.2%	0.72 (0.55–0.95)	0.02
Haemorrhage	1.2%	1.5%	0.79 (0.5–1.24)	0.3
Empyema	0.25%	0.48%	0.5 (0.14–1.76)	0.3
At least one complication	27%	34%	0.7 (0.62–0.78)	0.0001
Clavien-Dindo Classification				
IIIa or IIIb or IVa or IVb or V	4.6%	8.5%	0.5 (0.36–0.68)	0.0001
IVa or IVb or V	2.7%	4.9%	0.52 (0.37–0.74)	0.0001
Postoperative mortality				
30-day mortality	1%	1.3%	0.67 (0.38–1.2)	0.18
60-day mortality	1.4%	1.7%	0.78 (0.42–1.47)	0.4
90-day mortality	1.6%	1.9%	0.77 (0.45–1.34)	0.36

Severity of postoperative complications

We found that segmentectomy halved the risk of developing a severe postoperative complication (higher than grade IIIa in the Clavien–Dindo classification, meaning that the patient needs additional surgical management under local anaesthesia or more) (14). In their trial, Suzuki *et al.* used the Common Terminology Criteria for Adverse Events (CTCAE) to define their complications (10). They found no difference in the occurrence of complications needing additional surgical management or a prolonged hospital stay when they compared the two types of pulmonary resection. Handa *et al.* showed that patients were more likely to develop a grade IIIa complication or higher after lobectomy than after segmentectomy (9.6% vs. 3%, $P=0.076$), but the results did not reach significance, probably due to the study's small sample size (26).

Strengths and limitations

The main strengths of this study are the use of a national database, which provided a large number of patients and a homogeneous population. In addition, the large number of patients in both groups allowed us to make powerful

comparisons. The homogeneous population reduced the sample size needed for the matching comparison, and the reasonable length of the study period decreased historical bias.

However, any study involving a large database raises the question of the quality and exhaustiveness of the prospectively entered data such as comorbidities, and observational studies are notoriously full of missing values. Few details were available about the surgical technique, especially concerning the location of the resected segment, the type of the segmentectomy (simplex or complex), the value of the preoperative of diffusing capacity of the lung for carbon monoxide (DLCO), the value of the cardiopulmonary exercise testing, or postoperative predicted FEV1 value. We used Kernel matching to create comparable cohorts; however, we cannot be certain that the Kernel matching perfectly neutralized all of the confounding variables.

Conclusions

Anatomical segmentectomy is a surgical alternative that could reduce the occurrence and severity of postoperative complications. However, segmentectomy was not found to impact postoperative mortality at 30 days, 60 days or 90 days.

Acknowledgments

This work was performed on behalf of the French Society of Thoracic and Cardiovascular surgery (Société Française de Chirurgie Thoracique et CardioVasculaire – SFCTCV). We are grateful to all the French thoracic surgeons who participated in this study and have been listed in [Appendix 1](#). The authors would like to thank Suzanne Rankin (Dijon University Hospital) for reviewing the manuscript.

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/jtd-20-2203>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-20-2203>). JMB reports personal fees from INTUITIVE SURGICAL, outside the submitted work. PBP reports personal fees from INTUITIVE SURGICAL, personal fees from MEDTRONIC, outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional ethical approval and Individual informed consent were waived.

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Cite this article as: Berg E, Madelaine L, Baste JM, Dahan M, Thomas P, Falcoz PE, Martinod E, Bernard A, Pagès PB. Interest of anatomical segmentectomy over lobectomy for lung cancer: a nationwide study. *J Thorac Dis* 2021;13(6):3587-3596. doi: 10.21037/jtd-20-2203

Appendix 1

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