KJTCVS
The Korean Journal of Thoracic and Cardiovascular Surgery
https://doi.org/10.5090/kjtcs.2020.53.3.104
pISSN: 2233-601X eISSN: 2093-6516
Korean J Thorac Cardiovasc Surg. 2020;53(3):104-113

Clinical Research

Nodal Outcomes of Uniportal versus Multiportal Video-Assisted Thoracoscopic Surgery for Clinical Stage I Lung Cancer

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ARTICLE INFO
Received August 26, 2019
Revised October 18, 2019
Accepted October 30, 2019

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Background: Accurate intraoperative assessment of mediastinal lymph nodes is a critical aspect of lung cancer surgery. The efficacy and potential for upstaging implicit in these dissections must therefore be revisited in the current era of uniportal video-assisted thoracoscopic surgery (VATS).
Methods: A retrospective study was conducted in which 544 patients with stage I (T1abc–T2a, N0, M0) primary lung cancer were analyzed. To assess risk factors for nodal upstaging and to limit any imbalance imposed by surgical choices, we constructed an inverse probability of treatment-weighted (IPTW) logistic regression model (in addition to non-weighted logistic models). We also evaluated risk factors for early locoregional recurrence using IPTW logistic regression analysis.
Results: In the comparison of uniportal and multiportal VATS, the resected lymph node count (14.03±8.02 vs. 14.41±7.41, respectively; p=0.48) and rate of nodal upstaging (6.5% vs. 8.7%, respectively; p=0.51) appeared similar. Predictors of nodal upstaging included tumor size (odds ratio [OR], 1.74; 95% confidence interval [CI], 1.12–2.70), carcinoembryonic antigen level (OR, 1.11; 95% CI, 1.04–1.18), and histologically confirmed pleural invasion (OR, 3.97; 95% CI, 1.89–8.34). The risk factors for locoregional recurrence within 1 year were found to be number of resected N2 nodes, age, and nodal upstaging.
Conclusion: Uniportal and multiportal VATS appear similar with regard to accuracy and thoroughness, showing no significant difference in the extent of nodal dissection.

Keywords: Lung neoplasms, Nodal upstaging, Single port video-assisted thoracic surgery, Uniportal, Video-assisted thoracic surgery

Introduction

Mediastinal lymph node staging is an essential part of the assessment and management of patients with early-stage lung cancer. Since the extent of lymph node involvement is the most important prognostic factor in these patients, it heavily influences therapeutic strategies [1]. According to the current consensus and guidelines, preoperative invasive mediastinal lymph node assessment is recommended via endobronchial ultrasound-transbronchial needle aspiration, endoscopic ultrasound, mediastinoscopy, or video-assisted thoracoscopic surgery (VATS). Patients with peripherally-situated clinical stage IA tumors, normal-sized lymph nodes, and negative position-emission tomography and computed tomography studies (PET/CT) are exceptions [2]. However, clinical practice patterns seem to vary substantially and often depart from these guidelines. Inaccurate preoperative staging heightens the role of mediastinal node removal at the time of resection in staging [3,4].

Controversy lingers regarding the survival benefit of dissecting versus sampling mediastinal nodes, but systematic nodal dissection is recommended in all cases to ensure compliance with evidence-based guidelines adopted in Europe and the United States [1,5]. Although the extent of nodal dissection has yet to be stipulated, most current guidelines and studies recommend that at least 3 N2 nodes be examined, and to ensure pathologic N0 status, at least 6

nodes from the hilar and mediastinal stations should be removed [5,6].

Since the first VATS lobectomy for lung cancer (in the early 1990s), the feasibility, safety, benefits and oncologic outcomes of VATS have compared favorably with thoracotomy [7]. Advances in instrument technology and video-assisted surgery now allow for fewer ports than before (now 1 or 2). The first report of uniportal VATS was published in 2011. Subsequent data on clinical outcomes, feasibility, and safety have since dispelled concerns of inferiority [8-10]. However, single-port mediastinal lymph node dissection (MLND) presents a technical challenge that few studies have attempted to address [11,12].

The purpose of this study was to investigate uniportal and multiportal VATS in patients with clinical T1abc–T2a N0 lung cancer by analyzing differences in the extent of MLND and the incidence of nodal upstaging. We also assessed the likelihood and clinical implications of nodal upstaging.

Methods

Patient cohort

This retrospective review drew upon prospectively-collected institutional data. We identified patients who underwent surgical treatment of primary lung cancer with curative intent between August 2010 and October 2018. The grounds for exclusion were as follows: (1) T stage T2b or higher, (2) clinical N1 or N2 disease, (3) wedge resection or surgery with non-curative intent, (4) bilobectomy, and (5) surgical thoracotomy or conversion of VATS to open thoracotomy (Fig. 1). To emphasize the standard practice of lymph node dissection, we intentionally excluded data from patients who underwent wedge resection (n=45), bilobectomy (n=7), or VATS-to-thoracotomy conversion (n=10). We also excluded patients with sizeable (>40-mm) tissue-confirmed tumors that were preoperatively assessed as clinical stage I but proved instead to be stage II (n=9). One-sleeve lobectomy was categorized simply as lobectomy.

Both chest CT and PET/CT findings were used to define clinical N0 lung cancer. A lymph node with a short-axis diameter of less than 1 cm on an axial CT scan and no significant focal fluorodeoxyglucose uptake on PET/CT was defined as clinical N0 [7].

Locoregional recurrence was defined as recurrent disease at the bronchial stump, stapled margin, ipsilateral hilum or mediastinum, ipsilateral pleura, or ipsilateral chest wall

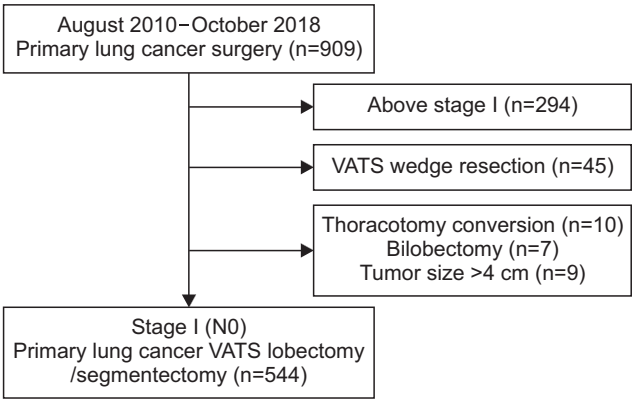

Fig. 1. Study flowchart, with counts and reasons for exclusion. VATS, video-assisted thoracoscopic surgery.

[13,14]. Early locoregional recurrence was defined in this study as recurrence within 1 year after surgery. Distant metastasis was equated with a recurrent tumor of the ipsilateral or contralateral lung, contralateral mediastinum, supraclavicular lymph node, or extrathoracic location. The first date upon which imaging studies raised suspicion of recurrence was considered the date of recurrence for our purposes.

This study was approved by the institutional review board of Seoul St. Mary's Hospital (approval no., KC19RESI0521). The requirement for the informed consent of individual patients was waived on the basis of the retrospective design of this study.

Surgical techniques used in video-assisted thoracoscopic surgery

Our uniportal VATS program began in 2017. Each patient was placed in the lateral decubitus position with a semi-flexed arm, as in multiportal VATS procedures. In our uniportal approach, a working incision of 3–5 cm was made at the fourth or fifth intercostal space at the anterior axillary line as described previously [15]. A 10-mm 30° thoracoscope was used. The procedure was otherwise similar to multiportal VATS, in which 2 (n=22), 3 (n=2), or 4 (n=367) ports were created. For 2-port and 4-port VATS, the camera ports were placed over the seventh and eighth intercostal spaces, respectively, on the mid-axillary line. The utility incision for 4-port VATS was made at the fifth intercostal space, with 2 instrumental ports at the seventh intercostal space anteriorly and the remaining 2 at the sixth intercostal space posteriorly.

https://doi.org/10.5090/kjtcs.2020.53.3.104

Statistical analysis

Baseline characteristics were expressed conventionally, using mean±standard deviation for continuous variables and frequencies with percentages for categorical variables. The distributions of continuous variables were compared via the Student t-test or the Mann-Whitney U-test, depending on the results of the normality test. The chi-square test or the Fisher exact test were utilized to compare categorical variables. Risk factors for nodal upstaging were assessed via binary logistic regression analysis. Receiver operating curve analyses were performed to calculate the area under the curve for the tumor size and serum carcinoembryonic antigen (CEA) level in the prediction of nodal upstaging.

Given the observational nature of this study, surgical allocation to either the uniportal or the multiportal group was not random. To address this, we first used propensity scores (PS) to balance baseline variables and maximize the balance between the 2 groups. Variables included in the PS model were those that (in our institutional experience) influenced the decision to perform uniportal surgery: age, sex, presence of chronic obstructive pulmonary disease or interstitial lung disease, clinical tumor-node-metastasis stage, and type of surgery planned (lobectomy or segmentectomy). Because the distribution of PS within the 2 groups differed considerably, and the study cohort was of limited size, inverse probability of treatment weighting (IPTW) was applied [16,17]. The IPTW method has been shown to outperform simple logistic regression in the context of case-mix adjustment. Weights were extracted from the PS model to calculate the IPTW, after which the IPTW was utilized in each case to produce an average treatment among the treated (ATT) estimate. The ATT estimate accounted for the unavoidable non-random selection of surgical patients and facilitated coherence in PS matching [18]. In the assessment of the clinical significance of nodal upstaging, considering the differences in follow-up time, we used early locoregional recurrence within a 1-year period after surgery as another endpoint. The factors associated with early locoregional recurrence were assessed with IPTW logistic regression analysis. Two-sided p-values less than 0.05 were used to indicate statistical significance, and variables that demonstrated statistical significance in univariate analysis were incorporated into a multivariate model. All computations were facilitated by R freeware ver. 3.6.1 (R Project for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

Results

General characteristics of the patients and clinical outcomes

Ultimately, 544 patients (men, 242; women, 302) qualified for this study, all diagnosed with clinical stage I (T1abc or T2a N0M0) lung cancer. The mean age was 63.91 years (range, 30–85 years). Uniportal VATS was preferentially performed over multiportal VATS in women (65.0% versus 52.2%, p=0.016) and in patients with lower forced expiratory volume in 1 second (93.0±15.66 L versus 96.6±17.83 L, p=0.037), lower diffusing capacity for carbon monoxide as a percentage of predicted value (92.1%±15.07% versus 88.1%±18.02%, p=0.015), and smaller tumor size (1.86±0.83 cm versus 2.11±0.83 cm, p=0.002). There were no group-wise differences in age; smoking history; history of tuberculosis, chronic obstructive pulmonary disease, or interstitial lung disease; or history of contralateral lung surgery or extent of surgery (segmentectomy versus lobectomy). The median follow-up time for the overall cohort was 34 months. The total number of dissected lymph node was 14.03±8.02 for the uniportal group and 14.41±7.41 for the multiportal group (p=0.48).

Detailed data on patient enrollees are shown in Table 1 according to the type of surgery and the number of ports. Among members of the lobectomy group, no differences were observed between the uniportal and multiportal groups with regard to the distribution of major demographic characteristics, underlying lung disease, tumor histotype, preoperative forced expiratory volume in 1 second, CEA level, or the location or size of the tumor. The same was true of the segmentectomy group, with the exception that T1a/b/c tumors were more prevalent in the uniportal lobectomy group than in the multiportal lobectomy group (p=0.003).

Surgical outcomes are presented in Table 2. Regardless of the type of surgery performed, there were no significant differences in terms of operative time, postoperative morbidity, adjuvant treatment, or crude locoregional recurrence. For each type of surgery, the uniportal group exhibited lower blood loss volumes and shorter hospital stays than the multiportal group. Operative mortality was 0.55% (3 of 544), including 2 patients in the uniportal lobectomy group (1.6%) and 1 patient in the multiportal lobectomy group (0.3%). The causes of death were pneumonia and acute respiratory distress syndrome. No deaths occurred in the segmentectomy group.

Table 1. Patient characteristics by type of surgery and number of ports

Characteristic	Lobectomy			Segmentectomy		
	Uniportal (n=124)	Multiportal (n=342)	p-value	Uniportal (n=29)	Multiportal (n=49)	p-value
Male sex	46 (37.1)	162 (47.4)	0.062	9 (31.0)	25 (51.0)	0.138
Age (yr)	64.19±11.20	63.68±10.09	0.637	66.79±9.64	63.06±9.16	0.092
Smoking (pack-years)[a]	26.49±18.76	33.86±20.14	0.025	33.07±15.28	30.35±21.32	0.459
Smoking status			0.236			0.726
Current smoker	5 (4.0)	29 (8.5)		2 (6.9)	4 (8.2)	
Ex-smoker	33 (26.6)	94 (27.5)		12 (41.4)	15 (30.6)	
Never smoked	86 (69.4)	219 (64.0)		15 (51.7)	30 (61.2)	
Tuberculosis history	11 (8.9)	30 (8.8)	0.999	5 (17.2)	3 (6.1)	0.239
Chronic obstructive pulmonary disease	3 (2.4)	19 (5.6)	0.245	2 (6.9)	1 (2.0)	0.552
Interstitial lung disease	3 (2.4)	17 (5.0)	0.346	1 (3.4)	4 (8.2)	0.646
Previous lung operation	2 (1.6)	0	0.070	3 (10.3)	6 (12.2)	0.999
Forced expiratory volume in 1 second (% of predicted)	94.13±14.66	97.18±18.03	0.088	88±18.85	92.76±15.98	0.239
Diffusing capacity for carbon monoxide (%)	92.63±15.23	88.18±17.75	0.014	89.69±14.35	87.24±19.94	0.566
Carcinoembryonic antigen (ng/mL)	2.63±4.80	2.74±5.51	0.139	3.77±11.17	1.77±1.56	0.587
Clinical T stage			0.003			0.194
Tis	4 (3.2)	12 (3.5)		4 (13.8)	7 (14.3)	
T1a	12 (9.7)	24 (7.0)		12 (41.4)	11 (22.4)	
T1b	61 (49.2)	121 (35.4)		11 (37.9)	20 (40.8)	
T1c	32 (25.8)	92 (26.9)		2 (6.9)	5 (10.2)	
T2a	15 (12.1)	93 (27.2)		0	6 (12.2)	
Tumor location			0.627			0.532
Right upper lobe	44 (35.5)	136 (39.8)		5 (17.2)	9 (18.4)	
Right middle lobe	11 (8.9)	31 (9.1)		0	0	
Right lower lobe	30 (24.2)	68 (19.9)		5 (17.2)	13 (26.5)	
Left upper lobe	18 (14.5)	61 (17.8)		11 (37.9)	20 (40.8)	
Left lower lobe	21 (16.9)	46 (13.5)		8 (27.6)	7 (14.3)	

Values are presented as number (%) or mean±standard deviation.
[a]Data were derived from 161 available patients.

Nodal upstaging

Pathologic outcomes are shown in Table 3. The overall incidence of nodal upstaging in this cohort was 8.09% (44 of 544). From the perspective of uniportal versus multiportal surgery, the number of resected lymph nodes differed among the resected lobes, as follows: the right upper lobe (RUL), 17.2±9.2 versus 14.4±7.7, respectively); right middle lobe (RML), 9.7±4.8 versus 14.3±7.5; right lower lobe (RLL), 15.9±4.8 versus 16.4±8.2; left upper lobe (LUL), 10.7±7.2 versus 12.8±6.5; and left lower lobe (LLL), 11.5±6.0 versus 14.0±6.1. After Bonferroni adjustment, statistical significance remained present only between the uniportal LUL versus multiportal RLL and uniportal RUL versus multiportal LUL pairs. Regardless of the type of surgery performed, uniportal and multiportal VATS showed no significant differences in either nodal upstaging (10 [6.5%] versus 34 [8.7%], respectively; p=0.5) or resected node counts (14.03 versus 14.41, p=0.48). Likewise, the nature of surgery had no significant impact on nodal upstaging (Table 3). More lymph nodes were dissected in the lobectomy group than in the segmentectomy group, but the lymph node totals at each station did not differ significantly by number of ports within the lobectomy or segmentectomy groups. No significant differences were observed in the frequency of single or multi-station nodal metastasis according to the number of ports (p=0.999), type of surgery (p=0.999), histological findings (p=0.758), or resected lobe (p=0.384).

Factors associated with nodal upstaging

The factors associated with nodal upstaging were analyzed using univariate and multivariate logistic regression methods. Additionally, to reduce the imbalances associated with choice of treatment, we calculated PS and constructed the IPTW model before logistic regression was performed

https://doi.org/10.5090/kjtcs.2020.53.3.104

Table 2. Clinical outcomes by type of surgery and number of ports

Variable	Lobectomy			Segmentectomy		
	Uniportal (n=124)	Multiportal (n=342)	p-value	Uniportal (n=29)	Multiportal (n=49)	p-value
Operation time (min)	146.40±42.02	141.40±41.56	0.194	150.60±40.78	171.10±44.54	0.056
Blood loss (mL)	78.14±109.59	180.9±275.52	<0.001	86.55±120.04	161±157.90	0.001
Numerical Rating Scale on postoperative day 1	3.06±1.71	2.02±1.77	<0.001	3.28±1.91	1.55±1.44	<0.001
Postoperative complications	19 (15.3)	61 (17.8)	0.619	6 (20.7)	11 (22.4)	0.999
Prolonged air leak	9 (7.3)	47 (13.7)	0.082	2 (6.9)	9 (18.4)	0.196
Pneumonia	2 (1.6)	6 (1.8)	0.999	2 (6.9)	0	0.135
Bleeding[a]	2 (1.6)	2 (0.6)	0.289	0	0	-
Chylothorax	1 (0.8)	6 (1.8)	0.681	2 (6.9)	0	0.135
Hoarseness	1 (0.8)	4 (1.2)	0.999	1 (3.4)	1 (2.0)	0.999
Others	2 (1.6)	4 (1.2)	0.659	0	1 (2.0)	0.999
Adjuvant treatments			0.523			0.999
None	116 (93.5)	313 (91.5)		28 (96.6)	46 (93.9)	
Chemotherapy	8 (6.5)	24 (7.0)		1 (3.4)	3 (6.1)	
Chemoradiation	0	5 (1.5)		-		
Hospital stay duration (day)	5.2±4.44	6.5±5.84	0.003	4.9±5.50	7.5±9.63	0.029
Locoregional recurrence	6 (4.8)	20 (5.8)	0.848	1 (3.4)	4 (8.2)	0.646
Distant metastasis	5 (4.0)	30 (8.8)	0.129	0	5 (10.2)	0.151
In-hospital death	2 (1.6)	1 (0.3)	0.345	0	0	-
Follow-up duration (mo)	14.2±6.36	52.0±25.94	<0.001	14.9±6.77	53.4±21.88	<0.001

Values are presented as mean±standard deviation or number (%).
[a]Bleeding was defined as that requiring transfusion.

Table 3. Pathologic outcomes by type of surgery and number of ports

Variable	Lobectomy			Segmentectomy		
	Uniportal (n=124)	Multiportal (n=342)	p-value	Uniportal (n=29)	Multiportal (n=49)	p-value
Tumor size (cm)	2.01±0.82	2.17±0.81	0.087	1.22±0.53	1.68±0.85	0.017
Histology			0.585			0.752
Adenocarcinoma	108 (87.1)	285 (83.3)		27 (93.1)	42 (85.7)	
Squamous cell carcinoma	10 (8.1)	33 (9.6)		1 (3.4)	3 (6.1)	
Others	6 (4.8)	24 (7.0)		1 (3.4)	4 (8.2)	
Grade of differentiation			0.650			0.856
Well	44 (35.5)	137 (40.1)		21 (72.4)	33 (67.3)	
Moderate	62 (50.0)	153 (44.7)		6 (20.7)	13 (26.5)	
Poor	17 (13.7)	45 (13.2)		2 (6.9)	2 (4.1)	
Unknown	1 (0.8)	7 (2.0)		0	1 (2.0)	
Pleural invasion (PL1+)	17 (13.7)	63 (18.4)	0.267	2 (6.9)	5 (10.2)	0.999
Nodal upstaging	9 (7.3)	33 (9.6)	0.540	1 (3.4)	1 (2.0)	0.999
Positive lymph node station			0.685			0.606
N0	115 (92.7)	309 (90.4)		28 (96.6)	48 (98.0)	
N1	3 (2.4)	17 (5.0)		0	1 (2.0)	
Skip N2	2 (1.6)	4 (1.2)		1 (3.4)	0	
N1+N2	4 (3.2)	12 (3.5)		-	-	
No. of resected N1 nodes	6.91±3.80	6.98±4.69	0.537	3.17±1.95	5.29±4.56	0.021
No. of resected N2 nodes	8.95±6.19	8.15±5.39	0.368	2.83±3.39	4.67±6.24	0.183

Values are presented as mean±standard deviation or number (%).

Table 4. Factors predicting nodal upstaging per univariate logistic regression: non-weighted and weighted model

Variable	Non-weighted		Inverse probability of treatment-weighted	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	0.999 (0.970–1.030)	0.953	1.011 (0.980–1.045)	0.499
Male sex	1.153 (0.618–2.140)	0.652	1.030 (0.541–1.938)	0.928
Smoking (ref: never)				
Current smoker	1.329 (0.377–3.642)	0.614	1.104 (0.277–3.213)	0.870
Ex-smoker	1.103 (0.537–2.161)	0.781	1.124 (0.540–2.227)	0.745
Tuberculosis history	1.011 (0.294–2.655)	0.984	1.025 (0.043–0.966)	0.966
Chronic obstructive pulmonary disease	1.590 (0.366–4.840)	0.466	1.356 (0.305–4.142)	0.635
Interstitial lung disease	0.988 (0.155–3.450)	0.987	1.000 (0.000–1.000)	>0.999
Pathology (ref: adenocarcinoma)				
Squamous cell carcinoma	1.409 (0.465–3.492)	0.496	1.627 (0.579–3.886)	0.307
Others	1.109 (0.258–3.301)	0.869	1.016 (0.218–3.140)	0.981
Forced expiratory volume in 1 second	0.991 (0.974–1.009)	0.343	0.991 (0.973–1.009)	0.336
Diffusing capacity for carbon monoxide	0.997 (0.979–1.015)	0.768	0.998 (0.980–1.016)	0.806
Carcinoembryonic antigen	1.075 (1.031–1.134)	0.003	1.116 (1.052–1.194)	0.001
Tumor size	2.204 (1.528–3.222)	<0.001	2.333 (1.600–3.463)	<0.001
Operation time	1.006 (0.999–1.012)	0.069	1.005 (0.998–1.012)	0.125
Uniportal surgery	0.734 (0.336–1.473)	0.408	0.904 (0.414–1.824)	0.788
Segmentectomy	0.266 (0.043–0.888)	0.071	0.278 (0.042–0.951)	0.088
Location (ref: right upper lobe)				
Right middle lobe	0.696 (0.106–2.652)	0.642	0.711 (0.110–2.703)	0.660
Right lower lobe	0.894 (0.327–2.253)	0.817	0.972 (0.362–2.439)	0.953
Left upper lobe	1.547 (0.656–3.587)	0.308	1.469 (0.604–3.488)	0.384
Left lower lobe	2.157 (0.908–5.048)	0.076	1.893 (0.770–4.539)	0.154
Pleural invasion	3.868 (1.975–7.411)	<0.001	4.190 (2.096–8.185)	<0.001
No. of dissected lymph nodes	1.052 (1.013–1.094)	0.009	1.059 (1.018–1.102)	0.004
No. of resected N1	1.085 (1.020–1.152)	0.008	1.084 (1.018–1.151)	0.010
No. of resected N2	1.042 (0.991–1.092)	0.096	1.051 (0.999–1.102)	0.046

OR, odds ratio; CI, confidence interval; ref, reference.

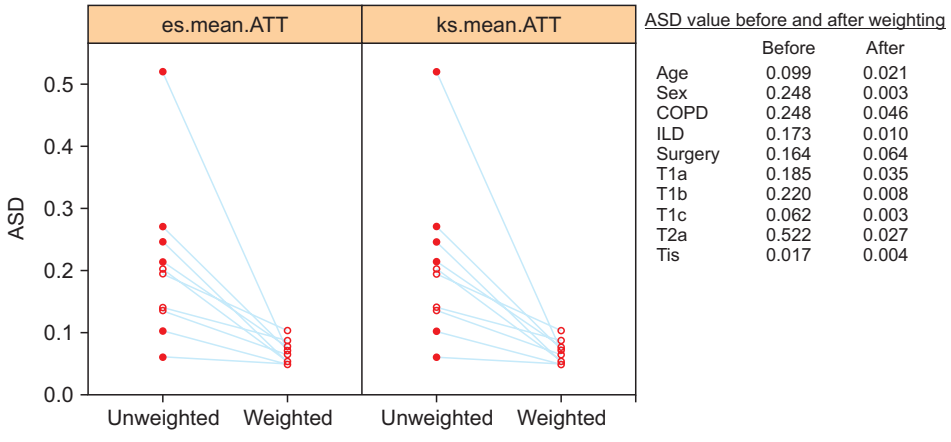

Fig. 2. Plot for absolute standardized differences before and after weighting. ASD, absolute standard difference; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

(Table 4). All standardized differences became <0.10, indicating that the model was effective in controlling covariate imbalance (Fig. 2). One limitation of PS matching is the exclusion of many control or treatment cases. To overcome this issue and strengthen the result, we adopted the IPTW method as an adjunct.

Upon univariate analysis, the non-weighted and IPTW model produced the same results regarding the presence or absence of statistical significance for each variable. The number of ports (uniportal versus multiportal surgery) and

https://doi.org/10.5090/kjtcs.2020.53.3.104

Table 5. Multivariate analysis of nodal upstaging: weighted and non-weighted model

Variable	Odds ratio (95% confidence interval)	p-value
Non-weighted model		
CEA	1.077 (1.030–1.132)	0.001
Tumor size	1.705 (1.131–2.584)	0.011
Pleural invasion	3.614 (1.737–7.422)	<0.001
Operation time	1.007 (1.000–1.014)	0.041
Dissected N1	1.069 (1.000–1.140)	0.043
IPTW model		
CEA (ng/mL)	1.101 (1.042–1.175)	0.001
Tumor size (cm)	1.783 (1.158–2.762)	0.010
Pleural invasion	3.820 (1.804–7.974)	<0.001
No. of dissected N1	1.071 (0.998–1.146)	0.050

Hosmer-Lemeshow test of IPTW model (p=0.210). McFadden R^2 index= 0.164.
CEA, carcinoembryonic antigen; IPTW, inverse probability of treatment-weighted.

type of surgery (segmentectomy versus lobectomy) did not impact nodal upstaging risk. However, larger tumor size, pathologic pleural invasion beyond grade PL1 (as visualized with elastic stain), and higher number of resected N1 nodes emerged as significant predictors of nodal upstaging after surgery.

To further increase the robustness of our findings, we conducted a multivariate analysis using all clinically relevant and statistically significant variables from the univariate models (Table 5). Larger tumor size, higher serum CEA level, and tissue-confirmed pleural invasion were found to be significantly associated with nodal upstaging in both the non-weighted and IPTW models. Longer operative time and higher N1 node count were also significant in the non-weighted model. Analysis of deviance in the non-weighted model indicated that tumor size was associated with the strongest reduction in deviance (deviance residual, 14.296; p<0.001) and thus was the strongest predictor of nodal upstaging, followed by the serum CEA level (deviance residual, 12.867; p<0.001) and pathologic pleural invasion (deviance residual, 10.241; p=0.001).

Receiver operating curve analyses were performed for CEA level and tumor size. The area under the curve for tumor size (0.704) was higher than that for serum CEA level (0.622). The cutoff values were 2.1 cm for tumor size (sensitivity, 75.0%, specificity, 60.8%) and 2.52 ng/mL for the CEA level (sensitivity, 48.8%, specificity, 74.4%).

Locoregional recurrence

The most common sites of locoregional recurrence during follow-up were the ipsilateral pleura and the mediastinal lymph nodes (Table 6). In the multiportal group, 3 patients developed recurrence at 2 locations: the parietal pleura and mediastinal lymph node in 1 patient, the pleura and chest wall in 1 patient, and the bronchial stump and chest wall in 1 patient. In the uniportal group, 1 patient experienced recurrence of the pleura and mediastinal lymph node, while the other patient developed recurrence of the pleura and chest wall. Univariate logistic regression analysis was performed to assess the factors related to locoregional recurrence within 1 year. Since recurrence occurred in only 9 patients, we did not perform a multivariate analysis. Nodal upstaging (OR, 5.776; 95% CI, 1.303–21.056; p=0.011), number of resected N2 nodes (OR, 1.105; 95% CI, 1.011–1.200; p=0.021), and age (OR, 1.258; 95% CI, 1.134–1.436; p<0.001) were found to be significant predictors of locoregional recurrence.

Table 6. Pattern of locoregional recurrence (number of cases with recurrence=31)

Recurrence site	Uniportal VATS (n=7)	Multiportal VATS (n=24)
Ipsilateral pleura	2	14
Ipsilateral mediastinal lymph node	5	8
Resection margin or remaining same lobe	1	1
Bronchial stump		2
Ipsilateral chest wall	1	2

Counting was based on the recurrence site, resulting in a difference between the values and the total number of patients in the lobectomy group. In addition, the number of recurrences refers to the number that occurred during the total study period.
VATS, video-assisted thoracoscopic surgery.

Discussion

Continued efforts towards less invasive surgery have fostered surgical innovations. Uniportal surgery was initially used for sympathectomy and was then applied to simple wedge resection, with Gonzalez-Rivas et al. [8] reporting the first uniportal VATS lobectomy in 2011 [19]. The safety and feasibility of uniportal VATS for primary lung cancer has since been validated [11,20].

Until now, most studies have focused on pulmonary resections via single-port lung surgery, which, despite its increasing popularity, raises some concerns regarding the completeness of surgical nodal staging. Indeed, operative methods for MLND have been proposed, and several reports from high-volume centers have demonstrated that the total number of dissected nodes remained the same or

exceeded those achieved using multiportal VATS [11,21,22]. In the present study, the count of dissected lymph nodes did not differ significantly according to the number of ports (uniportal group, 14.03±8.02; multiportal group, 14.41±7.41; p=0.48), a finding that aligned with prior studies. However, a critical issue is the clinical implication of the total number of dissected lymph nodes.

Nodal upstaging after surgery for lung cancer can be defined as the presence of unsuspected pathologic hilar (pN1) or mediastinal (pN2) disease detected during the final pathologic examination of surgical specimens [23]. According to the Cancer and Leukemia Group B prospective clinical trial (CALGB 9761), the incidence of nodal upstaging is 28% in clinical stage I lung cancer, 14% in stage II, and 14% in stage III [24]. More recently, an Italian VATS group reported nodal upstaging rates of 6.03% (N0 to N1) and 5.45% (N0 to N2) [25]. The overall incidence of nodal upstaging in our study was 8.09% (3.86% for N0 to N1, 3.13% for N0 to N1/2, and 1.11% for N0 to skip-N2 disease). The recommended number of nodes or stations for accurate nodal staging varies among sources. Some authors have proposed that 11–14 lymph nodes or at least 5 stations be resected [25,26]. The guidelines of the European Society of Thoracic Surgeons recommend systematic MLND for all resectable lung cancer, including at least 3 N2 stations [5].

Although the Italian group demonstrated a positive correlation between the number of resected nodes and the rate of upstaging, our data do not support this. A possible explanation is that the mean count of resected nodes in the present analysis was 14, which is larger than the recommended totals for accurate staging cited in several investigative reports. Moreover, the hilar or mediastinal lymph node totals we observed did not differ significantly according to the number of ports. However, the hilar node totals for segmentectomy were higher for multiportal than for uniportal VATS, perhaps reflecting the inherent difficulties of single-port nodal staging. The duration of follow-up after uniportal surgery was particularly limited, so more data are needed to reach a definitive conclusion.

Many researchers have explored risk factors for nodal upstaging, including those pertaining to patients (such as diabetes mellitus, history of tuberculosis, and connective tissue disorders) and to tumor-related factors (such as central location, higher T stage, higher standardized uptake value, and histotype) [23,26]. We did so as well and found that only tumor-related factors (namely serum CEA levels, lesion size, and tissue-confirmed pleural invasion) heightened the risk of nodal upstaging. Application of both a conventional logistic model and an adjunctive IPTW model (derived through calculation) confirmed the importance of tumor-related factors. Analysis of deviance reduction indicated that tumor size reduced deviance the most, followed by CEA levels and pleural invasion. Interestingly, the hilar node count proved to be a positive risk factor in the non-weighted model, despite showing a mere tendency in the weighted model. Nevertheless, the McFadden R^2 index was 16.4%, indicating the existence of other unknown factors affecting nodal upstaging. This study, can therefore only suggest that these factors might contribute to nodal upstaging, and further studies with larger patient cohorts should be performed to clarify the risk factors of nodal upstaging.

The role of serum CEA levels as a predictor of lymph node metastasis has been studied, and elevated serum CEA levels (>5.0 ng/mL) have been shown to be associated with upstaging and poor prognosis [27]. In addition, Koike et al. [28] proposed that a serum CEA level of 3.5 ng/mL or higher is associated with a higher risk of lymph node metastasis, even though that level fell within the normal range determined for that study.

In the present study, despite the limited follow-up duration after uniportal VATS, we evaluated the potential relationship between nodal upstaging and locoregional recurrence as a preliminary analysis. Our study showed that nodal upstaging, the number of resected N2 nodes, and patient age were related to locoregional recurrence. These relationships were statistically significant, but the wide 95% confidence intervals weaken the strength of these findings; therefore, further studies with longer follow-up periods and larger numbers of patients are warranted.

One interesting detail is that patients in the uniportal group felt more intense pain on postoperative day 1, as reflected by a higher numerical rating scale score. In uniportal surgery, the VATS instrument and thoracoscope must move within the same intercostal space, resulting in more pressure on the intercostal nerve and more pain. Moreover, the surgeons' learning curve in the uniportal group also may have played a role in the higher numerical rating scale score. These findings imply that the surgical procedure should be further elaborated.

In conclusion, uniportal and multiportal VATS procedures compared favorably in mediastinal nodal dissections performed during curative surgery for lung cancer. Tumor-related factors, specifically lesion size, serum CEA level, and pleural invasion (as visualized with elastic staining), were identified as risk factors of nodal upstaging in our cohort. Provided that MLND is adequate, the surgical technique alone is not predictive of nodal upstaging risk.

For segmentectomy, however, multiportal surgery may be a better choice.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

We would like to give special thanks to the biostatistics consulting team of our institute.

Funding

This study was supported by a Grant of the Samsung Vein Clinic Network (Daejeon, Anyang, Cheongju, Cheonan; Fund no. KTCS04-139).

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