



Two dimensional versus three dimensional video-assisted mediastinal lymphadenectomy: a meta-analysis

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Background: To investigate current role of three-dimensional video-assisted thoracoscopic surgery (VATS) and its differences from conventional flat video-assisted procedures for lymph node dissections in both pulmonary and esophageal cancers.

Methods: A PubMed Embase, Google Scholar, OpenDOAR research was carried out according to a prepeded Boolean function in order to speculate some difference in mean harvested lymph nodes, blood loss and postoperative chylothorax according to the techniques.

Results: Electing six articles, for a total of 1,262 patients (609 3D-VATS and 653 2D-VATS patients), significant differences favouring a 3D approach were found in mean node count [mean difference: 1.56; standard error (SE): 0.23; 95% confidence interval (95% CI): 1.11–2.01, difference freedom (DF) =1,260; $t=6.85$; $P<0.001$] and in a reduced intraoperative blood loss (mean difference: 11.07; SE: 1.22; 95% CI: 8.68–13.45, DF=1,260; $t=9.10$; $P<0.001$). Otherwise, a stroboscopic approach did not influence the pooled incidence of postoperative chylothorax (percentage difference: 0.07; $\chi^2=0.009$; 95% CI: -1.61–1.69, DF=1; $P=0.926$).

Conclusions: The management of the hilar and mediastinal lymphatic areas seems to be ameliorated by the adoption of three-dimensional video-assisted strategies potentially significantly influencing patients' outcome.

Keywords: Video-assisted thoracoscopic surgery (VATS); lung cancer; esophageal cancer; lymphadenectomy

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Introduction

On the attempt to reduce life-threatening postoperative morbidities in thoracic surgery, minimally invasive approaches, such as video-assisted thoracoscopic surgery (VATS), have been developed gaining wide acceptance worldwide due to their feasibility and safety as far as classical thoracotomy (1). However, conventional two-dimensional VATS approach carries certain disadvantages due to its technical features regarding optical resolution, pulmonary hilum visualization and issue concerning a flat two-dimensional camera rendering significantly affecting

spatial resolution and dissection plane identification (2). The goniometric characteristics of the pleural cavity (sharpen and deep angles) and the relative axial size of a two-dimensional triangulation have represented not inconsiderable critical elements in the minimally invasive management of lung cancer since its dawn. This assumption appears to be rather corroborated in the mediastinal compartment approach. In fact, previous reports expressed some concerns about radicality of VATS node harvesting which is intimately linked to its oncological effectiveness and patients' outcome in non-small cell lung cancer (NSCLC) (3,4). Beyond speculative and sometimes denied controversies, a video-

assisted approach should ensure an accurate nodal staging for further therapeutic decisions without understating some potential complications such as bleeding and postoperative chylothorax, although some technical features in gaining access to some mediastinal spaces (i.e., paratracheal and subcarinal one) still argues debate (4,5). If on the one hand some limits seem to be overpassed by a proper learning curve or surgeons' experience (6), on the other some technical limitation can influence surgical field visualization, view ranges and the exposition of structures (7). Some of these aspects seems to be overpassed with the adoption of three-dimensional technology in video-assisted procedures which are characterized by a magnified and deeper surgical field visualization due its stroboscopic visual perception allowing to reduce "blind" areas and by a high degrees of freedoms with a looking-around-the-corner-view facility resulting in an excellent spatial and hand-eye coordination (8) and making surgical dissection easier than in 2D visual rendering. Basing on this discussed topic and the theoretical effects on hilar and mediastinal node management in NSCLC patients, 3D- and conventional VATS dissections have been investigated through a systematic review and meta-analysis by evaluating their pooled effects on both oncological aspects and postoperative incidence of chylothorax according to these techniques.

Methods

Study design

A PubMed Embase, Google Scholar, OpenDOAR research was carried out by two investigators from the authors' panel in order to assay relevant and suitable report published up to Aug 31, 2018, according to the following Boolean function of medical subject heading (MeSH) terms: (((((((three-dimensional) OR 3D) AND two-dimensional) OR 2D) AND video-assisted thoracic surgery) OR VATS) AND lymphadenectomy) OR node staging) OR lymphatic staging)))))). The last search was run on October 25, 2018. All potential eligible articles were reviewed according to a two-phase process (title-abstract and full-text evaluation) and the following inclusion criteria: (I) video-assisted thoracoscopic lymph node dissection in NSCLC or esophageal cancer patients; (II) cohort analysis between two- and three-dimensional harvesting; (III) clearly description of surgical techniques and technological instrumentation; (IV) report of an exhaustive exploration of the mediastinal groves as far as hilar compartment; (V) proper definition of

the mean number of lymph node harvested; (VI) report of patients' surgical outcome, especially concerning bleeding and postoperative chylothorax and finally; (VII) article written only in English. Only retrospective monocentric or multicentric studies and prospective randomized-controlled trials (RCTs) were considered, the remaining ones (i.e., review, states of art, case reports and editorials) were excluded as their poor statistical relevance. Black-box, experimental model or geometrical analysis was also excluded. The remaining eligible reports were further analysed for data extraction by two independent reviewers to derive the following informations: authors, year of publication, country of publication, enrollment period, number of patients, primary disease, inclusion criteria (if reported), lymph node harvesting technique, devices or instrumentations and patients' outcome.

Endpoints

The primary endpoint for this meta-analysis was to assess any superiority of 3D-VATS lymph node dissection over conventional 2D-VATS.

Secondary endpoints included:

- (I) Video-assisted technology *vs.* paratracheal (stations #2–4) and subcarinal (station #7) dissection;
- (II) Postoperative blood loss;
- (III) Postoperative chylothorax.

Statistical analysis

The meta-analysis was conducted with Microsoft Excel 2016 (Microsoft®, Redmond, USA). All data were collected as absolute numbers (N), percentages (%), mean and standard deviation (SD) with their relative 95% confidence interval (95% CI). Statistical differences or correlations between groups were analysed according to the paired *t*-test both for categorical and continuous variables. For each endpoint, a summarized Forrest plot according was derived according to their mean difference (mean diff.), standard error (SE), 95% CI, *t*-statistic value or Chi-squared value (for proportions) and difference freedom (DF). A *P* value <0.05 was considered statistically significant.

Results

Data extraction process

According to the adopted Boolean function, one hundred

Table 1 Enrolled articles for meta-analysis

Author	Year	Country	Type of study	Period	N. patients			Primary disease	Inclusion criteria	Lymph node harvesting technique	3D surgical instrumentation
					Overall	3D	2D				
Li <i>et al.</i> (9)	2015	China	RS	2013–2014	93	45	48	Esophageal cancer	Up to stage III EC	LNRD	NR
Yang <i>et al.</i> (10)	2015	China	mPRS	2013–2014	300	150	150	NSCLC	Up to stage IIIA NSCLC	LNRD	Karl Storz 3D system
Hou <i>et al.</i> (11)	2015	China	RS	2013–2014	154	78	76	Esophageal cancer	NR	LNRD	Karl Storz 3D system
Dong <i>et al.</i> (12)	2016	China	RS	2013–2014	359	178	181	NSCLC	Stage I–IV NSCLC	LNRD	Karl Storz 3D system
Jiao <i>et al.</i> (13)	2017	China	RS	2013–2015	165	76	89	NSCLC	Up to stage IIIA NSCLC	LNRD	Aesculap Einstein Vision 3D
Huang <i>et al.</i> (14)	2018	China	RS	2015–2016	210	82	108	NSCLC	Up to stage IIIA NSCLC	LNRD	Karl Storz 3D system

RS, retrospective study; mPRS, multicentre prospective randomized study; NSCLC, non-small cell lung cancer; EC, esophageal cancer; LNRD, lymph node radical dissection; NR, not reported.

sixty-one papers were identified. Further twelve articles were included after other repositories investigation. Thereafter, one hundred thirty-nine were removed based on title or abstracts. Concerning the remaining twenty-seven potentially relevant articles, a second-phase analysis was carried out throughout a full-text evaluation. Only six articles resulted eligible for meta-analysis (9–14) (*Table 1*). In particular twenty-one were excluded due to: (I) form incompatibility (nine articles); (II) experimental model studies (four articles); (III) articles written in other languages than English and lacking of any translation (six articles); and (IV) lack of data making unsuitable extraction process. At the end of the analysis, 1,262 patients were enrolled for the study (609 3D-VATS patients and 653 2D-VATS patients) (*Figure 1*).

Studies' quality assessment

Quality analysis was carried out through the QUADAS-2 criteria panel, as reported in *Table 2*. Any source of bias was investigated by two reviewers and resulting in a high risk for selection bias according to standards in one article, whilst data in another one protocol were unclear. Similar issues were found evaluating applicability for both studies, as a result of an unclear patients' selection otherwise being enrolled for stage I to IV NSCLC (*Table 2*) (*Figure 2*). No resumable data could be assessed about surgeons' experience or skills in video-assisted approach, although high-volume centres were only enrolled.

Lymph node management technique

All the studies elected for analysis clearly reported lymph node harvesting technique. In particular each patient, both in the two-dimensional and three-dimensional arms, underwent radical mediastinal node dissection (9–14). Concerning with lung cancer, hilar stations (#10, #11) were included, while an en bloc resection with surgical specimen was reported in case of esophageal neoplasms (9,11). However, the Authors did not report their technique about the adoption of any energy device or any instrumentation for dissection.

Surgical and oncological data (Figures 3,4)

Number of harvested lymph nodes

The number of harvested lymph nodes for each cohort of patients was clearly reported in all six elected studies, accounting 1,262 patients (3D patient *vs.* 2D patients: 609 *vs.* 653). At the weighted-pooled analysis, no significant cumulative effect was found (7.37% *vs.* 23.77% *vs.* 12.20% *vs.* 28.53% *vs.* 13.07% *vs.* 15.06%, $P=0.694$). With a mean number of dissected nodes of 18.62 ± 3.53 and 17.06 ± 4.47 , respectively, there was a significant difference between cohorts (mean difference: 1.56; SE: 0.23; 95% CI: 1.11–2.01, $DF=1,260$; $t=6.85$; $P<0.001$) favouring a three-dimensional approach (*Tables 3,4*) (*Figure 3A*).

Paratracheal and subcarinal node dissection

Two studies reported influence of three-dimensional

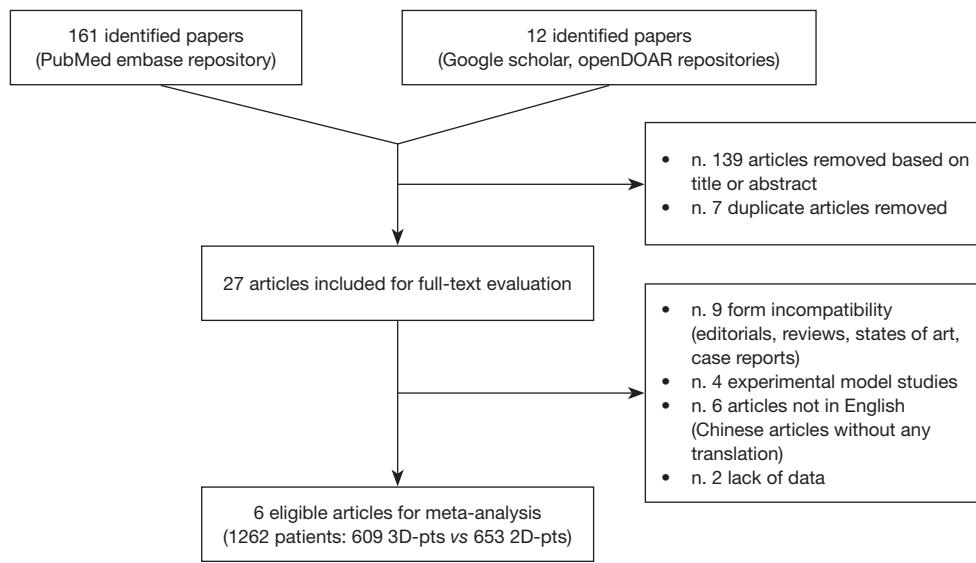


Figure 1 Flow chart selection process.

Table 2 QUADAS-2 selection process

Author	Year	Risk of bias				Applicability		
		Patients' selection	Study test	Standards	Timing	Patients' selection	Study test	Standards
Li <i>et al.</i> (9)	2015	L	L	L	L	L	L	L
Yang <i>et al.</i> (10)	2015	L	L	L	L	L	L	L
Hou <i>et al.</i> (11)	2015	L	L	U	L	U	L	L
Dong <i>et al.</i> (12)	2016	L	L	H	L	H	L	L
Jiao <i>et al.</i> (13)	2017	L	L	L	L	L	L	L
Huang <i>et al.</i> (14)	2018	L	L	L	L	L	L	L

L, low; U, unclear; H, high.

technology for specific mediastinal node areas. In particular, at the pooled analysis, no significant benefits were found to gain access to paratracheal compartment on the aspect of the mean number of dissected lymph nodes (#2–4 3D *vs.* 2D VATS: $P=0.619$). Otherwise, significant difference between technology was found by considering the subcarinal region (#7 3D *vs.* 2D VATS: $P=0.005$) (*Figure 4*).

Intraoperative blood loss

Intraoperative blood-loss estimation was reported in all the included studies, accounting 1,262 patients (3D patient *vs.* 2D patients: 609 *vs.* 653). At the weighted-pooled analysis, no significant cumulative effect was found (7.37% *vs.* 23.77% *vs.* 12.20% *vs.* 28.53% *vs.* 13.07% *vs.* 15.06%,

$P=0.694$). With a mean loss of 106.38 ± 23.78 mL in the 3D group and of 117.45 ± 19.30 in the conventional one, there was a statistical significant difference between cohorts (mean difference: 11.07; SE: 1.22; 95% CI: 8.68–13.45, DF=1,260; $t=9.10$; $P<0.001$) (*Tables 3,4*) (*Figure 3B*).

Postoperative chylothorax

Postoperative chylothorax was reported in four studies, enrolling 1,015 patients (3D patient *vs.* 2D patients: 486 *vs.* 529). At the weighted-pooled analysis, no significant cumulative effect was found (29.56% *vs.* 35.47% *vs.* 16.26% *vs.* 18.72%, respectively; $P=0.483$). With an incidence of 1.44% and 1.51% of chyle leak for 3D- and 2D patients, no augmented risks were found according to technological

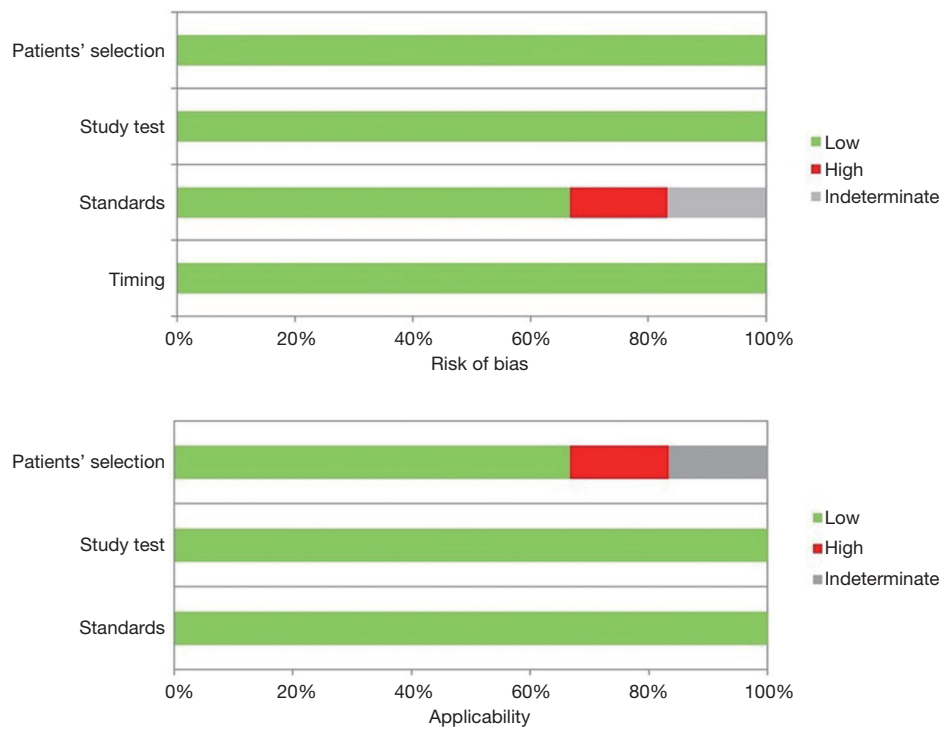


Figure 2 QUADAS-2 spreadsheet model.

supply (percentage difference: 0.07; $\chi^2=0.009$; 95% CI: -1.61–1.69, DF=1; P=0.926) (Tables 3,4) (Figure 3C).

Discussion

Two-dimensional VATS carries several disadvantages due to technical limits and anatomical issues. Concerning with instrumentation, the visual constraints as far as the lack of stereo-perception and difficulties in hand-eye coordination could significantly influence surgeons' performance and dissection phases in the operative theatre (15). Moreover, the undeniable geometric features of the thoracic cavity with reduced spaces and freedom grades of movements contribute to making uncomfortable and difficult some maneuvers that, only with an adequate learning curve and by means of expedients, may be accomplished. The absence of depth perception and spatial orientation have been recently countered by three-dimensional systems with an accuracy comparable to open surgery by the adoption of visual performance and motor skills resulting in an improved discrimination and recognition of targeted organs or regions (16,17). However, this technology is far to be widely accepted due to its high expensiveness and the requirement of dedicated operative setting (18). Moreover,

notwithstanding health expenditures and economic impacts, last generation 3D devices ensure several and not negligible benefits by reducing black-angle maneuvers and thus increasing patients' safety. An exhaustive and radical lymph node assessment is a cornerstone for the surgical management of both lung and esophageal cancer as being the most important prognostic factor for patients' outcome (19-21). In particular, metastatic nodes influence prognosis as absolute number of harvested glands and as their ratio upon N0 ones (22,23). Thereafter, every attempt to improve surgical dexterity and precision movements has to be advocated and in particular to gain access to some tedious mediastinal regions, such as the paratracheal and the subcarinal ones. In these lymph node stations a conventional flat vision could limit dissection and so oncological radicality in face of not negligible augmented risks of intraoperative complications from blind areas, such as bleedings. Speculating about surgical data and the effects of innovative stroboscopic resources with conventional video-assisted approaches, the mean number of harvested hilar and mediastinal lymph nodes significantly increased in the three-dimensional cohort (3D- vs. 2D-group: 18.62±3.53 vs. 17.06±4.47, 95% CI: 1.11–2.01, P<0.001) confirming feasibility of 3D lymphadenectomy. Differences could be

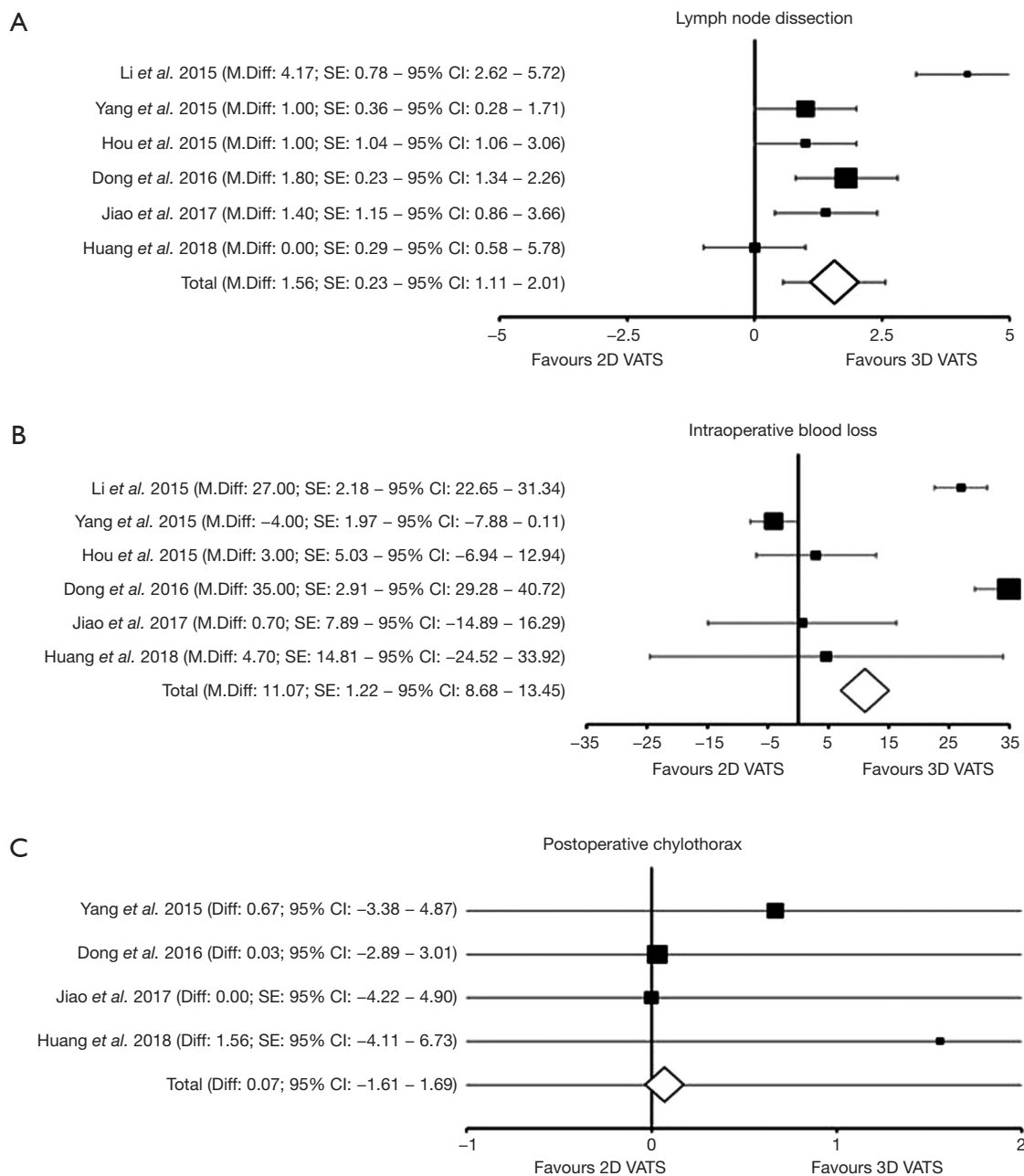


Figure 3 Forrest plots: (A) harvested lymph nodes; (B) intraoperative blood loss; (C) postoperative chylothorax.

explained upon the above mentioned technical properties allowing a safer and so a more extensive dissection among planes as far as an increased surgeon's safety to overpass beyond threatening fears to face with sudden complications. This aspect seem to be confirmed at the analysis of the subcarinal node dissection where a three-dimensional approach seems to ameliorate space assessment with an

increased mean number of harvested node (3D- vs. 2D-VATS: 3.89 vs. 2.73, $P=0.005$), as reported by Li *et al.* (9). In contrast, augmented reality does not seem to interfere with paratracheal space dissection (3D- vs. 2D-VATS: 7.50 vs. 6.00, $P=0.619$) and, as reported by Huang *et al.* (14), reasons should be found in anatomical issues rather than in technical aspects, as the region located in the upper

mediastinum and not disturbed by the sequences of pulmonary lobectomies. Moreover, paratracheal dissection classically is carried out at the end of the procedure with the surgical specimen extracted without spatial encumbrance and also a flat visualization of the surgical field allows the recognition of the anatomical landmarks above and below the azygos vein. In regard to intraoperative bleedings, a 3D approach significantly reduces losses (3D- vs. 2D-VATS: 106.38±23.78 vs. 117.45±19.30; 95% CI: 8.68–13.45, P<0.001) justifying a more accurate dissection and haemostasis of planes, especially around vascular

structures. In particular, this result should be corroborated only by technical aspects and by an increased dexterity in movements making a three-dimensional endoscopic technique closer to telerobotics rather than to conventional VATS (18). Another not negligible aspect to be considered is the risk of postoperative chylothorax, when facing lymphatics and their dissection. Historically, chyle leaks represent potentially serious complication of thoracic surgical procedures, especially after esophageal surgery with a cumulative incidence ranging from 0.5% and 4% (24–26), usually secondary to lymphatic cauterization failure, direct channel disruption or thoracic duct injuries. From our analysis, notwithstanding visualization and definition properties, last generation video-assisted strategies do not reduce its incidence, as being almost irrelevant (3D- vs. 2D-VATS: 1.44% vs. 1.51%, 95% CI: -1.61–1.69, P=0.926). In fact, putative causes should be traced on sealing or clipping techniques as far as proper dissection rather than the possibility to magnify surgical field and calling in the surgeon's accuracy and dexterity.

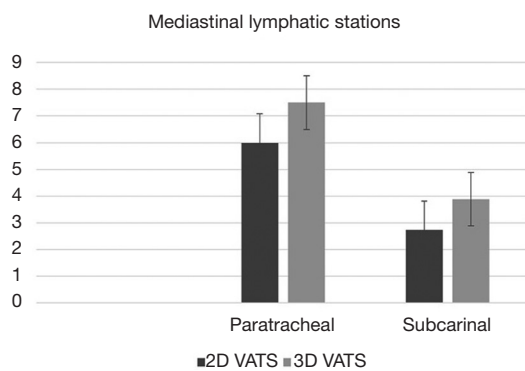


Figure 4 3D- vs. 2D VATS in paratracheal and subcarinal node dissection. VATS, video-assisted thoracoscopic surgery.

Limits of the study

Although a systematic approach, our evidences should be interpreted in the context of some limitations. In the first, most of eligible articles presented a low sample size and only

Table 3 Surgical and oncological data (3D- vs. 2D-VATS)

Author	Year	3D/2D patients	N. lymph nodes		N. paratracheal lymph node		N. subcarinal lymph node		Postoperative chylothorax		Intraoperative blood loss	
			3D (m + SD)	2D (m + SD)	3D (m + SD)	2D (m + SD)	3D (m + SD)	2D (m + SD)	3D, N (%)	2D, N (%)	3D (m + SD)	2D (m + SD)
Li et al. (9)	2015	45/48	13.13±3.43	8.96±4.05			3.89±2.59	2.73±1.08			68.20±10.70	89.80±10.40
Yang et al. (10)	2015	150/150	17.00±3.27	16.00±3.11					4 (2.67)	3 (2.00)	120.00±11.30	116.00±21.40
Hou et al. (11)	2015	78/76	17.00±8.60	18.00±3.30							124.00±35.80	127.00±25.70
Dong et al. (12)	2016	178/181	21.30±2.00	19.50±2.40					2 (1.12)	2 (1.10)	109.00±32.60	144.00±21.50
Jiao et al. (13)	2017	76/89	23.30±7.40	21.90±7.30					0 (0.00)	0 (0.00)	125.00±45.90	125.70±54.20
Huang et al. (14)	2018	82/108	19.00±2.00	19.00±2.10	7.50±1.03	6.00±0.91			3 (3.66)	1 (0.93)	97.50±84.80	102.20±111.90

VATS, video-assisted thoracoscopic surgery.

Table 4 Comparison between cohorts

Variable	3D VATS	2D VATS	M. Diff.	95% CI	DF	t	χ ²	P
N. lymph nodes	18.62±3.53	17.06±4.47	1.56	1.11–2.01	1,260	6.85		<0.001
Blood loss (mL)	106.38±23.78	117.45±19.30	11.07	8.68–13.45	1,260	9.10		<0.001
Chylothorax (%)	1.44	1.51	0.07	-1.61–1.69	1		0.009	0.926

VATS, video-assisted thoracoscopic surgery; CI, confidence interval; DF, difference freedom.

two of them enrolled more than three hundred patients. In the second, no data about surgeons' experience as far as the adoption of any energy device for dissection may be assessed. In the third, most of studies were retrospectively and single-center constructed. Moreover, most of them were strictly designed with ineluctable inclusion criteria clearly described. However, due to these aspects, an undeniable possibility of type 2 error should be considered.

Conclusions

Three-dimensional video-assisted approach in the surgical management of pulmonary or esophageal cancers ensures a better management of lymphatics and of their dissection with theoretical benefits both on short-term (bleedings) and oncological outcomes. New devices have overpassed historical limits of celioscopic procedures and, nowadays, seem to be closer to the fitness of open surgery rather in the past.

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Footnote

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