Systematic Review

Video-assisted thoracoscopic surgery versus open thymectomy for thymoma: a systematic review

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Background: Video-assisted thoracoscopic surgery (VATS) thymectomy is an increasingly utilized alternative to traditional open approaches for the resection of thymomas. Recent studies have suggested comparable survival and oncological efficacy as well as reduced perioperative morbidity when using the VATS approach. This current systematic review thus aimed to critically evaluate existing evidence for the efficacy and safety of VATS versus open (transsternal or transthoracic) thymectomy for thymomas.

Methods: Six electronic databases were searched from their date of inception to April 2015. Relevant studies were identified using specific eligibility criteria and data were extracted and analyzed based on predefined primary and secondary endpoints.

Results: Fourteen comparative observational studies with a total of 1,061 patients were obtained for qualitative assessment, data extraction and analysis. Five-year overall survival and 10-year recurrence-free survival was similar or higher in patients undergoing VATS compared to open thymectomy. On average, the VATS group also demonstrated reduced intraoperative blood loss (131.8 *vs.* 340.5 mL), shorter hospital stays (7.0 *vs.* 9.8 days), and lower rates of postoperative pneumonia (1.9% *vs.* 4.1%). The mean rate of conversion from VATS to open thymectomy was relatively low (3.1%), while 30-day mortality remained low in both the VATS and open groups (0 *vs.* 0.3%).

Conclusions: The current evidence suggests that VATS thymectomy for thymoma has at least equal if not superior oncological efficacy and survival outcomes, as well as reduced perioperative complications, compared to open surgery. Further adequately powered studies and future randomized trials are required to confirm these findings.

Keywords: Video-assisted thoracoscopic surgery (VATS); thymectomy; thymoma

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Introduction

While thymoma is a rare disease, it remains the most common primary mediastinal neoplasm in adults, with an estimated incidence of 0.15 cases per 100,000 (1). The overwhelming majority of thymic neoplasms are benign and slow-growing, and metastases are typically limited to the pleura, pericardium and/or diaphragm (1). Therefore, complete surgical resection is accepted as the mainstay of therapy, with median sternotomy currently considered to be the gold standard for resection approaches (2,3). However, interest has grown in minimally invasive surgical approaches, most notably video-assisted thoracoscopic surgery (VATS) thymectomy, as a means of reducing perioperative morbidity and mortality (3).

Recent institutional studies have associated VATS thymectomy with improved outcomes, including reduced postoperative pain, fewer complications such as bleeding and pneumonia, shorter hospital stays, better preservation of baseline pulmonary function, and superior cosmesis with the use of smaller surgical incisions (2,4). Furthermore, similar survival and recurrence rates have been demonstrated for VATS thymectomy compared to open thymectomy patients, reinforcing the rising popularity of the VATS approach as it continues to become increasingly used in centers worldwide (2,4).

Nonetheless, evidence for the efficacy, particularly long-term oncological outcomes, of VATS thymectomy compared to open surgery remains limited, with a current paucity of randomized controlled trials. The present systematic review thus aimed to summarize existing studies comparing VATS thymectomy to open thymectomy (transsternal or transthoracic). The primary outcomes of interest were overall and recurrence-free survival, while secondary endpoints included the incidence of postoperative complications and length of hospital stay.

Methods

Literature search

The present systematic review was performed according to recommended PRISMA guidelines (5,6). Six electronic databases, including MEDLINE, EMBASE, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), and Database of Abstracts of Reviews of Effects (DARE), were searched from their dates of inception to April 2015. To maximize the sensitivity of the search strategy, the following terms were combined: (VATS OR thoracoscopic OR thoracoscopy) AND (open OR sternotomy OR transsternal OR transthoracic) AND (thymus or thymoma or thymic or thymectomy) as either keywords or MeSH terms. The reference lists of articles retrieved were also reviewed in order to identify additional related studies.

Eligibility criteria

Comparative studies that reported any postoperative outcome of VATS thymectomy versus open (transsternal or transthoracic) thymectomy for thymoma were eligible for analysis. At least ten adult patients aged 18 years and over were required to be in each arm of the study. When institutions published duplicate studies with overlapping sample populations, only the most recent reports were included. Only studies published in the English language were selected. Case reports, conference abstracts, editorials, commentaries, pediatric or adolescent studies, and review articles were excluded.

Data extraction and critical appraisal

All data were extracted from article texts, tables and figures. Two independent investigators (A.X., R.T.) reviewed each article retrieved. Inter-reviewer discrepancies were resolved by discussion and consensus (A.X., R.T., K.P.). If the study reported medians and ranges we calculated the equivalent means and standard deviations (SDs) using the conversion method described by Hozo, Djulbegovic & Hozo [2005] (7). The studies were also qualitatively assessed using the critical review checklist formulated by the Dutch Cochrane Group and MOOSE guidelines (8) (*Table S1*). These checklist criteria included the clear definition of study population, outcomes and outcomes assessment; independent outcomes evaluation; adequate follow-up duration; no selective losses to follow-up; and identification of key confounders. The final results were reviewed by the senior investigator (T.D.Y.).

Statistical analysis

Conventional descriptive statistics were used to summarize the baseline demographics of included patients. Data were presented as raw numbers, percentages, or means with standard deviations unless otherwise indicated. Pooled averages were calculated for outcomes reported in at least three of the included studies. When not explicitly reported in the article text, rates of overall survival and recurrence-free survival were reconstructed for specific time points on digitized Kaplan-Meier curves using the software program, DigitizeIt v2.0.

Results

Quantity and quality of evidence

A total of 414 records were identified through the database searches. After eliminating duplicates and screening the studies based on abstracts 33 full-text articles were assessed using the eligibility criteria. Fourteen relevant studies were selected for analysis, all of which were observational, though two of these trials also used propensity score-matched groups (9,10) (*Figure S1*, *Table 1*).

A total of 1,061 patients were included in the analysis, with 540 undergoing VATS and 521 for open thymectomy. Individual sample sizes varied across the studies, with a median of 23.5 [12-125] for VATS and 22 [10-137] for open thymectomy. The mean length of follow-up similarly varied but was generally longer for open surgery, with a range of 24.4±8.8 to 99.4±27 months for VATS, and

Table 1 Characteristics of studies reporting on video-assisted thoracoscopic surgery versus open thymectomy for thymoma

First author	Year	Institution	Study period	Type of study	Sample size (n)	VATS (n)	Open (n)	Mean follow-up, entire cohort (months)	Mean follow-up, VATS (months)	Mean follow-up, open (months)
Chao	2015	Chang Gung Memorial Hospital, Taoyuan City, Taiwan	1991-2007	PSM	140 (96^{P})	61 (48^{P})	58^{TS} (48^{P}), 21^{TC}	53^{M}	66^{M}	95^{M}
Cheng	2005	Kaohsiung Medical University Hospital, Kaohsiung, Taiwan	1999-2004	OS	22	12	10	33.9±19.7	NR	NR
Chung	2012	Asan Medical Centre, Seoul, Korea	2002-2008	OS	70	25	45	NR	78.0±21.9	70.0±23.6
He	2013	First Affiliated Hospital of Nanjing Medical University, Nanjing, China	2006-2011	OS	33	15	18	$12\text{-}61^{R}$	NR	NR
Kimura	2013	Osaka University Hospital, Osaka, Japan	2002-2009	OS	74	45	29	NR	53.7±24.5	49.6±25.3
Liu	2014	National Taiwan University Hospital, Taipei City, Taiwan	1991-2010	OS	120	76	44	NR	61.9±52.0	69.71±68.4
Maniscalco	2015	Sant'anna Hospital of Ferrara, Ferrara, Italy	1995-2007	OS	27	13	14	123^{M}	101^{M}	129^{M}
Manoly	2014	Southampton General Hospital, Southampton, UK	2004-2010	OS	39	17	22	NR	30.5±14.3	35.0±20.2
Odaka	2010	Jikei University School of Medicine Tokyo, Japan	2000-2008	OS	40	22	18	NR	24.4 ± 8.8^{C}	56.2 ± 20.3^{C}
Pennathur	2011	University of Pittsburgh Medical Center, Pittsburgh, USA	1996-2008	PSM	40	18	22	36^{M}	27^{M}	58^{M}
Sakamaki	2014	Osaka Police Hospital, Osaka, Japan	1998-2011	OS	82	71	11	49^{M}	63.0 ± 38.0^{C}	57.5 ± 30.0^{C}
Tagawa	2014	Nagasaki University Hospital, Nagasaki; Oita Prefectural Hospital, Oita, Japan	1995-2007	OS	27	15	12	NR	99.4 ± 27^{C}	106.1 ± 32.8^{C}
Ye	2014	Shanghai Chest Hospital, Shanghai, China	2008-2012	OS	262	125	137	NR	35.8 ± 14.8^{C}	36.3 ± 14.8^{C}
Yuan	2014	Cancer Institute and Hospital of Chinese Academy of Medical Sciences, Beijing, China	2007-2013	OS	129	38	44^{TS}, 47^{TC}	NR	NR	NR

PSM, propensity-matched study; OS, observational study; ^{P}, propensity-matched number; VATS, video-assisted thoracoscopic surgery; ^{TS}, transsternal; ^{TC}, thoracotomy; ^{M}, median; MN, mean; ^{R}, range; ^{C}, converted from median and range to mean and standard deviation; NR, not reported.

35.0±20.2 to 106.1±32.8 months for the open approach. One study used a historical open thymectomy group (from 2000 to 2005) for comparison with VATS outcomes (2005-2008) (11).

Of the seven studies (9,11-17) that reported their eligibility criteria for either surgical approach, the majority limited their use of the VATS approach to those patients with a tumor diameter of less than 5 cm (12,14,16,17) or 6 cm (13), tumors located inferior and separate to the innominate vein (12,13,16), and/or little or no evidence of invasion or close proximity to vital organs including the heart and great vessels (9,11-16). Exceptions to these criteria, particularly tumors measuring over 5 cm that were still accessible through thoracoscopy, were reported by at least two studies (12,14). The first included study that used propensity-scores matched the VATS and open surgery groups for thymoma Masaoka stage and tumor size (9). The second such study matched for variables of tumor size, presence of myasthenia gravis (MG), and date of surgery (10).

Baseline characteristics

The baseline demographics are summarized in *Table 2*. The weighted mean age, proportion of male patients, and body mass index (BMI) were similar between VATS and open groups. The percentage of tumors classified as Masaoka stage I (60.2% *vs.* 58.6%) and II (39.6% *vs.* 40.1%) was also similar between VATS and open thymectomy patients, respectively. Only one study included thymomas in Stage III (VATS, n=0; open, n=5) and IV (VATS, n=1; open, n=1) (12). Histological grading (A-B3) according to World Health Organization guidelines was additionally comparable between the two groups, with only one study including one open thymectomy patient classified as grade C (17). Mean tumor size, as determined by either computed tomography or histopathology, was slightly larger at 5.6 cm (3.4-7.7 cm) in the open surgery group compared to 4.5 cm in the VATS group (3.2-6.6 cm).

Furthermore, a higher proportion of VATS patients had MG (24.9%) compared to open thymectomy patients (18.7%), although the range for both groups was large (0-100%), due to several studies incorporating MG into their inclusion (18) or exclusion criteria (11,12,17). The perioperative use of adjuvant therapy (radiotherapy and/or chemotherapy) appeared to be comparable in both groups (34.1% for VATS *vs.* 31.2% for open), although the range was similarly large (0-100%) across the studies.

Intraoperative characteristics

Differences were noted in the operative approaches and strategies for both VATS and open thymectomy across included studies (*Table 3*). Based on weighted means the majority of patients underwent a total or extended thymectomy with a higher proportion in the open thymectomy group (98.5%, range, 63.6-100%) than in the VATS group (79.9%, 40.8-100%). Correspondingly, a greater percentage of VATS patients underwent a 'partial' thymectomy (20.8%, 0-59.2%) compared to open thymectomy patients (1.5%, 0-36.4%). In the two studies that performed hemithymectomy or partial thymectomies for selected patients, the extent of resections was not clearly defined (9,15).

Most of the unilateral VATS thymectomy patients underwent a right-sided procedure (74%, 64-100%) rather than left-sided (26%, 0-36%). Four studies specified their surgical approach as always being from the side of the tumor (9,11,17,19), while an additional two studies preferred the right-sided approach except in cases of obvious left-sided thymoma (18,20). Maniscalco *et al.* [2015] reported that their VATS approach was mostly left-sided, although specific rates of use were not included (21). Eight studies included bilateral VATS approaches (9-11,13-16,19), while Tagawa utilized a cervico-xyphoidal-thoracic approach in an unspecified proportion of their patients (16). All open surgery groups utilized a midline sternotomy (n=474) except for a small proportion from the study by Yuan *et al.* [2014], which utilized a thoracotomy (n=47) (19).

The mean operative duration was similar between VATS (172 minutes, 117.0-249.8) and open thymectomy (173.6 minutes, 131.0-227.9) patients. The conversion rate for VATS was relatively low (3.1%), though this ranged from 0% to up to 11.8% in one study (22). Mean intraoperative blood loss was observed to be markedly higher in the open surgery group (340.5 mL, 75.0-484.8) compared to the VATS group (131.8 mL, 40.0-214.9). There were no cases of intraoperative mortality reported.

Postoperative characteristics

The postoperative outcomes are summarized in *Tables 4-6*. The length of hospital stay was, on average, longer for open surgery patients (9.8 days, 5.4-19.0) compared to VATS patients (7.0 days, 2.6-14.0). The length of intensive care unit (ICU) stay was similar between the two groups (1.4 days for VATS *vs.* 1.5 days for open), though this value should be

Table 2 Baseline demographics of participants in studies reporting on video-assisted thoracoscopic surgery versus open thymectomy for thymoma

First author	Approach	Age (years)	Male (%)	BMI	Masaoka stage I (%)	Masaoka stage II (%)	WHO histology (%)	Tumour size (CT)	Myasthenia gravis (%)	Adjuvant therapy (%)
Chao	VATS	50.7±0.4	50.0	24.9±3.6	35.4	64.6	A 8.3, AB 33.3, B1 10.4, B2 37.5, B3 10.4	5.8±1.8	26.0	37.5
	Open	50.8±1.4	54.2	24±3.8	35.4	64.6	A 6.3, AB 25, B1 8.3, B2 45.8, B3 14.6	5.7±1.7	26.0	33.3
Cheng	VATS	40.2±16.3	58.3	NR	0.0	100.0	NR	NR	50.0	100.0
	Open	47.7±8.5	40.0	NR	0.0	100.0	NR	NR	60.0	100.0
Chung	VATS	45.8±12.3	52.0	NR	72.0	24.0	A 16, AB 16, B1 44, B2 24	5.2±2.0×4.2±1.6×2.7±1.0^{PT}	0.0	NR
	Open	51.7±12.5	46.7	NR	66.7	20.00	A 11.1, AB 46.7, B1 31.1, B2 11.1	7.7±2.6×5.8±1.7×3.9±1.2^{PT}	0.0	17.8
He	VATS	54.2±11.9	46.7	24.5±2.4	NR	NR	NR	NR	100.0	33.3
	Open	48.6±8.9	61.1	23.7±3.4	NR	NR	NR	NR	100.0	50.0
Kimura	VATS	55±12	42.2	NR	91.1	8.90	A 11.1, AB 35.6, B1 31.1, B2 31.1, B3 4.4	4.8±2.1	31.1	NR
	Open	57±12	34.5	NR	58.6	41.4	A 3.4, AB 37.9, B1 44.8, B2 6.9, B3 6.9	6.5±2.5	31.0	NR
Liu	VATS	50.5±14.6	46.1	23.2±3.3	75.0	25.0	A 11.3, AB 49.3, B1 11.3, B2 18.3, B3 9.9	4.6±1.9^{PT}	46.1	NR
	Open	51.8±14.5	40.9	22.3±3.4	84.1	15.9	A 4.9, AB 51.2, B1 22, B2 14.6, B3 7.3	6.1±2.9^{PT}	31.8	NR
Maniscalco	VATS	59.4^{M}	53.8	NR	61.5	38.5	NR	3.5^{M}	38.5	100.0
	Open	64^{M}	50.0	NR	71.4	28.6	NR	6^{M}	35.7	0.0
Manoly	VATS	63.1±15.7	35.3	29.1±5.1	NR	NR	NR	NR	47.1	47.1
	Open	65.4±11.0	59.1	26.9±4.9	NR	NR	NR	NR	18.2	NR
Odaka	VATS	51.9±14.2	63.6	NR	68.2	31.8	NR	4.4±1.9	0.0	NR
	Open	51.1±13.2	38.9	NR	61.1	38.9	NR	4.9±2.2	0.0	NR
Pennathur	VATS	64^{M}	55.6	NR	27.8	72.2	NR	3.5±1.1	38.9	38.9
	Open	64^{M}	40.9	NR	40.9	59.1	NR	5.8±2.0	18.2	54.5
Sakamaki	VATS	56.0±17.5^{C}	38.0	NR	56.3	43.7	B2-B3 23.9	4.8±2.5^{C}	36.6	9.9
	Open	59.0 ±14.8^{C}	45.5	NR	36.4	63.6	B2-B3 27.3	7.2±3.2^{C}	27.3	9.1
Tagawa	VATS	51.4±16.0	46.7	NR	53.3	46.7	NR	3.6±1.0	6.7	26.7
	Open	50.9±15.0	25.0	NR	66.7	33.3	NR	3.8±1.3	66.7	16.7

Table 2 (*continued*)

Table 2 *(continued)*

First author	Approach	Age (years)	Male (%)	BMI	Masaoka stage I (%)	Masaoka stage II (%)	WHO histology (%)	Tumour size (CT)	Myasthenia gravis (%)	Adjuvant therapy (%)
Ye	VATS	51.9±13.0	52.0	NR	64.0	36.0	A 12.8, AB 68, B1 13.6, B2 3.2, B3 2.4, C 0	3.2±0.9	0.0	32.0
	Open	50.0±15.6	54.0	NR	65.7	34.3	A 10.4, AB 56.1, B1 14, B2 1.8, B3 0.6, C 0.6	3.4±0.7	0.0	29.9
Yuan	VATS	49.3±11.8^{C}	50.0	25.4±4.0^{C}	44.7	55.3	NR	6.6±2.6^{C}	13.2	NR
	Open	47.6±15.3^{C}	50.5	25.6±4.0^{C}	53.8	46.2	NR	7.3±2.6^{C}	15.4	NR
Weighted Mean	VATS	52.1	48.2	24.7	60.2	39.6	A 9.8, AB 46.8, B1 11.8, B2 9.3, B3 3.8, C 0	4.5	24.9	34.1
	Open	51.2	48.7	24.6	58.6	40.1	A 9.4, AB 51, B1 15.7, B2 6.7, B3 2.2, C 0.6	5.6	18.7	31.2
Range	VATS	40.2-63.1	35.3-63.6	23.2-29.1	0-91.1	8.90-100.0	A 8.3-16, AB 16-68, B1 10.4-44, B2 3.2-37.5, B3 2.4-10.4, C 0	3.2-6.6	0.0-100.0	9.9-100.0
	Open	47.6-65.4	25.0-61.1	22.3-26.9	0-84.1	15.9-100.0	A 3.4-11.3, AB 25-56.1, B1 8.3-44.8, B2 1.8-45.8, B3 0.6-14.6, C 0.6	3.4-7.7	0.0-100.0	0.0-100.0

VATS, video-assisted thoracoscopic surgery; ^{M}, median; BMI, body mass index; ^{C}, converted from median and range to mean and standard deviation; NR, not reported; WHO, World Health Organization; ^{CT}, computed tomography; ^{PT}, measured from histopathology specimens.

Table 3 Intraoperative outcomes in studies reporting on video-assisted thoracoscopic surgery versus open thymectomy for thymoma

First author	Approach	Full thymectomy (%)	Partial thymectomy (%)	VATS right-sided (%)	VATS left-sided (%)	Operation duration (min)	Conversion rate (%)	Blood loss (mL)	Operative mortality (%)
Chao	VATS	62.5	37.5	77.1	22.9	153±60	2.1	40±66	0.0
	Open	100.0	0.0	–	–	173±56	–	75±96	0.0
Cheng	VATS	NR	NR	NR	NR	193.3±79.6	0.00	119.2±70.6	0.0
	Open	NR	NR	–	–	207.5±85.8	–	238.5±110.2	0.0
Chung	VATS	100.0	0.0	64.0	36.0	117±48	7.1	NR	0.0
	Open	100.0	0.0	–	–	131±43	–	NR	0.0
He	VATS	100.0	0.0	100.0	0.0	202.3 ± 53.1	0.0	98.7±62.8	0.0
	Open	100.0	0.0	–	–	141.8±30.7	–	225.0±101.8	0.0
Kimura	VATS	NR	NR	NR	NR	197±102	NR	105±133	0.0
	Open	NR	NR	–	–	167±42	–	262±205	0.0
Liu	VATS	NR	NR	NR	NR	141.7±62.8	1.3	105.1±142.2	0.0
	Open	NR	NR	–	–	149.9±33.3	–	159.7±109.6	0.0
Maniscalco	VATS	NR	NR	NR	NR	138.0	0.0	NR	0.0
	Open	NR	NR	–	–	162.0	–	NR	0.0
Manoly	VATS	NR	NR	NR	NR	177.1±70.2	11.8	NR	0.0
	Open	NR	NR	–	–	151.7±63.3	–	NR	0.0
Odaka	VATS	NR	NR	72.7	27.3	194.0±61.8	0.0	100.6±76.5	0.0
	Open	NR	NR	–	–	180.9±43.3	–	208.1±236.4	0.0
Pennathur	VATS	NR	NR	NR	NR	NR	NR	NR	0.0
	Open	NR	NR	–	–	NR	–	NR	0.0
Sakamaki	VATS	40.8	59.2	NR	NR	208±58^{TT}, 136±65^{PT}	5.6	NR	0.0
	Open	63.6	36.4	–	–	191±29^{TT}, 176±96	–	NR	0.0
Tagawa	VATS	100.0	0.0	NR	NR	249.8±52.9	0.0	92.3±67.6	0.0
	Open	100.0	0.0	–	–	227.9±52.6	–	225.1±133.6	0.0
Ye	VATS	100.0	0.0	72.0	28.0	171±31.1	3.2	183.1±98.2	0.0
	Open	100.0	0.0	–	–	216±41.2	–	462.4±95.6	0.0
Yuan	VATS	NR	NR	NR	NR	146.8±67.5^{C}	NR	214.9±145^{C}	0.0
	Open	NR	NR	–	–	143.6±53.8^{C}	–	484.8±362.5^{C}	0.0
Weighted mean	VATS	79.9	20.8	74.0	26.0	172.0	3.1	131.8	0.0
	Open	98.5	1.5	–	–	173.6	–	340.5	0.0
Range	VATS	40.8-100.0	0.0-59.2	64.0-100.0	0.0-36.0	117.0-249.8	0.0-11.8	40.0-214.9	0.0
	Open	63.6-100.0	0.0-36.4	–	–	131.0-227.9	–	75.0-484.8	0.0

VATS, video-assisted thoracoscopic surgery; ^{TT}, total thymectomy; ^{PT}, partial thymectomy; ^{C}, converted from median and range to mean and standard deviation; NR, not reported.

Table 4 Postoperative outcomes in studies reporting on video-assisted thoracoscopic surgery versus open thymectomy for thymoma

First author	Approach	Length of hospital stay (days)	Length of ICU stay (days)	Chest drain duration (days)	Chest drain volume (mL)	30 day mortality (%)	Pneumonia (%)	Phrenic nerve injury (%)	Margin positive (%)	Reoperation (%)
Chao	VATS	5.8±2	NR	4.4±1.5	NR	NR	NR	NR	NR	NR
	Open	7.0±2.2	NR	4.9±1.9	NR	NR	NR	NR	NR	NR
Cheng	VATS	6.8±2.3	NR	4.2±2.1	NR	0.0	NR	NR	NR	NR
	Open	8.9±4.4	NR	4.6±2.1	NR	0.0	NR	NR	NR	NR
Chung	VATS	3.4±1.3	NR	1.8±0.9	NR	0.0	NR	NR	NR	NR
	Open	6.4±2.5	NR	3.6±2.0	NR	0.0	NR	NR	NR	NR
He	VATS	10.6±5.1	1.2±1.0	3.5±0.9	394.0±151.9	0.00	13.3	0.0	NR	NR
	Open	12.2±3.6	0.8±0.8	3.6±1.2	409.7±159.0	0.00	16.7	0.0	NR	NR
Kimura	VATS	14±9	NR	NR	NR	0.00	NR	NR	NR	8.9
	Open	19±13	NR	NR	NR	0.00	NR	NR	NR	NR
Liu	VATS	7.1±3.6	1.7±1.9	4.1±2.5	NR	0.00	NR	NR	0.0	NR
	Open	9.1±3.8	2.1±2.6	5.2±2.6	NR	2.30	NR	NR	0.0	NR
Maniscalco	VATS	2.6	NR	NR	NR	0.00	NR	7.7	7.7	NR
	Open	5.4	NR	NR	NR	0.00	NR	0.0	0.0	NR
Manoly	VATS	4.4±1.8	1.1±0.4	NR	NR	0.00	0.0	11.8	NR	0.0
	Open	6.4±4.6	2.0±1.2	NR	NR	0.00	0.0	0.0	NR	4.5
Odaka	VATS	4.6±1.7	NR	2±1	NR	NR	NR	NR	0.0	NR
	Open	11.2±3.6	NR	4.1±1.3	NR	NR	11.1	NR	0.0	NR
Pennathur	VATS	2.9±1.6	NR	NR	NR	NR	NR	NR	5.9	NR
	Open	6.2±4.2	NR	NR	NR	NR	NR	NR	0.0	NR
Sakamaki	VATS	NR	NR	NR	NR	0.00	NR	NR	NR	NR
	Open	NR	NR	NR	NR	0.00	NR	NR	NR	NR
Tagawa	VATS	NR	NR	NR	NR	0.00	NR	6.7	NR	NR
	Open	NR	NR	NR	NR	0.00	NR	NR	NR	NR
Ye	VATS	7.3±1.5	NR	3.2±0.8	311.8±122.0	NR	0.8	NR	0.0	13.6
	Open	12.4±7.6	NR	4.9±0.9	496.6±112.7	NR	2.2	NR	0.0	13.9
Yuan	VATS	6.4±2.8[C]	1.1±0.9[C]	4.9±2.0[C]	731.8±370.0[C]	NR	NR	NR	NR	NR
	Open	8.0±2.3[C]	1.2±1[C]	5.2±1.8[C]	1150.5±655[C]	NR	NR	NR	NR	NR
Weighted mean	VATS	7.0	1.4	3.6	408.4	0.0	1.9	6.7	0.8	11.2
	Open	9.8	1.5	4.8	732.1	0.3	4.1	0.0	0.0	NR
Range	VATS	2.6-14.0	1.1-1.7	1.8-4.9	311.8-731.8	0.0-0.0	0.0-13.3	0.0-11.8	0.0-7.7	0.0-13.6
	Open	5.4-19.0	0.8-2.1	3.6-5.2	409.7-1150.5	0.0-2.3	0.0-16.7	0.0-0.0	0.0-0.0	NR

VATS, video-assisted thoracoscopic surgery; [C], converted from median and range to mean and standard deviation; ICU, intensive care unit; NR, not reported.

Table 5 Overall survival outcomes in studies reporting on video-assisted thoracoscopic surgery versus open thymectomy for thymoma

First author	Year published	Approach	6 months	9 months	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
Chao	2015	NR												
Cheng	2005	NR												
Chung	2012	VATS	NR	NR	NR	100	NR	NR	100.0	NR	100.0	NR		
		Open	NR	NR	NR	98	NR	NR	98	NR	77	NR		
He	2013	VATS	NR											
		Open	NR	NR	94.4	NR								
Kimura	2013	VATS	100.0	100.0	100.0	100.0	100.0	NR						
		Open	100.0	100.0	100.0	100.0	100.0	NR						
Liu	2014	VATS	100.0	100.0	100.0	100.0	100.0	100.0	100.0	NR				
		Open	NR	NR	NR	NR	NR	NR	96.8	NR				
Maniscalco	2015	NR												
Manoly	2014	VATS	NR	NR	100	NR	83.3	NR	83.3	NR				
		Open	NR	NR	100	NR	93.8	NR	93.8	NR				
Odaka	2010	NR												
Pennathur	2011	NR												
Sakamaki	2014	VATS	98.1	98.1	98.1	96.8	96.8	96.8	96.8	96.8	96.8	96.8	96.8	96.8
		Open	90.7	90.7	90.7	90.7	90.7	79.1	79.1	79.1	79.1	79.1	79.1	79.1
Tagawa	2014	NR												
Ye	2014	NR												
Yuan	2014	NR												
	Range	VATS	90.7-100.0	98.1-100.0	98.1-100.0	96.8-100.0	83.3-100.0	NR	83.3-100.0	NR	NR			
		Open	NR	NR	94.4-100.0	90.7-100.0	NR	NR	79.1-98.0	NR	NR			

VATS, video-assisted thoracoscopic surgery; NR, not reported.

Table 6 Recurrence-free survival outcomes in studies reporting on video-assisted thoracoscopic surgery versus open thymectomy for thymoma

First author	Year published	Approach	6 months	9 months	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
Chao	2015	VATS	100.0	100.0	100.0	100.0	100.0	100.0	100.0	95.1	88.9	88.9	88.9	88.9
		Open	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	92.8	92.8	92.8	92.8
Cheng	2005	NR												
Chung	2012	VATS	100.0	100.0	100.0	100.0	NR	NR	96.0	96.0	96.0	NR		
		Open	NR	NR	NR	98.0	NR	NR	87.0	NR	77.0	NR		
He	2013	NR												
Kimura	2013	NR												
Liu	2014	VATS	NR	NR	NR	NR	NR	NR	96.9	NR				
		Open	NR	NR	NR	NR	NR	NR	92.2	NR				
Maniscalco	2015	VATS	100.0	100.0	100.0	100.0	100.0	100.0	100.0	NR				
		Open	100.0	100.0	100.0	100.0	100.0	100.0	100.0	NR				
Manoly	2014	VATS	100.0	100.0	100.0	NR	83.3	83.3	83.3	NR				
		Open	100.0	100.0	100.0	NR	85.2	NR	71.0	NR				
Odaka	2010	NR												
Pennathur	2011	VATS	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
		Open	100.0	100.0	100.0	100.0	100.0	83.0	83.0	83.0	83.0	83.0	83.0	83.0
Sakamaki	2014	VATS	98.5	98.5	98.5	96.9	95.0	95.0	92.4	92.4	92.4	92.4	92.4	92.4
		Open	90.5	90.5	90.5	90.5	90.5	79.5	79.5	79.5	79.5	79.5	79.5	79.5
Tagawa	2014	NR												
Ye	2014	NR												
Yuan	2014	NR												
	Range	VATS	98.5-100.0	98.5-100.0	98.5-100.0	96.9-100.0	83.3-100.0	83.3-100.0	83.3-100.0	92.4-100.0	88.9-100.0	88.9-100.0	88.9-100.0	88.9-100.0
		Open	90.5-100.0	90.5-100.0	90.5-100.0	90.5-100.0	85.2-100.0	79.5-100.0	79.5-100.0	79.5-100.0	77.0-92.8	79.5-92.8	79.5-92.8	79.5-92.8

VATS, video-assisted thoracoscopic surgery; NR, not reported.

interpreted with caution due to the large variation reported in individual studies. Both the duration of chest drainage and volume drained were lower in VATS patients compared to open thymectomy patients (3.6 *vs.* 4.8 days, and 408.4 *vs.* 732.1 mL respectively). Thirty-day mortality was low, at 0% for VATS, and 0.3% for open surgery.

Complications were variably reported, but higher rates of pneumonia were observed in the open group (4.1% *vs.* 1.9%), while the incidence of phrenic nerve injury was higher in VATS (6.7% *vs.* 0% in open surgery). A small proportion (0.8%) of VATS patients also demonstrated positive margins in resected specimens in contrast to none in the open surgery group. Other complications were insufficiently reported and thus not included in the analysis. The rate of reoperation for the VATS group was variable (0-13.6%) with an average of 11.2%, whilst it was inadequately documented for open surgery and therefore not reported.

The ranges of overall survival at 1, 2, and 5 years were similar or higher in VATS patients compared to open thymectomy patients (98.1-100%, 96.8-100%, and 83.3-100% in VATS *vs.* 94.4-100%, 90.7-100%, and 79.1-98.0% in open surgery, respectively) (*Table 5*). Small variations in survival rates are most likely attributable to inconsistent reporting and different time points documented across studies, with only four trials that examined 5-year survival (12,14,15,22). Recurrence-free survival at 6 months, 9 months, and yearly for up to 10 years was also predominantly similar or higher for VATS compared to the open surgery group (*Table 6*). In addition, this outcome was better reported in the studies analyzed, with seven trials that included recurrence-free survival up to at least 5 years (9,10,12,14,15,21,22). Only three studies reported recurrence-free survival at 10 years postoperatively (88.9-100% in VATS *vs.* 79.5-92.8% in open thymectomy) (9,10,15).

Discussion

Our results suggest that VATS thymectomy may be associated with similar, if not superior, overall and recurrence-free survival rates compared to open surgery. The VATS approach was also shown to potentially result in fewer complications such as bleeding and pneumonia, and shorter hospital stays. Furthermore, the average conversion rate was relatively low, at 3.1%. Subsequently, these findings reinforce those of existing reviews of the literature, though no previous publications have specifically focused on comparing VATS with open thymectomy for thymoma (1,2).

The majority of baseline characteristics, including demographics, use of adjuvant radiotherapy and/or chemotherapy, and tumor stage and grade were similar between the VATS and open groups. However, a key issue with comparing the two surgical approaches did arise from the non-random case selection in the studies. Although the criteria varied slightly across different trials, patients were generally reported as eligible for VATS if their tumor was less than 5 cm (12,14,16,17) or 6 cm (13) in diameter. Furthermore, most studies required the tumor to be sufficiently separate from the innominate vein and other vital organs, including the great vessels, heart, and trachea, with no evidence of local invasion (9,11-16). As a result, tumor size was on average greater in the open thymectomy patients compared to VATS (5.6 *vs.* 4.5 cm, respectively). This difference may have resulted in selection bias and potentially skewed results towards more positive outcomes for the VATS group.

It should be noted that two of the included studies used propensity-matching to adjust for the possible confounding effect of tumor size (10) and additionally, Masaoka stage (9), and still demonstrated similar or superior disease-free survival in VATS compared to open thymectomy patients at 5 years. Furthermore, exceptions to the VATS selection criteria were reported. A small proportion of patients with tumors over 5 cm in diameter still underwent VATS in at least three of the studies (11,12,14). The potential feasibility and safety of the VATS approach for bulky intrathoracic benign lesions over 5 cm size was moreover demonstrated by Gossot *et al.* [2007], albeit in a single-arm (23). Agasthian [2011] further showed that VATS thymectomy could be performed for 13 invasive Masaoka stage III and IV thymomas <5 cm in size, with only one recurrence over a median follow-up of 4.9 years (24). Evidently however, adequately powered randomized controlled trials are required to confirm the efficacy of VATS thymectomy compared to open surgery for a broader range of thymic tumor types (22).

Variations in surgical techniques were also observed across the studies. A greater proportion of VATS patients received a 'partial-' or 'hemi-' thymectomy (20.8%, range, 0.0-59.2) compared to open surgery patients (1.5%, range, 0.0-36.4). Although partial thymectomy may raise concerns about tumor recurrence in the remaining thymic tissue, proponents argue that this is extremely rare and that an unnecessarily wide resection for an early-stage lesion in a non-myaesthenic patient may increase the risk of operative complications (11,25,26). Moreover, in the current review, disease-free survival was still similar or superior in VATS patients compared to open thymectomy patients, despite variations in resection extent. This result also eventuated despite a small percentage of the VATS group demonstrating positive resection margins (0.8%) (10,11,14,21). Another concern with partial thymectomy has been that of post-thymectomy myasthenia gravis (PTMG); however, this complication was insufficiently reported in the studies included and therefore not presented in our analysis. Nonetheless, PTMG, which has an estimated incidence of 1-3%, has been shown to occur even after cases of extended thymectomy, suggesting that full resection is not necessarily more protective compared to partial thymectomy (27). Future studies comparing different extents of resection for thymoma are required to determine their respective efficacy and safety.

Inter-study variations in the approach to open thymectomy were likewise observed. Although the majority of studies exclusively utilized a midline sternotomy (n=474) a small proportion of patients (n=47) in the trial by Yuan *et al.* [2014] underwent a thoracotomy instead (19). Subgroup analysis in this trial revealed similar outcomes for the sternotomy versus thoracotomy patients, with the exception of greater blood loss and longer operation times for a sternotomy. Thoracotomy, conversely, was shown to have shorter operating times than for VATS. When the two open techniques were combined in a comparative analysis against VATS thymectomy, operative times were subsequently similar, although blood loss and length of hospital stay remained greater for open thymectomy (19). Although these subgroup differences may have influenced the results of the current review, their effect is likely to be minimal given the relatively small proportion of patients who underwent a thoracotomy.

Other factors to consider include potential complications of VATS, which, although inconsistently reported across the studies, included phrenic nerve injury (6.7% in VATS *vs.* 0% in open). The risk of these complications may well be increased in the initial stages of the learning curve associated with VATS thymectomy (21,22,28). In addition, VATS has been suggested to increase the risk of pleural dissemination and recurrence. Proposed mechanisms for this increased risk have included excessive manipulation of the thymoma in the restricted working space of the anterior mediastinum, making the tumor capsule more prone to tearing, as well as incision of the mediastinal pleura, which may facilitate seeding of tumor cells (29). Although lower rates of recurrence for VATS compared to open thymectomy were demonstrated in the current review, longer follow-up to at least 5 years in future studies is required to confirm this demonstration of equal, or potentially superior, oncological efficacy.

Limitations

This review had several limitations inherent to the studies analyzed. These included their non-randomized, observational nature, small sample sizes, and insufficient and/or inconsistent reporting of outcomes including long-term survival, recurrence rates, and postoperative complications. There was a particular paucity of data reported after 5 years of follow-up, restricting the types of statistical comparisons that could be made. As pooled averages could not be calculated, meta-analysis was not performed. As previously discussed, variations in study protocols, including eligibility criteria for VATS and surgical techniques for VATS and open thymectomy, may have also contributed to selection bias and heterogeneity in results. Qualitative evaluation using MOOSE criteria further demonstrated an apparent paucity of independent assessment of outcome parameters by at least two investigators and specification of trial inclusion and exclusion criteria, based on lack of reporting by their respective studies.

Conclusions and recommendations

VATS thymectomy is emerging as an increasingly feasible and efficacious alternative to open surgery for resection of thymomas. The present systematic review reaffirmed several potential benefits of VATS compared to open thymectomy, which included similar, if not superior, overall and disease-free survival, reduced blood loss, lower rates of complications such as pneumonia, and shorter hospital stays. However, given the limitations inherent in retrospective observational studies with small sample sizes, further adequately powered trials with longer-term follow-up and future randomized controlled trials are required to confirm the comparative safety and efficacy of VATS thymectomy for thymoma.

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Footnote

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

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Table S1 Qualitative assessment of studies reporting on video-assisted thoracoscopic surgery versus open thymectomy for thymoma

Assessment criteria	Chao	Cheng	Chung	He	Kimura	Liu	Maniscalco	Manoly	Odaka	Pennathur	Sakamaki	Tagawa	Ye	Yuan
Clear definition of study population[A]	No	No	Yes	Yes	Yes	No	Yes	Yes	No	No	No	No	Yes	Yes
Clear definition of outcomes and outcome assessment	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Independent assessment of outcome parameters[B]	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Sufficient duration of follow-up[C]	No	No	No	No	No	Yes	Yes	No	No	No	No	Yes	No	No
No selective loss during follow-up	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Important confounders and prognostic factors identified	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[A], inclusion and exclusion criteria required; [B], blinding during outcomes assessment, and assessment by multiple independent investigators required; [C], sufficient duration defined as at least 5 years postoperatively.

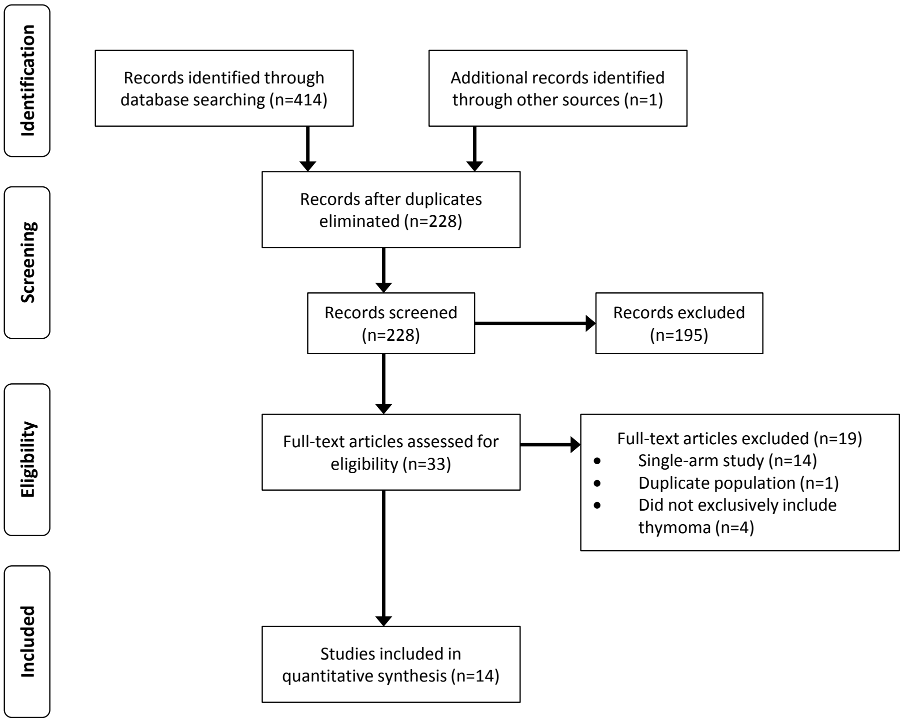

Figure S1 Search strategy for systematic review on video-assisted thoracoscopic surgery versus open thymectomy for thymoma.