Video-assisted thoracic surgery thymectomy versus sternotomy thymectomy in patients with thymoma: nationwide retrospective study in Japan.

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Running: VATS vs. sternotomy thymectomy

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Abstract

Background: This study was designed to evaluate the feasibility of video-assisted thoracoscopic surgery (VATS) and to compare the oncological outcomes of VATS with those of sternotomy in patients with thymoma.

Methods: The clinical outcomes of 2835 patients with thymic epithelial tumors treated between 1991 and 2010 in 32 Japanese institutions were collected retrospectively. We compared postoperative complications, positive surgical margins, location of recurrence, and survival between 140 of 142 VATS patients (VATS group) matched with 140 of 1294 sternotomy patients (ST group) using propensity scores.

Results: Postoperative complications were observed in 8 patients in the VATS group. The morbidity rate in the VATS group was not different from that of the ST group ($p = 0.25$).

Positive surgical margins were noted in 4 patients (3 in VATS group; 1 in ST group). There was no statistically significant difference in the recurrence rate between groups (median follow-up period: 3.7 years in VATS group; 5.2 years in ST group). In total the most frequent site of recurrence was pleural dissemination. In the VATS group, the 5-year recurrence-free survival rate was 93.8%, and the 5-year overall survival rate was 97.9%. There was no difference in the recurrence-free survival and overall survival

rates between the VATS group and the ST group ($p = 0.91$ and $p = 0.74$, respectively).

Conclusions: VATS thymectomy was feasible and comparable to sternotomy for the treatment of patients with thymoma with regard to morbidity, incomplete resection rate, and prognosis. However, additional follow-up is required to evaluate long-term outcomes.

Introduction

Thymectomy is the preferred standard treatment for thymoma. The traditional surgical approach involves total thymectomy by median sternotomy [1]. Complete surgical resection of a thymoma is the most important long-term prognostic factor in thymic malignancies [2–4]. Until recently, concern regarding incomplete surgical excision has limited the acceptance of video-assisted thoracoscopic surgery (VATS) for thymectomy. However, VATS represents a useful approach for the treatment of early stage thymoma. Recently, about 30% of thymectomies in Japan were performed using the VATS approach (Fig.1).

The surgical outcomes and technical benefits of VATS thymectomy have been previously reported [5], and limited data regarding the oncological outcomes of VATS thymectomy have been reported [6]. A nationwide registry of thymic epithelial tumors that was conducted by the Japanese Association for Research on the Thymus has enabled several previous studies and was utilized in the present study. The aim of this study was to evaluate the feasibility of VATS, and to compare the oncological outcomes associated with VATS and sternotomy-based thymectomies using data from the Japanese nationwide database.

Materials and Methods

Patients and data collection

Data was collected retrospectively from 2835 patients who underwent thymectomy between 1991 and 2010. Seventy-eight variables, including patient demographics, clinical diagnosis, surgical procedure, pathological diagnosis, perioperative therapy, and outcomes were investigated. The diagnosis of recurrence, follow-up schedule, and modalities used depended on the respective institution. Histological diagnoses were made according to the World Health Organization (WHO) classification of thymic epithelial tumors, and disease stage was determined according to the Masaoka staging system.

There were 2422 thymoma patients in the database. VATS thymectomy was performed in 349 patients and sternotomy thymectomy was performed in 1917 patients. The decision of surgical approach was non-randomized and depended on the respective institution. Patients who underwent a lateral thoracotomy and sternotomy surgery with VATS were excluded. Excluding patients without curative resection, treated with partial thymectomy, in Masaoka stage III and IV, and treated before 1994, there were 142 patients in the VATS group and 1294 patients in the ST group.

In these patients, the factors that influenced the decision as to whether to perform

VATS thymectomy including tumor size, Masaoka stage, age, WHO histological type, preoperative treatment (treatment for thymoma including chemotherapy, radiotherapy and pulse steroid therapy), postoperative treatment (treatment for thymoma including chemotherapy and radiotherapy), performance status, history of malignant disease, and the presence of myasthenia gravis were entered into a multivariable logistic regression model. The predicted probability derived from the logistic equation was used as the propensity score for each individual. Using the propensity score, 140 of 142 patients who underwent VATS thymectomy (VATS group) were matched with 140 of 1294 patients who underwent sternotomy (ST group).

Statistical analyses

We compared patient characteristics, tumor size, postoperative complications, recurrence location, recurrence-free survival (RFS), and overall survival (OS) between the groups. Categorical variables in each group were compared using the $\chi 2$ test or Fischer's exact test. A multivariate analysis of prognostic factors was performed using a Cox proportional hazard model. RFS and OS were calculated using the univariate Kaplan-Meier estimate probabilities, and differences between survival curves were analyzed with the log-rank test. The statistical analyses were conducted using SPSS

software Version 23 (IBM). In both the univariate and multivariate analyses, a p value of < 0.05 was considered statistically significant. This nationwide registry study was approved by the institutional review board of each participating institution.

Results

Patient characteristics

Patient characteristics are listed in Table 1. After propensity score matching, the VATS and sternotomy patients had similar characteristics. The only difference was that the patients who treated with extended thymectomy (en bloc resection of the anterior mediastinal adipose tissue including the thymus) in the VATS group were less than that seen in the ST group ($p < 0.01$).

The median follow-up period for the VATS group was 4.4 years. However, the median follow-up time in the VATS group was shorter than that seen in the ST group ($p < 0.01$), most likely because VATS had not been in clinical use for as long as the ST approach.

Outcomes and prognostic factors

During the follow-up period, 7 patients died. However no patient died within 30-days after surgery. In the VATS group, 1 patient died of MG and 1 patient died of cancer of a

different organ. On the other hand, 1 patient died of cancer of a different organ, 2 died from other causes, and 2 died from unknown causes in the ST group.

The 5-year OS rates were 97.9% in the VATS group and 97.1% in the ST group. The 5-year RFS rates were 93.9% in the VATS group and 95.0% in the ST group. There were no differences in the OS and RFS rates between the two groups ($p = 0.74$ and 0.91, respectively).

Recurrence locations

Recurrence locations are shown in Table 2. The most frequent recurrence location overall was the pleura, followed by local recurrence and metastasis. However, local recurrence and pleural dissemination were no more frequent in the VATS group than in the ST group (Table.2). Tumor size was a risk factor for recurrence in the VATS group (Table 3), but Masaoka stage was not a risk factor (Table 4).

Surgical margins

Curative (R0) resection was accomplished in 137 patients (97.9%) in the VATS group. All patients with a positive surgical margin in the VATS group had a microscopic positive margin (R1) (Table 3). All patients with R1 disease in the VATS group had a <

5cm diameter tumor and a Masaoka stage II thymoma (Table 3). There was no difference in the rate of R1 disease between the VATS group and the ST group (Table 2).

Postoperative complications

Postoperative complications are listed in Table 2. A total of 21 patients had postoperative complications, and the morbidity rate was similar in the VATS group compared with the ST group (6.1% vs. 9.6%, respectively; p = 0.25). The most frequent complications in the VATS group were MG crisis (1.5% in all patients, 4.4 % in patients with MG), heart disease (1.5%), and respiratory disease (1.5%).

A total of 114 patients had MG, and there was no difference in the incidence of postoperative MG crisis between the two groups (4.4% in the VATS group and 4.3% in the ST group, p = 1.0).

Discussion

Traditionally, sternotomy has been the standard approach for thymectomy. Many surgeons have been reluctant to use VATS for the resection of early stage thymomas because of the supposed increased risk of local recurrence, reduced safety margins after minimally invasive resection, possible rupture of the capsule, and seeding of the tumor

during endoscopic manipulations [7]. However, with surgical advances, the VATS technique for thymectomy has increased in popularity in patients with small thymomas and patients with MG [12].

Some studies have reported the advantages in surgical outcomes following VATS thymectomy. In previous reviews of VATS, VATS thymectomy demonstrated superior outcome in terms of hospital stay, intra-operative blood loss, and cosmetic satisfaction, when compared with open surgery [6, 9].

Because of the technical difficulty of VATS, complications have been a major concern for VATS thymectomy, but recent reports have not shown any major complications [10, 11]. Similarly, in the present study, the postoperative complication rate in the VATS group was not higher than that seen in the ST group (6.1% vs. 9.6%, $p = 0.25$), a finding consistent with the previous studies [10]. Compared with VATS, sternotomy has been associated with increased postoperative complications including more frequent pain, pulmonary compromise [6], wound complications, and sternal dehiscence [12].

In this study, there was no difference in morbidity between the two groups, and there were no difference between the groups in the incidence of wound infection, sternal infection, and respiratory complications. In particular, sternal infection and mediastinitis, severe complications after thymectomy, were not observed in the VATS

group.

Postoperative MG crisis is a serious complication associated with thymectomy in patients with MG. Meyer et al., reported that postoperative ventilation was required in 4.3% of patients with thymoma who underwent VATS thymectomy [11], which was comparable with our data showing that MG crisis was observed in 1.4% of VATS-treated patients. However, the MG crisis rates were not significantly different between the VATS and ST groups ($p = 1.0$). Because of the lack of randomized prospective clinical investigations, it is not clear whether a VATS thymectomy for MG has the same operative outcomes as a median sternotomy. Some reports have indicated that remission and palliation rates were equivalent between VATS and sternotomy-treated MG patients [11, 13]. Mayer et al. reported that 95.8% of VATS-treated patients showed complete stable remission, and 76.5% discontinued prednisone [11]. Furthermore, Zahid et al., [9] indicated that surgical management of MG was becoming increasingly recognized as an effective treatment option. The surgical treatment for MG requires an extended thymectomy, meaning an en bloc resection of the anterior mediastinal adipose tissue including the thymus. There were no differences in the between those patients undergoing total thymectomy and extended thymectomy in the VATS group (3.6% vs. 8.9% respectively, data not shown). Extended thymectomy by VATS can be performed as

safely as total thymectomy. Therefore, we believe that VATS thymectomy is a suitable treatment option for patients with MG who present with thymoma.

Pleural dissemination represents the typical recurrence pattern [14]. Pleural implants of a noninvasive thymoma may be caused by tumor cell seeding during tumor manipulation, especially if the mediastinal pleura have been opened [15]. Some authors have expressed concern that the risk of capsular rupture and subsequent pleural spread could be a drawback of VATS thymectomy [16]. Kimura et al. reported that tumor capsule injury was observed during VATS most frequently in patients with thymomas ≥ 5 cm in diameter [17]. However, many investigators agree that VATS thymectomy is technically feasible for thymomas ≤ 5 cm in diameter [18]. In the present study, tumor size ≥ 5 cm diameter was not a risk factor for a positive surgical margin in the VATS group ($p = 0.56$) (Table 3). Although the most frequent recurrences in the VATS group were pleural dissemination, the frequency of pleural dissemination was not different from that seen in the ST group (Table 3). VATS thymectomy has been considered to have a risk of pleural dissemination because the lateral mediastinal pleura is opened widely during VATS thymectomy. However, this result shows that if a negative surgical margin was achieved, the opening of the mediastinal pleura in VATS thymectomy does not appear to be a risk factor for pleural dissemination.

The recurrence rate in the VATS group was relatively low, possibly owing to the fact that the median follow-up time was shorter in the VATS group. Nevertheless, these data suggest that VATS thymectomy does not increase the risk of pleural dissemination.

In terms of oncological outcome, there are several reports of the oncological feasibility of VATS thymectomy for Masaoka stage I and II tumors. Jurado et al. reported that there was no difference in the 5-year RFS and recurrence rates between VATS and sternotomy-treated patients [10]. Sakamaki et al., found that, compared with sternotomy, VATS improved the 5-year OS, whereas the 5-year RFS was not different between the groups [16]. In the present study, the 5-year OS and RFS rates in the VATS group (97.9% and 93.9%, respectively.) were similar to those reported previously (5-year OS, 93.8–100%; 5-year RFS, 83.3–100%) [9, 11, 19, 20]. In addition, they were not significantly different from that seen in the sternotomy patients ($p = 0.74$ and 0.91, respectively). These results show that VATS thymectomy for Masaoka stage I and II tumors is as efficacious and safe as sternotomy.

When considering VATS thymectomy, tumor size is a major concern. Regarding the technical difficulty in handling the tumor, Girard et al., [20] stated that VATS was contraindicated for large tumors, whereas Youssef et al. suggested that VATS thymectomy was appropriate in tumors < 3 cm in diameter [21]. Several reports have

suggested that the indications for VATS thymectomy are more dependent on thymoma invasion into the great veins and pericardium, than on tumor size [9, 19]. Furthermore, Odaka et al. suggested that invasion into surrounding tissues was a greater risk factor when assessing resectability [9]. In this study, although there were more recurrences in patients with a > 5 cm thymoma, there were no differences in postoperative complications, positive surgical margins, local recurrences, and pleural dissemination between patients with a > 5 cm thymoma and those with thymomas ≤ 5 cm in the VATS group (Table 3). Currently there is no consensus regarding the maximum tumor size for VATS thymectomy [9], although to avoid capsule injury, careful attention should be given to larger thymomas. Overall, the present study indicates that thymoma size is not an absolute contraindication to VATS thymectomy.

Limitations

In many previous studies, limitations have included the length of the follow-up period. In fact, patients with thymoma tend to show long survival times. No patient died from thymoma during the course of this study, and only 0.2% patients died from thymoma in our entire database. However, the follow-up period could be considered short because thymoma is an indolent disease; longer follow-up durations might be necessary to

evaluate the final oncological outcomes.

Furthermore, as a non-randomized retrospective study, a patient selection bias could have existed.

Nevertheless, according to case-matched groups in patients undergoing thymectomy, VATS was a safe procedure that was not associated with any complications. Furthermore, for thymoma, in terms of complications, surgical margins, recurrence rates, OS, and RFS, VATS was as effective as sternotomy.

Conclusions

In conclusion, VATS thymectomy was a safe and feasible procedure for the treatment of thymoma with oncological outcomes and postoperative complication rates that were comparable to ST-treated patients.

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Table 1 Patient characteristics and clinical factors

Variables	All cases			Propensity score matched		
	ST	VATS	P value	ST	VATS	p value
Total no.	1294	142		140	140	
Age (years), mean	56.1±13.4	56.8±12.2	0.45	57.3±13.2	56.9±12.3	0.79
Sex			0.59			
men	561	65		59	63	0.72
women	732	77		81	77	
unknown	1	0				
Myasthenia gravis			0.44			0.45
no	909	96		86	94	
yes	376	46		51	46	
unknown	9	0		3	0	
Malignant disease			0.05			1.00
no	1179	124		118	122	
yes	97	18		18	18	
unknown	18	0		4	0	
Performance status			0.12			0.57
0,1	1073	110		103	110	
2,3,4,	209	30		34	30	
unknown	12	2		3	2	
Tumor size (cm), mean	5.7±4.0	4.4±2.8	< 0.001	3.9±1.8	3.9±1.7	0.81
WHO histology			0.19			0.71
A, AB, B1	885	89		85	89	
B2, B3	409	53		55	51	
Masaoka stage			0.013			0.63
I	614	83		76	81	
II	680	59		64	59	
Preoperative treatment			1.00			0.75
no	1249	138		133	136	
yes	36	4		5	4	
unknown	9	0		2	0	
chemotherapy	11	0	0.61	1	0	1.00
radiotherapy	7	0	1.00	1	0	1.00
steroid pulse therapy	22	4	0.35	3	4	1.00

Procedure			< 0.001			< 0.001
total thymectomy	507	86		52	84	
extended thymectomy	787	56		88	56	
Adjuvant therapy			0.073			1.00
no	1112	130		127	128	
yes	158	10		10	10	
unknown	24	0		3	2	
chemotherapy	5	0	1.00	0	0	1.00
radiotherapy	153	10	0.15	10	10	1.00
Follow up (years), median (range)	5.0 (0-18.0)	3.7 (0-15.9)	< 0.001	5.2 (0-18.0)	3.7 (0-15.9)	< 0.001

VATS, video-assisted thoracoscopic surgery; ST, sternotomy; WHO, World Health Organization.

Table.2 Endpoints in the VATS and ST groups

	ST (N = 140)	VATS (N = 140)	p value
Postoperative complications			0.25
no	112	129	
yes	13	8	
unknown	5	3	
Wound infection	2	0	0.23
Sternal infection, mediastinitis	1	0	0.48
Myasthenia gravis crisis	2	2	1.00
Nerve injury	1	1	1.00
Thrombosis	0	1	1.00
Respiratory complications	1	2	1.00
Bleeding	0	0	1.00
Cardiac complications	3	2	0.67
Others	4	0	0.05
Surgical margin			0.62
negative (R0)	139	137	
positive			
microscopic (R1)	1	3	
macroscopic (R2)	0	0	
Recurrence			0.72
no	130	136	
yes	4	3	
unknown	6	1	
Location of recurrence			
local recurrence	3	0	0.12
pleural dissemination	2	2	1.00
metastasis	0	1	1.00

ST, sternotomy; VATS, video assisted thoracoscopic surgery

Table 3 The effect of tumor size

		VATS group			ST group		
		> 5 cm	≤ 5 cm	p value	> 5 cm	≤ 5 cm	p value
Complication				1.00			0.51
	no	37	92		31	81	
	yes	2	6		2	11	
Positive margin				0.56			1.00
	no	40	99		42	97	
	yes	0	3		0	1	
Recurrence				0.02			0.58
	no	36	100		37	93	
	yes	3	0		2	2	
local recurrence				1.00			0.20
	no	39	100		37	94	
	yes	0	0		2	1	
pleural dissemination				0.08			0.50
	no	37	100		38	94	
	yes	2	0		1	1	
metastasis				0.28			1.00
	no	38	100		39	95	
	yes	1	0		0	0	

VATS, video-assisted thoracoscopic sternotomy; ST, sternotomy; CI, confidence interval

Table 4 The effect of Masaoka stage

		VATS group			ST group		
		stage I	stage II	p value	stage I	stage II	p value
Complication				0.28			1.00
	no	77	52		61	51	
	yes	3	5		7	6	
Positive margin				0.07			0.46
	no	81	56		76	63	
	yes	0	3		0	1	
Recurrence				1.00			1.00
	no	78	58		70	60	
	yes	2	1		2	2	
local recurrence				1.00			0.25
	no	80	59		69	62	
	yes	0	0		3	0	
pleural dissemination				1.00			0.21
	no	80	59		72	60	
	yes	1	1		0	2	
metastasis				1.00			1.00
	no	79	59		72	62	
	yes	1	0		0	0	

VATS, video-assisted thoracoscopic sternotomy; ST, sternotomy; CI, confidence interval

Figure legends

Fig 1.

Video-assisted thoracoscopic sternotomy approach vs. sternotomy for thymectomy over the duration of the study in multiple institutions participating in the Japanese Association for Research on the Thymus database.

Fig 2.

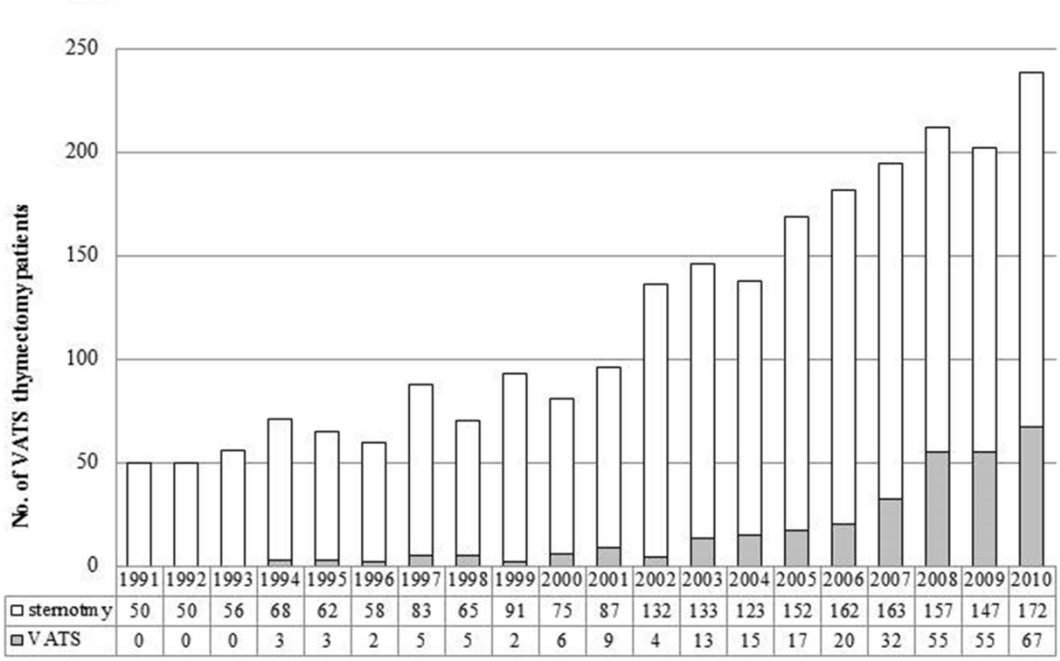
(A) Kaplan–Meier plot illustrating overall survival stratified by propensity score matched group (VATS vs. sternotomy). Time from thymectomy (years) plotted on x-axis.

VATS, video-assisted thoracoscopic sternotomy; ST, sternotomy; OS, overall survival

(B) Kaplan–Meier plot illustrating recurrence-free survival stratified by propensity score matched group (VATS vs. sternotomy). Time from thymectomy (years) plotted on x-axis.

VATS, video-assisted thoracoscopic sternotomy; ST, sternotomy; RFS, recurrence-free survival

Fig.1



	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
□ sternotmy	50	50	56	68	62	58	83	65	91	75	87	132	133	123	152	162	163	157	147	172
▨ VATS	0	0	0	3	3	2	5	5	2	6	9	4	13	15	17	20	32	55	55	67

Fig.2a

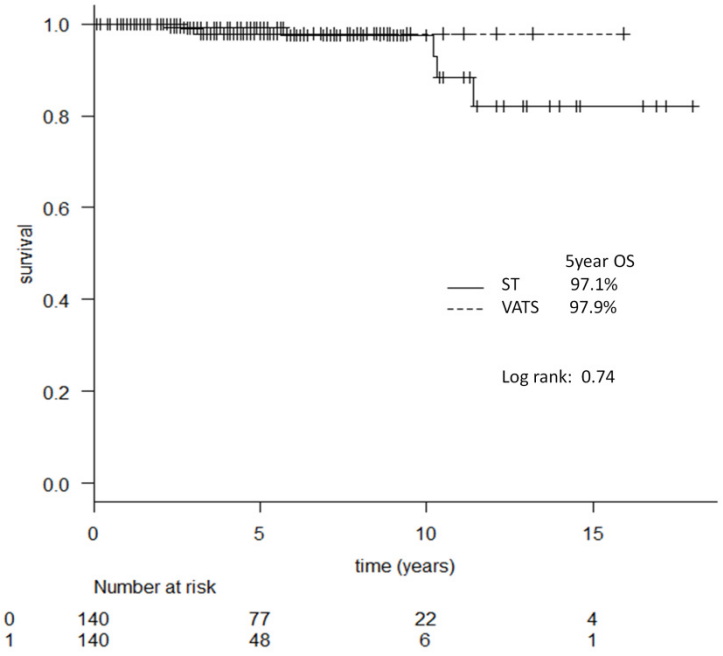
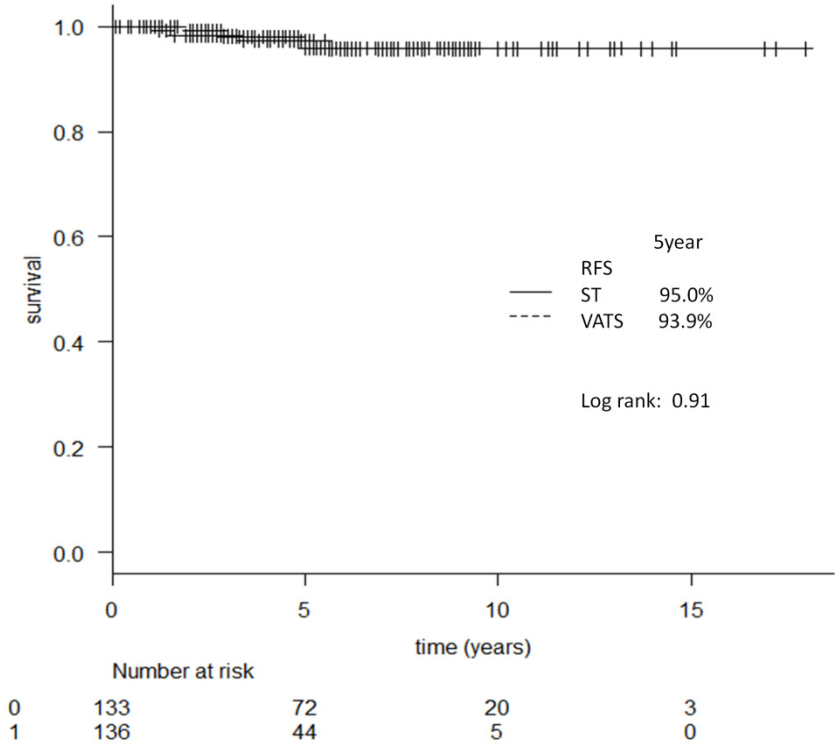


Fig2b


1.0
0.8
0.6
0.4
0.2
0.0
survival
5year
RFS
ST 95.0%
VATS 93.9%
Log rank: 0.91
0
5
10
15
time (years)
Number at risk
0 133 72 20 3
1 136 44 5 0