Lymph Node Dissection in Thymoma: Is it worth it?

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Word count (text): 3740

Disclosure: The authors declare no conflict of interest.

Abbreviations (in order of appearance in the manuscript):

TC = thymic carcinoma

NETT = Neuroendocrine thymic tumors

LND = Lymph Node Dissection

IASLC = International Association for Studies in Lung Cancer

ITMIG = International Thymic Malignancy Interest Group

JART = Japanese Association for Research in the Thymus

RYHTMIC = National Network for Thymic tumors and malignancies

UICC = Union for International Cancer Control

WHO = World Health Organization

ESMO = European Society for Medical Oncology

ITCH = Intra-thoracic chemo hyperthermia

CT = Computed tomography

^{18}F-FDG-PET = Fluorine-18-fluorodeoxyglucose positron emission tomography

SUVMax = Maximum Standardized Uptake Value.

FEV1 = Forced expiratory volume at 1 second.

RLN = Recurrent Laryngeal Nerve

OS = Overall survival

FFR = Freedom From Recurrence

VATS = video-assisted thoracic surgery

PN = phrenic nerve

ICU = Intensive Care Unit

SEER = Surveillance, Epidemiology, and End Results

Abstract *(251 words)*

Objectives: Lymph node dissection (LND) and nodal metastases in thymomas remain controversial and understudied. The aim of our study was to evaluate the incidence of nodal metastasis and the short term outcomes of systematic LND in thymomas.

Material and Methods: From December 2017 to September 2020, we performed 54 LND conducted according to the International Thymic Malignancy Interest Group (ITMIG) lymph node map. This group was compared to a historical control group of 55 patients who underwent surgery in our center from January 2015 to November 2017.

Results: LND was performed in 72% and in 5% of the cases in the study cohort group and historical control group, respectively. The number of lymph nodes retrieved was significantly higher in the study cohort group (3.89 per patient vs. 1.62, p=0.0021). In the whole population studied, nodal metastases were found in 3 patients (2.8% of all patients) with 5.6% in the cohort study group vs. 0% in the control group (p=0.12). Patients with nodal metastasis had larger tumors (> 7 cm), and a higher histology grade (B2 and B3). There was a trend towards higher risk of laryngeal nerve palsy in the cohort study group (9.3% vs. 1.8%, p=0.11).

Conclusion: Systematic LND increases the number of lymph node harvested and detects more lymph node metastases, which remains infrequent in thymomas. The impact of LND and the true prognostic significance of lymph node metastases remains controversial. Given the potential complications, LND or sampling should not be perfomed in small, encapsulated and low grade thymomas.

Keywords: Thymoma; Lymph Node Dissection; Lymphadenectomy; Nodal metastases; Lymph node metastasis

1. Introduction

Thymic tumors are rare thoracic malignancies, but represent the most common anterior mediastinal tumors [1]. The most frequent pathologic patterns are thymoma, thymic carcinoma (TC) and neuroendocrine thymic tumors (NETT). Complete R0 resection, when feasible, has the most significant impact on survival and recurrence rates [2]. The benefit of lymph node dissection (LND) in thymomas remains controversial and understudied [3–8]. Some studies underlined a low rate of lymph node metastasis, ranging between 0,5% [6] and 13.3% [8], justifying the decision of some centers to never perform LND for thymomas. By contrast, even though data are scarce, benefits of LND on TCs are more established. Nodal invasion is frequent (25% to 40%) and LND has a proven impact on survival and recurrence [3, 9, 10]. TC is also a known predictive factor of nodal metastasis in multivariate analysis [5, 7]. A recent survey conducted by the International Thymic Malignancy Interest Group (ITMIG) reported that LND of the N1 and N2 stations were performed in 50% and 21% of cases respectively for thymomas, and in 66% and 44% of cases respectively for TC [11]. Many studies mixed both histologies and therefore, results regarding thymomas alone remain controversial.

The International Association for Studies in Lung Cancer (IASLC) and the ITMIG proposed a new lymph node map for thymic malignancy and classification of the N component [12, 13]. ITMIG also suggested that anterior mediastinal nodes should be routinely removed along with the thymus. The group encouraged systematic sampling of deep nodes when resecting thymomas with invasion of mediastinal structures. For TC, a systematic removal of both N1 and N2 nodes is recommended during curative-intent resection [13]. Despite the unprecedented size of their retrospective database, the size of the N subgroups rapidly became smaller and the data was almost exclusively available from the patients of the Japanese Association for Research in the Thymus (JART). Thus, the proposed stage classification can be regarded as a step in an ongoing process. Further prospective studies are warranted to validate these recommendations.

To date, data on LND in thymoma are insufficient and complications are also poorly described. Therefore, we aimed at assessing the incidence of nodal metastasis and the short terms outcomes of systematic LND in thymomas.

2. Materials and Methods

2.1. Study design and patients

We conducted a retrospective cohort study between 2015 and 2020 at the Louis Pradel Hospital, Hospices Civils de Lyon, a national center of expertise for the management of thymic malignancies. All cases were discussed in RYTHMIC, the French National network dedicated to the management of thymic tumors, and the treatment principles followed the European Society for Medical Oncology (ESMO) guidelines [14]. Data were gathered and analyzed retrospectively by the investigators.

Patients were divided into two subgroups A and B. Group A included patients treated from December 2017 to September 2020, in which LND were performed in all cases of suspected thymic malignancies according to the ITMIG lymph node map. Patients with TCs were excluded. A total of 54 thymomas were included in group A. Group B was the control group and included patients treated between January 2015 and November 2017 and in which all thymomas who underwent surgery (n=55) were analyzed. In group B, LND was carried out only at the surgeon's discretion. Patients with micronodular thymomas or microthymomas found when the surgery was performed for myasthenia gravis were excluded, as were patients with recurrent thymomas. We included patients with pleural implants detected in pre-operative work-up who were treated with a multimodal therapy including thymectomy followed by pleurectomy and intra-thoracic chemo-hyperthermia (ITCH) [15]. We voluntarily chose to exclude TCs in this study because thymomas and TCs are different tumors types and the benefit of LND has already been established for TCs in the medical litterature [5, 7].

2.2. Lymph Node Dissection and staging

In group A, surgeons had to follow the lymph node map described by the IASLC/ITMIG [12]. Extra-thoracic lymph nodes were defined as M component [13]. LND was considered when at least one N2 station was intentionally harvested and sent for pathological examination separately. Invasion by direct extension was counted as nodal involment [13]. The extent of LND was at the surgeons' discretion, although they were encouraged to harvest as many nodes as possible. All patients with or without LND always had extended thymectomy with resection of the major part of the N1 stations. Thymomectomy alone was never performed. Invasion of neighboring organs was treated by

"en-bloc" resection. Tumor staging was based on the Union for International Cancer Control (UICC) staging system [12, 16] and the Masaoka-Koga classification [17]. Tumor histology was classified according to the 2015 World Health Organization (WHO) classification [18], and a second pathological examination was systematically performed through the RYTHMIC network.

2.3. Preoperative work-up

Preoperative work-up consisted of chest CT scan for all patients. Fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) coupled to a dedicated CT scan was performed in 41 cases in group A (76%) and in 35 cases in the control group (64%, p=0.21). Biopsy was performed in 12 cases (22%) in group A, and 10 cases (18%) in group B (p=0.64), before preoperative treatment or in the presence of uncertain diagnosis before potential resection of adjacent structures. Myasthenia gravis was observed in 22 patients in group A (40.7%) and 23 patients in group B (41.8%, p=1.00). Patient's preoperative characteristics are detailed in Table 1.

2.4. Follow-up

Follow-up and postoperative management were decided by the RYTHMIC tumor board, according to the European Society for Medical Oncology (ESMO) guidelines [14]. Early physical examination and chest CT scan were performed 3 to 4 months after surgery for all patients. A physical examination and a CT scan were performed every year for 5 years for complete resection of stage I-II, then every 2 years. For stage III-IV thymomas, and incomplete resections, follow-up exams were more frequent.

Operative mortality was defined as 30-day mortality or in-hospital mortality. Morbidity was defined as any complications above stage I in the Clavien Dindo Classification [19]. Recurrent laryngeal nerve (RLN) palsy had to be validated by nasofibroscopy. Overall survival (OS) was defined as the time from the date of operation to death from any cause. Freedom from recurrence (FFR) was defined as the time from the date of operation to the date of recurrence.

2.5. Statistical analysis

Statistical analysis was performed using GraphPad Prism Version 8.4.3 (471) (GraphPad Software, San Diego, CA). Categorical variables were analyzed using chi-square test, or Fisher's exact test for small samples. Continuous data were compared using Student's test (parametric test) or Mann-Whitney's test (nonparametric test). Overall survival rates were calculated using the Kaplan-Meier method, and a log rank test was used to calculate survival differences between the two groups. Statistical significance was accepted as a p value < 0.05.

3. Results

3.1. Patients' characteristics

A total of 130 thymic tumors were treated between January 2015 and September 2020. Sixty four patients with suspicion of thymic malignancies were enrolled in group A between December 2017 and September 2020. Group A included 54 histologically proven thymomas; 5 TCs, 3 thymoma recurrences. One micro thymoma and 1 micronodular thymoma were excluded. In group B, we reviewed all resected thymic malignancies from our database (n=66), all cases of thymomas (n=55) who underwent surgery between January 2015 and November 2017 were included. Six TCs, 1 NETT, 3 recurrences and 1 microthymoma were not included in the analysis. The flow chart of the study is described in Fig 1.

Patient's characteristics were statistically similar between the two groups for size, stages, and pathological examination (Table 2). Seventeen percent of patients in group A had invasive tumors (≥ pT2). Surgical approach was mainly open in both group with median sternotomy in 46% of cases in group A, vs. 42% in group B, manubriotomy in 44% vs. 45% of cases respectively, video-assisted thoracic surgery (VATS) in 7% vs. 9% of cases, thoracotomy in 0% vs. 2% of cases, and Masaoka approach in 2% in both groups. Follow-up was complete for all patients except one who was lost to follow-up 21 months after the surgery.

3.2. Lymph Node Dissection

All patients had extended thymectomy. In group A, LND was performed in 39 patients (72%). All patients in this group who did not have LND had macroscopically non-invasive tumors (pT1a in 12 patients (80%), pT1b in 2 patients (13.3%), and pT2 in 1 patient (6.7% of all cases)). Those patients with small tumors did not undergo LND due to the absence of nodes found during per operative exploration. In group B, 3 patients (5%) went through LND at the surgeon's discretion because of TC suspicion.

A total of 299 lymph nodes were harvested (average of 2.74 per patient). As expected, the number of lymph nodes retrieved was significantly higher in group A (210 nodes, 3.89 per patient vs. 89 nodes, 1.62 per patient, p=0.0021). The number of lymph nodes was also significatively higher for N2 stations in group A (p=0.0005), while it was similar for N1 stations (p=0.55). The rate of invaded lymph nodes in group A was 5.6% while not lymph nodes metastases where encountered in the control group (p=0.12). Nodal metastases were

found in 9 nodes, and all of them were located in N2 stations (lower para-tracheal, internal mammary, hilar nodes groups). The global incidence with lymph node metastasis was 2.8% in the whole population (Figure 3). In group A, minimally invasive approaches (manubriotomy and VATS) had significantly lower number of lymph nodes sampled than full-open procedures (2.75 vs. 5.1 lymph nodes per patient, p=0.027).

In the overall population, the rate of invaded lymph nodes was 10.3% for tumors with a diameter ≥7 cm, and 0% for tumors smaller than 7 cm (p=0.02). The nodal invasion rate was also significantly higher for advanced tumor with a stage ≥ T2 (14% vs. 1%, p=0.04) and for pleural/hematogenous metastases (40% vs. 1%, p=0.005). There was no difference in the rate of invaded lymph nodes across histological groups (p=0.24).

Focusing on group A only, the rate of invaded lymph nodes was 17.6% for tumors 7 cm or larger and 0% for tumors smaller than 7 cm (p=0.027). The nodal invasion rate was also significantly higher for patients with pleural/hematogenous metastases (50% vs. 2%, p=0.012).

All patients with positive LND actually required extensive resection with anatomical pulmonary resection due to direct invasion or metastatic invasion. 2 out of 3 had also vascular venous resection.

3.3. Early outcomes and complications

Median follow-up in group A and group B were 14.4 months (range 1.0 – 30.8) and 43.4 months (range 14.3 – 67.3), respectively, thus limiting the relevance of comparing outcomes. Operative mortality was not significantly higher in group A than in group B: one patient died 30 days after the surgery secondary to severe myasthenic crisis (1.9% vs. 0%, p=0.50). OS and FFR was similar in the two groups (p=0.41, p=0.36 respectively). Median survival was not reached (Fig 3). No patient died of thymoma. During the follow-up, five other patients died from other causes (septic shock, lung adenocarcinoma, dehydration on chronic diarrhea, and myasthenic crisis for 2 patients).

Post-operative complications occurred in 20% of the patients in group A. There were no differences between the two groups according to the Clavien Dindo Classification [19] (Table 4). RLN palsy was the most common complication. In group A, we had 5 RLN palsy (1 pT1a, 1 pT1b, 1 pT3 and 2 pT4). RLN palsy in the 2 pT4 patients were caused by tumor involvement or surgery of the primary tumor. In group B, we had 1 RLN palsy due to LND (pT3 tumor). There was a trend noticed for more RLN palsy in group A, but it did not reach

statistical difference (9.3% vs. 1.8%, p=0.11). Among the 5 RLN palsy in group A, one patient had RLN diplegia which was not life threatening. The phrenic nerve was resected for tumor invasion in 13% in each group.

In group A, 12 patients received adjuvant therapy (22%). Among them, 9 patients received radiation, and 3 underwent a sub-total pleurectomy with ITCH, one of which had also chemotherapy. In group B, 13 patients received adjuvant therapy (24%). All patients received radiation, and one patient also underwent sub-total pleurectomy with ITCH in addition of radiation.

Ultimately, only one patient (33%) was upstaged to stage IVb in the postoperative setting because of positive LND. He received post-operative radiation therapy. The two others had already been staged as IVb due to pericardial, pleural and pulmonary metastases, and were included in the ITCH program. One of which had also received chemotherapy, in addition for pulmonary metastases. Therefore, LND had no impact on the decision-making about adjuvant therapy.

4. Discussion

In the present study, we conducted a retrospective study to evaluate LND based on the ITMIG lymph node map. We have assessed LND in thymomas by comparing 2 homogeneous groups of patients over an equivalent time period. Seventy two percent of patients underwent LND in a study cohort group (group A) as compared to 5% in a historical control group (group B) for initially suspected TC. We identified a 5.6% rate in lymph node metastasis in group A whereas no lymph node metastases were founded in group B (5.6% vs. 0%, p=0.11). Although all patients had extended thymectomies, without N1 metastases. The global incidence of patients with lymph node metastasis was 2.8% in the whole population. Positive LND was found more frequently in patients with large tumor with diameter > 7cm (10.3%), with advanced tumor with a stage ≥ T2 (14%) or with pleural/hematogenous metastases (40%). LND does not appear to have a significant impact on the staging and does not influence the post-operative treatment. Moreover, no significant differences were found in overall survival and recurrence between the 2 groups. But, LND is not a harmless procedure. Indeed, RLN palsy occurred in 9.3% of group A.

The incidence of lymph node metastasis in thymomas is rare, advocating for absence of LND in few teams. To date, only few studies explored the metastatic lymph node involvement in thymomas, highlighting lymph node metastasis in 0.5 to 13.3% [4–8]. However, this low rate could be underestimated by the lack of LND performed in clinical practice. Our findings are consistent to the Japanese, Korean and Chinese database [3, 5, 7]. However, in the United States, Weksler *et al*. reported a far higher rate of metastatic lymph node invasion (13.3%) [8], probably over-estimated secondary to the inclusion of patients with advanced stages (55% of stage III-IV Masaoka-Koga classification) and with at least one lymph node analyzed. Our study also underlined a trend in the increase of nodal metastasis by intentional LND compared to our control group (5.6% vs. 0%, p=0.11). This statement has been corroborated for all thymic tumors combined in Fang's study (5.5% in their prospective cohort vs. 2.2% in their retrospective cohort; p=0.002) [7]. Hwang's studies also showed a higher nodal metastases rate with LND compared to the whole population incidence [4, 5].

Another important question is whether the identification of more nodal metastases should change postoperative care and the oncologic outcomes of patients with thymoma. In our purpose, LND does not appear to have a significant impact on tumor staging comparing to other studies where the occurrence of lymph node metastasis has led to upgrade to stage IV 65-80% of patients with lymph node invasion [5, 8]. In our study, only one patient with nodal

invasion (0.9% of all patients, 33% of N+ patients) was upgraded from stage III to IV, though it was only related to his N status, while the other N+ patients had already reached stage IV due to pleural and pulmonary metastases. LND does not seem to have influenced the need of adjuvant chemotherapy. Since the majority of tumors with positive nodes usually have high grade histology and high tumor stage, adjuvant radiation treatment should be performed anyway according to ESMO recommendations [14]. However, there are no current guidelines about adjuvant therapy for resectable thymomas with nodal invasion. Chemotherapy combined with radiation could be an option for such a disseminated disease and prospective studies are warranted to analyze the potential benefits of this treatment. Lymph node metastases seems to have an oncological impact in thymomas in some retrospective studies [3–5, 8] whereas LND has no positive effect on recurrence [5]. In our study, no significant differences were found in terms of overall survival and recurrence between the 2 groups. However, long term prospective studies are warranted to determine the oncological impact of LND.

Evaluation and dissection of N2 lymph nodes requires more extensive surgery. Our study is the first one to identify the occurrence of complications directly related to LND. The rate of global complications in the study cohort group was not significantly increased in comparison to the historical control group. However, a trend towards of more RLN palsy was encountered in group A (9.3% vs. 1.8%, p=0.11). RLN palsy in these patients, who are usually young professionals, have a negative impact on their quality of life. Monitoring of the recurrent nerves could be an option to prevent nerve damage as is it commonly carried out during thyroid surgery [20]. Precautions need to be taken during dissection of lower cervical stations, para-tracheal and the subaortic/aorto-pulmonary window.

Given the potential complications and the rarity of positive LND in thymomas, the main objective would be to target patients at risk of nodal metastases. We weren't able to perform risk factor analysis due to our small number of positive cases for thymomas. In all published series and risk factor analysis were always done mixing cases of thymomas, TCs and NETTs. Size (>6cm), high histologic grade (B3/TC), T categories T3-T4 were predictive factor of nodal metastases [5, 7]. However, no conclusion on thymomas only can be drawn. In our study, our findings are going in the same way. Positive LND was more frequently found in patients with large tumor with diameter > 7cm, with advanced tumor (stage ≥ T2) or with pleural/hematogenous metastases. We also observed that all thymomas with lymph node invasion were high grade (B2 and B3 thymomas). Pre-operative ^{18}F-FDG-PET/CT scan is a valuable tool to detect high grade thymoma or thymic carcinoma [21–24]. ITMIG's

prospective database showed that there is a relationship between primary tumor SUVMax and histologic type as well as Masaoka-Koga pathologic stage [25]. Therefore, patients with higher values of primary tumor SUVMax should undergo a diligent search for lymph node metastasis during workup and surgery. Also, surgical resection may be associated with systematic LND in these situations. Positive PET scanning nodes, they should be specifically removed. Finally, preoperative biopsy should be reassessed in invasive tumors, even when an upfront surgical resection is achievable, to confirm the diagnosis of TC. Then, it should encourage the surgeon to perform an extensive LND.

While most of the literature data used retrospective database with often incomplete or unclear data regarding LND and its complications, our study underlines the reality of thymic surgery and enables us to carefully consider the pattern of nodal metastasis in thymomas and LND. Despite of the described advantages, some limitations must be mentioned. First, the number of patients remains low. This probably explains why our study is not enough powerful to detect significant differences in complications and lymph node metastases rate. This low rate of nodal metastases is a consistent feature in the literature. Therefore, statistical meaning must be carefully interpreted regarding lymph nodes metastases in thymomas. Second, another limitation of our study is related to the retrospective design of the study and the incomplete rate of LND in group A (72%). Despite the will to perform as many LND as possible, 15 patients did not undergo LND because surgeons choose to not remove lymph nodes when the patient had a small non-invasive tumor without any nodes at the exploration. However, this rate of LND is the highest compared to other studies, with approximately 50% of N2 dissections [5, 7].

Definition of LND in thymoma is not fully delineated, particularly for the number of nodes groups and lymph nodes that should be harvested. In our study, we choose to consider LND when at least one N2 node was harvested, whereas dissection of the anterior region is often considered as LND. In fact, most of the N1 stations are harvested with extended thymectomy, which is recommended in thymic malignancies [14]. Dissection of the N1 stations is probably not sufficient when LND is required. Therefore, recommendations on the definition and the extent of LND are needed to ensure the true impact of LND in futures prospective studies.

It seems difficult now to draw firm conclusions about LND in thymomas. One of the interests of this study is to open the discussion, bearing in mind that the only short term benefit from LND is to detect more lymph node metastases, which remain rare in thymomas. Without clear recommendations, LND induced no change in adjuvant therapy, and had

probably no effect on survival and recurrences. Furthermore, serious complications can be related to LND. Hence, is performing LND in thymomas worth it? For small, encapsulated or non-invasive thymomas, we think that LND or sampling should not be performed. On the other hand, for invasive thymomas, the benefit of performing LND remains to be proven. Prospective multicentric studies are needed, and as our study is the first one to identify RLN palsy as specific complications related to LND, these complications should be reported in future studies.

5. Conclusions

Systematic LND increases the number of lymph node harvested, and detects more lymph node metastases, although it remains infrequent in thymomas. Surgical complications of LND are rare, but an increase in RLN injury was observed. Patients with lymph node metastases presented higher grade thymomas (B2/B3), larger tumors, more frequent invasion of adjacent structures and/or metastatic disease. Positive PET scan nodes must be specifically removed during surgery. However, the impact of LND and the true prognostic significance of lymph node metastases remains controversial. Given the potential complications, LND or sampling should not be proposed in small, encapsulated, low grade thymomas.

Thus, further larger prospective studies with standardized LND protocols are needed to better determine patients at a higher risk of lymphatic spread; the impact of nodal metastases on the risk of long-term recurrence and mortality has to be assessed.

Acknowledgments: The authors thanks Ms. Alexandra Pavan and Guillaume William Taylor for reviewing the English manuscript, and Ms. Carola Pierobon for reviewing the statistical data.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Tables

Characteristics	Group A, n (%) (n=54)	Group B, (%) (n=55)	p value
Male gender	23 (42.6)	26 (47.3)	0.70
Age, years, Mean, SD	59 +/- 14.4	62 +/- 13.5	0.24
Preoperative treatment			
Chemotherapy	6 (11.1)	4 (7.3)	0.53
Radiotherapy	0	0	NA
Biopsy	12 (22.2)	10 (18.2)	0.64
^{18}F-FDG-PET/CT			
n	41 (75.9)	35 (63.6)	0.21
Primary tumor FDG uptake	35 (85.4)	26 (74.3)	0.26
Median SUVMax, [range]	5.48 [2.2-15]	4.2 [2.5-10.9]	0.20
LN FDG uptake	8 (20)	3 (9.0)	0.21
Median SUVMax, [range]	4.3 [2-9.2]	3.5 [2.7-3.9]	0.52
FEV1,%	101	96.3	0.35
Comorbidities			
Myasthenia gravis	22 (40.7)	23 (41.8)	1.00
Other Auto-immune disease	7 (13.0)	4 (7.3)	0.36

Table 1. **Pre-operative characteristics in study cohort group (group A) and historical control group (group B)**.

CT: computed tomography. ^{18}F-FDG-PET: Fluorine-18-fluorodeoxyglucose positron emission tomography. SUVMax: Maximum Standardized Uptake Value. FEV1 : Forced expiratory volume at 1 second.

Characteristics	Group A, n (%) (n=54)	Group B, n (%) (n=55)	p value
Pathologic Size, mm [range]	63,1 [12-170]	53 [5-130]	0.11
Complete resection (R0)	49 (91%)	52 (95%)	0.49
WHO Classification			
A	2 (3.7)	6 (10.9)	0.27
AB	21 (38.9)	19 (34.5)	0.69
B1	1 (1.9)	2 (3.6)	1.00
B2	20 (37.0)	19 (34.5)	0.84
B3	9 (16.7)	8 (14.5)	0.80
Micronodular	0	1 (1.8)	1.00
Masaoka Koga stage			
I	15 (27.8)	15 (27.3)	1.00
IIa	11 (20.4)	14 (25.5)	0.65
IIb	12 (22.2)	15 (27.3)	0.66
III	11 (20.4)	10 (18.2)	0.81
IVa	2 (3.7)	1 (1.8)	0.62
IVb	3 (5.6)	0	0.12
pT descriptor			
1a	38 (70.4)	43 (78.2)	0.39
1b	7 (13.0)	7 (12.7)	1.00
2	1 (1.9)	3 (5.5)	0.62
3	6 (11.1)	2 (3.6)	0.16
4	2 (3.7)	0	0.50
Metastasis			
M0	49 (90.7)	54 (98.2)	0.11
M1a	4 (7.4)	1 (1.8)	0.21
M1b	1 (1.9)	0	0.50
pTNM stage			
I	44 (81.5)	50 (90.9)	0.18
II	1 (1.9)	2 (3.6)	1.00
IIIa	2 (3.7)	2 (3.6)	1.00
IIIb	2 (3.7)	0	0.24
IVa	2 (3.7)	1 (1.8)	0.62
IVb	3 (5.6)	0	0.12

Table 2. **Post-operative pathological characteristics in study cohort group (group A) and historical control group (group B)**.

WHO: World Health Organization

	Group A, n (%) (n=54)	Group B, n (%) (n=55)	p value
Clavien Dindo			
Grade II	7 (14.8)	10 (18.1)	0.80
Grade IIIa	2 (3.7)	0	0.24
Grade IIIb	0	0	NA
Grade IVa	1 (1.9)	1 (1.8)	1.00
Grade IVb	0	0	NA
Grade V	1 (1.9)	0	0.50
All	11 (20.3)	11 (20)	1.00
Nerves			
RLN Palsy	5 (9.3)	1 (1.8)	0.11
PN resection	7 (13)	6 (10.9)	0.78

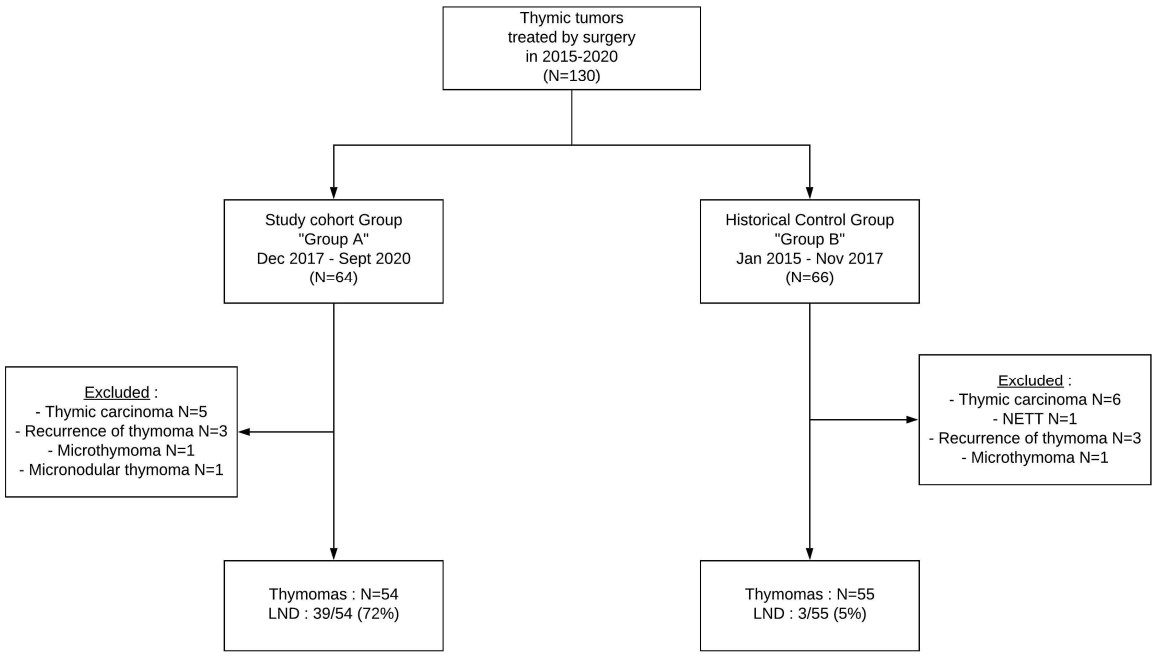
Table 3. Post-operative complication according to the Clavien Dindo classification [19] and nerve injuries in study cohort group (group A) and historical control group (group B). Grade I were not reported. There was no statistical difference between the 2 groups for all complications. Patient with recurrent laryngeal nerve palsy are more frequent in group A, but the difference didn't reach the statistical significance.

RLN = Recurrent Laryngeal Nerve, PN = phrenic nerve.

Figures

Figure 1. Flow chart illustrating the distribution of patients, based on time period and histological subtype.

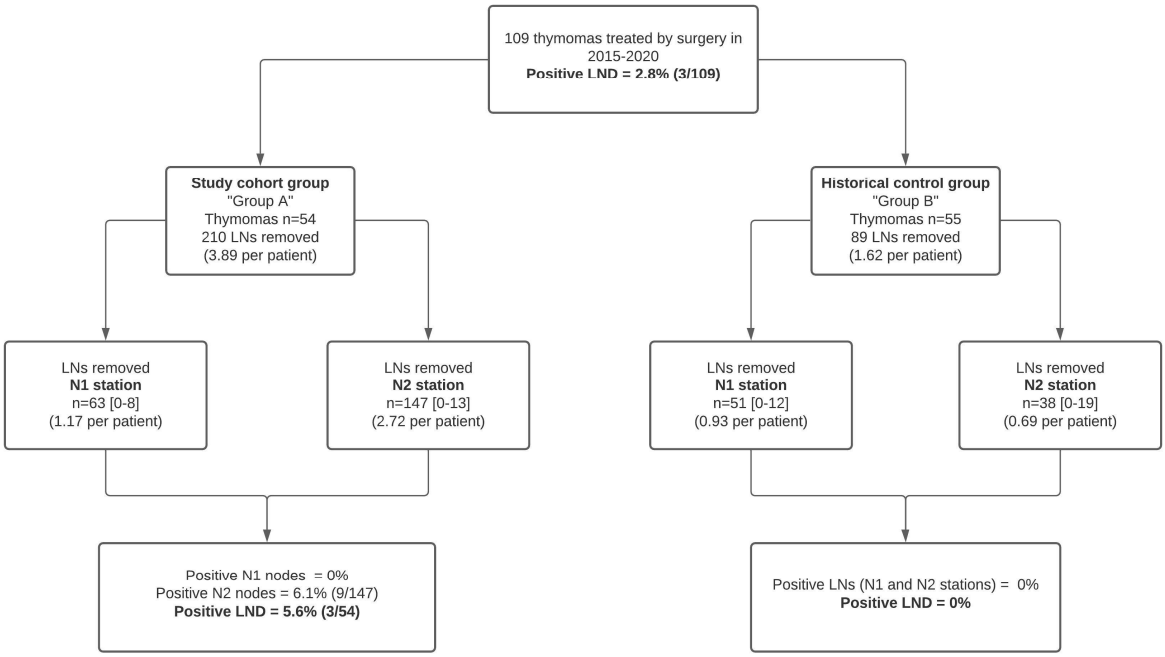
LND: lymph node dissection. LN: lymph node. NETT: neuroendocrine thymic tumor



<u>Figure 2:</u> Flow diagram showing the lymph nodes metastatic pattern in study cohort group (group A) and in historical control group (group B).

The number of lymph node retrieved was significantly higher in group A than in group B (p=0.0021). Patients with positive LND are more frequent in group A, without statistical significance (p=0.12).

LNs: lymph nodes; LND: lymph node dissection



<u>Figure 3</u>. Prognosis impact of lymph node dissection in thymomas between study cohort group (group A) and historical control group (group B).

(A) Overall survival curve on thymomas between group A and B (group A, red discontinue line; group B, blue continue line).

(B) Freedom from recurrence curve on thymomas between group A and B (group A, red discontinue line; group B, blue continue line).

LND: Lymph node dissection