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ABSTRACT SESSION 1: SURGICAL AND PATHOLOGICAL THEMES

ORAL1.01: LYMPH NODAL DISSECTION IN THYMIC TUMORS: PRELIMINARY RESULTS OF A MULTICENTER PROSPECTIVE STUDY

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Background: This study was to define the incidence and risk factors of lymph nodal metastases in thymic malignancies through a multicenter prospective observational trial by the Chinese Alliance for Research in Thymomas (ChART).

Methods: Between June 2014 and August 2015, patients without preoperative therapy, who underwent thymectomy and LN dissection for thymic malignancies were prospectively collected for the study. Incidence and pattern of lymph node metastasis was recorded and investigated. Stage analysis was carried out according to the ITMIG proposal for the UICC staging system. Results from this prospective observational study were then compared with the previously reported ChART retrospective study.

Results: Two-hundred and seventy-five patients from 15 hospitals were enrolled in the study. A total of 847 stations and 1347 LNs, with a mean number of 3.1 stations and 4.9 LNs, were dissected. Metastasis was confirmed in 41 nodes (3.04%) in 15 patients (5.5%). Nodal involvement in anterior region (N1) and deep region (N2) were 73.3% (11/15) and 60% (9/15), respectively, with 5 (33.3%) patients with concomitant N1 and N2 diseases. Multi-station metastasis was found in 6 (40%) patients, which was more often seen in NETT (37.5%, 3/8) than in thymic carcinoma (8.3%, 2/24) or thymoma (0.4%, 1/243) ($p<0.001$). Lymph node involvement was mostly ipsilateral to the location of the primary tumor, with only 2 cases of bilateral metastasis (both were neuroendocrine tumors). No nodal involvement was found in type A or B1 thymomas. Incidences of nodal metastasis in thymomas, thymic carcinoma, NETT were 2.1%, 25% and 50%, respectively ($p<0.05$). And incidences of nodal involvement increased significantly with increasing T, M categories as well as tumor size ($p<0.05$). Comparing with the results from the retrospective study, nodal involvement was more frequent in all histologic subtypes and in each T category (Table). In univariate analysis, WHO histologic type (p=0.000), T stage (p=0.001), and tumor size (p=0.011) were significantly associated with nodal metastasis. Upon multivariate analysis, only higher grade histology ($p=0.000$) and higher T stage ($p=0.02$) predicted greater likelihood of developing nodal metastases. If LN dissection were to be performed selectively in the 88 tumors above stage T2, or with B3 or higher histology (32% of the study population), nodal metastasis would have been missed in only 1 type AB tumor.

Conclusions: LN involvement in thymic malignancies after intentional dissection seems to be more common than previously recognized, when compared with retrospective study results. Nodal metastasis is more common in tumors with aggressive histology and advanced T stage, and often occursin multiple stations or regions. Systemic LN dissection for selected high risk group may be recommended.

Table Risk factors for nodal involvement and comparison between ChART retrospective and prospective studiesaccording to histologic subtype and T category.		
	Incidences of nodal metastasis (%)	
Variables	ChARTretrospective study	ChART prospective study
WHO histology type		
A	0	0
AB	0	2.4
B1	0	0
B2	0.4	1.6
B3	2.7	5.6
Ca	7.9	25
NETT	16.7	50
T stage		
T1a	0.3	2.0
T1b	0	8.3
T2	6.9	7.7
T3	8.5	18.4
T4	7.4	50
Multivariate analysis of risk factors predicting lymph nodal metastasis in ChART prospective study		
Variables	HR (95% CI)	*p Value*
Tumor size[a]	1.18 (0.94-1.482)	0.154
WHO histologic type[b]	5.625(2.479-12.764)	0.000
T stage (T1b-4 vs. T1a)	5.437(1.311-22.544)	0.02
Surgical approach (Open vs. VATS)	1.473(0.29-7.491)	0.641

[a]Analyzed as a continuous variable. [b]WHO histology type defined as NETT, thymic carcinoma, and thymomaAB+B1-3 CI, confidence interval; HR, hazard ratio; NETT, neuroendocrine thymic tumors

Keywords: risk factors, thymic malignancies, Incidence, lymph nodal metastases

ORAL1.02: PREOPERATIVE NEUTROPHIL-TO-LYMPHOCYTE RATIO IS AN INDEPENDENT PREDICTOR OF SURVIVAL IN THYMOMA

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Background: Previous studies have shown that preoperative peripheral neutrophil-to-lymphocyte ratio (NLR) is associated with a poor prognosis in patients with various cancers. The aim of this study was to investigate the prognostic role of preoperative NLR in patients with thymoma.

Methods: Retrospective review of patients who underwent surgical resection for thymic epithelial tumor. (N=240, 01/1974-12/2013) Exclusion criteria: received steroid therapy, thymic carcinoma or neuroendocrine tumor, recurrence of thymic epithelial tumor, incomplete resection and missing data. Preoperative NLR was measured within 3 months before surgery. We used the average value (1.81) as the optimal cut-off value for NLR. The patients were classified into two groups by NLR: low NLR (≤ 1.81) and high NLR (> 1.81). Kaplan-Meier methods and Cox proportional hazard models were used.

Results: One hundred and sixty patients were included in this analysis. Seventy-three patients were classified as high-NLR individuals. The recurrence-free survival was significantly worse in the patients with high NLR (p= 0.049). Time to progression was also significantly worse in patients with high NLR (p= 0.019). There was no significant difference in overall survival between high NLR group and low NLR group, however, among patients for invasive thymoma, patients with high NLR have worse prognosis in overall survival than those with low NLR (p= 0.046). In multivariate analysis for time to progression, high preoperative NLR (HR 4.099, 95%CI 1.095-15.34; p= 0.036), Masaoka stage (HR 5.454, 95%CI 1.185-25.11; p= 0.029) and WHO classification (HR 4.577, 95%CI 1.235-16.96; p= 0.023) were independently associated with poor survival.

Conclusion: Elevated preoperative NLR is associated with poor survival in patients who underwent surgery for thymoma. NLR may be a useful biomarker for predicting prognosis of patients with thymoma after surgery.

Patient characteristics	
Sex	Male 88, Female 72
Age	53 (15-83 yrs)
Masaoka stage	82 stage I, 51 stage II, 21 stage III, 6 stage IV
WHO classification	10 A, 42 AB, 47 B1, 43 B2, 16 B3, 2 Others

The recurrence-free survival after surgery

The overall survival of patient with invasive thymoma
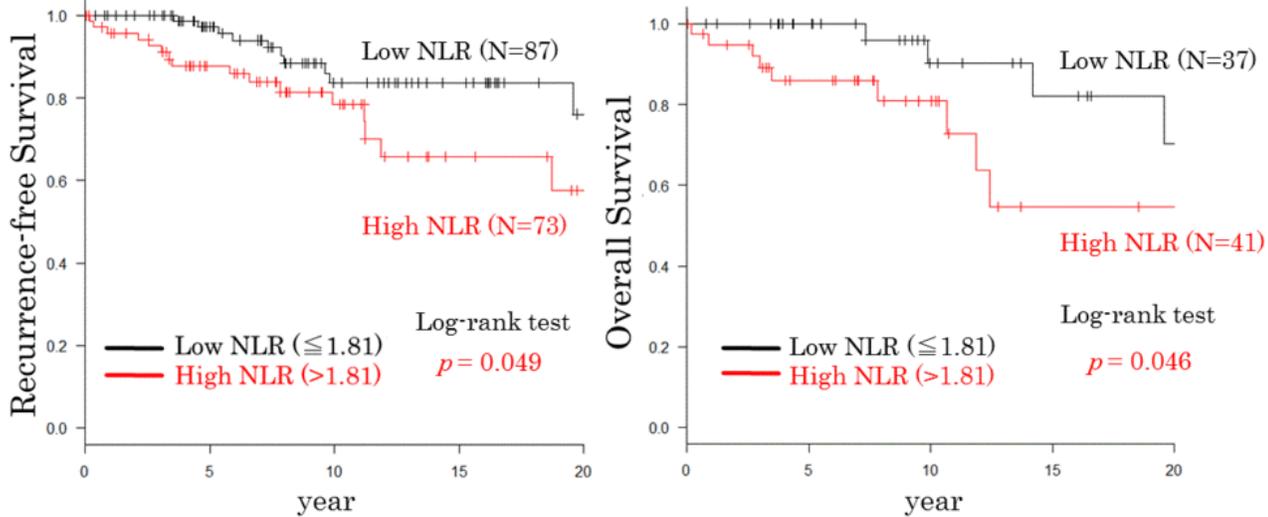
ORAL1.03: WHO CLASSIFICATION AND IASLC/ITMIG STAGING PROPOSAL IN THYMIC TUMORS: REAL-LIFE ASSESSMENT

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Background: Thymic epithelial tumors (TETs) are rare intrathoracic malignancies which are categorized histologically according to the World Health Organization (WHO) classification, recently updated in 2015 based on a consensus statement of ITMIG (Marx et al. J Thorac Oncol 2014;9:596), and for which the standard Masaoka-Koga staging system is intended to be replaced by a TNM staging system based on an IASLC/ITMIG proposal (Detterbeck et al. J Thorac Oncol 2014;9:S65). Objectives Our objectives were 1/ to analyze the feasibility of assessing ITMIG consensus major and minor morphological and immunohistochemical (IHC) criteria in a routine practice setting, and the diagnostic performance of those criteria for TETs histologic subtyping, and 2/ to assess the feasibility and the relevance of the proposed IASLC/ITMIG TNM staging system with regards to the Masaoka-Koga staging system.

Methods: This is a monocenter study conducted at the Lyon University Hospital, one of the largest centers for TETs in France. Overall, 188 consecutive TETs diagnosed in 181 patients since 2000 at our center were analyzed. Systematic pathological review of cases was conducted, and additional IHC stainings were performed as per ITMIG consensus.

Results: There were 89 (49%) men and 92 (51%) women; 57 (31%) patients presented with myasthenia gravis at time of diagnosis. There were 168 (89%) thymomas, including 9 (5%) type A, 67 (36%) type AB, 19 (10%) type B1, 46 (24%) type B2, and 27 (14%) type B3, and 20 (11%) thymic carcinomas (TC). After exclusion of necrotic and non-suitable specimens, 178 tumors were reviewed for ITMIG consensus major and minor criteria. Major criteria were identified in 100% of type A, AB, B1 and B2 thymomas. With regard to minor criteria, rosettes, glandular formations, subcapsular cysts, and pericytomatous vascular pattern were typical for type A thymomas, and were not identified in other subtypes. Expression of CD20 by epithelial cells was observed in 77% of type AB thymomas, and 14% of type A thymomas. Lobular growth pattern was present in all

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subtypes. Perivascular spaces were more frequent in type B thymomas (48% of cases) than AB thymomas (7% of cases). Medullary islands were identified in type AB (6% of cases), and type B2 thymomas (15% of cases). For type B3 thymomas, pink appearance at low magnification, lobular growth, lack of intercellular bridges and lack of expression of CD117 were presents in all cases. After exclusion of recurrent cases, fragmented tumors, and biopsies, Masaoka-Koga staging was assessable for 156 patients: there were 42 (27%) stage I, 55 (35%) stage IIa, 28 (18%) stage IIb, 22 (14%) stage III, 4 (3%) stage IVa, and 5 (3%) stage IVb tumors. After restaging according to the IASLC/ITMIG TNM classification, there were 127 (81%) stage I, 3 (2%) stage II, 17 (11%) stage IIIa, no stage IIIb, 5 (3%) stage IVa, and 4 (2%) stage IVb.

Conclusion: The comprehensive analysis of our well-characterized cohort of 188 TETs indicates the feasibility and the diagnostic value of the ITMIG consensus statement on WHO histological classification, and highlights the switch in staging when applying the IASLC/ITMIG staging proposal.

Keywords: thymoma, thymic carcinoma, WHO, ITMIG, IASLC

ORAL1.04: PATHOLOGICAL CENTRAL REVIEW OF 401 THYMIC EPITHELIAL TUMORS: THE RYTHMIC NETWORK EXPERIENCEPATHOLOGICAL CENTRAL REVIEW OF 401 THYMIC EPITHELIAL TUMORS: THE RYTHMIC NETWORK EXPERIENCE

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Background: RYTHMIC (Réseau tumeurs THYMiques et Cancer) is a nationwide network for TET appointed in 2012 by the French National Cancer Institute. The objectives of the network are management of clinical tumor board and central pathologic review of all cases. RYTHMIC Tumor Board is based on initial histopathological diagnosis.

Methods: Pathological central review of patients diagnosed with TET from January 2012 to May 2016 was made by a panel of 10 expert pathologists from the working group. Assessment of agreement or disagreement between the initial institution and the panel review was made according the WHO 2004/2015 and new ITMIG proposals for histologic typing and staging. Discordances were classified as "major" when they would have changed the therapy or management of patients according to the RYTHMIC guidelines.

Results and discussion: A total of 401 specimens were reviewed. Considering either histological subtype and/or staging, a total of 178 discordances in 159 patients (39%) were identified as follow: 118 concerning histological diagnosis and 60 regarding stage (Table 1). An underdiagnosis of AB and B2 thymoma as well as an underdiagnosis of invasive thymoma (stage IIB and stage III) were noticed. A total of 31 major discordances in 29 patients (7%) were identified: 19 patients for whom post-surgical treatment recommendation concerning adjuvant radiotherapy would have been changed and 10 patients for whom management of disease should have been modified. The most frequent disagreement among the major discordances was the sub-diagnosis of stage III reflecting the underlying difficulty of pericardial and/or mediastinal pleura histological invasion diagnosis. Additionally, major disagreement between the initial and panel pathology's stage and subsequent interpretation by the working group at national tumor board was found in 4 patients, enhancing the importance of an expert pathologist at the RYTHMIC network committee.

Conclusion: The RYTHMIC experience confirms the relevance of an expert histopathological panel diagnosis of thymic malignancies and for better decision-making in particular concerning post-operative radiotherapy to avoid over- or under-treatment of the patients. It also shows the importance of the diffusion to the pathologist community of the new updated ITMIG and WHO 2015 morphological and phenotypical criteria to improve reproducibility betweeen pathologists. . Table 1 : Discordance between initial pathologist diagnosis and

RYTHMIC review considering either histological subtype (A, AB, B1, B2, B3, epidermoid thymic carcinoma (TC), rare subtypes, TET NOS (thymic epithelial tumor Not Otherwise Specified), Not TET) or stage (I, IIA, IIB, III, IV) according to Masaoka Koga and detailed by ITMIG.

	A	AB	B1	B2	B3	TC	Rare	TET NOS	NOT TET	I	IIA	IIB	III	IV
Initial	16	10	25	23	18	8	5	13	-	24	13	17	4	2
Review	8	25	6	38	11	10	12	1	7	6	12	29	21	2

Keywords: misdiagnosis, misstaging, epithelial thymic tumors, expert pathology review

ORAL1.05: SPECIFICITY OF HISTOPATHOLOGICAL AND CLINICAL CRITERIA OF B3 THYMOMA VS EPIDERMOID THYMIC CARCINOMA

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Introduction: The differential diagnosis between B3 thymoma (TB3) and thymic carcinoma (TC) remains challenging. Our goal was to select, among morphological and immunohistochemical criteria, the most powerful features that discriminate TB3 from TC and to correlate them to clinical data.

Material: Among cases centrally reviewed by the pathologist panel from the French national thymic tumors network (Rythmic), 64 typical TB3 (n=23) and TC (n=41) were reexamined, using consensus criteria and two head microscope. For each case, we focused on lobular architecture (LA), nest-cord architecture (NA), perivascular spaces (PVS), severe cellular atypia (SCA), desmoplasia (D), budding (B), comedo-like necrosis (N), epidermoid differentiation (ED), stroma inflammation (I). Immunohistochemical study included TdT, CD5, CD117 and Glut1 expression. Clinical data of 62 patients were reviewed for clinical characteristics focusing on myasthenia/other autoimmune disorders, presence of systemic metastases at presentation, and pattern of recurrences (exclusively pleural or systemic).

Results: Table 1 summarizes morphological features:

	LA	NA	PVS	SCA	D	B	N	ED	I
TB3	23 (100%)	9 (39%)	19 (83%)	2 (9%)	8 (35%)	7 (30%)	1 (4%)	3 (13%)	3 (13%)
TC	3 (7%)	40 (98%)	1 (2%)	28 (68%)	40 (98%)	41 (100%)	9 (22%)	8 (20%)	33 (81%)

The best morphological features to discriminate TB3 versus TC were the presence of LA and PVS and the absence of inflammation and severe cellular atypia, whereas TC elementary lesions such as desmoplasia, nest-cord architecture, budding could be observed fairly in TB3. Immunohistochemical stainings shown a TdT expression in 100% of TB3 and none of the TCs, CD5 was positive in 4% of TB3 versus 85% of TC. CD117 was negative in all TB3 and positive in 93% of TC. 78% of the TCs coexpressed CD5 and CD117, whereas none of the TB3 coexpressed them. Glut1 staining exhibited a zonal pattern in 74% of TB3, a diffuse pattern in 90% of TC. It was negative in 22% of TB3 and 2% of TC, respectively. Eight patients (13%) had myasthenia, none of them were TC. Of the 22 (35%) cases with stage IVB disease at onset, only one was TB3. Recurrences were exclusively pleural in 11 cases (18%) including 8 TB3 and 3 TC, and were systemic in 26 cases (42%), including 1 TB3 and 25 TC. Survival data will be presented at the meeting.

Conclusion: Our study highlights several criteria that allow to distinguish TB3 from TC. Lobular architecture and peri-vascular spaces were TB3 features, whereas

nest-cord architecture, desmoplasia, stroma inflammation and budding were associated with TC diagnosis. Immunodetection of TdT was highly associated with TB3 diagnosis. The pattern of Glut1 staining, when expressed, was a good tool to differentiate TB3 from TC, as well as the coexpression of CD5 and CD117. Myasthenia had never been accounted in TC. Even if rare, stage IVB at presentation and systemic recurrence could not formally exclude TB3.

Keywords: B3 thymoma, epidermoid thymic carcinoma, morphology, immunohistochemistry

ORAL1.06: CARCINOID-/HEMANGIOPERICYTOMA-LIKE MORPHOLOGY OF A THYMOMA SUGGESTS MORE AGGRESSIVE TUMOR'S BEHAVIOR

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Background: The newest histological classification of World Health Organization (WHO, 2015) for mediastinal tumors introduces a new morphological variant of type A thymoma called "atypical" which seems to be more aggressive than conventional type. The most indicative feature of atypical variant is necrosis, some authors mention increased mitotic activity (>4/10 high power fields (HPF)) as well. We observed that necrosis in type A thymomas or type A component in other subtypes of thymomas more often accompanied the tumors with carcinoid-like/hemangiopericytoma-like (c-like/h-like) morphology so we decided to assess if this morphological pattern "*per se*" can predict the prognosis of the neoplasm.

Materials and Methods: Type A thymomas and thymic epithelial tumors of other subtypes which either contained distinct A component or do not but were rich in epithelial cells, were included into the study. The tumors with high number of lymphocytes intermingled with epithelial cells were excluded. The presence or lack of carcinoid-like/hemangiopericytoma-like morphology (round or oval rather than spindle cells, multiple rosettes, trabecular pattern, numerous slit-like or staghorn vessels, Fig.1) in A thymomas/components was noted.
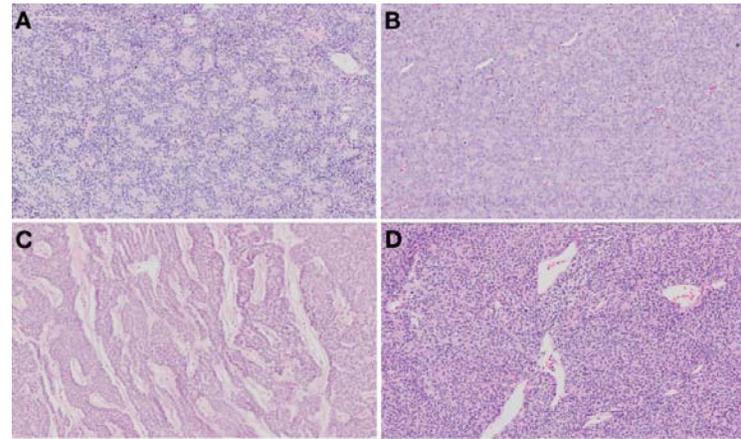
Fig. 1. Carcinoid-like (A, B, C) or hemangiopericytoma-like (D) pattern of type A thymomas.

All tumors were divided into two groups, more and less aggressive. The criteria of aggressiveness were: 1. confirmed aggressive clinical course (metastases, recurrent tumor); 2. higher stage (3 or 4) in Masaoka-Koga staging system; 3. histological type regarded as more aggressive: B3 or carcinoma. In all cases 3 parameters in immunohistochemical reactions were evaluated: mitotic index (number of mitotic figures/10 HPF in anti-PHH3 reaction), proliferation index (in "hot spots" as a percentage of positive cells in anti-Ki67 reaction) and GLUT-1 conspicuous expression (positive or negative).

Results: The results are shown in the Table

1.

Table 1. Proliferation index, mitotic index and GLUT-1 expression in more and less aggressive thymic epithelial tumors in comparison to type A thymomas with or without carcinoid-like/hemangiopericytoma-like morphology.	
Histological type	**No. of cases = 28 (All)**
A (pure)	5
AB with distinct A component	18
micronodular with A component	1
metaplastic	1
B3	2
micronodular thymic carcinoma with lymphoid hyperplasia	1

Parameter	More aggressive clinical course	Less aggressive clinical course	type A thymomas WITH c-like/h-like morphology	type A thymomas WITHOUT c-like/h-like morphology
No. (percentage) of cases	11 (39%)	17 (61%)	10 (40%)	14 (56%)
proliferation index (Ki-67) – median value	13	7,5	**10**	7
mitotic index (PHH3) – median value	12,5	8	**11,5**	5
GLUT-1 (+) expression - No. (percentage) of cases	6 (55%)	8 (47%)	6 (67%)	4 (29%)
Necrosis, no. (percentage) of cases	4 (36%)	3 (18%)	3 (33)	2 (14%)
type A thymomas WITH c-like/h-like morphology	5 (56%)	4 (44%)	X	X
type A thymomas WITHOUT c-like/h-like morphology	3 (21%)	12 (39%)	X	X

Conclusions: The results of our study show that proliferation and mitotic indices in type A thymomas with carcinoid-like/hemangiopericytoma-like morphology are higher than in type A thymomas without this pattern and in the group of tumors with less aggressive clinical course. Type A thymoma with carcinoid-like/hemangiopericytoma-like morphology more often showed aggressive clinical course. Although the results require precise statistical analysis, preliminary observations suggest that carcinoid-like/hemangiopericytoma-like pattern predisposes to more aggressive behavior of type A thymoma.

Keywords: histopathology, type A thymoma, prognosis, immunohistochemistry

ABSTRACT SESSION 2: IMAGING AND OUTCOMES STUDIES

ORAL2.01: DIFFUSION-WEIGHTED MR IMAGING FOR ASSESSMENT OF MEDIASTINAL LESIONS

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Purpose: Although diffusion weighted MR imaging (DWI) has been accepted as a valuable tool for malignancies, its role in the evaluation of anterior mediastinal masses has not been elucidated. The aim of this study was to evaluate the accuracy of DWI in distinguishing benign from malignant diseases and its performance in assessing thymic epithelial neoplasms (TEN).

Materials and Methods: After approval by our institutional review board, we retrospectively reviewed 38 patients with an anterior mediastinal mass who were referred for a chest MRI. DWI images were performed

with low- and high-b-values (b =0, 800 s/mm2) as well ADC maps. MRI analysis was performed qualitatively by one chest radiologist using apparent diffusion coefficient (ADC) measurements. Summary of ADC were provided in mean, SD, median, and range by different groups for each test (Table 1). Anterior mediastinal mass diagnosis was classified according to pathology diagnosis, and TEN were classified according to WHO classification and Masaoka-Koga staging system.

Results: Of the 38 study patients, 26 had malignant lesions and 12 had benign lesions. Malignant lesions included: thymoma (n=21), thymic carcinoma (n=2), and one of each: teratoma, lymphoma, and schwannoma. Benign lesions included: lymphangiona (n=1), thymic and pericardial cyst (n=7) and thymic hyperplasia (n=4). Of the patients with thymomas, 11 patients had early disease (stage I/II) and 10 had advanced disease (stage III/IV). We found that mean ADC value was statistically significant in differentiating benign from malignant masses (3.63 SD0.80 vs 2.30, SD=0.0.75, p<0.001), benign thymic masses from TEN (3.63, SD=0.80 vs 2.19, SD=0.66, p<0.0001) as well as in differentiating TEN from non-thymic mediastinal neoplasms (2.19, SD=0.66 vs 3.19, SD=0.93, p=0.0261). However, ADC values could not be used to differentiate low-grade thymomas, high-grade thymomas and thymic carcinomas according to WHO classification and early from late stage thymomas per Masaoka-Koga Staging System.

Conclusion: Our study shows that DWI is a valuable tool in differentiating benign from malignant lesions in the anterior mediastinum and is helpful in the evaluation of newly diagnosed mediastinal masses.
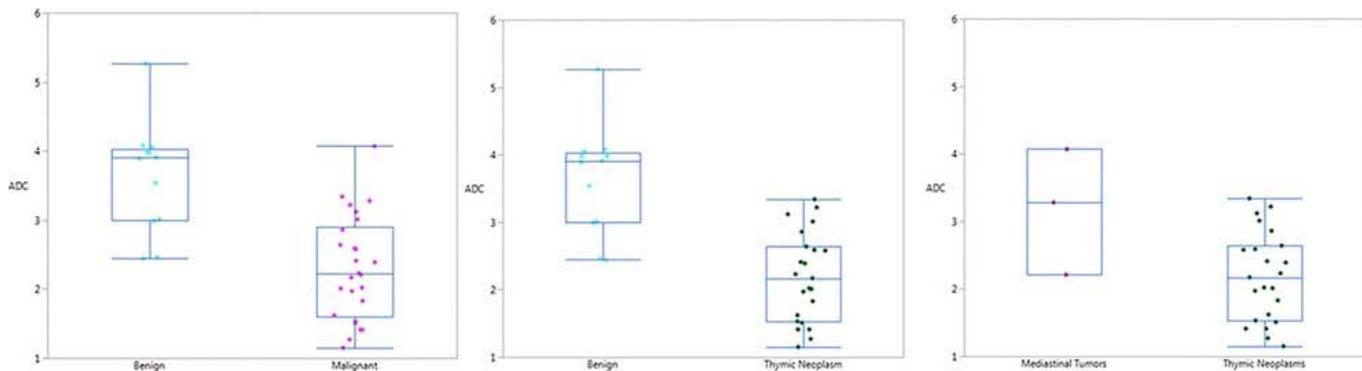
Boxplots of ADC demonstrating statistically significant p-values (=0.05). Benign versus malignant neoplasms (p-value <0.0001), benign versus thymic neoplasms (p-value <0.0001) and mediastinal tumors other than thymic malignancies versus thymic neoplasms (p-value= 0.0261).

Keywords: Thymic Epithelial Neoplams, Mediastinal lesions, Diffusion-Weighted Magnetic Resonance Imaging

ORAL2.02: QUALITY OF RESECTION AND OUTCOME IN STAGE III TETS: THE FRENCH RYTHMIC NETWORK EXPERIENCE

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Background: Stage III TET represents a heterogeneous population and their optimal approach remains unclear; most of the available literature is composed of small series spanned over extended periods of time. RYTHMIC (Réseau tumeurs THYMiques et Cancer) is a

French nationwide network for TET with the objective of territorial coverage by regional expert centers and systematic discussion of patients management at national tumor board. We reviewed our experience in stage III thymic tumors in order to evaluate the value of tumor board recommendations and multidisciplinary approach.

Methods: We conducted a retrospective analysis of patients (pts) with stage III TET discussed at the RYTHMIC tumor board from January 2012 to December 2015. Clinical, pathologic and surgical data were prospectively collected in a central database. Survival rates were based on Kaplan-Meier estimation. Cox proportional hazard models were used to evaluate prognostic factors for disease free survival (DFS) and overall survival (OS).

Results: 150 pts were included in the analysis. Median age was 64 years [18 – 91], 56% males, thymoma A-B2/B3-thymic carcinoma in 52% and 47% respectively; 12% presented with autoimmune disorder (76% myasthenia). Local treatment was surgery in 134 pts (90%) followed by radiotherapy (RT) in 90 pts; 26 pts received preoperative chemotherapy (CT). Complete resection rate (R0) was 53%. Among 38 pts considered non-surgical candidates at diagnosis, 26 pts became resectable after induction CT with a R0 rate of 58%; 12 pts received CT-RT and/or CT as primary treatment. Recurrence rate was 38% (n=57), first sites were pleural (n=32) and lung (n=12). The 5-year OS and DFS were 88% and 32% respectively. Gender (HR: 0.2 [95%CI 0.04 - 0.97] p=0.04), histology (HR: 0.19 [95%CI 0.05 - 0.70] p=0.02) and surgery (HR: 0.4 [95%CI 0.01 - 0.20]p<0.001) as primary treatment modality were significant prognostic factors for OS in multivariate analysis. Histology (HR: 0.5 [95%CI 0.30 - 0.90] p=0.02) and adjuvant RT (HR: 0.4 [95%CI 0.20 – 1.00] p=0.05) were significantly associated with DFS. Completeness of resection was not associated with survival in our cohort.

Conclusion: Surgery followed by radiotherapy improves outcome irrespectively of R0. Stage III TET not candidate to surgery should be reassessed for resection after induction chemotherapy.

Keywords: Outcome, TET, Stage III

ORAL2.03: RECURRENCE IN THYMIC MALIGNANCIES AFTER COMPLETE RESECTION: LONG-TERM OUTCOME FROM CHART DATABASE

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Abstract AIM: To investigate the risk of recurrence and its predictive factors in thymic malignancies after complete resection in large cohort of patients with long term follow-up. MATERIALS AND METHODS: The Chinese Alliance for Research in Thymomas (ChART) retrospective database was reviewed for the study. Pathological stage was reclassified according to the ITMIG proposal for the UICC staging. Only patients without pretreatment and with complete resection of stage I-IIIa tumors were included. Available follow-up data were reviewed to identify metastasis or recurrence. The sites of involvement and the time of involvement measured from surgery were recorded.

Results: Nine hundred and seven cases were retrieved, including 802 thymoma and 105 thymic carcinomas. With a median follow-up of 52 months (4- 147 months), the 10 year overall survival (OS) of the entire cohort was 89.5%, and the median OS was not reached. Metastasis and/or recurrence were noted in 53 (5.8%) patients. The 10 year OS of patients with and without recurrence were 95% and 43.7%, respectively (p<0.001). Local recurrence was more often seen in recurred thymoma patients (52.9%), while systemic dissemination was more frequently encountered in recurred thymic carcinoma patients (47.4%). In univariate analysis, WHO histologic type, T stage, surgical approach, extent of resection, postoperative radiotherapy and chemotherapy were significant associated with recurrence. However, in multivariate analysis, only WHO histologic type and UICC T stage were independent predicting factors for treatment failure (Table 1). Based on these results, a nomogram was established to predict the risk of recurrence after complete tumor resection (Figure 1).

Conclusions: The low incidence of recurrence after radical surgery reflected the indolent nature of thymic malignancies. Still, development of recurrence has a significant impact on long-term survival. The incidences and patterns of recurrence vary significantly across different histologic and stage groups, even in patients receiving complete resection. Establishment of a nomogram predicting recurrence after complete

resection may help identifying high risk patients and selecting potentially beneficial adjuvant therapies.

Keywords: recurrence, thymic malignancies, complete resection

ORAL2.04: LONG TERM HEALTH RELATED QUALITY OF LIFE IN PATIENTS WITH THYMIC MALIGNANCIES

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Background: There is limited health related quality of life (HRQOL) data in the literature for patients with thymoma and thymic carcinoma, particularly for long-term survivors following aggressive treatment.

Objectives: The goal of this study was to describe HRQOL in patients diagnosed with thymoma and thymic carcinoma, and evaluate how this is influenced by clinical and pathological characteristics.

Methods: As part of a cross-sectional study at a comprehensive cancer centre in Toronto, Canada, patients diagnosed with thymic malignancies were approached at clinic visits to completed questionnaires containing the EQ-5D instrument. HRQOL was evaluated through calculation of health utility (HU), scored from 0-1 and visual analogue scale (VAS), scored from 0-100. Clinical and pathologic information was abstracted from patient charts and comorbidities evaluated using the Charlson Comorbidity Index (CCI). Intra-individual variability among patients that completed multiple questionnaires was assessed using coefficient of variation.

Results: 87 patients completed a total of 177 questionnaires. The mean ± SEM HU scores for thymoma and thymic carcinoma were 0.79±0.02 and 0.80±0.03 respectively and the mean VAS scores were 69.6±6.7 and 70.8±2.9. The mean age was 58 and patients were approached at a mean of 64 months after diagnosis. Among all patients, the EQ-5D domains with the greatest proportion of patients reporting problems were pain/discomfort (50%) followed by anxiety/depression (47%), usual activities (45%), mobility (32%) and self care (10%). 36% of patients reported problems in ≥3 domains. HU and VAS scores did not vary significantly by stage, WHO classification or history of paraneoplastic syndrome. Patients with ECOG performance status of 0 had significantly higher mean HRQOL scores than those with ECOG ≥1 (HU 0.91±0.02 vs. 0.75±0.02, $p<0.001$; VAS 84.0±3.2 vs. 61.3±3.9, $p<0.001$). VAS scores were also higher among patients who were ≥65 ($p=0.009$) and those treated with radiation ($p=0.005$). HU scores were higher in patients who were ≥1 year since treatment completion (0.83±0.02 vs. 0.73±0.02, $p=0.03$), and among these patients, mean intra-individual variability for HU and VAS were 7% and 10% respectively. Within this subgroup of survivors, HU scores were higher among those with CCI≥4 ($p=0.02$) and VAS scores higher among radiated patients ($p=0.047$). Neither HU or VAS scores varied significantly by stage or pathology in these long-term survivors. Those treated for recurrence maintained relatively high HRQOL (HU 0.81±0.06, VAS 79.5±0.067.3) as did those treated with chemotherapy (HU 0.77±0.02, VAS 71.3±3.3).

Conclusions: Patients surviving from thymic malignancies report relatively high, stable long term HRQOL even after systemic treatment and/or treatment for recurrence. Overall HRQOL appears to be most greatly influenced by performance status and proximity to treatment. Age, radiation and comorbidities may also play a role whereas stage and tumour pathology were less important. Our data suggests that pain/discomfort and anxiety/depression are the most common problems in this population. More research is required to further assess specific HRQOL issues so that these patients can be best supported long-term.

Keywords: health related quality of life, health utility, survivorship

ABSTRACT SESSION 3: MEDICAL ONCOLOGY

ORAL3.01: CHEMOTHERAPY IN ADVANCED THYMIC EPITHELIAL TUMORS: INSIGHTS FROM THE RYTHMIC PROSPECTIVE COHORT

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Introduction: Thymic Epithelial Tumors (TET) are rare intrathoracic malignancies, which may be aggressive and difficult to treat. In the advanced setting, chemotherapy may be delivered as a primary/induction therapy before subsequent surgery or definitive radiotherapy, or as exclusive treatment in patients for whom no focal treatment is feasible, and/or in the setting of recurrences. As no randomized trial and a limited number of prospective studies are available, there is paucity of prospective, multicentre evidence regarding response rates and survival of patients. RYTHMIC is the nationwide network for TET in France, established in 2012. The RYTHMIC prospective database is hosted by the French Intergroup (IFCT), and prospectively collects data for all patients diagnosed with TET, for whom management is discussed at a national multidisciplinary tumor board (MTB) based on consensual recommendations. Primary, exclusive chemotherapy, and chemotherapy for recurrence accounted for 149 (11%), 37 (3%), and 67 (5%) questions of a total of 1401 questions raised at the MTB between 2012 and 2015. Methods All consecutive patients for whom chemotherapy and/or systemic treatment was discussed at the RYTHMIC MTB from 2012 to 2015 were identified from the RYTHMIC prospective database. In depth analysis of patients medical records and follow-up was conducted at each expert centre of the network. Main endpoints were response rates and progression-free and overall survival.

Results: At the time of analysis, data were available for 156 patients (80 thymic carcinomas, and 76 thymomas), for whom the management led to raise 283 questions at the MTB: 67 (24%) for primary chemotherapy, 35 (11%) for exclusive chemotherapy, and 181 (64%) for recurrences. For primary and exclusive chemotherapy, the most frequently administered regimen was CAP, producing response rates of 70% and 60%, respectively. A total of 104 patients received at least one line of chemotherapy for recurrence; 53 patients received second-line treatment, and 13 and 7 patients received third- and fourth line treatment. In the setting of first recurrence, carboplatine-paclitaxel combination was the most preferred regimen, administered to 54% of patients; overall response and disease control rates to systemic treatments for recurrences were 13% and 42% in thymic carcinomas, and 19% and 43% in thymomas (p=0.38 and p=0.92, respectively). Median recurrence-free survival after primary chemotherapy was 16.6 months; median progression-free survival after exclusive chemotherapy, and first-, second-, and third-line chemotherapy for recurrence were 6.0 months, and 7.6 months, 6.2 months, and 6.0 months. Median overall survival is not mature for patients treated with primary and exclusive chemotherapy; median overall survival after first-line chemotherapy for recurrence was 44.9 months.

Conclusion: Our data provide with a unique insight in the efficacy of chemotherapy for advanced thymic epithelial tumors in a real-life setting; our results may provide valuable information to further help the decision-making for better defining optimal therapeutic strategies.

**Keywords:** thymoma, thymic carcinoma, chemotherapy, targeted agents

ORAL3.02: DESIGNING NOVEL THERAPIES FOR CLINICAL TRANSLATION THROUGH PREDICTIVE SIMULATION FOR THYMOMA

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Abstract: Thymoma is a rare malignancy that tends to be slow growing, which makes preclinical model development challenging and limits the ability to validate drugs for clinical translation. One potential model for predicting benefit of drugs for patients with thymoma includes the use of computational simulation modeling. These simulated predictions can leverage the repurposing of approved drugs for clinical translation, either singly or in combination, for personalized cancer treatment. Currently, thymoma has no single genomic biomarker-guided strategy for treatment, and simulation modeling has the advantage of predicting drug sensitivities by accounting for the total molecular genomic aberrations of the tumor. We collaborated with Cellworks (San Jose, CA), which has a computational simulation model that models millions of cancer interactions simultaneously for drug personalization via annotation of genomic data of the patient's tumor and mechanism of actions of existing drugs. These simulation predictions were validated with the Indiana University IU-TAB1 patient-derived type AB thymoma

cell line. The IU-TAB1 cell line has a total of 1053 known gene aberrations (copy number variations) and these were used to create the IU-TAB1 thymoma simulation avatar. (Further genomic sequencing is ongoing). The simulation model predicted sensitivity to nelfinavir, a protease inhibitor used for the treatment of HIV, which is also known to inhibit AKT (Fig.1A-D). In IU-TAB1 cells, factors supporting nelfinavir sensitivity included overexpression of SRC, AURKA, and deletion of PPP2R2A, RASSF1, and NF1, which are predicted to increase AKT1 dominance. The simulation predictions were validated with *ex vivo* experiments on IU-TAB1

cells, including testing for tumor growth inhibition (Fig.1E), cell proliferation (Ki67; Fig.1F), cell viability (quantitation of DRAQ7 negative viable cells; Fig.1G), and apoptosis (cleaved caspase-3 levels; Fig1H). As predicted from the simulation model, AKT inhibition with nelfinavir inhibited proliferation (IC_{50} ~10µM) and increased apoptosis of IU-TAB1 cells (Fig.1F&1H, respectively). This supports the simulation approach to repurpose and clinically translate drugs for rare malignancies like thymoma and sets the stage for future applications for rational drug combinations.
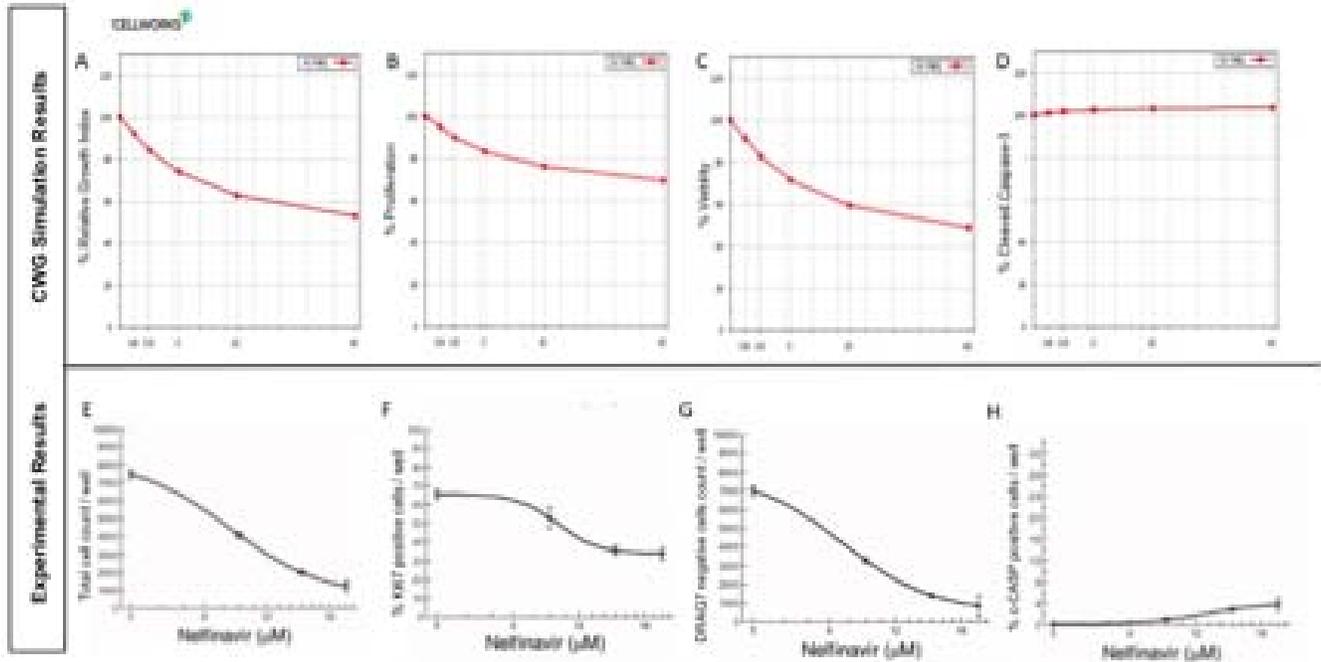
Keywords: thymoma, simulation, IU-TAB1, nelfinavir

ORAL3.03: SAFETY AND CLINICAL ACTIVITY OF AVELUMAB (MSB0010718C; ANTI-PD-L1) IN PATIENTS WITH ADVANCED THYMOMA

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Background: Thymic epithelial tumors have been shown to express programed death-ligand 1 (PD-L1), one of the determinants of response to PD-1/PD-L1-directed immune checkpoint inhibitor therapy. Avelumab (MSB0010718C) is a fully human, IgG1 anti-PD-L1 antibody under clinical development. We report safety and clinical activity in patients with relapsed thymic epithelial tumors enrolled in a phase I clinical trial (NCT01772004).

Methods: Patients previously treated with one or more standard therapies, no prior immune checkpoint inhibitors, and with no history of autoimmune disease were eligible. Treatment consisted of Avelumab at doses of 10-20 mg/kg iv q2 weeks until progression of disease or toxicity. Responses were assessed q6 weeks by RECIST 1.1. Correlative studies included PD-1, and PD-L1 evaluation in tumor samples by immunohistochemistry and peripheral blood immune subset analysis.

Results: 7 with thymoma and 1 with thymic carcinoma were treated with Avelumab; 3 patients with thymoma (2 B3, 1 B2/B3) received Avelumab 20 mg/kg; 4 patients

with thymoma (1 B1, 3 B2) and 1 patient with thymic carcinoma were treated at 10 mg/kg. Two (29%) patients with thymoma had a confirmed partial response (PR;1 at 20 mg/kg, and 1 at 10 mg/kg), 2 (29%) had unconfirmed PRs, 2 (29%) SD and 1 (14%) PD; the patient with thymic carcinoma had SD. Potential immune-related AEs (irAEs) occurred in 5 (63%) patients and included one or more of the following: muscle weakness, myalgia, myositis, respiratory muscle insufficiency, hoarseness, paresthesia, dysphagia, dyspnea, diarrhea and elevated creatine kinase. irAEs resolved rapidly and completely with oral steroids in 3 patients and incompletely in 1 patient. irAEs gradually resolved with additional medications (IVIG, cyclosporine A) in 1 patient. All 4 responders experienced irAEs (myositis in 3 patients, all after 1 dose of Avelumab and enteritis in 1 patient). Response was seen before or shortly after start of steroids in 3 patients suggesting response was related to Avelumab. Decreased CTLA4+ regulatory T cells and the ratio of granulocytic vs. monocytic myeloid-derived suppressor cells was seen post-treatment at the 20mg/kg dose.

Conclusions: Avelumab is active in patients with thymoma with 4 of 7 patients having objective responses accompanied by development of irAEs that were generally reversible with oral steroids. Further studies are needed to understand the mechanism of development of irAEs and determine the feasibility of immune checkpoint inhibitor therapy in patients with thymoma.

Keywords: Thymoma, Immune checkpoint inhibitor therapy, Immune-related adverse events, Myositis

ORAL3.04: NEOADJUVANT TREATMENT WITH PASIREOTIDE IN PRIMARY INOPERABLE THYMOMA TO REDUCE TUMOR SIZE

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Abstract: Long term prognosis in patients with inoperable thymoma (Masaoka III - IVa) or local recurrent thymoma depends on complete resection (R0). Somatostatin analogs have the capability to reduce tumor volume. Most thymoma express somatostatin receptors on the surface, detectable by nuclear medical methods. In combination with corticosteroids the effect may be enhanced. Pasireotide (SOM230 LAR) a somatostatin analog, has a high binding profile to human somatostatin receptor subtypes (sst), up to 30-40 times higher in sst1 + 5 and 5 times higher in sst3, only in sst2 the density is 2.5 times lower. SOM230LAR could offer a new neo adjuvant treatment option for unresectable thymoma. We performed a single-center, single-arm, open label phase II trial. Primary objective is tumor shrinkage defined as decrease in tumor volume > 20% compared to baseline. Secondary objectives are resection status (R0, R1, R2) and safety. Inclusion criteria: Patients with inoperable thymoma, defined as adherence to neighbored organs or suspicious to infiltrate neighbored organs or local metastasis therefore R0 resection cannot be expected/ >18 years/ WHO classification: A – B3, Masaoka II – IVa/ positive nuclear medicine detection of somatostatin receptor at the tumor surface. Treatment phase will last up to 6 months. The role of prednisolone as an additional drug in the treatment of thymoma is not clearly understood; therefore we started the SOM230 treatment if possible without prednisolon. Prednisolon was added to the therapeutic regimen after 8 weeks if the therapeutic response was not adequate. We treated 16 evaluable patients. Inclusion started 03/2012. WHO classification: AB- 1x, B1-1x,B2-4x, B3-6x, B1/2- 2x, B2/3-1x, 1 patient had to excluded, after reexamining histology diagnosis was changed from B3 to WHO Typ C(thymic carcinoma) , Masaoka Classification: III-1x, IVA-14x . 6/15 patients had at study inclusion a positive anti-AchR-ab. Tumor volume (V1) at the beginning ranged from 27ccm to 2213ccm, at the EOS from 9,68ccm to1514ccm. The most distinct volume reduction was from 2080ccm to 163ccm, however the tumor could finally not be removed because of infiltration of heart muscle. 1 patient was withdrawn from the study because of good response; early surgical removement of the tumor was possible. Thymomectomy was performed in 10 patients, 1 patient refused to be operated, 1 patient had tumor progression, in 3 cases tumor remained not resectable, therapy was subsequently changed. 1 patient died after EOS for unknown reasons after thymomectomy, autopsy was refused. Addition of prednisolon to the therapeutic regime had an significant positive effect on extra tumor shrinkage. Main side effects are gastrointestinal symptoms but AE CTS were consistently grade ≤2.), Neoadjuvant treatment with octreotide (Pasireotide, SOM230 LAR) in patients with primary unresectable thymoma and/ or local recurrent thymoma to reduce tumor size is safe and effective. Thymomectomy could finally performed in2/3 of the patients. This work was supported by Novartis/Germany

Abstract Session 4: Basic Science of Thymic Malignancies

ORAL4.01: MESOTHELIN: A NOVEL THERAPEUTIC TARGET FOR PATIENTS WITH THYMIC CARCINOMA

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Background: There exists a paucity of effective treatment options for patients with advanced thymic epithelial tumors (TETs). The cell surface antigen, mesothelin is overexpressed in a variety of solid tumors and has been successfully used as a target for tumor-directed therapy. We sought to determine the expression of mesothelin in advanced TETs.

Methods: Tumor samples were obtained from patients with histologically confirmed thymoma (T) or thymic carcinoma (TC) and analyzed for mesothelin expression by immunohistochemistry (IHC) using monoclonal antibody 5B2 (Novocastra/Leica, Bannockburn, IL). The pathologist performing the evaluation was blinded to clinical parameters and outcome. IHC staining was labeled as negative (no expression), or positive and the percentage of positive cells was estimated. Serum mesothelin was also estimated using the MesomarkTM assay (Fujirebio Diagnostics, Inc., Malvern, PA). Statistical analyses were performed to determine the association between tumor mesothelin expression, histology and survival.

Results: Seventy-one cases [42 (59%) TC; 29 (41%) T] were included in this series. Clinical characteristics: Median age, 51 years (range, 20-86), 38 (54%) patients were male, and 66 (93%) patients had stage IV disease. Results for 8 thymic neuroendocrine carcinomas (NETs) and 34 TCs without NE differentiation are reported separately. Mesothelin expression was observed in a greater proportion of TC (n=27, 79%) than T (n=3, 10%), (P<0.0001) and was absent in thymic NETs; 13 (38%) TCs showed strong and homogenous mesothelin expression in nearly all tumor cells. TC patients with mesothelin expression in >50% of tumor cells had significantly longer overall survival (median not reached) compared to patients with low or absent mesothelin expression (1.62 years; 95%CI: 1.26 to 5.01 years;
HR=4.46, 95%CI: 1.55 to 12.80; p=0.0026). Median serum mesothelin levels (ULN, 1.5nM/L) in patients with TC and T were 0.77 nM/L (range 0.09-2.53) and 0.90 nM/L (range 0.55-2.65) respectively.

Conclusions: Strong and homogenous expression of mesothelin is frequently observed in advanced TC, infrequently in T, and is absent in thymic NETs. Mesothelin-directed targeted therapies warrant further evaluation in patients with advanced TC.

Figure 1. Mesothelin immunostaining in TC. (A). 3+ membranous and cytoplasmic staining in 100% tumor cells. (B) 2-3+ membranous staining and cytoplasmic dots in 70% of tumor cells.

ORAL4.02: FGFR1 AMPLIFICATION IN THYMIC EPITHELIAL TUMORS (TET): A STUDY FROM 51 CASES

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Background: TET are rare tumors with variable aggressiveness and prognosis. More than 30% of the patients develop metastasis requiring systemic treatment (chemotherapy and/or targeted therapies). Recently, a phase I trial evaluating lucitanib (a VEGFR FGFR kinases inhibitor) showed tumor control in 86% of the patients. *FGFR1* amplification detected by fluorescence in-situ hybridization (FISH) is found in 20% of squamous cell lung carcinoma (SCLC) representing a potential therapeutic target of these tumors. In this context,

squamous cell thymic carcinomas (TC) showing an *FGFR1* amplification could be eligible to target therapy. We analyzed the presence of *FGR1* gene amplification in a series of TET.

Methods: Fifty-one specimens from surgically resected patients with diagnosis of TET discussed at RYTHMIC national tumor board from Jan 2009 to May 2015 were included for analyses. Specimens were centrally reviewed by a panel of 10 expert pathologists and diagnoses were made according to the WHO histological classification 2004/2015 and new ITMIG proposals for histologic typing. *FGFR1* amplification was performed by FISH (ZytoLight SPEC *FGFR1*/CEN 8 Dual Color Probe – Clinisciences). The slides were scanned and read using a semi automatized system (PathScan-FISH; Excilone) by two independent observers according to the Schildhaus score established in 2012 for *FGFR1* status assessment in SCLC. Cases were considered as *FGFR1* positive (amplified) under one of the following conditions (with (1–3) representing a high-level and (4) a low-level amplification): (1) the *FGFR1*/CEN8 ratio is ≥ 2.0 (2) the average number of *FGFR1* signals per tumor cell nucleus is ≥ 6 (3) the percentage of tumor cells containing ≥ 15 *FGFR1* signals or large clusters is ≥ 10% (4) the percentage of tumor cells containing ≥ 5 *FGFR1* signals is ≥ 50%

Results: Among 51 specimens (34 thymic carcinoma of squamous type and 17 B3 thymoma), 7/51 (14 %) tumors were *FGFR1* amplified according to the *FGRF1* FISH score described above [6/34 TC (18%) and 1/17 B3 thymoma (6%)]. All of these cases demonstrated low-level amplification, as defined by category (4) of the scoring system, with polysomy (≥ 2 CEN8 signals on average). *FGFR1*/CEN8 ratios were ranged from 1.01 to 1.5 (≤ 2).

Conclusion: In our series, *FGFR1* amplification detected by FISH was found in 18% of TC. This frequency is similar to the percentage of SCLC showing *FGFR1* amplification; however, unlike the SCLC's amplification level which is high in 80% of cases, TET's level amplification seems to be much lower and associated with a polysomy in all the cases. We demonstrated a subset of TET harboring a potentially targetable molecular aberration; further evaluation will elucidate whether VEGFR FGFR targeting could represent a successful strategy in this patients.

Keywords: FGFR1 amplification, therapeutic target, thymic carcinoma, thymic epithelial tumor

ORAL4.03: BORTEZOMIB AS A NOVEL TARGETED THERAPY FOR THYMIC CARCINOMA

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Background: Thymomas and thymic carcinomas (TCs) are rare epithelial tumors derived from the thymic gland. TCs are more aggressive and associated with early recurrence and metastasis. The current therapies for thymic cancers are not based on disease-specific biology. There is a great need to understand the complex pathology of these rare cancers and develop biology-driven therapeutic strategies. We have developed a gene signature that can accurately identify metastatic potential of thymoma and TCs (Gokmen-Polar et al., ITMIG 2013). Using this signature, we sought to develop effective targeted therapies for the prevention of metastasis in these cancers. We focused on a precision medicine methodology using approved drugs to enable faster clinical translation.

Methods: Combinatorial computational biology tools were applied at the genomic and proteomic level. Protein-protein interaction network has been performed using BIOGRID database and the genes constituting the pro-metastatic signature. Confirmation of the identified pathway-drug sensitivity has been carried out using the thymic carcinoma cell line (T1889; Ehemann et al: Int J Cancer 2008; courtesy of Dr. Rieker), and a patient-derived type AB thymoma cell line (IU-TAB-1, Gökmen-Polar et al, Lab Invest 2012). Independently, Cellworks' (San Jose, CA) predictive simulation modeling approach was used to model IU-TAB-1 and predict drug response.

Results: Combinatorial analysis of the pro-metastatic gene signature with the protein–protein interaction BIOGRID database identified that the ubiquitin proteasome pathway, the major pathway for intracellular protein degradation, presented an important role in metastasis of thymic carcinoma. In particular, three genes; STC2, JPH1 (both upregulated) and SLC9A2 (down regulated) converged on the ubiquitin-proteasome pathway. In confirmation of this finding, the thymic carcinoma cell line T1889 exhibited marked sensitivity (IC50 of 75 nM) to Bortezomib, an FDA approved

proteasome inhibitor. The thymoma cell line, IU-TAB-1, was modeled using Cellworks approach and predicted relative resistance to Bortezomib which was further confirmed using MTT assay. The proposed mechanism of resistance in the IU-TAB-1 cell line is due to dysregulation of ER stress pathway, and upregulation of beta catenin and Notch pathway. Conclusion: The ubiquitin-proteasome pathway is important therapeutic target in human thymic carcinomas. Bortezomib potently decreases survival of T1889 thymic carcinoma cells. Predictive simulation and combinatorial genomic and proteomic approaches beyond one gene one drug paradigm are essential for developing future precision medicine treatment strategies of patients with this rare malignancy.

Keywords: Thymoma, thymic carcinoma, targeted therapy, bortezomib

ORAL4.04: RECURRENT MUTATIONS AND COPY NUMBER ALTERATIONS IN THYMOMA

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Background: Characterization of the molecular alterations in thymomas is so far incomplete, and may lead to better understanding of tumorigenesis, prognosis, and therapeutic targets.

Methods: Demographic and clinical data from 43 patients who underwent surgical resection of thymomas was retrospectively reviewed. Paired tissue (tumor and matched normal) from the thymomas were evaluated by targeted exon capture (MSKCC IMPACT 341 gene panel) followed by deep coverage next generation sequencing. As there is a known clinical association between WHO subtype and survival outcomes in thymoma (A & A/B with the best prognosis, B1/B2/B3 worse), we performed an analysis in which samples were ordered by WHO subtype and associated with mutational status and copy number alteration.

Results: Pathologic tissue was available from 43 patients (M23:F20, age range 31-85) who during period of 7/97-5/14 underwent Ro (N=33), R1 (N=6), or R2 (N=4) resections. Induction therapy was chemotherapy in 20 pts and radiation in 0 pts. The median pathologic size was 7.2 cm (range 2.1-14). Somatic mutations were identified in 27 thymomas. Genes that are most commonly mutated are listed below, but recurrent

mutations were not identified between different patients and tumors.

WHO classification	Number specimens with mutations/#mutations and range freq
Type A	5 of 7; 8 (12-12%)
Type AB	7 of 7; 28 (14-28%)
Type B1	5 of 9; 11 (10-20%)
Type B2	6 of 12; 31 (6-6%)
Type B3	4 of 6; 21 (14-28%)

Most common mutations	Frequency
TP53	7.80%
FAT1	7.80%
ATM	7.80%
KMT2D	7.80%
EIF1AX	7.80%

Most common copy number alterations	
NTRK1 (AMP)	9.80%
SH2D1A (AMP)	5.90%
IKBKE (AMP)	3.90%
CXCR4 (AMP)	3.90%
PIK3CD (DEL)	3.90%

Conclusions: Targeted exon next generation sequencing of cancer genes in thymomas revealed a low frequency of mutations in our 341 gene panel and low number of copy number alterations. Extensive whole exome or whole genome sequencing in conjunction with transcriptome and/or epigenetic studies may offer further insight into the molecular mechanisms of this elusive entity.

Keywords: copy number alterations, thymoma, mutation, histologic grade

ORAL4.05: PD-L1 EXPRESSION IN THYMIC EPITHELIAL TUMORS: A COMPARATIVE ANALYSIS

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Introduction: Among thymic epithelial tumors, B3 thymoma (BT3) and thymic carcinomas (TC) are the most aggressive and are not always eligible to surgical treatment. Immunotherapy is promising, as it has been shown efficient in other malignancies. PD-L1 is a potential biomarker for immune checkpoint inhibitors (ICI). Its expression has been reported in some series on a limited numbers of patients with selected antibodies. We here aimed to analyze a large national series of TB3 and TC with a panel of available antibodies in order to assess the prevalence of PD-L1 expression, its prognostic value and to set up a reproducible test.

Methods: We retrospectively studied 104 patients with 115 samples of FFPE histologically confirmed B3T (57) and TC (58) mostly from the RYTHMIC French National Network. Clinical data were available for all patients. We analyzed and compared PD-L1, PD1, CD8 and PD-L2 expression and we performed correlation with tumor type and patient's outcome. Three different PD-L1 antibodies were tested; two of them considered as future companion tests in lung cancer. One of them was tested on two automates (table). We examined whole sections of tumors rather than tumor microarray to evaluate staining heterogeneity. We evaluated the percentage and intensity of epithelial and immune stained cells. Analysis was performed by expert pathologists within the RYTHMIC network.

Results: B3 thymomas epithelial cells had a higher and more diffuse expression of PD-L1 than in TC with a significant difference for a 50% cut-off with all the antibodies tested (see table, p<0.0001). The three antibodies targeting PD-L1 gave similar staining on the DAKO autostainer. PD-L1 staining on immune cells showed a low concordance between the antibodies and no significant difference between B3T and TC except with CST (Cell Signaling Technology) antibody. PD-L2 antibody did not stain any tumor epithelial cell. We found no significant statistical correlation between PD-L1 and PD1 and CD8 staining on immune cells. High PDL1 expression was correlated with a better overall survival after 48 months only for B3T (94% for positive versus 60% for negative B3T) and was not correlated with tumor staging.

Conclusion: Frequent PD-L1 expression in CT and particularly in TB3 paves the way for immunotherapy in these diseases. Moreover, we have set up reproducible immunohistochemical processes for three PD-L1 antibodies.

Target	Clone	Company	Automate	TB3*	TC*
PD-L1	E1L3N	Cell Signaling Technology	DAKO	84%	19%
PD-L1	22C3	DAKO	DAKO	78%	12%
PD-L1	SP142	Spring Biosciences	DAKO	82%	10%
PD-L1	SP142	Spring Biosciences	VENTANA	35%	6%

*percentage of positive sample with a 50% cut-off.

Keywords: thymic carcinoma, Immunotherapy, B3 thymoma, PD-L1

POSTER SESSION 1

P1.01: UPDATED INCIDENCE OF THYMIC EPITHELIAL TUMORS (TET) IN FRANCE AND CLINICAL PRESENTATION AT DIAGNOSIS

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Background: TETs are rare malignancies with an overall described incidence of 0.13 per 100.000 person-years. Given this, most of our knowledge is largely derived from small single-institution series. RYTHMIC (Réseau tumeurs THYMiques et Cancer) is a French network for TET created by INCa (French National Cancer Institute) with the objective of territorial coverage by 14 regional expert centers, systematic discussion of patients at national tumor board and collection of nationwide data within a centralized database. We reviewed our activity in 2015 in order to describe the epidemiology and main characteristics at diagnosis of thymic malignancies in France.

Methods: Through RYTHMIC, we prospectively collected all patients (pts) with new diagnosis of primary TET in France in 2015. Epidemiologic, clinical, pathologic and surgical data were prospectively collected within a centralized database. Histologic sub-type was centrally reviewed according to the WHO classification and stage by modified Masaoka-Koga classification. Fisher exact test was used for correlations.

Results: A total of 234 cases with new diagnosis of primary thymoma (T) or thymic carcinoma (TC) have been discussed at RYTHMIC national tumor board between Jan to Dec 2015. Among them, 58% were males; median age at diagnosis was 62 years [range 27; 86] for males and 61 years for females [range 24; 84];

20% of the pts presented an autoimmune disorder (AI); myasthenia gravis was the most common disorder in 76% of them. The incidence of AI per gender was not significantly different ($p=0.13$). History of previous malignancies was described in 15% of the pts, being prostate cancer, breast cancer and melanoma the most frequently observed. Any potentially relevant environmental exposure was declared for most of the pts. Histologic sub-type was characterized as follows: A / AB / B1 / B2 / B3 / TC in 7% / 23% / 13% / 24% / 9% / 16% respectively; neuroendocrine tumors and rare variants were observed in 8% of the pts. Stage I-II / III-IV tumors were observed in 63% / 37% of the pts respectively. Mediastinal pleura, mediastinal nodes and lung were the most common metastatic sites. Significant correlations were found between histologic sub-type (T vs TC) and presence of AI ($p=0.01$) and stage (I-II vs III-IV, $p=0.004$); no significant correlations were seen with gender ($p=0.27$). The median time observed between diagnosis and presentation at tumor board was 36 days [-131; 182].

Conclusion: The estimated incidence of TETS in France in 2015 is 0.35 per 100.000 persons, based in our activity. The inclusion in the RYTHMIC network is mandatory but is still based on physician's request. Although we might underestimate the incidence, it seems to be higher compared to other countries' registries. The high occurrence of previous cancer might underlie variations in environmental or genetic risk factors.

Keywords: Incidence, TET, France

P1.02: THE CURRENT ROLE OF ROBOTIC SURGERY FOR THYMIC TUMORS

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Background: Surgical therapy is the mainstay for multimodal treatment of thymic tumors. Minimally-invasive operation techniques have become more important, but remain to seem adequate only for early stage thymoma. A variety of different techniques includes transcervical, lateral and subxiphoid thoracoscopic techniques. Longer-term follow-up of larger series including more challenging cases is necessary to develop modern standards of treatment for thymoma.

Methods: A prospective study analyzed 81 cases of thymoma operated on for thymoma or thymic carcinoma. A standardized thoracocscopic operation was used with unilateral approach and robotic assistance (da Vinci system, Intuitive Surgical, Sunnivale, CA.). Inclusion criteria of stages I and II according to Masaoka-Koga were extended to thoracoscopic exploration and eventual resection also with suspicion of stage III. Feasibility and development of the operation technique, perioperative morbidity and mortality, survival, and recurrence were analyzed in all patients. The WHO – classification for thymoma was determined and correlated with presence and improvement of myasthenia gravis (MG). MG severity and improvement was classified according to the Myasthenia Gravis Foundation of America (MGFA) – classification.

Results: 81 cases (46 female, 56.8%) of thymoma were operated on with robotic thoracoscopic technique between 01/2003 and 06/2016. This was 14.6 % (81/553) of all robotic thymectomies. The mean age of all patients was 54.5 years, 55 patients with MG were at the same age. A Masaoka-Koga stage I,IIor III was found in 36,40, and 4 patients, respectively. The distribution of histogenetic stages (WHO) was as follows: A-11 (13.5%), AB-19, (23.5%), B1-17, (21%), B2-23, (28.4%), B3-8, (10%), 1 patient had a thymic carcinoma. The mean thymoma size of 45.8 mm was accompanied by a weight of the resected specimen of 89.1 g. Perioperative morbidity was 2.4% with no conversions. There was no thymoma-specific mortality and no recurrence of thymoma with a mean follow-up of 75 months. MGFA improvement stages of complete stable Remission or minimal manifestations were reached by 34/55 patients with MG.

Conclusion: During the last decade, thoracoscopic thymectomy has become widely adopted if not preferred for thymoma. Decision making favoring minimally-invasive surgery is based on symptoms, size, anatomical location and radiological morphology. The technical perfection of the advanced robotic assistance has led to inclusion of more challenging cases with adequate results.

Keyword: Robotic thymectomy for thymoma

P1.03: ROBOTIC THYMECTOMIES: 12 YEARS' SINGLE-CENTER EXPERIENCE

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Background: The three-dimensional robotic-assisted thymectomy is safe and feasible in patients with myasthenia gravis (MG) and an effective alternative technique for resection of mediastinal tumors. We want to report our surgical experience with robotic thymectomies in patients with MG and thymic epithelial tumors.

Methods: We retrospectively analyzed all 285 consecutive patients who underwent a robotic thymectomy using the da Vinci Robotic system (Intuitive Surgical, Inc, Sunnyvale, Calif) between April 2004 and May 2016. Analysis included procedure time, conversion rate, histological outcomes, hospitalization, morbidity and mortality.

Results: A total of 285 robotic procedures for mediastinal tumors or MG were performed in one academic hospital in the Netherlands, from April 2004 to May 2016. Mean procedure time was 143 minutes (44-413). In total, 93 thymomas were found (32.6%) of which 60 patients (64.5%) had concomitant MG and three patients had a thymus carcinoma (1.1%). Thymic carcinomas were only found in patients without MG (figure 1,2). Masaoka Koga staging of the thymic epithelial tumors: 24 stage I (25.8%), 30 stage IIA (32.2%), 21 stage IIB (22.5%), 12 stage III (12.9%), 5 stage IVA (5.4%) and 1 stage IVB (1.1%). Furthermore; we saw 93 patients with follicular hyperplasia (32.6%) of the thymus and 70 thymic remnants (24.6%). To a lesser extent, we did also see twelve thymic cysts (4.2%), three persistent thymus (1.0%), three fatty tissues (1.0%), two lipomas (0.7%), two teratomas (0.7%) and some more exceptional histological outcomes. The conversion rate is 5.3%; seven thoracotomies and eight sternotomies were required to remove the complete thymus. The median hospitalization was four days.

Conclusions: Robotic-assisted thymectomy is safe and feasible in patients with MG and thymomas with low conversion rate and no mortality. Our center shows also successful outcomes after a robotic thymectomy in late thymic epithelial thymomas: an unique strategy in comparison with other centers, which will perform a sternotomy in this specific population. A center bias is possibly caused by the role as an expertise center for patients with Myasthenia Gravis or a suspected thymoma.
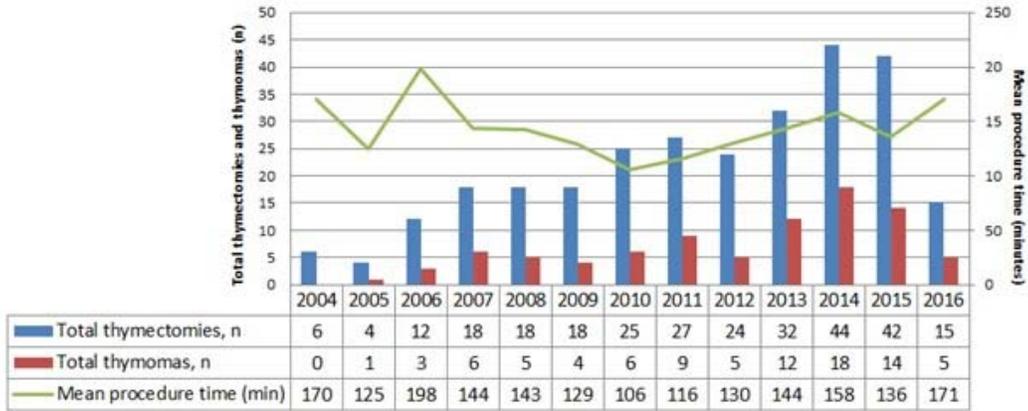
Legend:

Figure 1: Overview of total thymectomies, total thymomas and mean procedure time.
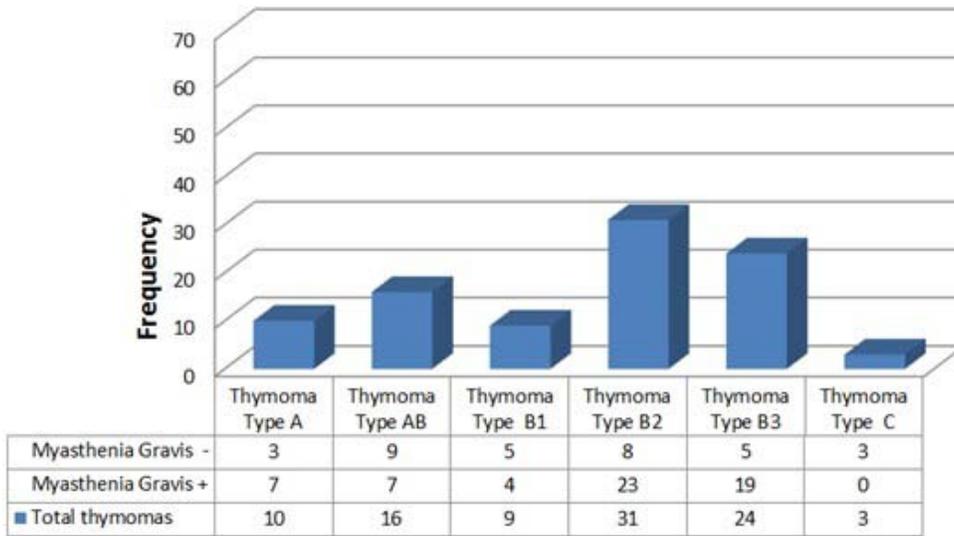
	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Total thymectomies, n	6	4	12	18	18	18	25	27	24	32	44	42	15
Total thymomas, n	0	1	3	6	5	4	6	9	5	12	18	14	5
Mean procedure time (min)	170	125	198	144	143	129	106	116	130	144	158	136	171

	Thymoma Type A	Thymoma Type AB	Thymoma Type B1	Thymoma Type B2	Thymoma Type B3	Thymoma Type C
Myasthenia Gravis -	3	9	5	8	5	3
Myasthenia Gravis +	7	7	4	23	19	0
Total thymomas	10	16	9	31	24	3

Figure 2: Thymomas with (+) and without (-) presence of Myasthenia Gravis

P1.04: ANALYSIS OF TREATMENT AND OUTCOME FOR RECURRENT THYMOMA

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Background: The optimal treatment of recurrent thymomas remains to be controversial. The objective of our study is to analyze treatment modality and outcome of recurrent thymoma in our hospital.

Methods: 52 recurrent thymoma patients out of 296 initial thymoma patients who underwent complete resection at our hospital between 2003 and 2013 were retrospectively enrolled. The extent of the recurrence was defined as local recurrence (mediastinum, lung, diaphragm or pleura with single neoplastic mass) and distant recurrence (pulmonary or pleural dissemination). Survival curves were calculated from the time of recurrence to the event of interest. Clinical variables with survival were estimated by Cox regression analysis and Kaplan–Meier survival analysis.

Results: Of 52 recurrent thymomas (18%, 52/296), 14 ones (22%) were found in the mediastinum as well as 25 (40%) in the pleura, 12 (19%) in the lung and 1 (2%) in the diaphragm. The extent of recurrence included 41 local recurrences and 11 distant recurrences. Therapeutically, surgical resection combined with adjuvant therapy were performed in 16 patients (13 local recurrences via complete resection plus radiotherapy and 3 distant recurrences via debulking surgery plus radiochemotherapy), and nonsurgical treatment was done in 36 patients (20 local recurrences and 2 distant recurrences via radiotherapy therapy, 4 local recurrences and 4 distant recurrences via chemotherapy, and 4 local recurrences and 2 distant recurrences via radiochemotherpy). During the period of follow-up (median: 103.5 months, range: 38-154 months), the 5-year and 10-year overall survival were 80% and 47% respectively. The univariate analysis found that local recurrence (HR: 0.196, 95% CI: 0.071–0.541, P=0.002) and surgical resection combined with adjuvant therapy for recurrent tumor (HR: 0.198, 95% CI: 0.045–0.873, P=0.032) were associated with higher survival after the development of the recurrence. The multivariate analysis found that only local recurrence was independently associated with higher survival (HR=0.172, 95% CI: 0.060–0.496, P=0.001). Survival curves stratified by the extent of recurrence and treatment are showed respectively in Fig 1 and Fig 2.

Conclusions: Local recurrence and resection of the recurrent tumor are associated with preferable prognosis. Surgical resection is recommended in patients with recurrent thymoma, with the possible use of adjuvant therapy.
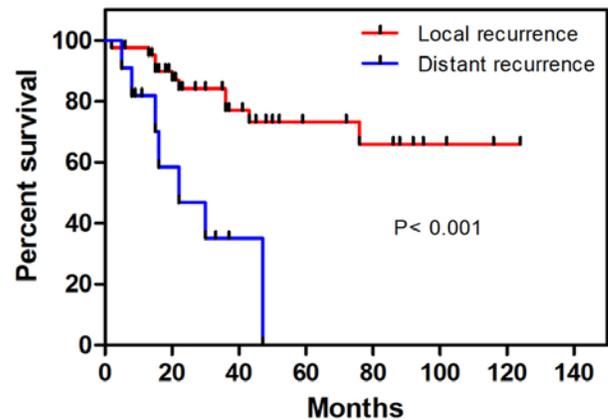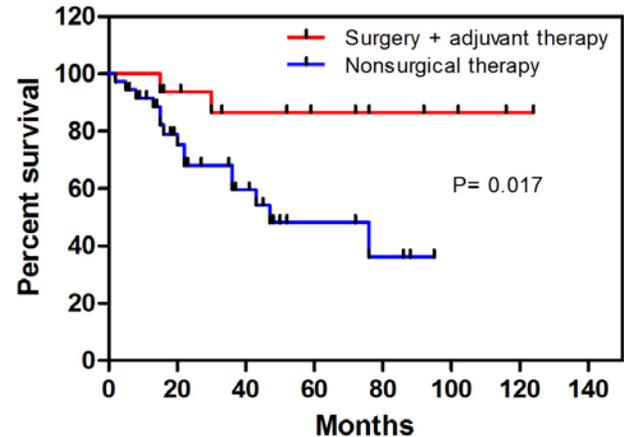

Fig 1

Fig 2

Keywords: survival, recurrent thymoma, treatment

P1.05: RESULTS OF SURGICAL INTERVENTION FOR THYMIC NEUROENDOCRINE TUMORS: A MULTICENTER STUDY

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Purpose: A thymic neuroendocrine tumor (TNET) is rare, with an approximate rate of incidence of 2–5% of all thymic epithelial tumors. Few comprehensive reports of treatment results have been presented. For the purpose clarifying the clinicopathologic characteristics of TNETs using forthcoming TNM Classification of Malignant Tumors, 8th edition, outcomes of TNET therapy were retrospectively examined using cases accumulated in a multicenter survey. Patients Thirty patients (25 males, 5 females, mean age 54.3±11.6 years) who underwent surgical resection or biopsy procedures at 10 institutions of the Thoracic Surgery Study Group of Osaka University and pathologically diagnosed with TNET were enrolled[no1] . Survival was estimated using the Kaplan-Meier method and analyzed by a log-rank test. Furthermore, univariate analysis was performed using Cox's proportional hazard model.

Results: Ten of the patients had symptoms such as chest pain or cough. The tumors were classified as typical carcinoid in 7, atypical carcinoid in 11, large cell neuroendocrine carcinoma in 3, and small cell carcinoma in 9. Induction therapy was performed in 2 cases. Twenty-eight patients underwent surgical resection and 2 surgical biopsy procedures. Twenty-seven patients underwent a macroscopically complete resection (MCR). The mean diameter of the resected tumors was 7.4±4.1 cm (range 1.5–18 cm). Classification according to Masaoka's staging was Stage I in 4, Stage II in 8, Stage III in 10, Stage IVa in 1, and Stage IVb in 7, while that according to the TNM staging system was Stage I in 12, Stage II in 2, Stage IIIa in 8, Stage IVa in 3, and Stage IVb in 5. Adjuvant therapy was performed for 10 patients. Thirteen had recurrence, with the most frequent site found to be osseous metastasis in 7, followed by dissemination in 6, lung metastasis in 6, cut-end r[no2] ecurrence in 1, and local lymph node metastasis in 1. Overall survival (OS) after 5 years was 81.4% and after 10 years was 54.3%, while relapse-free survival (RFS) was 57.9% and 12.9%, respectively. OS was significantly better in males (p=0.01) and patients who underwent MCR (p<0.01). In contrast, there were no significant differences in regard to Masaoka's classification, TNM stage, histologic type, tumor diameter, or Ki67 index. RFS was significantly better in males (p=0.009), and patients classified as TNM stage I or II (p=0.043). The rate of survival of those with recurrence after receiving therapy was 91.6% at 2 years and 25.4% at 5 years. Prognosis was better in patients with local recurrence as compared to those with distant metastasis.

Conclusion: The prognosis of patients with TNET was favorable in males and those treated with MCR. In contrast, there was no significant difference in regard to overall survival in relation to histologic type, TNM stage, and Masaoka's classification. The recurrence rate was high in cases with advanced TNM stage III or IV. For patients who underwent MCR, OS was relatively more favorable than RFS. We consider that patients with TNET can expect a certain period of cancer-bearing survival, though the disease has an intractable nature.

Keywords: thymic neuroendocrine tumor, surgical intervention,multicenter study, outcome

P1.06: CLINICAL FEATURES AND OUTCOMES OF 20 LYMPHOEPITHELIOMA-LIKE THYMIC CARCINOMAS

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Purpose: Thymic carcinoma (TC) is a rare malignancy, which accounts for about 14% of all thymic epithelial tumors. Among TCs, squamous cell carcinoma is the dominant subtype, while lymphoepithelioma-like thymic carcinoma (LEL-TC) represents a percentage of below 10%. There are controversies about the biological behavior and clinical outcome of LEL-TC due to the rarity. We reviewed 20 cases during the last 7 years in our hospital, and tried to draw an outline of this disease.

Methods: Between October 2009 and January 2016, totally 20 cases of LEL-TC patients had been treated in our hospital. All pathological slides were reconfirmed by Dr. Zhu L (pathologist). Medical records were reviewed to summarize patients' characteristics and treatment regimens. Phone calls were made to complete the follow-up information.

Results: There have been 20 patients involved in this retrospective study with an average age of 40 (11-67 years). It should be notified that there were two age groups of high incidence (10-30 years, 8 cases; 50-70 years, 9 cases). Female patients account for a higher ratio (12:8). According to Masaoka staging system, 2 patients were classified in stage Ⅰ ,5 in stage Ⅱ ,7 in stage Ⅲ and 6 in stage Ⅳ when initially diagnosed. The median diameter of all mediastinal tumors was 7.1 cm

(2.5-15cm). Seventeen (85%) patients received surgery-based treatment, and 10 of them (59%) achieved R0 resection. The other 3 patients were judged as inoperable and treated by chemoradiotherapy. In the surgery group, 76% (13/17) patients received post-operative radiotherapy, 59% (10/17) received adjuvant chemotherapy. During the follow-up (median time=55 months), 2 patients died. The 5-year survival rate of all patients was 89%, and the progression free survival rate (PFS) at 5-year was 68%. The most frequent failure pattern was lymph node metastasis (n=4) and pleural implant (n=2) .

Conclusions: Some previous studies recommended that LEL-TC should be grouped in high-grade TC because of poor prognosis. However, our results showed that LEL-TC demonstrated an indolent behavior and should be regarded as low-grade TC. Surgical resection is still the mainstay of treatment, and adjuvant chemoradiotherapy may have the potential benefit for invasive cases.

Keywords: lymphoepithelioma-like thymic carcinoma, surgery, prognosis, chemoradiotherapy

P1.07: LIMITED THYMIC RESECTION IS ACCEPTABLE FOR SMALL, EARLY STAGED, NON-MYASTHENIC THYMOMA PATIENTS

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Background: Thymic complete resection is thought to be the standard treatment for all thymic tumors. But the ideal resection for non-myasthenic early staged thymic tumors is not yet well understood. Therefore, we conducted a retrospective study to investigate the management of this unique scenario.

Methods: We retrospectively analyzed a total number of 118 early staged thymoma patients whom underwent a thymectomy and thymomectomy with curative intent January 2003 to December 2013 at our institution. Patients with myasthenia, thymic carcinomas, tumors with undetermined histology, and more advanced staged thymoma patients were exclude from this study. We compared disease free survival (DFS) according to the extent of thymic resection, Masaoka- Koga staging and the tumor size.

Results: 118 patients were staged as early thymoma. Complete resection was achieved in 100% in this group. Thymectomy was performed in 43(35.6%) patients and thymomectomy was performed 75(64.4%)patients. Type AB and B2 were the most common subtypes in thymectomy group, type AB was the most common in thymomectomy group. 74 patients were staged as stage I, among them, 57 (76%) had thymomectomy, and 17 (39.5%) had thymectomy. 44 patients were staged as stage II, 18 (24%) underwent thymomectomy, and 26 (60.5%) had thymectomy. 49(65.3%) patients with tumor size £3cm, underwent thymomectomy, and 9 (20.9%) underwent thymectomy. 26(34.7%) patients with tumor size >3cm underwent thymomectomy, 34(79.1%) underwent thymectomy. Comparing the disease free survival, we observed better DFS in patients with tumor size ≤3cm (P=0.023). In thymomectomy group, recurrence was observed 2 patients, and in thymectomy group, 3 had reoccurrence. Comparing DFS between two groups, there was no significant statistical difference in recurrence (p =0.250).

Conclusion: No difference in the rate of recurrence was observed in early staged non-myasthenic patients following extent of thymic resection and Masaoka-Koga staging. But early staged thymoma patients with tumor size >3cm, thymectomy is considered to be a better option.

Keywords: Thymomectomy, Non-myasthenic thymoma, thymoma, Thymectomy

P1.08: COULD THYMOMECTOMY BE AN OPTION FOR "SELECTED" NON-MYASTHENIC THYMOMA PATIENTS?

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Background: Complete resection is the mainstay of treatment for thymoma but few studies investigated the extent of resection of normal thymus. Extended thymectomy is considered the treatment of choice for myasthenic patients with thymoma while the optimal therapy for non-myasthenic is matter of debate. Aim of the study is to evaluate if thymomectomy may be an option for selected non-myasthenic patients.

Methods: Retrospective review on 160 consecutive thymoma patients observed at a single Institution in the period from March 1996 to September 2015. Exclusion criteria: C thymoma(15), biopsy(12), debulking surgery(5), myasthenia gravis(36). Ninety-two patients

were divided in two groups according to the extent of resection of the normal thymus: total thymectomy(70) and thymomectomy(22). Total thymectomy was the procedure of choice for suspected/proven thymoma. Thymomectomy was performed in selected patients in the following conditions: giant unilateral mass, totally cervical thymoma, not histologically proven small neoplasms, easily resectable through video-thoracoscopy and thymoma removed during surgery for lung cancer. Clinical-pathological data, oncological outcome and postoperative myasthenia gravis occurrence were compared.

Results: Patients and tumor characteristics are listed in the table. Only stage distribution was different between the two groups with prevalence of stage III in total thymectomy and stage IV in thymomectomy group. In total thymectomy group we performed 44(63%) isolated total thymectomy, 25(36%) en-bloc with lung/pleura/pericardium/vena cava and 1(1%) associated with resection of pleural-pericardial implants through median sternotomy 69(99%) or sterno-thoracotomy 1(1%). In the other group, patients received isolated thymomectomy 18(81%), associated with resection of pleural/pericardial implants 2(9%), en-bloc with pulmonary lobectomy and partial pleurectomy 1(5%) or with left extrapleural pneumonectomy 1(50%). Surgical approach was thoracotomy 14(63%), video-thoracoscopy 6(27%), cervicotomy 1(5%) and clamshell incision 1(5%). Complications in total thymectomy group were 14(20%): arrhythmia 7(10%),respiratory failure 3(4%), bleeding 2(3%), osteomyelitis 1(1%) and lymphorrhea 1(1%) while in thymomectomy group they were 2(9%): pericardial effusion 1(5%) and respiratory failure 1(5%). Perioperative mortality was zero. Outcome at a median follow up of 67 months (range 1-243 months) is summarized in the table. In three patients (one in total thymectomy and two in thymomectomy group) R0-resection was not achieved for multiple pleural implants. All these patients had a slow pleural disease progression, without mediastinal recurrence.

Conclusions: In selected non-myasthenic thymoma patients thymomectomy may have the same oncological outcome as total thymectomy; furthermore complete removal of the thymic tissue, in addition to tumor resection, doesn't seem to prevent postoperative myasthenia gravis occurrence. Multicentric thymomas are extremely rare and such event cannot be an indication for total thymectomy. Further investigations, by means of randomized-controlled prospective studies, should be warmly advised to confirm the data.

Variables	Total thymectomy (n=70)	Thymomectomy (n=22)	p-value
Gender M/F	38/32	12/10	0.983
Age(mean±SD)	61.9±12.1	62.4±14.3	0.610
Thoracic symptoms	22	9	0.412
Histology A/AB/B1/B2/B3	7/20/14/22/7	3/9/3/4/3	0.623
Tumorsize(mean±SD)	6.9±3	8.2±5.4	0.137
Tumor > 8 cm	30	10	0.830
Stage I/II/III/IV	39/19/11/1	10/8/0/4	**0.008**
Adjuvant therapy	14	3	0.486
Complications	14	2	0.239
Follow-up period	76months(1-243)	30months(9-115)	
Postoperative myasthenia gravis	8(11%)	0	0.097
Pattern of recurrence local/regional/distant	1/0/1	0/0/0	0.396
Deaths t. related/not related	2(3%)/8(11%)	0/3(14%)	0.706
Multiple thymoma	0	0	

P1.09: PROGNOSTIC VALUE OF PREOPERATIVE NLR AND PLR IN THYMIC CARCINOMA AFTER COMPLETE RESECTION

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Background: The evidence that cancer-related inflammation has a strong influence on outcome in cancer patients has increased and is consistent. Preoperative neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) have prognostic value in patients with various operable tumors. However, no previous studies have evaluated the association between NLR and PLR with the prognosis of thymic tumors. The purpose of our study was to investigate the prognostic value of preoperative NLR and PLR for patients with thymic carcinoma.

Methods: A total of seventy-nine patients who underwent complete resection of thymic carcinoma in the National Cancer Center/ Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College hospital between January 2005 and December 2015 were retrospectively enrolled. Differential leukocyte counts were collected before surgery, and the relationships of NLR, PLR, and other patient clinical variables with survival were estimated by Cox regression analysis and Kaplan–Meier survival analysis.

Results: During the follow-up period (median: 40 months, range: 1-130 months), the 1-, 3-, and 5-year disease-free survival rates were 78%, 57% and 44% respectively and the 1-, 3-, and 5-year overall survival rates of 96%, 79% and 60% respectively. The Cox univariate analysis found that a high level of NLR was associated with lower disease-free survival (HR: 3.385, 95% CI: 1.073–10.678, P=0.037) and lower overall survival (HR: 12.836, 95% CI: 1.615–101.990, P=0.016). The optimal NLR threshold of 4.1 could stratify the patients with high risk of recurrence or metastasis (P=0.026) and death (P=0.006). Meanwhile, the NLR value of >4.1 in those patients was associated with bigger tumor size (P=0.035) and more advanced Masaoka stages (P=0.040) compared with NLR ≤4.1. However, the PLR and other variables were not significantly associated with survival in thymic carcinoma patients.

Conclusions: Prognostic value of preoperative NLR is superior to PLR for survival in patients who underwent complete resection of thymic carcinoma. The preoperative NLR of >4.1 was significantly associated with larger tumor size, more advanced Masaoka stages and reduced disease-free survival and overall survival, but was not an independent predictor of survival in thymic carcinoma patients after complete resection.
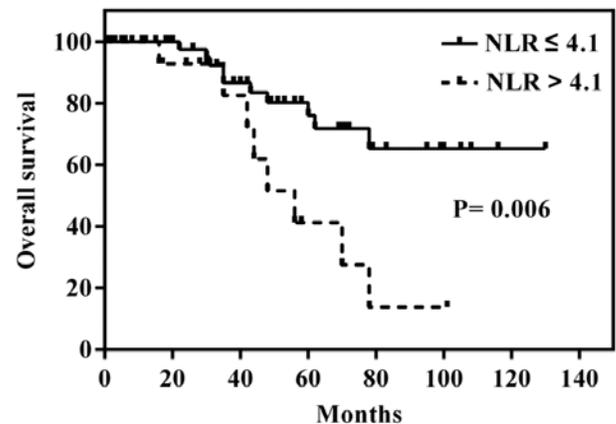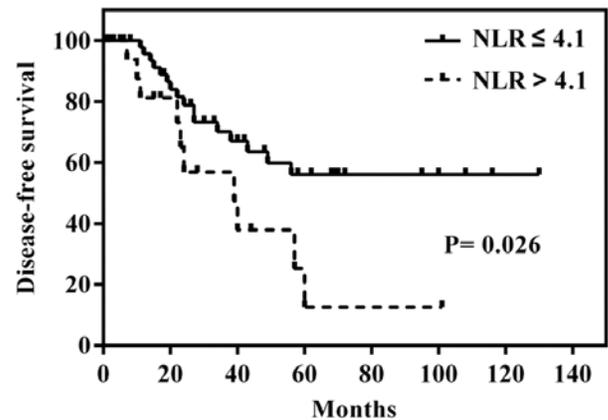
Keywords: thymic carcinoma, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, prognosis

P1.10: ASSOCIATIONS BETWEEN PD-L1 AND THYMIC EPITHELIAL TUMORS: A SYSTEMIC REVIEW AND META-ANALYSIS

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Abstract: The expression of programmed death ligand 1 (PD-L1) in tumor cells has been shown to play a significant role in destroying functions of tumor infiltrating T cell, which leads to antitumor immune evasion across various cancer types. However, whether PD-L1 is associated with the clinicopathological characteristics and prognosis of thymic epithelial tumors (TET) remains controversial. Therefore, we performed a systemic review and meta-analysis with studies published before June 2016 from PubMed, Web of Science, Embase, the Cochrane Library and the Chinese Biomedical Literature Database. A total of 315 TET cases, of which 255

(81.0%) were thymoma and 60 (19%) were thymic carcinoma, traced from 4 studies were included in the analysis. Positive PD-L1 expression are correlated with higher Masaoka stage (III/IV vs. I/II, RR 1.87, 95%CI 1.50-2.331, *P*< 0.001), and worse WHO histological type (B2/B3 vs. A/AB/B1, RR 1.74, 95%CI 1.38-2.19, *P*<0.001). Nonetheless, positive PD-L1 expression is not associated with thymoma or thymic carcinoma pathological type (thymic carcinoma vs. thymoma, RR 1.57, 95%CI 0.61-3.75, *P*= 0.367), and no relationship is observed between positive PD-L1 expression and patient gender, or completeness of surgical resection. Furthermore, positive PD-L1 is significantly related to the poor disease-free survival (HR 2.53, 95%CI 1.05-6.07), but has no impact on the overall survival (HR 0.76, 95%CI 0.38-1.52) of TET. In conclusion, the meta-analysis results suggest that positive PD-L1 in TET may indicate more aggressive histology and worse prognosis. Thus, anti-PD-L1 drugs may serve as potent therapeutic interventions in TET. However, because of the limited number of studies included, the results should be further identified by future updated or well-designed prospective studies.

Keywords: thymic epithelial tumor, Meta-analysis, programmed death ligand 1

P1.11: CLINICOPATHOLOGICAL ANALYSIS OF CYSTIC LESION OF THE THYMUS

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Background: Thymic cyst is the major pathology of cystic lesion in the thymus. We occasionally meet thymoma or other diseases associated with cysts. We retrospectively analyzed thymic cystic lesions resected surgically in our institution.

Materials and Methods: We examined pathological findings and medical records of the patients who had undergone resection of the thymic cystic mass during 1972 and 2015. We collected 46 cases for the analysis.

Results: Twenty-eight (61%) male and 18 female patients were included in the study group. Age at surgery ranged from 13 to 88 years (median 57 years). Diameter of the cysts were between 10 and 150 mm (median 40mm). Four patients were symptomatic (cough 2, fever 1, and chest pain 1), and other 42 were asymptomatic in the chest. Surgery had been performed because of the suspicion of mediastinal tumor (N=40), and concomitant resection at cardiovascular or lung surgery (N=6). Thirty-seven (80%) were unilocular, and 9 were multilocular cysts. Thymoma was associated with

the unilocular cyst in 6 patients, and seminoma in 1. Cystic wall was lined with squamous epithelium in 14 (30%), cuboidal-cylindrical epithelium in 18 (39%), and ciliated epithelium in 9 (20%). Differential diagnosis from bronchial cyst was a problem in the cysts lined with ciliated epithelium. Five of 6 thymoma was associated with cysts without lined epithelia.

Conclusions: In many cases of thymic cystic lesion accompanied by a thymoma may have different mechanisms of the thymic cyst without other lesions. Bronchial (or foregut) cyst might be more likely to occur in the thymic tissue.

Keywords: Thymus, cyst, thymoma, bronchial cyst

P1.12: WNT4 PROMOTES THYMOMA DEVELOPMENT THROUGH UPREGULATION OF FOXN1

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Objective: Wnt signaling pathway controls the development of thymic epithelial cell by regulating the expression of FoxN1, and the excessive activation of Wnt signaling pathway is related to the occurrence of tumors. The objective of this study is to know the mechanism of Wnt4 and FoxN1 in the pathogenesis of thymoma and the relationship between Wnt4, FoxN1 expression and malignant degree of thymoma.

Method: Choose 56 thymoma patients who had not been accepted preoperative chemotherapy and radiotherapy. Wnt4 and FoxN1 mRNA and protein were analyzed by RT-qPCR and immunohistochemistry, respectively, in thymoma tissues. Thymoma cells were cultured and transfected with siRNA plasmids targeting the Wnt4, JNK and FoxN1 gene. FoxN1 mRNA and protein expression was detected by PCR and western blot assay, and apoptosis analyzed using flow cytometric analysis.

Results: 1. Wnt4 and FoxN1 protein positive expression rate was 64.3% (36/56) and 58.9%（33/56）, the mRNA expression was 2.56±0.04、1.83±0.11 respectively. With the development of thymoma pathological classification and Masaoka staging, the protein positive expression rate and mRNA expression of Wnt4 and FoxN1 gradually increased and the difference was statistically significant (P < 0.05). 2.Wnt4、FoxN1 protein and mRNA expression in thymoma patients was positively correlated (P < 0.05), but no correlation whether

thymoma associated with myasthenia gravis. 3. After Wnt4, JNK and FoxN1 genes were interfered by siRNA technology, the inhibition rates were 56%, 72.6% and 78% respectively. The mRNA and protein expression of FoxN1 were decreased after downregulation of Wnt4 and JNK. 4. After Wnt4 and FoxN1 genes were interfered by siRNA technology, apoptosis rate was 13.78±0.35% and 15.32±0.46%, respectively, the difference compared with control group (5.96±0.31%) was statistically significant (P < 0.05) .

Conclusion: High expression of Wnt4 and FoxN1 may play an important role in the generation and development of thymoma. Wnt4 gene produced a marked effect in the upstream through the regulation of FoxN1. Combined detection of Wnt4 and FoxN1 can help us to evaluate the malignant degree of thymoma.
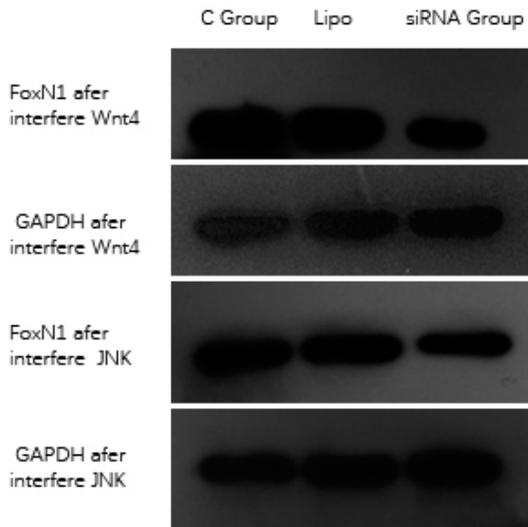
Fig.1 The Western bolt results of FoxN1 after downregulation of Wnt4 and JNK

Keywords: Wnt4, thymoma, FoxN1, siRNA

P1.13: ROLE OF F-18-CHOLINE PETSCAN IN RECURRENCE OF THYMIC EPITHELIAL TUMORS (TET)

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Background: Fluorine-18-fluorodeoxyglucose (F-18-FDG) PET/CT uptake in TETs is highly variable based on histology subtype. The fluorine-18-choline (F-18-choline) PET/CT scan represents an emerging important tool in the management of tumors with low glucose metabolism. There have been few sporadic case reports describing positive choline uptakes in TETs. The aim of this study is to evaluate the clinical use of choline PET/CT in a cohort of patients with TETs.

Methods: We conducted a retrospective analysis of patients with diagnosis of TETs who underwent an F-18-choline PET/CT exam in the course of their disease within two institutions from Jan 2012 to May 2016. Pathological and clinical data were extracted from electronic database and medical records. Images were acquired one hour after injection of 100 MBq radiolabeled choline. F-18-FDG exams with a mean standardize uptake value (SUV) higher than 4.5 and F-18-choline exams with uptake more than two times the physiologic value, were considered as positive. Choline SUV results were compared with F-18-FDG SUV and magnetic resonance imaging (MRI) findings when available by an expert radiologist.

Results: A total of 10 patients (pts) were included for the analyses. Among them, 8 pts were males; median age at diagnosis was 43 years [range 32 – 62], 8 presented an autoimmune disorder (62 % myasthenia gravis); 8 had thymoma (T) and 2 had thymic carcinoma (TC). All patients underwent choline PET/CT in order to evaluate suspected recurrence and /or progression. Positive choline PET/CT scans were observed in 7 pts with a median SUV of 6.5 [range 4.8 - 7.8] with the following histology subtype distribution: B1 / B2 / TC in 2 / 3 / 2 patients respectively. No significant correlations between a positive choline scan and existence of myasthenia gravis were seen (*p*=0.16). Negative choline PET/CT was observed in 3 pts with AB, B1 and B2 histology subtypes distribution. Five patients (50%) showed disagreement between F-18-FDG and F-18-choline scans results. Among them, 3 pts with a negative FDG PET/CT had a positive choline PET/CT showing an isolated recurrence amenable to local treatment in two of them; choline scan of the remaining patient showed disseminated progression excluding any local treatment. Diagnosis of mediastinal progression was suspected for 2 pts on positive mediastinal FDG uptake but excluded based on a negative choline scan and MRI findings; both of these patients had history of mediastinal adjuvant radiotherapy, a known common cause of false positive FDG uptake. Agreement was seen between both modalities for 4 pts confirming and excluding recurrence in 3 and 1 pts respectively.

Conclusion: Discordance between F-18-FDG and F-18-choline scans was observed for half of the patients. When FDG scan was negative, the addition of choline PET/CT impacted disease management in 75% of the cases, representing an alternative promising method in thymic malignancies with negative FDG PET/CT scan. History of adjuvant mediastinal radiotherapy could constitute a frequent cause of false positive FDG scan with negative choline findings; therefore, F-18-choline scan might also represent a useful exam to exclude mediastinal relapses in this scenario.

Keywords: PET Choline, Recurrence, TET

P1.14: POSTOPERATIVE RADIOTHERAPY IN THYMIC EPITHELIAL TUMORS: INSIGHTS FROM THE RYTHMIC PROSPECTIVE COHORT

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Background: Thymic Epithelial Tumors (TET) are rare intrathoracic malignancies, for which surgery represents the mainstay of the treatment strategy. Current practice for postoperative mediastinal radiotherapy is highly variable, and there is paucity of prospective, multicentre evidence. RYTHMIC is the nationwide network for TET in France, established in 2012. The RYTHMIC prospective database is hosted by the French Intergroup (IFCT), and prospectively collects data for all patients diagnosed with TET, for whom management is discussed at a national multidisciplinary tumor board (MTB) based on consensual guidelines. Whether postoperative radiotherapy (PORT) should be delivered was the most frequent question raised at the MTB over the past 3 years, accounting for 494 (35%) of a total of 1401 questions.

Objectives: Primary objectives were to assess whether decision made at the RYTHMIC MTB were consistent with that of RYTHMIC guidelines and actually implemented, and whether standard quality criteria of radiotherapy had been followed.

Methods: All consecutive patients for whom PORT was discussed at the RYTHMIC MTB from 2012 to 2015 were identified from the RYTHMIC prospective database. Analysis of patients medical records and follow-up was conducted at expert centers of the network.

Results: 285 patients were identified, 274 (52% men, 48% women) of whom strictly fulfilled inclusion criteria. Average age at time of TET diagnostic was 60 years. TET histology was thymoma in 243 (89%) cases – including type A in 11% of cases, type AB in 28%, type B1 in 17%, type B2 in 29%, and type B3 in 14% -, and thymic carcinoma in 31 (11%) of cases. Complete resection was achieved in 81% of patients. Masaoka-Koga stage was stage I in 29% of cases, IIA in 21%, IIB in 21%, III in 18%, and IVA/B in 11%. Decision of the MTB was consistent with guidelines in 221 (92%) assessable cases. Clinical situations for which PORT was indicated in accordance with guidelines (84 cases) were thymoma/R1 resection (30 patients), thymoma/R0 resection/stage III (22 patients), thymoma/R0 resection/stage IIB/type B2/B3 histology (11 patients), thymic carcinoma/R1 resection (6 patients), thymic carcinoma/R0 resection (13 patients), thymoma/R0 resection/stage IIA/type B3 histology (2 patients). Inconsistencies between decision of the MTB and guidelines – 20 (8%) cases - consisted of abstention related to poor general condition (10 patients), carcinoid histology (2 patients), discordance in staging (1 patient), and of delivery of radiotherapy related to peroperative tumor fragmentation (2 patients); for 5 patients who received PORT, a clear explanation for inconsistency with guidelines was not found, but those cases – 2 patients with type B2, stage IIA thymomas, and 3 patients with type AB, stage IIB thymomas - actually corresponded to those in a "grey zone" of guidelines. MTB decision for PORT was actually implemented for 99 (85%) of patients; most frequent reason for not delivering radiotherapy was prolonged delay since surgery.

Conclusion: Our data provide with a unique insight into the decision-making process for PORT in TET, highlighting the need for a systematic discussion at an expert MTB, while stressing the value of current available guidelines.

Keywords: thymoma, thymic carcinoma, Radiotherapy, staging

P1.15: EFFICACY OF SINGLE-PORT THORACOSCOPIC SURGERY FOR THYMECTOMY IN ANTERIOR MEDIASTINAL MASS

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Background: Single-incision thoracoscopic surgery is an alternative procedure used to performed thymectomy in patients with anterior mediastinal tumor, although conventional three- or four-port video-assisted thoracoscopic surgery is the recognized standard procedure. Single-incision thoracoscopic surgery is not yet popular when thymectomy is required during general thoracic surgery, including patients with anterior mediastinal tumor, because of the danger of collision between instruments during surgery. In addition, introducing all of the instruments through a single incision means that a relatively large incision is required, leading to less than satisfactory cosmetic outcomes. The purpose of this study was to show that our inhouse surgical method is a safe, alternative procedure for treating a thymectomy in patients with anterior mediastinal tumor.

Methods: A total of 249 patients with mediastinal tumor underwent mass excision of thymectomy. Among them, We excluded Open thoracotomy, sternotomy, posterior mediastinal tumor and MG thymoma.Remained 65 patients underwent surgical procedure to treat anterior mediastinal tumor from October 2009 to October 2016. Mean patient age was 49.6 ± 18.3 years; 27 patients were male and 38 were female. .All clinical data were analyzed retrospectively

	thymoma	thymic hyperplasia	thymic cyst	uninvoluted thymus	another	
Multi-port thymectomy	5	2	2	2	10	21
Single-port thymectomy1912	12	3	15	2	12	44
Total	17	5	17	4	22	65

Results: Mean operative time was 49.6 ± 18.3 minutes(multiport 136.33 ± 64.9, single port 93.86 ± 53.0), and the mean duration of chest tube drainage was 4.0 ± 1.5 days(multi 4.5 ± 1.5, single 3.8 ± 1.4). No complication was recorded. The Wong-Baker pain scores on postoperative days 0, and 5 were 2.4 ± 1.0, 2.3 ± 1.3, and 1.7 ± 0.83, respectively. The mean duration of hospital stay was 8.0 ± 3.5 days(multi 8.8 ± 5.1, single 7.6 ± 2.4).

Conclusions: Small single-incision thoracoscopic surgery for thymectomy in patients with anterior mediastinal tumor using a wound protector was safe and feasible and yielded acceptable outcomes for treating anterior mediastinal tumor and thymoma

Keywords: single-port thoracoscopic surgery,, mediastinal, Thymectomy

POSTER SESSION 2

P2.01: ENDEAVOUR TO EXPAND THE APPLICATION OF VATS FOR ADVANCED THYMOMAS

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Purpose：VATS shows some advantage over open surgery for early stage thymoma, but still controversial in advanced thymoma.

Methods: we introduced VATS in highly selected cases for the past few years. Up to now, we found that at least three situations could be candidates：1. mass oversize; 2. adjacent pericardiac or lung infiltrated; 3. close to left innominate vein, but not infiltrated. we have conceived corresponding solutions for these situations. For category 1, retrieving specimen via subxyphoid incision is preferred after dissection with a lateral approach; For category 2, resecting the pericardiac surrounding tumor with en-bloc procedure; For category 3, bilateral VATS will be introduced, and endoscopic staples may be applied to do angioplasty if necessary.

Results：From Jan, 2014 to May 2016, we have 89 surgical cases of thymic tumor, in which 50 VATS cases with stage Ⅰ or Ⅱ, 21 open procedure for advanced

stage and then 18 VATS for advanced cases which we considered as marginal candidate cases due to prior discussed situations: Category 1, 6 cases with tumor size > 7cm, the maximal size is 11cm; Category 2, 7 cases with pericardium or lung infiltrated; Category 3, 5 cases with mass close to the left innominate vein, but not infiltrated. 4 cases had myasthenia gravis. All the advanced cases were presented to the tumor workshop for thymic disease in our hospital, which included an experienced radiologist. Based on all the requrements from ITMIG consensus, all the cases had CT scan with contrast in mandatory and the radiologist joined the discussion for the resection possibility for every case.

For all the 18 cases, all the specimens were retrieved from subxyphoid pathway. No conversion to open surgery, average blood loss was 200ml, mean hospital stay was 5 days. We had one case of exploratory operation due to excessive drainage just 2 hours after first surgery, but found no active bleeding. No local recurrence up to now and all the cases are doing well during continuing follow-up.

Conclusion：VATS could be safe and effective procedure in some highly selected thymoma cases, which is based on decision making from a tumor workshop on thymic disease.
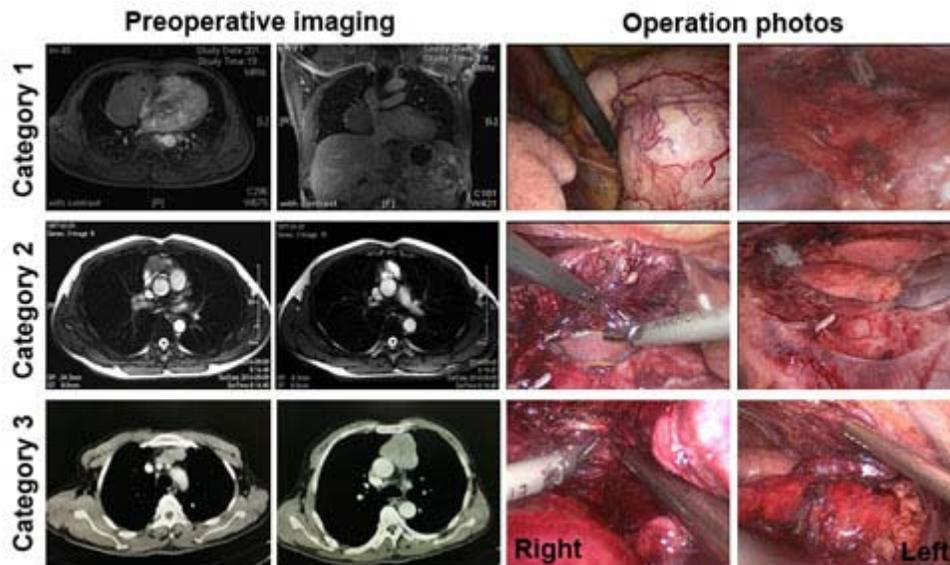
Table 1. The Clinical pathological characteristics of 18 Thymic tumor patients

Category	Case	sex	age	Paraneoplastic syndrome	WHO typing	Tumor oversize (cm) / Local violation (Lung or pericardium) / Close to left innominate vein			Operative approach
Category 1	1	M	41	No	B1	11 × 7 × 3			VATS (right)
	2	M	52	No	AB	8 × 5 × 2			VATS (left)
	3	F	29	No	AB	4 × 7 × 4			VATS (right)
	4	M	48	No	AB	5 × 7 × 3			VATS (left)
	5	F	37	MG	B2	8 × 3 × 1.5			VATS (right)
	6	M	48	NO	B3	8 × 4.5 × 2			VATS (right)
Category 2	1	M	29	MG	C		Pericardium		VATS (right)
	2	M	52	NO	C		Lung.pericardium		VATS (right)
	3	F	35	NO	B2		Pericardium		VATS (left)
	4	F	53	NO	B2		Pericardium		VATS (left)
	5	M	49	NO	AB		Pericardium		VATS (right)
	6	M	47	NO	B3		Lung.pericardium		VATS (left)
	7	M	34	NO	AB		Pericardium		VATS (right)
Category 3	1	M	32	MG	B2			Close to LIV #	VATS (bilateral)
	2	M	47	NO	AB			Close to LIV	VATS (bilateral)
	3	M	35	NO	2A			Close to LIV	VATS (bilateral)
	4	M	32	NO	AB			Close to LIV	VATS (bilateral)
	5	F	39	MG	B2			Close to LIV	VATS (bilateral)

Note: # LIV, left innominate vein. All the specimens were retrieved via subxyphoid pathway.

P2.02: MACROSCOPICALLY RESECTION FOLLOWED BY ENTIRE HEMITHORACIC RADIOTHERAPY FOR STAGE IVa THYMIC TUMORS

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Aim: To evaluate the safety of combined treatment consisting of visible tumor resection and postoperative entire hemithoracic radiotherapy (EHRT) for stage IVa thymic tumors.

Methods: Patients should meet the following criteria: 1) Mediastinal tumor with pleural masses or implants; 2) no distant metastasis. 3) no pericardial implants. Patients underwent sternotomy with or without thoracotomy to have all visible tumors removed. Four to six weeks after the surgery, a radiotherapy of 13Gy was scheduled to each patient in 13 fractions, with a target covering the entire hemithorax. The irradiation was conducted through opposing anterior-posterior field. Acute and late side effects were mainly observed. Short-term regional tumor control was also recorded.

Results: From November 2014 to March 2016, totally 8 patients have been enrolled in this study. There were 5 males and 3 females with a median age of 45 (29-70) years. Five patients were pathologically diagnosed via biopsy before surgery; another 3 were diagnosed based on resected specimen. The histological distribution was B2 in 5, B3 in 1 and squamous carcinoma in 2. Four patients received preoperative chemotherapy and 1 of them (25%) showed partial response in tumor volume. All patients underwent macroscopically resection, and one developed empyema 2 weeks post surgery, who recovered after continuous drainage. Radiotherapy was stared as scheduled for each patient and all of them finished the treatment except a 70-year-old woman with B2 thymoma, who showed deterioration of her myasthenia gravis (MG) symptoms after 9Gy/9 fractions and stopped at that dose. During the radiotherapy, 2 patients complained fatigue and nausea. No other severe side effects were recorded. During a median follow-up of 9 (3-19) months, no radiation-induced pneumonitis of more than grade 2 was found. One patient with squamous carcinoma developed new pleural nodules 12 months after EHRT, which was regarded as in-field recurrence. All other patients showed no sign of recurrence.

Conclusions: Macroscopically resection followed by low-dose EHRT is safe for stage IVa thymic tumors, but the long-term efficacy needs to be proved by longer follow-up. Patients with MG should by be managed carefully in this procedure.

P2.03: FEASIBILITY OF EXTENDED RESECTION COMBINED WITH PHOTODYNAMIC THERAPY IN STAGE IV INVASIVE THYMOMA

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Objective: Treatment of patients (pts) with pleural dissemination of thymoma or thymic carcinoma, Masaoka stage IVA, and pleural recurrence thymomas remains challenging and controversial. Photodynamic therapy (PDT) is a light based cancer treatment that can be delivered as an intraoperative adjuvant treatment. Aggressive debulking of the tumors and combination with photodynamic therapy as an intra-operation adjuvant therapy to this disease may provide better local control and prognosis. We reviewed our experience in a single institute after 10 years of following-up.

Methods: Between Oct 2006 to Dec 2010, 14 patients were included in this study. 6 patients with stage IVA thymoma (5 with MG), 8 patients with pleural recurrence thymomas (5 with MG and 2 with thymic carcinoma) underwent radical pleurodectomy (RP) and intraoperative PDT. Mean age was 45 yrs (range 22–60). No neoadjuvant treatment was performed for those 6 pts with newly diagnosed stage IVa thymomas. Other 8 pts with thymoma pleural recurrence all received chemotherapy and radiotherapy with persisted progression before PDT operation. All patients received macroscopic complete resection and intra-operative PDT

Results: There were one mortality due to pneumonia after 60 days post-operatively. At a median follow-up of 6 years, 6 pts have recurred (5 local; 1 distant), 6 pts are dead and 8 pts are alive (5 without recurrence with more than 6 years). Kaplan-Meier median recurrence-free survival (RFS) is 6 yrs. The median overall survival (OS) has not yet been reached and the 3-yr and 5-yr OS rate is 84% and 77% prospectively. For the 6 patients with newly diagnosed stage IVa thymoma, 5 are alive more than 6 years with only one has local recurrence received 2nd pleural PDT operation, and one was dead of MG crisis without evidence of tumor recurrence 5 years after operation.

Conclusions: Extend pleural resection combined with intra-operation PDT can be performed in select patients with stage IV and pleural recurrence thymoma with low morbidity and mortality and can result in excellent long-term survival.

Keywords: photodynamic therapy, Invasive thymoma

P2.04: DOSIMETRIC COMPARISON BETWEEN PHOTON AND PARTICLE THERAPY FOR BULKY THYMIC MALIGNANCIES /CASE REPORT

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Purpose: Radiotherapy (RT) plays an important role in the treatment of inoperable thymic malignancies. However, for bulky lesions, photon RT may lead to poor tumor control because radical dose often could not be delivered due to intolerable toxicities to organs at risk. Here we report the dosimetric comparison outcomes between photon and particle radiotherapy for five patients with bulky (>5cm) thymic malignancies.

Methodology: Five patients were enrolled for dosimetric comparison research. Tumor diameters varied from 5.0~17.7cm. The research prescription was 66GyE/22Fx for all plans. Intensity modulated RT was used for photon and beam scanning technique with fixed beams (horizontal or 45°) was used for particle therapy. Dosimetric parameters were acquired from Eclipse® for photon planning and from Syngo® for particle therapy.

Results: Compared with photon therapy, proton or carbon therapy significantly reduced the maximal dose of spinal cord, mean dose of lungs/heart/esophagus using paired student test. Moreover, particle therapy could also significantly reduce the V5, V10, V20 of lungs and V5, V10 of heart (Fig 1). For most of the patients, particle therapy even has room for dose escalation in order to improve tumor control of bulky lesions.

Case Report: 74 year-old male with stage III thymic atypical carcinoid, which is resistant to X-ray, presented with an inoperable bulky mass larger than 10cm. He received 44GyE/20fx proton and 21GyE/7fx carbon ion irradiation. The patient was followed up by CT review for tumor evaluation. The longest diameter of the tumor decreased gradually from 10.8cm to 8.1cm (about 25% reduction) in 6 month after irradiation (Fig.2). No grade >= 3 CTCAE (Common Terminology Criteria of Adverse Events) v4.0 toxicities were observed. Except grade 2 tachycardia and grade 1 radiation-induced pneumonitis, other toxicities (fever, nausea, skin reaction, and weight loss; all grade 1) all disappeared within 1 month after radiotherapy.

Conclusions: Dosimetric study showed that particle therapy has advantages for thymic malignancies in sparing lungs, heart, spinal cord and esophagus compared with photon therapy, especially in low dose area. Particle therapy has more chance to deliver radical dose to bulky mass. Further clinical outcomes are expected.
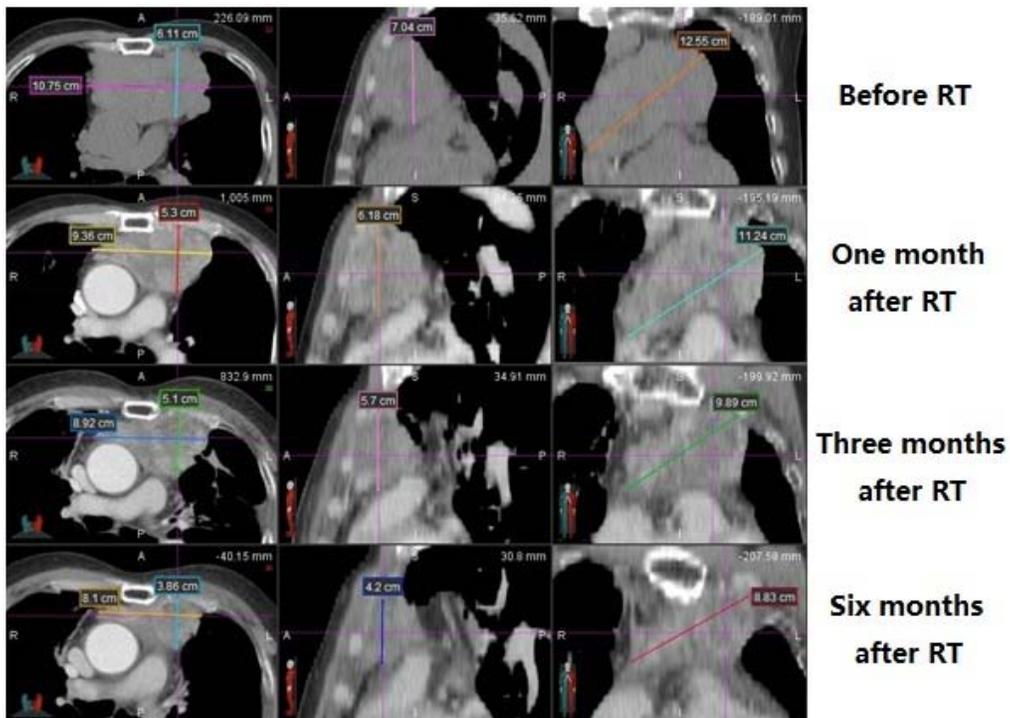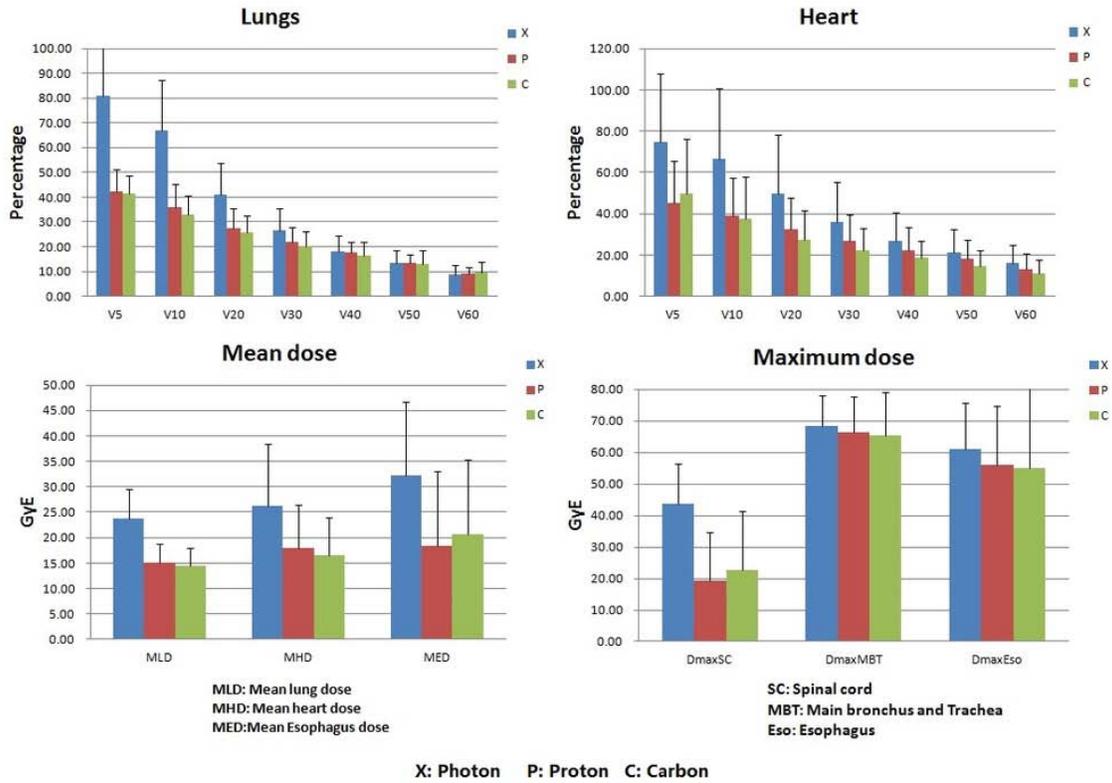
Lungs, Heart, Mean dose, and Maximum dose bar charts comparing Photon (X), Proton (P), and Carbon (C)

MLD: Mean lung dose
MHD: Mean heart dose
MED: Mean Esophagus dose

SC: Spinal cord
MBT: Main bronchus and Trachea
Eso: Esophagus

X: Photon   P: Proton   C: Carbon

Before RT

One month after RT

Three months after RT

Six months after RT

P2.05: DEFINITIVE RADIATION THERAPY FOR THYMIC MALIGNANCIES – THE MSKCC EXPERIENCE

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Introduction: The standard of care for thymic malignancies is surgical resection. Neoadjuvant or adjuvant chemotherapy and/or radiation therapy (RT) may be used in patients with advanced tumors. A small subset of patients, however, is inoperable, either unresectable because of extensive local invasion of critical organs or medically inoperable due to comorbidities. Here we sought to investigate the outcomes of inoperable patients treated with definitive RT.

Methods: We retrospectively reviewed an institutional database for patients with thymic malignancies who were treated without surgery or had surgery with gross residual disease and were treated with definitive RT. We included only patients who received a total dose of ≥4500cGy. Patients with thymoma and thymic carcinoma were included. Details about patient and treatment characteristics were collected. Local failure-free survival (LFFS), locoregional failure-free survival (LRFFS), and distant-metastases-free survival (DMFS) and overall survival (OS) were calculated using the Kaplan-Meier method.

Results: We identified 17 patients treated with definitive RT since 1988. The median age at diagnosis was 58 years (range 28 to 88 years). There were 13 thymomas (WHO subtype B1 in 3, B2 in 5, B3 in 3 and unknown in 2 patients), and 4 thymic carcinomas. All patients presented with advanced stage disease (stage III: 7; stage IV: 8; recurrent: 2). Median tumor size was 9 cm (range 4.5 to 13.7 cm). Three patients were treated with conventional fractionation using 2D, 2 with 3D, and 12 with intensity-modulated radiation therapy (IMRT) techniques to a median dose of 5940 cGy (range 4500 cGy to 6600cGy).
At the end of follow up 5 patients had died of thymic malignancy, and 5 remained without evidence of disease. Five had experienced local failures, 8 locoregional failures, and 5 distant metastases. The median OS was 6.1 years and 5-year OS 59%. Five-year LFFS was 64%, 5-year LRFFS 36% and 5-year

DMFS 61%.

Conclusions: Definitive RT can result in long-term survival even in a very advanced patient population.

Keywords: Unresectable, Definitive Radiation Therapy, thymoma

P2.06: METASTATIC THYMIC EPITHELIAL TUMORS : A CLINICOPATHOLOGICAL STUDY

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Background: Thymic epithelial tumors (TET) spread along lymphatic and/or hematogenous routes in a small percentage of Thymoma and more commonly in Thymic carcinoma cases. The rarity of metastases of TET poses diagnostic difficulties. The differential diagnosis might include epithelial, mesenchymal or haematolymphoid neoplasms. Moreover, unless they present at time of diagnosis, metastases specifically of thymoma often occur after a long disease-free interval, and the clinical information available to the clinician and pathologists could be scant or null. To increase the complexity, ectopic thymic tissue may occur, particularly along the embryonal route followed by primordial cells/thymic anlage, and TET may occur in ectopic sites. The knowledge about potential metastatic sites of TET is crucial to be able to diagnose these tumors correctly for proper treatment.

Methods: In the framework of the collaboration established by ITMIG, pathologists and oncologists from different Institutions searched their databases (DB) and Pathology reporting DBs for cases of metastatic TET. Only intrapulmonary, intrathoracic/non lymph nodal or extrathoracic metastases were considered. Cases were searched for over an average period of 15 years (Italian Pathologist DBs), 10 years (Clinical DB, Naples) or 16 years (Mayo Clinic Rochester). The search revealed 40 cases of metastatic TET in the Italian Pathologist's and Oncological DBs (material being available in 25 cases)

and 50 (17 thymic carcinomas, 33 thymoma) cases in the Mayo Clinic Pathology DB, respectively.

Results: Preliminary data indicated that Thymic carcinomas, through hematogeneous dissemination, often showed liver and/or bone marrow metastases. Thymoma metastases frequently occurred in lungs or or at laterocervical region lymph nodes; only few metastases occurred in other sites such as axilla, pelvis, ovary, kidney, pancreas and brain. Among WHO subtypes other than carcinomas, the B subtype appeared to give rise more frequently to metastatic disease. Metastatic thymoma were reported even 25 years after the primary diagnosis A differential diagnostic immunostain panel in cases suspicious for metastatic TET should include pancytokeratin, TdT and antibodies that might suggest thymic carcinoma, including CD5 and CD117.

Conclusions: In this multicenter study, DB's records and archival tissue biobank material of pathologically confirmed TET allowed the evaluation of metastases in a large series. This multicenter study could set the basis for subsequent characterization of biomarker expression in this subset of tumors.

Keywords: clinicopathological study, metastasis, thymoma, thymic carcinoma

P2.07: GOOD SYNDROM - A RARE PARANEOPLASTIC CONDITION IN THYMOMA PATIENTS

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Abstract: Good syndrome, first described in 1954 by Robert A Good, is a rare paraneoplastic, thymoma induced primary immundeficencie syndrome, caused by antibodies against B-cells at different stages of development and other blood cells. Immunoglobuline levels are reduced, susceptibility for bacterial, viral and fungal infections is increased. Good syndrome is frequently associated with other severe paraneoplastic disorders e.g. myasthenia gravis, alopecia areata, vitiligo, pytiriasis rosa pilaris, bronchiolitis, pneumonitis, pemphigus, total onychomadesis. Good syndrome in thymoma patients in the early phase often isundiagnosed, till severe opportunistic infections e.g. brochopneumonia, herpes and cytomegaly virus, pneumocystis carinii pneumonia, candida mucositis, gastrointestinal infection occur. Patient mostly have no mensurable numbers of B-cells in the periperal blood, defects in T-cell development and an inverse CD4/CD8-T-cell ratio We describe a group of 11 patients with thymoma associated paraneoplastic Good syndrome. All had a thymoma: (WHO-Classification AB 1x, B1 1x, B2 3x, B3 1x, B1/2 1x, B2/3 2x, 1x not exactly known), sex ratio is 1:1. in the majority of cases initial symptoms are bronchopneumonia, general weakness, anorexia, systemic infection, skin lesions, gastrointestinal infections and neurological symptoms. Additional haematological symptoms are anemia, thrombozytopenia,and agranulocytosis. Therapy of the Good syndrome is based upon replacement of immunoglobuline preparations (IgG or IgM) either iv or sc livelong, vigorous targeted treatment of all suspected infections, stimulation of granulocytes, erythrocytes and replacement of thrombocytes if indicated. It is surprising that in the case of required chemotherapy of the thymoma with PAC, blood values which were initially below normal level, improved nearly to normal. This supports the conception of the paraneoplastic, autoimmune origin of the syndrome. In general immunoglobuline therapy is not only replacement of deminished IgG but also a very vigorous immunomodulating/ immunosuppressive therapy of the autoimmune disorder. Sometimes however bone marrow stimulation with G-CSF or erythropoetin fails because granulopoesis or erythropoesis are nearly completly down regulated or even blocked. Subsequent replacement of the missing cells is nescessary till granulopoesis, thombopoesis or erythropoesis recovers from blocking. Life span is deminished, main reasons for premature death are intractable bacterial,viral or fungal infections, because anti-microbial treatment was started too late and not selective enough, iImmunoglobuline replacement was insufficient or simply diagnosis was not known or misdiagnosed.

Keywords: Good immunodeficieny syndrome, paraneoplastic disorders, thymoma associated syndroms, treatment of Good syndrome

P2.08: NON MYASTHENIC AUTOIMMUNE DISEASES ASSOCIATED WITH THYMOMA - A SINGLE INSTITUTIONAL EXPERIENCE

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Abstract: Non Myasthenia Autoimmune Disease in Association with Thymoma - A Single Institutional Experience Objectives: Thymomas are the most common mediastinal mass in adults, representing up to 50% of anterior mediastinal masses. The association between myasthenia gravis (MG) and thymoma has long been known. Besides MG, thymoma is also associated with other autoimmune diseases (AID), including pure red cell aplasia (PRCA), systemic lupus erythematosus (SLE), polymyositis, and Pemphigus. Little is known about the pathophysiology of non MG autoimmune disease and thymoma and the prognosis and follow up of patients at risk for AID after thymectomy. We reviewed 368 patients that underwent a thymectomy at our institution. The aims of the study were to evaluate both frequency and occurrence of non MG autoimmune disease in relation to the tumor course and risk factors for the occurrence of AID after thymectomy.

Methods: We retrospectively reviewed data from 368 patients that underwent a thymectomy at our institution between 2000-2016, for thymic carcinoma, thymic hyperplasia and thymoma. From this group of patients, we identified a cohort of 168 patients that had a thymectomy but did not have MG. 10 patients out of this cohort of 168 patients had a non MG autoimmune disease.

Results: Of these 10 patients, 8 patients had a non MG AID prior to a thymectomy, 1 patient had SLE, 1 had SLE and anti-phospholipid antibody syndrome, 1 had SLE and aplastic anemia, 1 had pure red cell aplasia, 1 had hashimotos thyroiditis, and 1 had sjogrens disease. 1 patient had jeuvenile polyarthiritis prior to having a thymectomy and developed atrophic gastritis after thymectomy. And 1 patient developed sjogrens disease after a thymectomy. One patient had seronegative AID with generalized constitutional symptoms (malaise, weight loss, joint pain, fever). Patient characteristics are shown in Table 1. Conclusions: A broad variety of AID, including SLE, pure red cell aplasia and thyroid disorders occurred both before and/or after thymectomy. None of the clinical or pathological features predicted the development of an AID after surgery. One patient that had an AID before thymectomy developed another AID after thymectomy and one patient did not have an AID before surgery developed an AID after thymectomy, suggesting that autoreactive T cells arising from a thymoma had been distributed to the peripheral immune system before the removal of the tumor. Interestingly one patient had seronegative AID and was symptomatic before surgery. More comprehensive studies including serological testing and genetic testing for single nucleotide polymorphisms (SNP's) are needed to better define the precise relationship between seropositive/seronegative AID and thymoma.

PATIENT CHARACTERISTICS			
Parameter	AID Before Thymectomy (*n*=8)	AID After Thymectomy (*n*=1)	AID Before and After Thymectomy (*n*=1)
Age (Years)	48 (34-72)	37	42
Sex (Female)	6	0	1
SLE Symptoms	3	0	0
Sjogren Symptoms	1	1	0
Generalized Constitutional Symptoms	1	0	0
Anti DS-DNA Antibodies	3	0	1
Anti SSRNA Antibodies	1	1	0
Anti ANA Antibodies	2	1	0
Anti Intrinsic Factor Antibodies	0	0	1
Anti Erythrocyte Antibodies	1	0	0
Resolution of Symptoms	8	0	0
Presence of Mediastinal Mass	8	1	1
VATS Thymectomy	3	0	0
Open Thymectomy	5	1	1
Complications	0	0	0

P2.09: IT IS THE PRESENCE OF PARANEOPLASTIC SYNDROME A GOOD PROGNOSTIC FACTOR IN THYMIC TUMOURS?

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Objective: The aim of this study is to describe our experience in management of thymic tumours and analyze the prognostic factors.

Methodology: descriptive and retrospective clinical and pathological data analysis of 42 patients with diagnosis of thymic tumour (thymoma, thymic carcinoma, thymic carcinoid), treated at our institution between 1990 and 2016. The analysis of progression-free survival (PFS) and overall survival (OS) is performed by Kaplan Meier and proportional hazards study with Cox regression. It was analyzed the presence of paraneoplastic syndromes, Masaoka stage, TNM staging and WHO classification as prognostic factors.

Results: Median age 55 years (27-86). Sex: 19 (45.2 %) women and 23 (54.8 %) men. WHO classification : 6 patients A (14.3%) 12 AB (28.6%) , 3 B1 (7.1%) and 7 -B3 B2 - C (16.7%) . 17 patients (40.5 %) were diagnosed at stage I Masaoka . 25 patients (59.5 % presented a paraneoplastic syndrome at the time of diagnosis ; 21 patients (50 %) with myasthenia gravis and 2 (4.76%) with aplastic anemia . The presence of paraneoplastic syndrome was higher in stage I (56%) and a better OS was correlated too with the presence of pananeoplastic syndrome (296 vs 66.5 months ; p .006 ; HR 0076) . In the analysis of PFS and OS it is significantly higher for patients with thymoma vs thymic carcinoma (PFS : 21 vs 89 months , p 0.036 ; OS: 239 vs 66 months ; P 0.000) .

Conclusions: The presence of paraneoplastic syndrome is more common in early stages and may be related with improved diagnosis and overall survival.

P2.10: THE UNEXPLORED PARADOX OF AUTOIMMUNITY AND IMMUNODEFICIENCY IN THYMOMAS: A MONOCENTRIC EXPERIENCE

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Background: The association between thymoma and severe alterations of the immune system is well known, although the pathogenesis remains unclear. The most common autoimmune thymoma related disease is myasthenia gravis (MG), with an incidence rate of 30–46%. A less common parathymic disease with an incidence rate of 5%, is Good Syndrome (GS), characterized by hypogammaglobulinemia and combined B and T cell immunodeficiency. The coexistence of autoimmunity and immunodeficiency added to the sequelae of treatments for tumour control such as surgery, radiotherapy and chemotherapy, causes life-threatening problems in the management of these patients, who require high expertise and multidisciplinary program that, up to date, are still lacking.

Methods: We conducted a retrospective analysis of thymoma patients with related immune disorders referred to the Rare Tumours Reference Center of University Federico II of Naples over a 10-year period. All the patients with GS diagnosis complicated by at least another immune alteration were evaluated for this report. Immunological features, histopathological diagnosis, additional malignancies and clinical outcome were registered. Results A total of 41 patients were identified, including 17 patients with a local disease (stage I-II according to Masaoka-Koga stage system) and 24 with an advanced disease (stage III-IV). 56.3% had a B2 thymoma. 23 cases presented with two immune disorders, 18 with three or more. The most common autoimmune disease was MG, diagnosed in 29 patients. In 90% MG required immunosuppressive drugs for more than one year. Plasmapheresis was not performed. Pure red cell aplasia (PRCA) was diagnosed in 12 patients and treated with high dose corticosteroids and oral cyclosporine. Only two non-responders patients received more aggressive immunosuppressive treatment such as alentuzumab and tacrolimus. Less common autoimmune diseases detected in this series were thyroiditis, lichen and Systemic Lupus erythematosus. Kaposi sarcoma, an immuno-related tumour, was seen in 2 patients. 35 patients died for severe infectious disease after prolonged hospitalization including viral pneumonitis, encephalitis, myocarditis and sepsis. Only 2 patients died for the autoimmune diseases, specifically, one patient with MG died for respiratoty

arrest and one with PRCA for evolving medullary aplasia. The estimated median overall survival time of all patients was 72 months. 6 patients are still alive.

Conclusion: The management of parathymic syndrome is still challenging. In this analysis of a 10-year period, Good syndrome has been diagnosed in 41 patients, highlighting that immunologic investigations, T cell subsets, B cell, and quantitative immunoglobulins should be considered a part of diagnostic search in patients with thymoma. Clinical outcomes depend on the severity of infections, associated hematologic and autoimmune diseases rather than the thymoma itself. The possible fatal infectious diseases in patients with both autoimmune condition and Good Syndrome treated by immunosuppressive agents, require high expertise and multidisciplinary program.

Keywords: Good syndrome, thymoma, autoimmune disease, high expertise

P2.11: ACTIVITY AND SAFETY OF ORAL ETOPOSIDE IN PRETREATED PATIENTS WITH METASTATIC OR RECURRENT TETS

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Objectives: Standard regimens in pretreated advanced TETs are lacking. Single agent responses have been reported with pemetrexed, gemcitabine and targeted therapies. Oral etoposide monotherapy has a favorable safety and efficacy profile in other tumor types. We assessed its activity and safety in advanced or recurrent pretreated TETs.

Methods: We conducted a retrospective analysis of patients with advance or recurrent TET treated with single agent oral etoposide at Gustave Roussy (GR) between 1992 and 2015. Data were collected from medical records. Efficacy was analyzed according to RECIST. Kaplan-Meier method was used to estimate progression-free survival (PFS) and overall survival (OS). Adverse events were assessed using NCI-CTCAE.

Results: Twenty patients were included. Median age was 62 years [range 34 - 88], 60% were male, 75% had thymic carcinoma (TC) and 25% had thymoma (T). Myasthenia gravis was reported in 15% of the patients. A median of 2 [range 0 – 7] prior chemotherapy regimens had been administered, with 60% exposed to etoposide (VIP 40%, carboplatin-etoposide 15%, BEP 5%). Median follow-up since etoposide introduction was

7 years [range 0.5 - 8.9]. Three of 18 evaluable patients achieved partial response and nine had stable disease, giving an overall response rate of 17% [T: 20%, TC: 16%] and a 67% disease control rate [T: 100%, TC: 54%]. Median PFS was 4 months [95%CI 3 - 14] and median OS was 41 months [95%CI 6 - 86]. Median PFS for T and TC were 21 months [95%CI 9 - 42] and 4 months [95%CI 2 - 4]; median OS were 99 months [95%CI 43 – not reached] and 13 months [95%CI 4 - 41], respectively. The most common grade 3-4 related events occurred in 9 patients (45%) and were neutropenia followed by anemia and thrombocytopenia.

Conclusion: Oral etoposide monotherapy is an active option for pretreated TET patients, with a manageable toxicity profile.

Keywords: TET, Metastatic, recurrent, Oral etoposide

P2.12: PROGNOSTIC IMPACTS OF ADJUVANT THERAPIES ON THYMOMA AND THYMIC CARCINOMA: A META-ANALYSIS

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Abstract: Adjuvant radiotherapy, chemotherapy or chemoradiotherapy have been administered to thymoma (TA) and thymic carcinoma (TC) since 1980s, however, their prognostic impacts remained controversial. Therefore, we performed a meta-analysis of published data to enhance the statistical power to demonstrate the effects of adjuvant therapies on the overall survival (OS) and disease-free survival (DFS) of patients with TA or TC. Studies in PubMed, Web of Science, Embase, the Cochrane Library and the Chinese Biomedical Literature Database that published before June 2016 were traced. A total of 18 studies with 8736 TA and 2162 TC patients were included in the meta-analysis. In general, adjuvant therapies are correlated with increased DFS (HR 0.74, 95%CI 0.58-0.94), but have no significant impact on OS (HR 0.81, 95%CI 0.65-1.01) of thymic tumor. In subgroup analysis, adjuvant radiotherapy is linked with improved DFS (HR 0.50, 95%CI 0.39-0.62) but not OS of TC; yet, adjuvant chemoradiotherapy was associated with the better OS (HR 0.58, 95%CI 0.35-0.96) of TC. Additionally, adjuvant therapies are correlated with favorable OS among TA patients at Masaoka staged II-III, or with R0 resection; and adjuvant chemoradiotherapy but not radiotherapy is related with increased OS (HR 0.60, 95%CI 0.46-0.79) of TA, however, no any positive result is yielded from the limited studies with DFS outcomes. In conclusion, the meta-analysis results suggest that chemoradiotherapy rather than radiotherapy acts as a potent adjuvant intervention for both TA and TC patients. However,

because of the limited number of studies concerning patients in different pathological stages included, the results should be further identified by well-designed prospective studies.

Keywords: Adjuvant therapy, Thymic malignancy, Overall survival, Disease-free survival

P2.13: MULTIMODAL TREATMENT OF ADVANCED STAGE THYMOMA: AN ITALIAN EXPERIENCE

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Objective: The optimal treatment for advanced stage Thymoma (AST) is still controversial. Complete resection (R0) has been shown to critically influence overall survival (OS) and recurrence development. Preoperative induction therapy (IT) has increased R0 and OS. The aim of this study was to evaluate the effect of IT treatment offered to primarily unresectable ATS.

Methods: This is a retrospective, multicentre study of unresectable patients with ATS treated between 2000 and 2014 in 4 Italian Institutions. Thymic Carcinomas were excluded. All patients were discusses at the local Multi-disciplinary Team (MDB). Tumor's upfront unresectablity was judged by surgeons on the basis of radiological imaging and local tumor's invasiveness. All patients had pre-treatment histological confirmation. The primary study end-points were OS and Cumulative Incidence of Recurrences (CIR); both were calculated using the Kaplan-Meier method. Differences in OS and CIR were assessed by the log rank test.

Results: A series of 38 ATS patients (Stages III-IVa) (22 males, 58%, mean age 55 years) were treated in 4 different Italian Institutions. Table 1 shows the patients characteristics. Pretreatment tumor biopsy was achieved in all; core biopsy (14 cases) and anterior mediastinotomy (15) were the most common procedures used. Tumor resection was performed through a sternotomy in 35 cases, a posterolateral thoracotomy in 1 and a combined approach in 2, respectively. After IT, 22 patients (58%) were Stage III, and 16 Stage IVa. R0 was achieved in 27 patients (87%). Overall 5 and 10-y survival were 74% and 65%, respectively. No significant difference in OS were observed for Stage III and IVa patients (Figure 1 A). Postoperative therapy (predominantly radiotherapy-RT-) was offered to 21 patients. Five-year CIR was 0.19; CIR significantly increased in Stage IVa Thymomas (P=0.026) (Figure 1 B).

Conclusions: Our results confirm, in a large cohort of patients, that a multimodal approach to primarily unresectable AST seems to increase OS and the chance to achieve a complete resection. CIR was statistically higher in Stage IVa Thymomas, even after adjuvant treatment. Future multicenter International randomized clinical trials are warranted to confirm those findings.
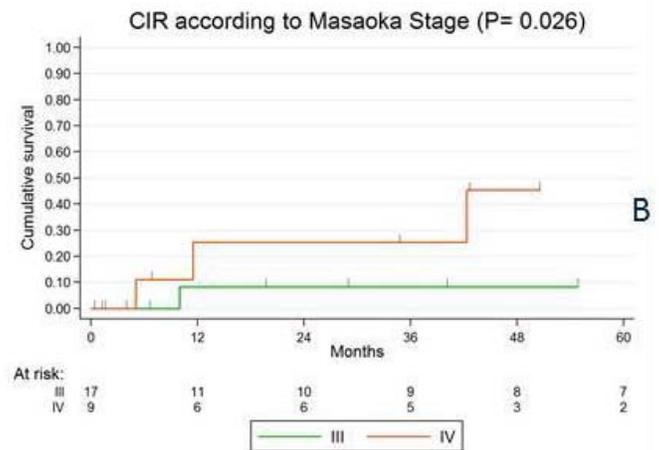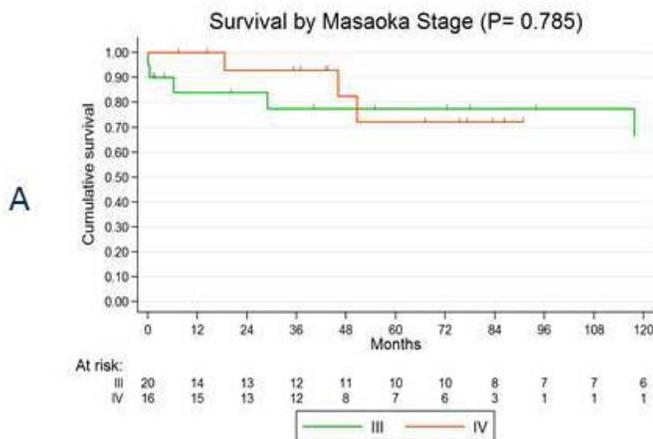
	Neoadjuvant CT	%
gender		
male	22	58
female	16	42
Symptoms/presentation		
asymptomatic	8	
autoimmune symptoms	4	
cough/dyspnea	8	
fatigue	5	
SVC syndrome	4	
other	9	
WHO histology		
A	1	3
AB	5	13
B1	3	8
B1/B2	2	5
B2	8	21
B2/B3	10	26
B3	5	13
other mixed forms	4	11
Masaoka-Koga stage		
III	22	58
IVa	16	42
Resection status		
R0	27	87
R1+R2	11	13
Invaded structures		
aorta	1	
lung	11	
SVC	11	
pericardium	6	
diaphragm	1	
other	7	
Adjuvant treatment		
none	16	
CT/RT	21	

P2.14: NEO-ADJUVANT PLATINUM BASED CHEMOTHERAPY IN LOCALLY ADVANCED THYMIC CARCINOMA

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Background: Thymic carcinoma is a rare malignant tumor. At present, cisplatin based doublet or triplet antitumor drugs are used in neo-adjuvant setting for advanced thymic carcinomas. However, no optimal chemotherapeutic regimen is well established and recent small case studies with carboplatin and paclitaxel doublet demonstrates the similar efficacy with less toxicity. We retrospectively evaluated effectiveness and toxicity of platinum based doublet chemotherapy for patients with advanced thymic carcinoma.

Methods: Between 2001 and 2011, we retrospectively identified 21 patients from hospital information system with pathologically confirmed advanced thymic carcinoma, who were treated with platinum based doublet chemotherapy followed by surgical resection. The most commonly used regimen being carboplatin plus docetaxel in 65% of the patients. Other regimens included cisplatin plus gemcitabine, carboplatin plus gemcitabine and cisplatin plus doxorubicin plus cyclophosphamide.

Results: The clinical response rate was achieved in 61.5 % of the patients. The disease control rate was achieved in 92% of the patients. The median progression-free survival was 7.9 months (95% CI 1.3–10.0) and median overall survival was 33.8 months (95% CI 8.3–45.9). The toxicity profiles of platinum doublets demonstrated grade 3-4 hematological and non-hematological toxicities in 18% and 24% of the patients respectively. No febrile neutropenia and toxic death was recorded.

Conclusion: We concluded that platinum doublet chemotherapy is active and tolerable for advanced thymic carcinoma in the front-line setting with regard to efficacy, toxicity, and usage in clinical setting.

Keywords: thymic carcinoma, neoadjuvant, platinum

P2.15: CLINICAL OUTCOMES FOR STAGE-IVB THYMIC SQUAMOUS CARCINOMA OF 48 CASES

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Purpose: The objective of this article is to retrospectively analyze the clinical survival of Ivb squamous thymic carcinoma.

Materials and Methods: We enrolled 48 patients of IVb squamous thymic carcinoma who were treated in our hospital from January 2008 to December 2014. There were 33 male and 15 female, mean age of 54 years (range 11-73). Thirty-five patients were diagnosed with lymph node metastasis (LM group), while five patients also with lung dissemination and two with bone metastasis. Distribution of metastasis sites when diagnose were lung (16 patients, 33%), bone (4 patients, 8%), lymph node (35 patients, 73%) and liver (2 patients, 4%). Twenty-nine patients were treated with surgical resection (surgical group), in which 22 were with lymph node metastasis and 7 were with oligo-metastatic lung or liver disease. Chemotherapy was performed in 40 patients and radiotherapy was performed in 42 patients.

Results: The median follow-up period from patients' first time diagnose was 30 months (7–66 months). Five-year overall survival rate was 12%, respectively. Five year OS for the surgery group was 12% while 16% for the non-surgery group (p=0.12). Five-year OS was 8% for the LM group and 33% for the NLM group (p=0.80). Three-year PFS was 9%. In the LM group, the OS rate was 12% for those patients who received operation while 0% for nonsurgical group (p=0.03)

Conclusion: Patients of IVb stage squamous thymic carcinoma were aggressive. Even patients with oligo lymph node metastasis had with poor overall survival. Surgical resection may lead to more favorable outcomes for IVb stage thymic carcinoma with lymph node metastasis.
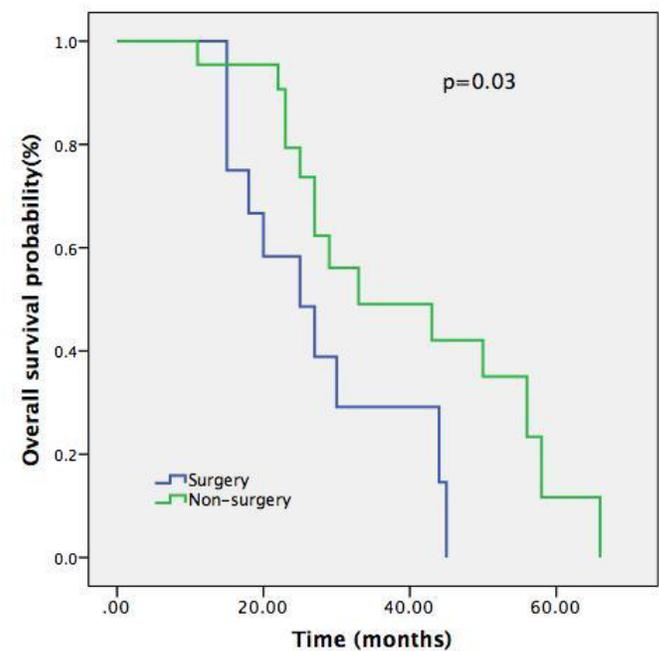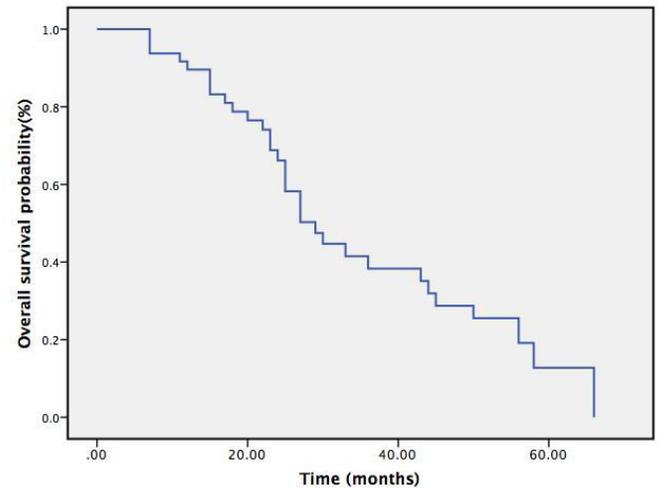
Keywords: Masaoka stage IV, thymic carcinoma

P2.16: THE EVOLVING ROLE OF SUNITINIB IN THE MANAGEMENT OF HIGHLY PRE-TREATED THYMIC CARCINOMA

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Background: The clinical management of thymic carcinomas, characterized by aggressive behaviour and poor prognosis, remains very challenging. The activity of sunitinib has been recently confirmed showing that tyrosine kinase inhibitors represent a novel strategy for the treatment of these rare malignancies. We performed a retrospective analysis of all patients with highly pre-treated thymic carcinoma who received sunitinib in an off-label modality.

Methods: Patients with highly pre-treated metastatic thymic carcinoma seen at the Rare Tumours Reference Center of University Federico II of Naples between January 2012 and February 2016 were identified. Only the patients who received sunitinib in the third line setting and beyond were included in this retrospective analysis.

Results: A total of 8 thymic carcinoma patients with a median age of 58 years (49-66) and a female:male ratio of 1:1 were identified, of whom 5 received sunitinib as 3rd line treatment, 2 as 4th line and 1 as 5th line. Sunitinib was firstly administered in all patients as the standard schedule of 50 mg daily, in 6-week cycles (4 weeks of treatment followed by 2 weeks without treatment). Sunitinib side effects were all manageable and tolerable, only one patient after 3 months of treatment, despite the clinical improvement of pain and dyspnea decided voluntarily to stop the treatment for fatigue G2. A dose reduction at 50 mg 2 weeks on/2 weeks off was made in 4 patients due to diarrhea G2 and thrombocytopenia G1. In the overall population, disease control rate was of 100%, overall response rate was 100% (3 patients achieved partial response, 5 patients stable disease). Median PFS in the whole population was 9 months (95% CI, 3-12 months). Six patients are still alive, of whom three are still on treatment with sunitinib. One patient has not yet reached the disease progression after 23 months of treatment. Conclusions: This small retrospective monocentric study shows sunitinib effectiveness for prolonged control disease in thymic carcinoma, despite the number of previous treatments. A personalized dose reduction can be used for managing highly pre-treated thymic malignancies with a low toxicity profile. Tyrosine kinase inhibitors with anti-angiogenic activity should be included routinely in the strategy for the treatment of refractory disease.

Keywords: sunitinib, thymic carcinoma, refractory disease, personalized schedule

P2.17: PLATINUM BASED CHEMOTHERAPY IN ADVANCED THYMIC EPITHELIAL TUMOURS: ALWAYS THE BEST CHOICE?

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Background: Standard chemotherapy for advanced thymic epithelial tumours (TETs) remains controversial due to the limited amount of available therapeutic evidence. The treatment choice is mainly based on few single-arm phase II trials and retrospective analyses with small numbers of patients. Up to date, there is a high consensus that the more effective drugs for the treatment of thymoma (T) are platinum and anthracycline, that can be basically used also in the setting of thymic carcinoma (TC), despite data regarding the responses reached in each histotype of TETs are widely lacking. In this retrospective study we highlight the need of a histology driven first line therapy in TETs.

Methods: In this monocentric retrospective analyses, data regarding first line platinum based chemotherapy in advanced TETs seen at the Rare Tumours Reference Center of University Federico II of Naples during a 10-year period, were analysed. The end point was the response rate to first line chemotherapy, comparing T with TC and B1-B2/B1/B2 with B2/B3-B3 T. Histotype and stage disease were assessed according to WHO 2004 classification and Masaoka-Koga staging system, respectively. RECIST criteria 1.1. were used for the evaluation of response disease. Results Thirty-four patients were identified, including 25 T and 9 TC. 29 patients received CAP (cyclofosfemide-cisplatin-anthracycline) schedule chemotherapy, 1 patient unsuited for anthracycline, had carboplatin-etoposide chemotherapy, the last 4 patients were treated with platinum-taxanes based schedule. The response rate was globally 44.11%. Specifically, response rate was 55.55% and 40% for TC and T respectively. Among T: B1-B2-B1/B2 T had a response rate of 25% while B2/B3-B3 T reached a response rate of 53.8%.

Conclusion: The key drugs for the treatment of thymic malignancies remain platinum and anthracycline although, in our small monocentric experience, there is a high rate of tumours that progressed after first line chemotherapy. The histotypes largely recognized as less aggressive seem to be less responders to platinum-anthracycline therapy. Further study are needed to predict the TETs platinum chemosensitivity and to define histology driven first line therapy.

Keywords: first line chemotherapy, histology driven, anthracycline, platinum

P2.18: PROPOSED PARADIGM FOR THE SECOND LINE TREATMENT IN THYMIC EPITHELIAL TUMOURS

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Background: Second line therapy for refractory thymic epithelial tumours (TETs) usually includes etoposide, ifosfamide, pemetrexed, octreotide, prednisone, 5-fluorouracil, gemcitabine, and paclitaxel, however, due to the rarity of these malignancies, prospective trials comparing the different agents in the literature are lacking and a decision making process has not yet been defined. In this retrospective analysis we stress the useful role of functional imaging in second line treatment choice.

Methods: Patients with progressed TET after first line platinum-based chemotherapy seen at the Rare Tumours Reference Center of University Federico II of Naples over a 5-years period were identified, and those who performed 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and 111In-octreotide SPECT (Octreoscan) before starting second line treatment, were included in this analysis. As for local clinical practice, the decision making of second line therapy was long acting somatostatin analogues (SST) (LAR Octreotide 30 mg/4weeks) plus prednisone (0.2 mg/Kg daily) in OctreoScan positive patients. A second line chemotherapy according the CAP-GEM schedule (capecitabine 650 mg/m^2 b.i.d. 14 days; gemcitabine 1000 mg/m^2 day 1,8 every 3 weeks) was administered in

OctreoScan negative patients. Response rate (RR), median time to progression (TTP) and toxicities were evaluated.

Results: Twenty-three patients including 8 thymic carcinoma (TC) and 15 thymoma (T), were identified. 18 patients, received LAR-SST plus prednisone, obtaining stable disease in 10 patients; partial response (PR) and progressive disease (PD) was registered in 5 and 3 patients, respectively. Reaching a median TTP of 12 months (95% CI, 3-84), a very tolerable toxicity profile was seen, with one case of hyperglycemia G1 and two of cholelithiasis G2. CAP-GEM chemotherapy was administered in 5 patients, obtaining partial response and progressive disease in 3 and 2 patients, respectively. A median TTP of 9 months (95% CI, 4-18) was achieved. Regardless the histotype, all the patients progressed to second line treatment presented with a high 18FDG uptake at the PET-CT scan baseline evaluation.

Conclusion: In our experience, functional imaging can play an important role to identify the best second line treatment in progressed TETs.

Keywords: functional imaging, second line treatment, somatostatin analogues, capecitabine

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