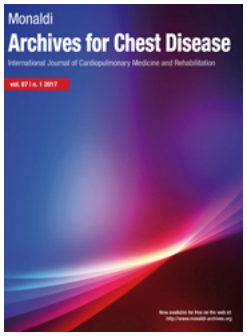

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Histopathological assessment of thymoma based on the World Health Organization 2021 classification with emphasis on transcapsular invasion: experience from a tertiary care center

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Contributions: SB, RM, conceived the idea, drafted the manuscript, and reviewed the histopathological diagnosis in all cases; SRB, conducted all clinical analyses and provided clinical data; SB, RM, SRB, critically revised the manuscript for important intellectual content. All authors contributed significantly and agree with the content of the manuscript. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Informed consent: waiver for informed consent was obtained from the Institutional Ethics Committee, since the current research involved already submitted tissue blocks, and no additional samples were procured from the patient. The manuscript does not contain any individual person's data in any form.

Patient consent for publication: This a retrospective study conducted over a period of 11 years where previously submitted tissue blocks were used and no fresh samples were obtained. Since the data is anonymized and the ethics committee has waived consent, additional patient consent for publication is not required.

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Abstract

Histological classification and staging are crucial in the management and prognostication of thymoma. With different staging systems used, the significance of transcapsular invasion is debatable, especially in light of pathological tumor-node-metastasis (pTNM) staging (American Joint Committee on Cancer, 8th edition). The objective of this study was to analyze the histological subtypes, transcapsular invasion, and clinical outcome of thymoma with regard to the World Health Organization (WHO) 2021 classification.

This retrospective study included all thymectomy specimens diagnosed as thymoma over a period of 10 years, from 2013 to 2023. Clinical details and histopathology slides were reviewed and histologically subtyped as per the WHO 2021 classification. Transcapsular invasion was assessed, and pTNM and modified Masoka staging were done. Descriptive statistics were used to summarize data.

A total of 45 thymoma cases were identified; two with extensive infarction were excluded. The mean age was 46.5 years (range 25-68 years); in this study, there were 28 males and 15 females with a male-to-female ratio of 1.8:1. Myasthenia gravis was the presenting feature in 31 (72.9%) cases. B2 and B3 subtypes constituted half of the cases (22/43), with mixed patterns in 4 (9.3%). A total of 9 cases showed macroscopic invasion, 80% being the B3 subtype, and out of the 23 cases that showed transcapsular invasion, the three most common subtypes are listed here, with B3 being the most common, followed by AB and B2. Masaoka staging showed 11 (25.5%) stage I, 22 stage IIa (51.1), 6 stage IIb (13.9%), 1 stage III (2.3%), 2 stage IVa (4.6%), and 1 stage IVb (2.3%). Follow-up available in 38 out of 43 cases (range 4-127 months) showed recurrence in one case of the B3 subtype, stage IVb. None of the stage I and stage II (as per Masoka staging) patients had recurrence. The Masaoka stage is a widely used staging system where transcapsular invasion is an important parameter for upgrading stage I to stage II. However, in the present study, Masaoka stage I and II patients had no recurrence, questioning the significance of capsular invasion for staging. Accurate histological subtyping in thymoma is challenging but can be achieved by adherence to the morphological criteria of the WHO 2021 classification.

Key words: histological subtype, morphology, prognosis, staging, capsular invasion.

Introduction

Thymomas are epithelial tumors of thymus with a reported incidence of 0.13 to 0.26 cases per 100,000 population every year [1,2]. Though these tumors are rare, they account for approximately 20-30% of the total antero-superior mediastinal tumors [1,3]. Thymic epithelial tumors include thymoma, thymic carcinoma and neuroendocrine neoplasms. Thymomas are most common among these accounting for 75-80% of tumors. They are mainly seen in fifth to sixth decade, rarely in children and have a slight female preponderance. Thymomas are frequently associated with autoimmune diseases, most commonly myasthenia gravis. Patients with thymomas are three to four times higher risk of developing synchronous malignancies [4]. Histological subtyping and staging are crucial in management and prognostication of thymomas [1,5,6]. Histologically thymomas are subtyped into five broad groups Type A, AB, B1, B2 and B3 based on morphological criteria defined by WHO for each subtype. The new protocol recommends to report thymoma with mixed patterns (more than one histological subtype) as the predominant component and the minor component (in increments of 10%) [3].

The modified Masaoka Koga staging system is the traditional staging system, first developed in 1981 with further amendment in 1994 and is till date a widely used staging system. This system takes into consideration the assessment of capsular invasion and invasion of adjacent structures [7]. A paradigm shift was seen in the staging of thymoma from traditional Masaoka-Koga system to TNM system by AJCC committee in January 2018. The AJCC staging is based on the proposal by the International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancy Interest Group (ITMIG) that is founded on the analyses of an international database with 10,808 patients from 105 sites [8,9]. The significance of transcapsular invasion in thymoma is debatable especially in the light of pTNM staging system in AJCC 8th edition [10-12].

Modern oncology practice relies on accurate pathological and clinical data. Though lot of progress has happened to bring uniformity in histopathology subtyping and staging of thymoma, relevance of some of these parameters in prognosis and management is not very clear, hence leading to subjectivity in reporting and different treatment protocols being followed. The TNM stage is already in existence since 2018, and lumps Masaoka stage I, II, part of III as TNM stage I, thereby questioning the clinical relevance of histopathological reporting of invasion of capsule, mediastinal fat and mediastinal pleura. The present study aims to understand the histomorphological subtypes of thymoma in detail based on the

morphological criteria given in WHO 2021 classification. Also we aim to study transcapsular invasion, which is a component of the traditional Masaoka staging and assess its role as a histolopathological parameter in thymoma.

Materials and Methods

Study design and population

This is a retrospective descriptive study. All cases diagnosed as thymoma on thymectomy specimens at Dept. of Pathology over a period of eleven years, from 2013 to 2023 were enrolled in the study. Exclusion criteria: cases of thymoma diagnosed on core biopsies, thymic epithelial tumors (other than thymoma),thymectomy specimens with no residual viable tumor (extensive sclerosis/infarction/post CT/RT), cases where slides & blocks were not available.

Data collection

The Laboratory information system (LIS) was reviewed to identify patients with a diagnosis of thymoma from January 2013 to December 2023 who have undergone thymectomy. The cases were studied retrospectively from the time of diagnosis of thymoma (clinical/histological) till the end of study period. Histopathology slides and immunohistochemistry slides (wherever available), of each case were retrieved from the archives of Pathology department and reviewed. Histopathological subtyping and transcapsular invasion was studied in each case. Tumors were divided into five main subtypes (A, AB, B1, B2 and B3) and mixed patterns (*Supplementary Figure 1*). Transcapsular invasion was analyzed in each case and Modified Masaoka Koga and pTNM staging was performed. Tumors with fibrous capsule of variable thickness and tumors that invade into, but not through, the capsule were considered encapsulated. Invasion of adjacent structures (pleura, pericardium, and lung) was also assessed.

Additional parameters recorded were tumor size, presence of medullary like areas/Hassall corpuscles, perivascular spaces, background lymphoid hyperplasia, LVI, surgical margins. Regional lymph node status was assessed, wherever available. The clinical details (like age, sex, associated paraneoplastic syndrome) were noted from the patient medical records. Follow up was done for each case from the time of diagnosis till the end of study period. Cases in which follow up data was not available (lost to follow up or death) were excluded from the survival analysis.

All clinical and histopathological parameters were recorded and statistical analysis was performed using SPSS version 25.0.

Statistical analysis

Categorical variables were presented in the form of number and percentage (%). Quantitative data with normal distribution were presented as the means ± SD and the data with non-normal distribution as median with 25th and 75th percentiles (interquartile range). The data normality was checked by using Shapiro-Wilk test. The cases in which the data was not normal, we used non parametric tests. Association between the quantitative variables was studied using Kruskal Wallis test and ANOVA test. For qualitative variables, Chi-Square test was used. Kaplan meier survival analysis curve was used for survival analysis and log rank test was used for comparison. p value of less than 0.05 was considered statistically significant.

Results

A total of 74 thymectomy specimens were submitted to Pathology department over the study period. Out of 74, 45 were diagnosed as thymoma. After excluding two cases with extensive infarction and no residual viable tumor, a total of 43 cases were enrolled in the present study. A male preponderance was noted (28 males, 15 females) with a male to female ratio of 1.8:1. The Age distribution varied from 25 to 68 years. Summary of clinical and histopathological characteristics is given (Table 1).

Gross findings

Tumor size has no significant association with histological subtype or stage of tumor (Figure 1).

Histopathological findings

The most common histological subtypes were B2 and B3 (22/43 cases; 51.1%) Mixed histological patterns (B2+B3) were observed in 4/43cases (Figure 2).

Type A/AB thymoma

The most common patterns of cell arrangement observed in Type A/AB thymoma were fascicular and storiform patterns (Figure 2A). The epithelial component was purely

spindle/plump shaped with moderate to dense lymphocyte density in Type AB thymoma (Figure 2B). Atypical features like hypercellularity, bizarre nuclei, necrosis or atypical mitosis were not identified in any of these cases. Perivascular spaces were observed in 16.2% (7/43) cases (Figure 2C).

Type B (B1-B3) thymoma

Type B1 and B2 thymoma looked blue while type B3 thymoma had a pink look on scanner view. The epithelial component was seen in the form of cells with round vesicular nuclei, clear chromatin and conspicuous central nuclei. B3 thymoma showed tumor cells in syncytial pattern, with one of the cases showed moderate to marked nuclear pleomorphism with pushing margins at the invasive front (Figure 2D,F).

Medullary like islands were noted in AB, B1 and B2 thymoma. Other regressive changes like presence of cholesterol clefts, foamy macrophages, extensive sclerosis and cystic change were also noted, but had no statistically significant association with any of the subtypes.

Transcapsular invasion in thymoma

23 cases showed microscopic transcapsular invasion through the capsule (53.49%) and nine cases has macroscopic/gross invasion into the peri-thymic fat (20.9%) (Figure 3).

Correlation of histological subtype with stage and other clinical/histomorphological parameters

Histological subtypes correlated well with the clinical stage (Modified Masaoka Koga and pTNM stage). Patients with type A and AB thymoma predominantly had lower clinical stage while patients with type B1-B3 and mixed pattern thymoma had higher clinical stage (Table 2 and *Supplementary Figure 2*).

Outcome and survival analysis

Follow up was available in 38 out of 43 cases. Survival analysis was done in 38 cases. 31 out of 38 patients (81.58%) were alive at the end of study period, while 7 (18.42%) patients had died (*Supplementary Figure 2*). Out of seven deaths, four deaths were attributed to myasthenic crisis, and in remaining cases, cause of death was not known. The median time to death was 4.5 months post surgery, with no significant association with histologic subtype or stage of the disease.

Recurrence was observed in only one case of Type B3 thymoma (1/38; 2.7%) which was Masaoka Stage IVb, with tumor involving pulmonary parenchyma. Patient defaulted the radiotherapy treatment and four years later, presented with pleural and pulmonary nodules, histologically confirmed as recurrence.

Kaplan Meier survival analysis curve showed no difference in overall survival between Masaoka Koga stage I and stage II patients (*Supplementary Figure 2*). Among the nine participants in Masaoka Koga Stage I, no events were observed, resulting in 100.00% overall survival at three, five years, and at the end of the study. In contrast, among the 25 participants in Stage IIA + IIB, five events (death) occurred, leading to overall survival rates of 87.16% at three years and 69.73% at five years and at the study's conclusion. The p-value of 0.188 suggests no statistically significant difference in overall survival between the two stages based on log rank test.

Discussion

Thymomas are uncommon malignancies which show morphological heterogeneity, thus making accurate histological subtyping difficult. Most of the studies defining the histological parameters and staging in thymomas are based on western literature. Few studies from India have assessed the clinic-pathological features of thymoma [13-16].

Global studies show a slight female preponderance over males for thymoma, however most of the Indian literature has shown a male predilection for thymic epithelial tumors [4,16-20]. In our study also we saw a male preponderance towards thymoma. Thymomas are common in 5^{th} and 6^{th} decades of life with a median age of 48 years and rarely seen in children. Our data showed a wide variation in age group from 25 to 68 years with a median age of 46 years.

Autoimmune disorders develop in thymoma in 30-50% cases either in pre or post–operative period. Most commonly associated disease is Myasthenia gravis, which was also seen in a high number in our study (72% patients). Thymoma derived autoreactive T cells and defective T helper regulatory cells are proposed factors behind this association [21,22].

Importance of histological subtyping?

Clinical stage, resection status and histological sub-class of thymoma are considered as important predictors of prognosis. The role of histological subtype as an independent predictor of prognosis and survival is controversial with a few studies showing significant 10

year disease free survival rate reduction from subtypes A, AB to B3 [23,24]; however some of the studies show shown a contrary result with no statistically significant association of DFS among the subtypes A and B [25,26]. Our study showed statistically significant association between the histological subtype and clinical stage, with type A and AB thymoma predominantly in lower clinical stage while type B1-B3 and mixed pattern thymoma in higher clinical stage.

Another criticism faced by histological subclassification is the reproducibility of the various subtypes among the pathologists. Recent WHO classification of thymoma has made an attempt to make the morphological criteria more objective by defining various cut-offs like three or more epithelial cell clusters in B2 subtype and use of Tdt immunostain to subclassify type A from type AB thymoma [4].

Type B thymoma

Type B2 and B3 were the most common subtypes in our study. Clustering of thymic epithelial cells (three or more cells) with lack of medullary like areas is seen in B2 thymoma. Cases with thick sections or staining problems can lead to ambiguity in diagnosis. Use of immunomarkers like CK can highlight those clusters (*Supplementary Figure 3*). Meshwork of epithelial cells as highlighted by cytokeratin is delicate in type B1 thymoma and is most dense in type B3 thyoma. Type B3 thymoma are distinguished from type B2 thymoma by lesser density of lymphocytes and arrangement of thymic epithelial cells in syncytial sheets imparting a pink looking appearance at low power in B3 thymoma.

Type A and AB thymoma

Type A thymoma are easier to diagnose in resection specimens They can be challenging in smaller biopsies as it requires exclusion of other spindle cell neoplasms of mediastinum and requires panel of IHC. Atypical Type A thymoma might be difficult at times to distinguish from type B3 thymoma with spindle morphology. This difficulty is yet to be addressed in the WHO classification of thymoma.

Cases where B like areas are intermingled, may be overlooked and mis-classified as type A thymoma. Careful relook at morphology and ancillary testing using Tdt immunostain can help classify such cases into subtye AB.

Transcapsular invasion and clinical stage

Masaoka Koga staging system [7,27] is still one of the most followed system worldwide until recently with the TNM staging system (AJCC 8th edition) being introduced in 2018 [8-9,28]. Till date, several staging systems proposed for thymoma took into account tumor capsule and invasion. Oncological implications of these staging systems have always been a matter of debate. In the present study, we tried assessing the role of transcapsular invasion and challenges faced, as a histolopathological parameter in thymoma. Our study is one the few Indian studies which took into consideration both Masaoka koga and TNM staging, in addition to histological subtypes.

TNM stage lumps Masaoka stage I, II, part of III as TNM stage I, thereby questioning the clinical relevance of histopathological reporting of invasion of capsule, mediastinal fat and mediastinal pleura. The Masaoka Koga stage can be influenced by variable sampling of the capsule and subjectivity in assessment of neoplastic involvement of extracapsular tissue from normal thymic tissue. Evidence from literature has shown no prognostic significance between the Masaoka Koga stage I and II patients [29,30], thus the clinical value of transcapsular invasion is still debatable.

The retrospective observational nature of the study with a limited small sample size and inadequate follow-up of all cases were the limitations of the present study which may have hindered the analysis of prognostic value of transcapsular invasion and Masaoka Koga stage I in thymoma patients. However, a strength of our study is that it is one of the few studies in literature to analyze both Masaoka and TNM staging, in addition to the histological subtype.

Conclusions

Thymoma as evaluated in our study were most commonly of B2 and B3 subtype followed by AB subtype. Majority of patients were in TNM stage I (93%) with good prognosis. Accurate histological subtyping can be achieved by adherence to strict morphological criteria by WHO. Adequate sampling of the tissue, strict adherence to morphological criteria ancillary techniques like IHC, wherever required, are the key factors to understanding the histological classes of thymoma. Further studies with more robust clinical follow-up data are required to assess the clinical significance of transcapsular invasion as a histological parameter.

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Online supplementary material:
Supplementary Figure 1. Histological subtypes, morphological criteria as per the World Health Organization 2021 classification of thymoma.
Supplementary Figure 2. A) Association of clinical stage with histological subtype; B) outcome distribution; C) survival analysis for stage I and stage II patients.
Supplementary Figure 3. Mixed subtypes of thymoma with varying proportions of B2 and B3 subtypes. CK 19 highlights denser meshwork of thymic epithelial cells in B3 areas (right side of the field, depicted by the arrowhead) as compared to B2 areas (left side of the field, pointed by arrow); Tdt shows lesser density of lymphocytes in B3 areas (100× magnification).

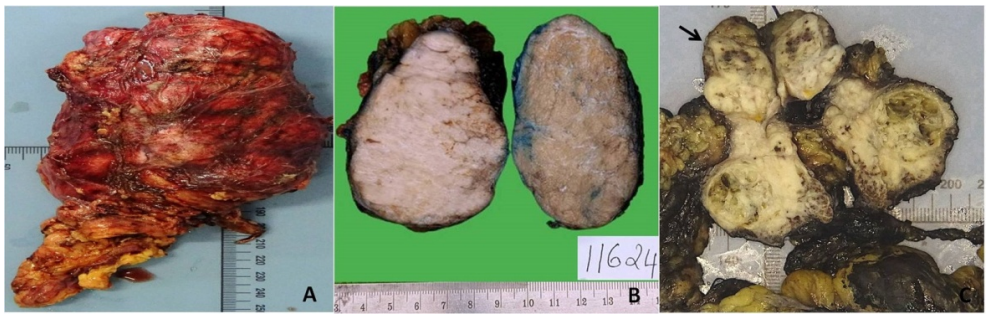

Figure 1. Gross photographs of thymectomy specimens. A,B) Photograph shows nodular external surface with lobulated homogenous cut surface; C) gross macroscopic invasion of tumor into the peri-thymic fat (as indicated by arrow).

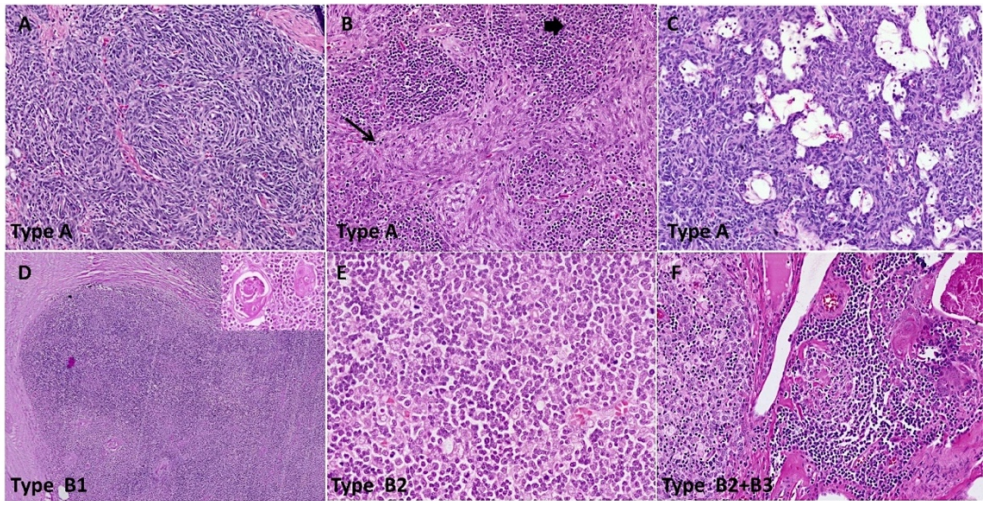

Figure 2. Morphological characteristics of various types of thymoma. A) Type A thymoma showing spindle cells in storiform pattern (H&E 100x magnification); B) type A areas with intermingled lymphocyte rich Type B areas (H&E 100x magnification); C) perivascular spaces in type A thymoma (H&E 100x magnification); D) type B1 thymoma – blue looking on scanner view with Hassall corpuscles (inset) (H&E, 40x magnification); E) type B2 thymoma showing clusters of thymic epithelial cells amidst dense lymphocytes (H&E, 400x magnification); F) mixed pattern thymoma with Type B3 on left side and Type B2 on the right side (H&E, 100x magnification).

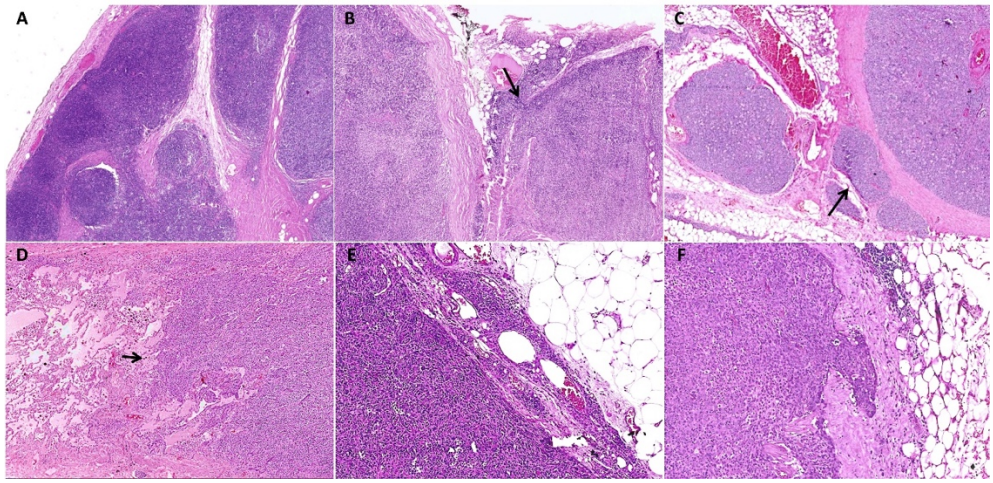

Figure 3 A) Encapsulated thymoma (H&E, 40x); B) direct invasion through capsule into perithymic fat (H&E, 40x); C) macroscopic invasion as separate tumor nodules in the perithymic fat (H&E, 40x); D) direct extension of the tumor into adjacent lung parenchyma (H&E, 100x); E,F) tumors with capsule deficient areas and tumor extension into the capsule but not through the complete thickness of capsule considered as encapsulated tumors (H&E, 40x).

Table 1. Distribution of clinical and histopathological characteristics.

Patient characteristics	n (%)	Mean ± SD	Median (25^{th}-75^{th} percentile)	Range
Gender				
Female	15 (34.88)	-	-	-
Male	28 (65.12)	-	-	-
Age(years)	-	45.98±12.3	46 (35.5-56)	25-68
Tumor size (cm)	-	5.71±3.29	5 (3.5-6)	2-19
Paraneoplastic syndrome				
Absent	11 (25.58)	-	-	-
Myasthenia gravis	31 (72.09)	-	-	-
ISAAC syndrome	1 (2.33)	-	-	-
Histological subtype				
A	7 (16.28)	-	-	-
AB	9 (20.93)	-	-	-
B1	1 (2.33)	-	-	-
B2	12 (27.91)	-	-	-
B3	10 (23.26)	-	-	-
B2 (80%) +B3 (20%)	2 (4.65)	-	-	-
B2 (90%) +B3 (10%)	2 (4.65)	-	-	-
Hassall corpuscles/medullary like areas	14 (32.56)	-	-	-
Perivascular spaces	20 (46.51)	-	-	-
Lymphoid hyperplasia	13 (30.23)	-	-	-
Involvement of capsule				
Absent	11 (25.58)	-	-	-
Macroscopic invasion through capsule	9 (20.93)	-	-	-
Microscopic invasion	23 (53.49)	-	-	-
Masaoka stage				
Stage I	11 (25.58)	-	-	-
Stage IIA	22 (51.16)	-	-	-
Stage IIB	6 (13.95)	-	-	-
Stage III	1 (2.33)	-	-	-
Stage IVA	2 (4.65)	-	-	-
Stage IVB	1 (2.33)	-	-	-
TNM stage				
Stage I	40 (93.02)	-	-	-
Stage II	1 (2.33)	-	-	-
Stage IVA	2 (4.65)	-	-	-

Table 2. Association of clinical and histopathological characteristics with histological subtype.

Characteristics	A (n=7)	AB (n=9)	B1 (n=1)	B2 (n=12)	B3 (n=10)	B2 (80%)+B3 (20%) (n=2)	B2 (90%)+B3 (10%) (n=2)	Total	p
Paraneoplastic syndrome									
Absent	2 (28.57%)	4 (44.44%)	1 (100%)	1 (8.33%)	2 (20%)	0 (0%)	1 (50%)	11 (25.58%)	
MG	5 (71.43%)	5 (55.56%)	0 (0%)	11 (91.67%)	7 (70%)	2 (100%)	1 (50%)	31 (72.09%)	0.285*
ISAAC syndrome	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	1 (2.33%)	
HC/medullary areas	1 (14.29%)	4 (44.44%)	1 (100%)	4 (33.33%)	1 (10%)	1 (50%)	2 (100%)	14 (32.56%)	0.089*
Perivascular spaces	4 (57.14%)	3 (33.33%)	0 (0%)	7 (58.33%)	4 (40%)	1 (50%)	1 (50%)	20 (46.51%)	0.91*
Lymphoid hyperplasia	2 (28.57%)	1 (11.11%)	1 (100%)	6 (50%)	2 (20%)	0 (0%)	1 (50%)	13 (30.23%)	0.257*
Involvement of capsule									
Absent	4 (57.14%)	2 (22.22%)	0 (0%)	4 (33.33%)	1 (10%)	0 (0%)	0 (0%)	11 (25.58%)	
Macroscopic invasion through capsule	0 (0%)	1 (11.11%)	1 (100%)	0 (0%)	4 (40%)	1 (50%)	2 (100%)	9 (20.93%)	0.021*
Microscopic invasion	3 (42.86%)	6 (66.67%)	0 (0%)	8 (66.67%)	5 (50%)	1 (50%)	0 (0%)	23 (53.49%)	
Masaoka stage									
Stage I	4 (57.14%)	2 (22.22%)	0 (0%)	4 (33.33%)	1 (10%)	0 (0%)	0 (0%)	11 (25.58%)	
Stage IIA	3 (42.86%)	5 (55.56%)	0 (0%)	8 (66.67%)	5 (50%)	1 (50%)	0 (0%)	22 (51.16%)	
Stage IIB	0 (0%)	1 (11.11%)	1 (100%)	0 (0%)	3 (30%)	1 (50%)	0 (0%)	6 (13.95%)	0.016*
Stage III	0 (0%)	1 (11.11%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.33%)	
Stage IVA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)	2 (4.65%)	
Stage IVB	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	1 (2.33%)	
TNM stage									
Stage I	7 (100%)	9 (100%)	1 (100%)	12 (100%)	9 (90%)	2 (100%)	0 (0%)	40 (93.02%)	
Stage II	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	1 (2.33%)	0.014*
Stage IVA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	1 (50%)	2 (4.65%)	