

Tateyama H, Sugiura H, Yamatani C, Yano M.
Expression of podoplanin in thymoma: its correlation with tumor invasion, nodal metastasis, and poor clinical outcome. Hum Pathol.
2011 Apr;42(4):533-40.

Christine Bekos

Podoplanin

- transmembrane glycoprotein
- many different synonyms (D2-40, gp38, T1 α , PA.A26, gp36, Aggrus, and M2A)
- first-identified as a marker of lymphangiogenesis due to its expression in lymphatic vessel endothelium
- Podoplanin was also noted in various malignancies

Pula B, Wojnar A, Werynska B, Ambicka A, Kruczak A, Witkiewicz W, Ugorski M, Podhorska-Okolow M, Dziegiel P. **Impact of different tumour stroma assessment methods regarding podoplanin expression on clinical outcome in patients with invasive ductal breast carcinoma.** Anticancer Res. 2013 Apr;33(4):1447-55.

Thymoma (WHO classification)

TABLE 5: Classification schemes for thymoma

WHO classification	Histogenetic classification (Müller-Hermelink)
A	Medullary thymoma
AB	Mixed thymoma
B1	Predominantly cortical thymoma
B2	Cortical thymoma
B3	Well-differentiated thymic carcinoma
C	Thymic carcinoma
Epidermoid keratinizing carcinoma (squamous cell)	
Epidermoid nonkeratinizing carcinoma	
Lymphoepithelioma-like carcinoma	
Sarcomatoid carcinoma	
Basaloid carcinoma	
Mucoepidermoid carcinoma	
Undifferentiated carcinoma	

A = atrophic, similar to that of an adult thymus; B = bioactive; C = cancer (with obvious signs of cell mitoses)

Material and methods

Table 1 Correlation between clinical stage and histological subtype of thymoma

Histological subtype	Clinical stage				
	I	II	III	IVa	IVb
A (n = 8)	7	1	0	0	0
AB (n = 40)	23	13	3	1	0
B1 (n = 15)	7	4	0	4	0
B2 (n = 23)	3	5	7	5	3
B3 (n = 15)	1	1	4	8	1
B1/B2 (n = 4)	0	3	1	0	0
B2/B3 (n = 6)	0	1	1	2	2
Total (N = 111)	41	28	16	20	6

Abbreviations: B1/B2, combined B1/B2 thymoma; B2/B3, combined B2/B3 thymoma.

NOTE. Thymomas were classified according to the WHO classification system, and clinical stage was determined according to the Masaoka staging system.

Immunohistochemistry

- D2-40 monoclonal antibody recognizes human podoplanin
- Semiquantitative assessment:
 - Negativ: no evidence of staining
 - Focally positive: 1% to 10% of tumor cells were positive
 - Positive: more than 10% of the tumor cells were positive

Results – Clinical features

Table 2 Correlation between podoplanin expression and clinicopathologic characteristics

Variable	Podoplanin			<i>P</i>
	Negative	Focally positive	Positive	
Subtype				<.0001
A (n = 8)	8	0	0	0
AB (n = 40)	36	4	0	10.0
B1 (n = 15)	11	3	1	26.7
B2 (n = 23)	7	11	5	69.6
B3 (n = 15)	5	7	3	66.7
B1/B2 (n = 4)	2	2	0	50.0
B2/B3 (n = 6)	1	2	3	83.3
Clinical stage				<.0001
I (n = 41)	36	4	1	12.2
II (n = 28)	21	4	3	25.0
III (n = 16)	5	10	1	68.8
IVa (n = 20)	8	9	3	60.0
IVb (n = 6)	0	2	4	100

Results – Clinical features

Age (y)					.400
<50 (n = 47)	28	12	7	40.4	
≥50 (n = 64)	42	17	5	34.4	
Gender					.260
Male (n = 52)	35	14	3	32.7	
Female (n = 59)	35	15	9	40.7	
Tumor size (cm)					.266
<5 (n = 21)	17	3	1	19.0	
5-11 (n = 60)	41	13	6	31.7	
>11 (n = 8)	4	3	1	50.0	
Myasthenia gravis					.361
Absent (n = 89)	58	22	9	34.8	
Present (n = 22)	12	7	3	45.5	

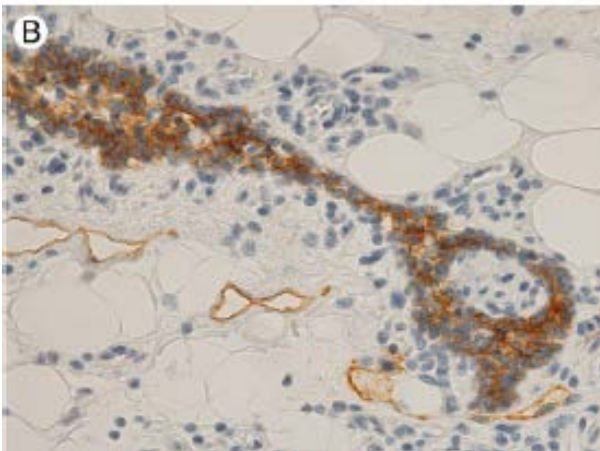
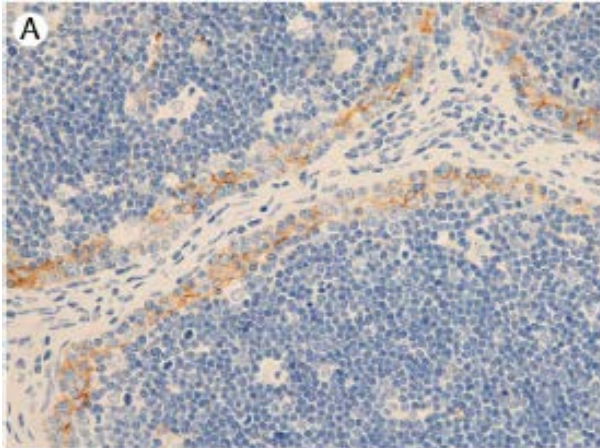
NOTE. Thymomas were classified according to the WHO classification system, and clinical stage was determined according to the Masaoka staging system.

Results – Clinical features

91 patients are alive during the period ranging from 0.5 to 23 years

8 patients died of disease, 12 patients died of other diseases

Results – Immunohistochemical features



Immunostaining for D2-40 in normal and involuted thymuses. The subcapsular epithelial cells of the normal thymus (A) and epithelial remnants of the involuted thymus (B) show positive staining for D2-40. Lymphatic endothelial cells also show D2-40 immunoreactivity (B)

Results – Immunohistochemical features

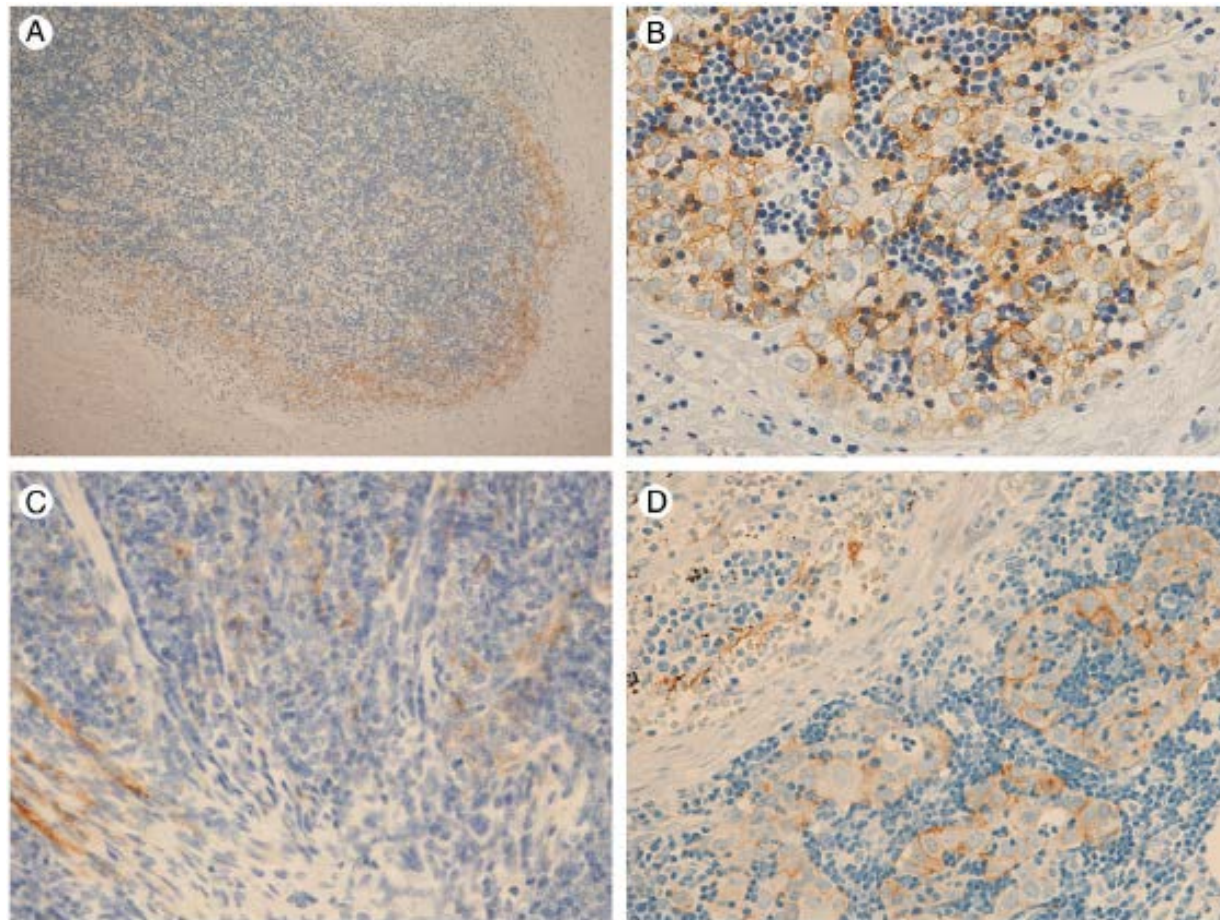
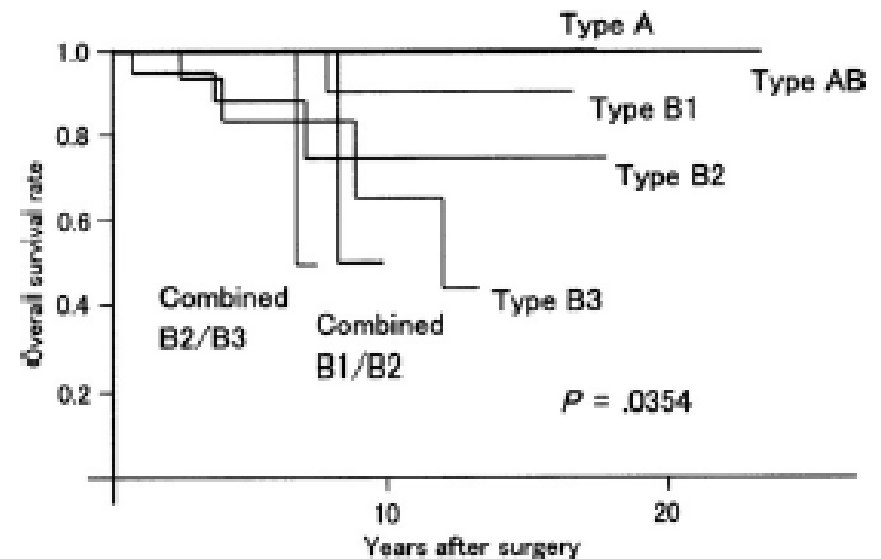
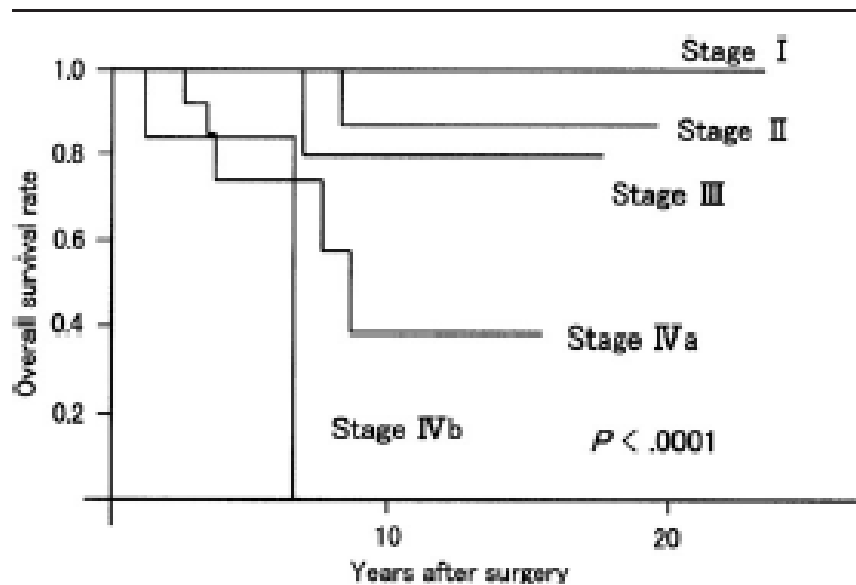


Fig. 2 Immunostaining for D2-40 in thymoma. (A) D2-40 is positive in the tumor cells in peripheral areas of type B2 thymoma. (B) Podoplanin is expressed on the cell membrane of the tumor cells. (C) Spindle cells of type A component and polygonal cells of type B-like component of type AB thymoma are positive for D2-40. (D) D2-40 is positive in the tumor cells within the lymph node.

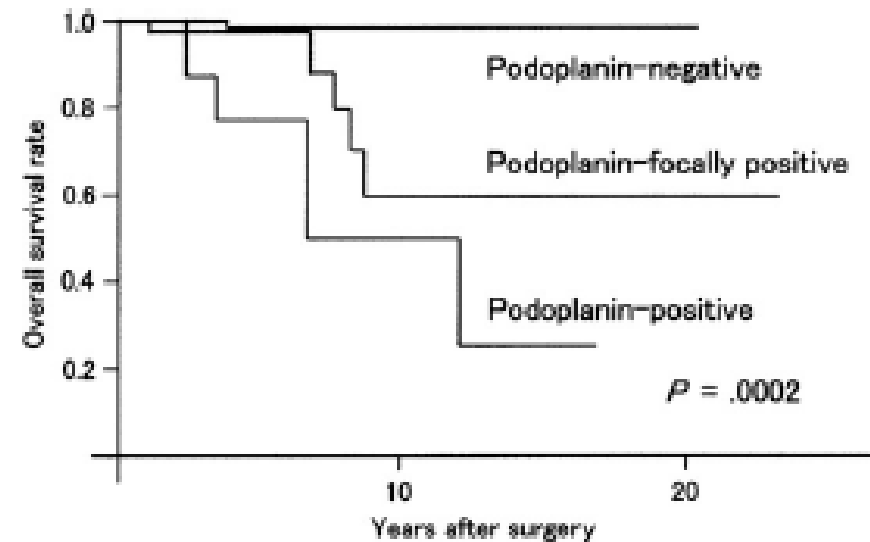
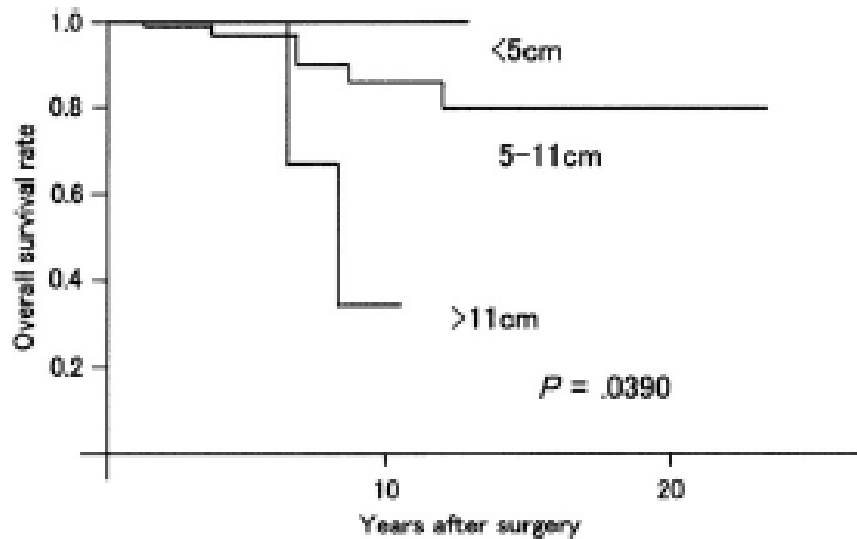
Results – Immunohistochemical features

- Lymphangiogenesis in and around thymomas was identified in only 9 cases: 2 type AB, 2 type B1, 3 type B2 and 2 type B3 thymomas.
- No significant correlation was apparent between lymphangiogenesis and histological subtype or clinical stage.

Results – Survival analysis



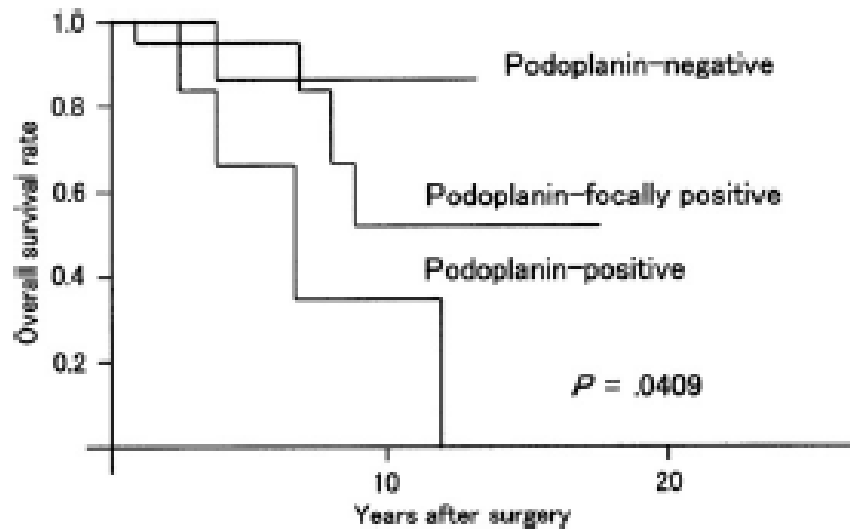
Results – Survival analysis



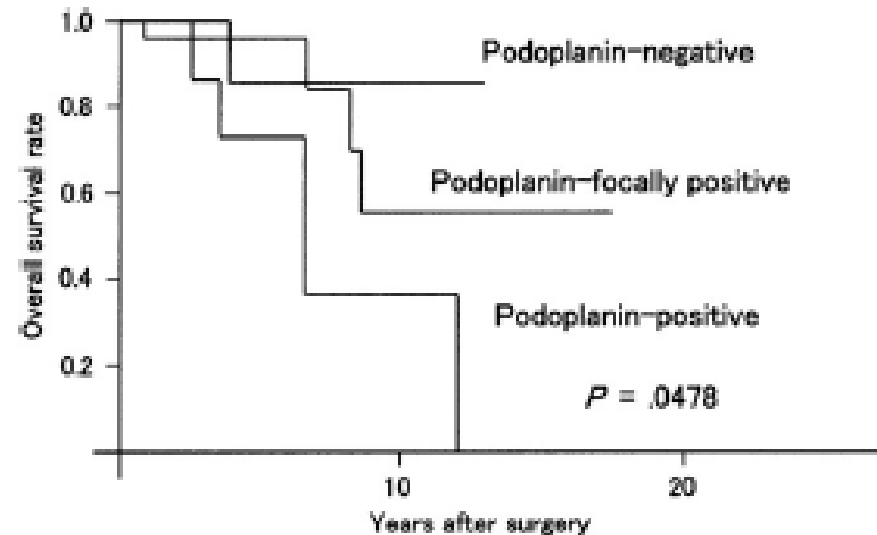
Results – Survival analysis

- In the present study, clinical stage ($P = .006$; relative risk, 37.77) and tumor size ($P = .037$; relative risk, 10.58) were proven to be independent predictive factors, whereas histological subtype ($P = .314$) and podoplanin expression ($P = .187$) were not prognostic factors.

Results – Survival analysis



survival rates of patients with stage III/IVa/IVb thymomas gradually worsened with increasing podoplanin expression



survival rates of patients with type B2/B3 thymomas gradually worsened with increasing podoplanin expression

Discussion

- Small number of deaths (n=9)
- Biological function of podoplanin is unclear
- Podoplanin expression was found in the tumor front or invasive nest and tumor cells within the lymph node
- Lymphangiogenesis was not identified in many thymomas
- Podoplanin expression seems to be associated with the invasive and metastatic potential of thymomas rather than proliferative activity

Discussion

- Podoplanin was detected in basal epidermal keratinocytes , showing characteristics of stem cells -> the subcapsular epithelium of the thymus may serve as stem cells for the thymic epithelium
- Thymomas may have their origin in these stem cells, which could explain the heterogenous morphology of these tumors