available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Thymic epithelial tumours: A population-based study of the incidence, diagnostic procedures and therapy ☆

Wouter K. de Jong[a,*], *Johannes L.G. Blaauwgeers*[b], *Michael Schaapveld*[c], *Wim Timens*[d], *Theo J. Klinkenberg*[e], *Harry J.M. Groen*[a]

[a]*Department of Pulmonology, University Medical Center Groningen, University of Groningen, P.O. Box 30.001, NL-9700 RB Groningen, The Netherlands*
[b]*Department of Pathology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands*
[c]*Comprehensive Cancer Center Northern Netherlands, Groningen, The Netherlands*
[d]*Department of Pathology, University Medical Center Groningen, University of Groningen, The Netherlands*
[e]*Department of Thoracic Surgery, University Medical Center Groningen, University of Groningen, The Netherlands*

ARTICLE INFO

Article history:
Received 16 August 2007
Received in revised form 22 October 2007
Accepted 7 November 2007

Keywords:
Thymic epithelial tumour
Population-based study
Incidence
Diagnosis
Therapy
Survival

ABSTRACT

The population-based incidence, diagnostic procedures, therapy and survival of thymic epithelial tumours were determined using the Netherlands National Pathological Archives and the Netherlands Cancer Registry. Excess mortality compared to the Netherlands standard population was estimated by relative survival analysis.

Between 1994 and 2003, 537 thymic epithelial tumours were diagnosed. The incidence of all thymic epithelial tumours was 3.2/1,000,000. Diagnosis was obtained by primary resection in 56% of cases. Survival data were available for 232 cases. Not only thymic carcinomas (type C) but also thymomas (types B1–B3) were associated with excess mortality. Cases that underwent resection (78%) had a better survival than non-operated cases (median survival >10 years versus 1.1 years, $p < 0.001$). Amongst the surgically treated cases ($n = 180$), the completeness of resection did not predict survival ($p = 0.53$).

Thymic epithelial tumours are rare. Excess mortality was observed in the majority of tumours. Surgery offers the best perspectives, even if the resection is incomplete.

© 2007 Elsevier Ltd. All rights reserved.

1. Introduction

Thymomas and thymic carcinomas are rare tumours but nevertheless are the most common neoplasms that arise from the thymus in the anterior mediastinum.[1] Thymomas originate from thymic epithelial cells. Although in thymomas epithelial cells lack cytological atypia, thymomas may behave as locally invasive tumours and can therefore be considered as potentially malignant. Whether they are truly malignant is still a subject of debate. Thymic carcinomas also arise from thymic epithelial cells, but they have both a malignant cellular appearance and behaviour. One-third to two-thirds of the thymomas are found in asymptomatic patients.[1] The most well-known paraneoplastic syndrome is myasthenia gravis, occurring in up to 45% of patients with a thymoma.[1,2]

A provisional diagnosis of a thymic tumour is based on clinical features and anatomical appearance on computed tomography (CT).[2] A definitive diagnosis of a thymic epithelial tumour is subsequently established by examination of tissue obtained through transthoracic needle or surgical biopsy, or

☆ This study was presented in part at the 43rd Annual meeting of the American Society of Clinical Oncology, Chicago, IL, June 1–5, 2007.

* *Corresponding author:* Tel.: +31 50 3616161; fax: +31 50 3619320.
E-mail address: w.k.de.jong@int.umcg.nl (W.K. de Jong).

0959-8049/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2007.11.004

after primary resection. Thymomas are also incidentally found during thoracic surgery for other reasons or during autopsy.[3] How often cytological aspirates or biopsy procedures precede resection and lead to accurate classification is unknown.

Thymic epithelial tumours are characterised by histological subtype and stage of the disease. Since 1999, the World Health Organisation classification is the most widely used histological classification system[4]; the term benign and malignant thymoma has fallen out of fashion. Thymic epithelial tumours are divided into six types, based on the predominant cell type. The Masaoka staging system is the most widely used clinical staging system for thymic epithelial tumours.[5] This system is based on the presence of local invasion in the thymus capsule and neighbouring organs, and on systemic expansion.

At present, the primary choice of treatment is resection.[1] The use of chemotherapy and/or radiotherapy, with or without surgery, is not standardised.[6] Several studies report that survival is strongly dependent on achieving a complete resection, histological classification and tumour stage.[7–11]

Our aim was to determine the incidence of all thymic epithelial tumours, and to evaluate the diagnostic procedures and the therapeutic interventions for these tumours in the Dutch population during a 10-year period.

2. Patients and methods

Data on cancer patients were anonymously collected by two nationwide databases. The Netherlands National Pathological Archives (PALGA) database registers all cytopathological and histopathological reports, and contains basic patient characteristics and diagnostic terms in line with the systematised nomenclature of medicine terminology.

The Netherlands Cancer Registry (NCR) records clinical and surgical data of all newly-diagnosed malignancies, with the exception of basal-cell skin cancer, and contains basic patient characteristics and clinical information such as tumour location, tumour stage, treatment and survival. Vital statistics were collected either directly from the patient's medical record or through linkage of NCR with the municipal population registries. Information from the PALGA and NCR databases were merged over a period from 1994 to 2003.

All procedures were performed according to Dutch privacy regulations. Because the study involved anonymised data that were routinely collected and explicitly did not involve the use of human subjects, consent was not specifically obtained and Institutional Review Board approval was not necessary.

3. Selection of cases from PALGA

An initial screening was performed in PALGA using the key words: 'thymoma, benign'; 'thymoma, malignant'; 'thymoma, lymphocyte-rich'; 'thymus, neoplasm'; 'thymus, benign' and 'thymus, malignant'. Between 1st January 1994 and 31st December 2003, 1244 hits matched the keywords. These 1244 hits originated from 750 cases, because in many cases more than one pathological specimen was recorded of the same tumour.

Of these 750 cases, 151 (20.1%) were excluded from the analysis because of other diagnoses, of which malignant lymphoma (49 cases, 6%) and carcinoid tumour of the thymus (31 cases, 4%) were the most common. Another 38 cases (5.1%) were excluded, because their thymic epithelial tumour was originally diagnosed before 1994. In 24 cases (3.2%), a definitive diagnosis was inconclusive or unknown. These categories were all excluded, leaving a total of 537 primary thymomas and thymic carcinomas.

4. Selection of cases from NCR

Over the same period, a total of 269 cases with a malignancy located in the thymus region (ICD code C.37.9) were collected from the NCR database. Cases were matched with the PALGA cases using date of birth, gender, and, if necessary, date of diagnosis.

Two hundred and thirty-two (86.2%) of the 269 cases with a thymus tumour according to NCR could be merged with PALGA data. Of these 232 cases, six cases had a histological diagnosis other than a thymic epithelial tumour according to NCR. In these cases the PALGA classification prevailed. Of the 37 unmatched cases, 26 had a histological diagnosis other than a thymic epithelial tumour according to NCR, mostly carcinoid ($n = 17$) or neuro-endocrine carcinomas ($n = 6$) of the thymus.

5. Tumour classification and staging

All tumours were histopathologically classified according to WHO criteria.[4] Older classifications were reclassified according to WHO by two independent observers (JLGB and WKdJ). Some neoplasms are composed of combinations of the various types, and are therefore considered combined thymomas (e.g. B2 + B3). These mixed presentations were classified according to the most aggressive type, which determines the prognosis.[7] For clinical staging the Masaoka system was used.[5]

5.1. *Diagnostic approach*

For each case the diagnostic procedures resulting in a definitive diagnosis of 'thymoma' or 'thymic carcinoma' were recorded. Diagnostic procedures were categorised as transthoracic fine needle aspirates for cytology, transthoracic needle biopsies, surgical biopsies, primary resection for histology or incidental findings at autopsy or surgery for other reasons. The completeness of a resection was recorded, as well as the dimensions and weight of the resected specimen. All resections were checked and only considered to be complete if no microscopical and/or macroscopical tumour residue was present.

5.2. *Statistical analyses*

The present study is a population-based study, encompassing the entire Dutch population of approximately 16 million inhabitants. The population at risk for each year was determined from the data from Statistics Netherlands.[12] Incidence rates were age-standardised using the European Standard Population as reference.[13] Trends in incidence rates were studied by calculating the Estimated Annual Percentage Change (EAPC).

Differences between groups were assessed by the χ^2 or Kruskall–Wallis test for categorical variables and the Mann–Whitney test for continuous variables.

Survival was calculated from the date of diagnosis until death or until end of follow-up and was estimated using the Kaplan–Meier method. Survival differences in subgroups were compared with the log-rank test.

Relative survival, the ratio of the observed to the expected survival, was considered as an estimator of the excess risk of death. The expected survival was calculated using age, gender and period matched mortality rates based on Dutch life expectancy tables.[12] Multivariate relative survival analysis was based on the estimation of the ratio of excess mortality rates.[14] All reported p-values are two-sided, the statistical significance level was set at a p-value <0.05.

6. Results

6.1. Characteristics

Of the 537 cases from the PALGA database, 275 (51%) were females. Median age at time of definitive diagnosis was 59 years (range: 1–94, interquartile range 48–70). Myasthenia gravis was present in 78 cases (15%). In 13 cases other paraneoplastic syndromes were observed (7 cases with pure red cell aplasia/aplastic anaemia, 6 cases with rarer syndromes such as hypogammaglobulinemia). The median largest tumour diameter was 7.5 cm (range 0.1–22 cm, $n = 298$), with a median weight of 213 g (range 20–2100 g, $n = 70$).

6.2. Incidence of thymoma and thymic carcinoma

During the 10-year period, 54 thymic epithelial tumours were diagnosed each year. The average annual incidence of all thymic epithelial tumours was 3.4/1,000,000 and the age standardised incidence was 3.2/1,000,000 (Table 1). Incidence was 2.2/1,000,000 for thymoma (types A, AB, B1 and B2) and only 0.3/1,000,000 for type C thymic carcinoma. Incidence rates for males and females were not different.

The incidence of thymic epithelial tumours did not increase over the 10-year period (3.2%, $p = 0.12$), but by excluding the first year of observation (1994), there was an increase of 6.0%, $p = 0.002$.

6.3. Tumour classification and staging

WHO types AB, B1 and B2 tumours were most common (Table 2). Thymic carcinoma (type C) was observed in 56 cases (10.4%). Cases with WHO types A and AB tumours were on average 5 years older than those with types B1 and higher ($p < 0.001$). The majority of cases had low Masaoka disease stages. Cases with thymic epithelial tumours of more malignant WHO types more often had a higher Masaoka stage at diagnosis than those with thymomas of less malignant WHO types (Table 2, $p < 0.001$).

6.4. Diagnostic approach

Primary resection as first definitive diagnostic approach was used in 302 cases (56%) (Table 3). Primary resection as first diagnostic procedure was more common in younger cases and cases with smaller tumours ($p = 0.002$ and $p < 0.001$, respectively). The percentage of primary resection as first diagnostic procedure gradually decreased with increasing Masaoka stage (76%, 75%, 46% and 23% from stages I to IV, respectively). In cases that were diagnosed with thymic carcinoma, the most frequently used first diagnostic procedure was a needle biopsy (20 of 56 patients, 36%).

A pre-operative pathological diagnosis was available in 24% of all cases that underwent a resection. A transthoracic needle biopsy was the most frequently used procedure to obtain a diagnosis before resection (in 64% of cases with a

Table 1 – Incidence of thymoma and thymic carcinoma (number, observed and age-standardised incidence and annual change of incidence) in the Netherlands 1994–2003

Year of diagnosis	Male		Female		Total		
	Number	Age standardised incidence[a]	Number	Age standardised incidence[a]	Number	Observed Incidence[b]	Age standardised incidence[a]
1994	29	3.83	31	3.67	60	3.91	3.79
1995	21	2.84	19	2.16	40	2.59	2.47
1996	19	2.48	19	2.18	38	2.45	2.33
1997	27	3.65	23	2.82	50	3.21	3.20
1998	21	2.70	31	3.43	52	3.32	3.13
1999	25	3.17	22	2.38	47	2.98	2.81
2000	28	3.50	27	2.93	55	3.47	3.21
2001	23	2.83	42	4.93	65	4.07	3.88
2002	34	4.05	32	3.66	66	4.10	3.84
2003	35	4.13	29	3.23	64	3.95	3.66
Total	262	3.32	275	3.14	537	3.41	3.23
EAPC[c]	–	+2.3% ($p = 0.266$)	–	+3.9% ($p = 0.196$)	–	–	+3.2% ($p = 0.120$)

a Age standardised incidence (based on European Standard Population[13]) per 1,000,000 person years.
b Observed incidence per 1,000,000 person years.
c EAPC, estimated annual percentage change.

pre-operative diagnosis), followed by surgical biopsy (25%) and needle aspiration for cytology (11%). Transthoracic needle biopsy was also the most frequently used method to obtain a diagnosis in cases that were not treated by resection.

Median time between preoperative diagnosis and subsequent resection was 37 days (interquartile range 21–84). The type of diagnostic procedure did not influence this time interval ($p = 0.58$).

Eventually, 419 of the 537 PALGA cases (78%) underwent a resection (Table 3). This resection was complete in 227 cases (54%), incomplete in 129 cases (31%) and completeness was unknown in 63 cases (15%). Of the 56 cases with thymic carcinoma, 28 (50%) underwent a resection.

Small changes in diagnostic procedures were observed when comparing the first five years of the 10-year study period to the last five years. The most important difference was a decrease in frequency of incidental finding of thymus tumours (both during autopsy and during thoracic surgery for other indications) from 10% to 2.4%.

6.5. *Myasthenia gravis*

Primary resection was more common as a first diagnostic procedure in cases with myasthenia gravis than in those without myasthenia gravis (90% and 51%, respectively, $p < 0.001$). Cases with myasthenia gravis were younger and had smaller masses than those without myasthenia gravis ($p = 0.001$ and $p = 0.004$, respectively). Only three of the 78 thymic epithelial tumours in cases with myasthenia gravis were not resected. Two of those three tumours were found at autopsy, the reason for withholding resection in the third case was unknown.

6.6. *Survival*

Survival data of 232 cases (43.2% of 537 cases) were available. Gender and age distribution were not significantly different from the complete study population. The 2, 5 and 10- year overall survival of all these thymic epithelial tumours combined was 75%, 69% and 40%, respectively.

WHO classification, Masaoka disease stage, resection and age (distributed into three groups) were significant prognostic factors of overall and relative 5-year survival (Table 4). Year of diagnosis (1994–1998 versus 1999–2003), gender and myasthenia gravis were not prognostic for survival (Table 4). Some adjoining histological types and disease stages had similar observed 5-year survival rates and could therefore be clustered (Fig. 1). Excess mortality was present in all WHO types except types A and AB (Table 4).

Resection was the most important independent prognostic factor for survival ($p < 0.001$). When resection, being related to disease stage, was excluded from multivariate analysis, WHO classification, Masaoka disease stage and age were independent prognostic factors ($p < 0.001$, $p = 0.010$ and $p < 0.001$, respectively).

6.7. *Treatment*

The majority of cases of which we had survival data ($n = 180$) was treated with surgery, or surgery combined with chemotherapy and/or radiotherapy. The 10-year survival of surgi-

Table 2 – WHO classification of thymic epithelial tumours distributed according to Masaoka clinical stages (n = 537)

	I	II	III	IV	Unknown	Total
A	20	15	6	2	20	63
AB	55	28	3	4	25	115
B1	28	20	9	5	25	87
B2[a]	19	27	19	15	17	97
B3[b]	12	12	11	13	15	63
C[c]	0	6	13	18	19	56
Unknown	8	14	7	5	22	56
Total	142	122	68	62	143	537

Classification is not equally distributed amongst tumour stages ($p < 0.001$).

Description of WHO classification (4): type A: medullary thymoma; type AB: mixed thymoma; type B1: predominantly cortical thymoma; type B2: cortical thymoma; type B3: well-differentiated thymic carcinoma; type C: thymic carcinoma.

Description of Masaoka clinical stages (5): stage I: macroscopically completely encapsulated lesion without capsular invasion; stage II: capsular invasion and/or invasion in surrounding fat or pleura; stage III: invasion in neighbouring organs (lung, great vessels, pericardium); stage IV: presence of pleural or pericardial dissemination, and/or presence of lymphogenous or haematogenous metastases.

a Including three combined B1 + B2 thymomas.

b Including eight combined B2 + B3 thymomas.

c Including one combined B3 + C thymoma.

Table 3 – Procedures leading to a definitive diagnosis of thymic epithelial tumours (n = 537)

First procedure	Number of cases	Percentage of total number of cases	Followed by resection	Percentage of total number of resections
Needle aspiration (cytology)	19	3.5	11	2.6
Needle biopsy (histology)	130	24.2	65	15.5
Surgical biopsy	52	9.7	26	6.2
Primary resection	302	56.2	302	72.1
Incidental finding during surgery for other indications	15	2.8	15	3.6
Incidental finding at autopsy	16	3.0		
Other	1	0.2		
Unknown	2	0.4		
Total	537	100.0	419	100.0

Table 4 – Univariate overall and relative 5-year survival with 95% confidence intervals

	Number	Overall 5-year survival in % (95% confidence interval (CI))	*p*-value*	Relative survival[a] in % (95% CI)	*p*-value[b]
Time of diagnosis			0.4463		0.1582
1994–1998	100	70.2 (61.9–79.6)		78.3 (66.7–87.4)	
1999–2003	132	69.8 (54.8–77.5)		74.0 (63.1–82.6)	
Gender			0.6816		0.8309
Male	122	70.3 (60.0–78.4)		78.4 (66.8–87.5)	
Female	110	67.2 (56.2–76.1)		71.7 (59.8–81.3)	
Age			0.0004		0.0135
<50	69	73.8 (60.2–83.5)		74.7 (61.0–84.4)	
50–69	116	74.8 (63.7–82.9)		79.8 (67.8–88.6)	
⩾70	47	46.8 (31.3–60.9)		64.4 (43.5–83.2)	
WHO classification			0.0001		0.0004
A	19	87.8 (59.4–96.9)		100 (69.9–111.9)	
AB	33	83.0 (63.8–92.6)		92.8 (71.2–103.6)	
B1	34	81.7 (61.0–92.1)		86.5 (64.7–97.4)	
B2	54	81.9 (66.6–90.6)		85.9 (69.8–95.2)	
B3	36	53.1 (32.8–69.8)		56.9 (35.5–74.5)	
C	36	37.8 (20.5–55.0)		42.6 (23.7–61.0)	
Unknown	20	59.7 (33.0–78.7)		70.9 (39.1–93.5)	
Masaoka stage			<0.0001		0.0028
I	25	82.9 (60.5–93.3)		91.2 (65.8–103.2)	
II	75	87.8 (75.7–94.1)		95.3 (82.2–102.1)	
III	53	57.6 (39.6–72.1)		63.2 (43.7–78.7)	
IV	50	55.6 (38.6–69.5)		59.7 (41.4–74.8)	
Unknown	29	49.9 (29.4–67.3)		56.3 (33.2–76.2)	
Tumour resected			<0.0001		<0.0001
Yes	180	80.1 (72.5–85.9)		87.7 (79.3–94.1)	
No	52	27.6 (14.1–42.9)		29.9 (15.3–46.3)	
Myasthenia gravis			0.1161		0.2280
Yes	27	82.3 (59.1–93.1)		88.9 (65.0–100.0)	
No	205	66.9 (58.9–73.7)		73.1 (64.4–80.6)	

a Relative survival, the ratio of the observed to the expected survival, was considered as an estimator of the excess risk of death compared to the standard population.
b Poisson regression analysis of relative survival rates, adjusted for follow-up time.
* Log-rank test.

cally treated cases was 52%; those not surgically treated ($n = 52$) had a median survival of 1.1 years (Fig. 1).

Resection was complete in 74 cases (41%), incomplete in 96 cases (53%) and unknown in 10 cases (6%). Cases with a complete resection did not have a better survival than those with an incomplete resection ($p = 0.53$) (Fig. 1). Cases with an incomplete resection more often received (neo)adjuvant therapy than those with a complete resection (64% versus 39%, $p = 0.002$). In cases with an complete resection, (neo)adjuvant therapy consisted of radiotherapy (25%), chemotherapy (7%) or chemoradiotherapy (7%). In cases with a incomplete resection, (neo)adjuvant therapy consisted of radiotherapy (50%), chemotherapy (10%) or chemoradiotherapy (4%).

7. Discussion

The present population-based study is the first to determine the incidence of all thymic epithelial tumours, with good coverage also of 'benign' lesions in comparison with many other studies. This study points out that in the Netherlands primary resection is the most frequently used procedure to obtain a definitive diagnosis of a thymus tumour. The majority of the thymic epithelial tumours is associated with excess mortality compared to the standard population. Remarkably, contradictory to previous publications, the completeness of resection was not predictive for overall survival.

The design of this population-based study had some limitations. First, it is a retrospective study; therefore the conclusions should be interpreted with caution. For example, the low prevalence of MG in our population could be a result of underreporting of co-existent diseases. However, one should realise that all large studies on thymic epithelial tumours were retrospective. Second, detailed information on the magnitude of incompleteness of resections was not available in all cases. Incomplete resections ranged from debulked large tumours to microscopical tumour residues. In addition, detailed information on the dosage, intensity and timing of (neo)adjuvant therapy was unavailable. Third, the occurrence of second

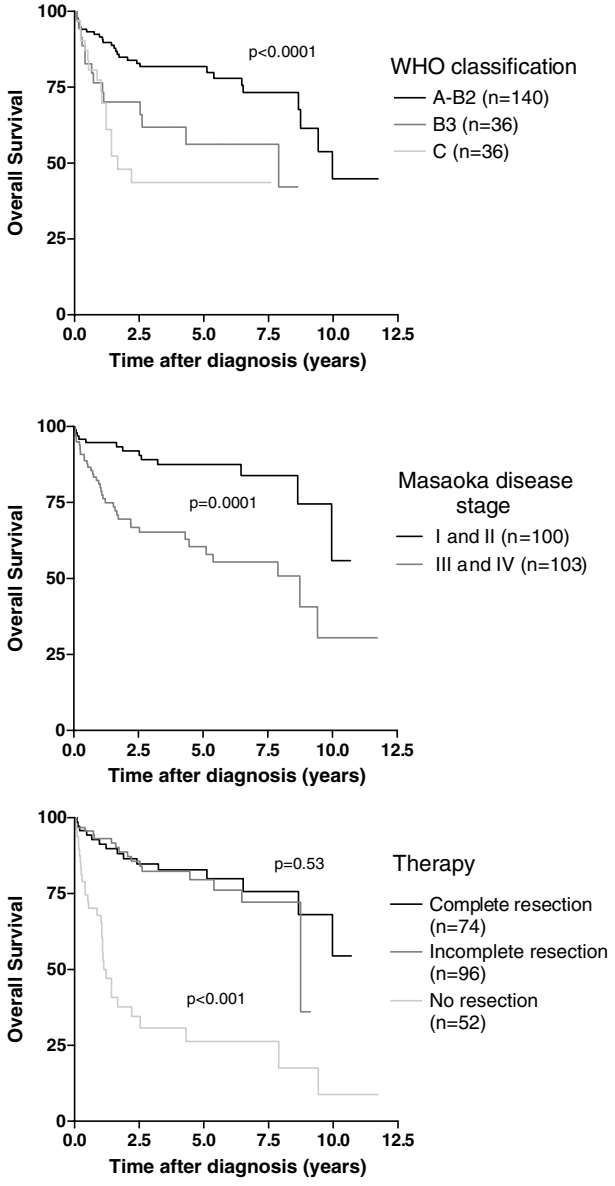

Fig. 1 – Overall survival curves of cases with thymic epithelial tumours distributed according to WHO classification (clusters A–B2, B3 and C, upper panel) or Masaoka disease stage (clusters I-II and III-IV, middle panel). Tumours with unknown classification (n = 20) or disease stage (n = 29) are not included, respectively. Overall survival curves according to treatment are displayed in the lower panel. Cases with a resection with unknown completeness (n = 10) are excluded. No resection versus resection $p < 0.001$, and complete resection versus incomplete resection $p = 0.53$.

primary tumours, which are common for thymomas[15] and may influence survival time, was not recorded.

The incidence for all thymic epithelial tumours in the Netherlands was 3.2/1,000,000. We observed that slightly less than half of all thymic tumours are collected by the Netherlands Cancer Registry, resulting in an incidence of only 1,5/1.000.000 for thymomas considered as malignant in that registry. In the United States, the Surveillance, Epidemiology and End Results (SEER) programme collects cancer incidence and survival data, thereby covering approximately 26% of the US population. Based on SEER data, an incidence of 1.5/1,000,000 (similar to NCR) for malignant thymomas was reported[16] without information about WHO types. Therefore, approximately 50% of all thymic epithelial tumours escape registration in cancer registries, probably because they are considered as benign tumours. Our data provide an increasing trend in the incidence of thymic epithelial tumours. This may be explained by the larger availability of CT-scans and more medical indications for performing CT scans leading to a decrease in incidental findings of thymomas. Overall, thymomas and thymic carcinomas are very uncommon, and the literature about diagnostic approaches and treatment is sparse.

Primary resection, i.e. resection without a pre-operative tissue diagnosis, was performed in the majority of cases and was associated with smaller tumours, younger age and the presence of myasthenia gravis. Pre-operative tissue diagnosis was obtained in only 24% of cases, which is less than was reported in the literature.[3,17] In cases that had a primary resection, especially in those with smaller masses or myasthenia gravis, a resectable thymic mass as assessed by CT scan was considered sufficient to proceed to thoracotomy without further diagnostics. A CT scan is very useful to assess the resectability of a localised tumour in the anterior mediastinum, but cannot differentiate between the different histological subtypes.[18] The presumed risk of dissemination of disease following a needle procedure may also favour immediate thoracic surgery without a pre-operative diagnosis. There is considerable disagreement in the literature about the risk of implantation metastases during transthoracic procedures.[2] In an analysis evaluating more than 68,000 transthoracic needle biopsies for different malignancies, the incidence of needle-track metastasis was only 0.012%.[19] Therefore, despite two case reports that describe implantation metastases,[20,21] the risk of seeding appears to be low.

Only 3.5% of all thymomas were diagnosed with a cytological procedure. The accuracy of cytology in diagnosing thymomas is limited, as this depends on the acquisition of both epithelial and lymphoid elements in one sample.[22] Cytology may provide some evidence for a thymic origin of the tumour but sampling error and tumour heterogeneity preclude proper typing and staging of the tumour. Therefore, histology is recommended.

Our results are in line with the studies from Germany, Japan, China and Italy in histological subtype frequencies of thymomas and thymic carcinomas.[7,9–11,23,24] Types AB and B2 were the most frequent, and type C thymic carcinoma represented about 5–15% of the disease spectrum. An other similarity between our findings and earlier studies[7,9,11,23–26] is that adjoining histological types and disease stages have comparable survival rates. Combining types A, AB, B1, and B2, as was recently proposed by Suster and Moran,[27] results in better separation of survival curves (Fig. 1). This is in line with the low reproducibility of the WHO classification between pathologists (interobserver agreement of only 0.49 for the B subtypes using κ statistics[10]) and the large heterogeneity of thymomas making classification prone to sampling errors.[28] The low reproducibility is also caused by the fact that

most pathologists see only one or two thymic epithelial tumours per year due to the low incidence.

In this study, as opposed to most other studies that report only on overall survival, we showed that the majority of thymomas is associated with a decrease in life expectancy because excess mortality was observed in WHO types B1 up to C and for Masaoka stages III and IV.

Resection is by far the best treatment option for patients with a thymic epithelial tumour,[7,8,23] although it is possible that not only tumour-related factors but also patient-related factors such as a worse performance status or co-morbid illnesses played a role in the decision not to operate, explaining the very poor survival for those patients without a resection. Contrary to earlier findings,[1,7,8,23] cases with a complete resection did not have a better survival than those with an incomplete resection. This may be due to the population-based design of our study compared to the single-centre design of most other studies. Also, in this study, more patients had an incomplete resection than in most other studies,[7,8,11] possibly due to our strict criteria for defining completeness. Patients with an incomplete resection received more (neo)adjuvant chemotherapy and/or radiotherapy than patients with a complete resection. It has been reported that postoperative adjuvant therapy decreases the recurrence rate in incompletely resected thymomas.[7] In addition, high overall survival rates were observed in patients with initially unresectable thymomas, who were treated with resection and postoperative radiotherapy after induction chemotherapy.[29,30] In conclusion, the present study points out that surgery offers the best perspectives for patients with thymic epithelial tumours, even if the resection is incomplete.

Conflict of interest statement

We declare that no conflict of interest exists for any of the authors.

Acknowledgements

This study was supported by the Netherlands National Pathological Archives (PALGA) and the Netherlands Cancer Registry (NCR).

REFERENCES

1. Detterbeck FC, Parsons AM. Thymic tumors. *Ann Thorac Surg* 2004;**77**:1860–9.
2. Thomas CR, Wright CD, Loehrer PJ. Thymoma: state of the art. *J Clin Oncol* 1999;**17**:2280–9.
3. Wilkins KB, Sheikh E, Green R, et al. Clinical and pathologic predictors of survival in patients with thymoma. *Ann Surg* 1999;**230**:562–72.
4. Rosai J, Sobin LH. Histological typing of tumours of the thymus. *World Health Organization. International histological classification of tumours*. 2nd ed. Berlin: Springer Verlag; 1999. pp. 9–14.
5. Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. *Cancer* 1981;**48**:2485–92.
6. Giaccone G. Treatment of malignant thymoma. *Curr Opin Oncol* 2005;**17**:140–6.
7. Strobel P, Bauer A, Puppe B, et al. Tumor recurrence and survival in patients treated for thymomas and thymic squamous cell carcinomas: a retrospective analysis. *J Clin Oncol* 2004;**22**:1501–9.
8. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. *Ann Thorac Surg* 2003;**76**:878–84.
9. Chen G, Marx A, Wen-Hu C, et al. New WHO histologic classification predicts prognosis of thymic epithelial tumors: a clinicopathologic study of 200 thymoma cases from China. *Cancer* 2002;**95**:420–9.
10. Rieker RJ, Hoegel J, Morresi-Hauf A, et al. Histologic classification of thymic epithelial tumors: comparison of established classification schemes. *Int J Cancer* 2002;**98**:900–6.
11. Okumura M, Ohta M, Tateyama H, et al. The World Health Organization histologic classification system reflects the oncologic behavior of thymoma: a clinical study of 273 patients. *Cancer* 2002;**94**:624–32.
12. Statistics Netherlands (CBS). <http://statlinecbsnl/StatWeb/>; 2006.
13. Parkin DM, Muir CS, Whelan SL. *Cancer incidence in five continents*, vol. III. IARC Scientific Publications; 1976.
14. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med* 2004;**23**:51–64.
15. Travis LB, Boice Jr JD, Travis WD. Second primary cancers after thymoma. *Int J Cancer* 2003;**107**:868–70.
16. Engels EA, Pfeiffer RM. Malignant thymoma in the United States: demographic patterns in incidence and associations with subsequent malignancies. *Int J Cancer* 2003;**105**:546–51.
17. Lardinois D, Rechsteiner R, Lang RH, et al. Prognostic relevance of Masaoka and Muller–Hermelink classification in patients with thymic tumors. *Ann Thorac Surg* 2000;**69**:1550–5.
18. Jeong YJ, Lee KS, Kim J, Shim YM, Han J, Kwon OJ. Does CT of thymic epithelial tumors enable us to differentiate histologic subtypes and predict prognosis? *AJR Am J Roentgenol* 2004;**183**:283–9.
19. Ayar D, Golla B, Lee JY, Nath H. Needle-track metastasis after transthoracic needle biopsy. *J Thorac Imaging* 1998;**13**:2–6.
20. Kattach H, Hasan S, Clelland C, Pillai R. Seeding of stage I thymoma into the chest wall 12 years after needle biopsy. *Ann Thorac Surg* 2005;**79**:323–4.
21. Nagasaka T, Nakashima N, Nunome H. Needle tract implantation of thymoma after transthoracic needle biopsy. *J Clin Pathol* 1993;**46**:278–9.
22. Wakely Jr PE. Cytopathology of thymic epithelial neoplasms. *Semin Diagn Pathol* 2005;**22**:213–22.
23. Rea F, Marulli G, Girardi R, et al. Long-term survival and prognostic factors in thymic epithelial tumours. *Eur J Cardiothorac Surg* 2004;**26**:412–8.
24. Rena O, Papalia E, Maggi G, et al. World Health Organization histologic classification: an independent prognostic factor in resected thymomas. *Lung Cancer* 2005;**50**:59–66.
25. Wright CD, Wain JC, Wong DR, et al. Predictors of recurrence in thymic tumors: importance of invasion, World Health Organization histology, and size. *J Thorac Cardiovasc Surg* 2005;**130**:1413–21.
26. Park MS, Chung KY, Kim KD, et al. Prognosis of thymic epithelial tumors according to the new World Health Organization histologic classification. *Ann Thorac Surg* 2004;**78**:992–7.
27. Suster S, Moran CA. Thymoma classification: current status and future trends. *Am J Clin Pathol* 2006;**125**:542–54.

28. Moran CA, Suster S. On the histologic heterogeneity of thymic epithelial neoplasms. Impact of sampling in subtyping and classification of thymomas. *Am J Clin Pathol* 2000;**114**:760–6.
29. Bretti S, Berruti A, Loddo C, et al. Multimodal management of stages III–IVa malignant thymoma. *Lung Cancer* 2004;**44**:69–77.
30. Kim ES, Putnam JB, Komaki R, et al. Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report. *Lung Cancer* 2004;**44**:369–79.