A Review of Prognostic Factors in Thymic Malignancies

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Prognosis is a central piece of information we would like to know when someone is diagnosed with a disease. Prognosis is affected by many factors. For a cancer, one important aspect is the anatomic extent of the tumor, typically described by a stage classification. Nevertheless, a stage classification system should not be confused with a system to predict prognosis—tumor stage is only one aspect. Prognosis is affected by the treatment given, by patient-specific factors (i.e., comorbidities), tumor-related factors, and others, collectively known as prognostic factors.

The International Thymic Malignancy Interest Group (ITMIG) is currently engaged in the development of a validated formal stage classification system for thymic malignancies, together with the International Association for the Study of Lung Cancer and under the auspices of the Union International Contre le Cancer (UICC) and American Joint Commission on Cancer (AJCC). Assessment of prognostic factors is an important corollary to development of an anatomic stage classification system. A review of the current literature identifying prognostic factors is an important baseline to have for this initiative.

The study and classification of prognostic factors, in general, is very rudimentary. Often there is confusion because people are not clear about the outcome in question: a factor may be prognostic relative to overall survival, to cure from the disease, to response to treatment, etc. Prognostic factors are often specific to a subgroup of patients and a particular setting: factors associated with prognosis for a patient with thymoma undergoing surgery may be different from that of a patient with thymic carcinoma undergoing chemotherapy and radiation. Prognostic factors can be divided into "domains" of tumor-related factors, host factors (i.e., that would be present in the patient even if there was no tumor), and environmental factors (including things such as access to optimal care). Furthermore, once we identify a prognostic factor, we immediately begin trying to change the outcome to be what we want to see (i.e., to undermine the predictive value of the prognostic factor). Finally, there are many statistical pitfalls and errors in the definition of prognostic factors, as discussed in another article in this issue.[1]

Despite deficiencies in our level of sophistication about the science of prognostic factors, the need to estimate future outcomes for patients is great. This article sets out to provide a review of the current state of affairs in the area of thymic malignancies.

METHODS

A search was conducted for English language articles reporting prognostic factors for survival or recurrence for thymoma or thymic carcinoma published from January 1, 1980, to December 31, 2010. This was supplemented with a review of reference lists of retrieved articles, recent book chapters and review articles, and articles identified independently by the authors. We did not evaluate prognostic factors relative to outcomes other than overall survival or recurrence mainly because there are only a few isolated studies.

Recurrence is probably the best measure of outcomes for thymic malignancies, as discussed in a recent landmark ITMIG article.[2] Unfortunately, few studies have addressed this. We included studies reporting disease-free survival in the analysis for recurrence, even though it is problematic to view a recurrence and (unrelated) death as equal end points.[2] Overall survival has been the most commonly used end point because it is easy to measure. Nevertheless, is not an ideal end point, because many patients with thymoma die of unrelated causes, and patients may survive for many years with recurrent disease.[2] Different studies have used different measures (e.g., overall survival and thymoma-specific survival), which can give quite different survival results. Nevertheless, as the analyses were designed to evaluate the relative prognostic value of different factors within a study, it is reasonable to combine the prognostic factor results from studies involving various survival measures.

A valid prognostic factor must have independent significance and, therefore, must be evaluated in conjunction with other factors. Because of this, only studies that reported multivariate analysis (MVA) were included. No restriction was placed on the method of MVA or the number or nature of factors considered. Nevertheless, only articles reporting on $\geq$75 patients were included. This is because a rough estimate suggests that at least 75 patients are needed to be

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able to assess three factors with a medium effect size at a power of 80%.[2]

We included studies reporting on a broad group of patients, who were mostly treated with surgery and sometimes additional modalities. To have an assessment of the patients involved, we included the rates of treatment with different modalities in the tables. Separate consideration of particular subgroups and settings in these studies is not possible, partly because of how the reported studies were done, and partly because the rarity of the disease precludes an appropriate statistical analysis of many subgroups. Furthermore, studies reporting on a specific cohort are so limited that it is difficult to draw any conclusions. Nevertheless, several studies reported an analysis including all patients and only resected patients; data from both were included.

We excluded duplicate publications or articles involving smaller cohorts that were subsequently also included in a larger updated cohort. Some institutions reported results on partially overlapping cohorts in which each article included some unique patients; in this case, we included both articles even though there was substantial overlap.

Data were extracted into tables, and factors were recorded as positive if reported to have a p value of ≤ 0.05 by MVA. Depending on how a MVA is conducted, there may be a high chance of false-positive results.[2] For example, the way a variable is divided (e.g., dichotomized) into groups for analysis also often results in an overly optimistic assessment of statistical significance (e.g., choosing the threshold by the best separation and then entering the variable into the multivariate model this way, which is known as "double-dipping").[1,2] As a crude approach to assessment of this risk, we grouped those studies in the tables in which dichotomization seems to have been done in a way associated with a risk of false-positive designation of a prognostic factor. It was not feasible to go beyond this to assess the actual risk.

There is also a chance of false-negative results, especially in studies of limited size, because the power of detection is low. Data were recorded as negative if reported as such with a p value of more than 0.05. A crude estimate of the ability to detect a difference according to the size of the study, number of factors analyzed, and the magnitude of the difference can be made.[2] We established a priori that to be counted as a negative result the study should have, as a minimum by this crude estimate, a power of detection of 80% for a medium effect size. In the end, however, we found that all studies of more than 75 patients satisfied this requirement.

Not all studies analyzed the same factors. Although the assessment of significance can be strongly influenced by which factors are left out of the analysis, no attempt was made to correct for this. We sought to be as inclusive as possible, and therefore, data were retrieved and accepted as reported. The reported data were recorded as positive, negative, or not assessed to provide a general overview of reported results. Furthermore, most reported series chose to dichotomize variables but not always at the same threshold. In an effort to be inclusive, we tried to combine the data if the thresholds were reasonably similar (and noted differences in the footnotes of the tables).

Some studies reported several multivariate analyses (e.g., by including or not including some factors or using different definitions). Again, to be inclusive and in the absence of criteria to define one as more valid than another, we included each as a separate entry in the tables. In addition, multivariate analyses in several of the studies were specifically done or redone excluding a particular factor because it had a dominant effect or was correlated to another factor, to study the value of a particular factor of interest.[3–8] This would seem to undermine the purpose of MVA to sort out which factors have the most important influence on survival and bias the study toward finding prognostic value (falsely?) in the factor of interest. When such studies did not report an analysis including all factors, we were forced to include all subset analyses (e.g., stage without histology or histology without stage). By including all subset analyses, we hoped to represent a more unbiased overall picture. Nevertheless, this illustrates the potential for bias in how studies are conducted. One study was excluded because a separate MVA was reported for practically each factor, tailored to exclude other factors that "hid" the significance of the factor of interest.[3] Because this study reported no overall MVA, the reported results were felt to be biased and were reported without sufficient detail to even be sure what had or had not been included in each.

To summarize the data, we calculated the percentage of multivariate studies that found a factor to be significant out of the number that analyzed it. This should be interpreted cautiously and qualitatively, because of the many reasons for false-positive and false-negative results that we cannot sort out from this literature review. Factors that were addressed in less than five and less than three studies of overall survival or recurrence, respectively, are not listed in the tables because the data are too limited to draw any meaningful conclusions.

RESULTS

The literature search and inclusion criteria outlined earlier resulted in a total of 29 studies reporting a MVA of prognostic factors for survival and 12 reporting this for recurrence. A few studies[4,8,9] reported more than one analysis; each of these analyses were included in the tables (in accordance with the criteria outlined in the Methods section). The results from the included studies are summarized in Tables 1 and 2 and Figures 1 and 2.

The patients included are not clearly described in most of studies. Nevertheless, they can be loosely thought of as the patients presenting to an institution for curative-intent treatment. Data regarding the treatment received are summarized in the tables. The majority of patients underwent surgery, approximately half also received radiotherapy (RT), and approximately 25% chemotherapy. A few studies deserve special mention: de Jong et al.[11] involved a population-based cohort in the Netherlands, Cowen et al.[22] involved only patients treated with RT, and in the series by Lucchi et al.,[25] all patients had myasthenia gravis (MG).

The factor most consistently identified as significant—for both recurrence and survival—is the stage. In most of studies, this was dichotomized as stages I and II versus III

TABLE 1. Multivariate Analysis of Factors Predicting Better Survival

Study	*n*	Treatment (%)			Factors Predicting Better Survival								No. of Additional Factors
		R_0	Ch	RT	Stage I, II	R_0	Hist Thym	Hist w/TC	Older Age[a]	Small Size	Male Gender	MG	
Studies with more robust statistical approaches													
Ruffini 10[10b]	255	87	2	45	0.001	—	NS	—	—	—	—	NS	—
de Jong 08[11c]	232	41	10[d]	33[d]	0.01	—	—	<0.001	*<0.001*[e]	—	NS	NS	1
Rieker 02[6]	218	77	14	39	<0.001	—	—	<0.03	NS	NS	NS	NS	2
Park 04[12]	150	69	—	—	<0.001	—	—	<0.02	NS	—	NS	NS	—
Venuta 97[13b]	148	—	33[d]	—	0.0001	—	NS[f]	—	0.001	—	—	—	2
Park 04[12]	133	77	—	—	0.006	NS	—	NS	NS	—	<0.04	NS	—
Kim 05[7g]	108	82	16	28	<0.03	NS	—	NS	NS	NS	NS	NS	—
Studies with less robust or unclear statistical approaches													
Kondo 03[14b]	1093	—	—	—	<0.001	<0.001	NS[f]	—	NS	—	NS	NS	3
Margaritoria 10[15]	317	93	—	38	NS	0.001	—	NS	NS	—	NS	NS	2
Regnard 96[9]	307	85	6	52	NS	0.00001	—	NS[f]	—	—	—	NS	—
Lewis 87[16b,g]	283	83	2	26	<0.05	<0.05	NS[f]	—	<0.05	NS	NS	NS	5
Regnard 96[9]	260	100	6	52	0.00001	—	—	NS[f]	—	—	—	NS	—
Okumura 02[17b,g]	243	95	10[d]	60[d]	<0.0001	NS	0.05	—	NS	—	NS	NS	1
Ströbel 04[18g]	228	67	17	32	<0.05	<0.05	—	<0.05	NS	NS	NS	NS	1
Fang 05[19]	204	88	—	—	<0.001	0.004	—	0.001	—	—	—	NS	—
Lee 07[20]	195	83	5	40	<0.001	NS	—	<0.001	NS	—	NS	NS	—
Rena 05[21b]	178	84	13	43	<0.04[d]	<0.02	<0.03	—	NS	—	NS	NS	1
Cowen 95[22b,h]	149	42	50	100	NS	(0.003)[i]	—	—	0.013	0.001[j]	—	NS	1
Wilkins 99[23]	136	68	7	37	NS[k]	<0.001	—	0.02[f]	*0.036*[e]	—	NS	0.005	4
Nakagawa 03[4b,g]	130	95	4	5	<0.01	NS	—	—	NS	0.01	NS	NS	—
Nakagawa 03[4b,g]	130	95	4	5	—	0.002	0.01	—	NS	0.001	NS	NS	—
Rea 04[24]	132	82	18	47	0.003	NS	—	0.0001	NS	—	NS	NS	2
Lucchi 09[25b,l]	123	95	17	73	0.04[m]	—	NS	—	NS	NS	NS	—	2
Blumberg 95[26]	118	73	32	58	0.003	0.0006	—	0.004[f]	NS	0.0001	NS	NS	—
Pan 94[27b]	112	80	—	—	<0.05	—	NS	—	—	—	—	—	—
Quintanilla 94[28b]	105	100	0	24	<0.05	—	<0.05[f]	—	NS	NS	NS	NS	1
Zisis 05[8b]	104	100	14	63	—	—	0.05	—	NS	—	NS	NS	2
Zisis 05[8b]	104	100	14	63	<0.05	—	—	—	*<0.02*[e]	—	NS	NS	2
Kondo 04[29]	100	84	28	37	0.04	<0.05	—	NS	NS	—	NS	NS	—
Kim 10[30n]	100	79	7	67	NS	—	NS	—	—	NS	—	—	—
Kim 08[31h]	100	78	45	100	0.04	NS	—	0.02	<0.03	—	NS	NS	4
Chalabreysse 02[5]	90	67	3	12	—	—	—	<0.001	NS	—	—	NS	—
Rieker 07[32]	77	74	30[d]	62	NS	0.001	—	0.001	NS	—	NS	NS	1
Summary: % positive[o]					**83%**	**63%**	**42%**	**67%**	**15/11%[p]**	**36%**	**4%**	**3%**	

Inclusion criteria: Studies from 1980 to 2010 of ≥75 patients reporting multivariate analysis of prognostic factors. Factors evaluated by <5 studies are not listed. Studies with "less robust statistical approaches" have used "double-dipping" methods to define dichotomization that carry a risk of a false-positive identification of a statistically significant result.

[a] Variously defined as >30 (Lewis, Cowen), >60 (Venuta), >47 (Park), >57 (Wilkins, Kondo, Rieker), >52 (Rena) or unspecified.
[b] Thymic carcinoma excluded.
[c] Population-based study.
[d] Estimated, not specifically reported.
[e] In this series, older age groups had significantly worse survival.
[f] Older, non-World Health Organization classification.
[g] Thymoma-specific survival.
[h] RT-based series.
[i] Biopsy only vs. resection .
[j] Defined as no mediastinal compression.
[k] Stage I vs. II–IV.
[l] MG-based series.
[m] Definition unclear.
[n] For thymoma type B only.
[o] Excluding values in parentheses.
[p] Associated with better survival in 15% and worse survival in 11%.
Ch, chemotherapy; Hist, histologic type; MG, myasthenia gravis; NS, not significant; R_0, complete resection; RT, radiotherapy; w/TC, with thymic carcinoma; Thym, thymoma.

TABLE 2. Multivariate Analysis of Factors Predicting Lower Rates of Recurrence or Disease-Free Survival

Study	*n*	Treatment (%)			Factors Predicting a Lower Recurrence Rate								No. of Additional Factors
		% R_0	Ch	RT	Stage I, II	R_0	Hist Thym	Hist w TC	Older Age	Small Size	Gender	MG	
Studies with more robust statistical approaches													
Ruffini 10[10a,b]	255	87	2	45	0.001	—	NS	—	—	—	—	NS	—
Rieker 02[6a]	218	77	14	39	<0.05	—	—	<0.05	NS	NS	NS	NS	2
Wright 05[33]	179	90	—	—	<0.0001	NS	—	0.003	NS	0.001	NS	NS	3
Huang 09[34]	112	73	67	43	(NS)[c]	<0.001	—	0.006	NS	NS	NS	—	2
Studies with less robust or unclear statistical approaches													
Margaritoria 10[15a]	317	93	—	38	<0.001	NS	—	NS	NS	—	NS	NS	2
Margaritoria 10[15a]	295	100	—	36	<0.001	—	—	0.003	NS	—	NS	<0.0001	2
Rena 05[21a,b]	178	84	13	43	0.01	0.0001	<0.02	—	NS	—	NS	NS	1
Cowen 95[22b,d]	149	42	50	100	0.04	(0.003)[e]	—	—	0.006	0.001[f]	—	NS	1
Blumberg 95[26]	118	73	32	58	0.03	NS	—	NS	NS	NS	NS	NS	—
Quintanilla-Martinez[28a,b]	105	100	0	24	0.03	—	0.03[g,h]	—	NS	NS	NS	NS	1
Kondo 04[29a]	100	84	28	37	0.002	0.05	—	NS	NS	—	NS	NS	—
Kim 10[30a,b,i]	100	79	7	67	0.002	—	NS	—	—	0.002	—	—	—
Kim 08[31a,d]	100	78	45	100	0.04	NS	—	0.01	NS	—	NS	NS	3
Summary: % positive[j]					**100%**	**43%**	**50%**	**63%**	**9%**	**43%**	**0%**	**9%**	

Inclusion criteria: studies from 1980 to 2010 of ≥75 patients reporting multivariate analysis of prognostic factors. Factors evaluated by <3 studies are not listed. Studies with "less robust statistical approaches" have used "double-dipping" methods to define dichotomization that carry a risk of a false-positive identification of a statistically significant result.

[a] Disease-free survival.
[b] Thymic carcinoma excluded.
[c] III vs. IV.
[d] RT-based series.
[e] Biopsy only vs. resection.
[f] Defined as no mediastinal compression.
[g] Older, non-WHO classification.
[h] Medullary, mixed, or cortical thymomas had lower recurrence rates than well-differentiated thymic carcinoma (undifferentiated thymic carcinoma was excluded from the analysis).
[i] For thymoma type B only.
[j] Excluding values in parentheses.

Ch, chemotherapy; Hist, histologic type; MG, myasthenia gravis; NS, not significant; R_0, complete resection; RT, radiotherapy; w/TC, with thymic carcinoma; Thym, thymoma.

and IV. In most of studies, Masaoka or Masaoka-Koga staging was used, and, in fact, in all staging systems, this dichotomization yields essentially the same cohorts of patients. It should be explicitly noted, however, that most of these multivariate analyses have not defined prognostic significance for stage I versus II, II versus III, III versus IVa, or for a sequential progression to worsening outcomes from I to IVb. Nevertheless, multiple studies do show progressively worse rates of recurrence and survival,[35] although questions have been raised whether the difference between stages I and II is significant.[36] Nevertheless, despite the limitations of these prognostic factor studies, it seems reasonable to view the stage of disease as a validated prognostic factor.

Another fairly consistent prognostic factor for both recurrence and survival is a complete resection. Obviously, it only makes sense to assess this factor in patients who are treated with surgery (i.e., a subgroup of all patients). Despite the fact that the rate of complete resection is clearly associated with tumor stage,[35] an R0 resection seems to carry independent significance by MVA.

The histologic subtype of thymic malignancy also seems to be important but is a bit more difficult to fully assess. First, different histologic classification schemes have been used, although more recently the World Health Organization system[37,38] has been the predominant one. Second is the issue of interobserver variation in assigning the histologic class.[39–41] The greatest problem comes from the fact that most studies reporting prognostic value for histologic typing have not reported exactly which subtypes account for the difference. Furthermore, the dichotomization used in most studies has been first chosen to maximize the difference and then tested for significance (i.e., double dipping). Uneasiness about the strength of the results is also fostered by the fact that the "best" dichotomization has yielded many different cutpoints in these studies. Thymic carcinoma seems quite consistently to have the worst survival, but whether this subtype has independent prognostic significance cannot be assessed from the data reported. We attempted to explore this by separating the MVA in cohorts that included or excluded thymic carcinoma. This shows that more studies including thymic carcinoma found prognostic significance (67%) for overall survival than if only thymoma was included (42%). Nevertheless, there is less difference when assessing recurrence.

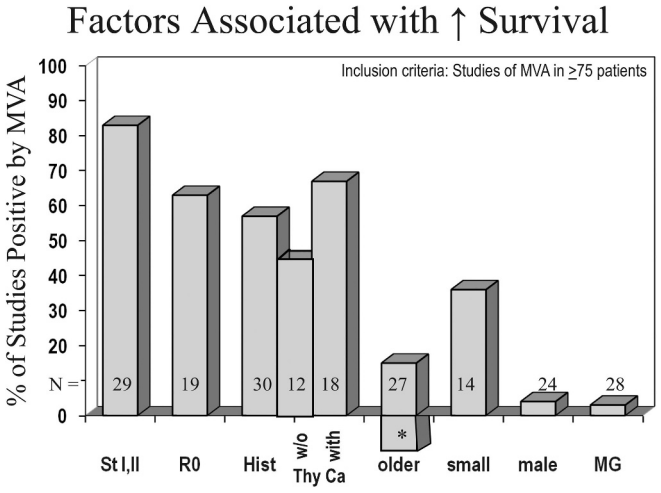

FIGURE 1. Factors associated with increased survival by multivariate analysis. Percentage of studies finding a factor prognostically significant for survival in multivariate analysis in studies of >75 patients from January 1, 1980, to December 31, 2010. *Percentage of patients showing that older patients had worse (not increased) survival. Hist, histologic typing; MG, myasthenia gravis; MVA, multivariate analysis; *N*, number of studies examining this factor; St, stage; Thy Ca, thymic carcinoma; w/o, without.

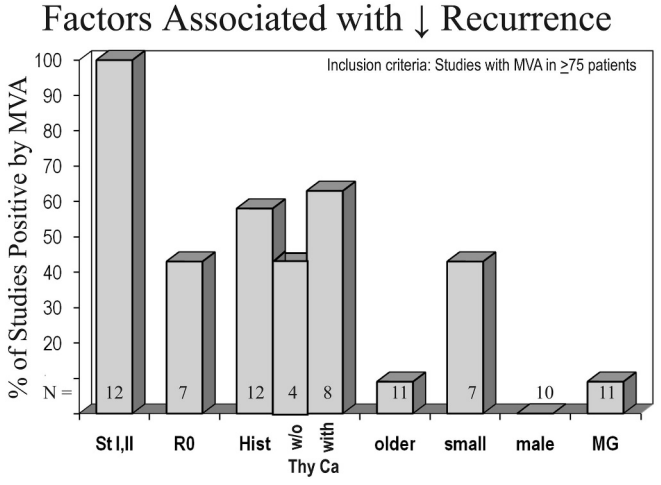

FIGURE 2. Factors associated with decreased recurrence by multivariate analysis. Percentage of studies finding a factor prognostically significant for recurrence or disease-free survival in multivariate analysis in studies of >75 patients from January 1, 1980, to December 31, 2010. Hist, histologic typing; MG, myasthenia gravis; MVA, multivariate analysis; *N*, number of studies examining this factor; St, stage; Thy Ca, thymic carcinoma; w/o, without.

The impact of age seems to be low. Age does not seem to have an impact on recurrence. One might predict that if there is no effect on recurrence, then older age would predict worse survival due to death from other causes. Nevertheless, several studies have found older age to be a good prognostic factor for overall survival, and a similar number found it predicted worse survival. The age threshold has been chosen at various cutpoints. Given the conflicting results, it is probably best to regard this factor as unlikely to be a valid prognostic factor.

A smaller tumor was found to be a good prognostic factor in a minority of studies for both recurrence and survival. Factors that do not seem to have prognostic significance for either survival or recurrence are gender and the presence of MG.

Many additional factors have been investigated sporadically (<5 studies). For overall survival, these include the time period (dichotomized periods),[11,13,15,16] the development of a recurrence,[8,18,24,31] the presence of parathymic syndromes other than MG,[14,16,21,24] symptoms,[16,23] comorbidity,[6,15] lymphoid hyperplasia,[6,28] remission of MG,[8,42] adjuvant RT,[9,42] adjuvant chemotherapy,[22] RT dose,[31] the presence of another nonthymic cancer,[23] great vessel involvement,[17] pleural invasion,[31] development of nodal metastases,[14] distant metastases,[14] Myasthenia Gravis Foundation of America (MGFA) class,[42] performance of a preoperative biopsy,[23] race,[23] cellular atypia or mitotic figures,[16] performance status,[32] and the sequence of multimodality treatment.[31] All these investigated factors were not found to be prognostically significant with the exception of one of four studies examining the time period,[13] one of four studies examining the appearance of a recurrence,[31] one of two studies examining remission of MG,[42] and one of one study examining the presence of great vessel involvement.[17]

Additional prognostic factors that have been investigated relative to recurrence (disease-free survival) in less than three studies include the time period,[15,33] performance of a preoperative therapy,[34] the use of adjuvant chemotherapy,[22] the sequence of multimodality treatment,[31] RT dose,[31] the presence of comorbidity,[6,15] parathymic syndromes other than MG,[21,33] lymphoid hyperplasia,[6,28] invasion of a vessel or structure,[33] pleural invasion,[31] and race.[34] All these factors were negative for prognostic significance except pleural invasion (in a single study).[31]

DISCUSSION

A conceptual framework to classify and integrate prognostic factors into a useful system is currently not available, and the thinking about how to approach this is evolving. The statistical approaches to define valid prognostic factors are much more developed, although not widely appreciated. Because the desire and need to predict outcomes are great, definition of prognostic factors cannot be simply delayed until the appropriate framework has been developed. Nevertheless, we must remember to view the definition of prognostic factors as an evolving process and take what we have at present with a grain of salt.

We attempted to address statistical weaknesses of existing studies to keep the results in proper perspective, but the ability to do this was limited. Overall, the methods used in most of the available studies carry a risk of identifying false-positive prognostic factors, which might not stand up to a more rigorous analysis. A review of the tables, however, suggests similar results in the studies with more versus less robust statistical approaches. Regarding false-negative re-

sults, we did not find that any reported analyses had a very limited power of detection because of trying to evaluate too many factors in a limited data set. Nevertheless, it should be noted that the size of the reported studies allows only detection of prognostic factors with a medium or large effect; the presence of a small effect on prognosis cannot be excluded for any factor.

Many of these studies spanned 20 or more years. Only a few studies analyzed the effect of the time period of treatment as a prognostic factor[11,13,15,16,33]; only one found a statistically significant difference.[13] Nevertheless, the ambiguities introduced by changes in practice over time and by inconsistencies in how various aspects of thymic malignancy have been defined reinforce the need to view this analysis of prognostic factors as preliminary.

The available data suggest that stage and completeness of resection can be viewed as validated prognostic factors. Furthermore, gender and the presence of MG can be accepted as not having prognostic significance. The effect of tumor size warrants further study. There are issues regarding what threshold to use (or series of thresholds?). Furthermore, there are issues of how size should be measured in a tumor that is typically not a round sphere.

The effect of tumor histology also requires further study. Survival curves from individual studies demonstrate quite consistently that thymic carcinoma carries a worse prognosis. Furthermore, this entity has been well recognized in all histologic classification systems. The multivariate studies that have included thymic carcinoma fairly consistently show prognostic value to histologic classification, whereas it is less clearly so when these patients are excluded. A discussion of issues associated with the histologic classification of thymic malignancies is currently ongoing. Therefore, it seems reasonable not to go beyond viewing thymic carcinoma as a validated independent negative prognostic factor and await further investigation before declaring other histologic features to be prognostically significant or not.

Because of the behavior of thymic malignancies, recurrence is a better measure of outcomes than overall survival. In general, the data on prognostic factors for recurrence (Table 2) parallel those for overall survival (Table 1). Nevertheless, the majority of studies have used disease-free survival as an end point, and this may at least partly explain the similar results. It is not wise to count death (from any cause) as the same as the development of a recurrence. Only four studies have focused specifically on recurrence.[22,26,33,34] This is clearly an area that must be addressed by future research on prognostic factors.

CONCLUSION

A review of the available data regarding MVA of prognostic factors in thymic malignancies demonstrates many limitations in our understanding of these. Tumor stage and completeness of resection are important for overall survival, whereas gender and the presence of MG are not. The effect of histologic classification other than identification of thymic carcinoma is unclear, as is the effect of tumor size. Future research on prognostic factors needs to focus on predictors of recurrence. Future research also should investigate novel factors such as biomarkers, as the number of factors that have been examined so far is rather limited. The infrastructure developed by ITMIG should significantly facilitate such investigations.

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