Editorial

Characterizing thymic tumors—how to track down rare diseases

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Awareness of rare diseases has increased over the past few decades. By the 3rd millennium, the keyword "orphan drugs" exceeded 100 hits in PubMed search. Nevertheless, no consensus in the definition of rare diseases has been achieved, even though a prevalence of 1 per 2,500 population might be considered (1). And still there is a dramatic lack of knowledge about rare diseases—for many reasons.

The rarity of a disease often leads to delayed diagnosis. Sufficient experience with these diseases is mostly reserved for experts at specialized centers. At the same time, there is a lack of reliable data on diagnostics, staging, therapy and prognosis.

Thymoma, thymic carcinoma and neuroendocrine tumors represent the typical malignancies of this organ. Their incidence is estimated as low as 0.17 per 100,000 (2). Thymic squamous cell carcinoma is one of 14 subtypes, accounting for 75% of thymic carcinoma. The lack of robust data reflects the rareness of these entities.

There are several approaches to this problem. A majority of scientific data comes from case reports. The thymus is an organ with a relatively low tumor burden. Thus, thymic tumors are often not mentioned in databases or subsumed under "other localizations" (3). Furthermore, studies of rare diseases often use scientific methods which are established for studies of common diseases—not infrequently with considerable problems. In a prospective randomized multicenter study, the subgroup of neuroendocrine thymic tumors could not be evaluated due to insufficient recruitment (4). Often, therapeutic concepts of rare diseases are also adopted from related and more common diseases. The resulting findings may be valuable but are subject to considerable uncertainty regarding their validity (5). The Surveillance, Epidemiology, and End Results (SEER) database is an important source of information about thymic tumors, but often relevant data are not captured (6). Retrospective analyses of the topic are subject to significant bias or do not allow discrimination of relevant subgroups (7-9).

For their recent article "Skeletal muscle and related protein expression as prognostic factors in thymic squamous cell carcinoma", Nakanishi *et al.* (10) chose two medical examination methods which stand for long-lasting assessability: computed tomography and histologically processed tumor tissue. They analyzed the prognostic impact of sarcopenia, represented by radiological psoas muscle index (PMI). Furthermore, immunohistochemical analysis was performed to determine the expression levels of the protein receptors fragile X-related 1 (FXR1) and programmed death ligand-1 (PD-L1).

FXR1 and PD-L1-levels showed no differences between the groups examined, indicating that these are not factors independently influencing the course of disease in thymic squamous cell carcinoma (TSQCC). The authors express the interesting hypothesis that addressing the extensive levels of FXR1 may be a promising therapeutic approach for sarcopenia.

For PMI the authors performed comprehensive statistics.

The group was divided into two, using the median PMI for cut off. The group with lower PMI was 10 years older (median 67; ranging from 54–79 years), than the younger group (median 57; range, 38–69). Bearing in mind that Hamaguchi *et al.* had reported, that PMI is significantly (P<0.001) lower in individuals ≥50 years than in younger men and women (11), the difference in overall survival (P=0.026) appears to be much more influenced by age than by PMI. As the raw data of PMI are not provided, it is difficult to compare to the sex-specific cutoff values published by Hamaguchi. Based on the information provided in the article, we estimate these values as 6.01 in the low PMI group and 9.01 in the high PMI group, which is within the limits of normal even for males.

It is worth reading the peer review comments, published by the *Journal of Thoracic Diseases* (10). The reviewers tend to state that one should rather conclude that PMI as well as PD-L1 and FXR1 levels are not reliable factors to assess the prognosis of TSQCC. We prefer this interpretation of the results, too.

However, one aspect of the work should be highlighted. The authors have examined numerous factors for their prognostic value, although this has regrettably not been discussed in detail. These are levels of tumor marker CYFRA 21-1, tumor size, lymph nodal metastasis status, Masaoga-Koga stage as well as TNM stage, resection status, differentiation and lymphoid infiltration. Lymph node metastases were associated (P=0.007) with a reduced 5-year disease free survival (DFS), but not overall survival (OS), which explains the non-significant tendency for lower DFS in higher Masaoka-Koga- and TNM-stages.

Quite surprising: in the univariate analysis the vast majority of factors, which we would intuitively consider as prognostic, shows neither an influence on DFS nor on overall survival. And R1 resection status resulted in a (not significant) better OS than R0 resection, as did lymphoid infiltration.

This may be explained partly by the small sample size. The quite good 5-year overall survival of more than 90% may contribute to these results as well, especially since this contrasts with the <60 % OS and DFS reported by other authors (7). But still we consider this a remarkable observation.

Concluding, it is the negative results that are the charm of this publication, providing valuable steps towards a better understanding of thymic squamous cell carcinoma. The authors are to be thanked for taking on the challenge of examining these factors for their prognostic value.

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