Editorial

How large databases may impact clinical practices for rare tumors—postoperative chemotherapy in thymic malignancies

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In this issue of the *Journal of Thoracic Disease*, Ma *et al.* report on the analysis of a cohort of 665 patients with advanced thymic epithelial tumors, looking at the long-term effects of postoperative chemotherapy on recurrence and survival rates (1). This cohort of the Chinese Alliance for Research in Thymomas (ChART) is the largest to date to investigate this question. Postoperative chemotherapy is actually not routine practice (2), as the vast majority of patients operated on for a thymic epithelial tumor do have early-stage disease (1,015 patients out of 2,306 cases in the ChART database), and/or receive primary/induction chemotherapy in the setting of advanced, non-resectable disease to subsequently achieve complete resection (3)—surprisingly a rare situation in the ChART database, only 68 out of 2,306 cases. Ultimately, the rationale for postoperative chemotherapy is limited in thymomas, as the risk of systemic metastases is low, ranging from 8% in stage I/II tumors, to 29% in stage III/IV tumors in the International Thymic Malignancy Interest Group (ITMIG) retrospective database (4); moreover, the majority of recurrences occur loco-regionally, in the pleura, with possible eligibility to re-resection. Meanwhile, recurrences, including systemic recurrences, are more frequent in thymic carcinomas, occurring in 29% of stage I/II cases, and in 51% of stage III/IV cases (4).

The results of the ChART database analysis confirm, with an even higher statistical power, that of previously reported series; postoperative chemotherapy was most frequently delivered in the setting of higher stage (27% of stage III, 56% of stage IV tumors)—and thus higher histological grade, type B3 thymomas (28% of cases) and thymic carcinomas (51% of cases), given the well established correlation between stage and histology in thymic epithelial tumors (5)—and incomplete, R2 resection (51% of cases, *vs.* 27–30% of R0–R1 cases).

This is in line with existing recommendations in the field. Especially, the Clinical Practice Guidelines of the European Society for Medical Oncology (ESMO) recommends postoperative chemotherapy to be administered after R2 resection of a thymoma, and to be systematically considered in stage II/III/IV thymic carcinomas, especially if not delivered as induction treatment (2). Actual evidence is sparse: only one prospective phase II study was conducted in advanced thymoma, showing, in 22 patients, the feasibility of multimodal strategy with induction chemotherapy, surgical resection, and radiation therapy, followed by consolidation chemotherapy with cyclophosphamide, doxorubicin, cisplatin and prednisone (6); in thymic carcinoma, recent reports from the ITMIG and European Society of Thoracic Surgery databases indicate that postoperative chemotherapy was delivered to 30% to 42% of patients, with unclear benefit (7,8); combination with radiotherapy was then reported in the majority of patients (7).

Those data also illustrate the difficulties in identifying the clinical relevance of retrospective data, even if large cohorts of patients are analyzed. In the ChART study, stratification analyses further indicate that patients who received postoperative chemotherapy or chemoradiotherapy had a significantly worse outcome, with recurrence rates of 46% *vs.* 26% in the non-chemotherapy group. As stated by the authors, postoperative chemotherapy may have preferably been administered for high-risk patients (thymic carcinoma histology, high stage, R2 resection), then hampering the statistical identification of its potential benefit. Indeed, in the propensity-matched analysis, no differences in the chemotherapy and non-chemotherapy groups were observed.

Ultimately, the analysis of large databases would be

facilitated if pre-defined treatment strategies are prospectively implemented on homogeneous subsets of patients, across multiple institutions, based on consensual guidelines. In France, RYTHMIC (Réseau tumeurs THYMiques et Cancer) is a nationwide network for thymic malignancies, which was appointed in 2012 by the French National Cancer Institute, as part of its rare cancer program. Since then, the management of all patients diagnosed with thymic tumors has been discussed on a real-time basis at a national multidisciplinary tumor board (MTB), which is organized twice a month basis using a web-based conferencing system. Decision-making is based on consensual recommendations that were originally established based on available evidence, and are updated and approved each year by all members of the network. A prospective database of all patients is hosted by the French Thoracic Cancer Intergroup. Overall, more than 1,000 patients have been enrolled, demonstrating the feasibility of a national MTB for thymic malignancies, that, besides ensuring patients an equal access to highly specialized management, provides with a comprehensive tool to monitor dedicated actions to improve the management of patients (9).

While prospectively ensuring the stringency of the decision-making at each step of the management of patients with thymic tumors, what represents a major commitment of multi-disciplinary teams, one limitation of such organization are the low levels of evidence and grades of recommendation of available guidelines. The ESMO Clinical Practice Guidelines, even if representing the most comprehensive recommendations for the management of thymic malignancies, are still based on level of evidence of III (prospective cohorts), IV (retrospective studies), and even V (expert opinions).

To conclude, the global and comprehensive effort of ChART has to be congratulated, emphasized, and should lay the foundations of prospective, controlled studies, possibly integrating innovative approaches such as adaptive, Bayesian designs. As a landmark of rare diseases, collaboration may make a success, and thymic malignancies represent a model of incremental effort in this setting.

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Footnote

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