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Mesothelioma and thymic tumors: Treatment challenges in (outside) a network setting

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ABSTRACT

The management of patients with mesothelioma and thymic malignancy requires continuous multidisciplinary expertise at any step of the disease. A dramatic improvement in our knowledge has occurred in the last few years, through the development of databases, translational research programs, and clinical trials. Access to innovative strategies represents a major challenge, as there is a lack of funding for clinical research in rare cancers and their rarity precludes the design of robust clinical trials that could lead to specific approval of drugs. In this context, patient-centered initiatives, such as the establishment of dedicated networks, are warranted. International societies, such as IMIG (International Mesothelioma Interest Group) and ITMIG (International Thymic Malignancy Interest Group) provide infrastructure for global collaboration, and there are many advantages to having strong regional groups working on the same issues. There may be regional differences in risk factors, susceptibility, management and outcomes. The ability to address questions both regionally as well as globally is ideal to develop a full understanding of mesothelioma and thymic malignancies.

In Europe, through the integration of national networks with EURACAN, the collaboration with academic societies and international groups, the development of networks in thoracic oncology provides multiplex integration of clinical care and research, ultimately ensuring equal access to high quality care to all patients, with the opportunity of conducting high level clinical and translational research projects.

Introduction

Rare thoracic tumors are defined as tumors originating from the lung, the pleura, or the mediastinum with low incidence [www.RARECARE.eu] and unusual histology [1]. Overall, these tumors account for about 11% of all primary thoracic tumors, whereas they correspond to more than 100 different histologic, clinical, radiologic, and prognostic entities [2]. Thoracic rare tumors are characterized by limited clinical and imaging descriptions, by the low number of experienced specialists for each tumor subtype, and by the limited amount of specific therapeutic data [1].

The recent establishment of the European Reference Network EURACAN provides an infrastructure of healthcare providers with high level of multidisciplinary expertise for the diagnosis, and the management and follow-up of patients with rare cancers, including rare thoracic tumors; the objective is to increase the quality of care, while building collaboration to develop clinical and translational research projects [www.ec.europa.eu/health/sites/health/files/ern/docs/erneuracan_factsheet_en.pdf].

Mesothelioma is the most frequent and thymic tumor is one of the rarest tumor types among rare thoracic cancers [2]; while patients have already been treated in dedicated networks in some European countries, initiatives have been taken at the European level to share clinical practices, analyze large databases, and develop common guidelines. However, at population level, hospital centralisation of rare cancer patients from seven different European countries, studied for the period 2000–2007 was not as expected,

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especially for patients with mesothelioma. The recently published study showed an annual mean admission hospital volume of 5 cases of mesothelioma, with a large variation across countries [2].

Epidemiological data

Mesothelioma

Malignant pleural mesothelioma (MPM) is a rare, aggressive cancer that develops from the surface mesothelium of the pleural cavity [2]. In Europe (EU28), about 11.000 new cases are diagnosed in a year with a crude incidence of 1.8/100,000 individuals per year [2], representing 3% of all thoracic cancers. The prevalence estimated for the year 2008 was 3/100,000 individuals, with 15,650 cases in EU28 [2].

This malignancy is strongly related to exposure to asbestos, and in fact more than 80% of cases are due to professional exposure [3].

There is a long latency (30–50 years) between exposure and disease presentation and in fact the highest incidence is reported in patients aged over 65 (7.8 100,000). For this reason, although asbestos has been banned in 55 countries for at least the last 20 years, a peak in incidence is expected in 2020–2030 in Western countries [3]. Unfortunately, the continued use of asbestos in developing countries and the inefficient disposal of the asbestos used in the past for buildings in the industrialised countries could lead to a new wave of MPM diagnosis in extended areas [3].

What about survival?

Thoracic mesothelioma has a very poor prognosis. In Europe, during the period 2000–2007, 1- 3- and 5-year survival was 39, 9 and 5%, respectively. Outcome was slightly better in young (25–64 years of age) than old patients (>65 years of age): at 3 years survival figure was 12% versus 7%. Survival was slightly better in females than males (3-year survival 12% versus 8%). A low, but significant, progress was reported for 1-year survival: from 34% (1999–2001) to 40% (2005–2007) [2].

Thymic malignancies

Thymic malignancies are rare cancers. In Europe, the annual crude incidence rates ranging from <1 (Northern Ireland, Scotland, Iceland, Lithuania) and between 2 and 3.5 per million individuals (Austria, Belgium, Italy, Malta, Spain, Switzerland and the Netherland). [www.RARECARE.eu, [4]]. In France, from the RYTHMIC data, incidence in 2015 was higher (3.4 per million individuals) [5]. Mean age at diagnosis is 50–60 years-old, but thymic malignancies may actually be diagnosed in children as well as in elderly patients [6]. There is no consistent gender predilection in thymomas overall, even if a slight female preponderance has been reported for type A, AB, and B1 subtypes in most studies.

No environmental or infectious factors have been demonstrated so far to play a role in the pathogenesis of thymic epithelial tumors. Reports on development of thymoma after radiation, solid-organ transplantation and HIV infection are rare; differential diagnosis with thymic rebound hyperplasia may be discussed in this setting [7]. Genetic risk factors may participate in the development of thymomas, given rare occurrence in case of familial background or association with cancer susceptibility syndromes, such as MEN1. Moreover, extra-thymic haematopoietic and solid cancers have been reported to occur, before and after thymoma diagnosis, at increased frequency [8].

Five-year survival of malignant epithelial tumors of thymus, as assessed for Europe for the period 2000–2007, was 64% [2], with large variation across type of tumor. The highest outcome (69%) was reported for malignant thymoma and the lowest (13%) for the undifferentiated cancer of thymus [www.RARECARE.eu].

Current strategies for mesothelioma and thymic tumors

Mesothelioma

The histological diagnosis of MPM is often complex due to the heterogeneity of this group of tumors. The three main histological subtypes are the epithelioid type, which is the most common (50–70%) and usually has more favorable prognosis; the sarcomatoid type (10–20%) that is the most aggressive; and the biphasic type (20–35%) that has both epithelial and sarcomatoid elements and has an intermediate prognosis [9]. Execution of biopsies is strongly advised in order to have a correct diagnosis that ideally should be performed by expert pathologist with the aim of reducing pitfall and diagnostic delays. Uncorrect diagnosis and in particular the inclusion of non-neoplastic lesions could explain the high survival for MPM in some European countries.

Due to the rarity and the complexity of the disease, each case should be evaluated in a multidisciplinary team in expert centers, consisting of a surgeon, a medical oncologist, pulmonologist, pathologist, nurses, palliative care specialist. The treatment strategy includes surgery in some cases, and chemotherapy for the majority of patients.

Surgery with radical intent may be offered to those patients with stage I–III disease, epithelial or biphasic histology and that are medically operable [10]. However, due to its location it is virtually impossible to obtain free resection margins, therefore the intent is often to remove all the visible tumor. Main surgical procedures, as defined according to the International Association for the Study of Lung Cancer [11] include:

- EPP (extrapleural pneumonectomy) that entails a complete en bloc removal of the involved pleura and the whole lung, sometimes extended to the diaphragm and pericardium;
- P/D (pleurectomy/decortication) that implies the removal of all gross tumor;
- Extended P/D that usually includes the resection of the diaphragm and pericardium if involved;
- Partial pleurectomy that implies the resection of part of the involved pleura, leaving gross tumor behind.

The prospective randomized Mesothelioma and Radical Surgery 1 (MARS 1) trial enrolled patients, who were treated with induction chemotherapy and then randomized between EPP and no EPP. In the feasibility study, 112 patients were enrolled over a 3-year period. Only 45% of patients (50/112) could be randomized after induction therapy, and 16 were randomly assigned to receive EPP. In this small group, mortality rate was 19% and median overall survival was 14 months, compared with 19 months for those not having EPP [12]. A subsequent trial was designed (MARS2) to assess the feasibility of randomization into P/D after induction chemotherapy (NCT02040272). Another trial with a similar design is ongoing in Italy (PASS trial) [www.meso.ospedale.al.it].

The combination of induction chemotherapy, surgery and radiotherapy (trimodality treatment) was studied in several trials, with inconsistent results. In a systematic review performed on 16 studies (including 5 prospective trials), median overall survival ranged from 13 to 47 months with acceptable perioperative mortality (0%–12.5%) [13]. However, a large prospective phase II trials of induction chemotherapy and EPP with or without radiotherapy has failed to show benefit in terms of survival with relevant toxicities, including one death from radiation pneumonitis [14]. The use of preoperative radiotherapy before EPP is being investigated,

and was proved to be feasible with potential prolonged survival [15,16]. More prospective trials are needed in order to assess the real benefit of radiotherapy and trimodality treatment.

For advanced MPM, systemic therapy should be offered to patients with good performance status (PS 0–2), medically inoperable or refusing surgery, or affected by stage IV disease or in sarcomatoid histology (any stage). In this setting radiotherapy can be considered for palliation of pain or to prevent sub cutaneous metastasis that can occur after local procedures. Surgery can be considered for pleural effusion management.

The standard for systemic treatment is represented by a combination of a platinum compound and a folate antagonist (pemetrexed) after 2 randomized phase III trial showed a survival advantage for the combination cisplatin-pemetrexed (overall survival of 12.1 months), and cisplatin-raltitrexed (overall survival of 11.4 months), compared to cisplatin alone (9.3 and 8.8 months, respectively) [17,18]. In a recent randomized phase III trial, the combination of cisplatin-pemetrexed-bevacizumab was compared to cisplatin-pemetrexed, showing an increased overall survival by 2.7 months (18.8 vs. 16.1 months) with a slightly higher toxicity rate (71% vs 62% of patients) [19]. Other acceptable combinations for first line chemotherapy include carboplatin and pemetrexed, that was assessed in 3 different phase II trials (median overall survival of 12.7, 14.0, and 14.0 months, respectively) [20–22].

Other options for patients include cisplatin-gemcitabine; for second-line treatment, single-agent pemetrexed (if not administered in first line setting; or as rechallenge in patients who had a good response to first line therapy), vinorelbine, and gemcitabine are possible. Immunotherapy seems potentially active in MPM. A checkpoint inhibitor, the anti-CTLA4 antibody tremelimumab, had shown interesting disease control rates in preliminary studies, but the phase IIb trial with tremelimumab vs. best supportive care in second and further lines has failed to show any advantage in unselected patients [23]. Other studies are ongoing with anti-PD-1/PD-L1 inhibitors, as well as with immunogenic therapy with intrapleural viral vectors and autologous dendritic vaccines. Research is also focusing on mesothelin-targeted treatments, including amatuximab, and anetumab ravtansine, anti-mesothelin immunotoxins (SS1P), mesothelin tumour vaccine (CRS-207), and chimeric antigen receptor T-cell targeted to mesothelin [24].

Thymic tumors

Thymic malignancies represent a heterogeneous group of cancers, which are classified according to the World Health Organization (WHO) histopathologic classification, that distinguishes thymomas from thymic carcinomas [25]; thymomas are further subdivided into different types (so-called A, AB, B1, B2, and B3) based upon the relative proportion of the non-tumoral lymphocytic component, and the resemblance to normal thymic architecture [25]. Thymic carcinomas are similar to their extra-thymic counterpart, the most frequent subtype being squamous cell carcinoma [25,26]. Staging of thymic tumors is currently based on the Masaoka-Koga system [27], that will be replaced by a TNM-based system for the 8th Edition of the AJCC/UICC staging classification of tumors starting 2018 [28]; the TNM staging may help to better define the resectability of the tumor.

The management of thymic epithelial tumors is a paradigm of cooperation between clinicians, surgeons, and pathologists from establishing the diagnosis to organizing the multimodal therapeutic strategy (Fig. 1) [7].

Surgery is the mainstay of the curative-intent treatment, as complete resection represents the most significantly favorable prognostic factor on overall survival [7,29]. Standard approach is median sternotomy, which allows the wide opening of the

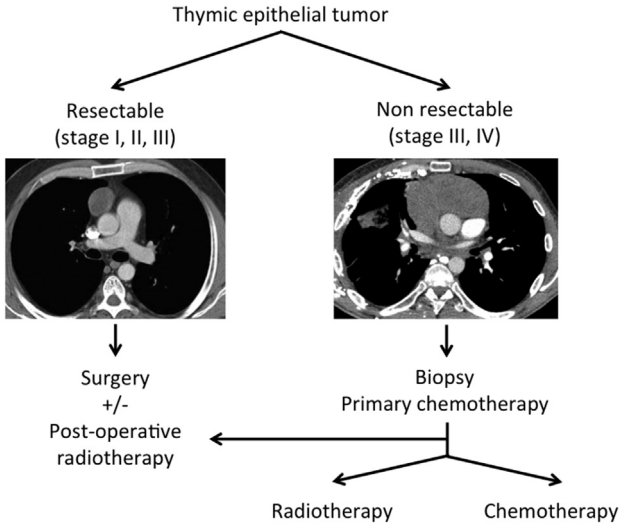

Fig. 1. Management strategies for thymic tumors.

mediastinum and both pleural cavities. Generally, complete thymectomy including the tumor, the residual thymus gland and perithymic fat is preferred; if the tumor is widely invasive, en-bloc removal of all affected structures, including lung parenchyma (usually through limited resection), pericardium, great vessels, nerves and pleural implants, should be carried out. Minimally-invasive surgery is an option for small tumors in the hands of appropriately-trained thoracic surgeons.

Radiotherapy may be delivered in the postoperative setting, aiming at reducing the risk of recurrence [7]. Stage and completeness of resection are thus the most relevant criteria in the decision-making, followed by histology.

Systemic treatment may be delivered in a curative-intent approach, for patients presenting with locally-advanced tumor at time of diagnosis, with invasion of intra-thoracic neighboring structures, and/or dissemination to the pleura and the pericardium, precluding upfront complete resection to be achieved. In such cases, chemotherapy has been used both to reduce the tumor burden - possibly allowing subsequent surgery and/or radiotherapy- and to achieve prolonged disease control [7,30]. In this setting, cisplatin-based combination regimens should be administered; combinations of cisplatin, adriamycin, and cyclophosphamide, and cisplatin and etoposide have been recommended, based on historical studies [7,31].

When the patient is not deemed to be a surgical candidate - either because R0 resection is not thought to be achievable, or because of poor performance status or co-existent medical condition, definitive radiotherapy is recommended part of a sequential chemoradiotherapy strategy [7]. Combination with chemotherapy (including cisplatin, etoposide chemotherapy and a total dose of radiation of 60 Gy) may be considered as well.

Chemotherapy is also a palliative-intent treatment of unresectable, metastatic, and recurrent tumors, which are more frequently thymic carcinomas than thymomas [7,29–31]. Again, cisplatin-based combination regimens with anthracyclins and/or etoposide are standard. No randomized studies have been conducted, and it is unclear which regimens are best; multi-agent combination regimens and anthracycline-based regimens appear to have improved response rates compared to others, especially the etoposide, ifosfamide and cisplatin combination [7,29–31]. Combination of carboplatin and paclitaxel is an option for thymic carcinoma, based on results of recent phase II trials [7].

Recurrences of thymic epithelial tumors should be managed according to the same strategy as newly diagnosed tumors. Complete resection of recurrent lesions represents a major predictor of favorable outcome, and surgery is then recommended in case of resectable lesion [7]. In non-resectable recurrences, several consecutive lines of chemotherapy may be administered when the patient presents with tumor progression. Preferred regimens for second-line treatment include carboplatin plus paclitaxel, and platin plus etoposide; capecitabine plus gemcitabine is an option [7,29–31]. Options for subsequent lines include pemetrexed, oral etoposide.

In the setting of advanced disease, multiple novel agents have been evaluated in thymic malignancies, with variable outcome. Sunitinib is an off-label option in the second-line setting, based on its antiangiogenic activity. Everolimus may be another option for refractory disease. Several trials assessing the efficacy of PD-1 checkpoint inhibitors are currently ongoing. Phase II studies of pembrolizumab were recently reported, collectively enrolling 63 patients, showing response rates of 24%, but occurrence of serious, autoimmune adverse events in 20%–30% of patients [32,33]. The off-label use of checkpoint inhibitors is currently not recommended.

Networks

The management of patients with mesothelioma and thymic malignancy requires continuous multidisciplinary expertise at any step of the disease. A dramatic improvement in our knowledge has occurred in the last few years, through the development of large databases, translational research programs, and clinical trials [34–38]. Access to innovative strategies represents a major challenge, as there is a lack of funding for clinical research in rare cancers and their rarity precludes the design of robust clinical trials that could lead to specific approval of drugs. In this context, patient-centered initiatives, such as the establishment of dedicated networks, are warranted. International societies, such as IMIG (International Mesothelioma Interest Group) and ITMIG (International Thymic Malignancy Interest Group) provide infrastructure for global collaboration, and there are many advantages to having strong regional groups working on the same issues [34–38]. There may be regional differences in risk factors, susceptibility, management and outcomes. The ability to address questions both regionally as well as globally is ideal to develop a full understanding of mesothelioma and thymic malignancies. Actually, diversity makes research in all the fields above discussed, more valuable.

National networks

In France, RYTHMIC (Réseau tumeurs THYMiques et Cancer; www.rythmic.org) 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 (Fig. 2) [38]. Since then, the management of all patients diagnosed with thymic tumors has been discussed on a bi-mensual 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 2000 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, and enroll patients in clinical trials. Similar thymoma-dedicated and mesothelioma-dedicated networks are now being implemented in France [www.e-cancer.fr/content/.../file/Resaux-nationaux-cancers-rares-adultes-2015.pdf] and in other European countries, such as Spain and Italy (the TYME collaborative group) [39,40].

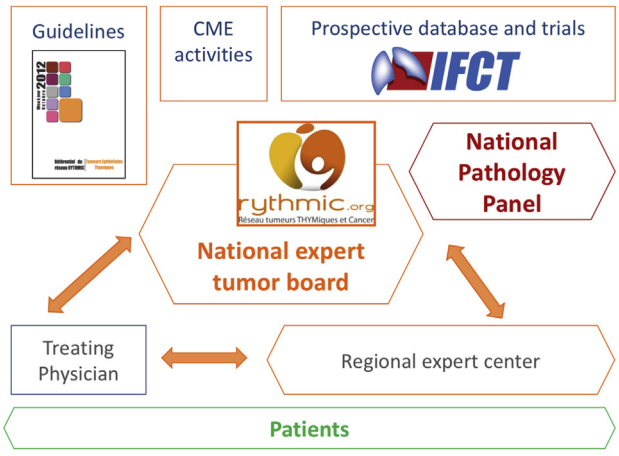

Fig. 2. Infrastructure of the French RYTHMIC network. Legends: CME: Continuous Medical Education.

Outside Europe, The Chinese Alliance for Research in Thymomas (ChART) and the Japanese Association for Research on the Thymus (JART) are national groups aiming at building and analyzing retrospective and prospective databases of thymic tumors cases [36,37].

International networks

The International Thymic Malignancies Interest Group (www.itmig.org) was created in 2010, and was endorsed and supported by the most representative medical and surgical societies around the globe [35]. The mission of ITMIG is to promote the advancement of clinical and basic science related to thymic malignancies. It provides infrastructure for international cooperation, trials, maintains close collaboration with other related organizations, and facilitates the spread of knowledge about thymic neoplasms. The achievements of ITMIG include 1)the development of standard definitions based on multidisciplinary consensus, regarding outcome measures, handling of surgical specimens, staging, surgical techniques, radiotherapy, and chemotherapy; 2) a significant contribution to the WHO histopathological classification update; and 3/ the establishment of an international, retrospective database of nearly 10,000 cases that has been a resource for descriptive studies, mostly driven by US-based investigators, as well as for the development of the 2018 TNM-based staging system as a backbone for the survival analyses of specific groups of patients [28]. A prospective database linked to a virtual tumor bank is underway.

The International Mesothelioma Interest Group was created in the early 90′, aiming at holding an international mesothelioma conference on alternate years, improving collaboration by generating a list of available research resources, and fostering international interest groups to address specific issues of importance, e.g. early diagnosis, thoracoscopy, comparison of national mesothelioma registers.

European networks

Research on mesothelioma and thymic malignancies has historically been driven by thoracic surgery societies, including the

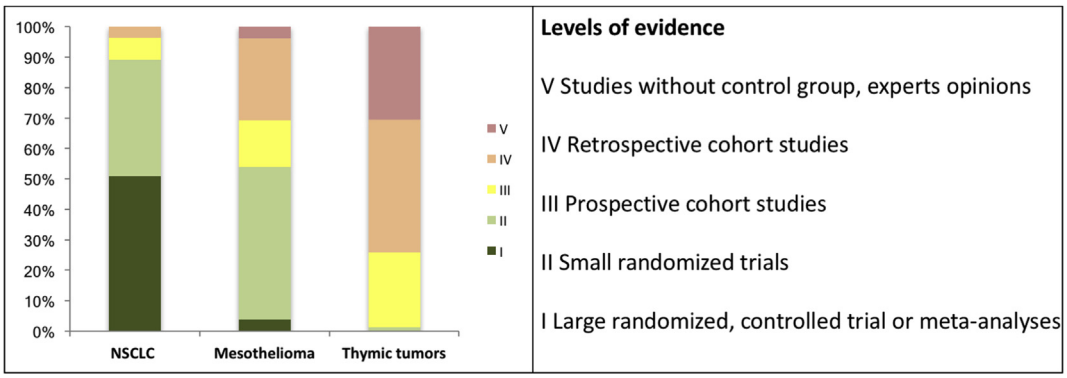

Fig. 3. Levels of evidence in the clinical practice guidelines of the European Society for Medical Oncology for non-small cell lung cancer, mesothelioma, and thymic tumors. Legend: NSCLC: non-small cell lung cancer.

European Society of Thoracic Surgery (ESTS) and the European Association of Cardio-thoracic Surgeons (EACTS) for thymic tumors; especially, the ESTS published multiple analyses on a retrospective cohort of patients, and is currently establishing a prospective database.

The European Society for Medical Oncology recently published the first multidisciplinary, comprehensive clinical practice guidelines for the management of mesothelioma and thymic tumors, integrating all the aspects of the management of the disease, from the diagnosis to the follow-up of patients [7,10]; as shown on Fig. 3, the level of evidence of thymic tumors recommendations is far lower than that of guidelines for non-small cell lung cancer and mesothelioma.

Within the European Reference Network EURACAN, the rare thoracic tumor domain – referred as to G8 domain - handles a network of 20 + healthcare providers; the objectives of EURACAN include the updating and the assessment of current guidelines, the development of educational programs, dissemination and communication with patients groups, and the establishment of research projects, from the diagnosis workup of the disease to the therapeutic strategies. Achieving the highest quality of patient care is the main objective of EURACAN, and the RYTHMIC model provides some practical tools to be implemented at the European level. The European network also provides an infrastructure for collaboration with diagnosis and pharmaceutical companies; one example may be the opening of dedicated cohorts in basket studies assessing new drugs, for which the network allows a better identification of patients and facilitates the recruitment in the trials [clinicaltrials.gov NCT03012620].

In Europe, through the integration of national networks with EURACAN, the collaboration with academic societies and international groups, the development of networks in thoracic oncology provides multiplex integration of clinical care and research, with the opportunity of conducting high level clinical and translational research projects, and ultimately ensuring equal access to high quality care to all patients. Within EURACAN the evaluation of outcome will be based on the use of cancer registry population data, the integration with clinical databases will be crucial to understand the extent of the access to standard treatment and to reduce the disparities.

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Conflict of interest statement

No disclosure for the authors.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2018.01.078.

References

[1] Girard N, Barbareschi M, Cordier JF, Murer B. What is a rare tumor, and how to deal with it clinically? Eur Respir Monogr 2007;39:85–133.
[2] Gatta G, Capocaccia R, Botta L, Mallone S, De Angelis R, Ardanaz E, et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. Lancet Oncol 2017 Aug;18(8):1022–39.
[3] Carbone M, Yang H. Mesothelioma: recent highlights. Ann Transl Med 2017;5:238.
[4] 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.
[5] Bluthgen M, Dansin E, Kerjouan M, Mazieres J, Pichon E, Thillays F, et al. Updated incidence of thymic epithelial tumors (TET) in France and clinical presentation at diagnosis. J Thorac Oncol 2016;12. S524.
[6] 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.
[7] Girard N, Ruffini E, Marx A, Faivre-Finn C, Peters S. ESMO Guidelines Committee. Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26(Suppl. 5):v40–55.
[8] Engels EA. Epidemiology of thymoma and associated malignancies. J Thorac Oncol 2010;5:S260–5.
[9] WHO histological classification of malignant pleural mesothelioma. In: Travis WB, Brambilla A, Burke AP, Marx A, Nicholson A, editors. World Health Organization classification of tumours of the lung, Pleura, Thymus and Heart. Lyon: IARC Press; 2015.
[10] Baas P, Fennell D, Kerr KM, Van Schil PE, Haas RL, Peters S. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26:v31–9.
[11] Rice D, Rusch V, Pass H, Asamura H, Nakano T, Edwards J, et al. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: a consensus report of the international association for the study of lung cancer international staging committee and the international mesothelioma interest group. J Thorac Oncol 2011;6:1304–12.
[12] Treasure T, Lang-Lazdunski L, Waller D, Bliss JM, Tan C, Entwisle J, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol 2011;12:763–72.
[13] Cao C, Tian D, Manganas C, Matthews P, Yan TD. Systematic review of trimodality therapy for patients with malignant pleural mesothelioma. Ann Cardiothorac Surg 2012;1:428–37.
[14] Stahel RA, Riesterer O, Xyrafas A, Opitz I, Beyeler M, Ochsenbein A, et al. Neoadjuvant chemotherapy and extrapleural pneumonectomy of malignant pleural mesothelioma with or without hemithoracic radiotherapy (SAKK 17/04): a randomized, international, multicentre phase 2 trial. Lancet Oncol 2015;16:1651–8.
[15] Cho BC, Feld R, Leighl N, Opitz I, Anraku M, Tsao MS, et al. A feasibility study evaluating Surgery for Mesothelioma after Radiation Therapy: the "SMART"

approach for resectable malignant pleural mesothelioma. J Thorac Oncol 2014;9:397–402.
[16] de Perrot M, Feld R, Leighl NB, Hope A, Waddell TK, Keshavjee S, et al. Accelerated hemithoracic radiation followed by extrapleural pneumonectomy for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2016;151:468–73.
[17] Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636–44.
[18] van Meerbeeck JP, Gaafar R, Manegold C, Van Klaveren RJ, Van Marck EA, Vincent M, et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European organisation for research and treatment of cancer lung cancer group and the national cancer Institute of Canada. J Clin Oncol 2005;23:6881–9.
[19] Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet 2016;387:1405–14.
[20] Katirtzoglou N, Gkiozos I, Makrilia N, Tsaroucha E, Rapti A, Stratakos G, et al. Carboplatin plus pemetrexed as first-line treatment of patients with malignant pleural mesothelioma: a phase II study. Clin Lung Cancer 2010;11:30–5.
[21] Ceresoli GL, Zucali PA, Mencoboni M, Botta M, Grossi F, Cortinovis D, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab as first-line therapy in malignant pleural mesothelioma. Br J Cancer 2013;109:552–8.
[22] Castagneto B, Botta M, Aitini E, Spigno F, Degiovanni D, Alabiso O, et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma (MPM). Ann Oncol 2008;19:370–3.
[23] Maio M, Scherpereel A, Calabrò L, Aerts J, Perez SC, Bearz A, et al. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. Lancet Oncol 2017;18:1261–73.
[24] Signorelli D, Macerelli M, Proto C, Vitali M, Cona MS, Agustoni F, et al. Systemic approach to malignant pleural mesothelioma: what news of chemotherapy, targeted agents and immunotherapy? Tumori 2016;102:18–30.
[25] WHO histological classification of tumours of the thymus. In: Travis WB, Brambilla A, Burke AP, Marx A, Nicholson A, editors. World Health Organization classification of tumours of the lung, pleura, thymus and heart. Lyon: IARC Press; 2015.
[26] Marx A, Ströbel P, Badve SS, Chalabreysse L, Chan JK, Chen G, et al. ITMIG consensus statement on the use of the WHO histological classification of thymoma and thymic carcinoma: refined definitions, histological criteria, and reporting. J Thorac Oncol 2014;9:596–611.
[27] Detterbeck FC, Nicholson AG, Kondo K, Van Schil P, Moran C. The Masaoka-Koga stage classification for thymic malignancies: clarification and definition of terms. J Thorac Oncol 2011;6:S1710–6.
[28] Detterbeck FC, Stratton K, Giroux D, Asamura H, Crowley J, Falkson C, et al. Staging and prognostic factors committee; members of the advisory boards; participating institutions of the thymic domain. The IASLC/ITMIG thymic epithelial tumors staging project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thorac Oncol 2014;9:S65–72.
[29] Girard N, Mornex F, van Houtte P, Cordier JF. Thymoma: a focus on current therapeutic management. J Thorac Oncol 2009;4:119–26.
[30] Girard N, Lal R, Wakelee H, Riely GJ, Loehrer PJ. Chemotherapy definitions and policies for thymic malignancies. J Thorac Oncol 2011;6:S1749–55.
[31] Girard N, Merveilleux du Vignaux C. Systemic treatment for thymic malignancies. Curr Opin Oncol 2017;29:112–7.
[32] Giaccone G, Thompson J, Crawford J, McGuire C, Manning M, Subramaniam DS, et al. A phase II study of pembrolizumab in patients with recurrent thymic carcinoma. J Clin Oncol 2016;34. suppl; abstr 8517.
[33] Cho J, Ahn MJ, Yoo KH, Lee H, Kim HK, Heo MH, et al. A phase II study of pembrolizumab for patients with previously treated advanced thymic epithelial tumor. J Clin Oncol 2017. 8521 (abstract).
[34] Girard N, Merveilleux du Vignaux C. How large databases may impact clinical practices for rare tumors-postoperative chemotherapy in thymic malignancies. J Thorac Dis 2016;8:1863–4.
[35] Huang J, Ahmad U, Antonicelli A, Catlin AC, Fang W, Gomez D, et al. Development of the international thymic malignancy interest group international database: an unprecedented resource for the study of a rare group of tumors. J Thorac Oncol 2014;9:1573–8.
[36] Detterbeck F. The impact of ChART on the science of thymic malignancies. J Thorac Dis 2016;8:1921.
[37] Okumura M. Trends and current status of general thoracic surgery in Japan revealed by review of nationwide databases. J Thorac Dis 2016;8:S589–95.
[38] Polo V, Girard N, Besse B. Thymic tumours: an update. Presse Med 2013;42:e311–6.
[39] Imbimbo M, Pasello G, Zucali P, Vitali M, Petrini I, Palmieri G, et al. The TYME network of expert centres presents the first Italian consensus conference for thymic epithelial tumours. Mediastinum 2017;1. AB053.
[40] Ruffini E, Venuta F. Management of thymic tumors: a European perspective. J Thorac Dis 2014;6:S228–37.