Editorial Commentary

The European Reference Network: the keystone for the management of rare thoracic cancers

Rocco Morra[1#], Antonio D'Ambrosio[1#], Erica Pietroluongo[1], Pietro De Placido[1], Liliana Montella[2], Vitoantonio Del Deo[3], Marianna Tortora[4], Sabino De Placido[1,4], Giovannella Palmieri[4], Mario Giuliano[1,4]

[1]Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy; [2]ASL NA 2 NORD, Oncology Operative Unit, "Santa Maria delle Grazie" Hospital, Pozzuoli, Italy; [3]Azienda Ospdaliera Universitaria Federico II di Napoli, Naples, Italy; [4]CRCTR Coordinating Rare Tumors Reference Center of Campania Region, Naples, Italy

[#]These authors contributed equally to this work.

Correspondence to: Mario Giuliano. Department of Clinical Medicine and Surgery, University of Naples Federico II, 80131 Naples, Italy. Email: m.giuliano@unina.it.

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Rare tumors are a heterogeneous group of malignancies, which show an incidence rate of <6 per 100,000 people per year, according to the definition of Surveillance of Rare Cancers in Europe (RARECARE) (1).

Overall, the estimated incidence of all rare tumors in Europe accounts for 24% of all cancers, with 5-year relative survival for all rare cancers of 48.5% (2).

Indeed, rare thoracic tumors include many entities: epithelial tumors of the trachea, rare epithelial tumors of the lung, epithelial tumors of the thymus, malignant pleural and pericardial mesothelioma, mediastinal germ cell tumors and mesenchymal tumors (*Table 1*) (1,3-5).

The incidence of these tumors in Europe is the highest in patients aged 65 years and older, with a crude rate of 1.4 per million per year for the epithelial tumor of the trachea, 1.7 per million per year for thymic epithelial tumors, among which malignant thymomas are the most common, and 16 per million per year for the malignant mesothelioma of pleura and pericardium. The 5-years relative survival rate is 14% for the epithelial tumors of the trachea, 65.6% for thymic epithelial tumors, and 5.4% for malignant mesothelioma (5). Detailed data on incidence, prevalence and survival of several types of rare thoracic tumors included in *Table 1* were reported in a study of the RARECARE working group, using a large patient database (5).

These malignancies present an intrinsic complexity in clinical management, both in the initial diagnostic phase, as well as in the treatment choice, due to scarcity of clinical practice guidelines and also to the lack of randomized clinical trials, which substantially limit treatment options. Moreover, to reduce the diagnostic delay and to improve the appropriateness of treatment choice, clinical centers with adequate patient volumes and expertise should be homogeneously accessible in different geographical areas, also to reduce healthcare migration (3,6,7).

Notably, the clinical complexity of rare thoracic tumors systematically requires multidisciplinary team discussion to reach the correct diagnosis and offer the best treatment.

In 2008, the European Commission launched the RARECARE project. This is a population-based cancer registry aiming at defining incidence, prevalence and long-term outcome of rare cancers. This project allows to study the epidemiology of these cancers in a large and heterogeneous population (8,9). The results of RARECARE registry led to a second project (RARECAREnet), which updated and enlarged the available information on rare cancers in Europe (10).

In addition, the Joint Action on Rare Cancers (JARC) launched in 2016, is another major European initiative, in which 34 partners from different countries belonging to the European Community are involved. This project, coordinated by the National Cancer Institute of Milan (INT), seeks to improve the epidemiological knowledge of rare cancers, to offer education to healthcare professionals and to ameliorate clinical management of these diseases, promoting the integration of translational research

Table 1 Rare tumors of the thoracic cavity (1,3-5)

Tier	Name
1	Epithelial tumours of trachea
2	Squamous cell carcinoma and variants of trachea
2	Adenocarcinoma and variants of trachea
2	Salivary gland type tumours of trachea
1	Epithelial tumour of thymus
2	Malignant thymoma
2	Squamous cell carcinoma of thymus
2	Undifferentiated carcinoma of thymus
2	Lymphoepithelial carcinoma of thymus
2	Adenocarcinoma and variants of thymus
2	Neuroendocrine tumors
2	Thymic carcinoma
2	Salivary gland like carcinoma
2	NUT carcinoma
1	Malignant mesothelioma
2	Mesothelioma of pleura and pericardium
1	Epithelial tumours of lung
2	Adenosquamous carcinoma of lung
2	Large cell carcinoma of lung
2	Well differentiated endocrine carcinoma of the lung
2	Poorly differentiated endocrine carcinoma of the lung
2	Squamous cell carcinoma with variants of lungs
2	Bronchiolo-alveolar carcinoma of lung
2	Undifferentiated carcinoma of lung
2	Salivary gland type tumours of lung
2	Sarcomatoid carcinoma of lung
1	Mediastinal Germ cell tumors
1	Mesenchymal tumors
2	Adipocytic tumors
2	Fibroblastic and myofibroblastic tumors
2	Vascular tumors
2	Skeletal muscle tumors
2	Peripheral nerve sheath and neural tumors
2	Tumors of uncertain differentiation

innovations into rare cancer care and ensuring sharing of best practices and equality of care across European countries (10).

An important milestone was set in 2017, when the European Reference Networks (ERNs) were established as a pan-European initiative to ensure and improve the most appropriate care for patients with rare or low prevalence diseases. It is expected that bringing together European reference centers within an official network, patients with rare diseases could get more often and more quickly access to expert care and that guideline development and research discoveries could be facilitated (11).

Twenty-four ERNs have been approved, involving more than 900 highly-specialized healthcare providers from over 300 hospitals in 26 EU countries (11,12).

There are four ERNs with an oncological focus: the ERN EuroBloodNet on rare hematological diseases, the ERN Genturis on genetic tumor risk syndromes, the ERN PaedCan on pediatric cancer (haemato-oncology), and the ERNs for Rare Adult Solid Cancer (ERN-EURACAN) (12).

At present, the ERN-EURACAN has 75 full members and affiliated partners from 24 countries, 30 associated partners and covers 10 disease domains, corresponding to the list of rare adult solid cancer (RARECARE) based on the international classification of disease (ICD-10) (12,13).

In agreement with the basic principles of the ERN, the objectives of EURACAN are to reduce disparities and guarantee equal access to the treatment for rare tumors among different member states of the European Community to increase the quality of care of rare cancer patients. All these purposes might be obtained through infrastructures with a high level of multidisciplinary expertise (5,13,14). The European network collects and edits available information through the creation of large cancer registry population data, which has contributed in recent years to a significant improvement in the knowledge of these tumors and produces new scientific evidence by conducting clinical and translational research.

Within the ERN-EURACAN, according to the last accessible assessment report, the rare thoracic tumor domain (G8 domain) is structured in 20 centers (*Table 2*) with expertise in the management of these rare tumors (15). The difficulties encountered in the management of rare thoracic cancers are in part in common with those encountered for other rare diseases and include the aforementioned lack

Table 2 List of expert centers for rare thoracic cancer (14)

Country	Istitution
Belgium	Antwerp University Hospital, Edegem
Italy	Azienda Ospedaliera Universitaria Senese, Siena
Italy	Azienda Ospedaliero–Universitaria Città della Salute e della Scienza di Torino, Turin
Luxembourg	Centre Hospitalier de Luxembourg, Luxembourg
Italy	Centro di Riferimento Oncologico di Aviano, Aviano
Italy	Rare Tumors Coordinating Center of Campania Region (CRCTR), Naples
Italy	Fondazione IRCCS Istituto Nazionale dei Tumori, Milan
France	Hospices Civils de Lyon, Lyon
France	Institut Gustave Roussy, Villejuif
Belgium	Institut Jules Bordet, Brussels
Italy	IRCCS San Martino–IST, Genoa
Italy	Istituto Fisioterapici Ospitalieri, Rome
Italy	Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola
Belgium	Leuven Cancer Institut, Leuven
Germany	Mannheim University Medical Center, Mannheim
Malta	Mater Dei Hospital, L-Imsida
The Netherlands	Netherlands Cancer Institute–Antoni van Leeuwenhoek, Amsterdam
Estonia	North Estonia Medical Centre foundation, Tallin
Estonia	Tartu University Hospital, Tartu
Germany	University Hospital Essen, Essen

of data about the biology of these groups of tumors, late diagnosis, pathological misdiagnosis, incorrect management, and absence of effective and standardized evidence-based treatment.

Since its establishment, the G8 domain has worked to overcome these pitfalls, through a vast range of activities, such as involving new reference centers, launching large projects for the creation of shared clinical databases in collaboration with other international groups (i.e., the International Thymic Malignancy Interest Group; ITMIG), promoting novel translational and clinical research programs through international collaborations, creating web-based-platforms for multidisciplinary case discussion, promoting different educational program for medical, radiation and surgical oncologists (16,17).

The discovery of aberrations in the oncogenic driver genome has changed the therapeutic algorithm of many tumors that need to be characterized by precision oncological methodology and could represent a keystone in the treatment of rare thoracic tumors that present little therapeutic possibilities. In this scenario, the EURACAN G8 domain recently launched a project named the real-world European registry to collect data from adult cancer patients harboring NTRK gene fusions and other rare actionable gene aberrations (TRacKING) together with a European registry to describe the management of patient with solid cancers harboring a NTRK fusion or other rare actionable fusion (17). In the same way other projects such as the lungNENomics and panNENomics on neuroendocrine tumors, and MESomics on mesothelioma, are carried out in partnership with the International Agency for Research on Cancer (IARC) with the establishment of the Rare Cancer Genomics group and focus on the molecular characterization of rare thoracic cancers. These projects will offer further information useful for dissecting the molecular biology of these tumors thus leading to

potential improvement in targeted drug development (17-19).

More recently, despite the difficulties related to the restrictions due to COVID-19 pandemic, officially declared on March 11th 2020 by the WHO, which affected negatively not only clinical and translational research activities, but also the diagnosis and treatment of oncological patients (20), the members of the ERN-EURACAN continued to support and help in the research and management of patients suffering from rare thoracic tumors.

Indeed, thoracic tumors, for their natural history and the treatment procedures, could cause serious respiratory and cardiovascular complications such as invasion of the lung and pleura, atelectasia due to compressive effect, reduced respiratory function due to surgical procedures that could be further aggravated by concomitant COVID-19 infection. A tailored risk assessment strategy for thoracic cancer patients, including those with rare tumors, has been recommended and several studies have been conducted, including the published study TERAVOLT, a longitudinal multi-center study on thoracic cancer patients who experienced COVID-19 (21).

Therefore, the networking of national Centers of competence at European level and the collaboration with various international groups represent the best option possibility to support rare tumor patients, as these diseases are heterogeneous in biological and clinical features, to have access to a correct, timely diagnosis, as well as to appropriate and most up-to-date care, including the possibility of having access to clinical trials and to the second opinion of specialists, guaranteeing equal access and better management.

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