



Mediastinal soft tissue sarcoma: dark sides and future lights

Giovannella Palmieri¹, Marianna Tortora¹, Sara Parola², Fernanda Picozzi², Margaret Ottaviano^{1,2,3}

¹C.R.C.T.R. Coordinating Rare Tumors Reference Center, AOU Federico II of Naples, Naples, Italy; ²Department of Clinical Medicine and Surgery, University Federico II of Naples, Naples, Italy; ³Oncology Unit, Ospedale del mare, Naples, Italy

Correspondence to: Giovannella Palmieri, CRTR Rare Tumors Reference Center, AOU Federico II of Naples. Via Sergio Pansini 5, 80131, Naples, Italy. Email: giovpalm@unina.it.

Comment on: Engelhardt KE, DeCamp MM, Yang AD, *et al.* Treatment Approaches and Outcomes for Primary Mediastinal Sarcoma: Analysis of 976 Patients. *Ann Thorac Surg* 2018;106:333-9.

Received: 08 November 2019; Accepted: 04 March 2020; Published: 30 June 2020.

doi: 10.21037/med.2020.03.02

View this article at: <http://dx.doi.org/10.21037/med.2020.03.02>

Soft tissue sarcomas (STS), are rare tumors of mesenchymal origin, account for 1% of all cancers (1). Even though these tumours may arise anywhere in the body, the most common primary sites are extremities and abdomen (2). STS of the mediastinum are very rare malignancies representing only <10% of primary mediastinal tumours and <1% of all STS (3-5).

The mediastinum is a complex anatomic space in which organ and major blood vessels reside with surrounding soft tissue elements. Mediastinal malignancies include epithelial tumours of thymic origin (thymoma and thymic carcinoma), lymphomas, germ cell tumours (GCT), metastasis arising from other sites and primary tumours originating from mesenchymal cell of the anterior, medium and posterior mediastinum. Moreover, recent findings confirmed also that spectrum and frequency of mediastinal lesions depends properly on mediastinal compartment, which identification may be helpful for the initial differential diagnosis of a mediastinal lesion (6).

To date, only few individual case report and small series of patients with STS of mediastinum have been reported (7,8). Owing to the complex anatomic features of mediastinum, often the mesenchymal tumours are detected at advanced stage, when vascular and lung compression symptoms arise.

Pathological definition of mediastinal sarcoma (MS) is often challenging and requires high expertise. Particular attention is needed especially in young male patients, since it must be considered that sarcomatous tissue may remain as the residual component or the metastatic vestige of burnt-out primary mediastinal GCT. The identification of isochromosome 12p could be helpful to confirm the origin

of MS (rhabdomyosarcoma and angiosarcoma subtype) from a GCT (9,10).

Pathologists should also take into account that sarcomatous area may be part of thymic-sarcomatoid carcinoma or pseudo-sarcomatous stroma in thymoma (11,12) (*Figure 1*).

Pachter *et al.*, in 1963, published a systematic review of the mediastinal soft tissue pathology (13), followed by the most recent two-part review by den Bakker *et al.*, based on the 2013 WHO classification of soft tissue tumours and the 2015 WHO classification of tumours of lung, pleura, thymus and heart (*Figure 2*) (14,15). The histo-pathological variety of MS has been recently enriched by the review of You-Li Wo *et al.*, with the description of the very rare entity of follicular dendritic cell sarcoma (FDCS) (16).

Complexity, rarity and literature data fragmentation make very difficult to define shared treatment strategy for the management of MS, therefore the study published by Engelhardt *et al.* is a reference and starting point for the knowledge of treatment approaches and survival outcomes of MS patients.

Analysing data from the National Cancer Database (NCDB), one of the largest cancer registries worldwide, the authors carried out the description of 976 patients affected by MS correlating the survival outcomes with treatment modality (no treatment, radiation and/or chemotherapy, surgery only, surgery and radiation, surgery and chemotherapy, and surgery and chemoradiation); surgery characteristics (R0, R1, R2, or unknown); tumour size (10 centimeters); histology subtype (hemangiosarcoma, leiomyosarcoma, synovial sarcoma, sarcoma not otherwise specified, malignant peripheral nerve sheath tumour

- GCT longstanding transformation mediastinal sarcoma → Iso-cromosoma 12p
- Metastatic from other site
- Thymic origin
- Primary origin by mesenchimal cell of the anterior, medium and posterior mediastinum

Figure 1 Mediastinal sarcoma origin. GCT, germ cell tumor.

and other); grade of tumour, patients and hospital-level characteristics (17).

The authors generated relevant points of interest that should be commented on.

First of all, as previously reported, the analysis confirmed a male predominance of disease and a poor prognosis with a five-year overall survival (OS) of only 14.8% in the entire cohort, but surprisingly, emangiosarcoma, rarely diagnosed in mediastinum (18), was reported as the predominant histotype.

Secondary, in this setting, this is the first study to examine the association between OS and treating facility characteristics or patient-specific social determinants of health, highlighting that factors like facility location, academic status, graduate medical education programs, educational levels of the patient and the insurance status, may impact on the survival outcome.

At last very remarkable is the authors' effort to correlate the delivered treatment to the survival outcome even in a highly heterogeneous cohort. As already acknowledged for sarcoma of other anatomic location and reported in previous case series of MS (19), surgery, also in this study, remains the primary therapeutic strategy, however, in this series, less than half of patients underwent surgical resection, likely because MS are frequently detected at advanced stage with invasion of vital structures, precluding resection. This anatomical peculiarity, however, should explain why the debulking surgery impacts positively on OS especially when followed by radiation therapy, differently from the sarcoma of other anatomic site, where the application of debulking surgery is still controversial.

Moreover, intriguingly, the radiotherapy was performed with the same rate in both patients with RO resection (28%) and with positive margin R1-R2 (30%), achieving the best 5 years survival ($P=0.002$) in patients who received R0 surgical resection and radiotherapy. Worthy of consideration is the uncertain role of chemotherapy, mainly because of the pathological heterogeneity, the lack of information about the delivered cytotoxic drugs, the inclusion of histo-type not chemo-sensitive and the

Adipocytic Tumors

- lipoma
- thymolipoma
- lipomatosis
- Lipoblastoma
- lipoma variants
- liposarcoma

Fibroblastic/miofibroblastic tumors

- aggressive fibromatosis/desmoid tumors
- solitary fibrous tumour
- other Fibroblastic/miofibroblastic tumors
- inflammatory myofibroblastic tumour

Fibrohistiocytic tumours

Smooth muscle tumours

Pericytic (perivascular) tumours

Skeletal muscle tumours

Vascular Tumours

- benign and intermediate-grade vascular tumours
- malignant vascular tumours

Chondro-osseous tumours

Ewing sarcoma/primitive neuroectodermal tumour (PNET)

Mediastinal Neural Tumours+

Nerve sheath tumours and tumours derived from the autonomic nervous system

- nerve Sheath/schwannian
- ganglionic/autonomous nervous system
- embryonal neural tube remnants
- neuroectodermal

Follicular dendritic cell (FDCS)

Figure 2 The most common primary mesenchimal tumours of the mediastinum.

absence of histology driven chemotherapy due to the time of data collection.

Conclusions

This the largest cohort of patients with MS ever reported, that identifies surgery as the cornerstone of therapy. Radiation therapy may offer some survival advantages, while the role of chemotherapy remains unclear. International reference centers with high expertise in the field of rare cancers should plan prospective registered database on the specific topic of MS in order to improve the current knowledge and provide a worldwide multidisciplinary consensus for the best treatment strategies.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Dr. Luigi Ventura (Thoracic Surgery, Surgical Unit, Department of Medicine

and Surgery, University Hospital of Parma, Parma, Italy).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/med.2020.03.02>). GP serves as an unpaid editorial board member of *Mediastinum* from Oct 2019 to Sep 2021. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/med.2020.03.02

Cite this article as: Palmieri G, Tortora M, Parola S, Picozzi F, Ottaviano M. Mediastinal soft tissue sarcoma: dark sides and future lights. *Mediastinum* 2020;4:9.