Review Article

Principles of medical and oncological management of giant masses of the mediastinum: a narrative review

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Background and Objective: Giant mediastinal tumors are represented by well-defined histological variants originating from different structures and compartments while their clinical presentation may be similar and characterized by the same set of symptoms, the well-known mediastinal syndrome (MS). In 80% of cases the MS is caused by malignant neoplasms, such as lung tumors, in 10–18% of cases by hematological neoplasms and in 2–3% by benign causes. In this review we investigated the medical treatment of main giant mediastinal tumors, focusing our interest on the objective response rate (ORR), as it represents the most suitable parameter to predict the volumetric reduction of the neoplasm and, consequently, the regression of their most severe complication, the MS. We will also cover the supportive and symptomatic treatment of MS.

Methods: We performed a deep analysis of the recent international literature published on PUBMED, UpToDate and Medline. The literature search was undertaken from origin until November 30th, 2021, and we only considered publications in English.

Key Content and Findings: Considering the variety of pathologies that can occur in the mediastinum, a rapid histological characterization of the neoplasm is mandatory. In fact, the treatment of these neoplasms includes different approaches, sometimes used in combination, which include chemotherapy, radiotherapy, and surgery. The vena cava syndrome (VCS), due to its high mortality, is considered an oncological emergency and, therefore, requires effective treatments carried out urgently, evaluated in multidisciplinary meeting.

Conclusions: The treatment of MS includes both antiblastic treatments and therapies directed to the symptoms. Among the former, chemotherapy, target therapy, radiation and surgery may be used, according to the etiology of MS. Among the latters, supportive therapies, interventional radiology procedures such as stenting may help manage this syndrome, despite the prognosis is poor in most cases and linked to the histology of the tumor, which therefore represents the most important prognostic factor.

Keywords: Giant mediastinal tumors; mediastinal syndrome (MS); precision medicine; oncological management

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Introduction

Giant mediastinal masses include benign or malignant tumors that can develop from structures located in the mediastinum or that pass through the mediastinum during development, as well as from metastases or lymphadenopathy of malignancies that arise elsewhere in the body (1).

The mediastinum is divided into compartments, each of which is characterized by the presence of specifics structures and, consequently, neoplasms.

The prevascular or anterior compartment of mediastinum is affected by thymic tumors such as thymomas, thymic carcinomas and thymic neuroendocrine tumors, germ cell tumors, lymphomas, thyroid and parathyroid tumors and metastases. The visceral or medial compartment includes lung tumors, lymphoma and metastases. In the last mediastinal compartment, the paravertebral or posterior, neurogenic tumors arising from dorsal root ganglia/neurons adjacent to intervertebral foramina and esophageal neoplasms can be observed (2).

While mediastinal tumors are represented by well-defined histological variants originating from different structures and compartments, their clinical presentation may be similar and characterized by the same set of symptoms proper of the well-known mediastinal syndrome (MS). In fact, in 80% of cases the MS is caused by malignant neoplasms, such as lung tumors [non-small cell lung cancers (NSCLCs) and small cell lung cancer (SCLC)], in 10–18% of cases by hematological neoplasms, such as lymphomas and in 2–3% by benign causes such as goiter or thyroid hyperplasia or vascular malformations such as aneurysm or cysts (3). A summary of the different cancer types causing MS is summarized in *Figure 1*.

The MS is classified according to the location of the lesion and the structures involved as follows: respiratory syndrome (trachea and bronchi), vascular syndrome (arterial or venous), neurological syndrome (vagus nerve, recurrent nerves, phrenic nerve, sympathetic chain) or digestive syndrome (esophagus). Symptoms of the syndromes are associated with the anatomic structures involved and superior vena cava syndrome (VCS) and airway obstruction represent the most severe complications of MSs and are considered a medical emergency. Treatment of MS is both directed against the tumors and to the symptoms. To tackle the tumor, chemotherapy, target therapy, radiation, surgery may be used, according to the etiology of MS (4).

Symptoms are treated with supportive therapies, for instance, interventional radiology procedures such as stenting may help manage this syndrome. However, the prognosis is poor in most cases. In fact, the median survival of patients with MS ranges from 6 to 9 months and it is linked to the histology of the tumor, which therefore represents the most important prognostic factor of the MS itself (5).

In this review we report the medical treatments of main giant mediastinal tumors, focusing our interest on the objective response rate (ORR). The ORR represents the most suitable parameter to predict the volumetric reduction of the neoplasm and, consequently, the regression of their most severe complication, the MS (*Figure 2*). We will also cover the supportive and symptomatic treatment of MS. We present the following article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-21-54/rc).

Methods

We performed a literature review on December 1st, 2021. The literature search was undertaken from origin until November 30th, 2021. Only studies published in English were considered. The databases used included UpToDate, Medline and PubMed. Article types included in the search criteria were retrospective, prospective, randomized control trial, case report studies, original research, meta-analyses, abstracts, and previous related reviews. The search terms used to identify relevant articles during screening included "Mediastinal tumors, Mediastinal syndrome, Superior Vena Cava Syndrome, NSCLC (Oncogene-addicted metastatic NSCLC, Non-oncogene-addicted localized NSCLC, Non-oncogene-addicted metastatic NSCLC), Small Cell Lung Cancer (SCLC), Thymic tumors (Thymoma, Thymic Carcinoma, Thymic Neuroendocrine tumor), Lymphoma, Rare tumor (Germ Cell Tumor, Mesenchymal tumor, Neurogenic tumor), Cancer of Unknown Primary, Medical non-oncological management," individually or in combination (*Table 1*).

Discussion

NSCLC

Lung cancer is the second most common malignancy and the first cause of death, regardless of sex, worldwide and NSCLC accounts for 80–90% of all lung cancers.

Although mediastinal lymph node involvement is common in patients with NSCLC, it often remains asymptomatic and

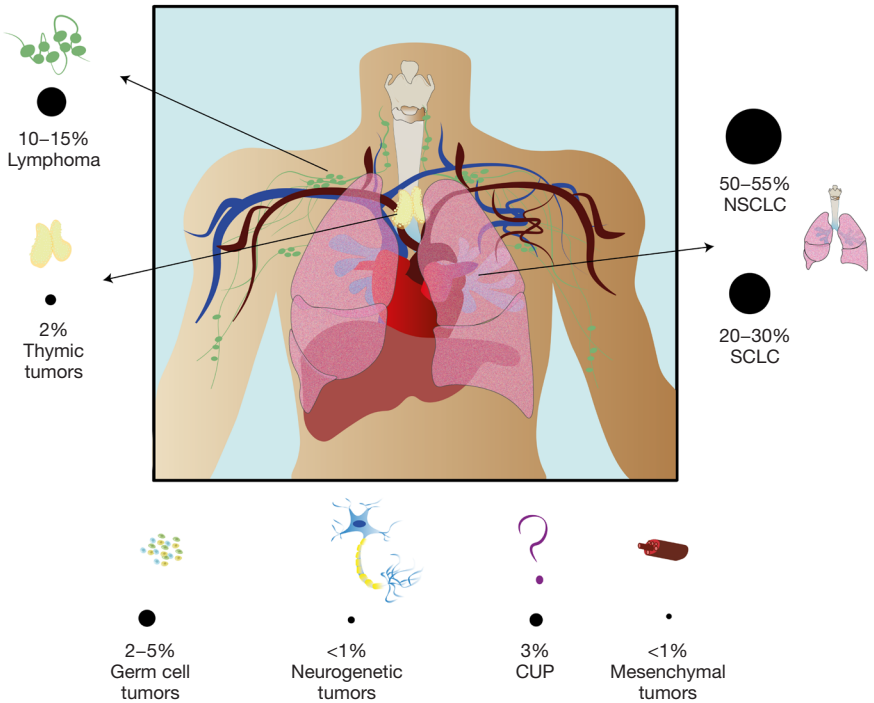

Figure 1 Different cancer types and their relative frequency in determining mediastinal syndrome. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; CUP, cancer of unknown primary.

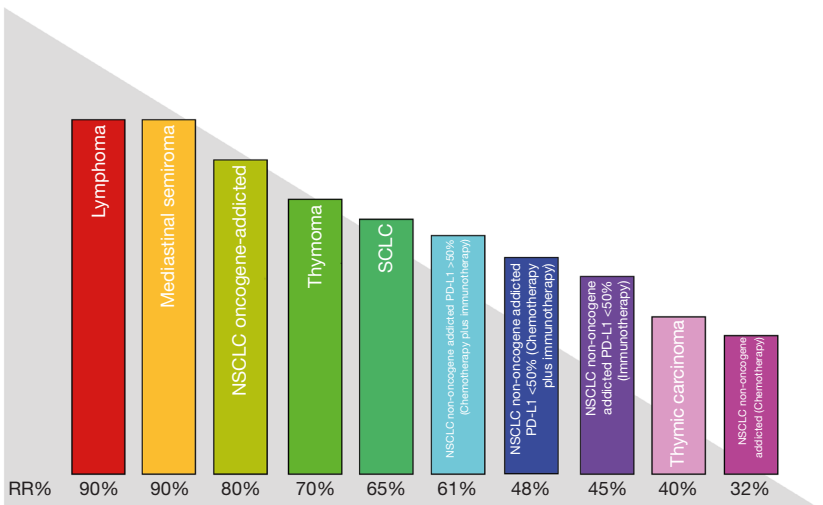

Figure 2 Response rate across different cancer types and treatments. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; PD-L1, programmed death-ligand 1; RR, response rate.

therefore is not a frequent cause of MS.

Oncogene-addicted metastatic NSCLC

Traditionally, chemotherapy represented the cornerstone of treatment for advanced diseases, until more recent years, when the identification of the so called "oncogene-addicted" NSCLC has radically changed the therapeutic algorithm for the advanced stages of this disease.

Table 1 The search strategy summary

Items	Specification
Date of Search (specified to date, month, and year)	December 1st, 2021
Databases and other sources searched	UpToDate, Medline and PubMed
Search terms used (including MeSH and free text search terms and filters)	Search terms: "Mediastinal tumors, Mediastinal syndrome, Superior Vena Cava Syndrome, NSCLC (Oncogene-addicted metastatic NSCLC, Non-oncogene-addicted localized NSCLC, Non-oncogene-addicted metastatic NSCLC), Small Cell Lung Cancer (SCLC), Thymic tumors (Thymoma, Thymic Carcinoma, Thymic Neuroendocrine tumor), Lymphoma, Rare tumor (Germ Cell Tumor, Mesenchymal tumor, Neurogenic tumor), Cancer of Unknown Primary, Medical non-oncological management"
Timeframe	From origin until November 30th, 2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	Inclusion and exclusion criteria: (I) English-language article; (II) Article types were retrospective, prospective, randomized control trial, case report studies, original research, meta-analyses, abstracts, and previous related reviews
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	The records were first screened for title or abstract by two independent reviewers (NC and FGD), and subsequently screened for full text. Debate over article selection was resolved with consensus

Appropriate morphological and biomolecular diagnosis are now essential to guide its therapy (6). Among these, the presence of EGFR and BRAF mutations and ALK and ROS1 rearrangements must always be assessed in patients with advanced NSCLC (stage IIIA–IV). Other agents targeting RET and NTRK rearrangements, MET exon 14, ERBB2 and KRAS G12C mutations are still available for patients carrying these targets. Oncogene-addicted diseases occur in 30% of NSCLC in western populations and are more frequent in young and non-smokers patients with adenocarcinoma histotype (6).

In the last fifteen years, several trials showed that first generation [Gefitinib (7) and Erlotinib (8)] and second generation [Afatinib (9)] tyrosine kinase inhibitors (TKIs) lead to an ORRs ranging 56–84.6% while Osimertinib, in the FLAURA trial, resulted in an ORR of 80%, matching the comparator arm represented by gefitinib or erlotinib (76%) (10).

ALK rearrangement affects 3–7% of NSCLC and occurs in young, non-smoking, male patients with adenocarcinoma histology (11). As for EGFR, ALK inhibitors are currently the main stay of systemic treatment, whit an ORR of 74–85% in patients treated with second generation TKIs and 62–74% in patients treated with first generation TKIs (12-14).

ROS1 rearrangements account for 1–2% of NSCLC cases and are specific for adenocarcinoma. Given the considerable clinicopathological overlap and homology between ROS1 and ALK, Crizotinib was also tested in ROS1-rearranged NSCLC where showed considerable clinical efficacy with an (ORR ~70%) (15,16). More recently, Entrectinib, a ROS1, NTRK and ALK inhibitor, has demonstrated clinical activity in crizotinib-naive ROS1-rearranged NSCLC, showing an even higher ORR of 77%.

Other targets with high sensitivity to the corresponding agent are BRAF, for whom the combination of dabrafenib and trametinib showed an ORR of 64% (17), MET, where capmatinib reached an ORR of 68% (in treatment-naïve patients) and 41% (in pre-treated patients) (18) and RET, with Selpercatinib and Pralsetinib achieving an ORR of 68–85% (19).

Larotrectinib, approved by FDA in 2018, based on data across a wide number of cancer types, shows an ORR of 81% among those patients with NTRK gene fusions, in a tumor-agnostic manner (20). Furthermore, Entrectinib was also approved by FDA regardless of tumor type, in patients with NTRK fusion. In STARTRK-1, 2, NG, this TRK inhibitor showed a consistent efficacy with ORR of 57% (21).

Less impressive were the results of KRAS G12C inhibitor Sotorasib, the first anti-KRAS G12C mutation, with an ORR of 54% in pre-treated patients (22).

Currently, however, not all molecularly targeted therapies can be prescribed except in the context of experimental protocols.

Non-oncogene-addicted localized NSCLC

In locally advanced non-oncogene-addicted NSCLC the options for surgery depend on the extent of the primary tumor and lymph node involvement. In fact, stages IIIA–IIIB represent a very heterogeneous group whose possible treatments are surgery followed by adjuvant chemotherapy, neoadjuvant chemotherapy followed by surgery or chemotherapy and radiotherapy, followed by durvalumab. The different therapeutic options must be evaluated within a multidisciplinary team. In patients with unresectable N2 disease, a combined treatment of chemo-radiotherapy at radical doses is indicated as the first option.

The neoadjuvant concurrent chemo-radiotherapy approach with combinations based on cisplatin plus third generation chemotherapy and RT 54–66 Gy aims to achieve presurgical downstaging, in particular at the lymph node level (23). Pathological complete response is 15–33% while lymph node clearance (N0) is 25–46% (24). Alternatively, patients who are unable to tolerate concomitant treatment or with high pathological volumes, can be treated with chemotherapy and sequential radiotherapy.

Non-oncogene-addicted metastatic NSCLC

The encouraging ORRs, seen in patients with oncogene-addicted disease, are not replicated in the non-oncogene-addicted group. Although the introduction of immunotherapy alone or in combination with standard histology-based chemotherapy, has increased the survival of these patients compared to standard chemotherapy, ORR are significantly lower than in patients with oncogene-addicted disease.

KEYNOTE-024 enrolled 305 patients with metastatic PD-L1 (TPS ≥50%) NSCLC who were assigned to either pembrolizumab as monotherapy or standard-of-care platinum-based chemotherapy. ORR was 45.5% in the pembrolizumab group compared to 29.8% in the chemotherapy group (25). Similarly, in Impower-110, atezolizumab was evaluated as first-line treatment in PD-L1 selected patients with advanced NSCLC, independent of tumor histology. This trial enrolled 572 patients with chemotherapy-naïve stage IV non-squamous or squamous NSCLC with PD-L1 expression ≥1% on tumor cells (TCs) or immune cells (ICs). ORR was 38.3% for patients treated with immunotherapy *vs.* 28.6% for patients treated with chemotherapy (26).

Subsequently, immune checkpoint inhibitors (ICIs) were evaluated as first-line treatment in combination with platinum-based chemotherapy. In Keynote-407 the addition of pembrolizumab improved the ORR, 57.9% *vs.* 38.4%. Similarly, the ORR was greater across all PD-L1 subgroups with the addition of pembrolizumab: 63.2% *vs.* 40.4% for PD-L1 negative, 49.5% *vs.* 41.3% for patients with PD-L1 of 1–49% and 60.3% *vs.* 32.9% for patient with PD-L1 ≥50% on TCs (27). Likewise, KEYNOTE-189 study showed that pembrolizumab plus pemetrexed-platinum significantly improved overall survival, progression-free survival, and ORR (47.6% *vs.* 18.9%) compared with placebo plus pemetrexed-platinum in patients with metastatic non-squamous NSCLC without sensitizing EGFR/ALK alterations, regardless of PD-L1 TPS (28).

It should be noted that an increasing amount of evidence is now questioning the efficacy of ICIs alone in patients with high tumor burden, regardless of cancer histology (29). A large number of these evidences come from lung cancer (30,31), with one study showing correlation between tumor burden and increased risk of hyperprogressive disease (meaning a sudden acceleration of tumor growth after being exposed to ICIs) in patients with large tumors (32). Considering the need of rapid shrinkage in the patients with giant mediastinal mass and that these cancers are, by definition, characterized by large volume, the use of ICIs monotherapy in such patients should be considered with caution and the combination with chemotherapy should be privileged, even in the presence of high PD-L1 expression.

In conclusion, the treatment of MS caused by NSCLC is based on molecular characterization. In fact, in oncogene-addicted disease, treatment with TKIs can determine a rapid and impressive response such as the so called "Lazarus effect" (33). Target therapy can lead to a reduction in tumor volume with consequent resolution of symptoms. In non-oncogene-addicted NSCLC, a combination treatment with ICIs and chemotherapy is recommended for metastatic disease, while concurrent or sequential chemo-radiotherapy is advised in locally advanced disease. Conversely, ICIs monotherapy should be handled with care.

SCLC

SCLC accounts for 10–15% of lung cancers. Despite the high chemosensitivity, the 10-year survival is 3.5%. Most SCLC arises from lobar or main bronchi and the most common manifestations is a large mass centrally located within the lung parenchyma or a mediastinal mass involving the hilus. Treatment of the limited-stage disease involves chemotherapy and radiotherapy with carboplatin/cisplatin + etoposide for 4 cycles and hyper-fractionated radiotherapy 45 Gy in 25–30 fractions.

Since small-cell tumors are centrally located, with mediastinal adenopathy, they account for the majority of cases of malignant SVC followed by squamous cell carcinoma, large-cell carcinoma, and non-Hodgkin's lymphoma. Treatment options include percutaneous stent placement, corticosteroids, radiotherapy, and chemotherapy as well as thrombolytics and anticoagulation; however, the rapid start of chemotherapy, in consideration of the excellent ORR, represents the best therapeutic approach. In their work, Chan *et al.* evaluated the improvement of VCS' symptoms after chemotherapy. They showed that 93% of patients enrolled in the study had significant improvement in symptoms of VCS after chemotherapy (34).

In extended disease (ED-SCLC) patients, the combination of immunotherapy plus chemotherapy showed to be superior in PFS and OS, either with durvalumab (35) and with atezolizumab (36), while chemo-ICIs combination failed to improve objective response both in terms of ORR and depth of response.

Thymic tumors

Thymoma

Thymomas are the most common tumors of anterior mediastinum and account for about 20% of mediastinal tumors. In most cases, thymomas are circumscribed masses, in other cases can be encapsulated, invade the mediastinum, or extend beyond the mediastinal pleura into lungs, pericardium, heart, large vessels, or involve the phrenic nerves. They may also be found as implants along the pleura, pericardium, and diaphragm (37).

Surgery represents the first treatment step, possibly followed by further post-operative treatments included radiotherapy and chemotherapy accordingly to the stage.

If, the lesion is judged unresectable or resectable with extended resection to other adjacent mediastinal structures, preoperative induction chemotherapy, discussed in a multidisciplinary setting, may be indicated. The suggested induction chemotherapy regimen is the combination of doxorubicin, cisplatin and cyclophosphamide (CAP regimen) for up to 4–6 cycles and the percentages of overall response rate reported in phase II studies with induction chemotherapy range from 69.6% to 77% (38). Alternatively, in patients not eligible for an anthracycline-containing chemotherapy regimen, the suggested scheme is the combination of cisplatin and etoposide.

In patients with metastatic and resectable disease, confined to the pleura and pericardium (stage IVA Masaoka or TNM IVA/M1a), induction chemotherapy is part of a multimodal approach, which can subsequently involve surgical treatment and radiotherapy. In patients with unresectable metastatic disease (Masaoka IVB and TNM IVB/M1b) or in any case not suitable for local treatment, systemic chemotherapy with palliative intent is indicated with regimens containing anthracyclines and platinum salts. They are associated with significantly higher ORRs (ORR 69.4%), when compared with regimens not containing anthracyclines (ORR 37.8%) (39,40). The suggested combination chemotherapy is CAP regimen for up to 6 cycles. Alternative regimens, represented by the combination of cisplatin and etoposide or carboplatin and taxol are considered in patients who are considered not fit for treatment with anthracyclines.

In patients progressing to first-line treatment and with good performance status, second-line chemotherapy with monochemotherapy or polychemotherapy has demonstrated an ORR ranging from 15% to 40%. Recommended treatments are the combination of gemcitabine and capecitabine, or single chemotherapy with paclitaxel, pemetrexed, ifosfamide, etoposide, gemcitabine or 5-fluoruracil (41-43). Regarding target therapies in thymoma, recent studies have evaluated anti-EGFR, anti-VEGF and Imatinib, demonstrating low ORRs (10–15%). Treatment with everolimus proved to be more promising albeit burdened with high toxicity (44). Immunotherapy with anti-PD1 and anti-PD-L1 showed ORRs of 28.6% and 29% respectively, again burdened by high severe toxicity (45), probably due to the predisposition of these patients to autoimmune disease (46).

Thymic carcinoma

Thymic carcinomas are more aggressive than thymomas; evidence of invasion of mediastinal structures is present in most of patients at diagnosis (47). As for thymomas, also in thymic carcinoma the standard treatment for resectable localized or locally advanced forms is represented by surgical treatment, followed by adjuvant chemo- and radiotherapy treatments. In patients with locally advanced unresectable disease (Masaoka III and TNM IIIA/T3 and IIIB/T4) induction chemotherapy treatment is indicated as part of a multimodal approach with curative intent, which includes a subsequent surgical and radiotherapy treatment in case of obtaining resectable disease, or definitive radiotherapy or concomitant chemo-radiotherapy. Phase II studies that evaluated the activity of induction chemotherapy treatments reported ORR rates of 69.6% to 77%. The recommended

treatment is the combination of carboplatin plus paclitaxel continued for 4–6 cycles (48).

In patients with metastatic disease (Masaoka IVA–IVB, or TNM IV/M1a-b), a systemic treatment with palliative chemotherapy is recommended. The meta-analysis of Okuma *et al.* analyzed pooled data from 4 prospective and 6 retrospective studies, they suggest that ORR rates are not significantly different between platinum and anthracycline salt regimens (41.8%) and schemes containing platinum salts but not anthracyclines (40.9%) (39). The suggested regimen is a multi-chemotherapy with carboplatin and paclitaxel for up to 6 cycles.

In patients progressing to first-line chemotherapy and with good performance status, second-line chemotherapy is indicated. Various studies report ORR ranging from 5% to 26% with sunitinib (49), combination of gemcitabine and capecitabine, anthracycline with or without cyclophosphamide, or monochemotherapy with pemetrexed, ifosfamide, etoposide, paclitaxel or 5-fluoruracil or a rechallenge with chemotherapy regimens containing platinum salts with or without anthracyclines. Low ORR rates (10–15%) were obtained in studies evaluating anti-EGFR and anti-IGFR treatments. More promising results were obtained with imatinib, lenvatinib (ORR 39%) and everolimus. Immunotherapy with pembrolizumab also demonstrated good ORRs with ORRs of 20–22% correlated with an acceptable toxicity profile (50).

Thymic neuroendocrine tumor

Neuroendocrine carcinomas of the thymus account for 2–4% of tumors of the anterior mediastinum. Three histological subtypes have been described: well-differentiated neuroendocrine carcinoma (formerly known as "typical carcinoid"), moderately differentiated neuroendocrine carcinoma (formerly known as "atypical carcinoid") and poorly differentiated neuroendocrine carcinoma (also known as thymic small cell carcinoma) (51). Furthermore, thymic neuroendocrine tumor may also be present in multiple endocrine neoplasia type 1 (MEN-1) syndrome. The treatment consists of total thymectomy and complete excision of the tumor, usually associated with radiotherapy and postoperative chemotherapy.

In typical advanced carcinoids, the standard treatment is somatostatin analogues. In patients with slowly progressive tumors, multiple locoregional management may represent the only anti-tumor strategy. In atypical carcinoids, first-line therapy is always based on somatostatin analogues (52). Treatment with everolimus (53), platinum salt-based chemotherapy (54), Peptide Receptor Radionuclide Therapy (PRRT) or INF alpha may be initiated following progression.

Lymphoma

A variety of lymphomas can occupy the mediastinum, either alone or as a clinically significant component of more widespread disease. The most common hematological diseases of mediastinum are represented by Hodgkin lymphoma (HL), diffuse large B cell lymphoma (DLBCL) and primary mediastinal large B cell lymphoma (PMBCL). Discovery a mediastinal mass is a common presentation of lymphomas, the mass may be asymptomatic or associated with chest pain or other symptoms.

Advanced HL is mainly treated with combination of chemotherapies. The evolution of modern cytotoxic combination regimens has been outlined in the introduction and establishment of ABVD (Doxorubicin, Bleomycin, Vinblastine and Dacarbazine) as the first-line treatment. This combination chemotherapy presents an ORR after accomplishment of the treatment of 92% (55). Even patients who are not cured with this therapy can often be rescued with alternate chemotherapy combinations, the novel antibody-drug conjugate brentuximab, or high-dose autologous or allogeneic hematopoietic stem cell transplantation (55). Also, the programmed death-1 inhibitors nivolumab and pembrolizumab have both demonstrated high response rates and durable remissions in patients with relapsed/refractory HL (56).

Diffuse large B-cell lymphoma is a common type of non-Hodgkin lymphoma (NHL), representing approximately 24% of new cases of NHL each year. The disease is aggressive, and patients typically present with rapidly enlarging lymphadenopathy and symptoms, necessitating immediate treatment. The most common up-front treatment is chemoimmunotherapy with R-CHOP regime (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), which leads to cure in approximately 50–60% of patients. Efforts to improve up-front therapy in DLBCL have combined biologic agents, including ibrutinib, bortezomib, or lenalidomide with R-CHOP with varying success (57). While most patients respond, 30–40% relapse or are unable to achieve remission with first-line treatment. In these cases, the prognosis is poor. Approximately 50% of patients with relapsed or refractory DLBCL have a response to second-line chemotherapy; up to 50% of these patients proceed to undergo autologous hematopoietic stem-cell transplantation in some settings, and of these,

approximately 30–40% remain progression-free 3 years after transplantation. Patients who progress after receiving R-CHOP receive combination salvage chemotherapy. Commonly used regimens, including R-ICE, R-DHAP, R-GDP, R-GemOx, O-DHAP, O-ICE, and DR-ICE (58).

PMBCL represents a distinct clinicopathologic disease that should have a separate management approach, compared with the other subtypes of DLBCL. These diseases have an elevated cure rate with current standard approaches. Because these mediastinal lymphomas are rare and have only been described relatively recently, there are very few studies to update on optimal up-front therapy. R-CHOP and MACOP-B-like regimens followed by mediastinal radiotherapy were associated with a 5-year PFS of 75–85%. More intensive regimens, like DA-EPOCH-R without mediastinal RT, have shown very promising results. Treatment with R-CHOP resulted in a 92% ORR (with 60% CR). Approximately 10% of PMBCL patients have refractory disease and may benefit from integration of novel therapies in the frontline setting.

In conclusion, these pathologies are characterized by a high ORR and significant proportion of patients may be cured with different regimens of polychemotherapies.

Rare tumor

Germ cell tumor

Mediastinal germ cell tumors can occur as primary neoplasms in the mediastinum. In adults, the most common site in order of frequency is the anterior mediastinum. Extragonadal germ cell tumors are classified as seminomas (termed dysgerminomas in women), non-seminomatous germ cell tumors (termed non-dysgerminomas in women), mature teratomas, and immature teratomas based upon histology. They occur far more often in men than in women and usually are diagnosed between the ages of 20 and 40 years. Most patients with mediastinal germ cell tumors are asymptomatic at presentation. Common signs and symptoms of these diseases may include fever, chills, weight loss, chest pain, dyspnea, and/or superior VCS.

Mediastinal seminomas constitute approximately one-third of malignant mediastinal germ cell tumors and 2–4% of mediastinal masses. Seminomas are sensitive to both cisplatin-based chemotherapy and radiotherapy. The recommended chemotherapy for non-metastatic disease is three cycles of BEP or four cycles of etoposide plus cisplatin (EP) without bleomycin. Patients with metastatic mediastinal seminoma should be treated with four cycles of BEP chemotherapy, except for patients with lung metastases who cannot tolerate bleomycin and should receive four cycles of VIP. The remission rate with chemotherapy and resection of residual masses was 92%.

Non-seminomatous germ cell tumors of the mediastinum contain yolk sac tumor, choriocarcinoma, and embryonal carcinoma. Mediastinal non-seminomatous tumors are aggressive and often metastatic at diagnosis. A multimodality approach is generally preferred and includes chemotherapy, followed by surgery. First-choice chemotherapy consists in four cycle of VIP (59). In the study of Joel *et al.*, partial response with elevated markers was observed in 20.5% of patients while partial response with no elevated markers in 35.2% (60). They concluded that survival outcomes among these patients have not changed dramatically, despite improvements in early diagnosis, availability of cisplatin-based chemotherapy, advancements in surgical expertise. In fact, the 5-year OS is 60%. They also showed that patients undergoing surgical resection have a better outcome when compared to those who did not undergo surgery (61,62).

Mature teratomas of the mediastinum are considered benign masses and usually tend to grow slowly. In other cases, the clinical manifestations include compression or obstruction of surrounding organs with symptoms like chest pain, cough, dyspnea, and bronchial obstruction. The treatment of mature mediastinal teratomas is surgical excision, and this is almost always curative. If only subtotal resection is possible, it is not clear that additional treatment with chemotherapy or radiation therapy offers any benefit, and observation is appropriate. Mature teratomas are relatively insensitive to both chemotherapy and radiotherapy.

Immature teratomas are rare and malignant diseases with a poor prognosis. Currently, there is no standard treatment for the mediastinal immature teratomas. Radical surgery is first-choice treatment, but the role of neoadjuvant and adjuvant chemotherapy remains uncertain. In fact, a combined approach of surgery and chemotherapy has often been recommended but the mediastinal malignant teratoma can be chemotherapy-resistant and cisplatin-based therapy may not be effective. However, for poor-risk tumors, first-line therapy usually involves chemotherapy followed by surgical resection of residual tissue (63). In fact, surgical resection of any residual mass is recommended to improve overall survival. The chemotherapy regimen includes a combination of bleomycin, etoposide, and cisplatin. Often, ifosfamide is substituted for bleomycin to avoid drug-induced lung injury. Overall complete remission rate and favourable response rate were not significantly different

between the two treatments, respectively 37% of VIP *vs.* 31% of BEP and 63% of VIP *vs.* 60% of BEP (64). However, VIP chemotherapy is preferred over BEP because these patients generally require thoracic surgery after chemotherapy and are at high risk for bleomycin-related postoperative pulmonary complications like pneumonitis and pulmonary fibrosis.

Mesenchymal tumor

Soft tissue tumours arising in the mediastinum are rare; their incidence is 2–5% of all mediastinal neoplasms. Mediastinal sarcomas may rise *de novo* or rarely as somatic-type malignancy in a mediastinal germ cell tumour. Mesenchymal tumors of mediastinum are adipocytic, fibroblastic/myofibroblastic, fibrohistiocytic tumours, soft tissue tumours arising as somatic components in germ cell tumours, mediastinal smooth muscle, skeletal muscle, vascular, chondro-osseous, and miscellaneous tumours of uncertain differentiation, including undifferentiated sarcomas. The most common sarcomas, developing in mediastinum, are rhabdomyosarcoma and angiosarcoma.

Angiosarcoma represents a rare subcategory of soft tissue sarcomas characterized by an aggressive clinical behaviour. Usually, radical surgery and adjuvant radiotherapy represent the keystone of treatment for patients with localized disease. However, despite a proper treatment, up to 50% of patients will develop a metastatic relapse. In patients affected by advanced angiosarcoma, there is evidence of efficacy with taxane in monotherapy or in combination with anthracyclines, with gemcitabine alone or with pazopanib (65). In the study of Italiano *et al.*, first-line single-agent doxorubicin and weekly paclitaxel seem to have similar efficacy in metastatic angiosarcomas. In fact, in doxorubicin group: 6% had complete response, 23.5% had partial response, 29.5% had stable disease, and 41% had progressive disease. In the weekly paclitaxel group: 13% had complete response, 40% had partial response, 29.5% had stable disease, 17.5% had progressive disease (66). Kollár *et al.* evaluated the efficacy of pazopanib, obtaining partial response rates of 20% and disease stability of 17.5%, representing a clinical benefit rate of 37.5% (67). D'Angelo *et al.* concluded that response rate was not significantly influenced by the type of first line therapy (25% for doxorubicin, 33% for liposomal doxorubicin, 31% for taxanes) and patients that receive anthracyclines and taxanes in combinations achieved ORR of 43% in comparison to 28% for the same agents in monotherapy (68). Recently, the development of tailored medicine has modified the systemic therapy of specific subgroups of soft tissue sarcoma, with remarkable efficacy. For instance, imatinib in advanced dermatofibrosarcoma protuberans, gemcitabine in leiomyosarcomas, trabectedin in myxoid/round cell liposarcomas, and mTOR inhibitors in perivascular epithelioid cell tumors (PEComas) (69-72).

Approximately 70% of the patients with rhabdomyosarcoma are diagnosed before the age of 10 years; in fact, is the most common soft tissue sarcoma in children, comprising 4.5% of all childhood cancer. Standard treatments of rhabdomyosarcoma include combination of chemotherapy (vincristine, actinomycin D, and cyclophosphamide/ifosfamide), radiation therapy, and surgical tumor excision. Although most patients with localized disease can be cured, the outcomes in those with metastatic or recurrent tumors remain poor. Currently, several clinical trials of immunotherapy and molecular target therapy showed efficacies in patients with soft tissue sarcomas.

Neurogenic tumor

Multicentric evidence shows that the incidence of mediastinal neurogenic tumors accounts on 4–15% of mediastinal lesions. These tumors can develop from mediastinal peripheral nerves, sympathetic and parasympathetic ganglia, and embryonic remnants of the neural tube. Neurogenic tumors are most frequent in the posterior compartment of the mediastinum (5% to 95% of all posterior mediastinal neoplasms), where they can cause neurologic symptoms by compression (55–75% of mediastinal masses) (73). The major categories of neurogenic tumors that may be encountered in the mediastinum, including schwannoma, neurofibroma, malignant peripheral nerve sheath tumors, ganglioneuroma and ganglioneuroblastoma (74). Nearly half of neurogenic tumors are asymptomatic, however, when they become larger in size, they can produce symptoms of compression, invasion, or spinal cord involvement. Most of intrathoracic neurogenic tumors are benign or low-grade malignant tumors.

Mediastinal schwannomas are benign neoplasms that originate from Schwann cells that usually affect patients of both sexes in the third and fourth decades of life. They are usually asymptomatic neoplasms but, in some cases, can cause compression and paralysis of peripheral nerves such as Pancoast syndrome or Bernard-Horner syndrome. Paragangliomas are rare mediastinal tumors that originate from the ganglia of the sympathetic nervous system and usually secrete catecholamines. Usually, radical surgery is the first-choice treatment of giant benign intrathoracic tumors. Instead, the treatment of malignant mediastinal

tumors is a research field of intensive investigation. Although the 5-year survival rate is low and curative surgery is usually not possible, adjuvant chemotherapy and radiotherapy can be used for metastatic disease.

Surgical resection is the treatment of choice in a large percentage of cases of neurogenic tumors. Furthermore, considering that schwannomas are usually benign diseases; mini-invasive approaches should be performed even when they arise as multiple simultaneous lesions or in unusual locations.

Cancer of unknown primary (CUP)

Tumors of unknown origin (CUP syndrome) usually manifest with distant metastases, with different clinical manifestations based on the organ involvement with a poor prognosis in most of the cases, and a median survival of about 8–12 months. The most common manifestations of CUP syndromes are metastases in the mediastinal and axillary lymph nodes, that can provoke MS. Disseminated metastases are seen in most cases (75–85%) while solitary metastases or metastases limited to lymph nodes are only observed in 15–25% of cases (75). In case of only a solitary metastasis or the incidence of a single lymph node, a local radical surgical or radiotherapy can be carried out with curative intent (76,77). Systemic therapy based on the finding of extensive pathological characterization is recommended for widely disseminated CUP syndromes. Standards of treatment for adenocarcinomas with no indication of enteral origin, and for undifferentiated carcinomas, are combination chemotherapy of platinum (cisplatin, carboplatin) and taxane, gemcitabine, irinotecan, or platinum-free combination therapies or monotherapies (78). Overall, the response rate in real CUP, meaning those in which the origin cannot be found even with advanced techniques, is around 20% (75,79).

Medical non-oncological management

The purpose of malignant SVC syndrome's management is to alleviate acute symptoms and treat the underlying disease. Treatment of the underlying cause depends on the histology of cancer while adjuvants medical therapy, including corticoids, diuretics and systemic anticoagulation will be administered regardless of cancer types.

Glucocorticoids (such as prednisone or methylprednisolone) may be helpful in two different settings of treatment of giant mediastinal tumors, causing MS. In the first setting, glucocorticoids can be used in steroid-responsive malignancies, such as lymphoma or thymoma, together with chemotherapy. In the other setting, high-dose glucocorticoids can minimize the risk of central airway obstruction secondary to edema in patients undergoing external beam radiation therapy and decrease the inflammatory response to tumor invasion by reducing edema surrounding the tumor (80).

Diuretics (such as furosemide) are recommended because they can reduce venous return to the heart which relieves the increased pressure and remove extra fluid from the body, although it is unclear whether small changes in right atrial pressure affect venous pressure distal to the obstruction. However, if diuretics do not alter symptoms, they should be stopped (81).

Anticoagulation is commonly used as primary prevention, but its benefit remains to be proven. In cases of proven thrombosis, systemic anticoagulation is generally recommended to limit thrombus extension (in the absence of contraindications) until definitive treatment can be undertaken (82).

Despite the wide variability depending on the underlying malignancy and the improvements of treatment, the median survival among patients who present malignant SVC syndrome remains approximately six months (83). In patients with advanced tumors and poor prognosis, palliative care should be initiated early (84).

Conclusions

In conclusion, considering the variety of pathologies that can occur in the mediastinum, a rapid histological characterization of the neoplasm is mandatory. In fact, the treatment of these neoplasms includes different approaches, sometimes used in combination, which include chemotherapy, radiotherapy, and surgery. Despite the great histological variability of mediastinal neoplasms, the clinical presentation and symptomatology is comparable and depends on the location of the mass and on the structures involved. Indeed, the main symptoms may be nonspecific such as chest pain or fever or may depend on the invasion or compression of vascular, nerve or respiratory structures, causing compression syndromes such as superior VCS. The VCS, due to its high mortality, is considered an oncological emergency and, therefore, requires effective treatments carried out urgently, evaluated in multidisciplinary meeting.

In advanced NSCLC, it is advisable to carry out molecular characterization by NGS (next generation

sequencing) or similar panels which evaluate the presence of genetic alterations, highly responsive to target therapy (EGFR, ALK, ROS1, BRAF, MET and RET). Target therapies with TKIs have an extraordinary ORR and produce a rapid reduction of neoplastic mass.

Non-oncogene-addicted NSCLC, treatment with anti-PD-1 in monotherapy have lower response rate, and a combination of chemotherapy and immunotherapy should be preferred. In these cancers, with concomitant superior VCS, loco-regional treatments including surgery, radiotherapy, stenting, and medical treatment based on corticosteroids, antithrombotic and diuretics may be considered as they may provide a rapid resolution of acute symptoms. Mediastinal tumors with high chemosensitivity are SCLC, lymphomas, and seminomas while the tumors sensitive to radiotherapy thymomas, thymic carcinoma, lymphomas, seminomas, and non-seminomas germ cell tumors. Other neoplasms including thymic, neurogenic, and mesenchymal tumors show poor sensitivity to chemotherapy and radiotherapy.

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