Review Article

When rarity meets thoracic cancers: a narrative review from ITMIG 2024

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Contributions: (I) Conception and design: M Ottaviano; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: M Ottaviano, E Pietroluongo; (V) Data analysis and interpretation: M Ottaviano, E Pietroluongo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background and Objective: Rare thoracic cancers (RTCs) comprise a heterogeneous group of malignancies characterized by low incidence, high histological diversity, and significant clinical challenges. Their rarity often results in delayed diagnoses, lack of standardized therapeutic approaches, and limited prospective clinical trials. The absence of robust data is compounded by the fragmentation of expertise across institutions, underscoring the need for centralized, multidisciplinary management and international collaboration. This article aims to provide an overview of three representative RTC models, highlighting their unique clinical, pathological, and therapeutic features, and to discuss strategies for optimizing clinical care.

Methods: A narrative review was conducted based on a targeted search of PubMed, MEDLINE, and major conference proceedings up to January 2025. The search focused on selected RTCs highlighted during the 2024 ITMIG annual meeting, using terms such as "SMARCA4-deficient undifferentiated tumors", "thymic neuroendocrine neoplasms", and "mediastinal germ cell tumors". Eligible sources included case reports, retrospective series, and narrative reviews. Only English-language publications were considered.

Key Content and Findings: We focus on SMARCA4-deficient undifferentiated tumors as examples of rare entities newly defined by molecular profiling; thymic neuroendocrine neoplasms as ultra-rare and biologically aggressive neoplasms; and mediastinal germ cell tumors, which share biological traits with their gonadal counterparts but exhibit unique clinical behaviors. Through these models, we highlight common themes in RTCs management, including diagnostic uncertainty, limited therapeutic options, and emerging directions.

Conclusions: We discuss the strengths and limitations of current evidence and future perspectives aimed at enhancing outcomes through dedicated registries and tailored therapeutic strategies.

Keywords: Rare thoracic cancers (RTCs); SMARCA4-deficient tumors; thymic neuroendocrine neoplasms (TNENs); mediastinal germ cell tumors (mediastinal GCTs)

Received: 15 April 2025; Accepted: 28 July 2025; Published online: 25 September 2025.

doi: 10.21037/med-25-22

View this article at: https://dx.doi.org/10.21037/med-25-22

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Introduction

Thoracic malignancies encompass over 100 different histotypes in the World Health Organization (WHO) 5th Classification of 2021, which covers tumors of the lung, thymus, heart, and pleura (1). Rare cancers, as defined by the European Rare Cancer Surveillance Project (RARECARE), represent a highly heterogeneous group of diseases with an incidence of fewer than six cases per 100,000 individuals annually (2). Overall, the estimated incidence of all rare tumors in Europe accounts for 24% of all cancers and, according to the results of RARECARE and Surveillance, Epidemiology, and End Results (SEER) databases, in Europe and the United States of America the 5-year survival is lower (48.5% and 55%, respectively) compared with all cancers with higher incidence (63.4% and 74%, respectively) (3). This worse survival may be mainly related to the lack of adequate and standardized treatments and delays in diagnosis (4). Rare thoracic cancers (RTCs) represent 8% of all thoracic malignancies (2,3), with a crude incidence in Europe of 6.8 per 100 000 people per year (2-4), while the SEER database reports an incidence of 0.22–0.25 cases per 100,000 per year for thymomas (5), 0.04–0.09 for mediastinal germ-cell tumors, and 0.03–0.80 for thoracic sarcomas (6), highlighting how this low incidence is the result of limited literature data with small case series and no prospective studies neither dedicated rare registry studies (7). The low frequency, the high prevalence of different subtypes, and the extreme unpredictability of clinical manifestation make RTCs an excellent challenge for most clinicians (8), who often have to manage complex decision-making processes. Tools largely proposed and accepted by the scientific community to try to fill the gap between common and RTCs are the centralization of diagnostic work-up and treatment in reference centers with high volume, expertise, and multidisciplinary approach (7). Moreover, worthy of consideration is that at the national and international level, some histological subtypes of RTCs may be studied in networks to organize individual efforts and make collation of personal experiences and global collaboration possible. The International Thymic Malignancy Interest Group (ITMIG), founded in 2010 and committed to research and guidelines development in the field of mediastinal cancers, has opened the way for building national-level infrastructure dedicated to reaching scientifically robust progress for rare cancers (9). The Italian network ThYmic MalignanciEs (TYME) is born in the wake of ITMIG to improve the current knowledge and provide a multidisciplinary consensus for the best treatment strategies for thymic epithelial tumors (TETs) (10). While significant efforts have been carried on scientific networking for TETs, which represent the most common mediastinal solid malignancies (8), most histological subtypes belonging to RTCs do not benefit from this organization, and data about them are based on small retrospective cohorts or cases reports (11). In this narrative review, we aim to discuss the epidemiology and the treatment strategies of three oncological models of RTCs selected by the scientific community of ITMIG for the 2024 annual conference to highlight the most critical emerging needs for RTCs: SMARCA4-deficient undifferentiated tumors (SMARCA4-dUT) as a model of rare entities characterized by new molecular profiles discoveries of common cancers; thymic neuroendocrine neoplasms (TNENs) a model of ultra-rare malignancies with an incidence rate less than one case per 100,000 individuals per year; mediastinal germ cell tumors (GCTs) as a model of rare cancers with unfavorable prognosis compared with gonadal counterparts. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-25-22/rc).

Methods

In this narrative review, we discussed the epidemiology, diagnostic complexity, and treatment strategies of selected RTCs presented at the 2024 ITMIG conference. A targeted literature search was conducted using PubMed, MEDLINE, and relevant conference proceedings up to January 2025 (*Table 1*). Search terms included “rare thoracic cancers”, “SMARCA4-deficient undifferentiated tumors”, “thymic neuroendocrine neoplasms”, and “mediastinal germ cell tumors”. No restrictions were applied regarding study design or publication status. Only articles published in English were considered. Given the rarity of the selected tumor subtypes, case reports, retrospective studies, and narrative reviews were included. Literature selection was performed independently by two authors, with disagreements resolved by consensus.

SMARCA4-dUT

SMARCA4-dUT are a rare and aggressive subgroup of thoracic malignancies characterized by mutations in the *SMARCA4* gene (12). While nosologically related to SMARCA4-deficient non-small cell lung cancer (SD-

Table 1 The search strategy summary

Items	Specification
Date of search	Up to January 31, 2025
Databases and other sources searched	PubMed, MEDLINE, major international conference proceedings (e.g., ITMIG Annual Meeting)
Search terms used	"Rare thoracic cancers", "SMARCA4-deficient undifferentiated tumors", "thymic neuroendocrine neoplasms", "mediastinal germ cell tumors"
Timeframe	From inception of each database to January 31, 2025
Inclusion and exclusion criteria	Included: English-language publications such as case reports, retrospective series, narrative reviews, and relevant conference abstracts
	Excluded: non-English publications, editorials without original data, and studies not focused on the selected rare thoracic cancers
Selection process	All articles were independently reviewed by two authors (M.O., E.P.). Discrepancies were resolved by discussion and consensus
Additional considerations	Selection was focused on tumor entities presented at the 2024 ITMIG meeting to ensure clinical and scientific relevance

ITMIG, International Thymic Malignancy Interest Group.

NSCLC), they remain a distinct entity. Indeed, SD-NSCLC accounts for approximately 5% of NSCLC cases and is characterized by aggressive clinical features and poor prognosis (13,14).

SMARCA4 is part of the SWI/SNF chromatin remodeling complex, which plays a critical role in suppressing tumor progression. These genes are among the most frequently mutated in human cancers, with alterations occurring in 20–24% of cases across various malignancies (15,16). These mutations are predominantly loss-of-function events, leading to disruptions in transcriptional regulation and DNA repair, thereby driving tumorigenesis. Thus, the defining molecular hallmark of SMARCA4-dUT is the mutation of *SMARCA4*, which leads to the loss of BRG1 protein expression (17). SD-NSCLC are usually adenocarcinomas and often form glandular structures showing a strong expression of cytokeratins in contrast to SMARCA4-dUT. The solid component does not differentiate between carcinoma and SMARCA4-dUT. Immunoexpression of SOX2, CD34, and SALL4 in SMARCA4-dUT is common but may not occur (18). In contrast, SD-NSCLC often harbors co-occurring mutations, including the KRAS G12C variant, which has therapeutic implications, particularly in the context of KRAS inhibitors (19).

Recent studies have further delineated the genomic and morphological distinctions of SMARCA4-dUT compared to other malignancies. For instance, while poorly-differentiated neuroendocrine carcinoma (NEC) and SMARCA4-dUT may share histological overlap and thoracic localization, SMARCA4-dUT lacks majority of the neuroendocrine markers (e.g., CD56 and chromogranin A), and is defined by the absence of BRG1 expression. Similarly, although morphologically similar to SMARCA4-dUT, malignant rhabdoid tumors are distinguished by SMARCB1/INI1 loss rather than SMARCA4 mutations (20). Another extensively studied and potentially targetable SMARCA4-deficient malignancy is small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), which shares notable morphologic, immunophenotypic, and molecular similarities with thoracic SMARCA4-dUT (21).

SMARCA4-dUT predominantly affects young males to middle-aged adults and is strongly associated with smoking history (18). These tumors are most frequently characterized by the presence of large, compressive masses localized within the mediastinum, pleura, or lungs, and they often present clinically with a constellation of symptoms such as dyspnea, chest pain, and superior vena cava syndrome, all of which are indicative of their highly invasive and infiltrative behavior (22). The prognosis for patients diagnosed with SMARCA4-dUT remains poor, as evidenced by a median overall survival (OS) of merely six months, further emphasizing the urgent need for novel and more effective therapeutic interventions to improve clinical outcomes (23).

From a histopathological perspective, SMARCA4-

dUT poses significant diagnostic challenges due to its morphological overlap with poorly differentiated carcinomas and carcinomas of unknown primary origin, and requires immunohistochemical confirmation using a well-defined panel of antibodies, as well as correlation of histological image with clinical and radiological findings .Recent advancements in molecular diagnostics, mainly through the application of next-generation sequencing (NGS), have greatly enhanced the ability to detect *SMARCA4* mutations along with associated co-alterations, thereby facilitating a more precise understanding of the molecular landscape of these tumors (14). Moreover, the development and refinement of liquid biopsy technologies, which enable the non-invasive detection and analysis of circulating tumor DNA (ctDNA), have emerged as tools for both the early diagnosis of SMARCA4-deficient malignancies and the real-time monitoring of treatment responses (24).

Radiologically, SMARCA4-dUT often presents as a large, heterogeneous mass with necrotic and calcified areas. While not pathognomonic, these features are distinctive and aid in diagnosis (25). These tumors exhibit a strong affinity for ^{18}F-fluorodeoxyglucose (FDG), rendering positron emission tomography (PET) a helpful imaging modality for clinical staging and disease monitoring, particularly in the context of assessing tumor burden and metastatic spread (26). These radiological characteristics alone are insufficient for a definitive diagnosis. However, when combined with clinical, histopathological, and molecular data, they enhance diagnostic accuracy and support therapeutic decision-making. The treatment management of SMARCA4-dUT is evolving in response to the challenges posed by the tumor's inherent resistance to conventional treatments. Surgery, while a potentially curative approach in localized Stage I disease, offers limited benefits in advanced stages due to high rates of recurrence and early metastases (27). Radiotherapy has similarly shown limited utility due to widespread resistance reported in several clinical cases (27). Preclinical data suggest that SMARCA4-knockdown lung cancer cells exhibit sensitivity to cisplatin, attributed to impaired DNA repair mechanisms (28). In real-world settings, responses are limited, likely due to BRG1 loss, which reduces chromatin accessibility and disrupts calcium signaling pathways critical for chemotherapy-induced apoptosis.

A retrospective study of SMARCA4-dUT and SD-NSCLC highlighted the poor outcomes associated with chemotherapy alone. Patients receiving exclusive chemotherapy had significantly lower progression-free survival (PFS) (median PFS: 2.73 months) than those receiving chemo-immunotherapy (median PFS: 26.8 months, P=0.0437) (29).

Indeed, immunotherapy has emerged as a promising strategy for SMARCA4-dUT, leveraging the tumor's high tumor mutation burden (TMB) and genomic instability, even without programmed death-ligand 1 (PD-L1) expression. Immune checkpoint inhibitors (ICIs) have demonstrated durable responses, with case reports describing rapid symptomatic improvements and significant tumor regression following their use (30,31). Naito *et al.* reported a complete response in SMARCA4-dUT patients who received nivolumab after three cycles of chemotherapy despite undetectable PD-L1 expression (31). Similarly, Yang *et al.* successfully treated a PD-L1-negative SMARCA4-dUT patient with a second-line therapy with tislelizumab, etoposide, and carboplatin after four cycles of liposomal paclitaxel and cisplatin failed. Both patients had a high TMB (32).

Currently, there is a lack of randomized controlled trials (RCTs) focused on SMARCA4-dUT, with most evidence coming from retrospective studies. Nonetheless, several targeted therapies are being researched for SMARCA4 deficiency. Xue *et al.* demonstrated that SCCOHT cells exhibit limited CDK4/6 activity and respond to CDK4/6 inhibitors, suggesting their potential repurposing for SMARCA4-deficient tumors. In a case report, a patient with SMARCA4-deficient SCCOHT responded well to the combination of abemaciclib and nivolumab after multiple failed treatments, and this sensitivity was later confirmed in NSCLC with SMARCA4 loss (33).

However, a nonrandomized trial showed limited clinical benefit of palbociclib and ribociclib alone in tumors with CDK4/6 pathway alterations, including SMARCA4-deficient cases (34). AURKA inhibitors have demonstrated increased efficacy in preclinical studies due to BRG1 loss, which sensitizes tumors to these agents (35). Similarly, ATR targeting replication stress responses show potential as a therapeutic strategy for SMARCA4-dUT (36). Lastly, oxidative phosphorylation (OXPHOS) inhibitors (010759) and PARP inhibitors have been explored, although clinical use is currently limited by toxicity and insufficient data (37,38).

SMARCA4-deficient undifferentiated tumors remain a clinical challenge due to their aggressive behavior and limited responsiveness to conventional therapies. However, recent advancements in immunotherapy, targeted agents, and combination strategies have highlighted new

potential avenues for therapeutic intervention. A deeper understanding of the molecular mechanisms underlying SMARCA4 deficiency will be essential to guide future research and improve clinical outcomes in this rare and aggressive tumor entity.

TNENs

TNENs are ultra-rare malignancies with an estimated incidence of 0.02 per 100,000 individuals (39). They represent only 2–5% of all thymic tumors and account for less than 0.5% of all neuroendocrine neoplasms (NENs) (40). These tumors are highly aggressive and have a poor prognosis, with approximately 50% of patients failing to reach a 5-year survival rate (41). Due to their rarity and histological complexity, accurate diagnosis remains challenging. TNENs typically occur in middle-aged individuals, with a slight male predominance and a preference for the white population (42). The 2021 WHO classification divides TNENs into two main categories based on their histopathological features: neuroendocrine tumors (NETs) grade 1 (typical carcinoid) and grade 2 (atypical carcinoid) (collectively referred to as TNETs); and NECs [small cell carcinoma and large cell neuroendocrine carcinoma (LCNEC)]. Typical carcinoids are well-differentiated tumors with a low mitotic rate, whereas atypical carcinoids exhibit higher mitotic activity and focal necrosis (43). Small cell carcinoma and LCNECs are highly aggressive neoplasms characterized by a high mitotic rate and extensive necrosis. Immunohistochemical markers, including chromogranin A, synaptophysin, CD56, retinoblastoma protein (RB), are used to differentiate TNENs. A newly described subset, NET G3, shares morphological characteristics with well-differentiated NETs but displays higher proliferative activity and distinct molecular features, including an intermediate Ki-67 index (44). Although this category is recognized in the gastro-entero-pancreatic (GEP) system, it is not formally included in the 2021 WHO classification for thymic tumors. Notably, in contrast to GEP and pulmonary NENs, the Ki-67 index is currently not used for diagnostic or grading purposes in TNENs (45). Given the limited data on "thymic NET G3", future studies should clarify its molecular characteristics, clinical behavior, and optimal therapeutic strategies, which are currently unexplored.

Additionally, distinguishing primary TNENs from metastatic pulmonary NENs remains a diagnostic challenge, particularly in the absence of definitive immunohistochemical markers. TNENs frequently present non-specific symptoms, including cough, chest pain, dyspnea, and superior vena cava syndrome due to their anterior mediastinal location. These tumors may also exhibit functional activity; in 25% of cases, they can present Cushing's syndrome due to ectopic adrenocorticotropic hormone (ACTH) production, while carcinoid syndrome is relatively rare (46). The potential association with autoimmune disorders and paraneoplastic syndromes related to the thymic gland further complicates the clinical presentation. Genetic testing for MEN1 should be considered in patients with TNENs, particularly in those with a family history of endocrine neoplasms or multiple primary NETs. This evaluation can guide screening for associated tumors in both patients and at-risk relatives, preventing misclassification of recurrences as new malignancies (43).

Imaging studies play a crucial role in the diagnosis and staging of TNENs. Computed tomography (CT) and magnetic resonance imaging (MRI) provide essential morphological details, while functional imaging with FDG-PET, particularly in highly aggressive tumors, and gallium-68 DOTA-(Tyr^3)-Octreotate (DOTATATE) PET/CT in more differentiated tumors, enhances diagnostic accuracy. Gallium-68 DOTATATE PET/CT has become particularly valuable in evaluating NETs. It facilitates the precise identification of tumors of somatostatin receptors (SSTRs), helping select patients for somatostatin analogs [somatostatin analogs long-acting release (SSA-LAR)] and peptide receptor radionuclide therapy (PRRT) (47). The management of TNENs requires a multidisciplinary approach involving thoracic surgeons, oncologists, radiologists, and pathologists. Surgery is the preferred primary treatment for all potentially radically resectable, well-differentiated TNETs, as complete resection significantly improves survival outcomes (48). Adjuvant therapy is generally not recommended for typical and atypical carcinoids unless there is a high risk of recurrence. Radiotherapy is mainly used for incompletely resected or unresectable TNENs, particularly in cases with local invasion or symptom burden. However, its impact on long-term survival remains uncertain (49).

The high recurrence rates of TNENs (40–70% at 5 years) highlight the need for effective systemic therapies, especially for high-grade subtypes. Several treatments have been explored for metastatic TNENs, including chemotherapy, targeted therapies, and PRRT. SSA-LAR are widely used in well-differentiated, SSTR-positive TNENs, particularly in slowly progressing or indolent disease. Although no

randomized trials evaluate SSA-LAR monotherapy in TNENs, data from pulmonary carcinoids suggest that this treatment may delay disease progression in well-differentiated tumors, particularly in low-grade NETs with SSTR expression (SPINET trial) (50). However, for progressive or high-grade tumors, SSAs are potentially combined with targeted agents [e.g., everolimus (EVE)] or PRRT.

Platinum-based chemotherapy remains the cornerstone of first-line treatment for high-grade TNENs, particularly LCNEC and small cell carcinoma. The most used regimen is etoposide combined with either cisplatin or carboplatin, which has shown an objective response rate (ORR) around 30% and a median PFS of 7.2 months in retrospective analyses (51). While cisplatin-based regimens are traditionally preferred due to their higher response rates, carboplatin-based regimens offer better tolerability, especially in patients with comorbidities or poor performance status (52). Second-line chemotherapy options for TNENs are not well established. Treatment decisions for platinum-refractory cases are guided mainly by evidence extrapolated from pulmonary and thymic NETs (53,54).

Among targeted therapies, the mTOR inhibitor EVE has demonstrated activity in pulmonary and TNETs. The LUNA trial evaluated pasireotide (PAS) and EVE in progressive bronchial and thymic carcinoids as monotherapy or combined. The PAS + EVE combination improved both PFS and biochemical PFS (BPFS) compared to monotherapies, suggesting a potential benefit in disease control (55). However, dose reductions were required in over 50% of patients, and 65.9% discontinued treatment due to disease progression.

The Phase III CABINET trial was a randomized, double-blind study evaluating cabozantinib versus placebo in patients with previously treated advanced NETs. The trial included two cohorts, one with pancreatic NETs (pNETs) and another with extra-pancreatic NETs (epNETs), including TNENs. In the epNET cohort [n=203], cabozantinib demonstrated a median PFS of 8.4 months, significantly improving over the 3.9 months observed in the placebo group (HR 0.38; 95% CI 0.25–0.59; P<0.0001). These findings highlight cabozantinib as a potential therapeutic option in advanced TNENs, particularly for patients progressing on SSAs and EVE (56).

PRRT is also being investigated as a promising therapeutic approach in TNENs. The phase 3 LEVEL trial (GETNE-T2217) is an ongoing study investigating the efficacy and safety of ^{177}Lu-edotreotide versus EVE in patients with advanced, well-differentiated NETs of lung or thymic origin. Eligible patients must have progressive, SSTR-positive NETs (WHO grade 1 or 2) and are randomized 3:2 to receive either six cycles of ^{177}Lu-edotreotide or daily EVE (10 mg) until disease progression or intolerable toxicity. The primary endpoint is PFS, with secondary endpoints including OS, ORR, and patient-reported outcomes (57). If positive, the LEVEL trial could position PRRT as a key therapeutic option for well-differentiated TNETs, particularly in patients progressing on SSAs or EVE, potentially redefining the treatment algorithm. Despite therapeutic advancements, TNENs management relies heavily on data extrapolated from extra-thymic NETs, underscoring the urgent need for dedicated trials and biomarker-driven approaches investigating the early integration of PRRT.

Mediastinal GCTs

Histopathogenesis and epidemiology

GCTs are the most common cancers among young adults, with less than 2% diagnosed over the age of 55–60 years (58). They represent a distinct category of solid tumors that are highly responsive to chemotherapy (59). Consequently, GCTs have a high cure rate, even in advanced stages, with nearly 80% of metastatic patients successfully treated with chemotherapy, radiotherapy, and surgery (60). Based on clinical presentation, pathology, and cytogenetics, human GCTs can be classified into five types: (I) teratoma/yolk sac tumor of infancy (mostly in females); (II) seminoma and non-seminomatous of young adults (mostly in males); (III) spermatocytic seminoma in older men, found solely in the testis; (IV) dermoid cyst, almost exclusively occurring in the ovary; (V) gestational trophoblastic tumors (61). Type I GCTs are more frequently found in extragonadal locations than in the gonads, whereas type II GCTs primarily occur in the gonads. Outside the gonads, type II GCTs are only identified in two areas: the anterior mediastinum and the midline of the brain, including the pineal gland and suprasellar regions (61). The anterior compartment of the mediastinum is the most common site for extragonadal GCTs, although cases involving the middle mediastinum have also been reported (62).

Primary mediastinal GCTs (PMGCTs) account for only 1–3% of GCTs and 16% of mediastinal tumors (63). They are predominantly found in males (3) and may be associated with metachronous testicular cancer within a 10-year timeframe in approximately 10% of patients (62).

The average age at diagnosis is between 25 and 35 years, and unlike testicular GCTs, there has been no recorded increase in incidence (63).

Clinical features and diagnostic considerations

Individuals with Klinefelter syndrome are particularly vulnerable, and this syndrome should be excluded in young patients diagnosed with PMGCTs (62). Women are less affected by PMGCTs and typically, though not always present with type I GCTs. The most common histotype found in both men and women with PMGCTs is mature teratoma, a pattern also observed in those with Klinefelter syndrome (61). PMGCTs generally present as an anterior mediastinal mass, associated with symptoms such as chest pain, shortness of breath, and cough. These tumors are primarily diagnosed in males, exhibiting a male-to-female ratio of 9:1 (64). Interestingly, PMGCTs may relate to Klinefelter syndrome and hematologic malignancies (58). In terms of histological features, non-seminomatous types are more prevalent than seminomas in PMGCTs, making up 60–70% of cases, with mature teratoma—which is often treated surgically—being the most common histotype.

In contrast, immature teratomas are a rarer and more aggressive subtype with worse outcomes (65,66). PMCGTs with seminoma histology demonstrate excellent cure rates, comparable to those of their testicular counterparts, with a 5-year survival rate surpassing 90% (65). Typically, they are slow-growing tumors and may present with elevated levels of beta-human chorionic gonadotropin (hCG), particularly if syncytiotrophoblast cells are present in the tumor, as well as elevated lactate dehydrogenase (LDH) at the time of diagnosis. Conversely, non-teratomatous non-seminomatous PMGCTs (NS-PMGCTs) are aggressive tumors with a poor prognosis and an estimated 5-year OS rate of approximately 40–50%.

They may have highly elevated levels of alpha-fetoprotein (AFP), which favours the diagnosis of yolk sac tumor component and beta-hCG, pointing to the coexistence of choriocarcinoma component (67-69). According to the most accepted theory, PMGCTs develop when germ cells halt their descent and remain in the anterior mediastinum, becoming malignant (58), which explains the presence of normal testes in these patients. Several similarities exist between testicular cancers and PMGCTs. Both cancers show the isochromosome 12p [i(12p)], a cytogenetic aberration found in approximately 80% of PMGCTs, regardless of the histological subtype (70). In challenging diagnostic cases, the persistence of i(12p), usually identified through fluorescence *in situ* hybridization, serves as a valuable tool for differentiating mediastinal masses, and confirming a diagnosis of PMGCTs (71,72). Additionally, PMGCTs, when compared to testicular GCTs, display a higher TMB and distinct pathogenic oncogene alterations, including TP53 (46%), c-KIT (18%), KRAS (18%), PTEN (11%), NRAS (4%), and PIK3CA (4%). These alterations are more commonly seen in NS-PMGCTs than in seminomas and non-seminomatous testicular GCTs (6).

Molecular pathogenesis and prognostic implications

Recent literature has emphasized the importance of TP53 mutations and MDM2 alterations in GCTs' cisplatin resistance. While TP53 mutations are mainly associated with PMGCTs, MDM2 amplifications are predominantly found in the testis (73). A retrospective multi-center study found TP53 genomic alterations in 56% of non-seminomatous tumors, which were linked to significantly shorter OS compared to patients with wild-type TP53 PMGCTs, suggesting a distinct genomic background associated with poor prognosis in PMGCT patients (73,74).

Treatment strategies

In the case of PMGCT diagnosis, the most appropriate treatment should be started as soon as possible, aiming for a curative intent. While the cure rate can reach 80% even in cases of extensive disease for seminoma PMGCT, this drops to 40–50% for patients with NS-PMGCTs, who often require a multimodal approach. PMGCTs with mature teratoma histology can be cured with surgery alone, resulting in an excellent prognosis. Teratomas with somatic-type malignancy are treated with surgery +/– chemotherapy, depending on the type and percentage of the transformed tumor (58). The complete or near-complete *en bloc* excision after normalized or decreased serum tumor markers (AFP; beta-hCG; LDH) plays a crucial role in curing patients with PMGCTs (64). Although NS-PMGCTs are less sensitive to cisplatin-based chemotherapies, patients are most often treated with standard-dose chemotherapy (SDCT), according to the BEP protocol (bleomycin, etoposide, cisplatin), or etoposide and cisplatin (EP), based on the IGCCCG risk group. Chemotherapy, according to the VIP schedule (etoposide, ifosfamide, and cisplatin), using ifosfamide

instead of bleomycin, should be considered as the primary option for the potential of subsequent thoracic surgery (65). For non-seminomatous histotype, it is recommended to administer four cycles of cisplatin-based chemotherapy followed by surgical resection of any remaining mediastinal mass, as the residual tumor could still contain viable germ cells, whether immature or mature, or teratoma with somatic differentiation, all of which are associated with a poor prognosis. Radiation therapy should be used in specific cases, such as managing brain metastases.

High-dose chemotherapy (HDCT) and future directions

The need for testing HDCT has been emphasized due to the known chemosensitivity of GCTs and the goal of achieving a higher rate of long-term remissions, even in cases with poor prognosis like NS-PMGCTs (64). Consequently, since the early 1970s, HDCT protocols have been evaluated in advanced GCT patients. However, it is crucial to acknowledge that NS-PMGCT serves as a negative prognostic indicator, suggesting unfavorable outcomes for patients undergoing HDCT and autologous stem cell transplantation (ASCT). Therefore, some specialists do not recommend HDCT for NS-PMGCTs (66), and the role of HDCT in PMGCTs remains debated due to the absence of well-defined prognostic indicators and the limited research available. Recently, results from the largest series of NS-PMGCTs treated with HDCT (including 69 adult males) have been reported, showing an OS of 43.3% at 2 years, and 34.7% at 5 and 10 years. An analysis of outcomes revealed that patients who received HDCT as initial therapy experienced better PFS and OS than those treated during subsequent relapses (with a 5-year PFS of 51.8% compared to 26.8% and a 5-year OS of 51.3% against 25.9%). Consequently, the authors propose that HDCT with ASCT could serve as a viable treatment option either after the first relapse or even as a front-line strategy (75). In conclusion, PMGCTs include heterogeneous histological entities with distinct clinical and molecular features that differentiate non-seminomatous and seminoma PMGCTs, with NS-PMGCTs being the poorest prognostic group due to their low sensitivity to cisplatin and greater tendency to relapse. For this patient population, optimizing therapeutic strategies is crucial for improving survival outcomes while preserving quality of life. Therefore, identifying biological and genetic factors to investigate novel therapies in centers with expertise in the care of GCTs should be essential for achieving better results (76).

Conclusions

RTCs represent a heterogeneous group of malignancies with distinct clinical presentation, molecular features, and treatment strategies. Despite the relative differences among the three models of RTCs here analyzed, a careful basal evaluation, with specific expertise in the context of multidisciplinary management in reference centers, is the best way to improve outcomes in these rare tumors. Additionally, international registries should be promoted in order to consolidate clinical data, facilitate patient recruitment, and support large-scale trials.

Acknowledgments

E.P. is supported by a scholarship from Associazione TUTOR for the academic year 2024–2025.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Malgorzata Szolkowska) for "The Series Dedicated to the 14th International Thymic Malignancy Interest Group Annual Meeting (ITMIG 2024)" published in *Mediastinum*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://med.amegroups.com/article/view/10.21037/med-25-22/rc

Peer Review File: Available at https://med.amegroups.com/article/view/10.21037/med-25-22/prf

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-25-22/coif). "The Series Dedicated to the 14th International Thymic Malignancy Interest Group Annual Meeting (ITMIG 2024)" was commissioned by the editorial office without any funding or sponsorship. M.O. reports speaker fees from MSD and Novartis; consulting fees and participation on an advisory board for Regeneron. P.A.A. reports receiving consulting fees from Bristol-Meyers Squibb, Roche-Genentech, Merck Sharp & Dohme, Novartis, Merck Serono, Pierre-Fabre, AstraZeneca, Sun Pharma,

Sanofi, Sandoz, Immunocore, Italfarmaco, Nektar, Boehringer-Ingelheim, Eisai, Regeneron, Daiichi Sankyo, Pfizer, OncoSec, Nouscom, Lunaphore, Seagen, iTeos, Medicenna, Bio-Al Health, ValoTx, Replimmune, Bayer, Erasca, Philogen, Biontech, and Anaveon. He also reports receiving support for attending meetings and travel from Pfizer, Bio-Al Health, Replimmune, MSD, and Pierre Fabre. In addition, he serves as President of Fondazione Melanoma Onlus (Naples, Italy) and the Campania Society of ImmunoTherapy of Cancer (SCITO), and is a Member of the Steering Committee of the Society for Melanoma Research (SMR), and a Member of the Board of Directors for the Society of Immuno-Therapy of Cancer (SITC). E.P. is supported by a scholarship from Associazione TUTOR for the academic year 2024–2025. The authors have no other 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-25-22
Cite this article as: Ottaviano M, Ascierto PA, Pietroluongo E. When rarity meets thoracic cancers: a narrative review from ITMIG 2024. Mediastinum 2025;9:23.