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Chinese Expert Consensus on the Diagnosis and Treatment of Inflammatory Myofibroblastic Tumor

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ABSTRACT

Inflammatory myofibroblastic tumor (IMT) is a rare spindle-cell neoplasm. IMT currently suffers from a paucity of standardized diagnostic and therapeutic guidelines. The Chinese expert consensus committee on the diagnosis and treatment of IMT formed an "Expert consensus on the diagnosis and treatment of inflammatory myofibroblastic tumor". This consensus was developed through a comprehensive synthesis of expert opinions, an extensive review of the literature, and a series of offline and online deliberations. The committee aspires that this consensus will enhance the therapeutic outcomes and prognosis for patients with IMT in the future.

1 | Introduction

Inflammatory myofibroblastic tumor (IMT) is a rare tumor composed of myofibroblasts with lymphoplasmacytic infiltration. IMT has a low potential for recurrence and metastasis, and it can originate from various organs, including the lungs, bladder, spleen, breast, pancreas, liver, colon, spermatic cord, prostate, peripheral nerves, and orbit. Expert Consensus Group on IMT developed this consensus based on the latest evidence and suggestions from experts and scholars to guide the diagnosis and treatment of IMT.

This consensus was registered on the International Practice Guideline Registry Platform (IPGRP) with the registration number PREPARE-2024CN902. The expert group members include clinicians from respiratory and critical care medicine, oncology, thoracic surgery, radiation oncology, gynecology, pathology, imaging, and so forth. All members of the consensus working group had declared no conflicts of interest related to the content of this consensus. The Delphi method was conducted to form nine recommendations through expert voting (see Table 1). For recommendations with disagreements, at least 50% of the participants agree, and the proportion of those holding the opposite opinion must be less than 20%. If this standard is not met, no recommendation is formed.

2 | Epidemiology

IMT is quite rare, and its exact epidemiological data are still unclear. Since its annual incidence is less than 1/1000000, IMT was defined as one of the "ultra-rare sarcomas" at the 2019 Connective Tissue Oncology Society Consensus [1]. IMT can occur at any age, and 50%–60% of IMT patients are children and adolescents. There is no significant gender difference in the incidence of IMT. IMT can occur in various sites of the body and organs. The most common site is the lung, and it can also occur in soft tissues, bones, abdominal cavity, pelvic cavity, retroperitoneum, head and neck, and less commonly in the esophagus, heart, and adrenal glands [2]. The etiology of IMT is still unclear. There are reports of IMT occurring after radiotherapy for non-small cell lung cancer, but the correlation between radiotherapy and IMT is still uncertain [3].

3 | Clinical Manifestations

The clinical manifestations of IMT are not specific. The symptoms of IMT vary depending on the anatomical location. Patients may present with fever and weight loss. Tumors in the respiratory tract may cause dyspnea and airway obstruction; tumors in the neck may cause hoarseness. Tumors in the gastrointestinal tract may lead to intestinal obstruction and constipation; liver tumors may cause jaundice and hepatosplenomegaly; urinary tract tumors may cause dysuria and hematuria. Uterine tumors may cause abnormal genital bleeding. Inflammatory markers are often elevated in IMT patients, such as increased C-reactive protein levels, accelerated erythrocyte sedimentation rate, leukocytosis, anemia, and thrombocytosis.

4 | Imaging Features

The most common site for IMT is the lung, and pulmonary IMT is also the most common primary pulmonary tumor in children. CT scan is the preferred imaging method. Pulmonary IMT usually presents as a lobulated lesion located in the peripheral lung, typically solitary (approximately 5% of cases are multiple). The lesions are commonly found in the lower lobes and often show heterogeneous enhancement on contrast-enhanced scans. (Figure 1A–C)Calcification may be present, especially in pediatric patients.

IMT can also occur in extrapulmonary sites, including the peritoneal cavity (liver, spleen, mesentery, gastrointestinal tract), urogenital system (kidneys, ureters, bladder, uterus, adnexa, and testes), head and neck, musculoskeletal system, nervous system, heart, and so forth. The imaging manifestations vary depending on the location. IMT usually appears as a solid or mixed echogenic mass with clear margins and possible internal blood flow signals on ultrasound. On the CT scan, it typically appears as a homogeneous or heterogeneous low-density mass with clear margins in most cases, and calcification may be visible in some cases. It often shows heterogeneous mild to moderate enhancement, with possible persistent delayed enhancement, indicating the presence of fibrosis within the lesion. (Figure 1D–F) CT is advantageous for observing calcification and the involvement of surrounding bone by the tumor. IMT typically appears as a hypointense mass in T1-weighted MRI, and heterogeneous hyperintensity in T2-weighted imaging depending on the degree of fibrosis and water content within the lesion. The central scar or myxoid areas show hyperintensity, while areas dominated by fibrous components show hyperintensity. IMT may show restricted diffusion in areas with high cellularity or fibrosis, resulting in hyperintensity on DWI. IMT may show delayed enhancement on enhanced scans.

Consensus 1: Imaging findings of inflammatory myofibroblastic tumors (IMTs) typically present as solitary masses, necessitating differential diagnosis from other common benign and malignant neoplasms in various anatomical locations. Contrast-enhanced CT or MRI, selected based on the optimal imaging modality for the specific tumor site, is recommended for further evaluation. Additionally, PET-CT may be utilized when indicated, providing critical insights for tumor staging and comprehensive assessment.

5 | Pathological Features

IMT is a rare tumor characterized by the proliferation of fibroblasts and myofibroblasts with infiltration of plasma cells, lymphocytes, and eosinophils. The pathological histology manifests in three patterns: (a) Nodular fasciitis-like, myxoid type: spindle-shaped fibroblasts/myofibroblasts proliferate within a myxoid edematous intercellular content; (b) hypercellular type: spindle-shaped fibroblasts/myofibroblasts are densely arranged in bundles; (c) hypocellular type: hyaline collagenous intercellular content with sparse spindle cells. (Figure 2A–C) One tumor may predominantly show one histological pattern or contain multiple patterns. Epithelioid inflammatory myofibroblastic sarcoma (EIMS) shows aggressive progression, with tumor cells presenting as large, round, epithelioid cells with vacuolated nuclei, and prominent nucleoli. The pathological diagnosis of IMT needs to be differentiated from various spindle cell tumors and reactive proliferative diseases, such as nodular fasciitis, gastrointestinal stromal tumors, follicular dendritic cell tumors, inflammatory fibroid polyps, and IgG4-related diseases. ALK immunohistochemical staining is recommended because of the high proportion of ALK fusion in IMT. (Figure 2D).

Consensus 2: IMT should be considered in the pathological diagnosis of spindle cell tumors with inflammatory cell infiltration, and multiple immunohistochemical markers,

TABLE 1 | Chinese expert consensus on the diagnosis and treatment of inflammatory myofibroblastic tumor.

Consensus number	Key points	Agreement	Disagreement	Abstain
1	Imaging findings of inflammatory myofibroblastic tumors (IMTs) typically present as solitary masses, necessitating differential diagnosis from other common benign and malignant neoplasms in various anatomical locations. Contrast-enhanced CT or MRI, selected based on the optimal imaging modality for the specific tumor site, is recommended for further evaluation. Additionally, PET-CT may be utilized when indicated, providing critical insights for tumor staging and comprehensive assessment	31	0	0
2	IMT should be considered in the pathological diagnosis of spindle cell tumors with inflammatory cell infiltration, and multiple immunohistochemical markers, including ALK, should be performed for diagnosis and differential diagnosis	31	0	0
3	Compared with immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and polymerase chain reaction (PCR), next-generation sequencing (NGS) offers a comprehensive and accurate approach to identifying gene rearrangements and their partner genes in inflammatory myofibroblastic tumors (IMT). Specifically, RNA-based NGS can provide detailed information on the entire spectrum of fusion partners involved in these rearrangements	30	0	1
4	Diagnosis and treatment of IMT often involve multiple disciplines, including respiratory and critical care medicine, medical oncology, radiology, pathology, thoracic surgery, general surgery, orthopedics, and gynecology. Multidisciplinary discussions are recommended to enhance capability of diagnosis and treatment	31	0	0
5	Patients with IMT suitable for surgery should conduct radical surgery as the main treatment	31	0	0
6	Postoperative head and neck IMT patients with high-risk features for recurrence can undergo adjuvant radiotherapy. Patients who have undergone partial resection or are unsuitable for surgery can receive radical radiotherapy combined with systemic therapy. Involved-field irradiation (without prophylactic lymph node irradiation) is recommended, with intensity-modulated radiotherapy (IMRT) technology preferred, and the radiation dose is controlled at 45-60Gy (conventional fractionation)	23	0	8
7	ALK-TKI was recommended for patients with IMT harboring ALK fusion who are not suitable for surgery; for patients with ROS1 fusion IMT who are not suitable for surgery, ROS1-TKI treatment can be attempted	25	0	6
8	Chemotherapy regimens based on anthracyclines, methotrexate, pemetrexed + platinum, and paclitaxel + platinum are recommended for patients with IMT	17	0	14
9	The diagnosis and treatment of IMT currently lack high-level evidence. It is recommended to conduct multicenter, prospective clinical studies	31	0	0

including ALK, should be performed for diagnosis and differential diagnosis.

6 | Molecular Characteristics

The incidence of ALK rearrangement is relatively high in children and adolescent patients with IMT. Approximately 50%–60% of IMT cases harbor ALK fusion. Additionally, other fusion genes have been detected, such as c-ros 1 (ROS1), neurotrophic tyrosine receptor kinase (NTRK), platelet-derived growth factor receptor (PDGFR), insulin-like growth factor 1 receptor (IGF1R), and RET fusion genes. Some fusion gene partners are associated with clinical features [4]. There are many fusion partners for ALK, such as TPM3, TPM4, CLTC, CARS, RANBP2, ATIC, NUMA1, SQSTM1, and so forth [5, 6]. It was

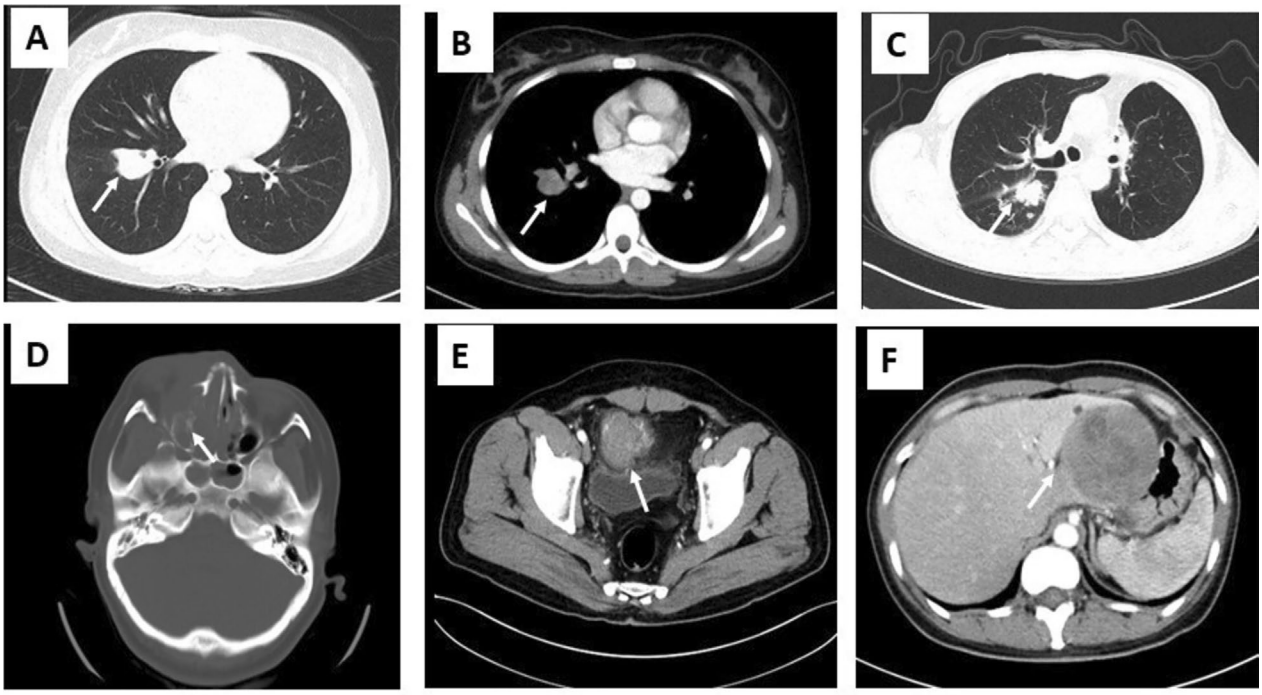

FIGURE 1 | CT Images of inflammatory myofibroblastic tumor: (A, B) Pulmonary inflammatory myofibroblastic tumor CT, showing a well-defined nodule in the right lung with heterogeneous enhancement in contrast CT; (C) Pulmonary inflammatory myofibroblastic tumor CT, showing a lobulated nodule; (D) Sinonasal inflammatory myofibroblastic tumor CT, showing an irregular soft tissue mass in the right sinus with surrounding bone destruction; (E) Pelvic inflammatory myofibroblastic tumor CT, showing a pelvic soft tissue mass with mild enhancement and slight surrounding exudation; (F) Hepatic inflammatory myofibroblastic tumor, showing a round low-density mass in the left lobe of the liver with heterogeneous enhancement.

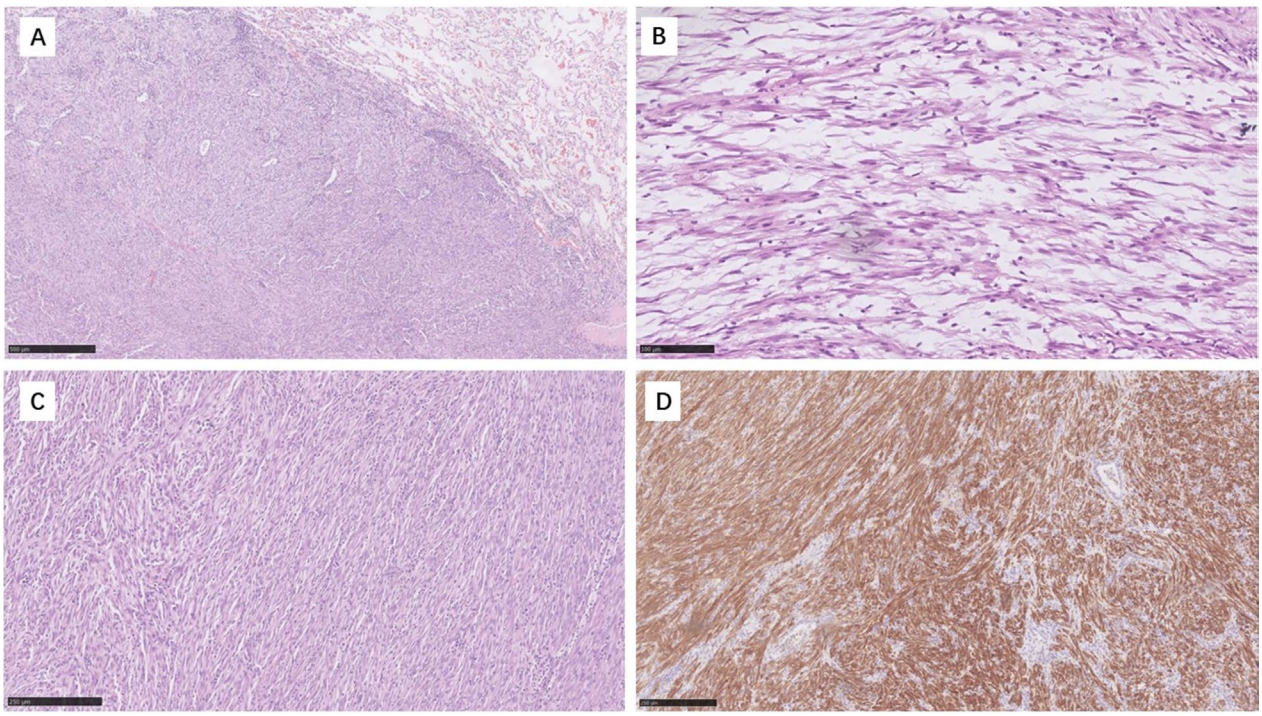

FIGURE 2 | Pathological Images of inflammatory myofibroblastic tumor: (A) HE staining of inflammatory myofibroblastic tumor, with tumor tissue in the lower left and lung tissue in the upper right; (B) HE staining of nodular fasciitis-like and myxoid inflammatory myofibroblastic tumor, showing scattered spindle-shaped fibroblasts and myofibroblasts within a myxoid edematous intercellular content; (C) HE staining of hypercellular inflammatory myofibroblastic tumor, with spindle-shaped fibroblasts and myofibroblasts densely arranged in bundles; (D) Positive ALK staining in immunohistochemistry.

reported that patients with ALK gene rearrangement in IMT often have a good prognosis; however, it was also reported that ALK positivity is associated with local recurrence of IMT. ALK-negative patients are more likely to have distant metastasis. The types of gene rearrangements in IMT tumors vary by location: in abdominal IMT, the incidence of ALK fusions with RANBP2 and CLTC genes is significantly higher than in other organs; ROS1 rearrangement is more characteristic in pulmonary IMT; NTRK3; and PDGFRb fusions are only detected in thoracic vertebral IMT. Detection of ALK fusion genes is important for predicting the prognosis of IMT patients, as well as the recurrence and metastasis of tumors.

Consensus 3: Compared with immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and polymerase chain reaction (PCR), next-generation sequencing (NGS) offers a comprehensive and accurate approach to identifying gene rearrangements and their partner genes in inflammatory myofibroblastic tumors (IMT). Specifically, RNA-based NGS can provide detailed information on the entire spectrum of fusion partners involved in these rearrangements.

7 | Prognosis

Most IMT patients have a good prognosis after radical treatment, and most recurrences occur in patients who have undergone non-radical surgery. The incidence of distant metastasis is approximately 5% [7]. There are limited prognostic factors currently. The impact of age on prognosis is still unclear [2]. Tumor size is associated with patient prognosis, with tumors > 6.5 cm indicating a poor prognosis [7]. Studies have shown that tumors larger than 11 cm are predictive of recurrence [8]. Pathological features such as necrosis, lymphatic invasion, high mitotic activity, increased cellularity, invasive margins, intercellular myxoid material, ganglion-like cells, and giant cells are associated with poor prognosis [8].

8 | Diagnosis

IMT can occur in various organs throughout the body. Currently, there is no specific staging system for IMT. The staging system for IMT can adopt the ninth edition of the TNM staging system of the American Joint Committee on Cancer (AJCC), referring to other types of tumors at the corresponding site.

Consensus 4: Diagnosis and treatment of IMT often involve multiple disciplines, including respiratory and critical care medicine, medical oncology, radiology, pathology, thoracic surgery, general surgery, orthopedics, and gynecology. Multidisciplinary discussions are recommended to enhance capability of diagnosis and treatment.

9 | Treatment of IMT

9.1 | Surgical Treatment

Surgery is the primary treatment for localized IMT. The standard surgical approach is complete resection with R0 margins. It was shown that complete resection of IMT leads to a good prognosis, with a 5-year survival rate of 91% [9]. Some patients experience tumor recurrence after surgery. The recurrence rate of IMT varies by location after complete resection, with a 2% recurrence rate for pulmonary lesions and up to 25% for extrapulmonary lesions. Prospective studies on adjuvant therapy after complete resection are lacking. Some patients with local recurrence who are suitable for surgery can undergo surgical treatment. Long-term follow-up is required after surgery.

Consensus 5: Patients with IMT suitable for surgery should conduct radical surgery as the main treatment.

9.2 | Radiotherapy

Radiotherapy can be applied as an adjuvant treatment for localized IMT in the perioperative period, including adjuvant radiotherapy and neoadjuvant radiotherapy [10, 11]. However, the indications are not yet established and are mostly applied to patients with close or positive surgical margins. A study on postoperative patients with localized head and neck IMT showed that for head and neck IMT patients with obvious invasive growth or other high-risk features (e.g., preoperative tumor size > 4.4 cm, maxillary sinus tumor, or preoperative neutrophil-to-lymphocyte ratio (NLR) > 1.958), postoperative adjuvant radiotherapy can improve overall survival [10]. There are also case reports showing that postoperative close-margin chest IMT patients can achieve long-term survival with 45Gy of postoperative adjuvant radiotherapy alone. Additionally, for patients who cannot tolerate surgery or have inoperable tumors, radical radiotherapy combined with systemic therapy can be performed [12–15]. However, due to the low incidence of IMT, the literature on radiotherapy is mainly case reports, with tumor locations covering the skull base, head, and neck, chest, and so forth. The recommended radiation dose is mostly 45-60Gy, usually combined with corticosteroids or other immunosuppressants, with follow-up ranging from 2 to 7 years, and a 5-year survival rate of over 70% [12].

There is currently no standard radiation field or dose for localized IMT patients. Based on clinical characteristics, it is recommended to perform involved-field irradiation, with the target area appropriately expanded around the tumor margin to include as many microfoci as possible, and intensity-modulated radiotherapy (IMRT) technology should be used whenever possible to protect surrounding normal tissues. The radiation dose mentioned in the literature is mostly 45-60Gy [11, 13, 14]. There are also case reports of low-dose 20Gy/10f combined with corticosteroids for head and neck IMT patients, [15] and attempts of ultra-low dose radiotherapy (4Gy/2f) for bilateral pulmonary recurrent IMT patients [16]. The former had a follow-up of 2 years, and the latter had a follow-up of over 6 months without recurrence or progression.

Consensus 6: Postoperative head and neck IMT patients with high-risk features for recurrence can undergo adjuvant radiotherapy. Patients who have undergone partial resection or are unsuitable for surgery can receive radical radiotherapy combined with systemic therapy. Involved-field irradiation (without prophylactic lymph node irradiation) is recommended, with intensity-modulated radiotherapy (IMRT) technology preferred,

and the radiation dose is controlled at 45-60Gy (conventional fractionation).

9.3 | Anti-Inflammatory Treatment

Case reports on corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) for IMT show tumor shrinkage after anti-inflammatory treatment [13, 17–19]. It was reported that the combination treatment of NSAIDs and chemotherapy for IMT was effective [20, 21]. However, it was also reported tumor progression in IMT patients treated with corticosteroids [22]. Since some studies included inflammatory pseudotumors or other reactive diseases, and due to the lack of prospective studies, the anti-tumor effect of anti-inflammatory treatment in IMT is still unclear.

9.4 | Targeted Therapy

A study of crizotinib for IMT demonstrated clinical responses in ALK-rearranged patients in 2010 [23]. A prospective clinical trial of crizotinib for IMT showed partial responses in 3 out of 7 IMT patients [24]. The expanded cohort of this trial recruited 14 IMT patients, with a response rate to crizotinib of 86% [25]. Long-term follow-up revealed that the median progression-free survival (PFS) for ALK-rearranged patients treated with crizotinib reached 18 months [26]. A number of case reports have been published on the treatment of IMT patients with ALK-TKIs, including crizotinib, ceritinib, alectinib, lorlatinib, and brigatinib [6, 27, 28]. In addition to ALK-targeted therapies, cases of targeted treatments for other fusion genes were reported. Case reports showed that crizotinib is effective in treating IMT harboring ROS1-rearranged [29, 30]. It was shown that IMT patients may harbor NTRK fusions [31]. Entrectinib was approved for the treatment of solid tumors with NTRK gene fusions. It was identified RET fusions in ALK-negative IMT patients [32]. Selpercatinib was approved in the United States for RET fusion solid tumors. However, data on targeted therapies for other targets in IMT are still limited and require further research.

Consensus 7: ALK-TKI was recommended for patients with IMT harboring ALK fusion who are not suitable for surgery; for patients with ROS1 fusion IMT who are not suitable for surgery, ROS1-TKI treatment can be attempted.

9.5 | Chemotherapy

Systemic therapy is applicable for advanced or inoperable IMT. Currently, due to the rarity of the disease and the lack of prospective data on the efficacy of chemotherapy, there is no established standard chemotherapy regimen for advanced IMT. Retrospective studies have shown that the overall response rate (ORR) for chemotherapy regimens based on anthracyclines or methotrexate ± vinorelbine/vincristine is approximately 50% [33]. It was reported that pemetrexed + platinum and paclitaxel + platinum have shown good efficacy in IMT [34, 35]. It is recommended to conduct chemotherapy clinical trials for IMT to detect efficacy.

Consensus 8: Chemotherapy regimens based on anthracyclines, methotrexate, pemetrexed + platinum, and paclitaxel + platinum are recommended for patients with IMT.

9.6 | Immunotherapy

About 69% of IMT tumors express PD-L1 [36]. Reports on the treatment of IMT patients with immune checkpoint inhibitors are very limited. One IMT patient achieved partial response after treatment with nivolumab [37]. One patient with nasopharyngeal IMT achieved partial response after treatment with toripalimab and sintilimab [38]. One patient with metastatic IMT achieved partial response after treatment with pembrolizumab and anlotinib [39]. The efficacy of Immunotherapy for IMT needs further exploration.

10 | Summary

IMT is a challenging disease. In addition to targeting ALK, more data on the efficacy of other TKIs, as well as chemotherapy and immunotherapy, are needed. It is crucial to summarize IMT cases. These data will not only help to better understand IMT, but also provide a rational targeted treatment strategy. Patients should be encouraged to participate in clinical studies. This consensus statement will be continuously updated with the accumulation of more evidence.

Consensus 9: The diagnosis and treatment of IMT currently lack high-level evidence. It is recommended to conduct multicenter, prospective clinical studies.

Author Contributions

Xiaoyan Si and Li Zhang participated in the design of the expert consensus. Shafei Wu, Rui'e Feng, Xuan Wang, and Hui Guan conceived of the expert consensus, and participated in its design, and other authors coordination and helped to draft the expert consensus. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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