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Evidence-based clinical consensus for the diagnosis and management of inflammatory myofibroblastic tumor

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Inflammatory myofibroblastic tumors (IMTs) are rare mesenchymal neoplasms with intermediate malignant potential, representing less than 1% of soft tissue tumors. They primarily affect children and young adults, most often arising in the abdominal cavity, retroperitoneum, or lungs. Although generally indolent, IMTs can aggressively invade local tissues, recur, and occasionally metastasize. Because 50% to 60% of these tumors harbor anaplastic lymphoma kinase (*ALK*) gene rearrangements, IMT is now recognized as a kinase-driven neoplasm.[1]

Broad sarcoma guidelines from 2021–2022 establish basic management principles for IMT, yet rapid therapeutic progress has outpaced these recommendations. Specifically, older guidelines lack detailed algorithms for utilizing next-generation sequencing to identify non-ALK fusions and deploying next-generation TKIs for crizotinib resistance. To address this gap, wesynthesizedexistingmultidisciplinaryguidelineswithrecentevidence,including the 2025 Chinese expert consensus, to provide an up-to-date IMT-specific clinical algorithm (Figure 1).[1-4] All recommendations herein are grounded in expert consensus and evaluated using standard evidence frameworks (Level of Evidence [LoE] I–V; Grade of Recommendation A–C).

DIAGNOSIS AND ASSESSMENT

While clinical presentation varies by anatomic site, 20% to 30% of patients develop a paraneoplastic systemic inflammatory syndrome (fever, weight loss, elevated C-reactive protein) that typically resolves following complete resection. Radiologically, these tumors often appear as lobulated, heterogeneous masses with variable contrast enhancement, making them difficult to distinguish from other soft tissue sarcomas on imaging alone.

Histologically, IMTs consist of proliferating fibroblastic and myofibroblastic spindle cells intermixed with a prominent inflammatory infiltrate (plasma cells, lymphocytes, and eosinophils). Notably, the highly aggressive epithelioid inflammatory myofibroblastic sarcoma (EIMS) subtype features plump epithelioid cells within an abundant myxoid stroma and carries a high risk of rapid recurrence and metastasis.

Molecular profiling is mandatory for both diagnosis and treatment planning. While ALK immunohistochemistry (IHC) serves as the first-line screening tool, negative IHC results necessitate further testing. Techniques such as RNA-based next-generation sequencing (NGS) or fluorescence in situ hybridization (FISH) must be used to detect cryptic *ALK* rearrangements or alternative actionable fusions (e.g., *ROS1*, *NTRK3*, *RET*, *PDGFRB*). Finally, baseline staging and multidisciplinary team (MDT) evaluation are required to assess tumor resectability and anticipated functional morbidity.

LOCAL THERAPEUTIC STRATEGIES

Complete surgical resection with negative margins (R0) remains the cornerstone for localized IMT. Following complete resection of node-negative localized disease, active surveillance is strongly recommended (LoE II, A). 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. Although robust evidence for adjuvant therapy following incomplete (R1/R2) resection is limited, ESMO guidelines recommend multidisciplinary team evaluation to weigh the use of re-excision, radiotherapy, or chemotherapy.[2] For patients following R1/R2 resection, repeat excision is the preferred strategy if anatomically feasible. Adjuvant radiotherapy plays a highly limited role; while it may be considered for adults with positive margins, it is strictly contraindicated in young children (< 3 years) due to severe developmental risks (LoE IV, C).[4]

SYSTEMIC THERAPEUTIC STRATEGIES

For advanced, unresectable, or metastatic IMTs, targeted therapy has replaced conventional chemotherapy as the preferred frontline approach. In *ALK*-positive disease, ALK inhibitors (e.g., crizotinib) show robust clinical activity and represent the standard first-line systemic treatment (LoE II, A). This approach is supported by prospective data demonstrating an 86% response rate and a median progression-free survival of 18 months among 14 patients with ALK-rearranged IMT treated with crizotinib.[4] In *ALK*-negative IMTs harboring alternative fusions, matched tyrosine kinase inhibitors (TKIs)—such as entrectinib or larotrectinib for *NTRK* fusions, and crizotinib for *ROS1* fusions—elicit strong objective responses. Although the optimal duration of TKI therapy remains formally undefined, continuous administration is currently recommended. Long-term follow-up data confirm that patients derive sustained clinical benefit and highly durable responses from prolonged treatment.

Systemic chemotherapy is reserved for patients lacking actionable mutations, or when targeted therapies are unavailable or contraindicated. Retrospective studies have demonstrated that both traditional anthracycline-based regimens and the MTX-V regimen (methotrexate plus vinorelbine or vincristine) yield a comparable overall response rate (ORR) of approximately 50%.[4] However, because MTX-V provides equivalent disease control with a more favorable long-term toxicity profile—particularly by avoiding the cumulative cardiotoxicity associated with anthracyclines—it has emerged as a preferred systemic option rather than just an alternative. (LoE IV, B).

RELAPSE/REFRACTORY MANAGEMENT AND FOLLOW-UP

ManagementofrelapsedorrefractoryIMTremainschallenging.Approximately 25% of extrapulmonary IMTs recur, with risk depending heavily on anatomic site and initial resectability. For patients progressing on first-generation ALK inhibitors due to acquired resistance mutations (e.g., *ALK* G1269A), next-generation agents (e.g., ceritinib or lorlatinib) are recommended.

In targeted therapy–refractory disease, next-generation ALK inhibitors such as ceritinib or lorlatinib serve as the primary salvage strategy.[5] Conversely, in cases of initial chemotherapy resistance, second-line chemotherapy regimens such as topotecan plus cyclophosphamide (TC) provide viable salvage options. Rituximab may also serve as a salvage strategy for ALK-negative recurrences featuring a prominent inflammatory infiltrate. Additionally, while high PD-L1 expression (~ 69%) supports a rationale for immune checkpoint blockade, responses to PD-1 inhibitors are limited to isolated case reports, rendering this approach strictly exploratory. Across all treatment lines, the high mortality associated with EIMS subtypes dictates aggressive, multidisciplinary intervention. Given the unpredictable nature of IMT recurrences, rigorous long-term surveillance is essential.

CONCLUSION AND OUTLOOK

Integrating molecular pathology has shifted IMT management from a purely surgical approach to a precision oncology paradigm. While consensus supports complete resection for localized disease and ALK inhibition for advanced cases, critical uncertainties remain—specifically regarding the optimal duration of TKI therapy, adjuvant strategies following incomplete (R1/R2) resections, and the validation of risk-stratified follow-up models. Given the rarity of this sarcoma, multicenter collaboration is crucial. Addressing these gaps mandates the establishment of prospective international registries, expanded RNA profiling to identify novel fusions in ALK-negative cohorts, and clinical trials investigating next-generation ALK inhibitors as upfront therapy, alongside salvage immunotherapies for refractory disease.

ABBREVIATIONS

ALK, anaplastic lymphoma kinase; DCR, disease control rate; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; MDT, multidisciplinary team; MTX-V, methotrexate and vinorelbine; NGS, next-generation sequencing; QoL, quality of life; TC, topotecan and cyclophosphamide; TKI, tyrosine kinase inhibitor; VDC, vincristine, doxorubicin, and cyclophosphamide.

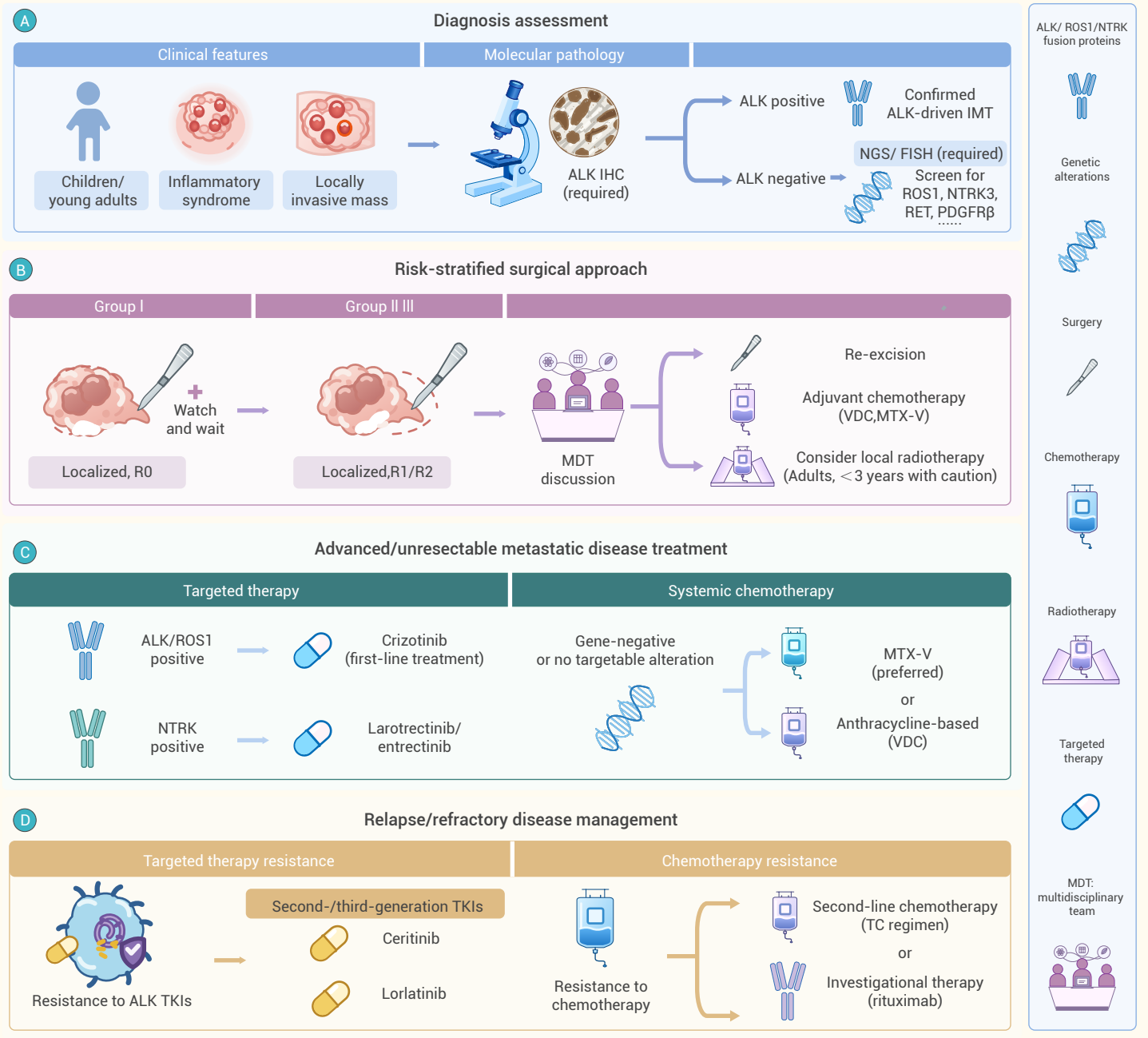


Figure 1. Comprehensive clinical management algorithm for inflammatory myofibroblastic tumor (IMT) (A) Diagnostic Assessment: Integrates clinical evaluation (including inflammatory syndrome and locally invasive mass) with obligatory ALK immunohistochemistry (IHC). ALK-negative cases necessitate reflex NGS or FISH testing to screen for alternative gene fusions, such as ROS1, NTRK3, RET, or PDGFRβ. (B) Risk-stratified Surgery: For localized disease with complete resection (R0, Group I), a active surveillance ("watch and wait") strategy is warranted. For cases with microscopic or macroscopic positive margins (R1/R2, Group II/III), multidisciplinary team (MDT) consultation is mandated to direct subsequent re-excision, adjuvant chemotherapy (e.g., VDC, MTX-V), or judicious local radiotherapy (administered with extreme caution in adults and children under 3 years of age). (C) Advanced/Unresectable Metastatic Disease Treatment: Guided by molecular profiling, target-positive tumors receive first-line targeted therapy (crizotinib for ALK/ROS1-positive; larotrectinib or entrectinib for NTRK-positive cases). Gene-negative or target-negative tumors are managed with systemic chemotherapy (preferably MTX-V or anthracycline-based regimens). (D) Relapse/Refractory Disease Management: Treatment strategies are dictated by the mechanism of prior resistance. Progression following targeted therapy is managed with second- or third-generation TKIs (e.g., ceritinib or lorlatinib), whereas chemotherapy failure is addressed via second-line chemotherapy (TC regimen) or investigational immunotherapies (e.g., rituximab).

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DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.