# Clinicopathological Analysis and Treatment of Inflammatory Myofibroblastic Tumor in Adult Patients: A Retrospective Study of 74 Cases

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## Abstract

Objective: Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal neoplasm with diverse behaviors occurring in soft tissues and visceral organs. The clinical and pathological features of IMT in adult patients are not well understood. This study highlights the importance of comprehensive diagnostics, including histopathology, immunohistochemistry, and genetic testing, in managing IMTs. High ALK positivity in lung IMTs suggests targeted therapies' benefit. ALK inhibitors should be considered for ALK-positive tumors. Regular follow-up is crucial due to relapse risk. Methods: We conducted a retrospective analysis of 74 patients diagnosed with IMTs at Peking Union Medical College Hospital between 2010 and 2023. Clinicopathological data, treatments, and outcomes were collected and analyzed. Results: Among the 74 patients (34 females, 40 males) at an average age of 50, the majority were asymptomatic. The most common tumor locations were the head and neck (24.1%), followed by lung (21.6%). Anaplastic lymphoma kinase (ALK) positivity was identified in 31% of cases, with the highest prevalence in lung IMTs (45.5%). Most patients underwent surgical resection, and some received postoperative treatments including radiotherapy, chemotherapy, or ALK inhibitors. The 1-year, 3-year, 5-year, and 10-year OS rates were 78.4%, 70.9%, 69.2%, and 69.2%, respectively. Limitations: This is a single-center retrospective study, and the characteristics of these patients may not be representative of all adult IMT patients. While the sample size of drug-treated patients is relatively small and heterogeneous, making further systematic analysis difficult. The mechanism of resistance to ALK inhibitors has not been determined. Conclusions: IMTs exhibit significant clinical heterogeneity, with lung IMTs demonstrated the highest rate of ALK positivity. While surgical resection remains the primary treatment modality, the observed rates of relapse and mortality underscore the necessity for more

effective therapeutic strategies. ALK inhibitor such as crizotinib should be consideration for ALK positive patients. A deeper understanding of the molecular characteristics of IMTs may help to enhance diagnostic accuracy and inform the development of improved treatment options.

## Full Text

## Preamble

### Clinicopathological Analysis and Treatment of Inflammatory Myofibroblastic Tumor in Adult Patients: A Retrospective Study of 74 Cases

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## Abstract

**Objective:** Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal neoplasm with diverse clinical behaviors that can occur in soft tissues and vis-

ceral organs. The clinical and pathological features of IMT in adult patients remain poorly understood. This retrospective study aimed to characterize these features and evaluate treatment outcomes in a large cohort of adult patients.

**Methods:** We conducted a retrospective analysis of 74 patients diagnosed with IMTs at Peking Union Medical College Hospital between 2010 and 2023. Clinicopathological data, treatment modalities, and clinical outcomes were systematically collected and analyzed.

**Results:** Among the 74 patients (34 females, 40 males) with a mean age of 50 years, the majority were asymptomatic at presentation. The most common tumor locations were the head and neck (24.1%), followed by the lung (21.6%). Anaplastic lymphoma kinase (ALK) positivity was identified in 31% of cases, with the highest prevalence observed in lung IMTs (45.5%). Most patients underwent surgical resection, and some received postoperative treatments including radiotherapy, chemotherapy, or ALK inhibitors. The 1-year, 3-year, 5-year, and 10-year overall survival (OS) rates were 78.4%, 70.9%, 69.2%, and 69.2%, respectively.

**Limitations:** This is a single-center retrospective study, and the patient characteristics may not be representative of all adult IMT patients. The sample size of drug-treated patients was relatively small and heterogeneous, limiting further systematic analysis. Additionally, the mechanisms of resistance to ALK inhibitors have not been determined.

**Conclusions:** IMTs exhibit significant clinical heterogeneity, with lung IMTs demonstrating the highest rate of ALK positivity. While surgical resection remains the primary treatment modality, the observed rates of relapse and mortality underscore the necessity for more effective therapeutic strategies. ALK inhibitors such as crizotinib should be considered for ALK-positive patients. A deeper understanding of the molecular characteristics of IMTs may enhance diagnostic accuracy and inform the development of improved treatment options.

**Keywords:** Inflammatory myofibroblastic tumors, Clinicopathological features, Anaplastic lymphoma kinase, Prognosis

## Introduction

Inflammatory myofibroblastic tumors (IMTs) are mesenchymal neoplasms with heterogeneous clinical presentations, ranging from benign solitary lesions to aggressive neoplasms with metastatic potential [1]. IMT primarily affects children and adolescents, with an average age of approximately 10 years; adult IMT is rare and has been infrequently reported in the literature [2]. IMTs can occur in both soft tissues and visceral organs. The diagnosis of IMTs relies on histopathology, immunohistochemistry (IHC), and gene fusion analysis. Histologically, IMTs consist of proliferating spindled fibroblastic or myofibroblastic

cells in a myxoid background and are categorized into three patterns: hypocellular/myxoid, fascicular, and hyalinized. Most clinicians use ALK IHC as a diagnostic tool because other markers such as desmin, SMA, and h-caldesmon have proven insufficiently reliable [3]. In cases where IMT is strongly suspected but ALK IHC is negative, further testing with fluorescence in situ hybridization (FISH), next-generation sequencing (NGS), or RT-PCR is recommended [3]. Regarding genetic fusions, ALK, ROS1, RET, and NTRK3 have been reported, with ALK being the most commonly involved [4].

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## 2. Methodology

Given that IMT has not been widely recognized in clinical practice, we analyzed its clinical, pathological, immunohistochemical, and molecular features along with treatment outcomes. This study compared ALK-positive and ALK-negative cases to assess clinical features and prognosis, aiming to enhance understanding of IMTs and improve diagnostic and therapeutic approaches.

We conducted a retrospective study of adult patients diagnosed with IMTs at Peking Union Medical College Hospital (PUMCH) from 2010 to 2023. Ethics approval was obtained from the Ethics Committee of Peking Union Medical College Hospital (No. I-22PJ674), and informed consent was exempted for this retrospective analysis. Data from 74 patients, including all relevant clinical, laboratory, and treatment information, were extracted from medical records and reviewed. IHC slides were re-examined for ALK expression using formalin-fixed paraffin-embedded sections by one of the authors (Xiaohua Shi). ALK immunohistochemistry was performed using anti-ALK antibody (D5F3, Cell Signaling, 1:50) with epitope retrieval by CC1 solution at pH 8.6 and 95°C for 64 minutes, followed by primary antibody incubation at 37°C for 40 minutes. Neoplasms showing any positive cytoplasmic and/or membranous staining in tumor cells were considered ALK-positive.

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## 3.1 Clinical Characteristics

Clinical features of the 74 IMT cases are summarized in Table 1 . The cohort comprised 34 females and 40 males with a mean age of 50.14 years. Most patients were asymptomatic, with only 11 patients (14.8%) presenting with weight loss. Systemic symptoms including fever, anemia, and weight loss were observed in 36 patients (40.7%) with large tumors, which also induced organ-specific symptoms: abdominal pain from abdominal tumors, headache and hearing loss from head and neck tumors, and cough and hemoptysis from lung tumors. Among the 74 cases, the most common locations were head and neck (n=18, 24.3%), followed by lung (n=16, 21.6%), limbs and trunk (n=11, 14.9%), and abdominal organs (n=10, 13.5%). Imaging studies revealed that IMTs were typically solid

tumors with smooth surfaces and no adhesion to surrounding tissues. Dynamic CT scans showed heterogeneous enhancement in early phases, while MRI scans exhibited hypointense signals on T1-weighted images and variable signals on T2-weighted images. Eleven patients underwent PET-CT examination, with SUVmax values ranging from 4.0 to 21.9.

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## 3.2 Pathological Features

Immunohistochemistry (IHC) was performed in 58 patients, and 31.0% of cases (n=18) showed positive ALK results (Table 3 ). The presence of fusion mutations was confirmed in two cases by next-generation sequencing (NGS), with 100% concordance between IHC and NGS results. Figure 2 [Figure 2: see original paper] compares the incidence of ALK-IHC positivity across different primary sites. Excluding less common sites, ALK positivity was highest in lung IMTs (6/15, 45.5%), followed by abdominal organs (2/9, 22.2%) and limbs and trunk (2/14, 14.3%). There was no significant difference in the occurrence of systemic symptoms between ALK-positive and ALK-negative groups (p=0.23).

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## 3.3 Treatment Strategy

All patients underwent biopsy or radical surgery (86.4% R0 resection, 9.5% R1/R2 resection, and 4.1% biopsy only), and most patients (82.4%) received no further postoperative treatment. Radiotherapy was administered to 10 patients following incomplete tumor resection due to unresectability, proximity to critical structures, or multiple lymph node metastases. Five patients received chemotherapy because of highly invasive tumors or progressive disease. Two patients have been maintained on glucocorticoid therapy to date. Of the 18 patients with unresectable disease, 3 were ALK-positive, with 2 receiving ALK inhibitors. One patient with highly heterogeneous tumor components remained stable after 6 years of treatment with lorlatinib and pembrolizumab. Another patient received crizotinib for 3 months but discontinued due to side effects and subsequently died from pericardial effusion caused by tumor progression.

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## 3.4 Prognosis

As of July 2024, the median follow-up time for all 74 patients was 59.9 months (95% CI, 49.0 to 70.8), with 46 patients alive, 6 deaths documented, and 22 patients lost to follow-up. Three patients experienced local recurrence 2 to 6 years after R0 surgery. Nine patients had disease progression within 1 year, with 3 dying from complications including pulmonary infection, hydropericardium, and epistaxis. Among these 12 patients with relatively poor prognosis, 5 were ALK-positive. The 1-year, 3-year, 5-year, and 10-year OS rates for all 74 patients were

78.4%, 70.9%, 69.2%, and 69.2%, respectively. Kaplan-Meier survival curves for IMT patients with and without ALK mutation are shown in Figure 3 [Figure 3: see original paper], with the log-rank test showing no significant difference. Patients who underwent R0 surgery had better prognosis compared with those who underwent R1/R2 surgery or biopsy only (Figure 4 [Figure 4: see original paper], $p = 0.0077$). Female gender ($p = 0.05$) and R1/R2 resection or biopsy only ($p = 0.03$) were correlated with poor prognosis, while age, primary tumor location, and ALK status were not statistically correlated with OS in univariate analyses.

## 4. Discussion

IMTs are myofibroblastic tumors of intermediate malignant potential occurring in both children and adults. To our knowledge, this study represents the largest analysis of adult IMTs to date. Systemic symptoms such as fever, anemia, and weight loss were present in 14.8% of our 74 patients, which is lower than previously reported [5]. IMTs can be discovered in both soft tissue sites and visceral organs. Our study reveals that head and neck, lung, abdominal organs, and limbs and trunk are common sites for IMTs in adults, with local symptoms being more frequent than systemic symptoms.

Consistent with our results, most CT imaging of IMTs shows lesions as soft tissue masses with clear boundaries, uniform or non-uniform density, occasional necrosis, and sometimes a thin capsule [6]. In several case reports, MRI scans have shown low specificity due to variations in the composition of mucus, inflammatory cells, and fibrous tissue, which affect signal intensity and enhancement patterns [7]. Several studies have reported cases of IMTs exhibiting increased 18F-FDG uptake, as these are metabolically active tumor masses with SUVmax ranging from 3.8 to 20.8, aligning with our data [8]. Preoperative differentiation of IMTs from other tumors is challenging due to non-specific histopathological features, necessitating confirmatory diagnostic testing. Histologically, IMTs comprise a proliferation of predominantly spindled fibroblastic/myofibroblastic cells in a myxoid background, typically associated with inflammatory infiltrates and low mitotic index. However, the presence of stromal edema and lymphocytic infiltrate is non-specific [3]. The unequivocal myxoid appearance of the tumor leads pathologists to consider a broader differential diagnosis including entities such as endometrial stromal sarcoma [3].

ALK is a transmembrane tyrosine kinase [9] expressed in the nervous system that plays a role in neuronal differentiation during embryogenesis. Additionally, ALK contributes to the oncogenesis of various tumors including leiomyosarcoma, alveolar rhabdomyosarcoma, and Ewing sarcoma [10, 11], making it a target for innovative therapeutic approaches [12]. ALK expression is highly specific for IMTs, and ALK-positive IMTs are reported to have high rates of rapid progression and recurrence, associated with a high grade of malignancy [13]. ALK

IHC staining is used to aid in the diagnosis of IMTs, with reported positivity in nearly 50% of cases [14]. However, only 31.0% of cases showed positive ALK IHC staining in our data, which may be due to bias from missing ALK staining data in early years. Fluorescence in situ hybridization (FISH), next-generation sequencing (NGS), and RT-PCR are used when ALK-IHC shows negative results. Our study revealed concordant results using these methods, aligning with previous studies [3].

ALK expression reportedly varies in sensitivity depending on tumor site [15]. Our study is the first to compare ALK-IHC positivity across different organs, revealing higher rates in lung and head/neck IMTs. This suggests a higher propensity for progression and recurrence in these sites and may warrant more frequent follow-up. Further data are needed for organs such as the kidney and thymus. Additionally, there were no statistical differences in age, systemic symptoms, or tumor-related symptoms between ALK-positive and ALK-negative patients.

It is widely acknowledged that IMT is an intermediate-grade, locally recurrent, and rarely metastasizing tumor, with a 5-year OS rate of approximately 77% [16]. A retrospective study of 59 patients found that ALK-negative IMTs were associated with death due to local disease [17], which aligns with our data showing that patients with ALK-negative tumors had worse OS. Complete resection remains the first-line treatment option. The efficacy of second-line options including nonsteroidal anti-inflammatory drugs (NSAIDs), high-dose corticosteroids, macrolide drugs, anti-inflammatory agents such as infliximab, chemotherapy, and radiotherapy—all of which may be associated with significant toxicity—remains to be determined [18, 19]. Our study showed that most patients (n=62, 83.8%) achieved full recovery from surgical treatment, and only 5 patients relapsed after R0 surgery.

Chaves et al. analyzed reports of ALK-negative cases receiving NSAIDs therapy and reported the striking result that NSAIDs were effective in treating 10 of 11 IMT cases [20]. A case report described an ALK-negative, IgG4-negative 73-year-old female with IMT who responded to macrolide drugs including clarithromycin [21]. For patients with incomplete resection or unresectable disease who show a high recurrence rate, effective systemic therapy is needed. Given that ALK gene rearrangements may drive IMT pathogenesis, especially in ALK-IHC positive patients, targeted treatment options have begun to be evaluated. The use of ALK inhibitors in IMTs has been restricted to case reports, so we summarized clinical features, responses, and side effects of related cases in Table 4 . Sixteen of the 17 cases showed ALK positivity by IHC, and most were confirmed to have ALK gene rearrangements. RANBP2 fusion proteins were more common (n=5) than EML4, DCTN1, NUMA1, CLTC, and TPM3 in these reports. The objective response rate was 70.6% (n=12), with one case showing stable disease and 4 cases showing progressive disease. The median duration of ALK inhibitor therapy was 14 months. Currently, crizotinib is the first-choice ALK inhibitor. A multicenter, non-randomized phase 2 trial recruited 20 patients diagnosed with IMTs and treated them with crizotinib 250 mg twice daily. Six of twelve

ALK-positive patients and one of seven ALK-negative patients achieved objective response, providing evidence for crizotinib efficacy in patients with IMTs [22]. When IMTs progress, ceritinib and alectinib are considered second-line options [23]. Side effects of ALK inhibitors focus on gastrointestinal reactions such as diarrhea and nausea, which are tolerated in most patients.

Our data support the high efficacy of ALK inhibitors in treating ALK-positive IMTs, with optimal efficacy observed in 2 patients who achieved partial response. However, with treatment progression, therapy-sensitive tumor cells are eliminated while therapy-insensitive cells dominate, altering tumor heterogeneity and leading to eventual tumor progression. Perhaps detecting tumor progression during targeted therapy could prompt re-examination with NGS to identify new mutations and help adjust treatment regimens to achieve precision therapy.

As Table 4 shows, the effectiveness and safety of ALK inhibitors have been preliminarily verified. Abdominal organ involvement rather than lung involvement at presentation may be associated with a more favorable response to ALK inhibitor therapy. There is also a high risk of publication bias, which increases the apparent efficacy of crizotinib, as exceptional responders are more likely to be published as case reports than non-responders. Disease progression on prior ALK inhibitor therapy is associated with poor response to subsequent ALK inhibition: both cases in Table 3 showed rapid disease progression [24, 25]. With further understanding of IMTs, clinicians may reveal a detailed classification from benign tumors to aggressive neoplasms and identify more effective treatments. Although the small number of cases is insufficient to establish treatment guidelines, the diversity in treatment response and highly variable behavior of these tumors underscores the need for close long-term follow-up.

The study has several limitations. First, this is a single-center retrospective study, and the patient characteristics may not be representative of all adult IMT patients. However, given the rarity of IMT in adults, prospective clinical trials have been virtually impossible. Second, the sample size of drug-treated patients is relatively small and heterogeneous, making further systematic analysis difficult. Third, the mechanisms of resistance to ALK inhibitors have not been determined.

## 5. Conclusion

Based on 74 cases at PUMCH, the incidence of IMTs is higher in the head and neck, abdominal organs, and lung compared to other sites. ALK IHC staining was positive in 31.0% of 58 cases, which is lower than the reported rate of 50%. IMTs in the lung and head and neck had higher ALK-IHC positivity rates, which may indicate easier progression and recurrence in these organs. We recommend that all patients undergo both IHC and gene rearrangement testing during diagnosis. When complete resection is not achieved or tumor progression occurs, ALK inhibitors such as crizotinib should be considered for

ALK-positive patients. Crizotinib has shown high objective response rates and durable responses in advanced adult patients with IMT. Next-generation ALK inhibitors may be a therapeutic option for crizotinib-resistant, ALK-positive IMT patients. With further understanding of IMTs, clinicians may reveal a detailed classification from benign tumors to aggressive neoplasms and identify more effective treatments.

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## 7. Conflict of Interest

We declare that we have no financial or personal relationships with other people or organizations that could inappropriately influence our work, and there are no professional interests of any nature or kind in any product, service, and/or company that could be construed as influencing the position presented in, or review of, the manuscript entitled.

*Note: Figure translations are in progress. See original paper for figures.*