ORIGINAL ARTICLE

PLEURAL SOLITARY TUMORS – LONG-TERM PROGNOSIS RELATED TO SURGERY AND CLINICOPATHOLOGICAL CRITERIA

Vânia Almeida[1, 2]*, Luis Veloso[3], Sara Cunha[4], Lina Carvalho[1, 2]

[1] Serviço de Anatomia Patológica do Centro Hospitalar e Universitário de Coimbra, Portugal
[2] Instituto de Anatomia Patológica e Patologia Molecular da Universidade de Coimbra, Portugal
[3] Instituto Politécnico de Coimbra, Escola Superior de Tecnologia e Gestão de Oliveira do Hospital, Portugal
[4] Serviço de Cirurgia Cardiotorácica do Centro Hospitalar e Universitário de Coimbra, Portugal

* **Corresponding author**: vaniafi@hotmail.com

Abstract

***Introduction**: Pleural solitary fibrous tumors (SFTs) are indolent mesenchymal neoplasias, generally with good prognosis, for which complete surgical resection is the gold standard. However, local recurrences and distant metastases are reported at variable rates. Risk-assessing criteria and models determining recurrence and metastatic risk have been proposed, and can impact on patient follow-up strategies.*

***Methods:** We conducted an observational study comprising a 12 years period to characterize a cohort of 20 surgically resected thoracic SFTs, and to retrospectively assess the prognostic value of England's histology criteria and Demicco's 4-tier model.*

***Results:** All tumors were pleural-based, 12 patients were women, and the mean age at diagnosis was 62.8 years. The median duration of follow-up was ten years, and at the end of the follow-up, all patients were alive, and no distant metastases were reported. Three cases (15%) had local recurrence at the median time of 89.3 months/7.4 years. The only case with an incomplete surgical resection relapsed. Collectively, tumors with worst prognostic features, specifically a positive margin or tumors with malignant histology or non-low-risk features, according to England's and Demicco's models, respectively, were associated with recurrence.*

***Conclusion:** These results confirm the importance of complete surgical resection of SFTs, and show that risk stratification criteria and models can predict important surgical outcomes such as recurrence. Moreover, they support a risk-based follow-up schedule, as patients with higher relapse risk can benefit from close follow-up.*

***Keywords**: Solitary Fibrous Tumor, Pleura, Pathology, Thoracic Surgery, Portugal, Survival Analysis*

INTRODUCTION

Solitary fibrous tumors (SFTs) are rare mesenchymal neoplasms that harbor the disease-defining NAB2::STAT6 gene arrangement. These mesenchymal neoplasms occur approximately equally in each sex, and are mainly diagnosed in individuals in the fifth and sixth decades of life. SFTs have been reported at almost every anatomic site, but most commonly occur in the thorax, predominantly arising from the visceral pleura, accounting for less than 5% of pleural neoplasms.

SFTs are generally slow-growing tumors, often discovered as an incidental finding, with a benign course. However, relapses and distant metastases are reported at variable rates, and can be as high as 45% in series with longer follow-up times.[1] Although complete surgical resection of the lesion is considered the best treatment strategy and the best predictor of survival, determining which tumors will behave aggressively is essential for patient surveillance. [2–4] This prognostic stratification has been a challenging task for both pathologists and clinicians, as no single factor taken in isolation provides strong predictive

value for the risk of recurrence, metastasis, or death. [5] For years, the characteristics described by England et al. – hypercellularity, nuclear atypia, mitoses, hemorrhage and necrosis – have been applied to identify tumors with malignant histology and, consequently, worst prognosis. [6] Other models have been proposed since [4,7–9], and, in the latest WHO classification of thoracic tumors (2020), the 3- and 4-variable risk stratification models by Demicco et al. [1,10] are recommended to determine metastatic risk in SFT, replacing the "typical" or "malignant" classic terms. These tools incorporate patient age, tumor size and mitotic activity (3-tier model) to which tumor necrosis was added to build the 4-tier model.

In this work, we conducted a retrospective study to characterize a cohort of thoracic surgically resected SFTs at Centro Hospitalar e Universitário de Coimbra (CHUC), and to assess the prognostic value of clinicopathological-based prognostic tools after an extended follow-up.

METHODS

Study design, patients, and collected data

This study was an observational and retrospective study of the investigator's initiative.

We collected data from all patients with SFT that underwent surgical treatment at Centro Hospitalar e Universitário de Coimbra (CHUC) from 2005 to 2016 (12 years). Patients with a first surgical intervention not included in the above period or whose surgery was not performed in our hospital, were excluded from the study.

Medical records were analyzed for age at surgery, sex, symptoms leading to diagnosis, tumor size (the largest gross tumor measurement on the resected specimen), operative approach, type of surgery, and tumor location.

Histopathological evaluation

A pathologist retrospectively examined the histopathological descriptions within the reports. If further clarification, particularly regarding details like mitosis, necrosis or immunohistochemistry results was deemed necessary, the pathologist reviewed the slides in the archives.

According to England's criteria [6], cases were classified as malignant when one or more of the following histological criteria was met: (1) mitotic count of more than four mitoses per 10 high-power fields (HPF), (2) presence of necrosis, (3) presence of nuclear atypia, (4) hypercellularity, or (5) presence of hemorrhage.

The 4-tier model was scored accordingly to Demicco et al. 10: (1) Patient age was scored as 0 if $<$ 55 years and 1 if $\geq$ 55 years, (2) mitotic activity was scored as 0 in the absence of mitotic figures/10 HPF, 1 if 1 – 3 mitotic figures/10 HPF, or 2 if $\geq$ 4 mitotic figures/10 HPF, (3) tumor size was scored as 0 when $<$ 5 cm, 1 if between 5 to $<$ 10 cm, 2 if between 10 to $<$ 15 cm, or 3 if $\geq$ 15 cm), (4) tumor necrosis was scored as 0 if $<$ 10% and 1 if $>$ 10%. Total scores were summed, and scores of 0 – 2 were considered low risk, 3 – 4 as intermediate risk, and 5 – 6 as high risk.

Follow-up and outcomes of interest

Follow-up was obtained from a retrospective review of the patient's medical records. Recurrence was defined as tumor reappearance in or adjacent to the tumor site of prior excision, and metastasis as distant tumoral dissemination. Overall survival, distant metastasis-free and recurrence-free survival were the outcomes of interest.

Statistical analysis

Statistical analysis was done using SPSS 28.0.1.1 (IBM, Chicago, USA).

The normal distribution of quantitative variables was evaluated through the Shapiro–Wilk test. Quantitative variables were described with minimum, maximum, and mean or median, while categorical variables were described as absolute numbers and/or percentages.

Mann-Whitney U test was used for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. All survival analyses were performed using the Kaplan-Meier method, with survival across groups compared using the log-rank test. P-values $<$ 0.05 were considered statistically significant.

RESULTS

Cohort description

We identified 20 SFTs, all pleura-based, in 12 women and eight men (ratio 1.5:1). Age at diagnosis ranged from 33 to 79, with a mean age of 62.8 years. Most patients (11/20, 55.0%) were asymptomatic, diagnosed as incidental findings in image studies. Six (30.0%) presented with tiredness/shortness of breath; for three (15.0%), thoracic pain was the main complaint.

The tumor's size varied from 2.2 to 18.5 cm, with a mean size of 8.4 cm. There are no statistical differences between the tumor's size and the reported symptoms ($U=57$, $p=0.52$).

Two patients had been subjected to a preoperative biopsy harboring a histopathological diagnosis of SFT. All patients were submitted to surgery with curative intent, and none were subject to chemotherapy or radiotherapy. Thoracotomy was the preferred approach, used in 17 cases (85%), uniportal video-assisted thoracic surgery (VATS) in two cases (10%), and sternotomy in one case (5%).

The surgical approach encompassed simple tumor excision in 14 cases (70%), with four necessitating atypical lung resection and two undergoing lobectomies. Notably, complete (R0) resection was successfully accomplished in 19 patients (95.0%). However, one case presented viable tumor cells on the margin during histopathological evaluation (R1). In this specific instance, the patient was a 33-year-old woman with a substantial tumor measuring 9.2 cm. Following the R1 result, the patient returned to her residency hospital for follow-up, and no immediate adjuvant therapy was administered. Remarkably, the patient sought our hospital again seven years later for a second intervention targeting the resection of tumoral implants.

All tumors had characteristic histopathological features of SFTs (Figure 1); by immunohistochemistry, all were diffusely positive for cytoplasmatic CD34, while CD99 and bcl2 were

Table 1 DeFilippi postoperative classification

Class	Description
1	Complete remission, no medications
2	Symptomatic, decreased medications
3	Improved, decreased symptoms or decreased medications
4	No change
5	**Worsening symptoms**

Table 2 Patients caracteristics - group A

	n = 12 (%)
Gender	
Women	10 (83%)
Men	2 (17%)
Mean age of surgery	48.9 years old (range 32-69)
Sympthoms prior to surgery	
Ocular (diplopy + ptosis)	12 (100%)
Generalises myasthenia	11 (91.7%)
Mean duration of the disease prior to surgery	33 months (range 1 week to 20 years)
Pathologic results	
thymoma	5 (42%)
hyperplasia	4 (33%)
normal thymic tissue	3 (25%)
The mean length of hospital stay	3.8 days (range 3-6 days)
The mean follow-up	27 months

additionally performed, respectively, in four and three tumors, all diffusely positive.

Prognostic models retrospectively applied showed that 15 tumors (75%) were benign according to England's criteria, and had a low risk of metastatic disease according to Demicco's 4-tier model. The other five cases (25%) had malignant histology by England's criteria, four of which scored as intermediate-risk tumors and one as high-risk tumors by Demicco's score (Table 1).

Clinical behavior

The median follow-up time was ten years, ranging from five to 17 years. All patients were alive at the last follow-up, and no distant metastases were reported.

Three cases (15%) had local recurrence, namely the one with incomplete surgical resection and two with malignant histology and intermediate or high risk by Demicco's score. The median recurrence time was 89.3 months/7.4 years (Table 2).

The only patient with an incomplete surgical resection had later developed pleural tumoral implants. Collectively, tumors with worse prognostic features, specifically a positive margin or tumors with malignant histology or non-low-risk features according to England's and Demicco's models, respectively, are associated with recurrence (Fisher's Exact Test two-tailed, p=0.02) (Figure 2).

Table 3 Results - group A

	n = 12 (%)
Complete remission with no medication	1 (8.3%)
Asymptomatic with decreased medication	2 (16.7%)
An improvement (decreased symptoms or decreased medications)	8 (66.6%)
No clinical improvement with prednisolone doses reduction	1 (8.3%),
No change in clinical outcome	1 (8.3%)
Slightly better symptoms but with a significant increase in medication doses	
Worsening symptoms	0 (0%)
Positive results on 1st post-op year	11 (91.7%)

DISCUSSION

In our series, patients' age at diagnosis and gender distribution align with other more extensive publications. Being indolent neoplasms, symptoms often emerge when SFTs exert pressure on organs and structures. In our cohort, symptoms do not depend on the tumor size. This unexpected result can be a consequence of the subjectivity of symptoms description, but perhaps is mainly related with one of the caveats of the study, which is inherent to its retrospective nature and its dependence on written registries, which may be incomplete.

In our work, all SFTs diagnosis were based on the histopathological slides and available supportive immunohistochemistry, namely CD34 and, in some cases, CD99 and bcl2. These immunomarkers are sensitive and usually show diffuse and strong expression in approximately 90% of cases, but have lower specificity [11]. STAT6 immunohistochemistry stain is an excellent surrogate marker of NAB2::STAT6 gene fusion, with excellent sensitivity and specificity, but was not available at our laboratory at the time of the diagnosis.

SFTs generally follow a favourable course; in our cohort, all patients were alive at the last follow-up, and no distant metastases were reported. In other published work, the rate of metastatic disease is highly variable, ranging from none to up to 30% [1,12–14] , which probably reflects different follow-up times and heterogeneity of primary locations of the series.

We identified three (15%) cases that recurred after surgical treatment, which is in line with major series in the

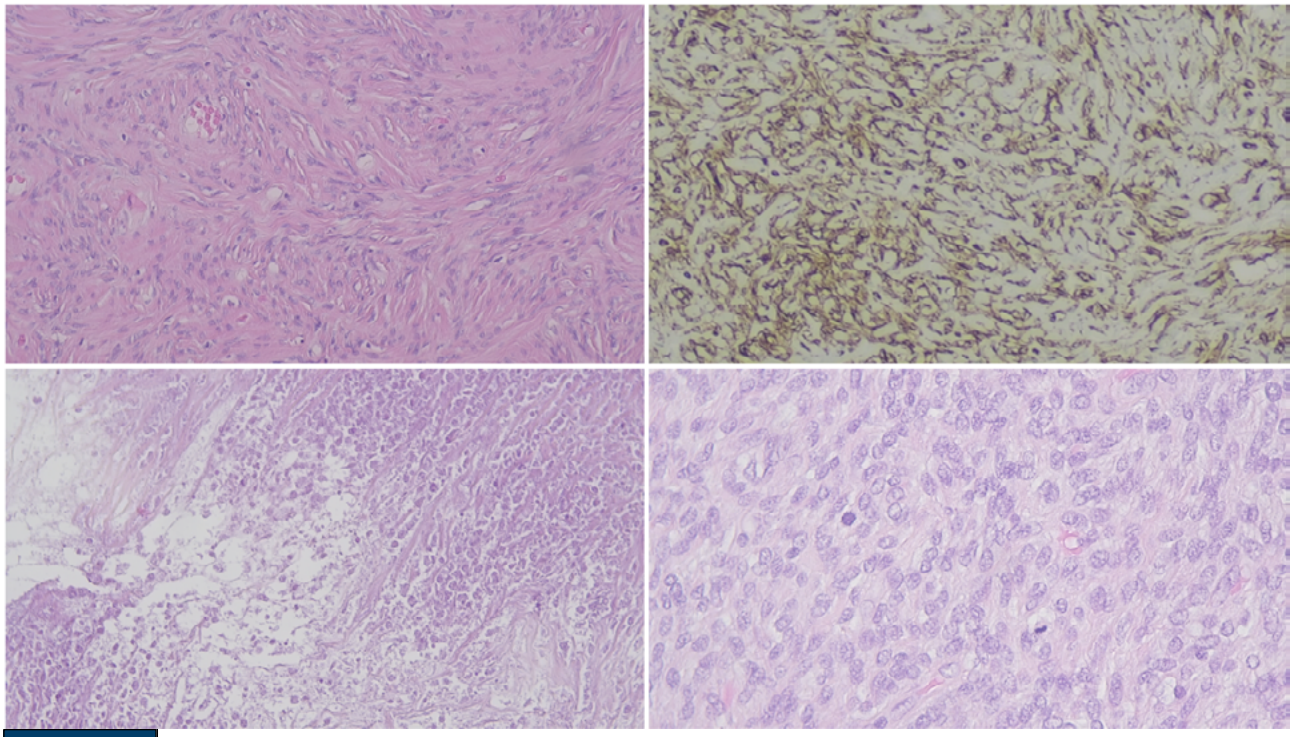

Figure 1 *Histological features of SFTs Most SFTs had fusiform spindle cell morphology with indistinct cell borders in a patternless pattern against collagenous background stroma and medium vessels (a, HE 100 x). All tumors were diffusively positive for CD34 (b, 200 x). Tumors with England's malignant histology or Demicco's non-low risk exhibit tumoral necrosis (c, HE 100 x), increased cellularity, and high mitotic count (d, HE 400 x)*

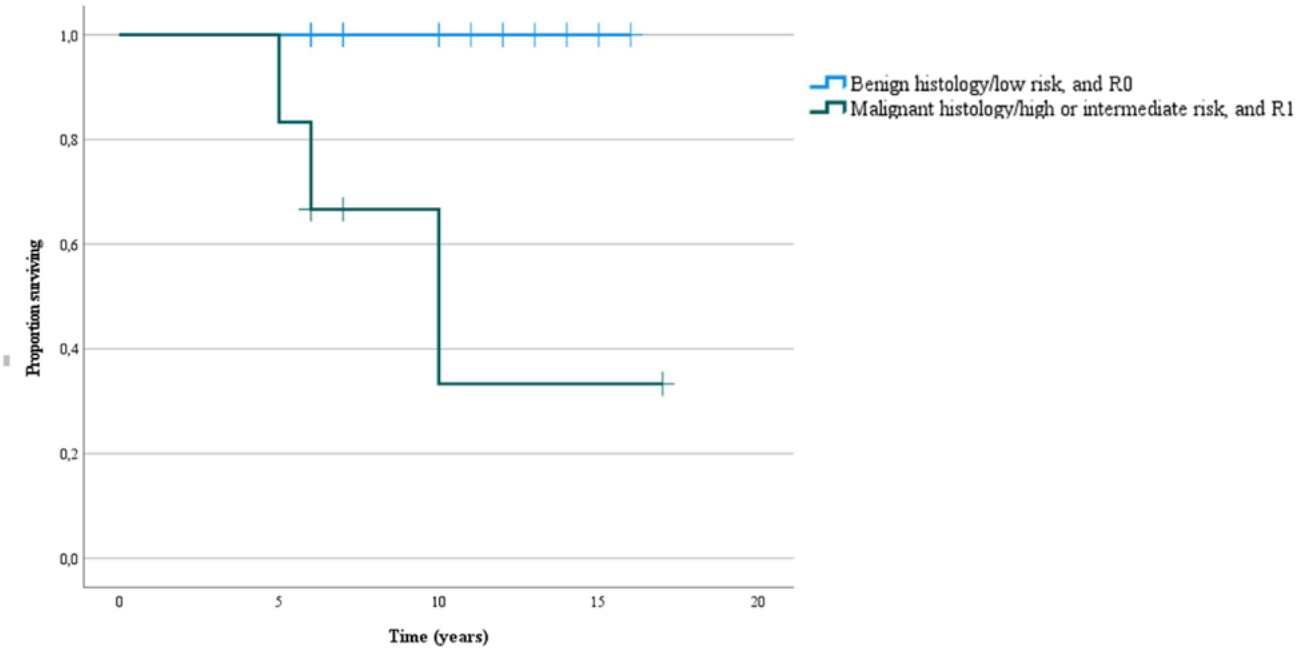

Figure 2 *Kaplan–Meier plot for time to recurrence by risk groups, p=0.02*

Table 1 **Parameters of the prognostic-risk models of the cases with malignant histology and non-low risk cases on Demicco´s score.**

	England's criteria						4-tier risk Demicco´s model *				
	4 mitoses per 10 high-power fields	Increased cellularity	Nuclear pleomorphism	Tumor necrosis	Hemorrhage	Classification	Patient age (years)	Tumor size (cm)	Mitotic count mitotic figure/10 HPF	Tumor necrosis (%)	Classification
Case 1	no	yes	no	yes	yes	**Malignant**	46 (0)	11.0 (2)	1 (1)	25% (1)	**Intermediate (4)**
Case 2	no	yes	yes	no	no	**Malignant**	65 (1)	18.5 (3)	<1 (0)	0 (0)	**Intermediate (4)**
Case 3	yes	yes	yes	yes	yes	**Malignant**	66 (1)	15.5 (3)	5 (2)	30% (1)	**High**
Case 4	no	no	no	yes	no	**Malignant**	69 (1)	13.5 (2)	<1 (0)	20% (1)	**Intermediate (4)**
Case 5	no	yes	no	yes	no	**Malignant**	77 (1)	14.0 (2)	2 (1)	25% (1)	**Intermediate (5)**

* Scores attributed to the 4-tier Demicco´s score are between parenthesis.

Table 2 **Characteristics of the cases with local recurrence**

	Complete resection	England's malignant histology	Demicco´s 4-tier risk model	Time to recurrence (months/years)
Case A	no	no	low	79/6.6
Case B	yes	yes	intermediate	66/5.5
Case C	yes	yes	high	123/10.25

literature. [15] In our work, the only case with an incomplete (R1) resection had a relapse, despite low risk on the models evaluated, highlighting the importance of complete surgical resection with negative margins. From the completely excised, all with malignant histology by England's criteria/ non-low risk features risk by Demicco's model were associated with relapse, which emphasizes the value of the models in predicting recurrence.

In our work both malignant histology by England's criteria and a non-low risk on Demicco's model identified the same cases. As both risk stratification models incorporate overlapping features, namely the mitotic index and tumor necrosis, we expected some agreement between the identified cases. It is important to state that Demicco's model is designed to predict metastatic disease, and is not intended to foresee local recurrence; however, in our series, non-low-risk cases were associated with local recurrence. We hypothesize that Demicco's model can stratify tumors and identify aggressive biological behavior that can either manifest as local recurrences or distant metastases.

In our series, one tumor demonstrated recurrence more than a decade after resection, whereas literature reports indicate pleural SFT recurrence at 17 years post-resection, with the longest documented time to recurrence being 23 years. [16,17] Our study, encompassing a median follow-up of 10 years, suggests that an extended surveillance period may uncover recurrences in tumors with persistent risk or identify distant metastases.

Identifying tumors prone to recurrence is crucial for implementing a rigorous follow-up schedule, facilitating early detection of relapse for prompt re-resection of local recurrence. Such interventions could achieve effective local control with minimal morbidity, particularly in fit patients.[18] Additionally, for patients at high risk of recurrence, considering adjuvant radiotherapy (RT) may be pertinent. While some series suggest favorable long-term outcomes with adjuvant RT, as reviewed by Bertoglio and colleagues[19], it's crucial to recognize that the current evidence doesn't conclusively establish a definitive benefit from adjuvant RT. Larger cohorts and further investigations are imperative to provide more comprehensive insights into the potential advantages of adjuvant RT in the context of SFTs.

CONCLUSION

Pleural SFTs are rare tumors whose biological behavior is still not completely understood. These tumors can recur and metastasize many years after surgical resection, requiring a long-term follow-up.

In our cohort, the tumors with either incomplete surgical resection or malignant histology according to England's criteria and a non-low risk in Demicco's 4-tier model were associated with local tumor recurrence. These findings underscore the significance of achieving complete excision in SFT cases. The risk stratification criteria and models not only aid in predicting critical surgical outcomes like recurrence but also advocate for a risk-based follow-up approach. This approach is particularly valuable for patients at a higher risk of relapse, enabling a more intensive follow-up to facilitate early detection and subsequent intervention, either through re-resection or consideration of adjuvant RT.

Conflict of Interest

The authors have no conflicts of interest to declare.

Acknowledgments

VA reviewed the histology, created the database, performed the statistical analysis, drafted the manuscript, and photographed the slides. LV extensively revised the statistical analysis and the manuscript. SC reviewed and harbored information from the clinical processes. LC was responsible for the diagnoses and reviewed the manuscript.

All authors participated in the design of the study. All authors read and approved the final manuscript.

Funding

No financial support was provided for this study.

REFERENCES

1. Demicco EG, Park MS, Araujo DM, Fox PS, Bassett RL, Pollock RE, et al. Solitary fibrous tumor: a clinicopathological study of 110 cases and proposed risk assessment model. Mod Pathol. 2012 Sep;25(9):1298–306.
2. Yanik F, Karamustafaoglu YA, Yoruk Y. Surgical outcomes and clinical courses of solitary fibrous tumors of pleura. Niger J Clin Pract. 2019 Oct;22(10):1412–6.
3. Sung SH, Chang JW, Kim J, Lee KS, Han J, Park SI. Solitary fibrous tumors of the pleura: surgical outcome and clinical course. Ann Thorac Surg. 2005 Jan;79(1):303–7.
4. Lococo F, Cusumano G, Margaritora S, Cardillo G, Filosso P, Cesario A. Tapias score for predicting recurrences in resected solitary fibrous tumor of the pleura: controversial points and future perspectives emerging from an external validation. Chest. 2015 Mar;147(3):e115–6.
5. Kazazian K, Demicco EG, de Perrot M, Strauss D, Swallow CJ. Toward Better Understanding and Management of Solitary Fibrous Tumor. Surg Oncol Clin N Am. 2022 Jul;31(3):459–83.
6. England DM, Hochholzer L, McCarthy MJ. Localized benign and malignant fibrous tumors of the pleura. A clinicopathologic review of 223 cases. Am J Surg Pathol. 1989 Aug;13(8):640–58.
7. de Perrot M, Fischer S, Bründler MA, Sekine Y, Keshavjee S. Solitary fibrous tumors of the pleura. Ann Thorac Surg. 2002 Jul;74(1):285–93.
8. Franzen D, Diebold M, Soltermann A, Schneiter D, Kestenholz P, Stahel R, et al. Determinants of outcome of solitary fibrous tumors of the pleura: an observational cohort study. BMC Pulm Med. 2014 Aug 12;14:138.
9. Gold JS, Antonescu CR, Hajdu C, Ferrone CR, Hussain M, Lewis JJ, et al. Clinicopathologic correlates of solitary fibrous tumors. Cancer. 2002 Feb 15;94(4):1057–68.
10. Demicco EG, Wagner MJ, Maki RG, Gupta V, Iofin I, Lazar AJ, et al. Risk assessment in solitary fibrous tumors: validation and refinement of a risk stratification model. Mod Pathol. 2017 Oct;30(10):1433–42.
11. Tariq MU, Din NU, Abdul-Ghafar J, Park YK. The many faces of solitary fibrous tumor; diversity of histological features, differential diagnosis and role of molecular studies and surrogate markers in avoiding misdiagnosis and predicting the behavior. Diagn Pathol. 2021 Apr 20;16:32.
12. Chu X, Zhang L, Xue Z, Ren Z, Sun Y e, Wang M, et al. Solitary fibrous tumor of the pleura: An analysis of forty patients. J Thorac Dis. 2012 Apr 1;4(2):146–54.
13. Tan F, Wang Y, Gao S, Xue Q, Mu J, Mao Y, et al. Solitary fibrous tumors of the pleura: A single center experience at National Cancer Center, China. Thorac Cancer. 2018 Dec;9(12):1763–9.
14. Salas S, Resseguier N, Blay JY, Cesne AL, Italiano A, Chevreau C, et al. Prediction of local and metastatic recurrence in solitary fibrous tumor: construction of a risk calculator in a multicenter cohort from the French Sarcoma Group (FSG) database. Annals of Oncology. 2017 Aug 1;28(8):1779–87.
15. Mercer RM, Wigston C, Banka R, Cardillo G, Benamore R, Nicholson AG, et al. Management of solitary fibrous tumours of the pleura: a systematic review and meta-analysis. ERJ Open Research [Internet]. 2020 Jul 1 [cited 2023 Jan 7];6(3). Available from: https://openres.ersjournals.com/content/6/3/00055-2020
16. Kovacs T, Waxman J. Recurrence of a malignant solitary fibrous tumor of the pleura 17 years after primary tumor resection – A case report. Respir Med Case Rep. 2019 Jul 2;28:100895.
17. Baldi GG, Stacchiotti S, Mauro V, Dei Tos AP, Gronchi A, Pastorino U, et al. Solitary fibrous tumor of all sites: outcome of late recurrences in 14 patients. Clinical Sarcoma Research. 2013 Apr 3;3(1):4.
18. Lahon B, Mercier O, Fadel E, Ghigna MR, Petkova B, Mussot S, et al. Solitary fibrous tumor of the pleura: outcomes of 157 complete resections in a single center. Ann Thorac Surg. 2012 Aug;94(2):394–400.
19. Bertoglio P, Querzoli G, Kestenholz P, Scarci M, La Porta M, Solli P, et al. Surgery for Solitary Fibrous Tumors of the Pleura: A Review of the Available Evidence. Cancers (Basel). 2023 Aug 18;15(16):4166.