Thoracic malignant solitary fibrous tumors: A population-based study of survival

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ABSTRACT

Introduction: This study characterizes the overall survival (OS) and cause specific survival (CSS) of patients with thoracic malignant solitary fibrous tumors.

Methods: Eighty-two patients with malignant solitary fibrous tumors of the lung, pleura or mediastinum, diagnosed from 2001-2007, were retrospectively analyzed using the population-based Surveillance, Epidemiology, and End Results database.

Results: Among 77 patients with available staging information, 42% (n=32) had localized disease, 31% (n=24) had regional disease extension (without nodal involvement) and 27% had regional-nodal (n=2) or distant (n=19) metastases. Cancer-directed surgery was performed in 85%; radiation was performed in 16%. The 1-year, 5-year and median OS were 87%, 49% and 4.6 years respectively. The 1-year, 5-year and median CSS were 89%, 61% and 5.7 years respectively. Less advanced stage and undergoing cancer-directed surgery were favorable prognostic factors. For localized, regional and distant stage the median OS was: not reached at 6.3 years, 4.4 years and 2.0 years respectively (P=0.021); the median CSS was not reached at 6.3 years, 5.0 years and 2.4 years (P=0.068). For patients undergoing versus not undergoing surgery, the median OS was 4.9 vs 0.9 years (P=0.053) and median CSS was 5.7 vs 0.9 years (P=0.011). Tumor size was not significant.

Conclusions: From a population-based analysis of patients with thoracic malignant solitary fibrous tumors, stage and cancer-directed surgery had the greatest impact on OS and CSS. While being amenable to surgery likely reflects more indolent disease and/or better performance status and cardiopulmonary function, the significantly favorable impact of surgery also likely reflects a therapeutic benefit.

KEY WORDS malignant solitary fibrous tumor, lung, pleural, population-based

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Introduction

Solitary fibrous tumors are rare primary malignancies arising from the submesothelial mesenchymal layer, mostly pleural in origin, though they can arise from extrapleual sites as well (1,2). These tumors often grow to a large size (3,4). Ten to 20% are classified as malignant, which are pathologically characterized by mitoses, necrosis, atypia and hypercellularity (5). Compared to benign solitary fibrous tumors, malignant tumors are characterized radiographically by larger size (6,7), and greater likelihood of PET positivity (6,7), and are characterized clinically by a greater likelihood of symptomatic presentation (6,8,9), more aggressive behavior, greater propensity to recur and/or metastasize, and poorer survival (1,5,6,8-10).

The present study offers a descriptive, retrospective analysis of patients with thoracic malignant solitary fibrous tumors, registered in the population-based Surveillance, Epidemiology, and End Results (SEER) database. This study was undertaken with the goal of better characterizing the overall survival (OS) and cause specific survival (CSS) of thoracic malignant solitary fibrous tumors and the risk factors affecting survival outcomes. This appears to be the first paper to analyze survival outcomes of patients registered in the SEER database with a diagnosis of malignant solitary fibrous tumors, and represents the largest series of these patients.

Methods

Patient database

The SEER Program collects information from population-based cancer registries throughout the United States. Serial registry data are de-identified and submitted to the United States National Cancer Institute on a biannual basis.

No potential conflict of interest.

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Patients were selected with the SEER Stat case listing session using the following criteria from the SEER database fields: "Site recode" = "pleura", "trachea or mediastinum" or "lung and bronchus"; and ICD-O-3 Hist/Behav="solitary fibrous tumor, malignant." Only patients actively followed were included (i.e. autopsy and death certificate only cases were excluded).

The "SEER historic stage A" and "summary stage 2000" variables of localized, regional (direct extension and/or nodal involvement) and distant (distant nodal sites and/or distant metastases) were used to stage patients. The SEER database also records whether or not a patient has undergone cancer-directed surgery, which the SEER program considers as any curative or palliative surgery that removes cancer, excluding biopsies which remove only a fragment or portion of tumor.

Statistical analysis

Stata version 9.2 (StataCorp, College Station, TX) was used for data analysis. Actuarial OS was calculated using the Kaplan-Meier method. For univariate analyses comparing OS between subgroups, the log-rank test was used. For multivariate analyses (MVA) assessing the significance and hazard ratios (HR) of prognostic variables, Cox proportional hazards models were used. *P* values <0.05 were considered significant.

Results

Patient and tumor characteristics

Table 1 summarizes the patient and tumor characteristics of the study patients. All patients had pathologic diagnosis of malignant solitary fibrous tumor. The median age at the time of diagnosis was 65 years. Fifty five percent are males. Of those with available staging information, 21 of 77 (27%) had nodal or distant metastases. Of the 56 without nodal or distant metastases, 32 (57%) were classified as "localized" stage disease. Tumor grade was not available in 84% of patients. Because only 2 patients had regional nodal disease, they are grouped with the regional via direct extension patients in the analyses below (regional stage group).

Among all patients, the follow-up ranged from 1 month – 6.8 years (median 2.2 years). Among patients alive at last follow-up, the median follow-up was 2.3 years.

Patient treatments

Cancer-directed surgery was performed in 85% of patients, radiation was performed in 16%, and both radiation and surgery were performed in 13%. Close to half (47%) of the patients underwent a radical-extent surgery (see Table 1 footnote).

Among patients with localized, regional and distant disease, 97%, 92% and 68%, respectively, underwent cancer-directed surgery (P=0.019), and among those patients undergoing surgery, 59%, 48% and 33% (respectively) underwent radical resection (P=0.53).

Among patients with lung and pleural primary sites, 79% and 90%, respectively, underwent cancer-directed surgery (P=0.18), and among those patients undergoing surgery, 57% and 44% (respectively) underwent radical resection (P=0.31)

Patient survival

The 1-year, 2-year and 5-year OS (Fig 1) of patients were 87%, 78% and 49% respectively. Median OS was 4.6 years. The 1-year, 2-year and 5-year CSS (Fig 1) of patients were 89%, 81% and 61% respectively. Median CSS was 5.7 years. Table 2 outlines the univariate analyses of variables potentially impacting OS and CSS. Significant and borderline significant (P<0.10) adverse prognostic factors included older age (for OS but not CSS), more advanced stage, and not undergoing surgery.

For localized, regional and distant stage the median OS (Fig 2a) was: not reached at 6.3 years, 4.4 years and 2.0 years respectively (P=0.021); the median CSS (Fig 2b) was not reached at 6.3 years, 5.0 years and 2.4 years respectively (P=0.068). For patients undergoing versus not undergoing surgery, the median OS (Figure 3a) was 4.9 vs 0.9 years (P=0.053), and the median CSS (Fig 3b) was 5.7 vs 0.9 years (P=0.011). While the OS and CSS of those patients treated without cancer-directed surgery plateaus (i.e. no deaths) beyond 1-year, only 3 patients are at risk beyond 1 year, and thus the calculated survival beyond 1-year reflects that of only a few patients.

Table 3 shows the Cox regression analyses, for which cancer-directed surgery and stage were significant for OS and CSS. Adding tumor size to the models did not appreciably impact the HRs or P values of stage and surgical resection, and tumor size remained not significant.

Discussion

From the present analyses of patients with malignant solitary fibrous tumors of the thorax, cancer stage and cancer-directed surgery of the primary site significantly impact OS and CSS. From Cox regression analyses, increments in stage were associated with a HR of ~1.8 for OS and CSS. Cancer-directed surgery was associated with a HR of 0.3 (>3-fold reduction in deaths) for OS and 0.2 (5-fold reduction in deaths) for CSS. While the actuarial OS and CSS of patients undergoing cancer-directed surgery is similar to those not undergoing surgery beyond 5-6 years (Fig 3), the small number of patients evaluable at these time points (particularly those not undergoing surgery) precludes any definitive conclusions about these findings.

Table 1. Patient and tumor characteristics

Total number	82
Age: median [range in years]	65 [26-91]
≤49	9 (11%)
50-59	16 (20%)
60-69	30 (37%)
70-79	19 (23%)
≥80	8 (10%)
Race	
White	72 (88%)
Black	4 (5%)
Other	5 (6%)
Unknown	1 (1%)
Gender	
Male	45 (55%)
Female	37 (45%)
Grade	
Well differentiated; Grade I	3 (4%)
Moderately differentiated; Grade II	5 (6%)
Poorly differentiated; Grade III to	
Undifferentiated; anaplastic; Grade IV	5 (6%)
Unknown	69 (84%)
Site	
Pleura	40 (49%)
Lung	38 (46%)
Mediastinum	4 (5%)
Summary Stage	
localized	32 (39%)
regional	26 (32%)
nodal involvement	2 of 26
distant	19 (23%)
unknown/unstaged	5 (6%)
Primary site size	
>2--≤5 cm	8 (10%)
>5--≤10 cm	22 (27%)
>10--≤15 cm	35 (43%)
>15--≤27 cm	5 (6%)
unknown/not recorded	12 (15%)
Surgery	
performed	70 (85%)
radical extent ‡	33
less than radical extent ‡	32
not otherwise specified	5
not performed	12 (15%)
Radiation	
performed	13 (16%)
not performed	68 (83%)
unknown	1 (1%)
Surgery performed; no radiation	59 (72%)
Radiation and surgery performed	11 (13%)
Radiation performed; no surgery	2 (2%)
No surgery or radiation	9 (11%)

Table 1 continues

Table 1. Patient and tumor characteristics(continued)

Percentages do not total 100% due to rounding; ‡ Radical resection in the table refers to SEER codes specifying "total removal" or "radical" resection, lobectomy or pneumonectomy

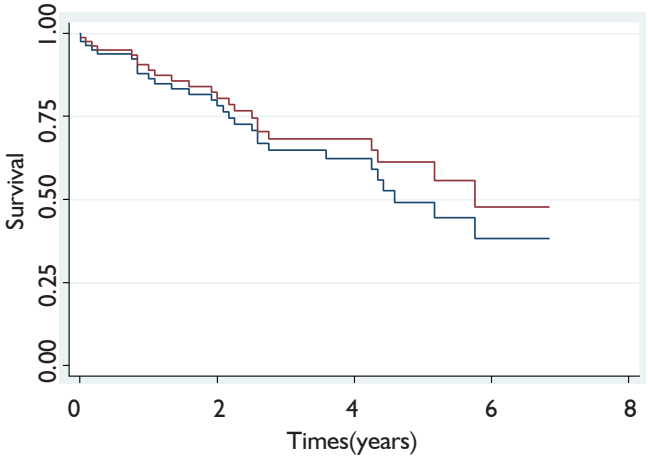

Fig 1. Kaplan-Meier overall survival (lower, blue curve) and cause specific survival (upper, red curve), among all 82 patients.

Table 2. p-values of univariate analyses of variables potentially affecting survival

Variable	OS	CSS
Age	0.063	0.32
Gender	0.46	0.57
Race	0.19	0.15
Tumor size	0.87	0.96
Primary site	0.83	0.74
Stage	0.021	0.068
Surgery of primary site	0.053	0.011
Radical versus less than radical surgery	0.19	0.063
Radiotherapy	0.44	0.25

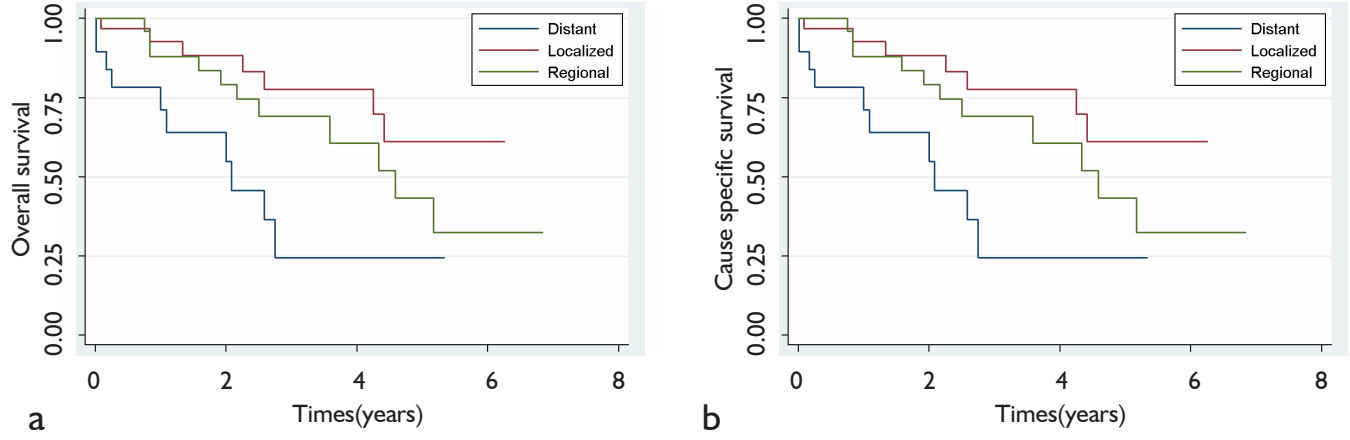

Fig 2. Kaplan-Meier overall survival (2a) and cause specific survival (2b), grouped by stage.

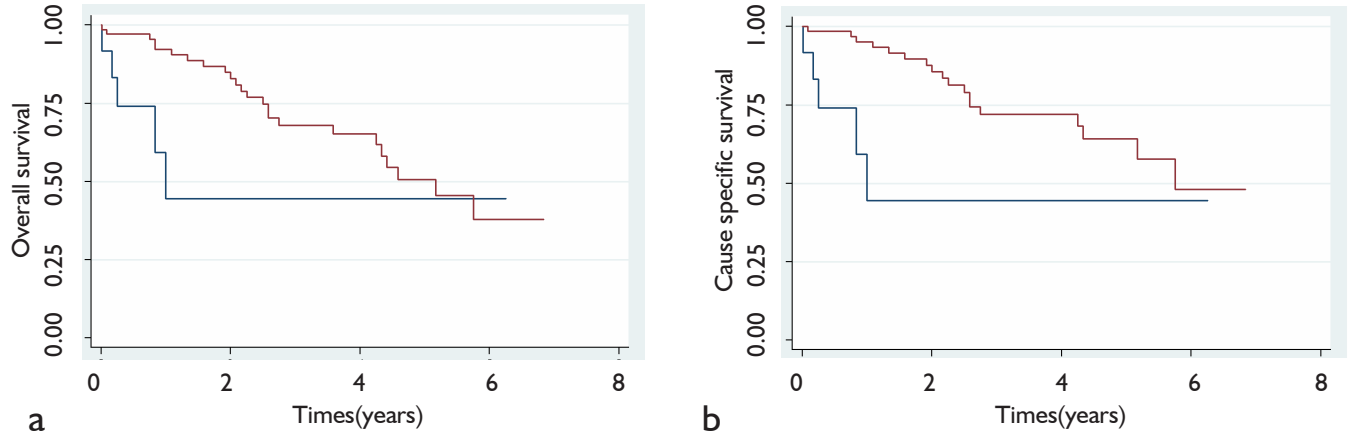

Fig 3. Kaplan-Meier overall survival (3a) and cause specific survival (3b), grouped by cancer-directed surgery. Those patients undergoing cancer directed surgery have the higher survival (at <5 years)

Table 3. Multivariate analyses of variables potentially affecting survival

Variable	OS			CSS		
	p value	HR	[95% CI]	p value	HR	[95% CI]
Age	0.13			not run		
Stage*	0.021	1.77	[1.02-3.05]	0.003	1.77	[1.02-3.05]
Surgery of primary site	0.019	0.20	[0.07-0.58]	0.041	0.20	[0.07-0.58]

* Localized, regional and distant assigned score of 1, 2 and 3 for model. HR represents risk associated with each increment in stage

Certainly, select patients whose tumors are not resected can experience a prolonged survival.

Malignant solitary fibrous tumors are generally larger than benign tumors (6-12), significantly so in some studies (8,10), though very large tumors can be benign. Perhaps larger tumors are more likely to have undergone genetic changes (13). While tumor size has been shown to be prognostic in retrospective series of patients with benign and malignant solitary fibrous tumors (5,10,11), this study which included only patients with malignant tumors, and others, including benign and malignant histologies (6,14), did not demonstrate an effect of size on survival outcomes.

The survival outcomes reported here are similar to that reported in a Mayo Clinic study (median survival of 4.6 years, and 5-year OS of 46%) which included 11 patients with malignant solitary fibrous tumors (8). In a study of 15 patients

with malignant solitary fibrous tumors from Memorial Sloan Kettering, the 5-year survival was reported to be 55% (10). A Korean study including 13 patients with malignant solitary fibrous tumors reported a median survival of 2.0 years (9). A French study reported a 5 and 10-year survival rate of 89% among 22 patients with malignant solitary fibrous tumors (of which only one did not undergo a complete resection) (15).

The observed OS and CSS benefit of cancer-directed surgery for malignant solitary fibrous tumors in this study likely reflects a combination of selection of patients who can tolerate surgery, more indolent disease being amenable to surgical resection and a therapeutic benefit from surgery. The Cox analyses which incorporate stage account for the extent of tumor (albeit with a spectrum of disease extent included within each stage group), and thus there is a possible therapeutic benefit of surgery. Other factors used to select patients for surgery, such as performance status, pulmonary function, cardiac function and comorbid conditions were not accounted for in these analyses, and also likely contribute to the survival benefit of surgery. Because of the retrospective nature of this study, it is not appropriately designed to address how extent of resection impacts outcome, though this data suggests that radical resection results in a trend towards better CSS versus less radical resections. Univariate analyses in this study suggest that undergoing radiation does not significantly impact survival outcomes, although, as described above for surgery, understanding the effect of radiation is complicated by the retrospective nature of this study. Clinical responses to radiation have been reported in the literature for benign (16), and malignant solitary fibrous tumors (17). The role of adjuvant radiation for solitary fibrous tumors is not known, though it has been suggested that malignant tumors can benefit from adjuvant radiotherapy (3,9).

Other weaknesses of the present study include the inability to ascertain progression/recurrence free survival and to account for other potentially relevant variables, such as performance status and tumor grade (which is reported in only 16% of patients, despite all having pathologic diagnosis). It must be acknowledged that there are complexities and uncertainties in the pathologic diagnosis of solitary fibrous tumors, which therefore limits the interpretation of retrospective analyses such as this study. It is possible that a pleura mesothelioma or, alternatively, a benign solitary fibrous tumors was misdiagnosed as malignant solitary fibrous tumors. The tumor pathology cannot be systematically reviewed, using modern immunohistochemistry techniques, to verify and specify the pathologic diagnosis. Likewise, radiographic imaging is not available to review, which can also assist in the diagnosis by either CT (18) or PET criteria (6,7).

The strengths of the study include the relatively large number of patients analyzed, from an unbiased population-based registry. Analyzing 82 patients allowed investigation of demographic, clinicopathologic and treatment-related variables. Nevertheless, the number of patients (and number of events) is too small to analyze outcomes grouped by stage.

Conclusions

From a hypothesis generating, retrospective, population-based registry analysis of patients with thoracic malignant solitary fibrous tumors, cancer stage and cancer-directed surgery appear to have the greatest impact on OS and CSS. While being amenable to surgery likely reflects more indolent disease and/or better performance status and cardiopulmonary function, the significantly favorable impact of surgery, when accounting for tumor size and stage may reflect a therapeutic benefit.

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