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Optimal Percent Myxoid Component to Predict Outcome in High-Grade Myxofibrosarcoma and Undifferentiated Pleomorphic Sarcoma

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Abstract

Background—Myxofibrosarcoma and undifferentiated pleomorphic sarcoma (UPS) are aggressive, genetically complex sarcomas. The minimum myxoid component used as a criterion for myxofibrosarcoma varies widely, so we determined the optimal myxoid component cutpoints for stratifying outcomes of UPS and myxofibrosarcoma. We also analyzed clinicopathologic factors associated with outcome.

Methods—Review of a prospective, single-institution database identified 197 patients with primary, high-grade extremity/truncal myxofibrosarcoma or UPS resected during 1992–2013. Histology was reviewed and percent myxoid component determined for each tumor. Disease-specific survival (DSS) and distant recurrence-free survival (DRFS) were analyzed using the Kaplan-Meier method, log-rank test, and Cox regression.

Results—Median follow-up for survivors was 6.4 years. In minimum *p*-value analysis of myxoid component, the best cutpoint for both DSS and DRFS was 5% (adjusted *p* 0.001), followed by 70%. Therefore, sarcomas with <5% myxoid component (*n*=69) were classified as UPS and those with ≥5% myxoid component (*n*=128) as myxofibrosarcoma. Five-year DRFS was 24% for UPS, 51% for 5–69% myxoid component myxofibrosarcoma, and 65% for ≥70% myxoid component myxofibrosarcoma. Myxoid component, tumor size, and age were independently associated with DSS; myxoid component and tumor size were associated with DRFS. Only tumor site was associated with local recurrence.

Conclusions—Percent myxoid component and tumor size are the two most important predictors of DSS and DRFS in high-grade myxofibrosarcoma and UPS. A 5% myxoid component cutpoint is an improved criterion for classifying myxofibrosarcoma. Myxoid component-based

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classification improves stratification of patient outcome and will aid in selection of patients for systemic therapy and clinical trials.

INTRODUCTION

Myxofibrosarcoma is a common type of soft tissue sarcoma that typically arises in the limbs of older patients. It was initially known as the myxoid variant of malignant fibrous histiocytoma, but was described as myxofibrosarcoma in 1997,¹ and since 2002 myxofibrosarcoma has been regarded by pathologists as a distinct tumor type that can be identified reproducibly.^{2–4} For distinguishing myxofibrosarcoma from undifferentiated pleomorphic sarcoma (UPS; also known as pleomorphic malignant fibrous histiocytoma or sarcoma NOS), a major criterion is the percent myxoid component.⁵ However, there is still controversy over the percentage of myxoid component to use for this cutpoint, and cutpoints in current use range from 10% to 50%.^{6–8}

The mainstay of therapy for patients with localized myxofibrosarcoma or UPS is surgery with or without radiation therapy. Overall 5-year survival after surgery is 60–70%, with approximately 35% of high-grade tumors resulting in distant metastasis, typically to lung, bone, or lymph nodes.^{6–9} Systemic chemotherapy has been employed for young patients with high-risk features and is associated with improved disease-specific survival in this group.¹⁰

Prognostic factors in myxofibrosarcoma and UPS have undergone only limited study. Overall survival, in retrospective studies, has been associated with age, size, and margin status. Additionally, local recurrence-free survival has been associated with margin status.^{6,11,12} In one study looking specifically at low-grade myxofibrosarcoma, a myxoid component of less than 75% was associated with worse disease-specific survival (DSS).⁶ A more systematic identification of pathologic features predictive of metastasis and survival would allow the treating physician to tailor neoadjuvant therapy to patients at highest risk of distant recurrence and to avoid overtreatment of patients at low risk.

We undertook a broad investigation into potential prognostic factors, including myxoid component, for three outcomes: DSS, distant recurrence-free survival (DRFS), and local recurrence. In addition, because of the lack of agreement over the percent myxoid component to differentiate UPS from myxofibrosarcoma, we sought to find the best cutpoint by finding what cutpoint best separates high-risk disease from lower-risk disease. To do this, we retrospectively analyzed patients with myxofibrosarcoma or UPS treated surgically at our institution. To make the group more uniform and to maximize the number of events, we included only high-grade tumors.

MATERIALS AND METHODS

Patients

The study cohort was drawn from patients diagnosed and operated on at Memorial Sloan Kettering Cancer Center between September 1992 and February 2013. We included all cases of high-grade primary extremity and superficial trunk tumors diagnosed as

myxofibrosarcoma or UPS that were not previously treated and had available histology slides (n=197). The study was approved by Memorial Sloan Kettering Cancer Center's institutional review board. Patients' data were retrieved from a prospectively maintained database.

Histologic Analysis

The tumors were prosected in a standardized manner and sampled as 1 section per cm of tumor. If the tumor showed a variegated appearance, additional sampling of the different regions was performed. Tumors less than 3 cm in size were sampled in their entirety. Histology slides of all the cases were reviewed by a sarcoma pathologist (N.A), and the diagnosis and grade were confirmed for each case. Briefly, high-grade myxofibrosarcomas are cellular neoplasms composed of cellular fascicles of spindled and pleomorphic tumor cells with increased mitoses and necrosis in a myxoid stroma. Undifferentiated pleomorphic sarcomas also show fascicles of spindle to pleomorphic cells but have little or no myxoid matrix.

The percent myxoid component was estimated both grossly and microscopically. The gross findings were reviewed from the pathology report so as to estimate the gross myxoid/gelatinous areas for each case. For the microscopic estimate, all of the H&E-stained tumor sections were reviewed for each case, an average of 5 slides/case (range, 3–15). Myxoid component was assessed as a percentage of tumor showing a background of myxoid stroma, regardless of degree of cellularity or grade. In contrast a solid (non-myxoid) component was defined as a compact area of increased cellularity embedded in a fibrous stroma and/or devoid of a myxoid background. The myxoid component was first estimated on each slide containing tumor and then estimated overall for each case. This percentage of myxoid component obtained microscopically was compared to the percentage of myxoid areas described grossly, in order to exclude any cases with substantial discrepancy between the gross and microscopic estimate of myxoid/gelatinous areas so as to avoid inappropriate sampling.

Statistical Analysis

For the study endpoints (DSS, DRFS, and local recurrence), times were defined as starting at the time of operation. For DSS, events were defined as deaths confirmed to be caused by the disease (86 among the 197 patients); patients were censored at the time of non-sarcoma deaths (19 patients) or their last follow-up. For DRFS, events were defined as distant recurrences (101 patients); patients were censored at the time of deaths without distant recurrence (22 patients) or last follow-up. Because of the high number of deaths without local recurrence, we analyzed local recurrence using competing risks methodology. Local recurrences (54 patients) were treated as events, deaths without local recurrence (69 patients) were treated as competing events, and those alive without local recurrence were censored at last follow-up.

The clinicopathologic variables examined were age, gender, tumor size, percent myxoid component, depth, margin, and site. For some analyses the continuous variables tumor size and age were dichotomized at the median value.

DSS and DRFS probabilities were estimated using the Kaplan-Meier method. The associations of clinicopathologic variables with these outcomes were examined using the log-rank test for categorical variables. Variables significant on univariate analysis at the 0.05 level were entered into a multivariate Cox proportional hazards model. The optimal cutpoint for the percent myxoid component was found using the minimum P value method in the univariate setting; the p-value for the optimal cutpoint was adjusted for multiple comparisons.¹³ Local recurrence was analyzed by cumulative incidence, Gray's k-test, and Fine & Gray regression. P-values <0.05 were considered significant. All analyses were performed using R version 3.1.1 (cran.r-project.org).

RESULTS

Cutpoint Analysis of Percent Myxoid Component

The study group consisted of 197 patients with primary, high-grade extremity or superficial trunk myxofibrosarcoma or UPS who were treated by surgical resection (Table 1). Median tumor size was 9.5 cm (range, 2.5 to 30), and median follow-up for survivors was 6.4 years (range, 0.3 to 14.8). The median myxoid component was 20% (range, 0% to 100%; Supplemental Figure 1). In no case did the percent myxoid component from the microscopic assessment differ substantially from the gross assessment of percentage of myxoid/gelatinous areas.

In a minimum p-value cutpoint analysis of myxoid component, the most significant cutpoint for both DSS and DRFS was 5%, followed by 70% (Figure 1). The analysis did not identify any significant cutpoints for local recurrence (data not shown).

The 5-year DSS differed significantly between patients with tumors of <5% myxoid component (36% vs. 60%; adjusted $p=0.001$), as did 5-year DRFS (24% vs. 58%; adjusted $p<0.001$) (Figure 2a,b). Based on these data, we propose that the percent myxoid component used as a criterion for myxofibrosarcoma be 5% myxoid component. Representative histologic images of high-grade myxofibrosarcoma and UPS are shown in Supplemental Figure 2. After we applied the 5% cutpoint, our cohort had 69 UPSs and 128 myxofibrosarcomas, 30 of which had previously been diagnosed as UPS.

The characteristics of patients with myxofibrosarcoma and UPS (as classified by the 5% cutpoint) are compared in Table 1. These groups were similar in clinicopathologic characteristics and local recurrence, but differed significantly in distant recurrence ($p<0.001$) and death from disease ($p=0.0011$).

Disease-Specific Survival Analysis

Among the entire cohort of 197 patients, 92 (47%) remain alive at last follow-up, and 86 (44%) have died of sarcoma. The actuarial DSS was 51% (95% CI, 44–60%) at 5 years and 48% (41–57%) at 10 years. In both univariate analysis (Supplemental Table 1) and multivariate analysis (Table 2), age, tumor size, and percent myxoid component (<5% vs 5%) were significantly associated with DSS. Supplemental Figure 3 shows DSS stratified by size for myxofibrosarcoma and UPS. Size ≥ 10 cm was associated with worse 5-year DSS for both myxofibrosarcoma (44% vs. 72%, $p=0.005$) and UPS (26% vs. 47%, $p=0.014$).

We then assessed the 70% myxoid component cutpoint from the minimum p-value analysis for its ability to stratify the myxofibrosarcoma subset by DSS. A myxoid component of 5–69% vs 70% was associated with a relative risk of 1.82 ($p=0.04$; adjusted $p=0.10$). The 5-year DSS was 66% (95% CI, 55–80%) for myxofibrosarcoma with 70% myxoid component compared to 52% (95% CI, 40–69%) for myxofibrosarcoma with 5–69% myxoid component ($p=0.05$; adjusted $p=0.10$); Kaplan-Meier curves are shown in Figure 2C. After we adjusted for tumor size, a 5–69% myxoid component was an independent predictor of worse DSS (Table 2).

Distant Recurrence–Free Survival Analysis

Among all 197 patients, 101 (51%) developed distant recurrence by the time of last follow-up. The actuarial probability of freedom from distant recurrence was 47% (95% CI, 40–55%) at 5 years and 40% (95% CI, 32–50%) at 10 years. In both univariate analysis (Supplemental Table 1) and multivariate analysis (Table 2), the only variables associated with DRFS were myxoid component and tumor size. Size 10 cm vs <10 cm was associated with worse 5-year DRFS for both myxofibrosarcoma (41% vs. 72%; $p=0.002$) and UPS (14% vs. 35%; $p=0.014$); Kaplan-Meier curves are shown in Supplemental Figure 3.

For DRFS, like DSS, the 70% myxoid component was a good cutpoint, with relative risk of 2.0 for myxofibrosarcomas of 5–69% vs. 70% myxoid component ($p=0.01$; adjusted $p=0.02$). The 5-year DRFS was 65% (95% CI, 54–79%) for myxofibrosarcoma with 70% myxoid component versus 51% (39–66%) for myxofibrosarcoma with 5–69% myxoid component (adjusted $p=0.02$) (Fig. 2D). On multivariate analysis, both tumor size and 5–69% myxoid component were associated with worse DRFS (Table 2).

Local Recurrence

All patients had complete surgical resections, and 54 (27%) developed local recurrence by their last follow-up. The cumulative incidence of local recurrence was 21% (95% CI, 13–28%) at 3 years and 25% (17–33%) at 5 years. In univariate analysis, tumor site was the only variable to significantly associate with local recurrence (Supplemental Table 2). The 5-year cumulative incidence of local recurrence was 18% for lower extremity tumors, compared to 36% for upper extremity tumors and 49% for truncal tumors (Figure 3; $p=0.001$).

DISCUSSION

Myxofibrosarcoma and undifferentiated pleomorphic sarcoma (UPS) are the most common and aggressive types of genetically complex sarcoma.^{3,14,15} Although myxoid component is a major criterion used to distinguish myxofibrosarcoma from UPS,² the myxoid component cutpoint is still controversial.^{6–8} Moreover, only limited information is available on factors to predict patients' outcomes. In our study of high-grade UPS and myxofibrosarcoma, we found that 1) 5% myxoid component is the best cutpoint for distinguishing patients at high risk of metastasis and disease-specific death from those at lower risk; 2) within the subset of patients with 5% or higher myxoid component, a 70% myxoid component cutpoint distinguishes moderate risk from low risk; 3) myxoid component and tumor size are independent prognostic factors for DSS and DRFS, both across UPS and myxofibrosarcoma

and specifically within the myxofibrosarcoma subset; and 4) only tumor site is prognostic for local recurrence.

In previous papers, the myxoid component cutpoint to distinguish UPS from myxofibrosarcoma has ranged from 10% to 50%.^{6–8} The cutpoint at our institution was originally 30% and more recently 10%. However, we found that the optimal cutpoint to discriminate risk is lower—only 5%. Therefore, we suggest that the myxoid component cutpoint used in the classification of myxofibrosarcoma vs UPS be 5%. Use of this cutpoint would make UPS, a diagnosis of exclusion, and would serve to classify patients into a more uniformly high-risk group. After applying this criterion to classify myxofibrosarcoma and UPS in our study group, we found that DRFS at 5 years was only 24% for patients with UPS, compared to 58% for patients with high-grade myxofibrosarcoma. Notably, for the 30 patients whose tumors were reclassified from UPS to myxofibrosarcoma as a result of our applying the 5% cutpoint, 5-year DRFS was 60%, almost identical to that of the myxofibrosarcoma group as a whole. This suggests that use of the 5% cutpoint will aid in assessing patient prognosis.

Looking specifically at patients with a >5% myxoid component, we showed that a myxoid component above 70% was significantly associated with better DSS and DRFS, even after adjusting for tumor size. A similar result has been reported for low-grade myxofibrosarcoma, with myxoid component above 75% associated with better DSS.⁶

Our results confirm prior studies that identify size as an important prognostic indicator for both myxofibrosarcoma and UPS.^{6,11,12,16–18} Size <10 cm was significantly associated with improved DSS and DRFS on multivariate analysis. Despite this association, among UPS patients, even those with small tumors had poor outcomes (35% DRFS at 5 years). Moreover, even in the subset with very small tumors (< 5 cm), patients fared poorly; of 13 patients, 8 (62%) developed distant recurrence and 6 died of their disease. Because these patient numbers are small, studies with a larger cohort are warranted to better define outcomes in patients with small UPS tumors.

The use of neoadjuvant/adjuvant chemotherapy for high-grade sarcoma remains controversial, given the diversity of sarcoma histologic types and their variable response rates to neoadjuvant chemotherapy. Our current practice at MSKCC is to treat selected patients with localized UPS and myxofibrosarcoma (>10 cm in size) with neoadjuvant chemotherapy prior to definitive surgical resection, as these patients are at particularly high risk of distant recurrence. The advantage of treating in neoadjuvant setting is that treatment response may be directly assessed after 2 cycles of chemotherapy, and, if local sarcoma progression has occurred, the patient may proceed directly to primary surgical resection and avoid the toxicity of further ineffective chemotherapy. Responding or stable tumors are treated with additional chemotherapy cycles followed by definitive surgery and radiation. However, the present study shows that, for tumors with <5% myxoid component (here classified as UPS), even a <10 cm tumor carries a substantial risk of metastases and disease-specific death. Therefore, we now suggest that patients with a small UPS, if they are less than 65 and fit, be considered for neoadjuvant chemotherapy (where response can be directly assessed) or enrolled in a clinical trial. On the other hand, patients with tumors with >5%

myxoid component (here deemed myxofibrosarcomas) that are less than 10 cm and tumors with 70% myxoid component have a 5-year DRFS of 65% or higher. Based on these data, we would recommend that patients with high-grade myxofibrosarcomas that are both <10 cm and of 70% myxoid component may be best managed with local surgery with or without radiotherapy and can avoid neoadjuvant chemotherapy. The risks and potential benefit of systemic neoadjuvant chemotherapy must be balanced against the probability of distant recurrence for the individual patient, particularly in the absence of definitive phase 3 trial data for UPS and myxofibrosarcoma subtypes.

For local recurrence, the only significant prognostic factor in our study was tumor site. Among both myxofibrosarcoma and UPS, lower extremity tumors had lower risk than upper extremity tumors and truncal tumors. These findings are in accord with a previous finding from our institution that, among all high-grade extremity sarcomas, rates of local recurrence were lower for lower extremity sarcomas.¹⁹ Margin status, however, has been the subject of conflicting reports on its ability to predict local recurrence of myxofibrosarcoma or UPS.^{11,12,17,18,19,20} In our dataset, local recurrence developed in 42% of patients who had an R1 resection, compared to 20% of patients with an R0 resection; however, this difference was not statistically significant ($p=0.064$), perhaps because our study included only 38 R1 patients.

On MRI, myxofibrosarcomas (particularly those with high percent myxoid component) frequently show curvilinear extensions of high T2 signal that also enhance, and on histopathologic examination these “tails” prove to represent fascial extension of tumor on histopathological examination.²¹ We have not yet studied the frequency of this tail finding in the relatively low myxoid component myxofibrosarcoma delineated in the present study. We think this will be important to examine in future work now that these new cut-points have been identified.

Our study has several limitations. The first is the cohort size of 197, which limits the power of statistical analyses. Large cohorts are difficult to assemble for rare tumors, and we note that ours is one of the larger cohorts in the literature on myxofibrosarcoma and UPS. A second limitation is the retrospective nature of the study. However, some of the disadvantages of retrospective studies were mitigated by the fact that clinical data were collected for a prospective database, and all pathologic data were reviewed for this study. This review was conducted by a single pathologist, which ensured uniform assessment of histologic type, grade, and percent myxoid component, but has the disadvantage that the assessments of other pathologists may differ. However, we believe that the 5% cutpoint may be easier to assess uniformly than the higher cutpoints in current use. Finally, our institution uses a two-grade system for sarcomas, whereas some other institutions use a three-grade system, such as FNCLCC grading.²² It is not clear how well our findings on high-grade disease apply to the intermediate grade in 3-tier systems; however, the percent myxoid component is not used as a criterion for grading in the FNCLCC system.

In conclusion, our results show that classification of UPS and myxofibrosarcoma on the basis of myxoid component improves risk stratification of patient outcome independent of size. A cutpoint of <5% myxoid component may be a useful criterion for enrolling patients

in clinical trials, e.g. for phase 2 trials of novel targeted agents with or without chemotherapy in the neoadjuvant setting. By including only high-risk patients, such trials would be expected to have more events and thus have greater power to detect a meaningful difference in outcome compared to historic controls. The molecular and biological features that drive the substantially higher rate of distant metastasis in the tumors with low myxoid component have yet to be identified, but this study now informs a consistent morphological cut-point to study this question. We are presently using a genome-wide analysis of the copy number alterations and transcriptional profiles to identify the molecular mechanisms and pathways driving myxofibrosarcoma and UPS tumorigenesis. Elucidation of these pathways will serve to identify new molecular prognostic markers and help prioritize drug targets for future therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Synopsis

Analyzing myxofibrosarcoma and undifferentiated pleomorphic sarcoma, we found a percent myxoid component of 5% to be the best cutpoint for differentiating patients by survival and recurrence. We therefore propose a myxoid component of 5% for an evidence-based definition of myxofibrosarcoma.

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Figure 1.

Minimum p -value cutpoint analyses for association between percent myxoid component and (A) disease-specific survival (DSS) and (B) distant recurrence-free survival (DRFS) (n=197). The vertical dashed lines indicate the cutpoints of minimum p -value.

Figure 2. Kaplan-Meier curves according to percent myxoid component. **(A)** DSS and **(B)** DRFS comparing UPS (<5% myxoid component, n=69) and myxofibrosarcoma (5–100% myxoid component, n=128). **(C)** DSS and **(D)** DRFS comparing myxofibrosarcoma with <70% myxoid component (n=59) vs. myxofibrosarcoma ≥70% myxoid component (n=69).

Figure 3.
Cumulative incidence of local recurrence (n=197) by tumor site.

Table 1

Clinicopathologic and treatment characteristics for 197 patients with primary high-grade myxofibrosarcoma (MXF) and undifferentiated pleomorphic sarcoma (UPS). The data are n (%) or median (range).

	All patients n=197	MXF (5% myxoid) n=128	UPS (<5% myxoid) n=69	P-value ^a
Age, years	66 (20–94)	64 (24–92)	69 (20–94)	0.14
Gender				0.10
Male	89 (45%)	52 (41%)	37 (54%)	
Female	108 (55%)	76 (59%)	32 (46%)	
Tumor size, cm				0.46
<10 cm	105 (53%)	71 (55%)	34 (49%)	
10 cm	92 (47%)	57 (45%)	35 (51%)	
Median (range)	9.5 (2.5–30)	9.5 (2.6–29)	10 (2.5–30)	
Tumor location				0.82
Upper extremity	32 (16%)	22 (17%)	10 (14%)	
Lower extremity	125 (63%)	79 (62%)	46 (67%)	
Trunk	40 (21%)	27 (21%)	13 (19%)	
Depth				1
Superficial	36 (18%)	23 (18%)	13 (19%)	
Deep	164 (82%)	105 (82%)	56 (81%)	
Margins				0.26
R0	158 (80%)	100 (78%)	58 (84%)	
R1	38 (19%)	28 (22%)	10 (14%)	
Local recurrence	54 (27%)	31 (24%)	23 (33%)	0.23
Distant recurrence ^b	101 (51%)	51 (40%)	50 (72%)	<0.001
Lung	91 (46%)			
Bone	14 (7%)			
Soft tissue	23 (12%)			
Other organs ^c	10 (5%)			
Death from disease	86 (44%)	45 (35%)	41 (59%)	0.0011
From metastatic disease	82 (42%)	42 (33%)	40 (58%)	
From local recurrence of chest wall tumor	4 (2%)	3 (2%)	1 (1%)	
Follow-up of survivors, years	6.4 (0.3–14.8)	5.7 (0.3–14.8)	8.6 (1.1–14.7)	

^aBy Fisher's test for categorical variables and Wilcoxon rank-sum test for categorical continuous variables.

^bThirty-one patients had distant recurrences to more than one location.

^cAdrenals, brain, and heart.

Table 2

Multivariate analysis of clinical and pathologic variables associated with disease-specific survival (DSS) and distant recurrence-free survival (DRFS) for the entire cohort and for the subset with myxofibrosarcoma.

Variable	DSS		DRFS	
	Multivariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Myxofibrosarcoma and UPS (n=197)				
% Myxoid component (<5% vs. 5%)	2.1 (1.4–3.2)	0.001	2.5 (1.7–3.8)	<0.001
Size (≥ 10 cm vs. <10 cm)	2.2 (1.4–3.4)	<0.001	2.2 (1.4–3.2)	<0.001
Age (≥ 65 vs. <65)	1.6 (1.1–2.5)	0.025	1.1 (0.7–1.6)	0.73
Myxofibrosarcoma only (n=128)				
% Myxoid component (<70% vs. 70%)	2.1 (1.2–3.9)	0.015	2.7 (1.5–4.8)	0.001
Size (continuous)	1.11 (1.05–1.16)	<0.001	1.12 (1.07–1.17)	<0.001

HR, hazard ratio