Beyond the Biopsy: High Rates of Grade and Diagnostic Discrepancy in Myxofibrosarcoma — A Single-Center Analysis

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Significance & Hypothesis: Myxofibrosarcoma (MFS) is among the most common soft tissue sarcomas in older adults and is characterized by marked intratumoral histopathologic heterogeneity. Accurate FNCLCC grading is essential for prognosis and treatment planning. This includes decisions regarding neoadjuvant radiation. The reliability of pre-operative biopsy grading in MFS and the clinical and procedural factors that predict discrepancies with final pathology remain poorly characterized. We hypothesized that biopsy-to-resection grade discrepancy in MFS is common, is not explained by procedural factors, and is most pronounced for biopsies initially called low-grade.

Innovation: This is the largest single-center analysis of biopsy-to-resection grade and diagnostic concordance in MFS reported to date. It is also the first to systematically evaluate predictors of grade upgrade in this histologically heterogeneous tumor. The findings reframe pre-operative MFS grading as a tumor-sampling problem rather than a technique problem.

Approach: We retrospectively reviewed adult patients with a final pathologic diagnosis of MFS who underwent pre-operative biopsy and surgical resection at a tertiary sarcoma referral center. Cases were identified through institutional query tools (EMERSE). The primary outcome was an upgrade in FNCLCC grade between initial biopsy and final pathology. Inter-rater agreement was quantified using quadratic-weighted Cohen's kappa with bootstrap 95% confidence intervals. Multivariable logistic regression identified independent predictors of upgrade, with biopsy modality (reference: excisional), biopsy location (internal vs. outside center), tumor size, age, and sex as covariates. Diagnostic discrepancy (initial diagnosis other than MFS) was assessed as a secondary outcome. Two-sided $p<0.05$ was considered statistically significant.

Results: Among 236 patients with paired biopsy and resection grades, 41 (17.4%) were upgraded, and 1 (0.4%) was downgraded on final pathology, yielding a quadratic-weighted κ of 0.77 (95% CI 0.69–0.85). Upgrade rate depended strongly on initial grade: 25 of 55 biopsy G1 cases (45.5%) and 16 of 78 biopsy G2 cases (20.5%) were upgraded, whereas only 1 of 103 biopsy G3 cases was reclassified (a downgrade). Seven patients (12.7% of biopsy G1) jumped two full grades from G1 to G3. In multivariable logistic regression (n=229, 39 events), no clinical or procedural variable independently predicted upgrade, including biopsy modality, biopsy location (outside vs. internal: OR 0.63, 95% CI 0.23–1.76, p=0.38), tumor size, age, or sex. Diagnostic discrepancy occurred in 65 of 236 patients (27.5%); the most common incorrect initial diagnoses were spindle cell sarcoma (n=21), undifferentiated pleomorphic sarcoma (n=11), and pleomorphic sarcoma (n=8).

Discussion & Impact: Pre-operative biopsy in MFS substantially undergrades nearly half of low-grade tumors and misclassifies more than one in four cases as a different sarcoma subtype. No procedural factor predicts an upgrade in our analysis, including whether the biopsy was performed at a high-volume sarcoma center or outside one. This suggests that tumoral heterogeneity and biopsy targeting, rather than technique, are driving grading error. Clinicians caring for MFS patients should interpret a low-grade initial biopsy with substantial caution, especially when imaging features suggest aggressive biology. Image-guided biopsy targeting strategies merit prospective evaluation.

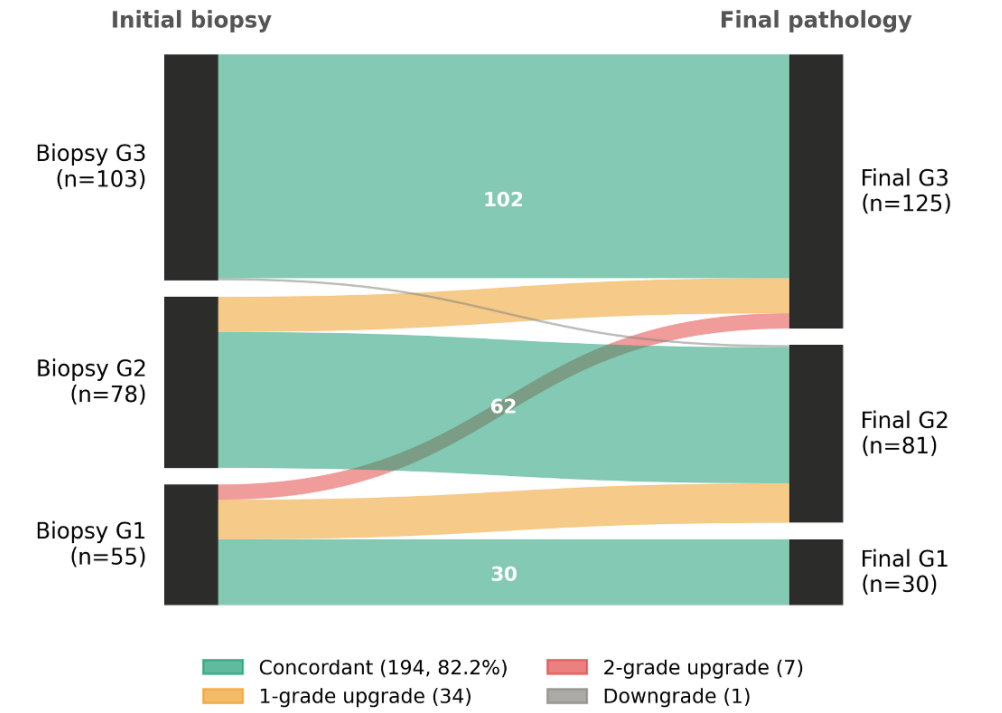
Figures (3 panels):

Figure 1. Sankey diagram of patient flow from initial biopsy FNCLCC grade to final pathology grade (n=236), illustrating the asymmetric pattern of upgrades concentrated in biopsy G1 cases.

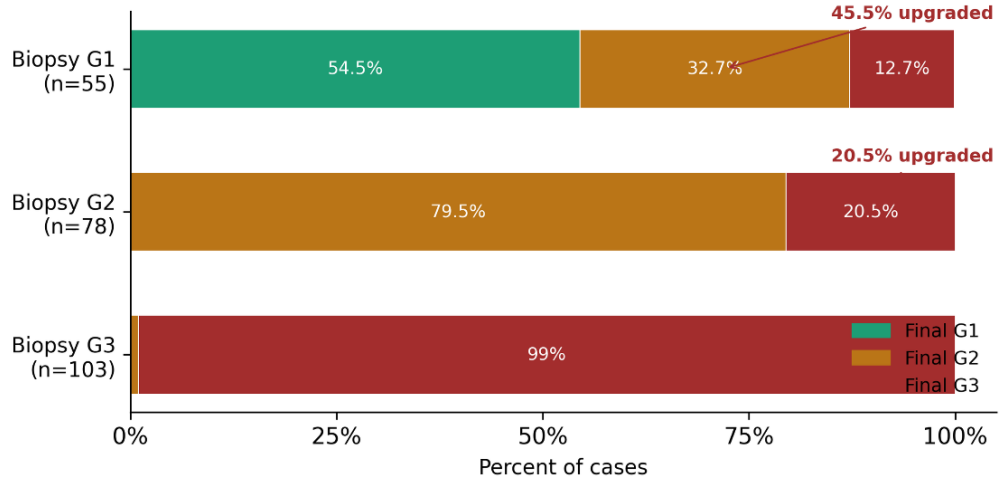
Figure 2. Stacked bar chart of final grade distribution within each initial biopsy grade, showing 45.5% upgrade rate for biopsy G1 and 20.5% for biopsy G2.

Figure 3. Forest plot of multivariable logistic regression results for predictors of upgrade, demonstrating that no clinical or procedural variable reached statistical significance.

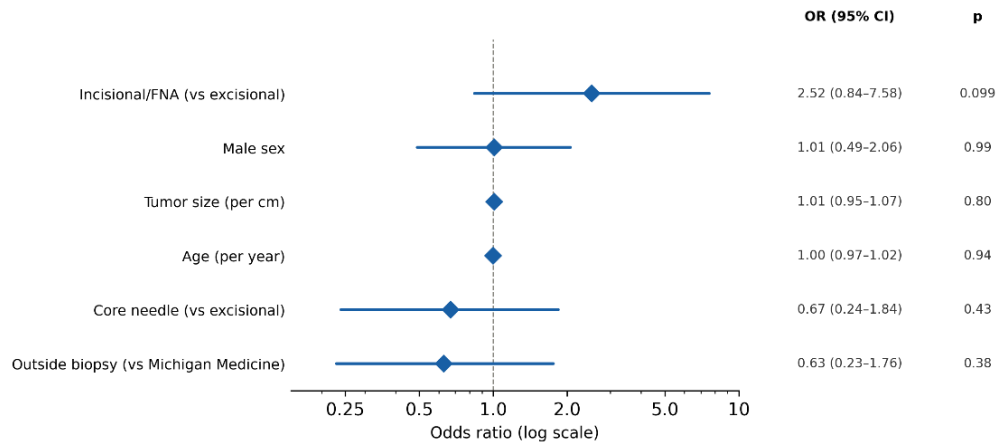
A


Initial biopsy
Final pathology
Biopsy G3 (n=103)
Biopsy G2 (n=78)
Biopsy G1 (n=55)
Final G3 (n=125)
Final G2 (n=81)
Final G1 (n=30)
102
62
30
Concordant (194, 82.2%)
1-grade upgrade (34)
2-grade upgrade (7)
Downgrade (1)

B


45.5% upgraded
20.5% upgraded
Biopsy G1 (n=55)
Biopsy G2 (n=78)
Biopsy G3 (n=103)
54.5%
32.7%
12.7%
79.5%
20.5%
99%
Final G1
Final G2
Final G3
0%
25%
50%
75%
100%
Percent of cases

C


OR (95% CI)
p
Incisional/FNA (vs excisional)
2.52 (0.84–7.58)
0.099
Male sex
1.01 (0.49–2.06)
0.99
Tumor size (per cm)
1.01 (0.95–1.07)
0.80
Age (per year)
1.00 (0.97–1.02)
0.94
Core needle (vs excisional)
0.67 (0.24–1.84)
0.43
Outside biopsy (vs Michigan Medicine)
0.63 (0.23–1.76)
0.38
0.25
0.5
1.0
2.0
5.0
10
Odds ratio (log scale)