Comprehensive Analysis of Adult NTRK-Rearranged Sarcomas: Clinical, Pathologic, Genomic Correlates

Michael Schwartz[1], Kieran Sweeney[2], Steven C. Smith[3], Kartik Angara[2], Celia E. Reynolds[4], Andrew Elliott[2], Matthew J. Oberley[2], Mark G. Evans[2], Armita Bahrami[1]

[1]Emory University School of Medicine, Atlanta, GA, USA, [2]Caris Life Sciences, Irving, TX, USA, [3]University of Virginia, Charlottesville, VA, USA, [4]Wake Forest Baptist Medical Center, Winston-Salem, NC, USA

BACKGROUND

NTRK1/2/3 gene fusions are oncogenic drivers in multiple tumor types and define several well-characterized pediatric neoplasms.

NTRK-rearranged mesenchymal tumors in adults are rare and their clinicopathologic spectrum remains incompletely defined.

Identification of NTRK fusions has therapeutic significance given the availability of selective TRK inhibitors.

This study examines the clinicopathologic feautres and genomic context of adult NTRK-rearranged sarcomas to better define their morphologic spectrum.

DESIGN

Caris Life Sciences database was retrospectively queried for sarcomas harboring pathogenic *NTRK1/2/3* fusions, screening 13,040 sequenced cases. Adult tumors were included; pediatric cases, infantile fibrosarcoma and GIST were excluded.

NTRK fusions were identified by RNA sequencing-based transcriptomic analysis.

Clinical data (demographics, tumor site and stage) were retrospectively extracted from pathology reports and available clinical records.

Histopathologic review of digitized H&E slides was independently performed by three pathologists, with consensus classification and grading using the FNCLCC system.

CONCLUSIONS

Adult NTRK-rearranged sarcomas are rare, identified in <1% of sequenced sarcoma cases in this large cohort.

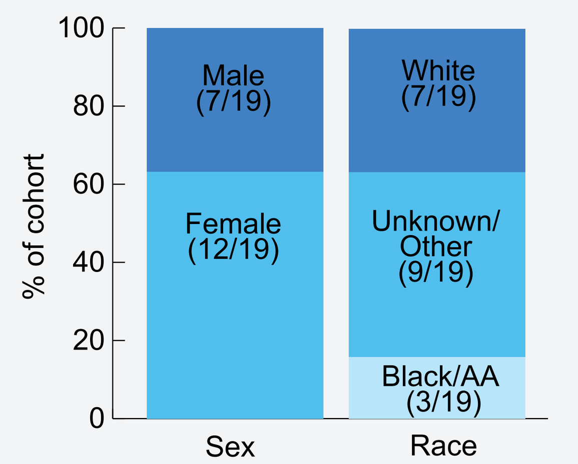
These tumors demonstrate broad morphologic heterogeneity, most often presenting as high-grade spindle cell sarcomas without distinctive lineage differentiation.

NTRK1 and *NTRK3* fusions occur with similar frequency, with diverse fusion partners and no dominant recurrent partner.

Given their nonspecific histologic appearance, recognition of these tumors requires a high index of suspicion and molecular testing, particularly in otherwise unclassified spindle cell sarcomas.

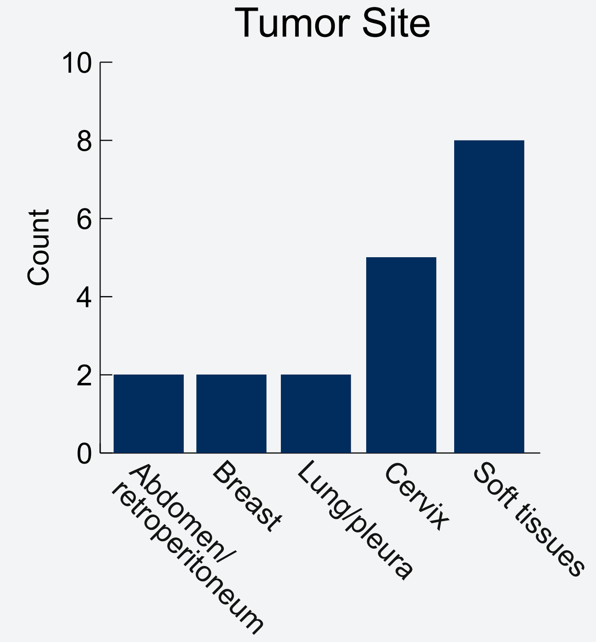
RESULTS

Cohort Demographic Characteristics (n=19)

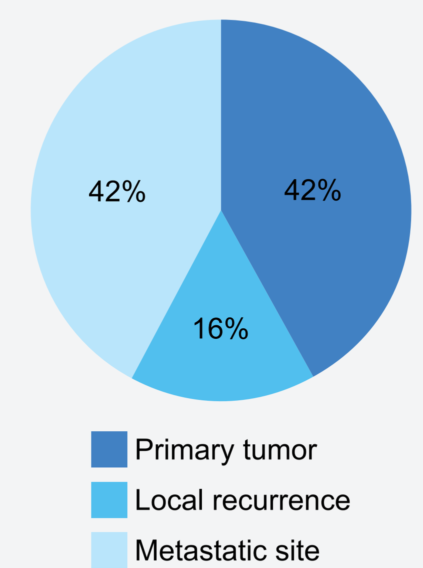


Tumor Clinical Features

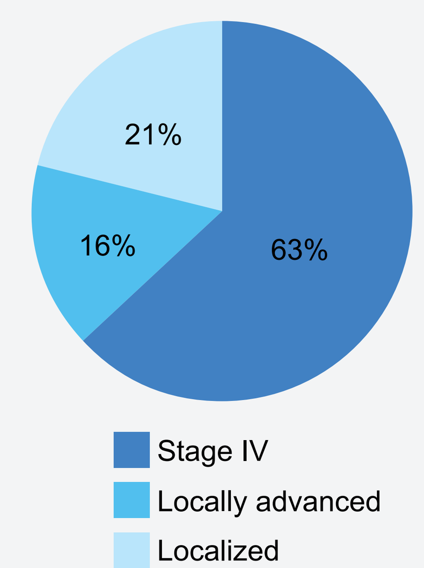
Tumor Site



Specimen Type

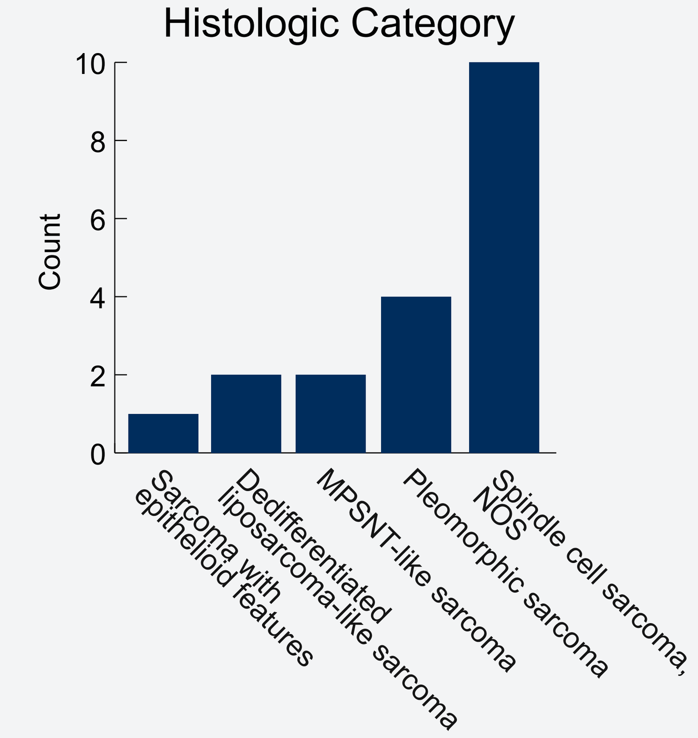


Stage at Diagnosis

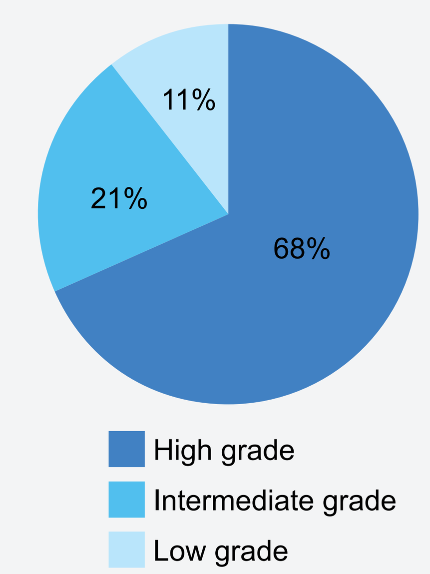


Tumor Pathologic Features

Histologic Category

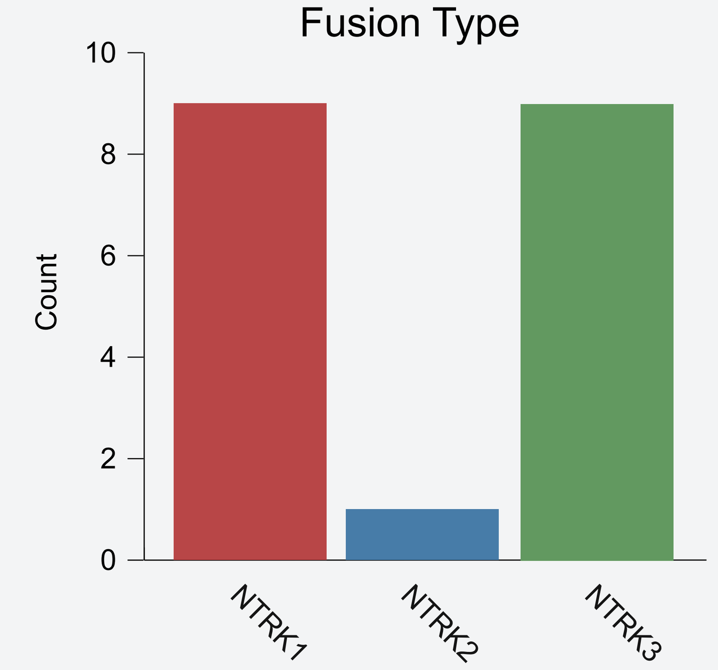


Histologic Grade



NTRK Fusion Data

Fusion Type

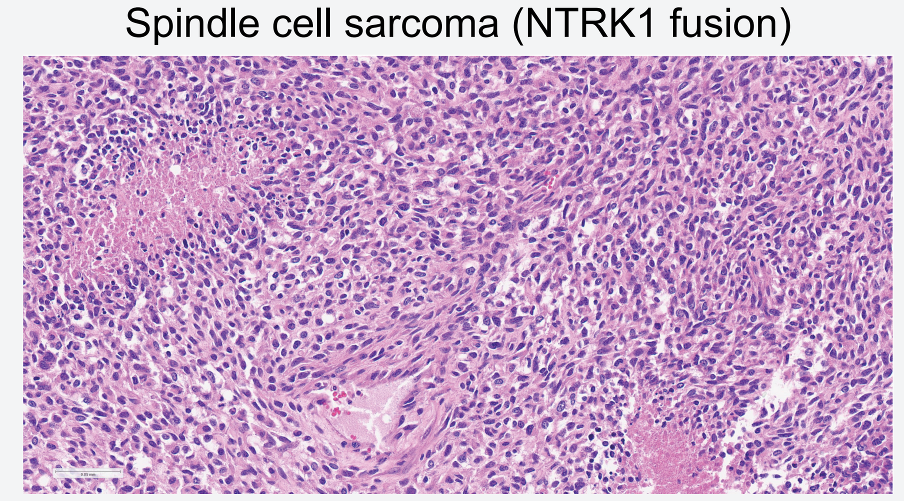


Fusion Partners

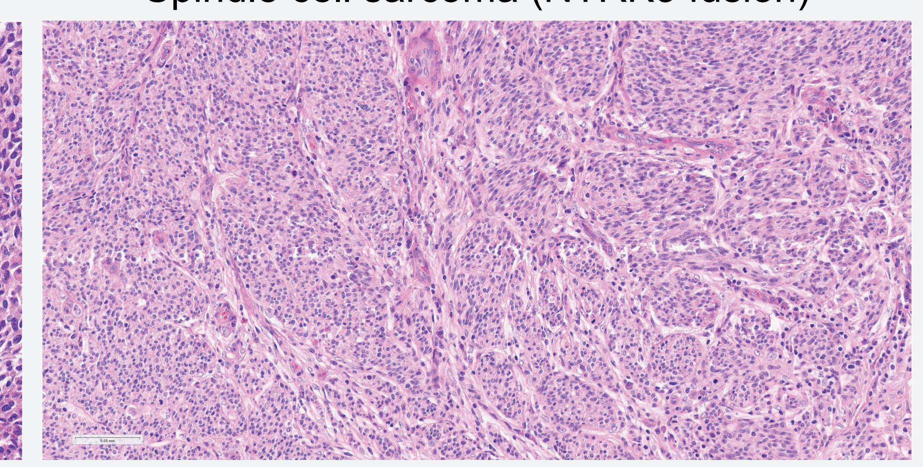
NTRK1	*NTRK2*	*NTRK3*
TPM3 (n=5)	*STRN* (n=1)	*TFG* (n=2)
ATF7-NPFF (n=1)		*EML4* (n=2)
NEF2D (n=1)		*AKAP13* (n=1)
TPR (n=1)		*ARNT2* (n=1)
NAV1 (n=1)		*ETV6* (n=1)
		HDAC4 (n=1)
		SNX25 (n=1)

Representative Histopathology

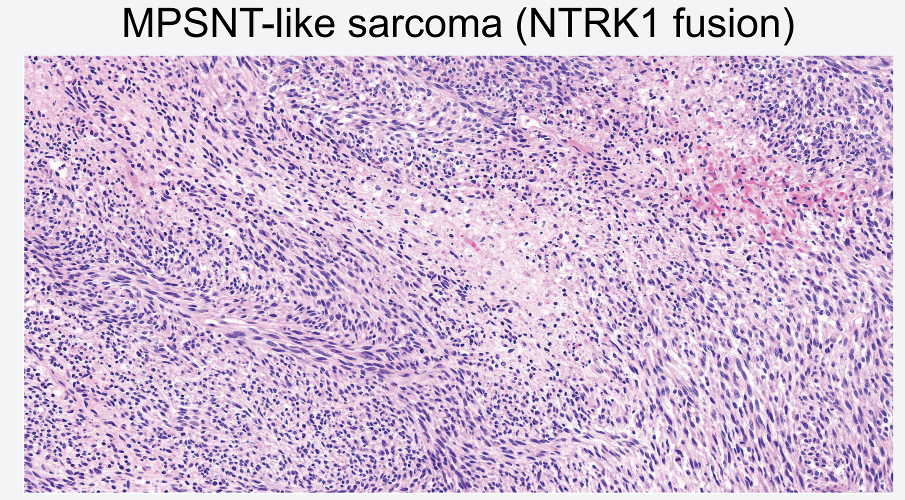
Spindle cell sarcoma (NTRK1 fusion)



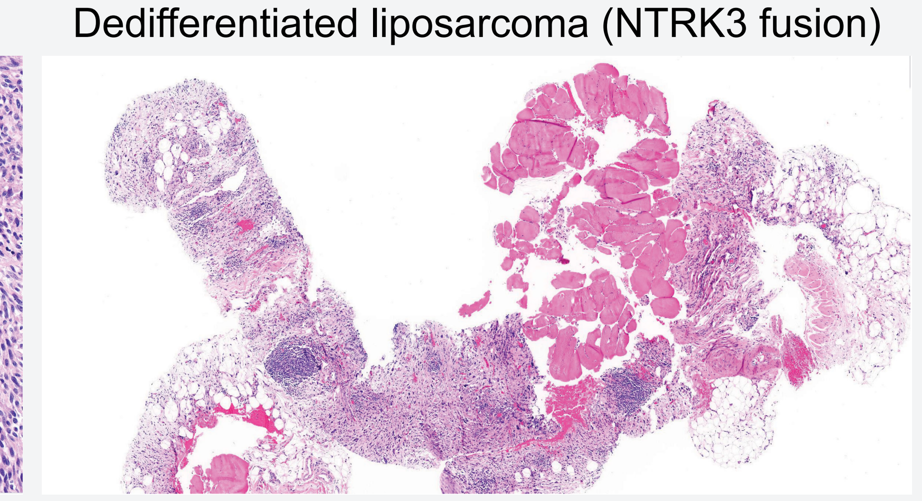
Spindle cell sarcoma (NTRK3 fusion)



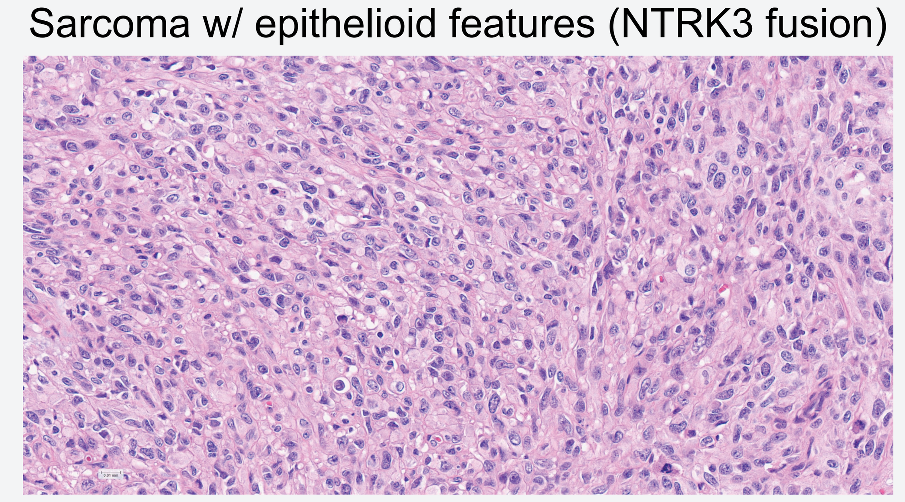
MPSNT-like sarcoma (NTRK1 fusion)



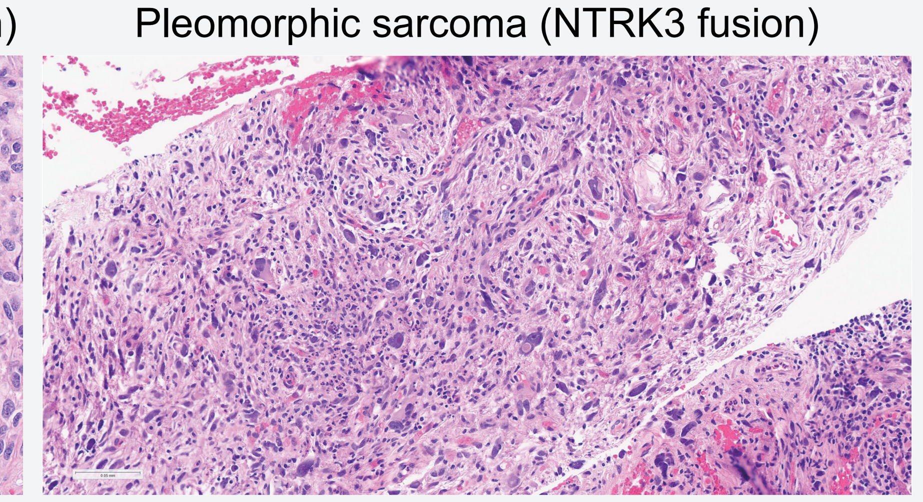
Dedifferentiated liposarcoma (NTRK3 fusion)



Sarcoma w/ epithelioid features (NTRK3 fusion)



Pleomorphic sarcoma (NTRK3 fusion)



MICHAEL SCHWARTZ: michael.schwartz@emory.edu