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Title: Has identification of pathognomonic translocations increased the reported incidence of translocation associated sarcomas over time?

Background: Translocations associated sarcomas (TASs) account for an estimated 20-30% of all sarcomas. Classic cytogenetic analysis identified sarcoma translocations beginning in the mid-1980s. Classic cytogenetic analysis is technically challenging, potentially limiting its diagnostic utility to highly expert centers. Subsequent identification of the transcription fusion product sequences permitted use of molecular diagnostic techniques including fluorescence in situ hybridization (FISH) and RT-PCR which may be performed on a wider array of tissue samples by a larger number of centers. It is unknown if sarcoma translocation or fusion product sequence identification impact the reported incidence of sarcomas. Cases that would have been previously labeled as a TAS are sometimes excluded by these analyses while new cases may be identified which would have been previously missed.

Questions: 1. Did the incidence of TASs reported in the Surveillance, Epidemiology, and End Results (SEER) program change after publication of translocation associations? 2. Did the incidence of TASs reported in SEER change after publication of the translocation fusion sequences?

Methods: Yearly incidences of eleven well defined TASs (n=19,639) reported in the SEER database (1973-2012) were determined using ICD-O-3 codes. Subgroup identification by location (e.g. extra-skeletal) and histologic subtype (e.g. pigmented DFSP) were determined when appropriate. Literature review identified the first publication dates of cytogenetic identification of the translocations and the translocation fusion product sequence. Average yearly incidences (for the preceding and succeeding 7 years) were calculated and t-test used to determine if significant differences exist.

Results: Pooled analysis of the TASs reveals that sequencing of the fusion product (p=0.005) but not cytogenetic identification of the translocation (p=0.20) correlated with a significant (9.4%) increase in the reported incidence. With exclusion of dermatofibrosarcoma protuberans (DFSP), a 23.3% (p=0.00003) increased incidence occurred after sequence publication. Synovial sarcoma diagnoses increased 53.7% (p=.0006) post-sequence publication. Myxoid liposarcoma (MLS) significantly decreased in incidence (12.4%, p=0.009) after identification of its associated translocation. Overall incidence of Ewing sarcoma family of tumors (ESFT) was not impacted by cytogenetic or sequence publication; however, extra-skeletal ESFT incidence increased 134% (p=0.0002) after publication of its fusion product sequence. Similarly, overall DFSP incidence was unchanged after translocation and sequence reporting, but non-skin DFSP cases increased 96% (p=0.0009) after identification of its translocation. Cytogenetic and sequence results are summarized in table 1 and 2 respectively.

Conclusions: This study demonstrates that publication of the translocation fusion product sequence correlates with a significant increase in the diagnosis of TASs as reported in the SEER database. The greater impact of sequence identification may result from the ability to use FISH and RT-PCR on small, paraffin embedded biopsy samples as opposed to the larger amounts of fresh tumor tissue required for classic cytogenetics. Cytogentic identification of the translocations correlated with a significant increase in several rare sarcomas including angiomatoid fibrous histiocytoma, extra-skeletal myxoid chondrosarcoma, desmoplastic small round cell tumor (DSRCT), epithelioid hemangioendothelioma, and infantile fibrosarcoma. In the case of DSRCT, translocation identification occurred one year after first description of the tumor, and for several other rare tumors translocation identification likely permitted wider recognition of the diagnoses among pathologists. Very rare or unusual sarcomas are also more likely to be referred to specialized centers where expert cytogenetics is available. MLS was the only tumor demonstrating a significant decrease after translocation or sequence publication. Prior

literature indicates that MLSs were over-diagnosed especially in the retroperitoneum. Limitations of the study include reliance ICD-O-3 codes and registry data. Some TASs such as inflammatory myofibroblastic tumor lack unique ICD-O-3 codes (necessitating exclusion from this analysis) while other sarcomas such as ESFT and synovial sarcoma require the combination of numerous codes. Another limitation is that the interval between translocation and sequence identification varied between 0 and 10 years with shortened intervals noted with more recent translocation discoveries. DFSP had only a 2 year discovery interval resulting in little difference between the translocation and sequence findings which is why overall results were reported with and without DFSP. Despite these limitations, we believe these data are clinically intuitive in light of the dramatically increased incidences of diagnostically challenging subgroups such as extra-skeletal ESFT and non-skin DFSP after sequence publication. We believe these data provide insight into adoption of new diagnostic technology for sarcomas and will be of use in predicting the impact of future molecular diagnostics upon sarcoma epidemiology.

Diagnostic Study, Level 2

Table 1. Average annual incidences of sarcomas before and after identification of their associated translocations.

Diagnosis	Publication Date	Before Translocation	After Translocation	p-Value 2 tailed
All Translocations	N/A	103.35	108.28	0.2014
All except DFSP	N/A	52.37	56.12	0.1315
Angiomatoid Fibrous Histiocytoma	2000	0.00	0.22	0.0001*
Alveolar Soft Part Sarcoma	1987	1.30	1.47	0.5761
Clear Cell Sarcoma	1990	1.77	1.90	0.6814
Myxoid Chondrosarcoma	1985	0.07	3.27	0.0010*
Dermatofibrosarcoma Protuberans (DFSP)	1995	50.98	52.17	0.6954
DFSP Non-skin	1995	4.66	9.12	0.0009*
DFSP Pigmented	1995	0.49	0.94	0.0842
Desmoplastic Small Round Cell Tumor	1995	0.06	0.30	0.0449*
Ewing Sarcoma Family of Tumors (ESFT)	1984	15.30	14.94	0.8367
ESFT Extra-skeletal	1984	1.73	2.44	0.3342
Epithelioid Hemangioendothelioma	2001	1.99	2.63	0.0065*
Infantile Fibrosacroma	1998	0.46	0.87	0.0121*
Myxoid Liposarcoma	1986	17.32	15.18	0.0094*
Round Cell Liposarcoma	1986	1.05	1.55	0.2021
Alveolar Rhabdomyosarcoma	1987	2.58	3.18	0.2246
Alveolar Rhabdomyosarcoma non-soft tissue	1987	0.32	1.49	0.0130*
Synovial Sarcoma	1987	9.98	9.66	0.7199

Notes: Incidences are reported in cases per 10,000,000. *denotes significant finding

Table 2. Average annual incidences of sarcomas before and after identification of their fusion product sequences.

Diagnosis	Publication Date	Before Sequencing	After Sequencing	p-Value 2 tailed
All Translocations	N/A	104.25	114.00	0.0047
All except DFSP	N/A	52.64	64.90	2.5E-5*
Angiomatoid Fibrous Histiocytoma	2007	0.19	0.12	0.2998
Alveolar Soft Part Sarcoma	2001	1.47	1.36	0.7066
Clear Cell Sarcoma	1993	1.77	2.11	0.2407
Myxoid Chondrosarcoma	1995	3.88	4.00	0.8575
Dermatofibrosarcoma Protuberans (DFSP)	1997	51.61	49.10	0.3999
DFSP Non-skin	1997	4.59	10.58	6.4E-7*
DFSP Pigmented	1997	0.70	1.07	0.0906
Desmoplastic Small Round Cell Tumor	1994	0.06	0.54	0.0904
Ewing Sarcoma Family of Tumors (ESFT)	1993	14.75	17.42	0.1033
ESFT Extra-skeletal	1993	2.75	6.45	0.0002*
Infantile Fibrosacroma	1998	0.46	0.87	0.0121*
Myxoid Liposarcoma	1993	15.18	17.12	0.0934
Round Cell Liposarcoma	1993	1.58	1.93	0.3890
Alveolar Rhabdomyosarcoma	1993	3.51	4.24	0.1855
Alveolar Rhabdomyosarcoma non-soft tissue	1993	1.41	1.15	0.4803
Synovial Sarcoma	1994	9.26	14.24	0.0007*

Notes: Incidences are reported in cases per 10,000,000; *denotes significant finding