Age as a factor in the molecular landscape and the tumor-microenvironmental signature of osteosarcoma

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Abstract

Background: Osteosarcoma (OS) incidence is characterized by a bimodal age distribution, with peaks in early adolescence and in adults > 65 years of age. In contrast to adolescents, OS in adults is frequently considered as a secondary neoplasm (i.e., transformation of Paget´s disease of the bone, radiation induced). Yet, the literature is scarce regarding the impact of age on the molecular landscape of OS. Herein, we sought to explore the association between age and the genomic profile as well as the tumor immune microenvironment (TME) in a large cohort of OS patients.

Methods: 208 specimens were centrally analysed at the Caris Life Sciences laboratory with DNA seq (NextSeq, 592 gene panel or NovaSeq, whole-exome sequencing), RNA seq (Archer fusion panel or whole-transcriptome sequencing) and immunohistochemistry (IHC). RNA deconvolution and differential expression analyses were performed using the Microenvironment Cell Populations counter method for quantification of immune cell populations and gene expression profiling. The cohort was stratified into three distinct age groups (< 25 years [n = 83], 25-45 years [n = 58], > 45 years [67]).

Results: Overall, the most frequently detected mutations were in TP53 (37%), RB1 (13%), ATRX (9%), TERT (6%), PTEN (5%), PIK3CA (4%) and KMT2D (3%). Copy number alterations were most frequently detected in CDK4 (12%), LRIG3 (11%), FLCN (11%), MDM2 (9%), CCND3 (9%), VEGFA (8%), TFEB (8%). Interestingly, age-based stratification revealed an increased frequency of FLCN (19.7 vs 4.7%, p < 0.01), CCND3 (13.9 vs 3.1%, p < 0.05), and HSP90AB1 (11.3 vs 0.0%, p < 0.01), alterations in patients < 25 years compared to > 45 years. TME analysis revealed that patients > 45 years have decreased B-cell abundance compared to patients < 25 years (2.9-fold decrease, p < 0.05) and 25-45 years (4.8-fold decrease, p < 0.05). Although not statistically significant, median transcriptional expression of PD-L1 was numerically increased in patients > 45 years (1.8-fold compared to 25-45 years, p = 0.17; 2.0-fold compared to < 25 years, p = 0.27), which was consistent with increasing rates of IHC PD-L1 expression with age (5.3%, 9.4%, and 17.5%, respectively, p = 0.06).

Conclusions: To the best of our knowledge, this study represents the largest cohort of molecularly characterized OS. Age-associated differences in the genetic landscape and TME composition, including increased gene amplifications observed in younger patients and decreased B-cell abundance in older patients, might suggest fundamental underlying molecular and biological differences.

Results

Table 1 – Baseline characteristics of the study cohort stratified by patient age

Characteristic	Overall	Subgroup by Patient Age		
		<25 years	25-45 years	≥45 years
Count (N)	208	83	58	67
Median Age N years (range)	31.0 (6 - 81)	17.0 (6 - 24)	33.0 (25 - 45)	64.0 (46 - 81)
Male % (N/Total)	62.5% (130/208)	69.9% (58/83)	60.3% (35/58)	55.2% (37/67)
Female % (N/Total)	37.5% (78/208)	30.1% (25/83)	39.7% (23/58)	44.8% (30/67)
Metastatic % (N/Total)	43.5% (84/193) [15 unclear]	50.6% (41/81) [2 unclear]	45.1% (23/51) [7 unclear]	32.8% (20/61) [6 unclear]

Figure 1. Genomic alteration landscape of osteosarcoma by patient age
Point mutations/indels (mut), copy number amplification (≥ 6 copies; amp), and gene fusions (fusion) detected in patient samples

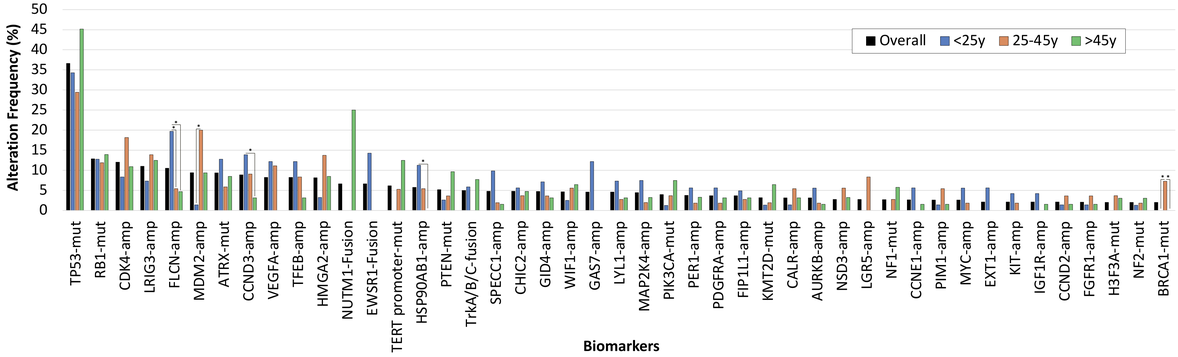


Figure 2 – Investigation of the tumor-microenvironment using the MCP counter. TMEs were largely similar between age-based subgroups. However, a B cell abundance was significantly lower in patients >45y

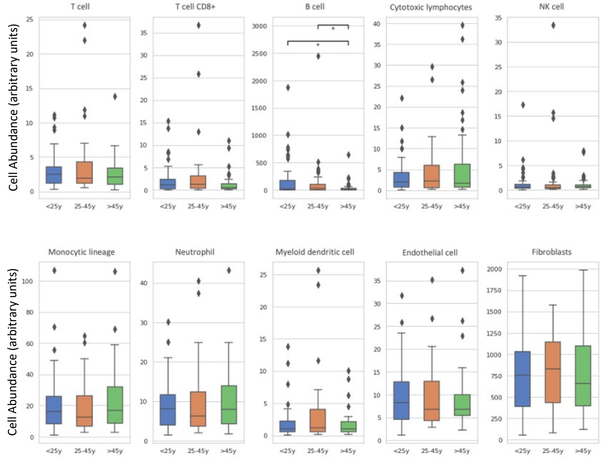
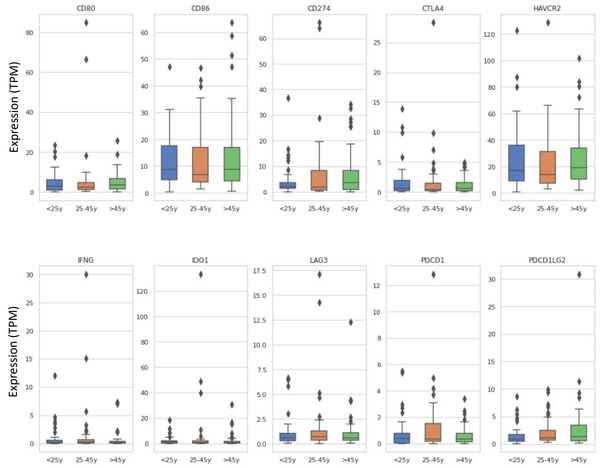


Figure 3 – Transcriptional profiling of immune-related genes
CD274 (PDL1) expression was highest in patients >45y, consistent with increased expression detected by IHC



Conclusions

- To the best of our knowledge, this study represents the largest cohort of molecularly characterized OS patient samples.
- Age-associated differences in the genetic landscape and TME composition, including increased gene amplifications observed in younger patients and decreased B-cell abundance in older patients, might suggest fundamental underlying molecular and biological differences.

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