Prognostic Role of TERT Mutations in Chondrosarcoma: Association with Dedifferentiated Tumors and Survival Outcomes

Authors: Alyan Zafar BS, Brooke M. Crawford MD/MBA, Sergio Jose Torralbas Fitz MD/MS, Francis J. Hornicek MD, H. Thomas Temple MD
Institutions: Department of Orthopaedics, University of Miami Miller School of Medicine, Miami, FL, United States.
Emails: Alyan Zafar BS- axz491@med.miami.edu**;** Brooke M. Crawford MD/MBA- bxc859@miami.edu**;** Sergio Jose Torralbas Fitz MD/MS- sjt96@med.miami.edu; Francis J. Hornicek MD- fjh21@med.miami.edu; H. Thomas Temple MD- htemple@med.miami.edu

a. Significance & Hypothesis: Chondrosarcoma is clinically heterogeneous, and the prognostic role of its genomic landscape is not fully understood. While Isocitrate Dehydrogenase (*IDH)* mutations are well-characterized, the impact of less frequent alterations—specifically Telomerase Reverse Transcriptase (*TERT)* promoter mutations—remains unclear. We hypothesize that *TERT* mutations correlate with increased tumor aggressiveness and poor clinical outcomes. This study aims to define the molecular landscape of chondrosarcoma and evaluate the prognostic significance of *TERT* mutations.
b. Innovation: This study integrates genomic profiling with clinicopathologic variables to determine whether *TERT* molecular alterations provide independent prognostic value beyond established risk factors. This work evaluates the independent prognostic impact of *TERT* alterations relative to tumor aggressiveness in chondrosarcoma.
c. Approach (Materials & Methods): In this retrospective cohort study of patients with chondrosarcoma, we integrated clinical, histological, and genomic data. Among patients with next-generation sequencing data (N=91) we assessed the mutation status of *IDH*, *TERT*, and *TP53*, alongside pathway-level alterations. Associations between *TERT* alterations and clinical tumor characteristics were evaluated using chi-square tests and logistic regression. Overall survival was analyzed via Kaplan-Meier curves and Cox proportional hazard models, adjusting for tumor type, grade, and size.
d. Results: Among patients with available genomic profiling, *IDH* mutations were identified in 52% of tumors. Additional alterations include *TP53* (16%), *TERT* (7.7%), epigenetic/chromatin (14%), and cell cycle proteins (8.8%) [Table 1]. Notably, *TERT* mutations were significantly more frequent in dedifferentiated chondrosarcomas (30%) compared to conventional (3.1%) and clear cell subtypes (0%), p=0.017 [Figure 1C+D]. *TERT* mutations were also strongly associated with higher tumor grade, occurring exclusively in grade 3 tumors (30.4% vs 0% in grade 2, $p < 0.001$) [Figure 1A+B]. Patients with dedifferentiated tumors demonstrated worse overall survival (HR 2.91, p=0.005) and a trend towards recurrence (OR 2.76, p=.076) [Figure 2C+D]. *TERT* mutations were associated with significantly worse survival in both Kaplan-Meier ($p = 0.0089$) and unadjusted Cox regression analysis (HR 7.02; $p = 0.024$) [Figure 2A+B]. However, after adjusting for tumor subtype, size, and grade, *TERT* was no longer an independent predictor of survival (HR 3.81; $p = 0.160$) [Figure 2E].
e. Discussion & Impact: *TERT* mutations are enriched in dedifferentiated chondrosarcomas and are associated with significantly worse survival in unadjusted analysis. The loss of significance in multivariable models indicates that *TERT* mutations are a proxy for tumor aggressiveness rather than an independent predictor of survival. *TERT* activation may promote tumor progression through telomere maintenance and enhanced proliferative capacity, aligning with its association in high-grade, dedifferentiated tumors. Clinically, these findings suggest that *TERT* mutations identify high-risk chondrosarcomas and may complement established clinicopathological factors to better characterize aggressive tumor biology. Though not independently prognostic, *TERT* status may still provide value in refining risk stratification when interpreted with tumor grade, type, and size. Further studies in larger, multi-center cohorts are necessary to validate these findings and determine the clinical utility of *TERT* mutations as an actionable biomarker.

Table 1. Genomic alterations across chondrosarcoma subtypes

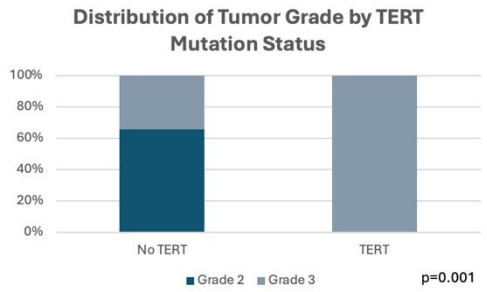
Characteristic	Tumor Type			Overall N = 91[1]
	Clear Cell N = 3[1]	Conventional N = 59[1]	Dedifferentiated N = 29[1]	
IDH				
No	3 (100%)	33 (56%)	8 (28%)	44 (48%)
Yes	0 (0%)	26 (44%)	21 (72%)	47 (52%)
NGS				
No	1 (33%)	27 (46%)	9 (31%)	37 (41%)
Yes	2 (67%)	32 (54%)	20 (69%)	54 (59%)
TP53				
No	1 (33%)	26 (44%)	12 (41%)	39 (43%)
Not tested	1 (33%)	27 (46%)	9 (31%)	37 (41%)
Yes	1 (33%)	6 (10%)	8 (28%)	15 (16%)
TERT				
No	2 (67%)	31 (53%)	14 (48%)	47 (52%)
Not tested	1 (33%)	27 (46%)	9 (31%)	37 (41%)
Yes	0 (0%)	1 (1.7%)	6 (21%)	7 (7.7%)
Epigenetic/Chromatin altered mutation				
No	2 (67%)	24 (41%)	15 (52%)	41 (45%)
Not tested	1 (33%)	27 (46%)	9 (31%)	37 (41%)
Yes	0 (0%)	8 (14%)	5 (17%)	13 (14%)
Cell cycle altered (CDKN2A, CDKN2B, RB1)				
No	2 (67%)	29 (49%)	15 (52%)	46 (51%)
Not tested	1 (33%)	27 (46%)	9 (31%)	37 (41%)
Yes	0 (0%)	3 (5.1%)	5 (17%)	8 (8.8%)

A)

	No TERT	TERT	Total
Grade 2	31 (65.9%)	0 (0%)	31
Grade 3	16 (34.1%)	7 (100.0%)	23
Total	47	7	54

Association between TERT mutation and tumor grade. TERT mutations were observed exclusively in Grade 3 tumors and were significantly associated with higher tumor grade (Fisher's exact p = 0.001).

B)



C)

	Clear Cell	Conventional	De-differentiated	Total
No TERT	2 (100.0%)	31 (96.9%)	14 (70.0%)	47
TERT	0 (0.0%)	1 (3.1%)	6 (30.0%)	7
Total	2	32	20	54

TERT mutations were most frequent in dedifferentiated chondrosarcomas (30.0%) compared to conventional (3.1%) and clear cell tumors (0%), demonstrating a significant association with tumor subtype (p = 0.017).

D)

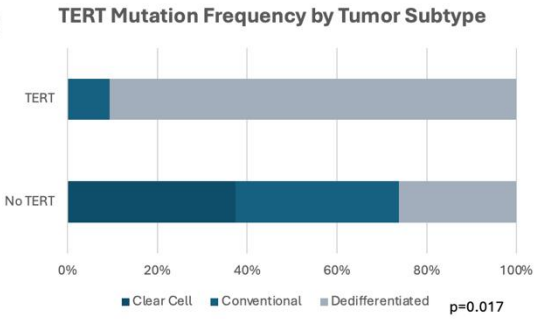


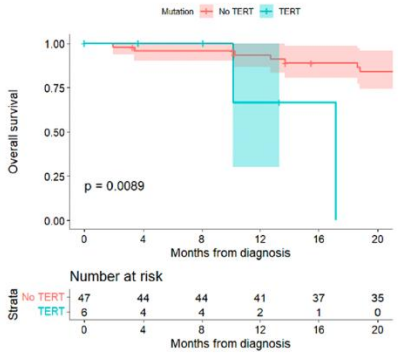
Figure 1. Association of TERT mutations with tumor subtype and grade in chondrosarcoma.
(A) + (B) Distribution of tumor grade within TERT mutation groups, confirming enrichment of grade 3 tumors in the TERT-mutated cohort (p= 0.001)
(C) + (D) Distribution of tumor subtypes by TERT mutation status, showing a predominance of dedifferentiated tumors among TERT-mutated cases (p= 0.017).

A)

	No TERT	TERT	Total
Alive at last follow-up	30 (63.8%)	4 (66.7%)	34
Dead	17 (36.2%)	2 (33.3%)	19
Total	47	6	53

Cox regression: HR =7.02 (1.30, 38.02), p = 0.024
Model: Survival ~ TERT mutation presence

B)

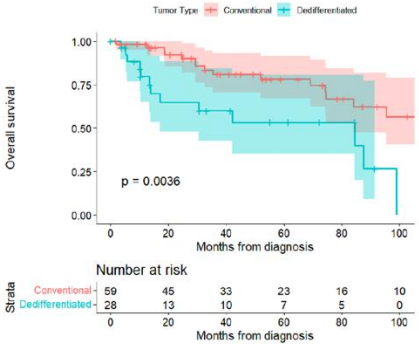


C)

Tumor Type	n	Deaths	Proportion	95% CI
Clear Cell	3	0	0%	(0%, 70.8%)
Conventional	59	15	25.4%	(15.0%, 38.4%)
Dedifferentiated	29	13	44.8%	(26.4%, 64.3%)

Cox regression (Conventional vs Dedifferentiated) HR = 2.91 (1.37, 6.18), p = 0.005
Model: Survival ~ Tumor Type

D)



E)

Variable	HR (95%)	P-value
Tumor grade	2.01 (0.61-6.63)	0.249
Tumor subtype	1.67 (0.59-4.73)	0.332
Tumor size (cm)	1.07 (0.95-1.20)	0.257
TERT Mutation	3.81 (0.77- 18.92)	0.160

Multivariable Cox regression analysis of overall survival

Figure 2. Survival outcomes and prognostic impact of TERT mutations and tumor subtype in chondrosarcoma.
(A) Survival outcomes by TERT mutation status, with unadjusted Cox regression demonstrating worse survival in TERT-mutated tumors (HR 7.02, p = 0.024).
(B) Kaplan–Meier analysis of overall survival stratified by TERT mutation status (log-rank p = 0.0089).
(C) Clinical outcomes by tumor subtype, with dedifferentiated tumors demonstrating higher mortality compared to conventional tumors (HR 2.91, p = 0.005).
(D) Kaplan–Meier analysis of overall survival by tumor subtype (log-rank p = 0.0036).
(E) Multivariable Cox regression analysis adjusting for tumor grade, subtype, and tumor size, demonstrating that TERT mutation was not independently associated with overall survival (HR 3.81, p = 0.160).