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Immunohistochemical Expression of IMP3 in Colorectal Adenocarcinoma: A Retrospective Analysis of Its Relation to Metastasis, Recurrence, and Prognosis

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Abstract **Objectives:** The protein Insulin-like growth factor II mRNA-binding protein 3 (IMP3) maintains mRNA stability thus enabling cellular multiplication as well as cell movement. The medical community links tumor progression in different malignancies to IMP3 overexpression. **Aims:** This research examines Insulin-like growth factor II mRNA-binding protein 3 (IMP3) expression patterns in colorectal carcinoma (CRC) tissue together with their impact on tumor properties as well as recurrence patterns and patient survival durations. **Methods:** The study examined 48 CRC patients after reviewing their follow-up reports along with histopathological data. The researchers performed immune staining of tumor tissue along with surrounding area using anti-IMP3 monoclonal antibody. An evaluation of IMP3 protein expression levels occurred between cancer cells and cells within the tumor stroma and this information was measured relative to common disease indicators as well as patient survival data. **Results:** Fourteen patients displayed IMP3 expression in tumor cells while ten patients and ten patients displayed IMP3 expression in tumor cells along with stromal cells respectively. Tumors displaying positive IMP3 in cancer cells demonstrated association with advanced Dukes stage and lymph node involvement, lymphovascular invasion and reduced both disease-free survival (39.87±9.25 months) and overall survival (43.79±9.27 months). Tumor cell IMP3 expression proved independent for survival prediction according to the multivariate analysis (HR = 4.96; p = 0.012). Results indicated that positivity of IMP3 markers within stromal tissue was directly associated with cancer recurrence occurrences. **Conclusion:** CRC patients often demonstrate high IMP3 expression levels which relates to increased chance of condition recurrence and decreased survival rates. Studying IMP3 represents both a promising candidate biomarker for assessment of patient risk levels as well as intervention aims. **Limitations:** The results of our study face limitations because the study used small numbers of participants in a single research center.

Key Words Colorectal carcinoma, IMP3, Cancer progression, Histopathological character

INTRODUCTION

The insulin-like growth factor II mRNA-binding protein family consists of three members; IMP1, IMP2, and IMP3 [1]. The gene of IMP3 is located on chromosome 7p11.2 and its corresponding protein is predominantly expressed in the developing muscle, epithelium, and placenta. In mature tissues, however, IMP3 levels are either low or undetectable. Notably, IMP3 is upregulated in tumor cells during carcinogenesis [2].

Several studies indicate that IMP3 expression could serve as an important prognostic marker in various human cancers, such as kidney, bladder, pancreatic

adenocarcinoma, gastric cancer, and non-small cell lung cancer, and is associated with aggressive behavior. Nonetheless, significant discrepancies remain regarding the frequency of its expression across different cancer types [3,4].

Even with the recent advancements in screening programs and the management of colorectal cancer patients, there remain numerous areas that need improvement. These include prevention, early diagnosis, identifying prognostic factors, and treating metastatic disease to develop a personalized approach [5].

The purpose of this study was to assess the clinical importance of IMP3 expression, as determined by immunohistochemistry, in colorectal carcinoma. The research predicts that CRC patients display worse clinical outcomes when tumor and stromal cells express positive IMP3 levels since it leads to higher recurrence rates and diminished survival durations. This study intends to explore the value of IMP3 expression evaluation through immunohistochemical analysis for prognostic and diagnostic purposes in CRC risk assessment.

METHODS

The study included 48 cases of primary colorectal cancer (CRC), which were collected retrospectively from archives of pathology lab. Patients didn't receive preoperative chemo or radiotherapy and with available follow up data, and pathological data were included in the study. All data were treated confidentially. All clinicopathological data of these cases regard age, size, multiplicity, histological type, metastasis (M), and TNM staging and survival data obtained from patient medical records and pathology reports. The study was approved by the research ethical committee of the university. As this is an exploratory retrospective analysis, a formal sample size calculation was not conducted. All eligible cases from the pathology archives that met inclusion criteria were included. Only patients who had not received prior neoadjuvant chemotherapy or radiotherapy were considered to ensure uniformity in histopathological characteristics and immunostaining response.

Serial sections from paraffin embedded blocks of tumor tissue and adjacent normal colon tissues were stained with H&E for recording the histopathological features and staging according to WHO 2010 classification, and tumor, lymph node, metastasis (TNM 8) system [6].

Immunostaining was performed using Anti-IMP3, mouse monoclonal antibody (1:200, clone sc-365640, concentrated, California). The stained slides were evaluated blindly to the patients' information. Staining was brown membranous and cytoplasmic and considered positive if >10% of tumor cells or stromal cells showed immunoreactivity. [7] All stained slides were independently evaluated by two pathologists blinded to clinical outcomes. In cases of discrepancy, consensus was reached. IMP3 expression was considered positive when >10% of tumor or stromal cells showed membranous/cytoplasmic staining, based on previously published scoring criteria.

The data analysis was conducted using R version 3.5.1 and SPSS version 23.0. For qualitative variables, Chi-square (X2) and Fisher's Exact Test (FET) were applied, while Student's t-test and Mann-Whitney U tests were used for continuous variables. A p-value of less than 0.05 was considered significant. The differences in overall survival (OS) and disease-free survival (DFS) between groups were evaluated using the log-rank test, and Kaplan-Meier survival curves were plotted. Univariate and multivariate Cox proportional hazards regression analyses were performed to determine the hazard ratio (HR) and 95% confidence interval (CI).

RESULTS

The study included 48 patients with colorectal cancer (CRC); the mean age is 57.52±12.86 years with range, 36-81-years. All patients were followed for >60 months or until mortality. At the end of follow-up, 16 patients died. Eighteen of the patients (37.5%) were female, and 30 (62.5%) were male. Most cases RT side 24 (50%) and19 (39.58%) were in LT side and rectum. More than half of cases were G2 (56.25%), followed by G3 (31.25%), 21/43 (43.75%) were T2 followed by 27.08% were T3 extending to subserosa. LN deposits were detected in 27/48 (56.25%). Distant metastasis was reported clinically and radiologically in 9 cases. 33.33% of cases showed lympho-vascular invasion (LVI). Twenty-nine cases (60.4 %) showed relapses of tumor (Table 1).

Immunohistochemical Expression of IMP3 in CRC samples

In normal colonic mucosa epithelial cells did not show any IMP3 staining**.** In neoplastic cells IMP3 showed membranous and cytoplasmic staining with varying intensity and either focal or diffuse (Figure 1). IMP3 expression in tumor cells alone encountered in 14 cases, in stromal cells alone in 10 cases, coexpression in tumor cells and stromal cells in 10 cases. There was Significant correlation between IMP3 expressions in tumor cells and stromal cells (Table 1). Kaplan-Meier survival curves showed that positive tumor cell IMP3 expression was associated with significantly shorter disease-free and overall survival. However, stromal IMP3 expression, while significantly correlated with recurrence, did not show a statistically significant difference in survival outcomes.

Correlation analysis

Expression of IMP3 in tumor cells was positively correlated with advanced Dukes staging, depth of invasion (T4 and T3 versus T2 and T1), presence of LN deposits presence of LVI, relapse of tumor, and percentage of dead patients at the end of follow up period. Expression of IMP3 in stromal cells showed no significant correlation to all clinicopathological features except relapse (Table 2).

Clinical and survival analysis

Relapse of tumor after complete resection was recorded in 39.58% of cases. DFS was 46.54±9.04; (30-66) in patients

Table 1: IMP3 expression in CRC with relation to clinicopathologic features and patients' outcomes.

Variable		Total	IMP3 tumor negative (no. = 24)		IMP3 tumor positive (no. = 24)		P-value
			No.	%	No.	%	
Age (years)	≤55	19 (39.58%)	8	33.33	11	45.83	0.38
	>55	29 (60.42%)	16	66.67	13	54.17	
	Mean±SD; (range)	57.52±12.86; (36-81)	61±12.62; (37-81)		54.04±12.4; (36-80)		0.06
Gender	Female	18(37.5%)	10	41.67%	8	33.33%	0.55
	Male	30 (62.5%)	14	58.33%	16	66.67%	
Site	RT	24 (50%)	13	54.17%	11	45.83%	0.49
	Trans	5 (10.42%)	1	4.17%	4	16.67%	
	LT	19 (39.58%)	10	41.67%	9	37.5%	
Type	Adeno	31 (64.6%)	17	70.83%	14	58.33%	0.33
	Mucinous	9 (18.8%)	2	8.33%	7	29.17%	
	Signet	5 (10.42%)	3	12.5%	2	8.33%	
	Anapl	3 (12.5%)	2	8.33%	1	4.17%	
Grade	1	5(10.42%)	3	12.5%	2	8.33%	0.63
	2	27(56.3%)	15	62.5%	12	50%	
	3	15 (31.25%	5	20.8%	10	41.7%	
	4	1 (2%)	1	4.2%	0	0	
Dukes Stage	A and B	17 (35.42%)	12	50%	5	20.83%	0.05
	C and D	31 (64.58%)	12	50%	19	79.17%	
Tumor depth	T and T2	29 (60.4%)	18	66.7%	11	45.8%	0.04
	T3 and T4	19 (39.58%)	6	33.33	13	54.2%	
N	0	21(43.75%)	13	54.2%	8	33.33%	0.04
	N1 and N2	27(56.25%)	11	45.8%	16	66.7%	
M	0	39 (81.25%)	22	91.67%	17	70.83%	0.14
	1	9 (18.75%)	2	8.33%	7	29.17%	
Lympho vascular invasion	Present	16 (33.3%)	11	45.83%	5	20.83%	0.05
	Absent	32 (66.7%)	13	54.17%	19	79.17%	
Relapse (recurrence)	Yes	29	18	75.0	11	45.83	0.04
	No	19	6	25.0	13	54.17	
DFS duration (months)	Mean±SD; (range)	46.54±9.04; (30-66)		39.87±9.25; (20-53)			0.01
OS (months)	Mean±SD; (range)	49.67±9.14; (35-66)		43.79±9.27; (24-66)			0.03

IMP3: Insulin-like growth factor II mRNA binding protein 3, OS: Overall survival, DFS: Ddisease free survival. P-value at <0.05 was set to be significant

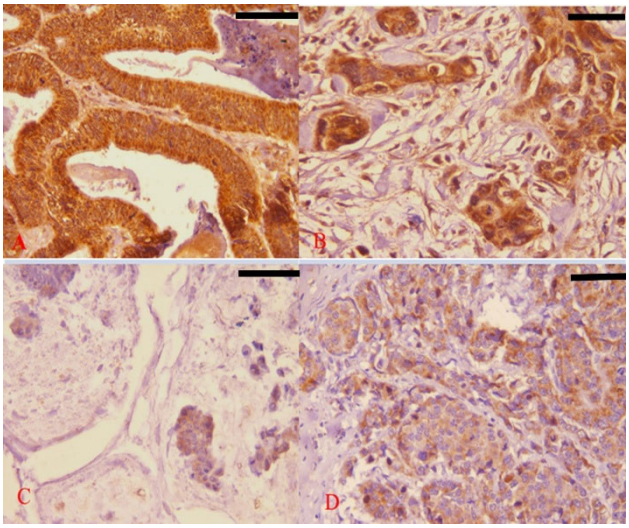

Figure 1: A showing immunohistochemical staining for IMP3 with diffuse strong positive staining of tumor cells in well differentiated colorectal carcinoma (scale bar: 20 µm). B: Diffuse strong staining in tumor cells and stromal cells in moderately differentiated colorectal carcinoma (scale bar: 10 µm). C: Moderate staining of tumor cells in mucinous colorectal adenocarcinoma (scale bar: 20 µm). D: Poorly differentiated adenocarcinoma showed moderate positive staining of tumor cells (scale bar: 20 µm).

Table 2: Association of IMP3 expression in stroma cells and clinicopathological prognostic factors of colon cancer.

Variable		IMP3 stroma negative (no. = 36)		IMP3 stroma positive (no. = 12)		Test	P-value
		No.	%	No.	%		
Age (years)	≤55	14	38.89	5	41.67	X2 = 0.03	0.86
	>55	22	61.11	7	58.33		
	Mean±SD; (range)	57.89±12.98; (37-81)		56.42±13.03; (36-80)		t = 0.34	0.73
Gender	Female	13	36.11	5	41.67	X2 = 0.12	0.73
	Male	23	63.89	7	58.33		
Site	RT	18	50.0	6	50.0	FET	0.71
	Trans	3	8.33	2	16.67		
	LT	15	41.67	4	33.33		
Type	Adeno	23	63.89	8	66.67	FET	0.32
	Mucinous	5	13.89	4	33.33		
	Signet	5	13.89	0	0.0		
	Anapl	3	8.33	0	0.0		
Grade	1	23	11.11	1	8.33	FET	0.91
	2	19	52.78	8	66.67		
	3	13	33.33	3	25.0		
	4	1	2.78	0	0.0		
Stage	I and II	13	36.1	4	33.33	FET	1.00
	III and IV	23	63.9	8	66.7		
Tumor depth	pT1 and pT2	23	63.9	6	50	FET	0.69
	pT3 and pT 4	13	36.1	6	50		
N	Absent	16	44.44	5	41.67	FET	0.82
	Present	20	38.89	7	33.33		
M	0	29	80.56	10	83.33	FET	1.00
	1	7	19.44	2	16.67		
Lympho-vascular invasion	Absent	22	61.11	10	83.33	FET	0.29
	Present	14	38.89	2	16.67		
Relapse (recurrence)	Yes	25	69.44	4	33.33		0.04
	No	11	30.56	8	66.67		
DFS	Mean±SD; (range)	44±9.08; (20-66)		40.83±11.31; (24-65)			0.32
OS	Mean±SD; (range)	47.53±8.89; (33-66)		44.33±11.49; (24-65)			0.33

IMP3: Insulin-like growth factor II mRNA binding protein 3, OS: Overall survival, DFS: Disease free survival, X^2: Chi-square test, t- student t test and FET: Fisher's Exact test, p-value at <0.05 was set to be significant

with negative IMP3 in tumor cells, compared to lesser DFS [39.87±9.25; (20-53)] in patients with positive expression (P = 0.01). Overall survival was 49.67±9.14; (35-66) in patients with negative IMP3 in tumor cells, compared to 43.79±9.27; (24-66) with positive expression (Table 1). Stromal expression of IMP3 was significantly correlated to relapse of CRC but no difference in DFS, or OS between tumors with IMP3 positive stromal cells and tumors with IMP3 negative stromal cells (Table 2).

Kaplan-Meier analysis and the log-rank test reveal significant difference in disease-free, however no significant difference in overall survival rates among patients with IMP3 expression in tumor cells and with IMP3 negative tumor cells (Figure 2).

Univariate analysis showed significant IMP3 expression in tumor cells, however, no relation of IMP3 expression in stromal cells to DFS or OS. Multivariable analysis revealed that IMP3 expression in tumor cells, grading of tumor, and LVI are independent predictors for survival. Both short OS and DFS were associated with IMP3 expression in tumor, high grade of tumor, and presence of LVI (Table 3).

DISCUSSION

CRC functions as a significant worldwide health issue because survival results vary through molecular and histopathological characteristics. Using IMP3 as a new biomarker would improve both patient risk evaluation and individual treatment planning methodologies. Research results showed that IMP3 protein expression within cancer cells directly correlated with aggressive tumor features which included lymph node metastasis and high tumor stage and invasion of lymphatic vessels combined with poorer patient survival data. The presence of IMP3 protein in stromal tissue linked positively to cancer recurrence though it did not influence survival chances. This suggests that stromal IMP3 may play a role in reshaping the microenvironment of tumors [8].

Numerous studies have explored the prognostic significance of IMP3 in various types of cancer, yielding

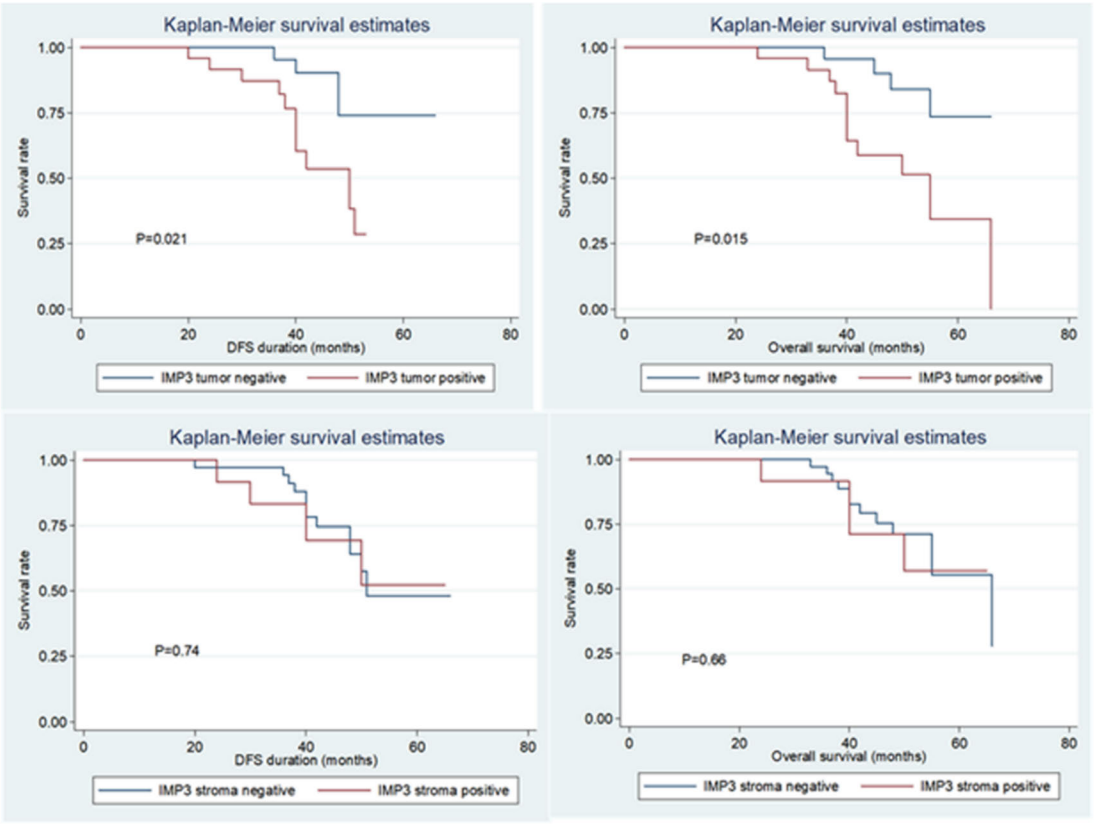

Figure 2: Kaplan–Meier curves of DFS and OS by tumors cells showed significant difference between tumors with IMP3 negative tumor cells VS tumors with IMP3 positive tumor cells. Also, Kaplan–Meier curves of DFS and OS showed no significant difference between tumors with IMP3 negative stromal cells VS tumors with IMP3 positive stromal cells, IMP3: Insulin-like growth factor II mRNA binding protein 3, OS: Overall survival, DFS: Disease free survival

Table 3: Predictors of overall survival and disease-free survival

	Univariate analysis			Multivariate analysis		
Parameters (no. = 48)	HR	95%CI	P	HR	95%CI	P
IMP3 tumor (negative vs positive)	4.13	1.31 to 12.96	0.015	4.96	1.41 to 17.40	0.012
IMP3 stroma (negative vs positive)	1.29	0.41 to 4.05	0.66			
Age (years) (≤55 vs>55)	1.29	0.47 to 3.56	0.62			
Gender (female vs male)	0.66	0.24 to 1.84	0.43			
Site	1.00					
RT	4.50	1.12 to 18.17	0.03			
Trans LT	0.91	0.30 to 2.72	0.87			
Type	1.00					
Adeno	5.74	1.47 to 22.43	0.01			
Mucinous	1.18	0.14 to 9.56	0.87			
Signet Anapl	11.01	1.93 to 62.88	0.007			
Grade*	2.67	1.27 to 5.61	0.009	2.59	1.23 to 5.44	0.012
Stage	1.48	0.85 to 2.58	0.17			
Tumor size	1.15	0.66 to 2.01	0.62			
N	1.27	0.67 to 2.44	0.46			
M (No vs yes)	2.92	0.98 to 8.73	0.05			
Lympho-vascular invasion (absent vs present)	1.16	0.41 to 3.26	0.78	3.19	0.99 to 10.30	0.052
Relapsed (no vs yes)	1.75	0.63 to 4.87	0.28			

IMP3: Insulin-like growth factor II mRNA binding protein 3, OS: Overall survival, DFS: Disease free survival, HR: Hazard ratio, CI: 95% confidence interval

inconsistent and debated findings [9-10]. IMP3 plays a role in cancer by enhancing the expression of target genes, either by preventing mRNA degradation or by promoting mRNA translation, including direct binding to the mRNAs of cyclins D1 and D3. Additionally, IMP3 facilitates tumor cell invasion and migration by targeting molecules associated with epithelial–mesenchymal transition, such as E-cadherin, Slug, and vimentin [11]. Some evidence also suggests that IMP1 and IMP3 help maintain tumor cell subpopulations with stem cell-like characteristics [10].

Most of the studies focused on IMP3 expression in tumor in CRC patients [12-13]. However, few studies assessed the role of stromal cells IMP3 in CRC progression and its clinical relevance in CRC. In this study we evaluated IMP3 expression in tumor cells and stromal cells and their relation to patients' outcomes.[14] Co-expression of IMP3 in both tumor and stromal cells was recorded in 10 cases, with significant correlation between tumor cell and stromal cell expression of IMP3. Tumor cell expression of IMP3 showed significant association with depth of invasion, LVI, LN deposits and advanced stage. However, clinicopathological features didn't show any correlation to IMP3 in stromal cells.

In agreement with our results, previous studies noted that tumoral expression of IMP3 was significantly associated with T-classification, LN deposits and tumor budding, however, they recorded IMP3 expression in (72.3%) of tumors while stromal expression of IMP3 in 18.5%. They found stromal expressions of IMP3 were associated with TNM stage, LN deposits, LVI and infiltrating tumor border [14]. Lin *et al.* [13] reported in addition IMP3 expression in tumor cells with large tumor, and highKi-67 labeling index. In contrast our study, along with others, noticed no relationship between the grade of the tumor differentiation and IMP3 immunoreactivity [12,15]. Accumulating evidence supports the profound effect on cancer progression, metastasis, and therapy resistance [16] Also, stroma was the main source of IMP3 in some cancers, suggesting that IMP3 acted as a mediator of stromal-epithelial interactions [17].

Burdelski *et al.* [18] discovered that IMP3 positivity appeared in 21.9% of urinary bladder cancers and 63.4% of colon tumors. There were notable correlations between IMP3 and advanced stage and grade in urinary bladder cancers, high grade and advanced esophageal adenocarcinomas, and decreased survival in adenocarcinomas of the lungs, stomach, and pancreatic cancers. In contrast, our study showed that expressed IMP3 in stromal cells showed no correlation to patient survival but significant relation to relapse of CRC. previous studies reported role of elevated IMP3 expression in fibroblast-to-myofibroblast differentiation and recurrence in CRC [19].

Consistent with previous findings, we demonstrated that positive IMP3 expression in tumor cells predicted a poor clinical outcome in CRCs in form of relapse, death of patients, shorter DFS, and overall survival, moreover stromal IMP3 was correlated to relapse of CRC. These results support the usefulness of IMP3 expression in tumor and stromal cells as predictors for relapse and survival in CRC [12-13].

Normally, IMP3 is expressed in a few individual cells of glandular epithelium, lymphatic tissues, and placenta [20]. In the present study, we found no immunoreactivity in normal colon tissues, however variable and heterogenous expression in tumor cells, so IMP3 protein could be used in a panel with other markers for diagnosis of colonic cancer especially in debatable biopsies [18]. The study reveals promising results although it contains some shortcomings that affect its effectiveness. The research had limited statistical power because the data collected at one organization enrolled only a small number of participants. Tumor heterogeneity together with potential selection bias affect the expression patterns of IMP3. The reliability of test results is affected by inconsistencies between different laboratories that use immunohistochemistry protocols. Additional extensive multicenter studies comprising substantial patient groups need support to verify the results obtained.

CONCLUSIONS

The research shows that IMP3 expression occurs at high frequency in colorectal carcinoma tissues that affect tumor cells and produces strong correlations with disease stage progression and recurrence events and unfavorable survival outcomes. The connection between IMP3 expression in stromal tissue and cancer recurrence indicates a need to study tumor-stroma interactions better even though stromal IMP3 expression did not affect patient survival. The research indicates that IMP3 utilizes potential as both a valid prognostic biomarker and therapeutic target in colorectal cancer. The exact relation of IMP3 to tumor progression and therapy resistance warrants investigation through future prospective research and functional test evaluations.

Conflicts of Interest

The authors declare no conflict of interest.

Ethical Statement

All patient data were anonymized and handled confidentially. Ethical approval for the study was obtained from the institutional research ethics committee, and data access was restricted to the study investigators in accordance with data protection guidelines.

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