RESEARCH ARTICLE

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PIK3CA Polymorphisms in Cervical Cancer: Differential Impact of rs6443624 and rs141178472

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Abstract

Background: Cervical cancer remains a major cause of mortality in low- and middle-income settings. We assessed whether two PIK3CA single-nucleotide polymorphisms (SNPs) rs6443624 (A/C) and rs141178472 (C/T) are associated with disease risk, clinicopathological features, and survival. **Materials and Methods:** In a prospective case control study at a tertiary center, 154 participants were enrolled (77 cases, 77 controls). Genomic DNA was isolated from FFPE cervical tumors (QIAamp DNA FFPE Tissue Kit) and genotyped using TaqMan allelic discrimination. Clinicopathological variables (FIGO stage, histology, grade, treatment, tumor-infiltrating lymphocytes [TILs]) were abstracted from records. Genotype distributions were compared by Pearson chi-square. Associations with clinicopathological features used chi-square/Fisher's exact as appropriate; ANOVA compared age across genotypes. Overall survival (OS) was estimated by Kaplan–Meier and compared with the log-rank test; mean OS with SE and 95% CI is reported. **Results:** Cases were predominantly locally advanced at presentation and squamous histology; most were moderately differentiated. rs6443624 differed significantly between cases and controls (χ^2=21.1, p<0.001), with CC over-represented in cases and CA less frequent. rs141178472 showed no significant case control difference (χ^2=2.9, p=0.086). For OS, rs6443624 showed a significant genotype effect (log-rank χ^2=23.45, p=0.001): AA had the poorest survival, CA the longest, CC intermediate. rs141178472 was not associated with OS (χ^2=1.06, p=0.588). Genotype clinicopathological correlations for stage group, grade, TILs, and treatment were non-significant or inconsistent, with some comparisons limited by small sample sizes. **Conclusion:** The PIK3CA rs6443624 variant appears to influence both susceptibility and prognosis in cervical cancer, highlighting its potential as a biomarker for molecular risk stratification. Validation in larger, multi-center cohorts incorporating HPV/p16 assessment and extended follow-up is warranted to confirm its clinical relevance.

Keywords: PIK3CA- cervical cancer- single-nucleotide polymorphism- rs6443624- survival analysis

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Introduction

Cervical cancer remains a major global health challenge, ranking as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related death among women worldwide, with approximately 660,000 new cases and 350,000 deaths reported in 2022 [1]. The burden is disproportionately higher in low- and middle-income countries (LMICs), which account for 88–90 % of cases and fatalities [2]. In India, GLOBOCAN 2020 estimated around 123,907 new cases and 77,348 deaths, corresponding to 20 % of global incidence and 22.6 % of global mortality [3]. The age-standardized incidence rate (ASIR) in India was noted to be approximately 18 per 100,000 women, exceeding many global averages. Invasive cervical carcinomas predominantly arise from the transformation zone, with squamous cell carcinoma accounting for 80–90 % of cases [4]. The median age at diagnosis for squamous cell carcinoma is typically between 51 and 58 years [5]. Established risk factors include early onset of sexual activity, multiple sexual partners, early age at first childbirth, prolonged oral contraceptive use, and persistent infection with high-risk human papillomavirus (HPV) types [5]. HPV infection is the central driver in cervical carcinogenesis, wherein oncogenic proteins E6, E7, and E5 disrupt the regulatory pathways governed by

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p53 and pRb, and facilitate immune evasion [6]. Beyond HPV, molecular alterations are pivotal in cervical cancer progression. Mutations in several cancer-related genes PIK3CA (approx. 40 %), KMT2D (26 %), KMT2C (26 %), LRP1B (14 %), and FBXW7 (13 %), mostly involve the PI3K-AKT pathway and contribute to oncogenesis [7, 8]. PIK3CA encodes the p110α catalytic subunit of PI3K, a key enzyme in the conversion of PIP2 to the second messenger PIP3, subsequently activating AKT and promoting proliferation and survival [9]. PIK3CA mutations feature in around 15 % of all human cancers [10]. Single nucleotide polymorphisms (SNPs) in the PIK3CA gene, especially in its miRNA regions, have been linked with susceptibility to cervical and precancerous lesions [11]. A large-scale study involving 1,402 participants identified two such SNPs rs107822 in miR-219a (C allele: OR = 1.29) and rs2292832 in miR-149 (C allele: OR = 0.77) demonstrating significant associations with cervical cancer risk [12]. Moreover, PIK3CA mutations are prevalent across populations; for example, among Chinese patients, mutation frequencies (~37 %) align closely with those observed in Caucasians (TCGA data), and are frequently accompanied by mutations in DNA repair genes like BRCA1/2 and TP53, as well as TERT and FGFR3 [13]. Such alterations have implications for treatment response, including chemoradiation resistance and tumor recurrence. The PI3K/AKT pathway also influences cancer metabolism, especially aerobic glycolysis and GLUT4-mediated glucose transport, further promoting oncogenic growth. However, the specific metabolic consequences of mutant PIK3CA in cervical cancer remain insufficiently explored [14]. In various cancers including breast, endometrial, colorectal PIK3CA mutations are frequent; in cervical cancer, they are implicated in resistance to cisplatin and radiotherapy, reducing treatment efficacy [15]. Given the advent of targeted therapies, identification of molecular subtypes becomes critical. PIK3CA inhibitors (e.g., buparlisib) are currently under clinical evaluation for cervical carcinoma across stages I–III, aiming to overcome PI3K-mediated treatment resistance [16]. Retrospective analyses of patients receiving concurrent chemoradiotherapy (CCRT) showed that PIK3CA mutations (~12 %) were associated with poorer cancer-specific and overall survival compared to wild-type counterparts [17]. While SNP rs6443624 has been associated with decreased cancer risk in bladder cancer and rs141178472 with increased colorectal cancer risk, data on these specific SNPs in cervical cancer especially in the Indian context are lacking [18]. This highlights a critical gap, which the present study seeks to address by examining the association between rs6443624 and rs141178472 in the PIK3CA gene with cervical cancer susceptibility and its clinical outcomes.

Materials and Methods

Study Setting and Design

This tertiary care hospital- and laboratory-based prospective observational case control study was conducted in the Department of Pathology, Lucknow, in collaboration with the Centre for Advanced Research, Department of Obstetrics and Gynaecology, Department of Medical Oncology, King George's Medical University (KGMU), Lucknow. The study was carried out over a period of one year. The research protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to enrolment.

Sample Size Calculation

A total of 154 subjects (77 cases and 77 healthy controls) were included. The sample size was estimated using the formula by Fleiss (Formula 3.19) as cited in Lin et al. (2014), considering a two-sided significance level (1-α) of 90%, a power (1-β) of 80%, a ratio of unexposed to exposed participants of 1:1, an outcome prevalence of 10% in the unexposed group and 25% in the exposed group, and an odds ratio of 3.07. The calculated total sample size was 154 participants.

Inclusion and Exclusion Criteria

Cases included histopathologically confirmed cervical cancer with adequate formalin-fixed paraffin-embedded (FFPE) tissue available for molecular analysis, who provided informed consent. Controls were age-matched healthy females with no history of malignancy. Patients refusing consent, those with concurrent malignancies, or those with inadequate tissue for molecular testing were excluded.

Clinical and Pathological Data Collection

For this prospective study, demographic details, clinical profiles, radiological findings, and liquid-based cytology results for cervical cancer cases were recorded at the time of patient enrolment. All cases underwent histopathological evaluation of cervical biopsy or surgical specimens in the Department of Pathology, King George's Medical University. FFPE tissue blocks obtained during routine diagnostic work-up were processed according to standard laboratory protocols. Portions of the remaining archived tissue were subsequently retrieved for molecular analysis.

DNA Extraction from FFPE Tissues

Genomic DNA was extracted from FFPE cervical tissue samples using the QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol, with optimization for FFPE material. Prior to DNA extraction, manual microdissection was performed under a stereomicroscope to selectively enrich tumor areas and minimize contamination from adjacent non-neoplastic tissue. Hematoxylin and eosin (H&E)-stained reference sections were reviewed by a pathologist to confirm the presence and proportion of tumor cells, and only samples with adequate tumor content were processed. Briefly, 1–8 tissue sections (5–15 μm thickness, 20–50 mm² area, ≤20 mg tissue) were placed in sterile microcentrifuge tubes, deparaffinized with xylene, and washed twice with 96–100 % ethanol. Samples were air-dried at 37 °C to remove residual ethanol. Tissue digestion was performed in ATL buffer with Proteinase K at 56 °C for 1-3 hours (or overnight) until complete

lysis, followed by a 90 °C incubation for 1 hour to reverse formalin cross-linking. After brief centrifugation, the lysate was mixed with AL buffer and ethanol, applied to QIAamp MinElute columns, and centrifuged to allow DNA binding. Columns were sequentially washed with AW1 and AW2 buffers, followed by an optional ethanol wash to remove residual salts. DNA was eluted in 50–60 µL of AE elution buffer. All centrifugation steps were performed at room temperature. DNA concentration and purity were measured using spectrophotometry prior to genotyping.

SNP Selection and Genotyping

Allelic discrimination for PIK3CA rs6443624 (A/C; Chr3:179,179,886, GRCh38) and PIK3CA rs141178472 (C/T; Chr3:179,234,393, GRCh38) was performed using TaqMan SNP Genotyping Assays (Thermo Fisher Scientific) on a real-time PCR platform. Custom VIC/FAM-labelled probes and proprietary primer sets supplied by the manufacturer were used. The reaction mixture (25 µL) contained 1.25 µL of 20× SNP Genotyping Assay Mix, 12.5 µL of 2× TaqMan Universal PCR Master Mix, 6.25 µL of nuclease-free water, and 5 µL of genomic DNA. The thermal cycling profile included: pre-read at 60 °C for 30 s, enzyme activation at 95 °C for 10 min, 40 cycles of denaturation at 95 °C for 15 s and annealing/extension at 60 °C for 1 min, followed by a post-read at 60 °C for 30 s. Real-time fluorescence data were recorded in each cycle. Genotype calls were assigned from allelic discrimination plots in the instrument software; samples with ambiguous clustering or no-calls were re-run. Internal controls and duplicate samples (≥5%) were included across plates. Call rate was ≥98%, with complete high-confidence genotypes retained for analysis.

Genotype Calling and Quality Control

Allelic discrimination plots were generated using the real-time PCR system's proprietary software, allowing clear distinction between homozygous wild-type, heterozygous, and homozygous variant genotypes. For each SNP, genotypes were categorized as homozygous wild-type (reference allele homozygote), heterozygous, and homozygous variant (alternate allele homozygote) according to GRCh38/dbSNP notation (rs6443624: A/C; rs141178472: C/T). Samples with ambiguous clustering or no amplification were re-tested to ensure accuracy. Final genotype calls included in the analysis were high-confidence, with complete genotype coverage achieved for all 154 participants.

Survival outcomes and analysis

The primary time-to-event endpoint was overall survival (OS), defined as the interval (in months) from diagnosis (or start of first-line therapy, when specified) to death from any cause; patients alive at last contact were censored on that date. Survival analyses were conducted in the subset with complete follow-up (n=73). Survival functions were estimated by Kaplan–Meier. In keeping with the reporting format of our results, we present KM mean OS with standard error (SE) and 95% confidence intervals (Greenwood's formula). Genotype groups were compared with log-rank (Mantel-Cox) tests within each SNP (three-group comparison: wild-type, heterozygous, homozygous variant). Where a genotype category contained very few patients (e.g., rs141178472 CC), results were interpreted cautiously.

Statistical analysis

Continuous variables were summarized as mean ± SD and categorical variables as counts (percentages). Case–control comparisons of genotype distributions (3×2 tables) were performed using Pearson's chi-square test; results are reported as χ^2 with two-sided p-values. Associations between genotype and clinicopathological features (e.g., FIGO stage group], histologic grade, tumor-infiltrating lymphocytes, primary treatment) were assessed using Pearson's chi-square for 3×k contingency tables; when any expected cell count was <5, Fisher's exact (Freeman–Halton) was used. Age across genotype strata was compared with one-way ANOVA. Survival endpoints included overall survival (OS) and progression-free survival (PFS), measured from diagnosis (or start of first-line therapy when applicable) to death/recurrence, with censoring at last contact. Survival functions were estimated by Kaplan–Meier; group differences by genotype were tested with the log-rank (Mantel–Cox) test. For presentation, KM mean survival with standard error (SE) and 95% confidence intervals (Greenwood's formula) are reported. Analyses used available cases (missing categories shown and excluded from hypothesis tests). All tests were two-sided with α=0.05. Statistical analyses were conducted using SPSS (v26) and R (v4.x).

Results

Baseline clinicopathological features are summarized in Table 1. The cohort's mean age was 56.6 years (SD 11.3), with most patients in the 50–59 and 60–69-year groups. Presentation was predominantly locally advanced (LACC 80.5%), led by stage IIB; early stages (IA–IB2) comprised 19.5%. All tumors were squamous cell carcinoma. Most were moderately differentiated, with well- and poorly differentiated tumors infrequent and one case of unknown grade. Treatment patterns reflected stage, with radiotherapy-based management most common, followed by Wertheim hysterectomy and cold conization. Tumor-infiltrating lymphocytes were mainly moderate (48.1%) or mild (41.6%), with dense infiltration in 10.4%.

Genotype–clinicopathological associations

As summarized in Table 2, rs6443624 showed a borderline association with FIGO stage (χ^2=5.66, p=0.0589), with AA skewed toward advanced disease (87.5% advanced) and CA more frequent in early stages (58.1% early). For rs141178472, the overall association with FIGO stage was significant (χ^2=7.86, p=0.0197); however, this pattern was driven by sparse strata (TC n=5, all early; CC n=2, all advanced) and should be interpreted cautiously. Neither SNP demonstrated a significant relationship with tumor-infiltrating lymphocytes (rs6443624: χ^2=4.51, p=0.3418; rs141178472: χ^2=3.85, p=0.4268) or with histologic grade.

Table 1. Baseline Clinicopathological Characteristics of Cases (n = 77)

Characteristic	Category	n	%
Age (years), mean ± SD	n=77	56.6 ± 11.3	
Age group (years)	30–39	6	7.8
	40–49	14	18.2
	50–59	30	39.0
	60–69	20	26.0
	70–79	4	5.2
	80–89	3	3.9
FIGO stage	IA	5	6.5
	IB1	7	9.1
	IB2	3	3.9
	IIA	20	26.0
	IIB	27	35.1
	IIIA	7	9.1
	IIIB	7	9.1
	IVA	1	1.3
Stage group	LACC	62	80.5
	ESCC	15	19.5
Histology	Squamous cell carcinoma	77	100
Histological grade	Well differentiated	6	7.8
	Moderately differentiated	69	89.6
	Poorly differentiated	1	1.3
	Unknown	1	1.3
Primary treatment modality	Radiotherapy-based	50	64.9
	Wertheim hysterectomy	10	13.0
	Other/Not specified	9	11.7
	Cold conization	8	10.4
Tumor-infiltrating	Mild	32	41.6
	Moderate	37	48.1
	Dense	8	10.4

Percentages are column values for each category. ESCC, early-stage cervical cancer; LACC, locally advanced cervical cancer.

Overall survival: OS analysis included 73 patients with 29 deaths (event rate ~40%). The overall Kaplan–Meier (KM) mean OS was 8.06 months (SE 0.47; 95% CI 7.14–8.98) (Table 3). For rs6443624, KM curves separated clearly across genotypes (log-rank χ^2=23.45, p=0.001, Figure 1). The AA group (n=7) experienced the highest mortality (100%) and the shortest mean OS (3.57 months, SE 0.53; 95% CI 2.53–4.61), with early and steep decline of the survival curve. The CA group (n=31) had the lowest mortality (29%) and the longest mean OS (9.24 months, SE 0.57; 95% CI 8.12–10.36). The CC group (n=35) was intermediate (mortality 37.1%; mean OS 8.08 months, SE 0.64; 95% CI 6.83–9.33). Confidence intervals for AA versus CA/CC were widely separated, indicating a materially worse outcome for AA; intervals for CA and CC overlapped, suggesting no clear difference between those two strata by KM means. For rs141178472, there was no significant difference in OS between genotypes (log-rank χ^2=1.06, p=0.588, Figure 2). Mean OS estimates were 7.98 months for TT (SE 0.49; 95% CI 7.02–8.94), 9.60 months for TC (SE 1.17; 95% CI 7.31–11.89), and 6.00 months for CC (SE 2.00; 95% CI 2.08–9.92). The very small numbers in TC (n=5) and CC (n=2) produced wide confidence intervals, and the survival curves largely overlapped, limiting inference. Together, these data indicate a significant genotype survival association for rs6443624 (driven by the poor outcomes in AA), whereas rs141178472 shows no discernible prognostic effect in this cohort (Table 3).

Discussion

Cervical cancer remains a leading cause of cancer mortality in low- and middle-income countries, despite the availability of organized screening and prophylactic HPV vaccination programs. In our cohort, most women presented with locally advanced disease, reflecting the persistent gaps in public awareness, screening uptake, and timely referral. This mirrors global disparities, where

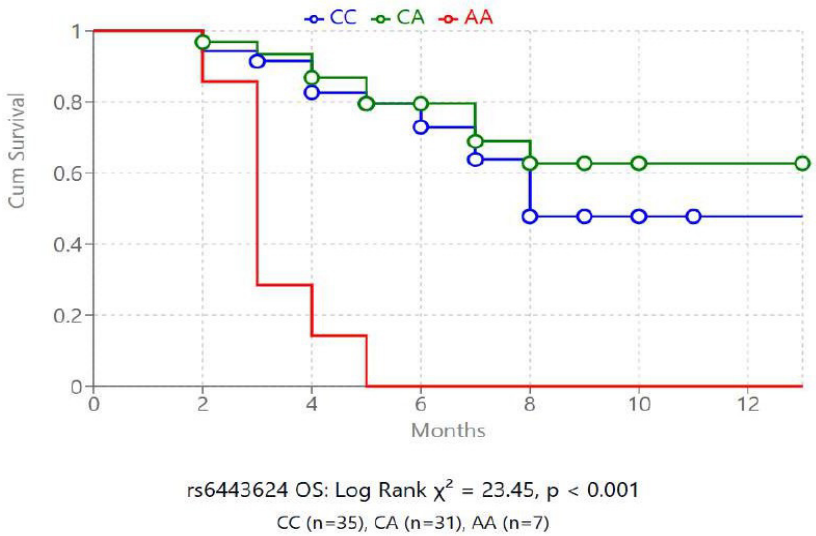

Figure 1. Overall Survival by PIK3CA rs6443624 Genotype (Kaplan–Meier). Kaplan–Meier curves for overall survival (months) stratified by rs6443624 genotypes: CC (blue), CA (green), AA (red). Analysis set: n=73 (CC=35, CA=31, AA=7); events=29. Group comparison by log-rank (Mantel–Cox): χ^2=23.45, p < 0.001, showing a significant difference in OS across genotypes

Table 2. Combined Genotype Distribution Across Clinicopathological Features

SNP	Clinicopathological feature	Genotype	Breakdown (n, row %)	χ^2 (p-value)
rs6443624	FIGO stage (Early I–IIA vs Advanced IIB–IV)	CC	Early 16 (42.1%); Advanced 22 (57.9%)	5.66 (0.0589)
		CA	Early 18 (58.1%); Advanced 13 (41.9%)	
		AA	Early 1 (12.5%); Advanced 7 (87.5%)	
rs141178472	FIGO stage (Early I–IIA vs Advanced IIB–IV)	TT	Early 30 (42.9%); Advanced 40 (57.1%)	7.86 (0.0197)
		TC	Early 5 (100.0%); Advanced 0 (0.0%)	
		CC	Early 0 (0.0%); Advanced 2 (100.0%)	
rs6443624	Tumor-infiltrating lymphocytes (TIL)	CC	Mild 18 (46.2%); Moderate 17 (43.6%); Dense 4 (10.3%)	4.51 (0.3418)
		CA	Mild 13 (41.9%); Moderate 16 (51.6%); Dense 2 (6.5%)	
		AA	Mild 1 (14.3%); Moderate 4 (57.1%); Dense 2 (28.6%)	
rs141178472	Tumor-infiltrating lymphocytes (TIL)	TT	Mild 29 (41.4%); Moderate 34 (48.6%); Dense 7 (10.0%)	3.85 (0.4268)
		TC	Mild 3 (60.0%); Moderate 1 (20.0%); Dense 1 (20.0%)	
		CC	Mild 0 (0.0%); Moderate 2 (100.0%); Dense 0 (0.0%)	
rs6443624	Histologic grade (WD/MD/PD)	CC	WD 4 (10.3%); MD 35 (89.7%); PD 0 (0.0%)	2.49 (0.6463)
		CA	WD 2 (6.7%); MD 27 (90.0%); PD 1 (3.3%)	
		AA	WD 0 (0.0%); MD 7 (100.0%); PD 0 (0.0%)	
rs141178472	Histologic grade (WD/MD/PD)	TT	WD 5 (7.2%); MD 63 (91.3%); PD 1 (1.4%)	5.44 (0.2451)
		TC	WD 0 (0.0%); MD 5 (100.0%); PD 0 (0.0%)	
		CC	WD 1 (50.0%); MD 1 (50.0%); PD 0 (0.0%)	

p-values from Pearson χ^2 tests on the full contingency table for each SNP-feature block. Row percentages are calculated within genotype rows.

implementation of preventive strategies remains uneven. The World Health Organization's Global Strategy for Cervical Cancer Elimination ("90-70-90" by 2030) targets 90% vaccination coverage among girls by age 15 years, screening of 70% of women at least twice by age 45 years, and appropriate treatment for 90% of those diagnosed, emphasizing the urgent need to strengthen prevention and early detection initiatives [19]. Among 77 histologically confirmed cases and 77 healthy controls, the age distribution skewed to middle-older adulthood (mean 56.6 ± 11.3 years), with >80% postmenopausal, and the majority staged as IIB–IIIA at diagnosis. Tumors were predominantly squamous cell carcinoma and moderately differentiated. These patterns echo prior reports from India and other resource-constrained settings, where late presentation is common [20, 21] and contrast with cohorts from developed settings reporting higher proportions of early-stage disease [22].

At the genetic level, we observed a marked case-control difference in PIK3CA rs6443624: CC was enriched among cases (50.6% vs 20.8%), CA was depleted (40.3% vs 76.6%), and AA was infrequent (9.1% vs 2.6%), yielding a

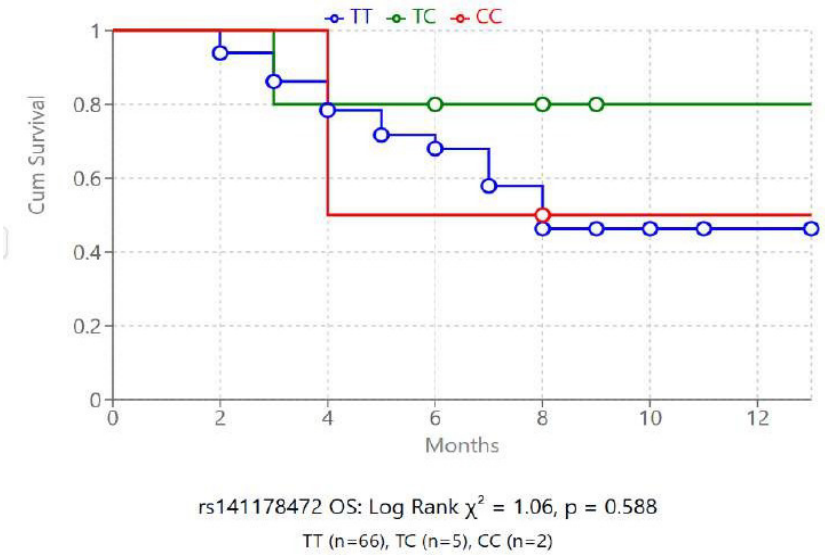

Figure 2. Overall Survival by PIK3CA rs141178472 Genotype (Kaplan–Meier). Kaplan–Meier curves for overall survival (months) stratified by rs141178472 genotypes: TT (blue), TC (green), CC (red). Analysis set: n=73 (TT=66, TC=5, CC=2); events = 29. Group comparison by log-rank (Mantel–Cox): $\chi^2 = 1.06$, p = 0.588, indicating no significant difference in OS among genotypes

Table 3. Overall Survival by PIK3CA Genotypes (Kaplan–Meier), with Log-Rank p-values

SNP	Genotype	Total (n)	Events (n)	Mortality %	Mean OS (months)	SE	95% CI	Log-rank χ^2 (p)
rs6443624	AA	7	7	100	3.57	0.53	2.53–4.61	23.45 (0.001)
	CA	31	9	29	9.24	0.57	8.12–10.36	
	CC	35	13	37.1	8.08	0.64	6.83–9.33	
rs141178472	TT	66	27	40.9	7.98	0.49	7.02–8.94	1.06 (0.588)
	TC	5	1	20	9.6	1.17	7.31–11.89	
	CC	2	1	50	6	2	2.08–9.92	
Overall (all genotypes)	—	73	29	39.7	8.06	0.47	7.14–8.98	—

Mean OS and SE are Kaplan–Meier estimates. P-values are from log-rank (Mantel–Cox) tests comparing genotypes within each SNP. The log-rank χ^2 (p) is shown once per SNP.

highly significant overall comparison (χ^2=21.1, p<0.001). By contrast, rs141178472 showed no significant overall case-control difference (χ^2=2.9, p=0.086), consistent with a low minor-allele frequency in our population. Clinicopathologic correlations (stage group, grade, TIL category, and treatment) did not show robust, reproducible signals after accounting for small cell sizes; exploratory stage differences for rs141178472 were driven by sparse strata and should be interpreted with caution. In survival analyses, rs6443624 genotypes differed significantly for OS (log-rank χ^2=23.45, p=0.001). Patients with AA had the poorest outcomes (mean OS 3.6 months, 95% CI 2.5–4.6), whereas CA and CC showed longer OS (~9.2 and 8.1 months, respectively). For rs141178472, OS did not differ significantly across genotypes (log-rank χ^2=1.06, p=0.588), likely limited by very small TC/CC strata (n=5 and n=2). The survival analysis was based on short-term follow-up data, which may not fully capture long-term survival differences or late recurrence patterns. Extended longitudinal follow-up would provide a more definitive assessment of prognostic significance.

Our observations are directionally consistent with the established role of PIK3CA in cervical carcinogenesis and treatment response. Large genomic studies identify PIK3CA among the most frequently altered genes in cervical cancer, with pathway activation linked to oncogenic signaling and therapeutic resistance [23]. In real-world cohorts, PIK3CA mutations have correlated with inferior survival or radio-chemoresistance; for example, Lachkar et al. reported poorer cancer-specific survival in mutated vs wild-type tumors [24] and Martell et al. associated PIK3CA mutation with worse OS in univariate analysis [24]. In a Chinese series evaluating genomic correlates of neoadjuvant therapy response, PIK3CA alterations were common and co-amplification with SOX2 associated with relapse [22]. Separately, Akt-pathway SNPs (e.g., rs4558508, rs1130233, rs7259541) have been linked to chemoresistance, highlighting the broader PI3K/Akt axis in treatment outcomes [25]. Histology-specific trends are also reported, Liu et al. found higher PIK3CA mutation frequency in SCC vs adenocarcinoma aligning with our SCC-predominant cohort [26].

Biologically, PI3K pathway activation promotes proliferative signaling and survival, mediates glucose metabolism reprogramming, and has been implicated in cisplatin and radio resistance [27, 28]. These mechanisms plausibly underlie the worse OS among rs6443624 AA carriers in our series and support ongoing trials of PI3K inhibitors in cervical cancer [29]. If validated, rs6443624 could serve as a prognostic marker and aid risk-stratification for patients receiving standard chemoradiation. Given emerging data on PI3K/Akt inhibitors, genotype-informed enrolment in trials may help identify subgroups that benefit from pathway blockade. Conversely, rs141178472 does not appear to be prognostically informative in our cohort, though power was limited by rare variant counts. While the association of rs6443624 with disease susceptibility and survival appears robust, other genotype–phenotype correlations should be interpreted cautiously given the small subgroup sizes. These exploratory observations nevertheless provide useful direction for hypothesis-driven future work.

Limitations:

This study has few limitations. It was conducted at a single tertiary-care center with a modest sample size, which may have limited the statistical power to detect weaker associations, particularly for the less frequent rs141178472 genotypes. The absence of HPV testing represents a key limitation, as HPV status is a major etiological factor in cervical cancer and could not be included in adjusted analyses. Short follow-up duration restricts interpretation of long-term survival trends, and potential confounding from treatment heterogeneity or stage variation cannot be excluded. Future multi-center studies incorporating HPV genotyping or p16 immunohistochemistry, comprehensive molecular profiling (including tumor mutational burden and immune parameters such as TILs), and longer follow-up are warranted to validate and expand upon these findings.

In conclusion, this prospective case–control study identified a significant association between the PIK3CA rs6443624 polymorphism and cervical cancer susceptibility, with the homozygous variant genotype linked to poorer overall survival. In contrast, rs141178472 showed no consistent association with disease risk or prognosis. No meaningful correlations were observed between genotype and clinicopathological features such as stage, histologic grade, or tumor-infiltrating lymphocytes, and most patients presented with locally advanced disease, reflecting persisting challenges in early detection. These findings suggest that rs6443624 may

serve as a potential biomarker for risk assessment and prognostic stratification, reinforcing the oncogenic role of PI3K pathway dysregulation in cervical carcinogenesis. However, the study's single-center design, modest sample size, limited follow-up, and absence of HPV data warrant cautious interpretation. Validation in larger, multicentric cohorts with integrated HPV/p16 assessment, extended follow-up, and molecular profiling is essential to confirm the clinical applicability of PIK3CA variants and to inform personalized therapeutic strategies targeting the PI3K pathway.

Author Contribution Statement

Harshi Srivastava, Shivanjali Raghuvanshi, Shalini Bhalla, Nitu Nigam: contributed to conceptualization, data curation, statistical analysis, writing original draft preparation; Shivanjali Raghuvanshi, Shalini Bhalla, Snehkiran Raghuvanshi: funding acquisition; supervision, data collection and analysis, and manuscript review and editing. Harshi Srivastava, Shivanjali Raghuvanshi, Shalini Bhalla, Alok Singh, Ajay Singh, Nisha Singh; clinical samples: Nisha Singh

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If any scientific Body approved it/ if it is part of an approved student thesis

Study was approved by the isntitutional ethics committee of the institute.

Availability of data (if applicable to your research)

Data will be available on request from corresponding author.

How the ethical issue was handled (name the ethical committee that approved the research)

Study protocol was approved by the institutional ethics committee of the King George's Medical University, Lucknow wide approval number 1379/Ethics/2023 dated 05/09/2023 (Ref. Code: XIX-PGTSC-IIA/P53)

Any conflict of interest

None.

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