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L1CAM Is Not a Predictive Factor in Early-stage Squamous-cell Cervical Cancer

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Abstract. *Aim: Our study aimed to assess expression of L1 cell adhesion molecule (L1CAM) in early-stage cervical squamous-cell cancer as a prognostic factor. Patients and Methods: This retrospective, single-institution study included 154 patients who underwent radical hysterectomy for early-stage squamous cell cervical cancer between 2007 and 2017. Tumor samples from 154 patients were available for L1CAM analysis by immunohistochemistry. Among all patients, radical abdominal hysterectomy was performed in 144 cases. Results: L1CAM expression was positive in 24 tumors (15.6%) of the whole group. In relation to the grade of differentiation and the presence of lymphovascular invasion, L1CAM expression did not show an association (p=0.154 and p=0.306, respectively). The disease-free interval and overall survival also did not significantly differ between L1CAM-positive and L1CAM-negative cases (p=0.427 and p=0.240, respectively). For histopathological characteristics, L1CAM-positive cases had a significantly higher median tumor size (p=0.015). Even in the selected group of 115 cases without nodal infiltration, L1CAM status had no effect on the relapse rate during follow-up. Conclusion: Our study did not confirm the results of previous studies showing L1CAM expression to be a negative prognostic factor in cervical cancer. In our study, increased L1CAM expression in early-stage squamous-cell cervical cancer was not associated with adverse prognosis regarding disease recurrence, disease-free survival, nor overall survival. L1CAM expression was correlated only with the size of the tumor.*

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According to the World Health Organization, cervical cancer (CC) is the third most common malignant disease in women, and its incidence and mortality are increasing worldwide. In 2018, about 570,000 cases were diagnosed, and 311,000 women died. The incidence is often higher in developing countries (1, 2). The main histological subtype is squamous-cell carcinoma, comprising around 80%. Other histological subtypes are rare (2).

CC is a disease caused predominately by human papillomavirus infection. The persistence of human papillomavirus infection is the most potent risk factor (especially its high-risk variants). Treatment planning follows the European Society of Gynecological Oncology, the European Society for Radiotherapy and Oncology, and the European Society of Pathology recommendations based on knowledge of prognostic factors. For the early stages of CC, surgery with varying degrees of radicality is the primary treatment. Fertility-sparing surgery can be considered for patients with incomplete fertility plans. For advanced stages, prior radiotherapy or chemotherapy is indicated (3).

Generally known prognostic factors are tumor size, lymphovascular space invasion (LVSI), extra-cervical spread of disease, and histological type (3). However, these factors

Table I. *Patient characteristics (n=154) according to expression of L1 cell adhesion molecule (L1CAM).*

		L1CAM*		
		Positive (n=24)	Negative (n=130)	*p*-Value
Stage#, n (%)	pT1a	0 (0.0)	11 (8.5)	0.455[a]
	pT1b	21 (87.5)	102 (78.5)	
	pT2a	3 (12.5)	17 (13.0)	
Diameter, mm	Median (IQR)	27.5 (22.8-34.3)	20.0 (10.0-30.0)	**0.015**[b]
	<20	4 (16.7)	57 (43.8)	
	20-40	18 (75.0)	56 (43.1)	
	≥40	2 (8.3)	17 (13.1)	
Grade, n (%)	1	2 (8.3)	31 (23.8)	0.154[a]
	2	15 (62.5)	76 (58.5)	
	3	7 (29.2)	22 (16.9)	
	Unknown	0 (0.0)	1 (0.8)	
LVSI, n (%)	Yes	7 (29.2)	54 (41.5)	0.306[a]
	No	17 (70.8)	72 (55.4)	
	Unknown	0 (0.0)	4 (3.1)	
Recurrence, n (%)	Yes	5 (20.8)	20 (15.4)	0.728[a]
	No	19 (79.2)	109 (83.8)	
	Unknown	0 (0.0)	1 (0.8)	

IQR: Interquartile range; LVSI: lymphovascular space invasion. [a]Chi-square test of independence or Fisher's exact test; [b]Mann-Whitney test. Statistically significant *p*-values are shown in bold. *Cases were classified as L1CAM-positive when over 10% of tumor cells were positively stained. #Eighth edition of the TNM classification, 2016.

are not specific. To date, no specific molecular marker associated with higher incidence of relapse and mortality in patients with CC has been established. Consequently, current research is aimed at finding a specific molecular marker, detectable in serum or tumor tissue, to help define patients with a high risk of early recurrence and metastasis.

Adhesion molecules are transmembrane glycoproteins that mediate connection and communication both between cells and between cells and their intercellular matrix. They are activated by an external signal that changes their structure. The signal is transmitted through the cytoplasmic membrane to inside the cell nucleus, and subsequently regulates changes in the cytoskeleton, gene transcription, and cell differentiation. The L1 cell adhesion molecule (L1CAM) belongs to the family of immunoglobulin-like molecules and is physiologically involved in the development and plasticity of the nervous system (4-8).

Pathological *de novo* expression of L1CAM in tumor cells activates the epithelial–mesenchymal transition (EMT) and increases malignant cell motility, invasiveness and tumor angiogenesis. Ultimately, it contributes to the process of metastasis and leads to chemoresistance (9-13). EMT is a multistep morphological process during which static epithelial cells lose intercellular junctions and apicobasal polarity. They turn into mesenchymal cells capable of migration. EMT is triggered by L1CAM binding to cell receptors of the so-called canonical Wingless/Int-1 (WNT)/β-catenin signaling pathway. The WNT protein changes the conformation of the surface receptor Frizzled. With the participation of other cofactors, the sequestration of β-catenin in the cytosol is inhibited through ubiquitination and proteasomal degradation. Subsequently, β-catenin accumulates in the cytosol, is translocated to the nucleus, and affects nuclear gene transcription. This the strongly deregulated activation of the canonical WNT/β-catenin signaling pathway is considered the initial event in carcinogenesis (14-16).

Historically, L1CAM was first mentioned in oncology as a strong prognostic factor for developing metastases in malignant melanoma (17, 18). Subsequent studies presented L1CAM expression in several other tumor types (*e.g.*, colorectal cancer, kidney cancer, pancreatic cancer, and others) as a molecule associated with an unfavorable prognosis (19-21).

Table II. *Recurrence type according to expression of L1 cell adhesion molecule (L1CAM) (n=25 patients with recurrence).*

	L1CAM	
Recurrence, n (%)	Positive (n=5)	Negative (n=20)
Isolated	1 (20.0)	7 (35.0)
Multiple	4 (80.0)	11 (55.0)
Unknown	0 (0.0)	2 (10.0)
Distant	2 (40.0)	2 (10.0)
Pelvic	1 (20.0)	10 (50.0)
Both	2 (40.0)	8 (40.0)

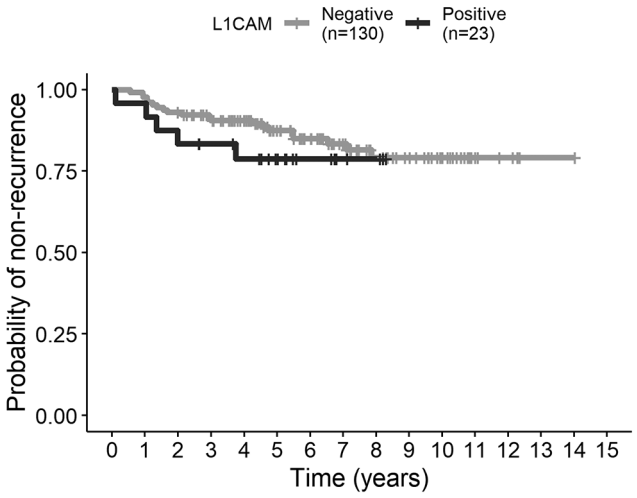

Figure 1. *Kaplan-Meier curves displaying the estimated probability of non-recurrence according to L1 cell adhesion molecule (L1CAM) positivity considering all patients. In patients without recurrence, the time to the last follow-up visit or to death was considered. Recurrence data for one L1CAM-negative case were unknown. No significant difference was found in survival without recurrence between L1CAM-positive and -negative patients (log-rank test, p=0.427).*

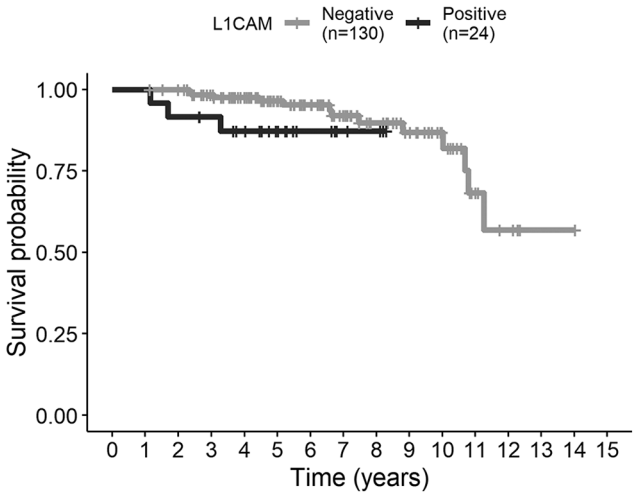

Figure 2. *Kaplan-Meier curves displaying the estimated probability of overall survival according to L1 cell adhesion molecule (L1CAM) positivity considering all patients. The time to last follow-up visit or to death was considered. No significant difference was found in survival between L1CAM-positive and -negative cases (log-rank test, p=0.240).*

Concerning gynecological oncology, several works confirmed the negative predictive influence of L1CAM in endometrial cancer (22-27). However, only a few studies have so far dealt with the survey of L1CAM expression in CC (28-30). Our study aimed to analyze L1CAM expression in a cohort of patients with squamous-cell CC and to clarify its prognostic value.

Patients and Methods

This was a retrospective, single-institution study that included 154 patients diagnosed with squamous-cell CC who underwent surgery and follow-up at the Gynecologic Oncology Centre of University Hospital Ostrava between 2007 and 2017. All included patients had preoperative International Federation of Obstetrics and Gynecology (FIGO) stage I and IIa (2018 FIGO classification) (31).

Patients with other histological types of tumors were excluded from the study. This study was approved by the local Ethics Committee (approval number 400/2020). We enrolled 154 patients aged 26-81 years, including 134 diagnosed with FIGO stage I disease and 20 patients with stage IIa. The cohort grading distribution was 33 tumors of grade 1, 91 of grade 2, and 29 of grade 3. The majority of tumors measured more than 2 cm (n=93), and LVSI occurred in patients with 61 tumors (Table I). Radical abdominal hysterectomy was performed in a total of 144 patients, the rest of the patients underwent a minimally invasive surgery.

After surgery, patient follow-up consisted of clinical examination, blood sampling, and ultrasound examination. When recurrence was suspected, another imaging method was added, and the focus was confirmed by biopsy.

Clinic visits were performed every 3 months for the first 2 years, every 6 months until the fifth year, and annually until the end of follow-up. Local or distant recurrences were defined as the appearance of histologically or radiologically proven malignant tissue. The cases where this follow-up was not performed were excluded from the database.

The median total length of follow-up of the patients from surgery to the end of the study was 70 months (range=30-171 months), and 19 patients died. The cases where this follow-up was not performed were excluded from the database (n=4).

Recurrence occurred in 25 patients with local pelvic metastases, distant metastases, or combined metastatic processes (in 12, 4 and 10, respectively) (Table II).

Pathological processing. The immunohistochemical procedure used was initially described by Bosse *et al*. (22). Immunohistochemical evaluation of L1CAM and scoring were performed by only one experienced pathologists dedicated for this study. Only unequivocal membranous staining was considered specific. A case was classified as L1CAM-positive when over 10% of tumor cells were positively stained (27).

Statistical processing. Quantitative variables are described as medians and interquartile ranges (lower and upper quartiles); qualitative variables are presented as absolute and relative frequencies (%). Between-group differences were analyzed with the chi-square test of independence for contingency tables, Fisher's exact test, or Mann-Whitney test. Kaplan-Meier curves and the log-rank test were used for analysis of overall survival (time from the primary surgery to the death or the last follow-up visit) and disease-free survival (time from the primary surgery to recurrence,

the last follow-up visit or death). The significance level was set at 0.05 and statistical analysis was performed using R software (version 4.2.3).

Results

A total of 196 eligible patients were identified, but it was impossible to analyze histopathological samples from 42 cases; thus, the final number of patients included was 154. Of the 154 patients, L1CAM expression was positive in 24 tumors (15.6%). A significantly higher median tumor size was found in L1CAM-positive cases (p=0.015). In contrast, L1CAM expression did not affect the degree of differentiation nor the presence of LVSI (p=0.154 and p=0.306, respectively) (Table I).

In our cohort, recurrence occurred in 25 cases, of which five were L1CAM-positive and 20 were L1CAM-negative; there was no difference between these two groups (p=0.728). L1CAM positivity did not affect the character of relapse (pelvic or distant) or the number of relapses (isolated or multiple) (Table II).

In the statistical analysis, we selected a group of 115 cases without nodal infiltration (74.7%). During follow-up, 14 patients experienced relapse but only two of these patients were L1CAM-positive (14.3%). Among cases without relapse, we found L1CAM positivity in 14 (14%). Regarding L1CAM expression, there was no significant difference in relapse during follow-up in this selected group (p>0.999). Finally, we did not note a significant difference between L1CAM-positive and -negative groups in disease-free survival (p=0.427), nor in overall survival (p=0.240) (Figure 1 and Figure 2). In the patients who underwent radical abdominal hysterectomy, L1CAM expression also did not influence disease recurrence.

Discussion

In our work, we focused on studying L1CAM protein expression in patients with early-stage squamous-cell CC and its influence on the prognosis. We included 154 patients with preoperative FIGO stage I and IIa disease who underwent surgery and subsequent follow-up visits at the Gynecological Oncology Center of the University Hospital of Ostrava.

Our results showed that the disease-free and overall survival did not differ significantly between the L1CAM-negative and L1CAM-positive groups (p=0.427 and p=0.240, respectively). Based on the result of the Laparoscopic Approach to Cervical Cancer trial, which showed worse survival in patients who underwent radical hysterectomy by a minimally invasive approach, and to avoid this potential bias, we recalculated DFI and overall survival only for patients who underwent radical hysterectomy by an open approach (32). Even in the group treated with radical abdominal hysterectomy only, L1CAM expression did not affect the incidence of recurrence.

In contrast to our research, all previous studies showed L1CAM positivity in patients with CC to be associated with more aggressive tumor form, more frequent recurrence, and worse disease-free survival.

Schrevel *et al*. presented their results in 2017, with the most extensive cohort of 372 patients. Overall, 21% of patients were L1CAM-positive (n=80). During the observation period (median=88 months), they confirmed the association of increased expression of L1CAM with shorter disease-free interval (p=0.017). This association was even stronger in patients not treated with adjuvant radiotherapy (n=185, p=0.004) (27).

In 2020, Carvalho *et al*. published the results of a retrospective observational study with only 71 patients, where L1CAM-positive tumors made up 28.2% (n=20). This study confirmed a worse disease-free interval in L1CAM-positive patients, with an average of 137.1 months *versus* 184.8 months, respectively (p=0.032). The median length of follow-up was 66.2 months. However, the overall survival of the patients was not significantly different (p=0.220) (29).

Finally, Elfeky *et al*., at the beginning of 2021, presented the results of a prospective study with only 62 patients. The increased expression of L1CAM was confirmed in 24 patients (38.7%). There was a significantly positive association between patient mortality and L1CAM level (19.5 times higher mortality in the L1CAM-positive group) (30).

In our cohort, concerning the tumor pathological characteristics, only tumor size as a known prognostic factor for squamous-cell carcinoma was related to L1CAM expression – L1CAM-positive cases had a higher median tumor size. We did not find such a relationship with LVSI. Although the majority of tumors presented intermediate or poor differentiation, this did not reflect significantly in L1CAM expression either.

One strength of our present study was that it included an unselected cohort of patients who underwent treatment at a tertiary care center, following a standardized surgical technique and regular follow-up. Moreover, we focused only on squamous-cell histology. A weakness of our study was its retrospective design and the small number of recurrences. As in all studies focusing on cancer with limited malignant potential, we faced the statistical dilemma of calculating survival rates based on a limited number of disease-specific events during follow-up.

Conclusion

In conclusion, regarding disease-free and overall survival, and recurrence, our data do not follow the findings of previous studies on L1CAM expression in CC. In contrast to previous studies, we observed L1CAM expression in patients with squamous-cell carcinoma. Our study did not confirm the hypothesis that L1CAM expression of tumor is a

negative prognostic factor for metastatic involvement and early disease recurrence in patients with squamous-cell CC.

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Conflicts of Interest

None of the Authors has any conflicts of interest to declare.

Authors' Contributions

JK designed the research study. VJ and VL, and MR performed the research. MR and JK analyzed the data. MR wrote the article. AK performed the statistical analysis and analyzed the data. All Authors read and approved the final article.

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