Prognostic significance of L1CAM in cervical cancer: A narrative review

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Cervical cancer remains a major contributor to cancer-related mortality among women worldwide, despite substantial progress in prevention and treatment strategies. While established prognostic factors such as tumor size, lymphovascular space invasion, and nodal status guide clinical decision-making, they lack sufficient specificity for individualized risk stratification. Consequently, there remains an unmet need for robust biomarkers capable of reliably predicting recurrence and treatment response. L1 cell adhesion molecule (L1CAM), a neural adhesion protein implicated in epithelial–mesenchymal transition (EMT), tumor invasion, and metastasis, has emerged as a candidate prognostic marker in several solid tumors, including gynecologic malignancies. Its role in cervical cancer, however, remains insufficiently defined. This narrative review synthesizes preclinical evidence and clinical studies evaluating L1CAM expression in cervical cancer, with an emphasis on its biological rationale, methodological challenges, and prognostic significance across different disease contexts. Data from early-stage and from locally advanced disease were critically appraised. Most early-stage studies have not demonstrated an independent prognostic effect of L1CAM, although associations with adverse histopathological features have been reported. In contrast, recent multicenter evidence suggests that high-level L1CAM expression (≥50%) may predict inferior pelvic control in patients undergoing chemoradiotherapy, underscoring a potential context-dependent prognostic role. Current evidence emphasizes the need for standardized immunohistochemistry protocols, prespecified positivity thresholds, and integration of L1CAM assessment with other. Prospective, adequately powered studies are essential to validate L1CAM as a clinically actionable biomarker and to determine whether its incorporation into prognostic models can enhance treatment personalization in cervical cancer.

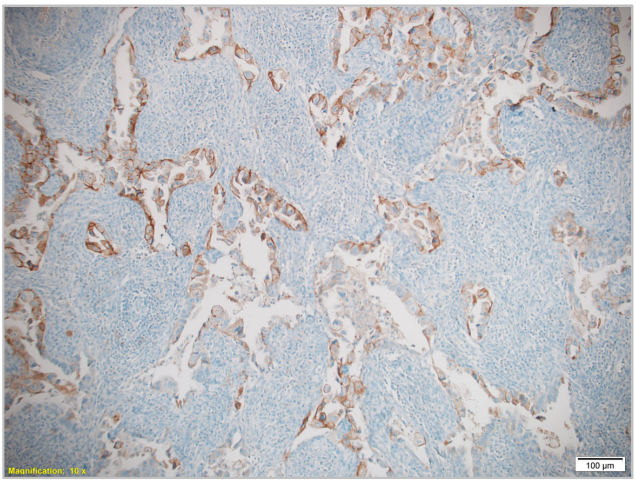
PROGNOSTIC SIGNIFICANCE OF L1CAM IN CERVICAL CANCER: NARATTIVE REVIEW

Cervical cancer remains a major contributor to cancer-related mortality among women worldwide, despite substantial progress in prevention and treatment strategies.

The identification of reliable serum- or tissue-based biomarkers capable of predicting early recurrence and metastatic potential remains a critical unmet need in cervical cancer management.

L1CAM has emerged as a promising candidate due to its mechanistic involvement in epithelial–mesenchymal transition and its established association with adverse clinical outcomes across multiple malignancies.

Current evidence does not yet support the validation of L1CAM as an independent prognostic biomarker in cervical cancer. However, a context-dependent prognostic signal has been observed in locally advanced disease treated with concurrent chemoradiotherapy and MRI-guided brachytherapy, particularly when a ≥50% expression threshold is applied.



To enable clinical implementation, rigorous validation in prospective, adequately powered, stage-specific studies is required – employing standardized immunohistochemical protocols, predefined clinical endpoints, and integrated assessment of PD-L1/p16 status.
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INTRODUCTION

Cervical cancer (CC) is the fourth most common malignancy among women. Incidence and mortality display divergent trajectories – rising steadily in low- and middle-income countries, yet falling sharply in settings with effective screening and vaccination programmes[1,2].

Persistent infection with high-risk human papillomavirus (HPV) remains the principal driver of disease; additional contributors include multiple sexual partners, early sexual debut (coitarche), smoking (including passive exposure), co-infections (e.g. *Chlamydia trachomatis*, HIV), and immunosuppression[2,3].

Management is typically delivered by multidisciplinary teams in line with international recommendations[4,5]. Early-stage disease is primarily managed surgically, whereas advanced stages are treated with radiotherapy, chemotherapy, chemoradiotherapy, immunotherapy, or palliative approaches. Established prognostic factors included in TNM/FIGO staging (tumour size, extracervical spread, nodal involvement) lymphovascular space invasion (LVSI) and histological type, though none provides the full picture.

The identification of reliable serum- or tissue-based biomarkers capable of predicting early recurrence and metastatic potential remains a critical unmet need in cervical cancer management. L1CAM has emerged as a promising candidate due to its mechanistic involvement in epithelial–mesenchymal transition and its established association with adverse clinical outcomes across multiple malignancies.

L1 cell adhesion molecule (L1CAM, CD171)

L1CAM is a transmembrane adhesion molecule of the immunoglobulin superfamily that mediates cell-cell and cell-matrix adhesion and transduces extracellular signals, thereby orchestrating cytoskeletal dynamics, gene expression, and differentiation[6,7]. Physiological roles span neural development and plasticity, embryogenesis, cell differentiation, and maintenance of tissue integrity[6,7]. In tumours, de novo expression sets off multiple signalling cascades – most notably canonical Wnt/β-catenin –promoting EMT, angiogenesis, migration, invasion, and ultimately contributing to metastasis and treatment resistance[8-12]. L1CAM also shapes cytoskeletal architecture and regulates the expression of other adhesion molecules, thus paving the way for invasion[6,7].

Epithelial-mesenchymal transition (EMT)

EMT is a multistep process in which epithelial cells lose polarity and intercellular junctions, adopt a spindle-like morphology, and acquire migratory potential[13,14]. Hallmarks include suppression of E-cadherin and nuclear accumulation of β-catenin, which in turn switches on transcription of genes driving proliferation and invasiveness (e.g. c-MYC, CCND1/Cyclin D1, MMP family) (ref.[13-16]).

L1CAM in oncology

L1CAM was first implicated in malignant melanoma as a strong predictor of metastasis[15]. Since then, it has repeatedly been linked to poor prognosis across multiple solid tumours[6,16]. In gynaecological oncology, it is most extensively studied in endometrial carcinoma, where L1CAM marks out a high-risk subgroup[17]. In contrast, investigations exploring the prognostic significance of L1CAM in cervical cancer remain scarce and insufficiently characterized.

NARRATIVE REVIEW

Data extraction and synthesis

Two reviewers independently screened and extracted study characteristics and outcomes; discrepancies were resolved by discussion. Given the considerable heterogeneity of available data, we opted for a narrative synthesis.

PROGNOSTIC SIGNIFICANCE OF L1CAM IN CERVICAL CANCER

Early-stage surgery cohorts

Across early-stage, surgically managed cohorts, results are mixed and largely point towards the absence of an independent prognostic effect of L1CAM. After an initial retrospective signal suggesting increased risk of locoregional relapse[18], subsequent studies failed to replicate an adverse impact on Disease Free Survival (DFS)/ Overall Survival (OS) or recurrence – including a 154 patients squamous-cell carcinoma series managed surgically[19] and a 35-patient HPV-associated adenocarcinoma/adenosquamous cohort[20]. In a stage IB cohort, L1CAM expression was more frequent in adenocarcinomas than in squamous histotypes and correlated with larger tumours and inferior DFS, albeit without an independent effect on OS (ref.[21]). Taken together, the early-stage literature does not support L1CAM as a stand-alone prognostic marker.

Locally advanced disease

In the multicentre BIOEMBRACE cohort (n=264) of locally advanced cervical cancer treated with concurrent chemoradiotherapy and MRI-guided brachytherapy (CRT/MRI-IGBT), high-level L1CAM expression (≥ 50%) was independently associated with inferior pelvic control (HR 5.5; 95% CI 1.3–23.3; P=0.02) (ref.[22]). By contrast, PD-L1 > 1% predicted worse local control, while p16 negativity and MRI-defined tumour necrosis were linked to poor response at brachytherapy[22]. These findings suggest that both treatment context (CRT/MRI-IGBT in LACC) and the positivity threshold (≥ 50% vs. ≥ 10%) critically shape the observed prognostic role of L1CAM.

Methodological sources of heterogeneity

Observed discrepancies most likely stem from methodological heterogenity: stage composition and treatment context (early surgery vs. CRT/MRI-IGBT), IHC antibody clone and platform, pre-analytical handling, and positivity thresholds (≥ 10% vs. ≥ 50%) (ref.[17-22]), as well as whether scoring emphasises the invasive front. Standardised IHC protocols and prespecified cut-offs val-

ues are essential prerequisites for validation across different clinical settings.

DISCUSSION

Summary of evidence

Overall, the body of evidence points to a context- and cut-off–dependent prognostic signal for L1CAM. Early-stage surgical cohorts do not consistently demonstrate an independent prognostic effect, whereas high-level expression (≥ 50%) (ref.[22]) may single out patients at heightened risk of pelvic failure in locally advanced disease managed with CRT/MRI-IGBT (ref.[22]). Histological subtype emerges as a critical determinant of L1CAM expression and prognostic relevance. Studies that stratified by histology, such as Romanová et al.[19], Klát et al.[20], and Mancusi de Carvalho et al.[21], offer more solid insights into subtype-specific behaviour. Squamous cell carcinomas generally display lower L1CAM positivity compared with adenocarcinomas and adenosquamous variants. This discrepancy may constitute a fundamental factor contributing to the heterogeneity of outcomes observed in studies involving mixed cohorts. Staging likewise shapes the observed prognostic effect. Early-stage disease, typically managed surgically, shows variable L1CAM expression and limited independent prognostic value. By contrast, in locally advanced disease treated with chemoradiotherapy and MRI-guided brachytherapy (as in the BIOEMBRACE study) (ref.[22]), a clearer association emerges between high L1CAM expression and poor pelvic control. To improve the translational applicability of L1CAM, future investigations should systematically integrate histological subtyping and staging parameters.

Clinical implications and guidelines

Routine L1CAM testing is not currently endorsed by major guidelines (ESGO/ESTRO/ESP 2023; NCCN 2025) (ref.[4,5]). In research settings, immunohistochemical evaluation should be rigorously standardized, including specification of antibody clone, analytical platform, and scoring methodology at the invasive front. Thresholds for positivity – such as ≥50% – must be prespecified, and interpretation should be contextualized with respect to tumor stage, treatment history, PD-L1 and p16 expression status.

Limitations

The current evidence base is hampered by small sample sizes, retrospective study designs, and heterogeneity in staging, histology, and treatment. Methodological variability in IHC (clone, platform, pre-analytical handling, thresholds) and inconsistent endpoints (DFS, OS, pelvic/local control) not only preclude robust meta-analysis but also open the door to residual confounding.

CONCLUSIONS

Current evidence does not yet support the validation of L1CAM as an independent prognostic biomarker in cervical cancer. However, a context-dependent prognostic signal has been observed in locally advanced disease treated with concurrent chemoradiotherapy and MRI-guided brachytherapy, particularly when a ≥50% expression threshold is applied. To enable clinical implementation, rigorous validation in prospective, adequately powered, stage-specific studies is required – employing standardized immunohistochemical protocols, predefined clinical endpoints, and integrated assessment of PD-L1/p16 status.

Search strategy and selection criteria

We conducted a targeted narrative search of MEDLINE/PubMed, Embase, and Scopus from 1 January 2005 to 1 September 2025, using combinations of "L1 cell adhesion molecule"/"L1CAM"/"CD171" and "cervical cancer"/"cervix" with "prognosis"/"survival"/"recurrence." We included human studies evaluating tumour L1CAM expression and clinical outcomes; both retrospective and prospective cohorts using IHC (or validated transcriptomic thresholds) were eligible. We excluded case reports, abstract-only publications, animal-only studies, and non-English reports.

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