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Integrating Clinical, Histopathological, and Molecular Predictors of Malignant Transformation in Oral Leukoplakia: A Narrative Review

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ABSTRACT

The most prevalent potentially cancerous oral condition is oral leukoplakia (OL), but reported rates of malignant transformation (MT) vary widely, which complicates follow-up and management. This narrative review examines clinical, histopathological and molecular predictors of MT in OL, including the consistency of associations, methodological limitations, challenges and research gaps. Pooled MT estimates are about 6.6-7.2% although individual cohorts range from 4% to 21.7%. In pooled analyses, non-homogeneous lesions, lateral tongue location, and epithelial dysplasia are most strongly associated with MT, whereas tobacco and demographics remain inconsistent. DNA ploidy and p53 have the most molecular support but act only as adjuncts, while other markers remain preliminary. Current evidence supports stratifying patients into higher and lower-risk groups however cannot yet predict transformation in individual patients. A consensus-based definition, prospective multicenter cohort studies, and externally validated models are necessary for future study.

Keywords: oral leukoplakia; malignant transformation; oral potentially malignant disorders; dysplasia grading; biomarkers; risk stratification

INTRODUCTION

Oral leukoplakia (OL) is the most prevalent oral potentially malignant disorder (OPMD) worldwide, although its prevalence differs greatly among populations and geographic regions. The term OPMD indicates a higher risk of cancer without suggesting that all lesions will change. The WHO defines it as a mostly white plaque of dubious hazards following the exclusion of other recognized illnesses that have no effect on the risk of cancer [1,2].

It is clinically significant that OL may develop into an OSCC, however, reported rates of malignant transformation (MT) vary widely, making evidence-based follow-up and management challenging [2]. Consequently, risk classifications are important: patients at high risk require stricter monitoring, whereas those at low risk may be spared intense intervention. Typically, three types of predictors are examined. Clinical predictors include location, type of lesion, and tobacco exposure. The primary focus of histopathological predictors is the grade of epithelial dysplasia. Proteins, DNA content, and non-coding RNA's among examples of molecular predictors, many of which have been proposed [3,4]

There is a lot of conflicting evidence at this time. The findings on primary studies grading systems, smoking, and biomarker performance differ, yet meta-analyses demonstrate a number of clinicopathological factors of MT [5,6,7]. Numerous studies additionally conflate OL with other OPMDs or dysplastic lesions of diverse origins, complicating interpretation. By emphasizing how strong and enduring associations are, methodological limitations, significant challenges, and current research gaps, this narrative review aims to review the available data regarding clinical, histopathological, and molecular predictors of malignant transformation in oral leukoplakia. It explains why results differ and separates association from prediction.

DISCUSSION

Oral Leukoplakia Definition, Diagnosis, and Malignant Transformation Rates

Given that OL is an exclusion diagnosis, this includes recognizing normal variants of the oral mucosa; in one cohort of healthy elderly patients, fissured tongue (93.1%) and coated tongue (58.6%) were the most frequent. The clinician's ability to rule out other

white lesions are crucial to its diagnosis [1,2,8]. There is variation in reported MT rates. A pooled MT proportion of 6.64% (95% CI 5.21-8.21) was estimated through a meta-analysis of 55 studies involving 41,231 OL patients, and there was no discernible variation over time. An earlier-period comparison in that review yielded 5.35% prior to 1978, 7.06% between 1979 and 2007, and 6.97% more recently [9]. The need to distinguish subtypes is further highlighted by an umbrella review that found roughly 6% in OL versus 48% in proliferative verrucous leukoplakia (PVL) [2]. Another meta-analysis of 26 studies estimated a pooled MT proportion of 7.2% (95% CI 5.5-9.1) [10]. From 4% in one Brazilian cohort to 8.8% in another Brazilian multicenter sample, individual cohorts vary greatly [5,7], and 21.7% in an oral leukoplakia retrospective single-center series with an average follow-up of approximately 149.9 months [11]. The pattern indicates that variations in definition, follow-up duration, and referral setting, rather than solely biology, have been at least partially accountable for rate differences. This study is the first reason why comparing their findings is a challenge.

Clinical Predictors of Malignant Transformation

Lesion Type

Non-homogeneous lesions exhibit the highest association with MT among the documented clinical characteristics. In comparison to homogeneous lesions, a meta-analysis of 55 cohorts revealed a pooled relative risk of 4.23 (95% CI 3.31- 5.39), with MT of 21.88% in non-homogeneous lesions and 5.02% in homogeneous lesions [9]. Similarly, a single retrospective cohort of 221 patients with oral leukoplakia reported MT in 61.1% of non-homogeneous lesions compared with 18.2% of homogeneous lesions, with a significant association in the univariate analysis (HR 4.57, 95% CI 1.88-11.13). However, this association was no longer statistically significant after multivariable adjustment (HR 2.79, 95% CI 0.95-8.24; p = 0.063) [11]. As a result, the direction is consistent, but the estimate for the cohort is imprecise because it only includes 18 lesions, which are also heterogeneous.

Site

Tongue location was associated with a higher risk of MT, with a pooled relative risk of 2.04 (95% CI 1.72-2.41). The lateral border of the tongue showed a similarly elevated risk (RR 2.09, 95% CI 1.48-2.95), with an MT proportion of 12.71% among tongue lesions [9]. However, findings from a single-center cohort were less conclusive. Although tongue lesions had an MT proportion of 23.3%, their association with MT was not statistically significant compared with buccal mucosal lesions (HR 2.89, 95% CI 0.90-9.20). The percentage of coarse MT was higher in gingival lesions and multifocal lesions (46.1% and 47.4%, respectively) [11]. Overall, pooled evidence supports an association between tongue location and MT, whereas findings from the individual cohort were less conclusive. Variations in the study population, sample size, follow-up length, and lesion location distribution may be the cause of these discrepancies.

Smoking: etiological factor versus prognostic predictor

Although this effect is not exclusive to oral leukoplakia, smoking tobacco is linked to an elevated risk of head and neck malignancies as well as oral leukoplakia [12]. Its value as a predictor must therefore be judged by outcomes among patients who already have OL, not by its role in causing the lesion. A correlation with malignant transformation (MT) is suggested by pooled data (RR 1.64; 95% CI 1.25–2.15; I^2 = 83.8%) [8]. The meta-analysis's authors came to the conclusion that there is a markedly increased risk in cases with big, non-homogeneous lesions on the tongue's lateral border that are accompanied by epithelial dysplasia, especially in smokers. This implies that rather than functioning as a stand-alone risk factor, smoking may interact with the lesion's features. Cohort study results are less reliable. In one long-term cohort study, smoking was only linked to MT in a univariate analysis (HR 4.93) and did not show up as an independent predictor; however, 115 of the 221 patients' smoking status was unknown [11]. In a multicenter Brazilian study, non-smoker status was among the factors associated with a higher risk of transformation [7]. In a Japanese cohort of 200 patients with dysplastic leukoplakia, the 5-year cumulative MT was 9.3% in non-smokers and 3% in smokers, but the difference was not statistically significant (13 versus 2 events; P=0.15) [12].

Smokers and non-smokers also appear to differ biologically. Non-smokers in that cohort were order, more often female, and had more PD-L1-positive lesions and more CD163+ cells. The authors proposed that OL is much more prevalent in smokers, so a lesion arising in a non-smoker may follow a different route, and that smoking status was recorded only at diagnosis without accounting for cessation [12]. Although smoking is an established risk factor for OL and oral squamous cell carcinoma (OSCC), its independent prognostic value for MT remains uncertain. There is also no evidence linking smoking status to molecular markers linked to MT. For example, PD-L1 positivity was associated with MT among non-smokers, whereas baseline ZNF582 methylation levels were higher in smokers, although smoking status itself did not predict disease progression [12,13].

Other factors

There is still conflicting evidence on sex and age. Age and gender did not significantly increase the risk of malignant transformation, but non-homogeneous lesions (RR 4.23; 95% CI 3.31–5.39), greater extent (RR 2.08), location on the tongue's lateral border (RR 2.09), smoking (RR 1.64; 95% CI 1.25–2.15), and epithelial dysplasia (RR 2.75). Accordingly, a retrospective cohort of 485 patients with oral leukoplakia (>6 months of follow-up) treated by CO2 laser excision found no significant difference in malignant transformation between male and female patients [14]. In some subtypes, localization and histology are especially important: in the group of patients with proliferative leukoplakia from 2025, higher dysplasia grade was significantly associated

with malignant transformation, and the tongue was the most common site of transformation [15]. Additionally, an "umbrella review" shows that oral leukoplakia (6%) has a far lower transformation rate than proliferative verrucous leukoplakia (48%) [2].

Histopathological Predictors of Malignant Transformation

Presence and grade of dysplasia

Epithelial dysplasia is associated with MT across designs. One of the variables linked to an increased risk was dysplasia, according to the meta-analysis [9]. In the oral subgroup of a long-term cohort, dysplasia and dysplasia grade were independent predictors of MT, whereas transformation was infrequent in non-dysplastic lesions (5.1%) and in lesions that were not biopsied (3.9%) [11]. Risk appears grade-dependent in some data: in a head-to-head comparison, severe Oral epithelial dysplasia (OED) carried an HR of 13.7 (P = 0.02), whereas moderate OED did not show an increased risk [16]. This finding concerns an OED population rather than OL specifically.

Grading systems. Comparison gives divergent conclusions, summarized in Table 1.

TABLE 1: Comparison of dysplasia grading studies.

Study	Population	Finding
Sperandio dkk., 2023	OL, Brazil	3-tier OR 9.23 vs binary OR 3.49; kappa 0.47 vs 0.139 [5]
Mahmood dkk., 2023	75 OED (development); 121 OED, 4 centers (validation)	WHO AUROC 0.68 vs binary AUROC 0.72 for MT, with overlapping Cis [17]
Ellonen dkk., 2025	612 OED, Finland	No significant difference in prediction (p = 0.060); MT 7.8% [6]
Hankinson dkk., 2025	OED, UK	Binary HR 4.67; six-point HR 5.28; two-point did not stratify [16]

Because of this, the results that are now available are conflicting when it comes to the superiority of any one approach, but they generally concur that manual treatment (MT) carries a higher risk in higher-risk groups. This divergence may reflect differences in study populations (leukoplakia vs. dysplastic lesions), pathologist agreement, sample sizes, and MT definitions.

Interobserver variability

Kappa values were 0.42 for the WHO system, 0.31 for the binary system, 0.17 for the two-point system, and 0.41 for the six-point system [16]. In a smaller single-center study in which two pathologists independently graded 89 cases of leukoplakia, interobserver agreement was moderate for the WHO system (κ = 0.46) [18]. A worldwide survey also demonstrated that the three-tier system is the one most commonly used by pathologists and that grading is affected by the frequency of reporting and the amount of clinical information available [19]; this again underlines the subjectivity of the grading of dysplasia and the inherent limitations of the system in terms of predicting MT.

Aside from the difficulties in identifying the dysplasia grade, the lack of dysplasia is not a reliable indicator of low risk on its own. In a long-term cohort of 4 of 79 (5.1%) oral leukoplakia lesions without dysplasia went on to undergo malignant transformation [11]. So, the absence of dysplasia doesn't rule out the possibility of MT.

Molecular Predictors of Malignant Transformation

Protein markers

173 putative protein biomarkers were found in a meta-analysis of 142 studies (mostly utilizing IHC and ELISA methodologies). The majority of these were related to processes of cell death, cell proliferation, and apoptosis. Only 12 were found in both tissue and biofluid. There may not yet be agreement on what constitutes a trustworthy molecular biomarker due to the abundance of possible biomarkers. In the quantitative synthesis, PD-L1, MDM2, and MUCIN-4 all had significantly higher expression in OSCC than in leukoplakia (moderate certainty of evidence). These are all differences between the two disease states, not evidence of their ability to predict future malignant change [3].

At the mechanistic level, wild-type p53 contributes to apoptosis of initiated cells, whereas mutant p53 is associated with transformed cells [20]. A meta-analysis of 24 studies (1,210 patients) found that p53 overexpression was associated with a roughly 2-fold increased risk of malignant transformation (RR 1.88, 95% CI 1.39-2.56) in an umbrella review of systematic reviews. The evidence was rated as low certainty due to publication bias (Egger's p = 0.01) and considerable heterogeneity (I = 56%), while the association continued in leukplakia subgroups and seemed unaffected by dysplasia severity [2]. A scoping review of systematic reviews reported a similar estimate specific to leukoplakia (RR 2.22, 95% CI 1.35-3.64) [21]. Primary data on individual markers remain limited. In a prospective study of 73 excised leukoplakias, p53, p63, podoplanin, and Ki-67 were all higher in recurrent lesions, but only p53 was significantly higher, and combined high p53 and p63 predicted recurrence (HR 2.48, 95% CI 1.13-5.44). Recurrence is only a surrogate outcome. Only three patients in this cohort, all from the group with recurrences, went on to develop cancer [22].

The evidence that is currently available about the Ki-67 value is mostly cross-sectional. Secondary evidence

shows expression rising progressively from normal mucosa to leukoplakia to oral cancer. A retrospective study of 35 samples likewise found a rise from normal mucosa to dysplasia to OSCC, with mild dysplasia not significantly different from normal mucosa [21], [23]. This shows association with histological grade, not prospective prediction. In the prospective leukoplakia cohort above, Ki-67 showed a nonsignificant upward trend in recurrent lesions and did not correlate with recurrence [22]. Genetic alterations have been found in histologically normal-appearing tissue at the margins of oral malignant lesions, indicating that histopathology alone cannot identify all at-risk areas [24].

Intraoral immune response and malignant transformation

The systemic immunological status is also reflected in the oral mucosa; for example, lesions in the oral cavity are frequently the first sign of immune system weakness in the event of an HIV infection [25]. The immunological milieu beneath the epithelium (subepithelium) has been generally overlooked in predictive research involving oral lesions (OL), despite the fact that the previously described predictors describe the epithelium or the patient's condition. It seems to play two roles: regulatory T cells (Tregs) help to create an immunosuppressive environment, while CD8+ T cells may be an attempt to eradicate dysplastic cells [26]. Immune checkpoint signaling is the best-documented feature. PD-L1 is more abundant in OSCC than in leukoplakia [3], and proliferative verrucous leukoplakia (PVL) showed higher PD-L1 than localized leukoplakia, together with more CD8+ T cells and Tregs; high PD-L1 scores were associated with poorer cancer-free survival [27]. This fits the much higher transformation proportion of PVL than OL (48% vs 6%) [2], although causality cannot be inferred. Within OL, PD-L1 positivity was associated with transformation only in non-smokers, whose lesions also contained more CD163+ macrophages

Macrophages add a further layer: a systematic review supports an active role for macrophages in immune suppression and in the transition from oral potentially malignant disorders to OSCC [28]. Together with [12], this suggests that immune features may help explain why smoking is an inconsistent predictor [11,12], as lesions in non-smokers may follow a biologically different route. The evidence remains exploratory. There is presently no evidence in the form of a systematic review evaluating immune evasion in OL [21], the hazard ratio for PD-L1 is based on just 15 events [12], and the majority of the data are cross-sectional or retrospective in character. Immune markers should therefore be read as biological context rather than validated predictors, and prospective OL-only cohorts with standardized immune panels are needed.

DNA ploidy

In a prospective cohort, DNA ploidy was associated with MT in OL in univariate analysis; adding it increased model predictive power, but no predictor was associated with MT in PVL [29]. Both ploidy and the WHO classification-based grading system are linked to the clinical course of potentially malignant oral disorders (OPMDs); the AUC value for ploidy is 0.617, which rises to 0.688 when combined with WHO grading [30]. Citing a meta-analysis that revealed a hazard ratio (HR) of 14.10 for aneuploid leukoplakias compared to diploid leukoplakias, an "umbrella review" backed by moderate-quality evidence identified DNA aneuploidy as the most promising biomarker [2,31]. On the other hand, a 2025 meta-analysis that compared diagnostic accuracy to histopathology revealed an AUC value of 0.49, a sensitivity of 0.71, and a specificity of 0.31 [32]. Ploidy is therefore not appropriate as a stand-alone, independent test, even though it can offer additional information.

Other candidate markers

For PD-L1, a single-center retrospective cohort of 200 patients with dysplastic leukoplakia (15 transformations) found that PD-L1 positivity in non-smoking patients carried a 6.97-fold higher hazard of malignant transformation (95% CI 2.14-22.7), while PD-L1-positive lesions in smokers were too few to analyze [12]. The wide interval and small number of events mean this is an association rather than a validated prediction. A systematic review of microRNA signatures reported nine consistently dysregulated miRNAa in progressing leukoplakia, notably miR-21 and miR-31, but the evidence was graded as very low certainty [4]. For genomic markers, loss of heterozygosity has been assessed in only two small retrospective studies, with differing loci (9p versus 5q, 6p, 6q and 11q) [33]. For methylation, a hospital-based cohort of 171 patients with normal mucosa or OPMD found that higher baseline ZNF582 and PAX1 methylation was associated with progression, but there were only 11 cancers and 4 advanced histological progressions [15]. Single nucleotide polymorphisms (SNPs) linked to chronic inflammation have also been proposed as genetic markers of susceptibility and prognosis in oral cancer [34]. In addition to tissue markers, 25 patients with head and neck cancers had non-invasive measurements of oxidative markers in their saliva (malondialdehyde, glutathione, and superoxide dismutase), which were linked with the degree of radiation-induced mucositis [35]. This was not an OL cohort and did not assess malignant transformation, so its relevance here is limited to showing that salivary sampling is feasible.

All things considered, none of these indicators have been verified in a separate prospective cohort.

METHODOLOGICAL APPROACHES USED IN CURRENT RESEARCH

TABLE 2: Common methodological approaches in studies of malignant transformation (MT) in oral leukoplakia.

Approach	Measures	Strengths	Limitations	Reasonable conclusion
Study design				
Retrospective cohort	MT among treated or referred patients	Feasible; large samples and long follow-up (e.g., 221 OL, 149.9 months [11]; 485 OL [14])	Referral and single-center bias; incomplete records (smoking status unknown in 115/221 [11]); differing MT definitions	Association, not prediction
Prospective cohort	MT or surrogate outcome with predefined predictors	Predictors and follow-up defined in advance [22,29].	Small samples and few events (only 3 transformations among 73 lesions [22]); recurrence used as surrogate outcome [22]	Stronger prognostic inference, but underpowered
Systematic review/meta-analysis, umbrella review	Pooled MT rates and risk ratios	Pooled estimates from large datasets (55 studies, 41,231 patients [9]); allows OL vs PVL comparison [2].	High heterogeneity (I^2 = 83.8% for smoking [9]); publication bias and low certainty for some markers [2]; mixed OL, OED, and OPMD populations	Pooled association
Exposure/biomarker assessment				
Dysplasia grading (WHO 3-tier, binary, six-point)	Architectural and cytological atypia	Best-established predictor and widely used [19].	Moderate to poor interobserver agreement (κ 0.17-0.46 [16], [18]; inconsistent superiority between systems [5,6,16,17]	Risk category, not individual certainty
IHC / ELISA protein markers	Protein expression (p53, Ki-67, PD-L1, etc.)	Accessible; broad candidate screening (173 proteins [3])	No consensus among candidates; only 12 shared between tissue and biofluid [3]; evidence mostly cross-sectional (e.g., Ki-67 [21,23])	Association
DNA ploidy	aneuploidy	Modest discrimination alone (AUC 0.617), improved when combined with grading (AUC 0.688) [30] associated with MT in OL [29]	Modest accuracy (AUC 0.49, sensitivity 0.71, specificity 0.31 [32]); results differ between studies [2,31].	Adjunct, not stand-alone
miRNA, LOH, and methylation assays	miRNA signatures, allelic loss, gene methylation	Candidate markers beyond protein level [4], [13,33].	Very low certainty [4]; only two small LOH studies with different loci [33]; few events (11 cancers in 171 patients [13])	Exploratory association
Analytical approach				
Cox regression and ROC analysis	Time-to-event risk (HR), discrimination (AUROC)	Handles follow-up time [11]; quantifies discrimination [17].	Depends on an even number (e.g., 15 events [12]); significance is often lost in multivariate models [11]	HR/AUC need external validation

Taken together, the methods listed in Table 2 are more appropriate for examining correlations than for forecasting. Prospective cohort studies, on the other hand, are better suited for prognostic purposes, even though they usually have smaller sample sizes and fewer events [22]. Retrospective cohort studies and pooled analyzes provide the largest sample sizes, but they are vulnerable to selection bias (referral bias), inconsistent definitions of MT, and heterogeneity across studies [2,9,11]. Histological grading and molecular markers add risk information, yet with limited reproducibility or low certainty of evidence [3,4,16,18,33], and DNA ploidy appears to function as an adjunct rather than a stand-alone test [30,32]. Because hazard ratios and AUC values rest on few events, they require external

validation before being applied to individual patients [11,12]. Therefore, current evidence consistently supports stratifying patients into higher- and lower-risk groups, but it is not yet sufficient to predict transformation in individual patients. This will require larger prospective cohorts, standardized MT definitions and follow-up, and external validation of candidate markers.

MAJOR CHALLENGES

Challenge 1: heterogeneity of definitions, designs, and populations.

Studies differ in how OL, MT, follow-up, and the study population are defined. The evidence that is currently available shows that rates of malignant transformation (MT) vary from 4% to 21.7% among different cohorts [5,7,11]; pooled estimates from multiple meta-analyses are 6.64% and 7.2%, respectively [9,10]. Additionally, proliferative verrucous leukoplakia (PVL) is linked to some predictors [29] and has a substantially greater transformation rate than oral leukoplakia (OL) (about 48% versus 6%) [2]. Oral epithelial dysplasia (OED) instances or a combination of different potentially malignant oral disorders (OPMDs) have been included in some grading studies [6,16,30]. There is no agreed-upon definition for malignant transformation, OL is a diagnosis of exclusion, and long-term surveillance is expensive. The impact itself is pooling and comparison across studies are limited. Implications: adopt consensus definitions [1,2], report OL separately from other OPMDs, and standardize the MT definition and minimum follow-up.

Challenge 2: limited reproducibility and validation of predictors

The predictors with the most support are subjective or not externally validated. Ploidy alone has limited discriminative ability (AUC 0.617; 0.688 when combined with grading) [30], PD-L1 estimates have wide confidence intervals [11], pathologists' approaches vary [16,18], and [19], and interobserver agreement regarding grading is low to moderate (κ 0.17–0.46). The large number of candidate proteins (173) also indicates a lack of convergence [3]. Because samples are small, single-center, and mostly retrospective, and shared validation cohorts are likely lacking, markers remain associations that cannot support individual decisions, and progress will require multicenter prospective cohorts, calibrated or digital grading, and external validation of combined clinical-histological-molecular models.

RESEARCH GAPS AND UNRESOLVED QUESTIONS

Standardized definitions

Reported MT rates vary with definition, follow-up, and referral setting [5,7,9,10,11], but it remains unknown how much of this variation is biological, which affects every pooled estimate. As a result, future studies should use a consensus-based cohort made up only of patients who have oral lesions (OL), using a standard definition for these lesions.

Dysplasia grading

Higher grades are generally associated with greater MT risk, yet it is still unclear which system performs best [5,6,16,17] and how to improve observer agreement [16,18,19]. Because grading drives management, future research should focus on multi-observer validation, consensus reporting, and digital approaches.

Molecular validation

DNA ploidy is associated with MT in OL [29,30], and PD-L1 positivity with MT in non-smokers [12], but it remains unknown whether they improve prediction beyond clinical and histological data in externally validated models. Thus, a prospective model that includes clinical, histological, and genetic predictors along with external validation is necessary for clinical translation.

Under-studied markers

A systematic review of miRNA signatures exists, but its certainty is very low [4], and the performance of LOH [33] and methylation markers in OL-specific cohorts is unknown, since these markers have mostly been tested in few, small, or mixed-lesion studies. Primary OL cohort studies are needed to address this.

Population coverage

Primary cohorts in this review come from a limited set of regions, with Brazilian samples prominent [5,7], so it remains unknown whether MT risk and predictors differ in other populations. Because regional exposure may modify risk, multicenter regional studies are needed.

Follow-up

The follow-up period varies from a minimum of six months [14] to an average of almost 149.9 months [11]; the precise minimum follow-up period for OL is currently unknown. Since short follow-up may miss later MT, long and standardized follow-up is needed.

CONCLUSION

Current evidence suggests that non-homogeneous lesion type, lateral tongue location, and epithelial dysplasia are the clinical and histopathological factors most strongly associated with malignant transformation in oral leukoplakia in pooled analyses, whereas the independent roles of tobacco and demographics remain uncertain or inconsistent. Determining the dysplasia grade is undoubtedly helpful, but it has drawbacks, most notably only mediocre reproducibility, and no grading system has been proven to be unquestionably better than the others. Among molecular candidates, DNA ploidy and p53 have the most support but remain adjunctive and are limited by low certainty of evidence, while PD-L1, miRNA, LOH, and methylation markers remain preliminary and unvalidated. Overall, the evidence supports stratifying patients into higher-and lower-risk groups, which can guide surveillance intensity, but it is not yet sufficient to predict transformation in individual patients.

The two main issues are the low reproducibility and validation of predictors and heterogeneity in terms of definitions, design, and populations. Priorities for future research include consensus definitions, multicenter prospective cohorts with long follow-up, calibrated grading, and externally validated models that combine clinical, histological, and molecular data.

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