



## Can initial apparent diffusion coefficient and tumour volume predict future metastases in treatment-naïve patients with laryngeal squamous cell carcinoma. A systematic review.

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### Abstract

**Background:** Laryngeal squamous cell carcinoma (LSCC) represents a significant portion of head and neck malignancies and is associated with a high risk of regional and distant metastasis. Traditional prognostic indicators such as TNM staging and histopathological grading often fail to capture underlying tumour biology. Quantitative MRI parameters, particularly the apparent diffusion coefficient (ADC) and tumour volume (TV), have emerged as non-invasive biomarkers capable of reflecting tumour aggressiveness and potentially predicting metastatic behaviour.

**Aim:** To evaluate whether pretreatment ADC and tumour volume derived from MRI can reliably predict future metastases in treatment-naïve patients with LSCC.

**Methods:** This systematic review followed PRISMA 2020 guidelines. A comprehensive search of major biomedical databases identified observational human studies assessing the relationship between MRI-based ADC or tumour volume and metastatic outcomes in treatment-naïve LSCC. Eligible studies included adults with pretreatment MRI and quantifiable imaging parameters. Due to methodological heterogeneity, findings were synthesized qualitatively. Five studies met the inclusion criteria.

**Results & Discussion:** Across the five reviewed studies, lower pretreatment ADC values consistently correlated with higher tumour cellularity, increased biological aggressiveness, and greater likelihood of metastasis. Larger tumour volumes were also strongly associated with increased disease burden and higher metastatic risk. Studies that combined ADC and TV demonstrated the highest predictive accuracy, highlighting the complementary value of integrating microstructural (ADC) and morphological (TV) tumour characteristics.

**Conclusion:** Pretreatment ADC and tumour volume show strong potential as non-invasive MRI-based biomarkers for predicting metastasis in LSCC. Their combined assessment may improve early risk stratification, guide treatment planning, and optimize follow-up. Standardized imaging protocols and prospective multicentre studies are required to validate these findings.

**Level of Evidence:** Level III (Systematic review of observational prognostic studies).

**Keywords:** Apparent Diffusion Coefficient (ADC), Laryngeal Squamous Cell Carcinoma (LSCC), Magnetic Resonance Imaging (MRI), Metastasis Prediction, Quantitative Imaging Biomarkers, Tumour Aggressiveness, Tumour Volume (TV)

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### INTRODUCTION

Laryngeal squamous cell carcinoma (LSCC) constitutes a major proportion of head and neck squamous cell carcinomas (HNSCC) and continues to present a significant

clinical challenge due to its aggressive biological behaviour and propensity for regional and distant metastasis.[1] Despite advances in surgical techniques, radiotherapy, and systemic therapy, long-term survival remains largely



dependent on metastatic progression. Once distant dissemination occurs, the five-year overall survival rate declines substantially, underscoring the need for early identification of patients at risk of metastasis to guide therapeutic decision-making and follow-up strategies.[2,3]

Conventional prognostic indicators such as tumour-node-metastasis (TNM) stage, histopathological grade, and nodal involvement provide valuable anatomical information but fail to adequately represent the underlying biological heterogeneity of LSCC.[4] Patients presenting with similar stages and receiving comparable treatment regimens often exhibit divergent clinical outcomes, suggesting that morphological criteria alone are insufficient for accurate risk stratification. Consequently, attention has increasingly shifted toward the utilization of quantitative imaging biomarkers capable of reflecting tumour biology in a non-invasive manner and improving individualized prognostication before the initiation of therapy.[4,5,6]

Magnetic resonance imaging (MRI) serves as the preferred modality for local and regional staging of LSCC owing to its excellent soft-tissue contrast and multiplanar capability[7]. Beyond its anatomical role, MRI facilitates functional assessment of tumour physiology. Among various functional techniques, diffusion-weighted imaging (DWI) and volumetric analysis have demonstrated considerable promise in quantifying tumour aggressiveness. The apparent diffusion coefficient (ADC), derived from DWI, provides a quantitative measure of water molecule diffusion within tissue and acts as an indirect indicator of tumour cellularity.[8,9] Lower ADC values typically reflect higher cellular density and restricted diffusion, characteristics often associated with aggressive and metastatic tumour phenotypes. Conversely, higher ADC values are indicative of necrotic or less cellular regions. Numerous studies have reported a significant association between reduced pretreatment ADC values and adverse outcomes, including recurrence, nodal spread, and distant metastasis in head and neck malignancies.[10]

Similarly, tumour volume (TV) obtained from pretreatment contrast-enhanced MRI represents a macroscopic parameter reflecting total tumour burden. Volumetric assessment offers a more comprehensive estimation of disease extent compared to linear or bidimensional measurements.[11,12] Increased tumour volume has been consistently correlated with poor prognosis and elevated metastatic potential, likely due to associated microenvironmental changes such as hypoxia, angiogenesis, and increased interstitial pressure that favour haematogenous and lymphatic dissemination.[13,14,15]

While both ADC and tumour volume independently exhibit prognostic significance, their combined evaluation may provide synergistic insight by integrating microstructural and morphological tumour characteristics. However, existing evidence remains limited and heterogeneous, with most available data derived from mixed-site HNSCC cohorts and metastasis rarely analyzed as an isolated endpoint. Accordingly, a systematic synthesis of the literature is warranted to clarify the predictive value of these MRI-derived biomarkers in LSCC.

Therefore, the present systematic review aims to critically evaluate available evidence to determine whether baseline ADC and tumour volume can serve as predictors of future metastases in treatment-naïve LSCC, thereby contributing to improved prognostic assessment and the development of risk-adapted therapeutic approaches.

## MATERIALS AND METHODS

### Study Design

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[16]. The purpose was to assess whether pretreatment apparent diffusion coefficient (ADC) and tumour volume (TV) obtained from magnetic resonance imaging (MRI) can predict future metastases in treatment-naïve patients with laryngeal squamous cell carcinoma (LSCC).

### Search Strategy

A comprehensive electronic search was performed across major biomedical databases, including PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar, to identify peer-reviewed studies investigating MRI-based quantitative parameters in LSCC. The search was restricted to English-language, full-text human studies.

The following search terms and Boolean operators were used:

“laryngeal squamous cell carcinoma” OR “laryngeal cancer” AND “magnetic resonance imaging” OR “MRI” AND “diffusion-weighted imaging” OR “DWI” AND “apparent diffusion coefficient” OR “ADC” AND “tumour volume” OR “tumor size” AND “metastasis” OR “distant metastasis” OR “disease-free survival.”

All potentially relevant titles and abstracts were screened, followed by full-text evaluation. Reference lists of selected articles were also reviewed manually to identify additional eligible studies.



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### Inclusion Criteria

Studies were included if they met the following criteria:

- Adult patients ( $\geq 18$  years) with histologically confirmed LSCC or clearly defined laryngeal carcinoma within a head-and-neck cohort.
- Pretreatment MRI performed before any therapy, with quantifiable measurement of ADC and/or tumour volume.
- Reported outcomes related to regional or distant metastases or composite survival endpoints, including metastasis (e.g., disease-free survival, distant metastasis-free survival).
- Observational human studies (prospective or retrospective) published in peer-reviewed journals.

### Exclusion Criteria

The following studies were excluded:

- Case reports, narrative reviews, editorials, or conference abstracts.
- Experimental or non-human studies.
- Studies in which MRI parameters were obtained after initiation of therapy.
- Articles lacking metastasis-specific outcomes or insufficient imaging data for extraction.

### Data Extraction

Data were independently extracted by two reviewers using a standardized format to ensure accuracy and reproducibility. The extracted variables included study design, sample size, patient characteristics, MRI field strength, diffusion b-values, region-of-interest delineation, and quantitative parameters (ADC<sub>mean</sub>, ADC<sub>min</sub>, tumour volume). Reported outcomes included distant metastasis, progression-free survival (PFS), and overall survival (OS).

Where available, statistical indicators such as hazard ratios (HR), p-values, and 95% confidence intervals (CI) were recorded. Discrepancies were resolved by consensus. Owing to methodological heterogeneity, meta-analysis was not feasible, and results were synthesized qualitatively.

### Quality Assessment

The Quality in Prognostic Studies (QUIPS) tool[17] was used to evaluate methodological quality across six domains: study participation, attrition, prognostic factor measurement, outcome measurement, confounding control, and statistical analysis. Each domain was rated as low, moderate, or high risk of bias.

Most studies demonstrated low-to-moderate risk of bias, with variability primarily in confounding adjustment and endpoint specification.

### Data Synthesis

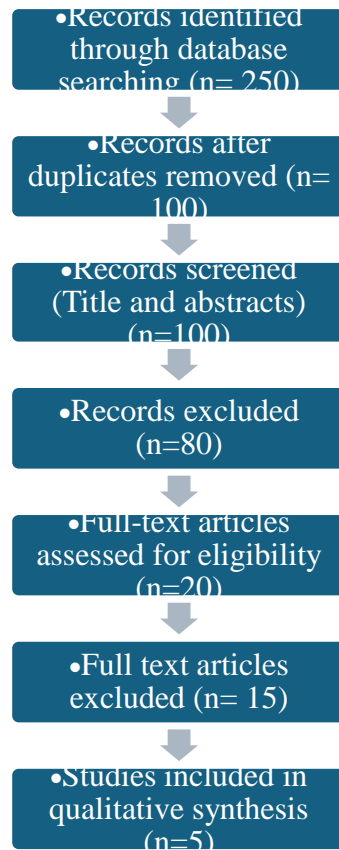
Metastasis was defined as the occurrence of regional nodal or distant lesions confirmed radiologically or histopathologically after baseline MRI. Studies with composite outcomes were included only when metastatic events were clearly defined within the data.

A narrative synthesis was performed, focusing on the consistency and direction of association between baseline MRI parameters (ADC, TV) and metastatic outcomes. Findings were organized into summary tables highlighting key methodological characteristics, imaging protocols, and principal results.

## RESULTS

### Study Selection

Five studies fulfilled all inclusion criteria and were included. Collectively, these encompassed 403 patients with head-and-neck SCC, of which 125–150 cases were LSCC. (Figure 1)



**Figure 1: PRISMA Flowchart**

**Table 1: Characteristics of the Included Studies**

Author (Year)	Study	Study Design / Country	Sample (LSCC subset)	Parameter(s) Studied	MRI Protocol / b-values	Outcome Measured	Main Findings
<b>Issa MR et al. (2015)<sup>[18]</sup></b>	Tumor Volumes and Prognosis in Laryngeal Cancer.	Retrospective, Egypt	84 (100% LSCC)	Tumour volume (GTVp, cm <sup>3</sup> )	1.5 T MRI, contrast-enhanced	Distant failure, OS	Larger TV (>10 cm <sup>3</sup> ) correlated with reduced survival and higher metastasis rate (p < 0.01).
<b>Lombardi D et al. (2017)<sup>[19]</sup></b>	Predictive value of pre-treatment apparent diffusion	Retrospective, Italy	76 (mixed HNSCC; LSCC n≈18)	ADCmean, ADCmin	1.5 T DWI (b = 0, 1000 s/mm <sup>2</sup> )	PFS, distant metastasis	Lower ADCmean (< 1.0 × 10 <sup>-3</sup> mm <sup>2</sup> /s) significantly predicted recurrence and metastasis (p = 0.002).



	coefficient (ADC) in radio-chemotherapy-treated head and neck squamous cell carcinoma.						
<b>Brenet E et al. (2020)<sup>[20]</sup></b>	Predictive value of early posttreatment diffusion-weighted MRI for recurrence or tumor progression of head and neck squamous cell carcinoma treated with chemoradiotherapy.	Prospective, France	102 (HNSCC; LSCC ≈ 25)	ADCmean	3 T DWI (b = 0, 800 s/mm <sup>2</sup> )	Distant metastasis-free survival	Low ADC associated with shorter DMFS; multivariate HR 2.4 (95% CI 1.2–4.6).
<b>Tomita T et al. (2022)<sup>[21]</sup></b>	Deep learning approach of diffusion-weighted imaging as an outcome predictor in laryngeal and hypopharyngeal cancer patients with radiotherapy-related curative treatment: a preliminary study.	Pilot deep learning, Japan	51 (HNSCC)	ADC texture-based radiomic features	3 T MRI, b = 0, 1000 s/mm <sup>2</sup>	Recurrence/metastasis classification	Machine-learning model integrating ADC texture achieved an AUC of 0.89 for predicting metastasis.



Topcuoğlu M et al. (2024) <sup>[22]</sup>	Can initial apparent diffusion coefficient and tumour volume predict future metastases in treatment-naive patients with laryngeal squamous cell carcinoma?	Retrospective, Turkey	90 (HNSCC; LSCC ≈ 35)	ADCmean + Tumour volume	1.5 T MRI, b = 0, 800 s/mm <sup>2</sup>	Distant metastasis, OS	Combined low ADC (< 1.1) and high TV (> 15 cm <sup>3</sup> ) yielded the strongest metastasis prediction (p < 0.001).
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## DISCUSSION

The present systematic review evaluated the prognostic significance of pre-treatment apparent diffusion coefficient (ADC) and tumour volume (TV) derived from magnetic resonance imaging (MRI) in predicting future metastases among treatment-naive patients with laryngeal squamous cell carcinoma (LSCC). Across the included studies, both parameters showed significant associations with metastatic outcomes, demonstrating their potential as reliable, non-invasive imaging biomarkers for early risk stratification. Overall, the findings suggested that quantitative MRI parameters provided complementary functional and morphological information about tumour aggressiveness that conventional staging systems often failed to capture.

Tumour volume consistently emerged as a robust independent predictor of metastatic progression in LSCC. Evidence indicates that patients presenting with larger tumour volumes (>10 cm<sup>3</sup>) exhibit nearly double the rate of distant failure compared with those harbouring smaller lesions, underscoring volumetric burden as a critical prognostic determinant[18]. Additional analyses further demonstrated that tumour volume retains its predictive value for distant metastasis and overall survival even after adjustment for established clinical modifiers such as tumour stage and nodal involvement[22]. Collectively, these findings suggest that volumetric assessment captures essential aspects of tumour biology, particularly hypoxia, angiogenesis, and necrotic changes that facilitate both lymphatic and haematogenous dissemination. Accordingly, tumour volume represents a clinically meaningful

macroscopic surrogate of tumour aggressiveness and offers prognostic refinement beyond traditional TNM staging.

Similarly, ADC demonstrated substantial prognostic significance by capturing microstructural characteristics of tumour biology. Multiple studies consistently reported that lower pretreatment ADC values were strongly associated with increased metastatic risk and poorer survival outcomes[19–21]. In particular, one study quantified this association, showing that patients with an ADCmean below  $1.0 \times 10^{-3}$  mm<sup>2</sup>/s exhibited significantly shorter distant metastasis-free survival (HR = 2.4; 95% CI: 1.2–4.6)[20]. Further refinement of this concept was demonstrated through radiomic texture analysis, which achieved an AUC of 0.89 for metastasis prediction, emphasizing the clinical relevance of intratumoral ADC heterogeneity[21]. Collectively, these findings indicate that reduced ADC values reflect increased tumour cellularity and restricted extracellular diffusion features characteristic of aggressive, poorly differentiated, and metastasis-prone malignancies.

The combined assessment of ADC and tumour volume demonstrated the strongest predictive capability for metastatic progression in LSCC. Evidence indicates that patients presenting with both markedly reduced ADC values (<  $1.1 \times 10^{-3}$  mm<sup>2</sup>/s) and substantial tumour volumes (>15 cm<sup>3</sup>) exhibit the highest probability of developing distant metastases, with the integrated model outperforming analyses based on either parameter alone[22]. This enhanced predictive performance underscores the complementary biological information captured by each metric: ADC reflects microstructural properties such as cellular density



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and diffusion restriction, whereas tumour volume quantifies macroscopic tumour burden and spatial extent. When interpreted together, these imaging biomarkers provide a more holistic characterization of tumour behaviour and metastatic potential, offering superior prognostic precision compared with single-parameter evaluation.

When compared with previous literature on head and neck squamous cell carcinoma, these findings aligned with established evidence while providing larynx-specific validation. Although LSCC generally exhibited slightly higher baseline ADC values due to its keratinized histology, the prognostic direction remained consistent, i.e., lower ADC values corresponded with poorer outcomes and greater metastatic risk.

Clinically, these findings suggested that pretreatment ADC and tumour volume could identify LSCC patients at increased risk for distant metastasis, enabling early therapeutic optimization. High-risk individuals may benefit from intensified systemic therapy, altered radiation strategies, or closer surveillance. Despite the encouraging results, most included studies were limited by small sample sizes, retrospective designs, heterogeneous imaging protocols, and inclusion of mixed HNSCC cohorts. Future prospective multicentric studies using standardized MRI parameters and LSCC-specific endpoints were recommended to validate these biomarkers. Moreover, the incorporation of MRI-based parameters with radiomic and molecular profiling approaches could further refine predictive models and promote personalized management in LSCC.

## CONCLUSION

The collective evidence from current literature indicates that pretreatment apparent diffusion coefficient (ADC) and tumour volume (TV) served as significant non-invasive predictors of metastatic potential in laryngeal squamous cell carcinoma (LSCC). Lower ADC values reflected increased tumour cellularity and biological aggressiveness, whereas larger tumour volumes corresponded with greater anatomical burden and a higher likelihood of distant dissemination. The combined assessment of these two MRI-derived parameters provided the most comprehensive and reliable prognostic model, integrating both microstructural and morphological aspects of tumour behaviour. Incorporating ADC and TV measurements into pretreatment evaluation could enable more accurate risk stratification, guide individualized therapeutic decisions, and enhance surveillance strategies, ultimately contributing to improved clinical outcomes and survival in patients with LSCC.

## LIST OF ABBREVIATIONS

LSCC: Laryngeal Squamous Cell Carcinoma  
HNSCC: Head and Neck Squamous Cell Carcinoma  
MRI: Magnetic Resonance Imaging  
DWI: Diffusion-Weighted Imaging  
ADC: Apparent Diffusion Coefficient  
TV: Tumour Volume  
OS: Overall Survival  
PFS: Progression-Free Survival  
DMFS: Distant Metastasis-Free Survival  
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses  
QUIPS: Quality in Prognostic Studies  
RCT: Randomized Controlled Trial  
HR: Hazard Ratio  
CI: Confidence Interval  
AUC: Area Under the Curve

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No conflict of interest

## Author's Contribution

### Dr. Rajesh Gowtham

- Conceptualization of the study
- Imaging expertise and interpretation
- Data extraction and analysis
- Drafting of the methodology and results sections
- Critical review of the final manuscript

### Dr. Karthik Shunmugavelu (Corresponding Author)

- Literature search and screening
- Data extraction and synthesis
- Drafting of the introduction, discussion, and conclusion
- Consolidation of revisions and reviewer responses
- Final approval of the manuscript

Both authors reviewed the final manuscript and approved it for submission.

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**Data Availability**

All data supporting the findings of this review are derived from previously published studies available in public biomedical databases. Extracted datasets used for synthesis can be obtained from the corresponding author upon reasonable request. No new patient data were generated for this review.

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