Laryngoscope Investigative Otolaryngology

WILEY

REVIEW OPEN ACCESS

Tumor Growth Rate in Head and Neck Squamous Cell Carcinoma: A Scoping Review

Gilles Delahaut[1] | Florent Jamme[2] | Bruno Krug[3] | Jean-François Daisne[4] | Samantha Hassid[1] | Sebastien Van der Vorst[1]

[1]ENT and Head & Neck Surgery Department, CHU UCL Namur site de Godinne, Yvoir, Belgium | [2]Cervico-facial carcinology department, Gustave Roussy, Villejuif, France | [3]Nuclear Medicine department, CHU UCL Namur site de Godinne, Yvoir, Belgium | [4]Oncologisch Centrum Antwerpen, Iridium Netwerk-ZAS Augustinus, Wilrijk, Belgium

Correspondence: Gilles Delahaut (gilles.delahaut@chuuclnamur.uclouvain.be) | Florent Jamme (florent.jamme@outlook.com)

Received: 10 September 2025 | **Revised:** 22 May 2026 | **Accepted:** 23 May 2026

Keywords: head and neck squamous cell carcinoma | prognostic impact | scoping review | time to treatment initiation | tumor growth rate | tumor growth velocity | tumor progression

ABSTRACT

Objective: This scoping review evaluates the current literature on tumor growth rate in head and neck cancer patients and its potential prognostic value on survival, loco-regional control and recurrence (PROSPERO registration CRD42022370828).

Review Methods: PubMed, Embase, and Scopus were searched for publications between 1990 and November 5th 2025. Studies providing measures of treatment-naïve HNSCC tumor growth, estimated from tumor volume derived from two pre-therapeutic scans and/or related outcome evaluations, were included. The risk of bias was assessed using the QUIPS tool. Data analysis was summarized in tables and reported following the PRISMA-ScR recommendations.

Results: Thirteen papers met the inclusion criteria. Among them, eight provided an actual growth rate, and nine conducted a statistical analysis of survival outcomes. There was significant heterogeneity in study design, imaging technique, volume measurement, growth rate calculation, confounding factors, and prognostic impact. Overall, despite some studies suggesting a correlation between tumor kinetics and survival and loco-regional control, there is insufficient data to conduct a proper meta-analysis or to confirm tumor growth rate as a valid predictor.

Conclusion: Tumor kinetics could influence treatment planning and therapy for HNSCC patients in a more personalized way. However, even though some authors have shown a significant impact of Tumor-specific growth rate (TSGR) on survival and loco-regional control, important heterogeneity across articles on this topic fails to yield consistent results, making it difficult to achieve good risk stratification. Recommendations for future research were summarized.

Level of Evidence: NA.

1 | Introduction

Head and neck cancer ranks as the fifth most common cancer, with approximately 140,000 new cases and 70,000 deaths reported annually in Europe. Approximately 90% of these cases are squamous cell carcinomas (HNSCC) [1]. Despite recent progress, their evolution and patients' clinical outcomes are difficult to predict at the time of diagnosis. Although the Tumor Node Metastasis (TNM) staging system remains the primary prognostic tool—drawing on clinical, radiological, and pathological data—its ability to accurately predict tumor progression and treatment response is often limited due to the significant heterogeneity of these cancers. However, there is still no consensus on establishing proper risk stratification.

Gilles Delahaut and Florent Jamme contributed equally to this study.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2026 The Author(s). *Laryngoscope Investigative Otolaryngology* published by Wiley Periodicals LLC on behalf of The Triological Society.

To address this gap, various predictive markers from diagnostic imaging techniques (CT, MRI, PET) have been investigated. Among them, nodal status is well validated, and extranodal extension was recently incorporated into the TNM staging. Tumor volume (TV) also has a predictive value for radiotherapy (RT) response in locally advanced HNSCC [2–4]. However, there is still no consensus on establishing proper risk stratification. Metabolic parameters derived from FDG-PET, such as metabolic TV or total lesion glycolysis, are also promising predictive factors [5, 6]. Recently, MRI parameters (diffusion/perfusion) and quantitative imaging (radiomics) have also been investigated as potential predictors. Despite recent advancements, most of these imaging parameters remain debated and have not been validated for clinical routine [7, 8]. Predicting disease progression and clinical outcome with precision remains a considerable challenge.

In recent decades, expanding indications for RT and multimodal treatments, along with the increasing number of diagnostic tests, have extended the time-to-treatment initiation (TTI) in many countries [9]. This delay has raised concerns that it could affect the prognosis of patients with rapidly growing tumors. A systematic review and meta-analysis confirmed that a prolonged waiting time before RT significantly increases the risk of local recurrence [10]. Accelerating treatment planning to avoid upstaging of HNSCC during TTI remains a major consideration [11]. In addition, clinicians frequently encounter tumors with highly variable growth patterns. Tumor growth (TG) rate is presumably an in vivo reflection of in vitro aggressiveness markers, such as high proliferation capacity, increased angiogenesis, and increased glucose uptake, but also depends on anatomical constraints in the head and neck area. Determining in vivo tumor kinetics (TK) could be a key to improving patients' risk stratification in the era of personalized medicine, allowing de-intensification protocols for slow-growing tumors or fast-track treatment planning for aggressive tumors. It could also help better determine the place of induction therapy in the treatment of HNSCC.

This scoping review aims to identify and synthesize the available literature on the prognostic relevance of imaging-based TK in patients with head and neck squamous cell carcinoma (HNSCC).

2 | Methods

This scoping review was primarily designed and registered as a systematic review (PROSPERO registration CRD42022370828). Given the limited number of studies and significant methodological heterogeneity, the research team decided to present the information in a scoping review. It is reported in accordance with the PRISMA-ScR guidelines (Appendix 1).

To comprehensively map and evaluate the existing evidence, this scoping review is structured around two complementary research questions:

1. "Which imaging-based methods have been used to quantify tumor kinetics in patients with squamous cell carcinoma of the oral cavity, oropharynx, larynx, and hypopharynx?"
2. "What is the prognostic value of imaging-derived tumor kinetics in these patients?"

A comprehensive search was conducted through Pubmed, Embase, and Scopus for articles in English or French published from 1990 to 5 November 2025. Search equations are detailed in Appendix 2. Included studies addressed either the estimated TG rate/velocity in HNSCC or the predictive performance of TG rate on survival and loco-regional control in treatment-naïve patients (oral cavity, larynx or pharynx). These had to measure changes in tumor size between two imaging acquisitions, including volumetric measures from CT, MRI or PET-CT.

The following were excluded:

- Unreviewed papers, narrative reviews, conferences, case reports, abstracts, posters, technical notes.
- Tumors from other head and neck sites (thyroid, salivary, nose and paranasal sinuses, cutaneous, nasopharynx, esophagus).
- Animal studies.
- Patients treated before or between both acquisitions.

Two authors (F.J. and G.D.) independently screened articles, resolving disagreements by consensus or with a third reviewer (S.V.d.V). The selection process is detailed in a PRISMA flowchart (Figure 1).

Quality and risk of bias (RoB) were evaluated using an adapted QUIPS tool [12] (Table 1 and Appendix 3). The authors applied it to the original article's main topic—not specifically to the TGR evaluation—to assess the general quality of the papers. Disagreements were resolved by consensus or by a third reviewer's (S.V.d.V) input.

Data extraction encompassed study type, population characteristics, imaging parameters (modality, injection, acquisition equivalence, delay, and interobserver agreement), tumor size measurement (technique and results), TG kinetics (TK) (e.g., tumor-specific growth rate [TSGR] and doubling time [DT]) and their prognostic relevance, and statistical analysis. Data were extracted by a first author and validated by a second author.

3 | Results

Results are summarized (Table 2), and complete data extraction is disclosed in supplemental materials (Appendix 4).

3.1 | Studies Selection, Quality Assessment, and Population

The search was complex due to the lack of a standardized vocabulary and inconsistency in TK parameters (TG velocity, TSGR, tumor DT ...) in the literature. The search in PubMed, Embase, and Scopus yielded in 22,019 articles, of which 4421 duplicates, 2611 non-English/French records, and 97 ineligible

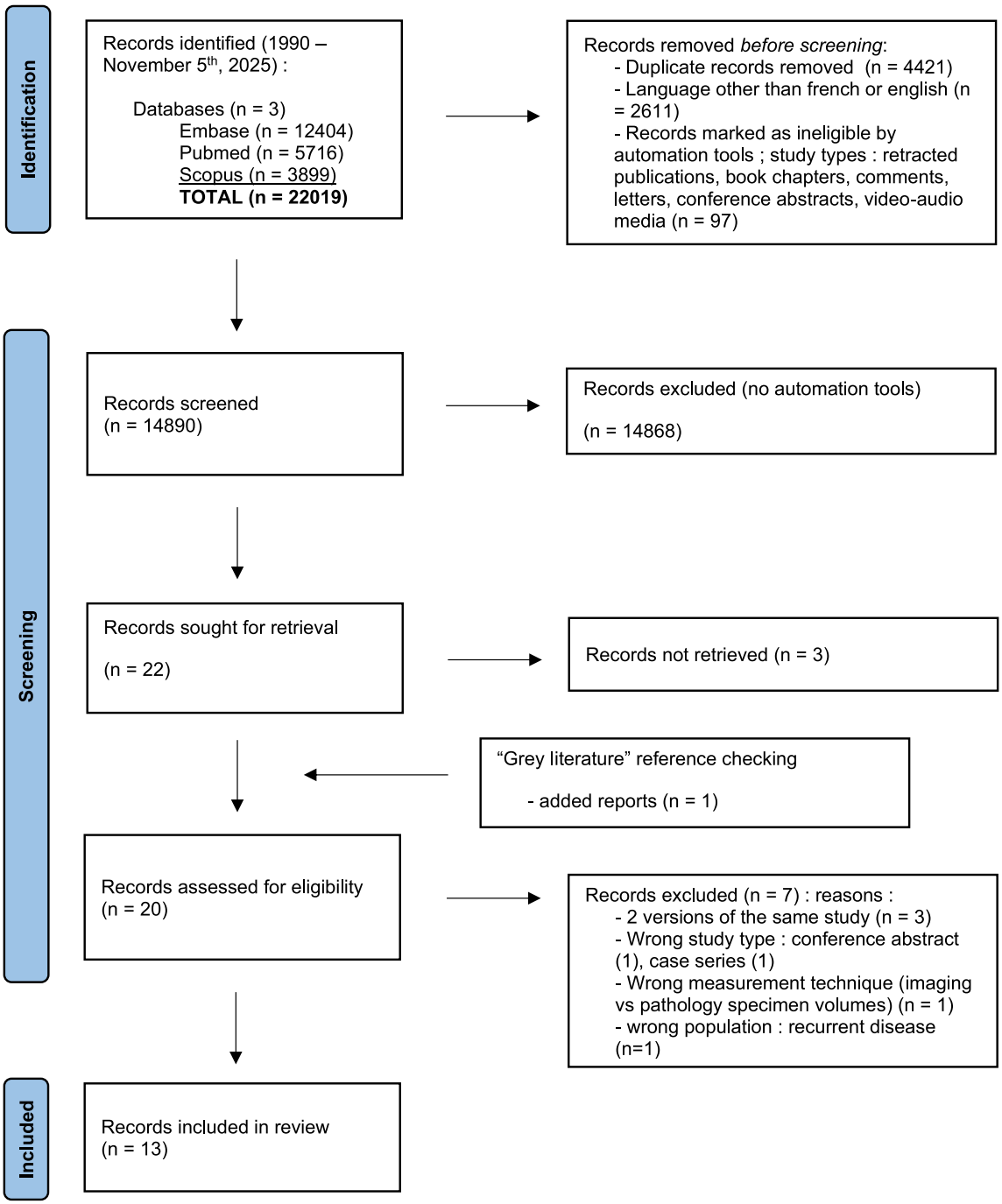

FIGURE 1 | Selection flowchart. Flow diagram of studies selection and eligibility assessment.

study types (retracted publications, book chapters, comments, letters, conference abstracts, video-audio media) were removed using automation tools, leaving 14,890 for screening. After a title and abstract review by both authors, 22 articles were shortlisted. Further full-text analysis allowed the exclusion of three studies for which full-text couldn't be obtained. Seven other studies were excluded: three were second unpublished versions of a selected study, one was a conference abstract observing patients with relapsing HNSCC receiving immunotherapy [26], one compared imaging volumes to pathological specimen volumes [27] and the last two didn't match the study type criteria (one was a conference abstract [28] and the other was a case series [29]). One additional paper [17] was identified by reference checking (grey literature) and added, resulting in a final selection of 13 studies.

The 13 studies, published between 2003 and 2024 were predominantly retrospective cohort studies, except for one retrospective diagnostic test accuracy study [16] and one prospective observational cohort study [14]. All were single-centre studies.

During the RoB evaluation, six studies were classified as low risk-of-bias [13, 15, 16, 20, 22, 24], six as moderate risk [14, 17, 18, 21, 23, 25], and one as high risk [19] (Appendix 3).

TABLE 1 | Risk of bias assessment (QUIPS tool)—summary.

Biases	Murphy [13]	Kishan [14]	Zumer [15]	Dejaco [16]	Delahaut [17]	Dejaco [18]	Waaijer [19]	Van Bockel [20]	Roldan [21]	Perni [22]	Jensen [23]	Zhang [24]	Fujima [25]	Global "Risk of bias"
1. Study participation	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Low	Low	Low	Low	Low	Low	Low
2. Study attrition	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Moderate	Low	Low
3. Prognostic factor measurement	Low	Low	Low	Low	Moderate	Moderate	Moderate	Low	Moderate	Low	Low	Moderate	Moderate	Moderate
4. Outcome measurement	Low	Moderate	Low	Low	Low	Low	Moderate	Low	Low	Low	High	Low	Low	Moderate
5. Study confounding	Low	Moderate	Moderate	Moderate	High	Moderate	High	Low	High	Moderate	Moderate	Low	High	High
6. Statistical Analysis and Reporting	Low	Low	Low	Low	Low	Low	Low	Low	Moderate	Low	Low	Low	Low	Low
Global "Risk of Bias"	Low	Moderate	Low	Low	Moderate	Moderate	High	Low	Moderate	Low	Moderate	Low	Moderate	

Key concerns in most studies included selection bias, attrition bias, and measurement bias. The major RoB lied in the absence of confounding factor evaluation in most studies.

Most studies had small sample sizes, with only four including more than 100 patients, and none provided statistical power calculations. We noticed that the RoB evaluation was also higher in low-volume studies. Selection criteria typically included primary HNSCC cases referred for curative RT or chemoradiotherapy (RCT) with at least two comparable pre-therapeutic imaging studies. Patients' mean age ranged from 56 to 68 years, and males were predominant (sex ratio from 2.0:1 to 10.2:1). Data on tobacco and alcohol use was largely unreported. Three studies included P16 status in their analyses.

3.2 | Measurement Techniques and Tumor Kinetics

Most diagnostic and simulation imaging were performed using CT scanners (mostly with contrast infusion), with occasional use of MRI or PET-CT. Strict imaging equivalence between diagnostic and pre-therapeutic scans was observed in only three studies. In some studies, the same modality was used, with minor discrepancies limited to slice thickness and inter-slice distance. The other main acquisition technique differences were window leveling and patient positioning, with and without thermoplastic masks. Delineation was usually performed by consensus between two or more observers, by a first observer with validation by a more experienced radiologist/radiation oncologist, or by a combination of both. The median interval between scans ranged from 19 to 42 days.

TV was mainly measured using two methods: the "slice-by-slice segmentation" method (manual delineation of the tumor area on each slice, multiplied by the inter-slice distance and summed) and the ellipsoid approximation based on the tumor's largest diameter across three orthogonal axes. It was mainly applied to the primary tumor volume (PTV) but sometimes also to the cervical lymph nodes identified as pathological according to predefined malignancy criteria (nodal tumor volume; NTV), or to both combined (total tumor volume; TTV).

Interobserver discrepancies in TV measurement were evaluated in only one study [18], which compared the ellipsoidal approximation with the segmentation method. The study showed that the ellipsoidal approximation using the three largest tumor axes produced PTV comparable to those from the summation of areas technique, with only a slight 8% underestimation, and with excellent inter- and intra-observer reproducibility. Fujima et al. [25] compared the largest tumor area, evaluated on a single slice at the same level in both acquisitions.

TG was evaluated using TV measurements over the time interval between the two acquisition sets. It was approximated using either an exponential (six studies) or a linear growth model (six studies), with one study not specifying the model. Terminology and calculation methods for TK showed significant heterogeneity (Appendix 5), with different approaches applied to PTV, NTV, or TTV, depending on the study design.

TABLE 2 | Results synthesis.

Authors	Dejaco	Dejaco	Delahaut	Fujima	Jensen	Kishan	Murphy
Year of publication	**2015**	**2019**	**2019**	**2017**	**2007**	**2014**	**2015**
Study characteristics							
Type of study	Diagnostic test accuracy study—comparative cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Non randomized prospective cohort study	Retrospective cohort study
Quality rating[a]	2	3	3	3	3	2	3
Sample size	74	123	19	55	61	12	85
Inclusion criteria	HNSCC[b] Treatment naive Advanced stage III/IV CUP[c] Two available CT[d]	HNSCC Any stage CUP available CT	OSCC[e] Treatment naive Measurable tumor volume Two available imaging	HNSCC Treatment naive MRI[f] Two comparable pretherapeutic imaging	HNSCC Treatment naive RT/RCT[g] Two Comparable imaging	HNSCC Treatment naive RT/RCT	OSCC Treatment naive RT/RCT Two available imaging Measurable primary Known P16/ smoking status
Exclusion criteria	Nose and paranasal sinuses cancer Stage I/II	Salivary or naso-sinusal cancer	M1 stage Previous HNSCC No contrast injection	Nasopharynx cancer Salivary cancer Recent biopsy	Nasopharynx cancer Salivary cancer	NA	Other HNSCC Non squamous Surgery/ palliative treatment < 7 days interval between scanners
Imaging parameters							
Modality	CT + contrast	CT + contrast	CT + contrast	CT + contrast MRI	CT MRI	CT CBCT	MRI CT + contrast
Interval between acquisitions	24.4 ± 13.4 days	29 ± 21 days	42 days [12; 72]	34.2 ± 4.15 days [25; 43]	28 days [5; 95]	13 days [7; 40]	35 days [8; 314]

(Continues)

TABLE 2 | (Continued)

Authors	Dejaco	Dejaco	Delahaut	Fujima	Jensen	Kishan	Murphy
Year of publication	**2015**	**2019**	**2019**	**2017**	**2007**	**2014**	**2015**
Tumor volume measurement	Slice by slice segmentation Ellipsoid approximation Cuboid approximation	Ellipsoid approximation	Slice by slice segmentation (GTV)[j]	Largest tumor surface on one slice	Ellipsoid approximation	Slice by slice segmentation (GTV)	Slice by slice segmentation (GTV)
Tumor kinetics							
Relative PTV[k] increase	28%	NA	56.3% [−8%; 194%]	Maximum volume increase/30 days = 30.5%/30 ± 20.1 days	NA	Median = 16.04% ($p = 0.024$) Mean 19.13% [8.03; 47.41%]	NA
Tumor growth calculation	SGR[l] = ln(V_1.V_2)/t	SGR = ln(V_1.V_2)/t	TGV[m] or NGV[n] = 100[($V_2 - V_1$)/V_1]/t	$V_2 = V_1(\text{Growth}^o)^{(t/30)}$	NA	Relative increase in size = ($V_2 - V_1$)/$V_1 \times 100\%$	TSGR[p] = ln2/DT
Relative PTV progression rate	0.97%/day (±0.49)	1.8% ± 1.8%/day [−2.6; 8.6]	1.84%/day [−0.23; 12.9]	"Discovery group": 1.15%/day "Validation group" 1.02%/day	NA	Median 1.23%/day Mean 1.47%/day	Median: 0.74%/day
PTV doubling time (DT)	NA	Mean = 43 days 75th perc = 85 days 25th perc = 24 days	Mean = 286 days [7; 1282] Median = 100 days	NA	NA	NA	NA
Prognostic impact							
Tumor growth stratification: cut-off values	NA	Slow: < 0.3%/day Intermediate: [0,3–3] %/day Rapid: > 3%/day	1%/day	For OS[r] [137.8–139.4]%/day For PFS[s][136.3–137.6]%/day	NA	NA	0.74%/day
LRC[u]	NA	NA	NA	NA	NA	NA	NA
OS	NA	Not correlated	NA	Not significatively correlated $p > 0.05$	NA	NA	3 year-OS Inversely correlated ($p < 0.001$)

(Continues)

TABLE 2 | (Continued)

Authors	Dejaco	Dejaco	Delahaut	Fujima	Jensen	Kishan	Murphy
Year of publication	**2015**	**2019**	**2019**	**2017**	**2007**	**2014**	**2015**
DSS[x]	NA	NA	No significant correlation HR = 2.2	NA	NA	NA	NA
DFS[y]	NA	NA	No significant correlation HR = 2.2	NA	NA	NA	Inversely correlated ($p < 0.001$): In univariate regression: T-stage, tobacco usage, P16-, T volume In multivariate regression: TSGR
PFS[z]	NA	No correlation	NA	Correlated ($p < 0.05$)	NA	NA	NA

Authors	Perni	Roldan	Van Bockel	Waaijer	Zumer	Zhang
Year of publication	**2016**	**2020**	**2014**	**2003**	**2020**	**2024**
Study characteristics						
Type of study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study
Quality rating[a]	3	3	3	3	3	3
Sample size	101	39	131	13	52	105
Inclusion criteria	OSCC Treatment naive Curative RT/RCT Two available imaging Measurable tumor Minimal 2-weeks interval No interval treatment	LSCC[h], HSCC[i] Treatment naive RT/RCT Two available imaging Measurable tumor Known smoking status	LSCC Treatment naive RT/RCT Two available imaging Measurable tumor	OSCC M0 stage treatment naive curative RT/RCT 2 Available imaging	HNSCC Treatment naive curative RT/RCT Two comparable imaging	LSCC Treatment naive RT/CRT Two available CT

(Continues)

TABLE 2 | (Continued)

Authors	Perni	Roldan	Van Bockel	Waaijer	Zumer	Zhang
Year of publication	**2016**	**2020**	**2014**	**2003**	**2020**	**2024**
Exclusion criteria	Other HNSCC Non squamous Improper image format	Other HNSCC Non squamous Unknown smoking < 7 days interval between scanners	Other HNSCC Non squamous Previous RT Artifacts/ improper image	Other HNSCC Non squamous Unknown smoking status	T1N0/T2N0 glottic LSCC Other histologies Artifacted/ improper imaging	< 18 years old M1 stage
Imaging parameters						
Modality	CT + contrast PET-CT	CT + contrast MRI PET	CT + contrast MRI PET	CT + contrast MRI PET	CT + contrast	CT + contrast
Interval between acquisitions	27 days [14; 137]	22 days [7; 170]	25.7 ± 11.6 days	Mean 34 days Median 35 days [12 days; 47 days]	Median 19 days [3; 108 days]	
Tumor volume measurement	Slice by slice segmentation (GTV)	Slice by slice segmentation (GTV)	Slice by slice segmentation (GTV)	Slice by slice segmentation (GTV)	Slice by slice segmentation (GTV)	Slice by slice segmentation (GTV)
Tumor kinetics						
Relative PTV^{k} increase	NA	NA	NA	70% [11%; 235%]	NA	NA
Tumor growth calculation	$TGV = 100[(V_2 - V_1)/V_1]/t$	$TSGR = \ln 2/DT$	$TGR^{q} = \ln(V_2 - V_1)/t$	NA	Tumor relative increase $rate = (V_2 - V_1)^{(1/t)}$	$TGR = V_2 - V_1/t$
Relative PTV progression rate	0.65%/day [0–9.37]	0.93%/day	NA	NA	Mean 3.2%/day Median: 1.03%/day [0.99; 1.41]	NA
PTV doubling time (DT)	112 days [61–266]	NA	NA	Mean 96 days [21; 256]	19 days [2; 659]	NA
Prognostic impact						
Tumor growth stratification: cut-off values	TGV: 1%/day DT: 80 days	Median: 0.93%/day 75th percentile: 2.18%/day [0.043; 7.31]	Mean: 0.3 ln(cc/day)	NA	1%/day	OS: 0.036 mL/day RFS^{t}: 0,082 mL/day

(Continues)

TABLE 2 | (Continued)

Authors	Perni	Roldan	Van Bockel	Waaijer	Zumer	Zhang
Year of publication	**2016**	**2020**	**2014**	**2003**	**2020**	**2024**
LRC[u]	5year-LRC[v]: correlated Univariate regression: HR[w] = 16.9 ($p = 0.004$) Multivariate regression: HR = 38.9 ($p = 0.02$)	No significant correlation ($p > 0.05$)	No significant correlation	NA	Not correlated	Correlated OR = 7.4 (95% CI, [1.89–29.8])
OS	5year-OS: Univariate regression: HR = 10.1 ($p < 0.0001$) Multivariate regression: HR = 17.2 ($p = 0.04$)	Stratified on the median: no significant correlation Stratified on the 75th percentile: Correlated HR = 2.12 [1.16–11.42] ($p = 0.018$)	Correlated after univariate regression HR = 1.9 [1.2; 3.2]	NA	NA	Correlated HR 1.43 (95% CI, [0.63–3.26])
DSS[x]	NA	NA	NA	NA	not correlated	NA
DFS[y]	NA	No significant correlation ($p = 0.786$)	Correlated (Univariate regression only) HR = 2.4 [1.3; 4.4] Significant confounding factors: age, differentiation, T-volume	NA	Not correlated	NA
PFS[z]	NA	NA	NA	NA	NA	NA

Note: (a) According to the Quality Rating Scheme for Studies and Other Evidence modified from the Oxford Centre for Evidence-based Medicine for ratings of individual studies. (b) HNSCC: head and neck squamous cell carcinoma. (c) CUP: carcinoma of unknown primary. (d) CT: computed tomography. (e) OSCC: oropharyngeal squamous cell carcinoma. (f) MRI: magnetic resonance imaging. (g) RT: radiation therapy/CRT: chemoradiotherapy. (h) LSCC: Laryngeal squamous cell carcinoma. (i) HSCC: hypopharyngeal squamous cell carcinoma. (j) GTV: gross tumor volume. (k) PTV: primary tumor volume. (l) SGR: specific growth rate. (m) TGV: tumor growth velocity. (n) NGV: nodal growth velocity. (o) Growth: defined as the estimated % increase in TV after 30 days. (p) TSGR: tumor specific growth rate. (q) TGR: tumor growth rate. (r) OS: odd survival. (s) PFS: progression-free survival. (t) RFS: recurrence-free survival. (u) LRC: loco-regional control. (v) 5year-LRC: LRC at 5 years follow-up. (w) HR: hazard ratio. (x) DSS: disease specific survival. (y) DFS: disease-free survival. (z) PFS: progression-free survival.

Values for absolute and relative TG rates showed high variability between patients across studies. Median values were also heterogeneous, with median relative growth rates ranging from 0.65% to 1.84% per day, while DT ranged from 19 to 286 days for PTV and from 41 to 99 days for NTV. In studies with only oropharyngeal tumors, the growth rate was around 1% with a DT of around 100 days. Progression was evaluated according to TNM staging systems or RECIST criteria in two papers, showing 17 to 26% TNM upstaging and 30% to 73% volume increase according to RECIST (> 20% progression in TTV over 5 main targets).

3.3 | Prognostic Impact and Stratification

Nine studies evaluated prognostic outcomes, with follow-up periods ranging from 22 to 59 months, as reported in five papers. Various cut-off values of TK parameters were used to assess the prognostic significance:

- Dejaco et al. [18] found no significant correlation between TSGR and OS or progression-free survival (PFS), using stratification between slow (< 0.3%/day), intermediate (between 0.3% and 3%/day), and fast (> 3%/day) growing HNSCC.
- Perni et al. [22] found in univariate analysis that the linear TGV of OPSCC at a cut-off value of 1%/day (DT = 80 days) was the only predictor of the 5 years OS (HR 10.1), 5 years LRC (HR 16.9), and 5 years metastasis-free survival (HR 5.24). In multivariate regression, TGV > 1%/day remained the only significant predictor of local control and the strongest independent predictor of metastasis-free survival.
- Delahaut et al. [17], applying the same TGV formula and cut-off as Perni to 19 OPSCC patients, did not find a significant correlation with disease-free survival (DFS) and disease-specific survival (DSS).
- Roldan et al. [21] stratified TSGR on its median (0.93%/day) and its 75th percentile (2.18%/day). Only the latter had a significant association with 2-, 3- and 5-year OS (HR 2.12) and a non-significant trend with DFS. It wasn't correlated to local recurrence-free survival (RFS).
- Zumer et al. (excluding T0/T1 glottic SCC) could not find any significant association between the linear relative increase rate with a cut-off at 1%/day and LRC, DSS and DFS.
- Murphy et al. [13] reported in OPSCC that TSGR at 0.74%/day correlated with 3-year OS and DFS in OPSCC patients in uni- and multivariate analysis.
- Van Bockel et al. [20] found that TGR was significantly correlated to OS and DFS in laryngeal SCC patients when treated as a continuous variable but lost significance when adjusted for N-stage.
- Zhang et al. [24] identified a significant correlation between survival- and recurrence-related TGR and both overall survival (OS) and RFS, using cut-off values of > 0.036 and > 0.085 mL/day, respectively, for population stratification.
- Fujima et al. [25] reported a statistical correlation between their version of relative tumor increase and DFS but not with OS.

When a positive correlation with TGR was found, it was generally with OS. Given the heterogeneity of the parameters analyzed and the stratification used, no meta-analysis could be performed based on these results. We can infer that studies with positive correlations were more likely to be withdrawn from RCTs with larger sample sizes, lower RoB scores, and proper segmentation and calculation methodology.

Several factors correlated with TK, although results were inconsistent across studies. Notable covariates included proliferation markers (e.g., Ki-67, EGFR, CD44), initial tumor and nodal volumes, time interval between scans, laryngeal subsites in LSCC, N-stage, T-stage, tobacco use, p16 status, RTOG 0129 risk groups and tumor differentiation. These factors showed varying degrees of influence on TK, with contradictory results.

4 | Discussion

Reviewed studies span the past 20 years, reflecting a growing interest in TK as imaging technologies and RT have become more prevalent. Ethical challenges in studying cancer treatment delays contribute to the scarcity of prospective or randomized studies on this topic. To overcome these limitations, this scoping review aims to discuss the limitations of existing literature and the different aspects to consider in the design of future work in this field.

The sample size was generally small, even with extended recruitment periods, due to challenges such as unavailable comparable imaging or difficulties in defining TVs because of unclear boundaries or imaging artifacts. Defining the target population—general HNSCC patients versus those undergoing RT or chemoradiotherapy (RCT)—is essential for future studies. To date, most studies have focused on RT-selected patients, taking advantage of a second acquisition opportunity for simulation CT. This results in an overrepresentation of higher-stage tumors and an under-representation of oral cavity squamous-cell carcinomas (OCSCC) due to fewer RT indications. Moreover, small tumors (e.g., T1–T2 glottic cancers) are inherently more challenging to detect and delineate. That represents a possible selection bias that may affect TG. If possible, every measurable tumor should be included to better understand TK in the general population. More generally, TK in surgical or metastatic patients could be evaluated if they benefit from a second set of imaging before treatment initiation, even if that condition could also raise some ethical limitations. Tumor sub-site in the head and neck was used in many studies as an inclusion or exclusion criterion. Tumor location might also represent a potential confounder as subsites may influence prognostic. In few studies, Sino-nasal and salivary SCC and carcinomas of unknown primary were part of the cohort. These are rare entities that should be treated in a subgroup or excluded from further study. For oropharyngeal cancers (OPSCC), HPV status must be included in a subgroup analysis, as it is a crucial prognostic factor influencing overall and PFS [30].

Whatever imaging modality (CT, MRI, PET/CT) is used, increasing reproducibility and improving comparability between acquisitions requires standardizing imaging protocols across institutions and, if possible, using the same scan in a fixed

position. Despite these efforts, random measurement errors are an unavoidable reality in TV delineation. Interobserver and intraobserver variability are well-known and studied parameters in gross TV and organs at risk delineation. Although guidelines exist [31], inconsistencies persist, even among experienced professionals [32, 33]. As mentioned, unresolved issues remain regarding spatial resolution, measurement errors, and the actual TG rate. Currently, it is challenging to determine the minimal interval between scans needed to distinguish random measurement variability from actual progression. Combining the observations of at least two qualified observers with verification by a radiologist or radiation oncologist appears to be the most reliable approach. Future studies should compare this method with automated or semi-automated delineation tools to establish the most accurate technique. While time-consuming, the "slice-by-slice summation" technique is the most accurate for evaluating TV, especially in head and neck cancers.

Although the study by Dejaco et al. [16] demonstrated its accuracy in the head and neck, the ellipsoid approximation—developed for more uniform TG in abdominal and pulmonary areas—could apply less to the head and neck region due to the irregular growth patterns of the tumors in this area, constrained by natural barriers. It could be useful clinically as it is easier and quicker than the slice-by-slice delineation technique. Its validity should be further confirmed. Heterogeneity in measurement methods prevented a meaningful meta-analysis of TV increase across studies.

Although some studies also measured NTV because of its prognostic relevance, factors such as hemorrhage, necrosis, and inflammation can skew these measurements by overestimating the actual viable neoplastic tissue [34]. Until nodal volume assessments become more accurate, it is advisable to rely on N-stage or RECIST criteria rather than nodal volume when studying TK.

Variability in growth calculations was notable, as many studies employed linear rather than exponential models. The latter are more accurate for evaluating three-dimensional TG. Among proposed TK formulas, Mehrara's TSGR offers a more accurate reflection of exponential growth patterns than DT, which can be distorted by short intervals or measurement uncertainties [35]. If DT is calculated, median values are more suitable than averages. Although tumor expansion is related to the number of proliferating cells, there are additional roles for anatomical constraints, the tumor microenvironment (including necrosis and nutrient intake), and the immune response in cancer progression, which induce uncertainties and fluctuations in the calculation of TG rates that mathematical models cannot fully account for. Even if they are less accurate, linear models are easier to use and allow a good approximation of TG at a specific point in cancer evolution. In every model, prolonging the time interval and increasing measurement precision yield better growth rate estimates.

In addition to the heterogeneity in mathematical models, discrepancies in population and measurement methods have rendered comparisons of TGR between studies meaningless. Nevertheless, the authors highlight the need for subgroup analysis by location and for HPV-positive patients with OPSCC.

Regarding the potential prognostic impact of TGR, analyses revealed significant variability, likely due to differences in population characteristics and methodological heterogeneity. Despite these inconsistencies, most high-quality and high-volume studies reported a negative impact of rapid TG on local recurrence control (LRC), OS, and DFS. In those studies, results were more significant when stratifying by high-risk tumors or combining them with validated risk scales (e.g., the RTOG 0129 study's risk groups [36]).

However, prognostic analysis revealed considerable heterogeneity across studies, complicating the interpretation of the data. Different TK calculation methods and inconsistent outcome measures (e.g., survival vs. local control) hindered comparability. Currently, the available data are insufficient to confirm a predictive impact of TGR on oncological outcomes.

Several studies have also evaluated confounders and other factors that may correlate with TGR. Key factors that may correlate with TSGR include initial tumor stage and volume, tobacco use, age, and HPV status (in OPSCC). One study also found a correlation between TGR and Ki67, a well-known histopathological marker of cell proliferation [18]. Nevertheless, inconsistent results across studies necessitate more controlled trials to confirm these associations.

TGR as a prognostic tool shows promising results in many studies with appropriate methodology, but these studies suffer from major heterogeneity in their design. Aside from the design, we also outlined many limitations in the calculation of TGR itself and in the arbitrary choice of its cut-off in the evaluation of its prognostic impact in the previous paragraphs. Let's recall the lack of data on p16 status, the selection bias towards large-volume tumors due to the majority of patients treated with radiation, which may have a strong impact on tumor biology, the lack of standardization in imaging acquisition that may hinder comparability between scans, the variability in segmentation, and the delay before treatment, all of which are confounding factors that must be part of further investigation.

Identifying factors correlated with TK is crucial for developing a robust prediction tool based on multiple parameters. Moreover, TK are currently available only after a time interval. If any predictive capacity is demonstrated, their clinical use would be more appreciated at the time of diagnosis, before the treatment decision. Using those parameters, alone or in combination, to predict TG and aggressiveness could be a step forward in personalized cancer care. Those factors, available at diagnosis, could include imaging parameters (such as T volume, MRI diffusion parameters, radiomics algorithms, and metabolic parameters), biological parameters (Ki-67, differentiation, p16, and genomics), or clinical data (age, tobacco use, and T-stage). More research is needed in the future to investigate these elements.

5 | Conclusion

This scoping review revealed significant heterogeneity in study design, imaging techniques and volume measurement for TK in HNSCC. These discrepancies do not allow results to be

synthesized and a systematic review and meta-analysis conducted. Despite some studies suggesting a potential impact of TK on survival and loco-regional control, there is currently insufficient evidence to use TGR to predict treatment outcomes or guide personalized treatment planning. It is therefore necessary to conduct more high-quality, controlled trials and, eventually, prospective studies with large sample sizes to be more definitive about the role of TK in HNSCC.

To achieve this, the authors propose the following recommendations:

- Standardization of Imaging Protocols: Consistent imaging techniques across institutions are essential for comparability.
- Accurate Volume Measurement: The slice-by-slice summation technique should be preferred, despite its time-consuming nature, because of its accuracy. The ellipsoid approximation of TV requires further validation in controlled studies due to its convenience for clinical use.
- Interobserver Agreement: Aim for consensus among multiple qualified observers, with verification by experienced radiologists or oncologists.
- Subgroup analysis is crucial for OPSCC (HPV), as it significantly influences prognosis.
- Stratified Analysis: High-risk tumors should be identified using established risk scales, and TSGR should be the preferred metric to DT.
- Study of Prognostic Factors: Future studies should investigate the impact of TK on outcomes, adjusting for variables such as T-stage, TV, tobacco use, age, and P16 status.

Acknowledgments

This review was conducted as part of G. Delahaut's thesis, which was supported by a grant from Fondation Mont-Godinne. ChatGPT 4.0 (OpenAI) was used on 19 September 2024 solely to reduce the overall word count. Both co-authors take responsibility for the integrity of the content of this review, which was an original creation. The review was checked after AI usage to ensure that no pertinent information was lost or altered. It was also used to assist in refining and validating the literature search equations.

Funding

This review has been realized as a part in G. Delahaut's thesis which was delivered a Grant from *Fondation Mont Godinne*.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. A. Jemal, T. Murray, E. Ward, et al., "Cancer Statistics, 2005," *CA: A Cancer Journal for Clinicians* 55 (2005): 10–30.

2. R. Kurek, A. Kalogera-Fountzila, K. Muskalla, et al., "Usefulness of Tumor Volumetry as a Prognostic Factor of Survival in Head and Neck Cancer," *Strahlentherapie und Onkologie* 179, no. 5 (2003): 292–297, https://doi.org/10.1007/s00066-003-1017-0.

3. A. Strongin, S. Yovino, R. Taylor, et al., "Primary Tumor Volume Is an Important Predictor of Clinical Outcomes Among Patients With Locally Advanced Squamous Cell Cancer of the Head and Neck Treated With Definitive Chemoradiotherapy," *International Journal of Radiation Oncology, Biology, Physics* 82, no. 5 (2012): 1823–1830, https://doi.org/10.1016/j.ijrobp.2010.10.053.

4. G. A. Plataniotis, M. E. Theofanopoulou, A. Kalogera-Fountzila, et al., "Prognostic Impact of Tumor Volumetry in Patients With Locally Advanced Head-And-Neck Carcinoma (Non-Nasopharyngeal) Treated by Radiotherapy Alone or Combined Radiochemotherapy in a Randomized Trial," *International Journal of Radiation Oncology, Biology, Physics* 59, no. 4 (2004): 1018–1026, https://doi.org/10.1016/j.ijrobp.2004.01.021.

5. G. Creff, A. Devillers, A. Depeursinge, et al., "Evaluation of the Prognostic Value of FDG PET/CT Parameters for Patients With Surgically Treated Head and Neck Cancer: A Systematic Review," *JAMA Otolaryngology. Head & Neck Surgery* 146, no. 5 (2020): 471–479, https://doi.org/10.1001/jamaoto.2020.0014.

6. P. Bonomo, A. Merlotti, E. Olmetto, et al., "What Is the Prognostic Impact of FDG PET in Locally Advanced Head and Neck Squamous Cell Carcinoma Treated With Concomitant Chemo-Radiotherapy? A Systematic Review and Meta-Analysis," *European Journal of Nuclear Medicine and Molecular Imaging* 45, no. 12 (2018): 2122–2138, https://doi.org/10.1007/s00259-018-4065-5.

7. S. Payabvash, "Quantitative Diffusion Magnetic Resonance Imaging in Head and Neck Tumors," *Quantitative Imaging in Medicine and Surgery* 8, no. 10 (2018): 1052–1065, https://doi.org/10.21037/qims.2018.10.14.

8. L. G. Marcu, P. Reid, and E. Bezak, "The Promise of Novel Biomarkers for Head and Neck Cancer From an Imaging Perspective," *International Journal of Molecular Sciences* 19, no. 9 (2018): 2511, https://doi.org/10.3390/ijms19092511.

9. C. T. Murphy, T. J. Galloway, E. A. Handorf, et al., "Increasing Time to Treatment Initiation for Head and Neck Cancer: An Analysis of the National Cancer Database," *Cancer* 121, no. 8 (2015): 1204–1213.

10. Z. Chen, W. King, R. Pearcey, M. Kerba, and W. J. Mackillop, "The Relationship Between Waiting Time for Radiotherapy and Clinical Outcomes: A Systematic Review of the Literature," *Radiotherapy and Oncology* 87, no. 1 (2008): 3–16.

11. A. Coca-Pelaz, R. P. Takes, K. Hutcheson, et al., "Head and Neck Cancer: A Review of the Impact of Treatment Delay on Outcome," *Advances in Therapy* 35 (2018): 153–160.

12. J. A. Hayden, D. A. van der Windt, J. L. Cartwright, P. Côté, and C. Bombardier, "Assessing Bias in Studies of Prognostic Factors," *Annals of Internal Medicine* 158, no. 4 (2013): 280–286.

13. C. T. Murphy, K. Devarajan, L. S. Wang, et al., "Pre-Treatment Tumor-Specific Growth Rate as a Temporal Biomarker That Predicts Treatment Failure and Improves Risk Stratification for Oropharyngeal Cancer," *Oral Oncology* 51, no. 11 (2015): 1034–1040.

14. A. U. Kishan, J. Cui, P. C. Wang, M. E. Daly, J. A. Purdy, and A. M. Chen, "Quantification of Gross Tumour Volume Changes Between Simulation and First Day of Radiotherapy for Patients With Locally Advanced Malignancies of the Lung and Head/Neck," *Journal of Medical Imaging and Radiation Oncology* 58, no. 5 (2014): 618–624.

15. B. Žumer, M. Pohar Perme, S. Jereb, and P. Strojan, "Impact of Delays in Radiotherapy of Head and Neck Cancer on Outcome," *Radiation Oncology* 15 (2020): 1–10.

16. D. Dejaco, C. Url, V. Schartinger, et al., "Approximation of Head and Neck Cancer Volumes in Contrast Enhanced CT," *Cancer Imaging* 15 (2015): 1–9.

17. G. Delahaut, S. Témam, J. Ambroise, Y. Tao, F. Janot, and S. Van der Vorst, "Prognostic Impact of Tumor Growth Velocity in Head and Neck Squamous Cell Carcinoma Treated by Radiotherapy: A Pilot Study," *Head & Neck* 41, no. 9 (2019): 3041–3048.

18. D. Dejaco, T. Steinbichler, V. H. Schartinger, et al., "Specific Growth Rates Calculated From CTs in Patients With Head and Neck Squamous Cell Carcinoma: A Retrospective Study Performed in Austria," *BMJ Open* 9, no. 2 (2019): e025359.

19. A. Waaijer, C. H. Terhaard, H. Dehnad, et al., "Waiting Times for Radiotherapy: Consequences of Volume Increase for the TCP in Oropharyngeal Carcinoma," *Radiotherapy and Oncology* 66 (2003): 271–276.

20. L. W. van Bockel, G. M. Verduijn, E. M. Monninkhof, F. A. Pameijer, and C. H. Terhaard, "The Importance of Actual Tumor Growth Rate on Disease Free Survival and Overall Survival in Laryngeal Squamous Cell Carcinoma," *Radiotherapy and Oncology* 112, no. 1 (2014): 119–124.

21. C. S. Roldan, J. J. Chen, M. M. Fareed, et al., "Impact of Primary Tumor-Specific Growth Rate on Treatment Failure for Nonoropharyngeal Head and Neck Cancers," *Laryngoscope* 130, no. 10 (2020): 2378–2384.

22. S. Perni, A. S. Mohamed, J. Scott, et al., "CT-Based Volumetric Tumor Growth Velocity: A Novel Imaging Prognostic Indicator in Oropharyngeal Cancer Patients Receiving Radiotherapy," *Oral Oncology* 63 (2016): 16–22.

23. A. R. Jensen, H. M. Nellemann, and J. Overgaard, "Tumor Progression in Waiting Time for Radiotherapy in Head and Neck Cancer," *Radiotherapy and Oncology* 84, no. 1 (2007): 5–10.

24. F. G. Zhang, S. Viswanathan, C. Zhang, et al., "Association of Tumor Growth Rate With Overall Survival and Recurrence Among Patients With Laryngeal Squamous Cell Carcinoma," *Head & Neck* 47 (2024): 23–33, https://doi.org/10.1002/hed.27888.

25. N. Fujima, T. Sakashita, A. Homma, et al., "Non-Invasive Prediction of the Tumor Growth Rate Using Advanced Diffusion Models in Head and Neck Squamous Cell Carcinoma Patients," *Oncotarget* 8, no. 20 (2017): 33631–33643.

26. C. Suzuki, N. Kiyota, Y. Imamura, et al., "Relationship Between Tumor Burden to Growth Rate and Treatment Outcomes of Nivolumab for Patients with Head and Neck Squamous Carcinoma, 2019 ASCO-SITC Clinical Immuno-Oncology Symposium," *Journal of Clinical Oncology* 37, no. suppl (2019): 68, https://ascopubs.org/doi/10.1200/JCO.2019.37.8_suppl.68.

27. J. G. Wihlidal, K. Y. Tay, S. D. MacNeil, et al., "Demographic and Pathologic Factor Regression to a Growth Rate Model of p16-Negative Oral Cavity Squamous Cell Carcinoma," *Laryngoscope Investigative Otolaryngology* 7, no. 5 (2022): 1384–1390.

28. M. Dziemianowicz, C. T. Murphy, K. Devarajan, et al., "Evaluating the Impact of Node-Specific Growth in Patients With Node-Positive Oropharyngeal Cancer," *International Journal of Radiation Oncology, Biology, Physics* 96, no. 2 (2016): E368–E369, https://doi.org/10.1016/j.ijrobp.2016.06.1558.

29. Y. Miyasaka, Y. Kusano, N. Mizoguchi, et al., "Development of a Tumor Growth-Responsive Robust Planning Method for Head and Neck Cancer in Carbon-Ion Radiotherapy," *Anticancer Research* 44, no. 11 (2024): 5113–5122, https://doi.org/10.21873/anticanres.17336.

30. K. K. Ang, J. Harris, R. Wheeler, et al., "Human Papillomavirus and Survival of Patients With Oropharyngeal Cancer," *New England Journal of Medicine* 363, no. 1 (2010): 24–35.

31. C. L. Brouwer, R. J. Steenbakkers, J. Bourhis, et al., "CT-Based Delineation of Organs at Risk in the Head and Neck Region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG Consensus Guidelines," *Radiotherapy and Oncology* 117, no. 1 (2015): 83–90.

32. J. van der Veen, A. Gulyban, and S. Nuyts, "Interobserver Variability in Delineation of Target Volumes in Head and Neck Cancer," *Radiotherapy and Oncology* 137 (2019): 9–15.

33. J. van der Veen, A. Gulyban, S. Willems, F. Maes, and S. Nuyts, "Interobserver Variability in Organ at Risk Delineation in Head and Neck Cancer," *Radiation Oncology* 16 (2021): 1–11.

34. K. P. Chu, J. D. Murphy, T. H. La, et al., "Prognostic Value of Metabolic Tumor Volume and Velocity in Predicting Head-And-Neck Cancer Outcomes," *International Journal of Radiation Oncology, Biology, Physics* 83, no. 5 (2012): 1521–1527.

35. E. Mehrara, E. Forssell-Aronsson, H. Ahlman, and P. Bernhardt, "Quantitative Analysis of Tumor Growth Rate and Changes in Tumor Marker Level: Specific Growth Rate Versus Doubling Time," *Acta Oncologica* 48, no. 4 (2009): 591–597.

36. C. Fakhry, Q. Zhang, M. L. Gillison, et al., "Validation of NRG Oncology/RTOG-0129 Risk Groups for HPV-Positive and HPV-Negative Oropharyngeal Squamous Cell Cancer: Implications for Risk-Based Therapeutic Intensity Trials," *Cancer* 125, no. 12 (2019): 2027–2038, https://doi.org/10.1002/cncr.32025.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix 1** Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist. **Appendix 2** Database search equations. **Appendix 3** Risk of bias assessment (QUIPS) detailed. **Appendix 4** Results. **Appendix 5** Doubling time (DT) and tumor growth kinetics formulae in selected reports.