Systematic Review

# Nodal tumor volume as a prognostic factor for head and neck squamous cell carcinoma: a systematic review

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## 1. Abstract

**Introduction**: Several studies suggest that there is an association between the metastatic nodal tumor volume and the clinical outcome in patients with solid cancers. However, despite the prognostic potential of nodal volume, a standardized method for estimating the nodal volumetric parameters is lacking. Herein, we conducted a systematic review of the published scientific literature towards investigating the prognostic value of nodal volume in the carcinomas of head and neck, taking into consideration the primary tumor site and the human papillomavirus (HPV) status. **Methodological issues**: For this purpose, the biomedical literature database PubMed/MEDLINE was searched for studies relevant to the relationship of nodal volume to the treatment outcome and survival in head and neck squamous cell carcinoma (HNSCC) patients. Collectively, based on stringent inclusion/exclusion criteria, 23 eligible studies were included in the present systematic review. **Results**: On the basis of our findings, nodal volume is suggested to be strongly associated with clinical outcomes in HNSCC patients. Of particular note, there is an indication that nodal volume is an independent factor for further risk stratification for recurrence-free survival in patients with squamous cell carcinoma of the pharynx (oropharynx and hypopharynx). Extranodal extension (ENE) and HPV status should be also taken into consideration in further studies.

## 2. Introduction

Accumulating evidence suggests that the presence of metastatic lymph nodes represents the most accurate predictor of clinical outcome for patients with head and neck squamous cell carcinoma (HNSCC) [1, 2]. Furthermore, human papillomavirus (HPV) infection (primarily type 16) is considered to be a prominent risk factor and an important prognostic indicator for HNSCC patients. Hence, HNSCC can be classified into two distinct types, HPV-positive and HPV-negative, with distinct mutational landscape, response to clinical treatment, and survival outcomes [2]. In a

study by Gillison *et al*. (2012) [3], conducted in the United States, it has been demonstrated that there is a shift in the primary site distribution of HNSCC, with a steady increase of oropharyngeal squamous cell carcinoma (OPSCC) and a decline in cancers of the larynx and hypopharynx. This change is consistent with a decrease in tobacco use and the exposure to high-risk oncogenic HPV [3, 4]. Notably, there are distinct patterns of geographic variation in HPV-related oropharyngeal cancer, with higher prevalence in Western Europe; there are limited recent data available for Eastern Europe, Asia or Africa [5].

The prognostic value of the nodal tumor parameters including the extranodal extension (ENE) or extracapsular spread (ECS), the lymph node ratio (LNR) and the number of positive nodes (pN) in HNSCC, has been thoroughly investigated through systematic reviews and large-scale studies [6–9]. ECS was found to have a negative effect on HPV-negative OPSCC and is recognized as a major criterion for the selection of high-risk HNSCC patients undergoing adjuvant chemotherapy in post-operative settings [7]. Moreover a combination of the ECS status and LNR value was found to have improved prediction power of outcomes in HPV-negative HNSCC patients [6]. The volume of the metastatic lymph nodes is another parameter that is considered to be of prognostic importance, given that a nearly linear relationship between the clonogenic tumor cell number and tumor control has been observed [10]. As far as the gross tumor volume (i.e., primary and nodal tumor volume) is concerned, there is a growing number of studies supporting its strong association with clinical outcomes and recurrence in HNSCC patients. Moreover, several studies suggest that tumor volume is the most important predictor of head and neck cancers, even superior to the Tumor, Nodes, Metastasis (TNM) staging [11, 12]. Of particular importance, in spite of the prognostic capacity of nodal volume, there is not currently a consensus regarding the measurement of nodal volumetric parameters, as highlighted by Lodder *et al.* [13].

The American Joint Committee on Cancer (AJCC) classification offers a reliable method for differentiating HNSCC patients with different prognoses. To date, TNM represents a staging system mainly focused on operability. TNM considers, in its prognostic stratification, only two-dimensional lymph nodes' measurements or not at all, lacking quantitative volumetric evaluation of the tumor load. However, volumetric parameters are of great importance especially in the modern radiation therapy era where they could be useful in improving the accuracy of decision making in precision radiotherapy, than the simple measurement of the maximal diameter of regional lymph nodes. In the eighth TNM/AJCC edition several changes were introduced regarding the TNM staging classification for head and neck cancers. These changes are associated primarily with technical advances in diagnosis and treatment, as well as evolving knowledge regarding the prognosis and risk stratification of head and neck cancer patients from research and observational studies (e.g., inclusion of depth of invasion as a predictor for OSCC, inclusion of ENE for all non-viral head and neck cancers etc.) [14, 15]. Nonetheless, despite the significant advancements in diagnostic and therapeutic strategies that have taken place over the last years, the prognosis of HNSCC remains largely unfavorable, with a cumulative 5-year overall survival (OS) rate of 45–55% in patients with locally advanced HNSCC [16]. Therefore, research should be directed toward the identification of robust prognostic factors for the risk stratification of HNSCC patients.

Herein, we performed a comprehensive and updated systematic review of the literature on the prognostic value of nodal volumetric parameters, with respect to different primary sites, for HNSCC.

## 3. Methodological issues

This systematic review was performed by following the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement [17] (Fig. 1). The bibliographic database PubMed/MEDLINE [18] was searched manually for relevant published studies reporting the association between nodal tumor volumes and prognosis in head and neck cancers, using the keywords: ((((((((((volum*) OR "Lymph Nodes/diagnostic imaging" [Mesh])) AND (((("Head and Neck Neoplasms" [Mesh]) OR "Squamous Cell Carcinoma of Head and Neck" [Mesh])) OR hypopharyngeal))) NOT esopha*) NOT thyroid) NOT parathyroid) NOT sinonasal) NOT melanoma) NOT gland) NOT nasopharyn*. Regarding the primary tumor site, studies on neoplasms of the nasopharynx were not included in this systematic review, as they constitute a distinct epithelial malignancy entity with different etiology, pathogenesis and progression. Sinonasal squamous-cell carcinomas were not included as well, as their etiology, epidemiology, clinical features, and genetic profiles are quite distinct from those of the main head and neck cancer localizations, such as larynx, pharynx, and oral cavity cancers. The eligibility criteria for including studies in the present review were the following: (i) studies reporting the association between clinical outcomes and the nodal volume (not the total tumor volume), (ii) studies including separate analyses for each primary tumor site so as to minimize any confounding factors, and because of the diverge tumor imaging and volume measuring methods used across studies.

Studies were excluded from this review based on the following exclusion criteria: (i) no separate analyses for primary sites and nodal volumes were performed, (ii) no precise pretreatment volumetric analysis, and/or where other radiographic parameters were used, (iii) reviews, case reports, editorials, commentaries.
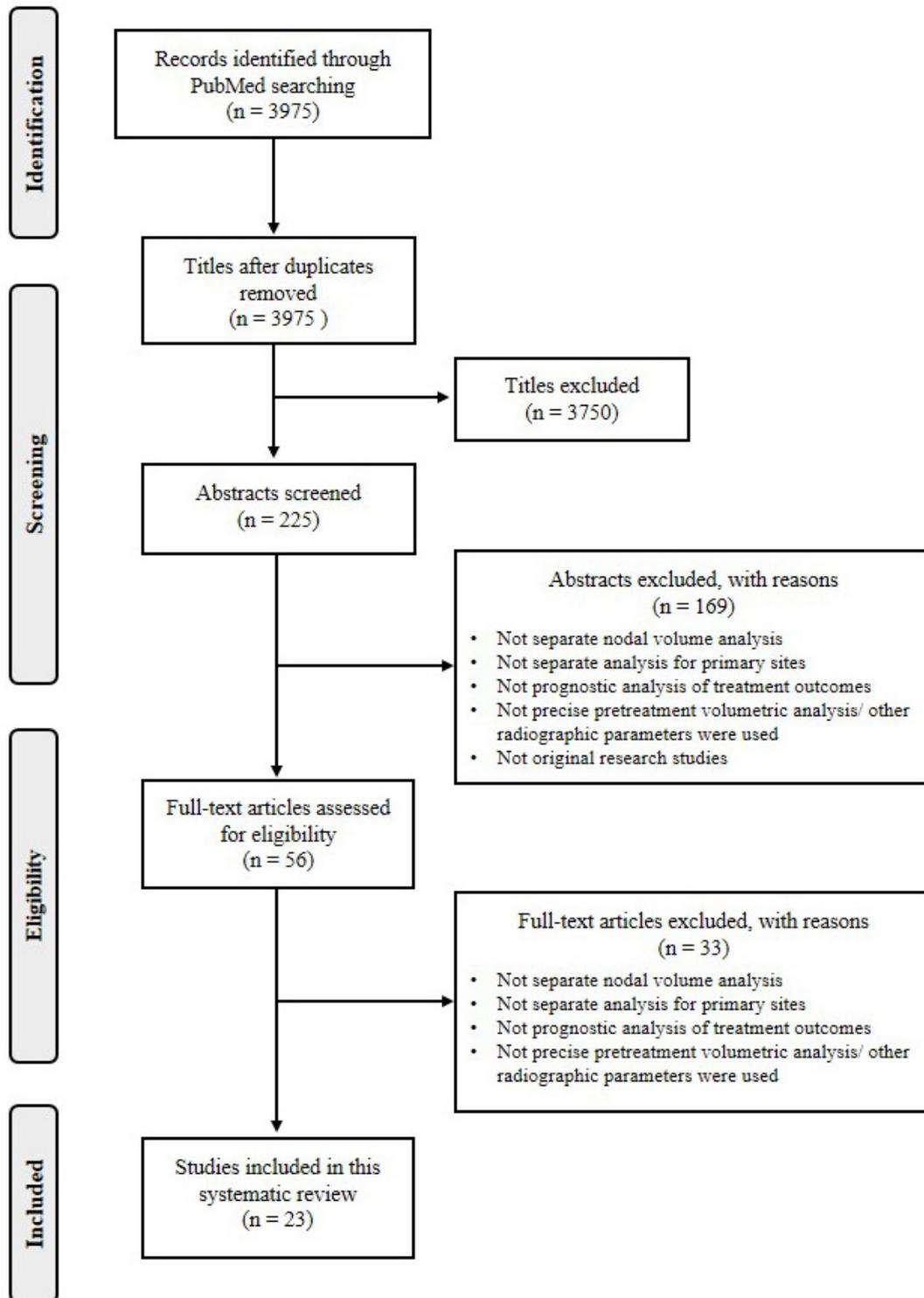
**Fig. 1. PRISMA process flow diagram for study selection.**

The quality of the retrieved studies was assessed independently by two authors (PTM. and AP). Any disagreement between PTM. and AP was resolved by a third investigator (EK). Respective data were extracted from the eligible studies and recorded into an *ad hoc* Excel worksheet.

## 4. Results

Collectively, 3975 relevant records were retrieved from PubMed (up to 6 February 2021). After initial screening, 3750 titles and 169 abstracts were excluded because they were irrelevant to our study. A total of 56 full-text articles were assessed for eligibility. By applying strict

**Table 1. Main characteristics of the eligible studies included in the systematic review.**

| First author, year | Primary site; cancer stage | Imaging technique; volume type | Type of treatment | Number of patients (N); Follow-up period | Volumetric groups | Treatment outcome; Survival statistic (95% CI), $p$ value |
|---|---|---|---|---|---|---|
| Martens, 2021 [19] | Oropharyngeal, hypopharyngeal; Stages I–IV, with HPV status | PET-CT, DCE MRI; DCEGTV (cm$^3$) | curative (chemo) radiotherapy | N = 70 (Oropharyngeal = 56, hypopharyngeal = 14); Mean 22.1 months (interquartile range 14.3–29.4) | mean nodal volume in DCE MRI ± SD, in patients with recurrence: 6.4 ± 4.7 cm$^3$; no proposed volumetric group; HPV-negative group (n = 44 patients) | no significant differences in PET-CT volumetry; LRFS; OS HR = 1.18 (1.03–1.36), $p$ = 0.018; HR = 1.20 (1.0–1.4), $p$ = 0.027 |
| Fujii, 2019 [20] | Laryngeal, hypopharyngeal; Stages III/IV | PET-CT; nMTV (SUV ≥2.5) | Total laryngectomy and neck dissection | N = 88 (Hypopharyngeal = 61); ≥12 months | High risk Nmtv ≥11.3 mL; Intermediate risk ENE (+), Nmtv <11.3 mL; Low risk ENE (−), Nmtv <11.3 mL | OS; HR = 8.2 (2.5–31.9), $p$ = 0.0004; HR = 4.4 (1.4–16.7), $p$ = 0.01; Reference group |
| Safi, 2018 [21] | OCSSC; Stages III/IV (T4b excluded) | CT; NV | Comprehensive neck dissection (level I to V), and postoperative radiotherapy for locally advanced disease | N = 100; ≥3 months | NV >6.86 cm$^3$ | LR; HR = 20.926 (4.824–90.774), $p$ < 0.001 |
| Okazaki, 2018 [22] | Hypopharyngeal; Stages III/IV | PET-CT; nMTV (SUV ≥3.0) | Definitive RT (>50 Gy) +/− chemotherapy | N = 61; Median 21.7 (2.2–103.3) months | In the subgroup of MTV-T <19.9 mL (N = 40 patients); Cut-off value of nMTV = 73.5 mL | OS, DSS; HR = 1.01 (1.00–1.03), $p$ = 0.014; HR = 1.02 (1.00–1.03), $p$ = 0.012 |
| Dua, 2018 [23] | Pharyngeal (OPC, hypopharyngeal), no HPV status; Stages III/IV | CT; TNV | Definitive concurrent chemoradiotherapy | N = 87 (OPC = 57); Median 18 (6–33) months | OPC, TNV >15 cc | RC; AUC = 0.974 (0.939–1.000), $p$ = 0.001 |
| Carpén, 2018 [24] | OPC, with HPV status; Stages I–IV | CT; nGTV | Definitive chemoradiotherapy or IMRT | N = 91, p16 (+) = 72; ≥31 months | p16 (+) (nGTV as a continuous variable); p16 (+) Ngtv >26 cm$^3$ (dichotomized by its mean); p16 (+/−) (nGTV as a continuous variable) | DDFS, LRC; HR = 1.02 (1.01–1.03), $p$ = 0.005, HR = 1.03 (1.01–1.05), $p$ = 0.007; HR = 9.86 (1.05–93.03), $p$ = 0.046, ns; HR = 1.02 (1.00–1.04), $p$ = 0.022, HR = 1.02 (1.00–1.04), $p$ = 0.017; no differences found when nGTV was dichotomized by its mean value |

**Table 1. Continued.**

| First author, year | Primary site; cancer stage | Imaging technique; volume type | Type of treatment | Number of patients (N); Follow-up period | Volumetric groups | Treatment outcome; Survival statistic (95% CI), *p* value | |
|---|---|---|---|---|---|---|---|
| Zhang, 2016 [25] | OCSSC; | PET-CT; | Surgery with or without radiotherapy or chemoradiotherapy | N = 122; | na | DFS | |
| | Stages I–IV | nMTV (SUV $\geq$2.5) | | Mean 2.4 (1.3–5.2) year | | ns | |
| Kim, 2016 [26] | HPV-positive OPC; | PET-CT; | Surgery +/− radiotherapy or chemoradiotherapy | N = 86; | In high-risk patients (n = 54) with nMTV >10.8 cm$^3$ predicted statistically significant poorer DFS | DFS | LR |
| | Stages II–IV | nMTV(SUVmax >40%) | | Median 47.9 (5.1–102.6) months | | HR = 1.09 (1.03–1.16), *p* = 0.004 *p* = 0.007 | ns |
| Davis, 2016 [27] | HPV-positive OPC; | CT; nGTV | Definitive chemotherapy and IMRT | N = 53; | na | DFS | |
| | Stages III/IV | | | Mean 29 (4–76) months | | HR = 1.021 (1.008–1.035), *p* = 0.001 (not clear if multivariate analysis was performed) | |
| Lin, 2015 [28] | Pharyngeal (OPC and hypopharyngeal), no HPV status; | CT, PET-CT; | IMRT +/− concurrent chemotherapy | N = 91, OPC = 49; | na | NRFS | DFS |
| | Stages III/IV | nGTV, nMTV (SUV $\geq$2.5) | | Median18 (6–69) months | | ns | ns |
| Kendi, 2015 [29] | OCSSC; | PET-CT; | Surgery +/− radiotherapy or chemoradiotherapy | N = 36; | na | LRFS | |
| | Stages I–IV | nMTV | | Median 24.1 (8–44.5) months | | ns | |
| Vainshtein, 2014 [30] | OPC with HPV status; | CT, PET-CT; | IMRT with concurrent chemotherapy +/− adjuvant neck dissection | N = 198, HPV (+) = 184 | na | LRF | |
| | Stage III/IV | nGTV | | | | ns (significant only in univariate analysis) | |
| Ng, 2014 [31] | Pharyngeal (OPC and hypopharyngeal), no HPV status; | CT, PET-CT; | IMRT with concurrent chemotherapy | N = 69 (OPC = 37); | na | 3-year neck control | |
| | Stages III/IV | nGTV, nMTV (SUV >2.5) | | $\geq$12 months, Median 31 (7–49) months | | ns (significant only in univariate analysis) | |
| Kikuchi, 2014 [32] | OPC with HPV status; | PET-CT; nMTV | Surgery +/− radiotherapy or chemoradiotherapy or radiotherapy +/− chemotherapy | N = 47 p16 (+) = 29; | Nmtv $\geq$55 cm$^3$ versus <55 cm$^3$ | DFS | DSS |
| | Stages I–IV | | | Median 30 (3–89) months | | ns | HR = 5.0 (na), *p* = 0.04 |
| Janssen, 2014 [33] | Laryngeal; | CT; nGTV | chemoradiotherapy | N = 270; | na | RC | |
| | Stages II–IV | | | Median 44 (2–84) months | | ns | |

**Table 1. Continued.**

| First author, year | Primary site; cancer stage | Imaging technique; volume type | Type of treatment | Number of patients (N); Follow-up period | Volumetric groups | Treatment outcome; Survival statistic (95% CI), *p* value |
|---|---|---|---|---|---|---|
| Alluri, 2014 [34] | HPV-positive OPC; | PET-CT; nMTV | Concurrent chemoradiotherapy or surgery or combination of both | N = 70; | na | EFS |
| | Stages III/IV | | | Median 25 (3–97) months | | No multivariate analysis (significant only in univariate analysis) |
| Lok, 2012 [35] | OPC, no HPV status; | CT; nGTV | IMRT +/− concurrent chemotherapy | N = 340; | na | RC |
| | Stages I–IV | | | Median 34 (5–67) months | | ns |
| Chen, 2009 [36] | Hypopharyngeal; | CT; nGTV | Radiotherapy plus concurrent chemotherapy | N = 76; | na | NRFS |
| | Stages III/IVA | | | Median 37 (13–95) months | | ns |
| Tsou, 2006 [37] | Hypopharyngeal; | CT; nGTV | Radiotherapy plus concurrent chemotherapy | N = 51; | na | LC |
| | Stages III/IV | | | Mean 24.55 (5–76) months | | significant only in univariate analysis |
| Chao, 2004 [38] | OPC, no HPV status; | CT; nGTV | Definitive IMRT | N = 31; | na | DFS          LRC |
| | Stages I–IV | | | ≥2 years | | Exp (B) = 1.06 (1.02–1.10), *p* = 0.05     Exp (B) = 1.02 (1.00–1.04), *p* = 0.01 |
| Hermans, 2001 [39] | Tonsillar, no HPV status; | CT; nGTV | Radiotherapy | N = 112; | Ngtv >14.5 mL | RC |
| | Stages I–IV | | | Mean 33 (2–121) months | | significant only in univariate analysis |
| Kawashima, 1999 [40] | Pharyngolaryngeal (oropharynx, pyriform sinus and supraglottic larynx), no HPV status; | CT; Nd | Definitive radiotherapy | N = 48; | Nd ≥3 cm versus Nd <3 cm predicted statistically significant poorer RC | RC          Cause specific survival |
| | Stages I–IV | | | ≥2 years, median 32.7 (12.4–68.6) months | | *p* < 0.001          ns |
| Jakobsen, 1998 [41] | Laryngeal, pharyngeal (no HPV status); | CT; Volumes of tumor burden of lymph node metastases | Radiotherapy | N = 280, Larynx = 71, Pharynx = 209 | NV >100 cm$^3$ | DSS |
| | Stages I–IV | | (except in 10 patients with laryngeal carcinoma who were subjected to surgery) | | | significant only in univariate analysis for each subsite |

Abbreviations: AUC, area under the ROC curve; CT, computed tomography; DCE, dynamic contrast-enhanced; DFS, disease-free survival; DSS, disease-specific survival; EFS, event-free survival; Exp (B), exponentiation of the B coefficient; HR, Hazard ratio; IMRT, intensity-modulated radiation therapy; LC, local control; LR, locoregional recurrence; LRC, locoregional control; LRF, locoregional failure; LRFS, locoregional recurrence-free survival; MTV-T, metabolic tumor volume of primary tumor; Nd, diameter of a sphere of which the volume is equal to the sum of volumes of the metastatic adenopathies; nGTV, nodal gross tumor volume; nMTV, nodal metabolic tumor volume; NRFS, nodal relapse-free survival; NV, nodal volume; OCSCC, oral cavity squamous cell carcinoma; OPC, oropharyngeal carcinoma; OS, overall survival; PC, pharyngeal carcinoma; PET-CT, positron emission tomography-CT; RC, regional control; SUV, standardized uptake value; TNV, total nodal volume. *na: not available data; *ns*: not significant in univariate analysis.

**Table 2. Results grouped by primary tumor site, HPV status, proposed volumetric subgroups and significantly affected, by metastatic nodal volume, treatment outcome on multivariate analysis.**

| Primary tumor site | Number of related studies | Total number of patients in all related studies | | High-risk patient volumetric subgroups proposed by study | Significantly affected treatment outcome |
|---|---|---|---|---|---|
| Oropharynx | 13 studies [19, 23, 24, 26–28, 30–32, 34, 35, 38, 39] | | HPV (+) | nGTV >26 cm$^3$ [23] | LRFS [19], RC [23], LRC [38], DFS [26–28], DSS [32] |
| | | 1227 | 518 | nMTV >10.8 cm$^3$ in high-risk patient group (positive margin section, ≥5 metastatic nodes and/or pT3/4 disease) [26] | |
| | | | HPV (−) 83 | | |
| | | | No HPV status 626 | TNV >15 cc [23] | |
| Hypopharynx | 8 studies [19, 20, 22, 23, 28, 31, 36, 37] | 367 | | Nmtv ≥11.3 mL [20] | OS [20, 22], DSS [22] |
| | | | | Nmtv ≥73.5 mL in the MTV-T <19.9 subgroup [22] | |
| Larynx | 3 studies [20, 33, 41] | 368 | | | ns |
| Oral Cavity | 3 studies [21, 25, 29] | 258 | | NV >6.86 cm$^3$ in stage III/IV (T4b excluded) patients [21] | LR [21] |

inclusion and exclusion criteria, 23 studies were included in this systematic review (Fig. 1). The basic characteristics of the included studies are summarized in Table 1 (Ref. [19–41]), where the following information was recorded: first author's surname and year of publication; primary tumor site; cancer stage; imaging method for tumor detection; type of tumor volume; type of therapy administered to patients; total number of patients; follow-up period; volumetric groups of patients; clinical treatment outcome; survival analysis statistic (e.g., hazard ratio) and the corresponding 95% confidence interval (CI) for the clinical outcome.

The majority of the studies included in this review focused on squamous cell carcinomas of the pharynx (oropharynx, hypopharynx or both) (Table 1, Ref. [19–41]; Table 2, Ref. [19–39, 41]). In all of those, nodal tumor volumetry was assessed using pre-treatment imaging (CT, PET-CT, MRI). In most of the studies, the volume of the primary tumor and the involved metastatic lymph nodes were automatically measured using a radiotherapy treatment planning software, within a region of interest contoured at workstation software, preferably by two readers (i.e., radiologist or nuclear medicine physician or head and neck radiation oncologist or otolaryngologist). None of the studies included information about the volumetric parameters for the surgical specimen. In addition, among the MRI studies screened for eligibility, only two studies had conducted concise volumetric analysis. However, only one MRI study [19] was included in this review, while the other study failed to meet the inclusion criteria, as nodal volumes were studied separately for ipsilateral and con-

tralateral nodes [42]. In the volumetric analyses where CT was used, nodal gross tumor volume (nGTV) was the most frequently used term to describe the cumulative metastatic lymph node volume. In those studies where the PET-CT parameters were analyzed, we presented results related only to nodal metastatic tumor volume (nMTV) and not the total lesion glycolysis (TLG), or the mean or maximum standard uptake value (SUV$_{mean}$, SUV$_{max}$). This was based on a recently published systematic review and meta-analysis by Bonomo and coworkers (2018) [43], where it was suggested that pretreatment MTV is the only metabolic variable with a significant impact on patient outcome in locally advanced HNSCC treated with concomitant chemoradiotherapy. In the same study, it was also pointed out that because of the heterogeneity and the lack of standardized methodology, the optimal cut-off values could not be determined accurately.

Most of the eligible studies on OPC were published after 2014 and included data associated with the HPV status (Table 1). Notably, in these studies, the vast majority of the OPC patients were HPV-positive. The results of HPV-positive OPC patients indicate a potentially significant prognostic value of the nodal volumetric parameters. However, there is a disagreement about the terminology used for end-points to define treatment failure and the level of significance for each end-point in the treatment outcomes. Disease-free survival (DFS) is the end-point mostly associated, with statistical significance, to nodal volume. In order to further our understanding on the prognosis of HPV-positive OPC patients, a meta-analysis would be use-

ful, though this might be difficult due to the heterogeneity in the available studies. Conversely, there are limited data in the current literature supporting the potential use of nodal volume in the prognosis of HPV-negative patients with OPC. Nonetheless, in the most recent study selected for this review [19], which included patients with pharyngeal carcinomas, a separate analysis was also conducted for the HPV-negative group. Interestingly, nodal volume in dynamic contrast-enhanced (DCE) MRI was significantly associated with recurrence-free survival (RFS) in multivariate analysis.

Regarding hypopharynx alone, an association between nodal volume and treatment outcomes was found mainly in univariate and not in multivariate analyses; for oral cavity a significant association was observed only in the advanced stages (III and IV) of squamous cell carcinomas (Table 1).

None of the studies included in the present review used the 8th edition TNM/AJCC classification for staging head and neck cancer patients, whilst only one clearly included ENE in multivariate analysis [20]. In the same study, which included mostly patients with hypopharyngeal squamous cell carcinoma, it was demonstrated that there is a statistically significant risk for patients with large nodal tumor volumes, regardless the presence of ENE [20].

In some studies patients were stratified into high-risk volumetric subgroups [20, 21, 23, 25, 44, 45]. The great majority of these studies (5 out of 6) focused on carcinomas of the pharynx (two studies [20, 45] on hypopharyngeal SCC and three studies [21, 23, 25] on oropharyngeal SCC). The proposed nodal volume cutoffs appeared to vary slightly among the studies of the oropharynx (nGTV $>26$ cm$^3$ [23] vs nMTV $>10.8$ cm$^3$ in high-risk patient group [25] vs TNV $>15$ cc [21]), whereas in studies of the hypopharynx they vary considerably (nMTV $\geq 11.3$ mL [20] vs Nmtv $\geq 73.5$ mL in the MTV-T $<19.9$ subgroup [45]). In an effort to explain the observed differences, we focused on the treatment modalities used in each of these studies. Interestingly, the low volumetric cutoff of 11.3 mL, in a study be Fujii and colleagues [20] regarding hypopharyngeal SCC, concerned those patients treated surgically with total laryngectomy and neck dissection. On the other hand, the considerably high volumetric cutoff of 73.5 mL in the study by Okazaki and coworkers [22] concerned patients with low volume (MTV-T $<19.9$) primary hypopharyngeal tumor treated with definitive radiotherapy +/- chemotherapy. In line with the aforementioned observation the lowest proposed volumetric cutoff in the oropharyngeal SCC studies, according to Kim *et al.* [26], where HPV (+) patients with OPC were again treated surgically with curative resection followed by postoperative radiotherapy or chemoradiotherapy.

## 5. Discussion

In this systematic review, we focused predominantly on the detection of groups of patients (regarding both the primary tumor site and the HPV status) where the nodal tumor volume can be used as a prognostic imaging biomarker for HNSCC patients. Notwithstanding, articles screened for eligibility in this review, apart from the heterogeneous methods applied for volume measurements, they also had other limitations which did not allow us to assess the prognostic value of nodal volumetric parameters. Full-text articles reporting the total tumor volume (both primary plus nodal tumor volume) instead of the nodal volume separately were also screened in this review, while the majority of those contained all primary tumor sites with no separate analysis for each one of them. Another serious limitation of our study was the lack of multivariate analyses in many of the studies examined for eligibility. Notably, even two studies [42, 46] which include multivariate analysis regarding the prognostic significance of nodal volumes failed to meet our inclusion criteria. In particular, Ljumanovic *et al.* [42] conducted only separate analysis regarding ipsilateral and contralateral lymph node volume and Vergeer *et al.* [46] did not include a separate analysis of the primary tumor site.

In order to minimize the aforementioned limitations so as to avoid any confusion and hasty conclusions, we considered as eligible only the articles where the nodal tumor volume was separately analyzed for each primary tumor site. In those articles, we investigated whether there is a statistically significant ($p$ value $< 0.05$) relationship of nodal volume, based on multivariate analysis, with treatment outcome and survival (e.g., locoregional recurrence, disease specific survival, regional control, locoregional control, disease-free survival, nodal relapse free survival, locoregional failure, locoregional recurrence-free survival, event-free survival). The most commonly used covariates in multivariate analysis, were the following: age, sex, N-stage, T-stage, Union for International Cancer Control (UICC) clinical stage and therapy related information (e.g., radiotherapy dose, concurrent chemotherapy). Notably, the smoking status was considered as a covariate in approximately one-third of the studies [19, 25, 27, 29, 30, 34, 45], whereas alcohol consumption was considered only in two studies [19, 29]. Eastern Cooperative Oncology Group Performance Score (ECOG) was considered as covariate only in two studies [24, 36] and Charlson Comorbidity Index (CCI) were considered as covariates only in two and one studies, respectively [24]. Pretreatment hemoglobin levels, were also considered as covariates in only two studies [21, 31]. Among those studies where patients were mainly surgically treated [20, 24, 25, 29], the only study that considered as a covariate information related to surgical specimen's lymphovascular and perineural invasion, was the one by Kim *et al.* [26], which regarded patients

with p16-positive oropharyngeal squamous cell carcinoma who received curative resection. Regarding HPV status, in oropharyngeal carcinomas studies, the HPV status was either used as a covariate or HPV positive and HPV negative cases were studied separately. In those patients where a statistically significant association was found, we further examined whether a risk stratification based on nodal volume was conducted and if any nodal volume cut-off values were proposed. As such, patients were divided into volumetric groups with different prognosis.

The identification of volumetric groups of patients might have potential utility in clinical decision making for locally advanced head and neck cancers. Of note, in the case of treatment de-escalation for HPV-positive oropharyngeal cancers, the first results from De-ESCALaTE HPV, an open-label randomized controlled phase 3 trial [47], showed that compared to the standard cisplatin regimen, cetuximab had a significantly detrimental effect on tumor control, thereby leading to the suggestion that combinatorial therapy of cisplatin and radiation should be used as the standard of care for HPV-positive low-risk patients who are able to tolerate cisplatin. Low-risk patients were defined according to the Ang classification [48], that is, the patient-derived tumor cells had to be p16-positive on p16 immunohistochemistry, and the patients had to be non-smokers or have a self-reported lifetime cigarette history of less than 10 pack-years.

Moreover, volumetric stratification might be more appropriate for patients where different treatment modalities were used. The observed differences in the proposed volumetric subgroups concerning patients with carcinomas of the oropharynx and hypopharynx, indicate that in surgically treated patients with pharyngeal carcinomas, lower nodal volumetric cutoffs should be used for the risk stratification of those patients and more aggressive postoperative treatments might be proven beneficial. However, this has to be further investigated, separately for HPV (+) and HPV (−) cases, in large-scale studies.

In high-risk patients, immunotherapy could also be used in the adjuvant setting, even for newly diagnosed cases of metastatic nodal disease. Such therapeutic protocols are in line with recent data supporting the use of immunotherapy with checkpoint inhibitors, such as Nivolumab and Pembrolizumab, in recurrent and/or metastatic HNSCC [49].

Nodal volumetric analysis in patients with oropharyngeal, both HPV-positive and HPV-negative, and hypopharyngeal carcinomas appears to represent a challenging and promising field for research. Of particular note, in a quite recent systematic review [44], it was shown that the locoregional recurrence rates for HPV-negative (26%) patients are significantly higher (i.e., almost three times higher) as compared to HPV-positive (9%) OPSCC patients. This finding, in combination with the results of a multicentric study by Culie *et al.* (2021) [45], wherein primary surgical treatment in patients with p16-negative OPSCC was found to be associated with improved overall survival (OS), disease-specific survival (DSS) and RFS, further supporting that patients with p16-negative OPSCC represent a group at high risk for recurrence, and metastatic nodal tumor volume could serve as an independent and decisive factor for risk stratification. The need remains, though, for standardizing the measurement of nodal volume. Hitherto, volumetry is mainly assessed by CT and PET-CT, albeit in surgically treated patients. Tumor volumetric data can also be derived from the histopathological analysis of neck dissection surgical specimen. The development of deep learning neural network algorithms might also be useful for the risk stratification of patients regardless of the volumetric method used. Furthermore, the release of the new edition of TNM classification for head and neck cancers should be taken into consideration in future meta-analyses. In order to clarify whether and in which groups of patients the addition of nodal volume could improve the predictive capacity of the 8th edition of the TNM/AJCC, values of variables referring to the TNM classification should be updated accordingly, before conducting multivariate analysis.

## 6. Conclusions

In the present study, we have conducted a systematic review in order to assess further the prognostic potential of nodal tumor volume in the cancers of the head and neck, taking into consideration the lack of a standardized protocol for measuring the nodal volume. Based on our findings, nodal volume could be considered as a candidate imaging biomarker for monitoring and predicting diverse clinical outcomes in HNSCC patients. Future studies should focus on determining a standard methodology for assessing nodal volumetric parameters and their potential utility in the imaging, prognostication and treatment of head and head cancers. Moreover, further research is required, where both the ENE and the HPV status will be taken into consideration in patients with pharyngeal squamous cell carcinomas, in order to identify possible subgroups of patients with considerably higher risk for locoregional recurrence, who might benefit from different therapeutic and/or post - treatment follow-up approaches.

## 7. Author contributions

AGG and EK conceived the study; AGG, PTM and EK designed and supervised the study; PTM and AP analyzed the data; PTM, AP, RÜ, IM, AGG and EK wrote the manuscript; PTM, AP, RÜ, IM, AGG and EK revised the manuscript. All authors reviewed and approved of the final manuscript.

## 8. Ethics approval and consent to participate

Not applicable.

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## 11. Conflict of interest

The authors declare no conflict of interest.

## 12. References

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