



# Tumor volumes predict prognosis in head and neck cancer: a meta-analysis

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**Background:** Head and neck cancers (HNCs) are the 6th most common cancer worldwide and account for 4% of malignancies. Recent studies implied that tumor volumes play a useful prognostic role in HNC. This meta-analysis based on published studies was performed with the aim of obtaining an accurate evaluation of the relationship between tumor volume and prognosis of HNC.

**Methods:** A comprehensive search strategy was used to search relevant literature in PubMed, EBSCO and ISI Web of Science. The correlation between tumor volume and HNC prognosis was analyzed. This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and using STATA Version 12.0.

**Results:** Finally, fifteen eligible studies consisting of 2,447 participants were included. We found that HNC with a primary gross tumor volume (GTVp) larger than the cut-off value were associated with an increased risk of local control failure (pooled HR =1.34; 95% CI =1.22–1.47). For the longtime survival, a larger GTVp was significantly associated with disease free survival (DFS) (pooled HR =1.34; 95% CI =1.23–1.46) and overall survival (OS) (pooled HR =1.27; 95% CI =1.17–1.37). On PET-CT, the primary tumor metabolic tumor volume (MTVp) was associated with local control (pooled HR =3.51; 95% CI =1.87–6.59), DFS (pooled HR =5.70; 95% CI =4.30–7.5) and OS (pooled HR =4.13; 95% CI =2.63–6.47).

**Conclusions:** The GTVp and MTVp were highly significant in evaluating local control, OS and DFS of patients with HNC and might be a useful adjuvant and complementary index for a new T staging system in HNC.

**Keywords:** Head and neck cancer (HNC); primary tumor volumes; prognosis

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## Introduction

Head and neck cancer (HNC) encompasses multitudinous malignancies, including laryngocarcinoma, oral carcinoma and nasopharyngeal carcinoma (1). Tobacco and alcohol abuse and human papillomavirus (HPV) infection are two primary causes of HNC. HNC was commonly prevalent in several countries around the world, with an estimated prevalence of HNC in 4% of malignancies and

more frequently in China in approximately 4.8–6.1% of malignancies (2,3). The clinical management of HNC requires precise diagnosis, accurate staging and a standardized multidisciplinary treatment approach. The HNC stage at diagnosis predicts prognosis and guides treatment decisions; American Joint Committee on Cancer TNM staging classification was used as a basis for clinical oncology practice. However, due to various tumor sites and specific anatomic regions of HNC, tumor staging is not

sufficient and usually generates error (4). Therefore, many concerns have been raised regarding the weakness of T staging for several HNC sites.

Recently, several studies implied that anatomic primary tumor volumes on CT or MRI and primary gross tumor volume (GTVp) play a meaningful predictive role for HNC long time prognosis. Strongin *et al.* conducted a study including 78 participants with stage III–IV oropharyngeal, laryngeal or hypopharyngeal cancer; patients with GTVp <35 mL had significantly improved local control (71% *vs.* 41%), as well as the long-term survival, like progression free survival (61% *vs.* 33%), and overall survival (OS) (84% *vs.* 41%) rates (5). Those small retrospective studies implied that anatomic tumor volumes on imaging tests have prognostic value for HNC patients (6). With advancements in imaging technologies, positron emission tomography-computed tomography (PET-CT) has been used in HNC diagnosis and clinical staging, although routine PET-CT scan for staging of cancer remains controversial. However, PET-CT is helpful in accurately evaluating distant metastasis and therapy response by tumor metabolic and morphological changes (7,8). Currently, in many studies using PET-CT to calculate primary tumor volume, named primary tumor metabolic tumor volume (MTVp), MTVp was defined as tumor volume with elevated fluorodeoxyglucose (FDG) uptake (7,9). Several studies also suggested that MTVp as a novel parameter in PET-CT has potential to become a standardized prognostic indicator (10,11).

From the literature, it appears that tumor volume (GTVp and MTVp) is a significant factor associated with outcomes in HNC. However, the prognosis role of tumor volume (GTVp and MTVp) in HNC is controversial and limited according to the previous investigations. This comprehensive meta-analysis was conducted to accurately evaluate of the relationship between tumor volume (GTVp and MTVp) and the prognosis of HNC.

## Methods

### Literature search

Initially, the systematic literature search was performed by using the electronic databases PubMed, ISI Web of Science, and EBSCO up to January 2016. This search strategy utilized the following selected common tags: “HEAD AND NECK CANCER” and “TUMOR VOLUMES” and “PROGNOSIS”. The language was limited to English,

and unpublished results and abstracts were not included. Hand search was also conducted according to reference lists of relevant articles and reviews for additional relevant researches.

### Eligibility criteria

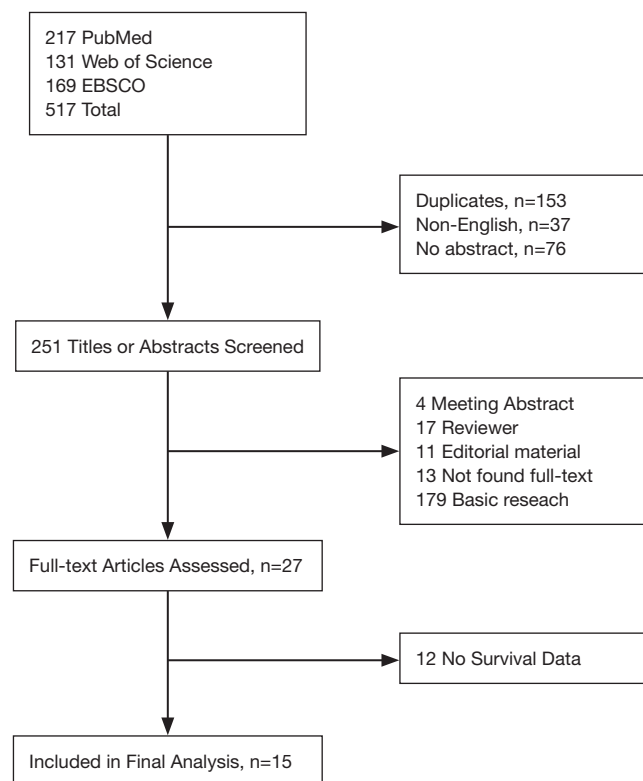
Eligible studies include randomized controlled studies or observational studies that reported estimates of the associations between primary gross tumor volume (GTVp or MTVp) and HNC prognosis. Included studies in this analysis should meet all of the following criteria: (I) articles evaluating the association between tumor volume (GTVp or MTVp) and HNC parameters such as clinicopathological characteristic and long-term prognosis (OS or DFS) of HNC; (II) articles containing sufficient information to estimate of hazard ratios (HRs) and 95% confidence intervals (CIs); and (III) English papers and full text available. Studies were excluded based on the following: (I) duplicate publications; (II) reviews, editorials, clinical guidelines, case reports, comments or letters and meeting abstract; (III) lacking relevant data.

### Data extraction and quality assessment

Relevant data were extracted from each eligible study in a standardized manner: first author's name; publication year and country; average age of participants; duration of follow-up; sample size; tumor volume (GTVp or MTVp) detection methods and cutoff scores; tumor stage; tumor location; and local control rate, five years OS and disease-free survival (DFS) rates. Data extraction conflicts were resolved through discussion. The cutoff value for the tumor volume (GTVp or MTVp) varied among the included articles; we defined large tumor volume (GTVp or MTVp) value according to receiver operating characteristic (ROC) curve analysis from original articles. Newcastle-Ottawa Quality Assessment Scale (NOS) was adopted to assess included studies quality, when scores greater than six were judged as high-quality studies.

### Statistical analysis

Statistical analysis was conducted to calculate the pooled HRs with 95% CI to evaluate tumor volume (GTVp or MTVp) predict prognosis in HNC. Analysis endpoints for survival outcomes including local control rate, OS and DFS. Q test and  $I^2$  test were used to assess the heterogeneity of



**Figure 1** Flow diagram of study identification. 517 potential articles were acquired from PubMed, ISI Web of Science and EBSCO. After screened for eligibility by duplication and language, 266 studies were excluded. 224 records were excluded after titles and abstracts screened. Finally, 27 articles were reviewed. Due to insufficient of survival data, we removed 12 papers. Finally, 15 observational retrospective studies were included.

included studies. The DerSimonian-Laird method (random-effects model) was applied when statistical heterogeneity was found ( $I^2 > 50\%$  or  $P < 0.10$ ). While, Mantel-Haenszel method (fixed-effects model) was considered when  $P > 0.1$  and  $I^2 < 50\%$ . Funnel plots, Begg's and Egger's tests were performed to assess the publication bias on the reported outcomes. All statistical analyses were following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. And performed with STATA software (Version 12.0, Stata Corporation, College Station, TX, <http://www.stata.com>).

## Results

### Eligible studies characteristics

Initially, 517 potential articles were retrieved utilizing electronic database searches above. Those potentially relevant articles were screened for eligibility by duplication

and language, and 266 studies were excluded. Two hundred and twenty-four records were excluded after titles and abstracts screened. Finally, 27 articles were reviewed. Among these papers, 12 were removed because they did not provide survival data. Totally, 15 observational retrospective studies were included (5,10-23). And the detailed search steps are described in *Figure 1*.

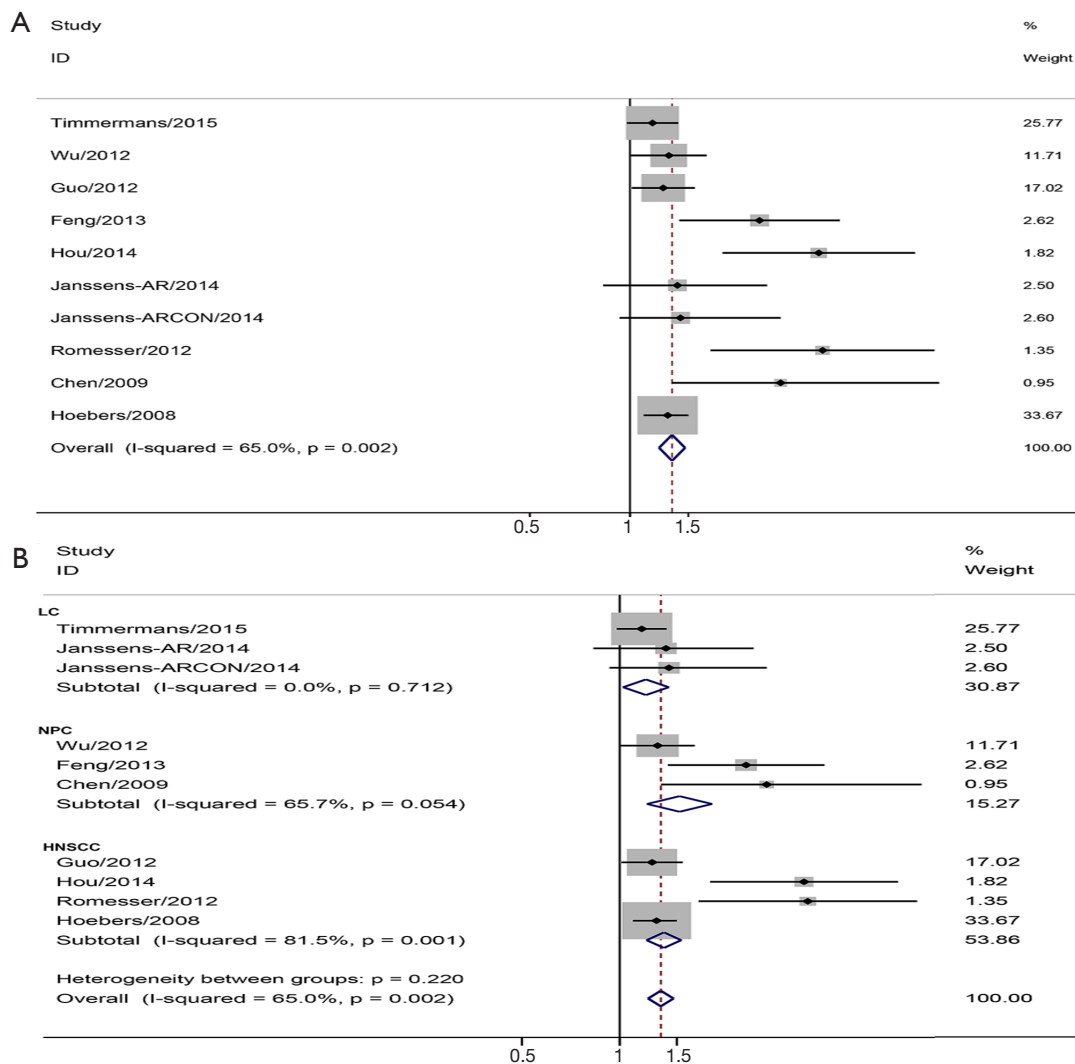
Major features of these 15 eligible studies (approximately 2,447 patients) were summarized (*Table 1*). The sample size range from 30 to 694 (median: 163). Median follow-up was 45 months (range: 18 to 62.2 months). Four studies were from the Netherlands, three from the USA, one from Germany, and seven from Asia (five studies in China and two from Korea), covering most areas around the world.

### Evaluation of the GTVp

The detection and definition method of tumor volume

Table 1 Characteristics of the included studies

Source	Year	Country	Cancer location	Study	Number (M/F)	Age (y)	Follow-up (m)	Median volume	Survival data	NOS score
Timmermans (12)	2016	Netherlands	LC (T3-T4)	Retrospective	166 (124/42)	61.9±11.3	37 (13.8-74)	11.6 (5.7-21.3)	Local control, OS, DFS	7
Wu (16)	2013	China	NPC	Retrospective	305 (241/64)	43 [13-78]	78 [6-126]	16.47 (1.04-146.86)	Local control, OS, DFS	8
Noji (13)	2015	Netherlands	HNSCC	Retrospective	78 (45/33)	-	18 [9-25]	7.3 (2.7-14.6)	DFS	6
Guo (18)	2012	China	NPC	Retrospective	694 (534/160)	43 [13-78]	59.1 (3.1-104.9)	29.1 (4.6-92.3)	Local control, OS, DFS	8
Feng (17)	2013	China	NPC	Retrospective	363 (285/78)	48 [16-78]	63 [9-82]	31.5 (1.8-112.4)	Local control, OS, DFS	7
Strongin (5)	2012	USA	HNSCC (III-IV)	Retrospective	78 (67/11)	57.5 [38-82]	22.6 (2.4-65.9)	38.7 (3.1-123.2)	OS, DFS	6
Hou (14)	2015	USA	HNSCC (LA)	Retrospective	30 (23/7)	59.8 [48-79]	-	34.7±24.2	Local control, OS	6
Janssens (15)										
AR	2014	Netherlands	LC (cT2-4)	Retrospective	137 (109/28)		44 [2-84]	3.6 (0.4-57.7)	Local control	7
ARCON	2014	Netherlands	LC (cT2-4)	Retrospective	133 (108/25)		59 [18-84]	3.5 (91.0-65.2)	Local control	7
Romesser (10)	2012	USA	HNSCC	Retrospective	41 (31/10)	58.9±10.3	24.2 (2.7-56.3)	GTVp: 22.2 (1.5-162.5) MTV: 7.2 (0.40-43.5)	Local control, OS, DFS	6
Seol (11)	2010	Korea	HNSCC	Retrospective	59 (56/3)	65 [47-81]	-	MTV: 23.5 (1.2-170.8)	OS, DFS	6
Chen (20)	2009	Tai Wan	NPC	Retrospective	76 (74/2)	57 [36-79]	37 [13-95]	33.4 (3.8-152.4)	Local control, DFS	6
Hoebbers (21)	2008	Netherlands	HNSCC	Retrospective	46 (34/12)	61 [40-85]	40 [23-69]	28 [9-112]	Local control, OS, DFS	6
Chang (23)	2003	Tai Wan	HNSCC	Retrospective	52 (32/20)	46 [16-75]	62.2 (2.8-84.4)	19.15 (3.23-131.82)	DFS	6
Kurek (22)	2003	Germany	NPC	Retrospective	107 (100/7)	61 [34-87]	43	32.5 (2.1-220.1)	OS	7
Chung (19)	2009	Korea	NPC	Retrospective	82 (69/13)	53.8 [11-70]	-	39 (1.9-231.9)	Local control, OS, DFS	7



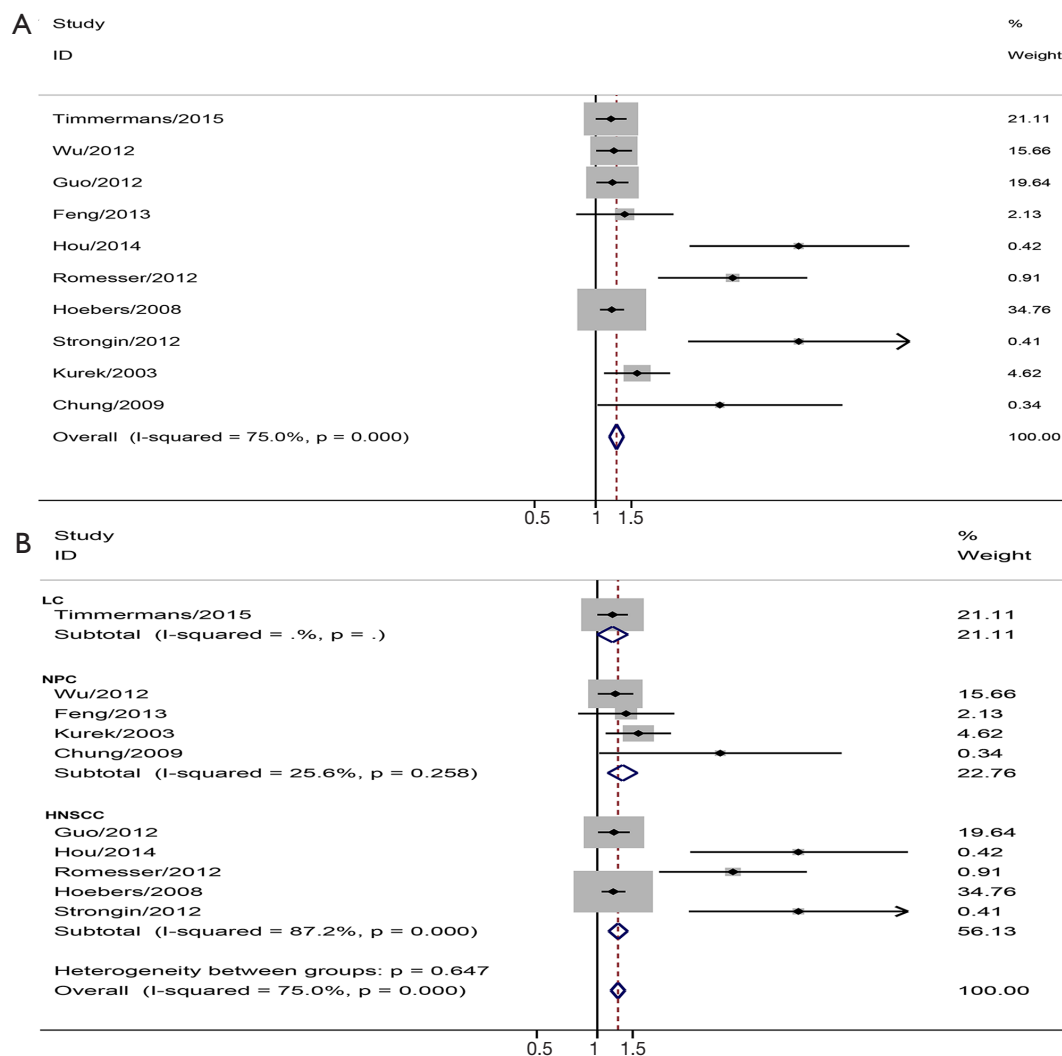
**Figure 2** Forest plots showing results of studies on the impact of primary tumor volume (GTVp) of local control. (A) Impact of GTVp on local control of patients with head and neck cancer; (B) subgroup analysis of GTVp on local control of patients with different location of head and neck cancer.

(GTVp or MTVp) used in the included studies were imaging techniques. Among the 15 studies, two articles used PET-CT, whereas computed tomography (CT) and/or magnetic resonance imaging (MRI) was used in 12 studies, and one study used both CT and PET. The cut-off value for larger tumor volume depended on ROC curve analysis, the median cutoff value of GTVp was 24.48 mL (range: 8.38 to 48 mL).

**GTVp predicts local control**

Nine studies provided the association between GTVp and

HNC local control, including two studies on laryngeal cancer (LC), three studies on nasopharyngeal cancer (NPC), and four articles on squamous cell carcinoma. The combined analysis from the published data showed that larger GTVp was significantly associated with worse local control rate (pooled HR =1.34, 95% CI =1.22–1.47). Next, we found that heterogeneity existed (I<sup>2</sup>=65%, P=0.002) (Figure 2A). Furthermore, the subgroup analysis was conducted according to location of HNC, two studies including three datasets were about LC demonstrated that larger GTVp was correlated with poor local control (pooled HR =1.21, 95% CI=1.03–1.42), NPC (pooled HR =1.53,



**Figure 3** Forest plots showing results of studies on the impact of primary tumor volume (GTVp) of overall survival (OS). (A) Impact of GTVp on OS of patients with head and neck cancer; (B) Subgroup analysis of GTVp on OS of patients with different location of head and neck cancer.

95% CI =1.22–1.93) and HNSCC (pooled HR =1.37, 95% CI =1.21–1.55) (Figure 2B).

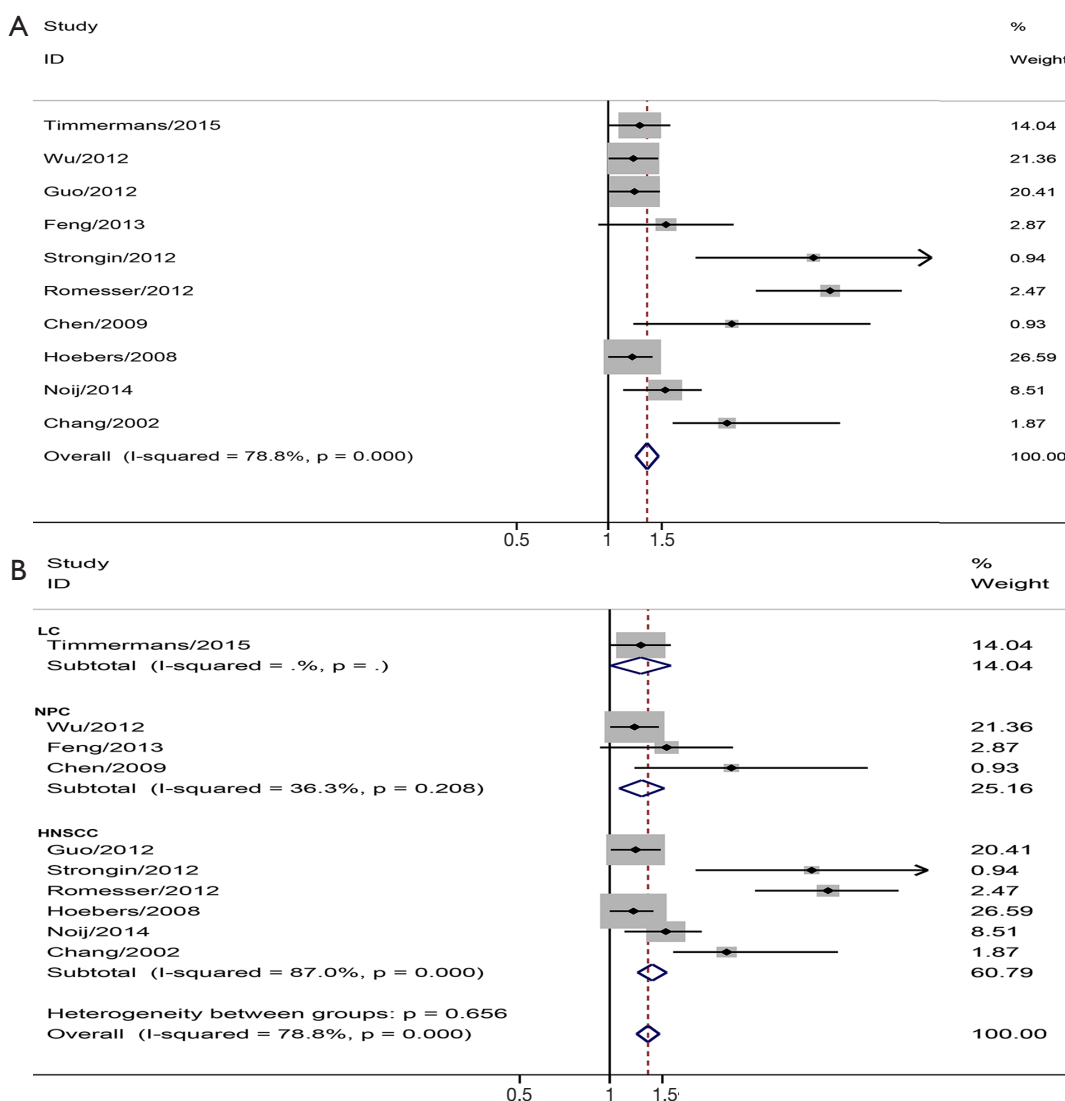
### GTVp implies OS

There were ten studies assessing GTVp and OS of HNC. The pooled analysis found that larger GTVp could predict a worse OS rate (pooled HR =1.27, 95% CI =1.17–1.37). Next, we found that heterogeneity existed ( $I^2=75\%$ ,  $P=0.000$ ) (Figure 3A). Subgroup meta-analysis was performed by the location, four studies on NPC demonstrated that larger GTVp was correlated with

unfavorable OS (pooled HR =1.34, 95% CI =1.13–1.58), LC (pooled HR =1.19, 95% CI =1.00–1.42) and HNSCC (pooled HR =1.77, 95% CI =1.14–1.41) (Figure 3B).

### GTVp and DFS

Ten included articles assessed the relationship between GTVp and DFS of HNC. The pooled analysis found that a larger GTVp was significantly associated with a poorer DFS rate (pooled HR =1.34, 95% CI =1.23–1.46).  $I^2=78.8\%$  indicated heterogeneity was existed ( $P=0.000$ ) (Figure 4A). Subgroup meta-analysis was conducted according to HNC



**Figure 4** Forest plots showing results of studies on the impact of primary tumor volume (GTVp) of disease free survival (DFS). (A) Impact of GTVp on DFS of patients with head and neck cancer; (B) subgroup analysis of GTVp on DFS of patients with different location of head and neck cancer.

location, three studies on NPC demonstrated that a larger GTVp was correlated with a poorer DFS (pooled HR =1.28, 95% CI =1.08–1.52), LC (pooled HR =1.27, 95% CI =1.01–1.60) and HNSCC (pooled HR =1.39, 95% CI =1.24–1.55) (Figure 4B).

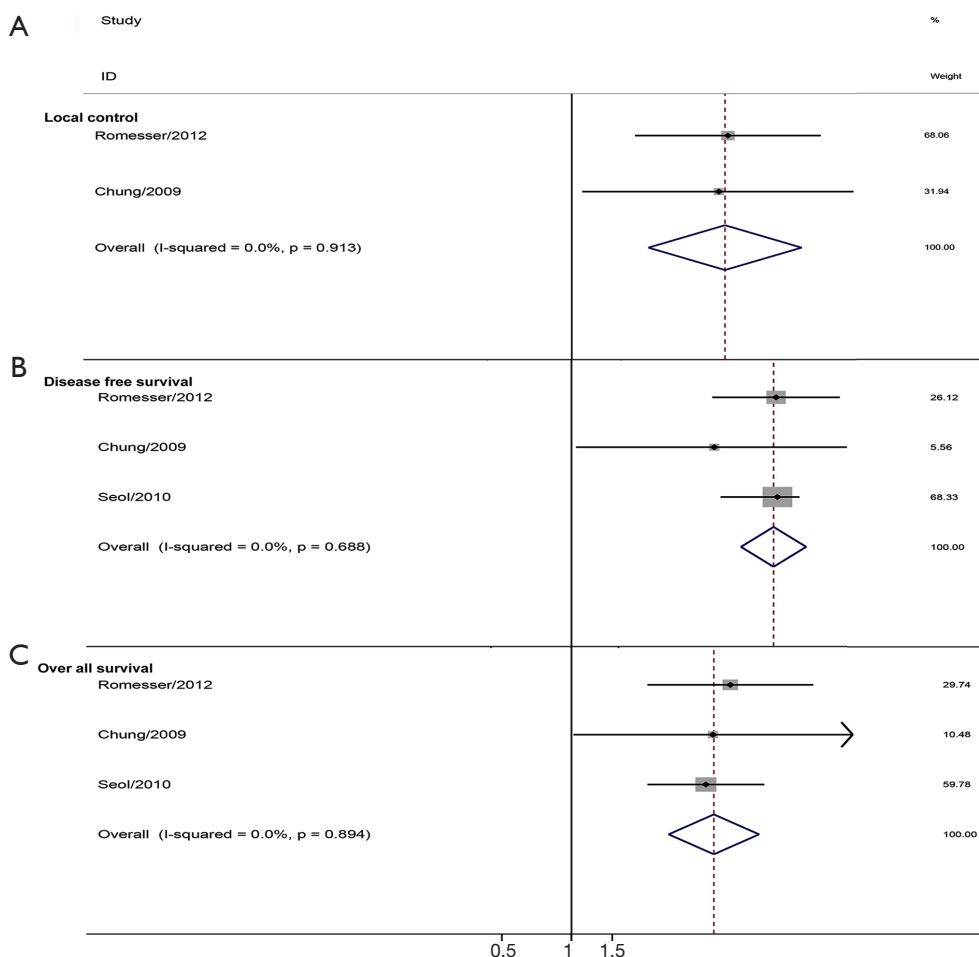
**MTVp in HNC**

Three studies assessed the MTVp and HNC. The combined analysis found that a larger MTVp was significantly associated with a poorer local control (pooled

HR =3.51, 95% CI =1.87–6.59). For longtime survival, a larger MTVp also correlated with a poorer OS (pooled HR =4.13, 95% CI =2.63–6.47), and an unfavorable DFS (pooled HR =5.70, 95% CI =4.30–7.5) (Figure 5).

**Publication bias**

Begg’s rank correlation and Egger’s weighted regression methods were used to investigate the publication bias of included studies. Analysis results indicted no significant publication bias was found in this meta-analysis (data not



**Figure 5** Meta-analysis of impact of metabolic tumor volume (MTVp) on the survival of head and neck cancer patients. (A) Impact of MTVp on local control of patients with head and neck cancer; (B) impact of MTVp on OS of patients with head and neck cancer; (C) impact of MTVp on DFS of patients with head and neck cancer. OS, overall survival; DFS, disease free survival.

shown). However, publication bias might exist and difficult to confirm because of the limited studies included.

**Discussion**

The present systematic literature review and meta-analysis studied the published data to examine the tumor volumes (GTVp or MTVp) on predict prognosis of HNC and included fifty studies with 2,447 patients. This comprehensive analysis incorporated the most recent data, used both random and fixed effects models, and yielded the evidence that GTVp on CT/MRI (GTVp) is a marker of poor prognosis. These results not only observed on local control, but also OS and DFS. Similarly, tumor volume also could be assessed by PET-CT, named MTVp. The pooled

analysis implied that a larger MTVp also indicted a worse prognosis.

According to National Comprehensive Cancer Network (NCCN 2016) guideline, the T classification plays a major role in HNC treatment decisions (1). However, T classification was dependent on clinical examination, laryngoscopy, CT or MRI, which was not sufficient to predict survival in clinical practice. The clinical T stage of HNC is not representative of tumor burden; many T stages have a wide range of tumor burden, but guidelines lack of further nonsurgical sub-grouping for clinical stages, helping oncologists to select therapy methods and to predict survival outcomes. In addition, basic studies indicated that HNC with large volumes usually have more clonogenic tumor cells, tumor volume could be an ideal surrogate for tumor



burden. A larger volume indicates a greater tumor burden and requires larger doses of radiation or chemoradiotherapy to acquire radical cure (16). Previous studies demonstrated that volumetric staging system was superior to TNM stage system in correlating long-term survival in any site of HNC undergoing definitive intensity modulation radiated therapy (IMRT) (24). Furthermore, Studer's retrospective research adopted the volumetric stratification to divide clinical T4 HNC into four volume subgroups (1 to 15 *vs.* 16 to 70 *vs.* 71 to 130 *vs.* >130 mL); they found that the OS was 90%/72%/58%/18% for V1/2/3/4, respectively. Those results implied that volumetric staging could potentially predict outcomes for different volume sizes in HNC (25).

Recently, evidence regarding the prognostic impact of tumor volume and as a supplement for T stage in HNC was increasing. However, the exact relationship was not well established, and tumor volume was not being used for clinical practice. There are many reasons why it is hard to draw a final conclusion. First, due to malignancy, tumors might be more aggressive and finally grow into irregularly shapes. Therefore, the accurate measurement of the tumor volume is difficult under conventional imaging examinations (e.g., CT and MRI). Second, the cut-off value of tumor volume was difficult to define; among the eligible studies in this meta-analysis cut-off values were different (median cutoff value was 24.48 mL, range from 7.3 to 48 mL). Various assessment software and different treatment methods might account for cutoff value biases (26,27). Furthermore, all the studies were retrospective studies; no prospective randomized trials performed to verify the prognostic impact of tumor volume on HNC. The therapy methods adopted in the included studies were radiotherapy or chemoradiotherapy, but the tumor stages and location varied. The unavoidable differences in baseline characteristics in each study might also explain the controversial results in association between tumor volume and HNC survival.

Furthermore, studies indicated that total HNC volume is a major prognostic factor, it mainly impacted by hypoxic volume, while not by non-hypoxic volume (8). Advancements in imaging technologies have significant implications for the use of measured tumor volumes, especially for molecular imaging (e.g., PET-CT). MTVp appears to be a trend to instead of GTVp. PET-CT could accurately assess the metabolic tumor volume in HNC not influenced by irregularly shaped tumors, and MTVp measurements do not need special software and was acquired easier than GTVp. Furthermore, in our analysis,

the results revealed that a small advantage of MTVp (OS: HR =4.13, 95% CI =2.63–6.47) was that it is better than GTVp (OS: HR =1.27, 95% CI =1.17–1.37) as a prognosis factor. Therefore, MTVp is an exciting parameter as metabolic information provided by the PET-CT scan, which could help more accurately measure tumor volume.

Limitations might remain in this study. Firstly, the method and cut-off values for assessing GTVp and MTVp are inconsistent. Secondly, some heterogeneity observed across studies could not be completely accounted for despite the use of appropriate meta-analytic techniques with random-effect models. Finally, because this is a literature-based analysis, inevitable could cause publication bias due to several negative results not been published.

## Conclusions

Results from this analysis demonstrated that tumor volume (GTVp or MTVp) was a useful prognostic marker, and HNC patients with larger tumor volumes are associated with unfavorable local control and long-term survival. It is recommended that tumor volume should be included in a new staging system combined with TNM classification to provide oncologists predict long-term survival. Without doubt, further studies to assess the standard measurement and improve new imaging technologies are urgently needed.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2017.07.14>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## References

- Pfister DG, Spencer S, Brizel DM, et al. Head and Neck Cancers, Version 1.2015. *J Natl Compr Canc Netw* 2015;13:847-55; quiz 856.
- Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9-29.
- Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016;66:115-32.
- Issa MR, Samuels SE, Bellile E, et al. Tumor Volumes and Prognosis in Laryngeal Cancer. *Cancers (Basel)* 2015;7:2236-61.
- Strongin A, Yovino S, Taylor R, 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. *Int J Radiat Oncol Biol Phys* 2012;82:1823-30.
- Chen MK, Chen TH, Liu JP, et al. Better prediction of prognosis for patients with nasopharyngeal carcinoma using primary tumor volume. *Cancer* 2004;100:2160-6.
- Hoeben BA, Troost EG, Span PN, et al. 18F-FLT PET during radiotherapy or chemoradiotherapy in head and neck squamous cell carcinoma is an early predictor of outcome. *J Nucl Med* 2013;54:532-40.
- Dunst J, Stadler P, Becker A, et al. Tumor Volume and Tumor Hypoxia in Head and Neck Cancers. *Strahlenther Onkol* 2003;179:521-6.
- Geets X, Daisne JF, Tomsej M, et al. Impact of the type of imaging modality on target volumes delineation and dose distribution in pharyngo-laryngeal squamous cell carcinoma: comparison between pre- and per-treatment studies. *Radiother Oncol* 2006;78:291-7.
- Romesser PB, Qureshi MM, Shah BA, et al. Superior prognostic utility of gross and metabolic tumor volume compared to standardized uptake value using PET/CT in head and neck squamous cell carcinoma patients treated with intensity-modulated radiotherapy. *Ann Nucl Med* 2012;26:527-34.
- Seol YM, Kwon BR, Song MK, et al. Measurement of tumor volume by PET to evaluate prognosis in patients with head and neck cancer treated by chemo-radiation therapy. *Acta Oncol* 2010;49:201-8.
- Timmermans AJ, Lange CA, de Bois JA, et al. Tumor volume as a prognostic factor for local control and overall survival in advanced larynx cancer. *Laryngoscope* 2016;126:E60-67.
- Noij DP, Pouwels PJ, Ljumanovic R, et al. Predictive value of diffusion-weighted imaging without and with including contrast-enhanced magnetic resonance imaging in image analysis of head and neck squamous cell carcinoma. *Eur J Radiol* 2015;84:108-16.
- Hou J, Guerrero M, Suntharalingam M, et al. Response assessment in locally advanced head and neck cancer based on RECIST and volume measurements using cone beam CT images. *Technol Cancer Res Treat* 2015;14:19-27.
- Janssens GO, van Bockel LW, Doornaert PA, et al. Computed tomography-based tumour volume as a predictor of outcome in laryngeal cancer: results of the phase 3 ARCON trial. *Eur J Cancer* 2014;50:1112-9.
- Wu Z, Zeng RF, Su Y, et al. Huang Prognostic significance of tumor volume in patients with nasopharyngeal carcinoma undergoing intensity-modulated radiation therapy. *Head Neck* 2013;35:689-94.
- Feng M, Wang W, Fan Z, et al. Tumor volume is an independent prognostic indicator of local control in nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. *Radiat Oncol* 2013;8:208.
- Guo R, Sun Y, Yu XL, et al. Is primary tumor volume still a prognostic factor in intensity modulated radiation therapy for nasopharyngeal carcinoma? *Radiother Oncol* 2012;104:294-9.
- Chung MK, Jeong HS, Park SG, et al. Metabolic tumor volume of (18F)-fluorodeoxyglucose positron emission tomography/computed tomography predicts short-term outcome to radiotherapy with or without chemotherapy in pharyngeal cancer. *Clin Cancer Res* 2009;15:5861-8.
- Chen SW, Yang SN, Liang JA, et al. Prognostic impact of tumor volume in patients with stage III-IVA hypopharyngeal cancer without bulky lymph nodes treated with definitive concurrent chemoradiotherapy. *Head Neck* 2009;31:709-16.

21. Hoebbers FJ, Pameijer FA, de Bois J, et al. Prognostic value of primary tumor volume after concurrent chemoradiation with daily low-dose cisplatin for advanced-stage head and neck carcinoma. *Head Neck* 2008;30:1216-23.
22. Kurek R, Kalogera-Fountzila A, Muskalla K, et al. Usefulness of tumor volumetry as a prognostic factor of survival in head and neck cancer. *Strahlenther Onkol* 2003;179:292-7.
23. Chang CC, Chen MK, Liu MT, et al. Effect of Primary Tumour Volumes in Early T-Stage Nasopharyngeal Carcinoma. *J Otolaryngol* 2003;32:87.
24. Studer G, Rordorf T, Glanzmann C. Impact of tumor volume and systemic therapy on outcome in patients undergoing IMRT for large volume head neck cancer. *Radiat Oncol* 2011;6:120.
25. Studer G, Glanzmann C. Volumetric stratification of cT4 stage head and neck cancer. *Strahlenther Onkol* 2013;189:867-73.
26. Arens AI, Troost EG, Hoeben BA, et al. Semiautomatic methods for segmentation of the proliferative tumour volume on sequential FLT PET/CT images in head and neck carcinomas and their relation to clinical outcome. *Eur J Nucl Med Mol Imaging* 2014;41:915-24.
27. Bhatia KS, King AD, Yu KH, et al. Does primary tumour volumetry performed early in the course of definitive concomitant chemoradiotherapy for head and neck squamous cell carcinoma improve prediction of primary site outcome? *Br J Radiol* 2010;83:964-70.

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