Original Article

Prognostic factors and the role of locoregional treatment in patients with distantly metastatic hypopharyngeal cancer: a retrospective cohort study based on SEER database

Wenlun Wang[#]**, Hongwei Zheng**[#]**, Lisheng Yu, Lihong Zhang**

Department of Otorhinolaryngology-Head and Neck Surgery, Peking University People's Hospital, Beijing, China

Contributions: (I) Conception and design: L Yu, L Zhang; (II) Administrative support: L Yu, L Zhang; (III) Provision of study materials or patients: W Wang, H Zheng; (IV) Collection and assembly of data: W Wang, H Zheng; (V) Data analysis and interpretation: W Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors have contributed equally to this work and should be considered as co-first authors.

Correspondence to: Lisheng Yu, MD. Department of Otorhinolaryngology-Head and Neck Surgery, Peking University People's Hospital, Beijing, China. Email: lishengyuent@163.com; Lihong Zhang, MD. Department of Otorhinolaryngology-Head and Neck Surgery, Peking University People's Hospital, Beijing, China. Email: lihongzhangent@163.com.

Background: There is increasing evidence that locoregional treatment (LRT, surgery or/and radiotherapy) for the primary tumor can improve survival in some cancers with systemic dissemination. This study aimed to investigate the survival benefit of LRT and prognostic factors in patients with hypopharyngeal cancer with distant metastasis.

Methods: A retrospective population-based analysis was performed using the Surveillance, Epidemiology, and End Results database. Cox regression analysis was used to account for the imbalance of baseline covariates. The Kaplan-Meier method, log-rank test, and competing risk analysis were used to compare survival outcomes between treatment patterns.

Results: Four hundred and sixty-three eligible patients were included in the analysis with a median overall survival of 7 months. LRT plus systemic therapy was the most common treatment modality (47%) and was associated with the most prolonged survival compared with other treatment methods (log-rank test, P<0.001). In multivariate analysis, bone metastasis, liver metastasis, and treatment were identified as independent prognostic factors for survival. Patients receiving LRT and systemic therapy had a 35% reduced risk of death compared with patients receiving systemic therapy (HR =0.65, 95% CI: 0.39–0.92, P=0.028). Further subgroup analysis and competing risk analysis also confirmed this survival trend favoring LRT and systemic therapy. Interestingly, interaction analysis revealed that only age variable affected the treatment effect and younger patients (<65 years) were more likely to benefit from LRT plus systemic therapy.

Conclusions: Our results suggest that bone metastasis, liver metastasis, and treatment were prognostic factors for the survival of patients with metastatic hypopharyngeal cancer. Patients with distant metastasis are often treated with systemic therapy for a palliative intention. In our work, LRT plus systemic therapy was associated with improved survival compared with systemic therapy alone in selected patients. Particularly, patients younger than 65 years may be the potential subpopulation that can benefit from LRT with improved survival.

Keywords: Hypopharyngeal cancer; SEER database; distant metastasis; radiotherapy; surgery

Submitted Oct 13, 2021. Accepted for publication Dec 24, 2021.
doi: 10.21037/apm-21-2953
View this article at: https://dx.doi.org/10.21037/apm-21-2953

Introduction

As is well known, hypopharyngeal cancer is one of the most malignant cancers in the head and neck region. Hypopharyngeal cancer accounts for 3% of all head and neck malignancies (1). The vast majority of hypopharyngeal cancers are squamous cell carcinoma. Hypopharyngeal cancer has aggressive biological traits and is often asymptomatic due to its concealed location. At the time of initial diagnosis, seventy percent of patients with hypopharyngeal cancer present with advanced-stage (2), and up to 13% of the patients develop distant metastasis (3). The 5-year overall survival (OS) was about 13.5% for hypopharyngeal cancer with distant metastasis (4), while it was estimated to be 52.3% for patients without distant metastasis (5). Remarkable advancements in multidisciplinary approaches have led to substantial improvements in locoregional control for hypopharyngeal cancer in recent years (6), but treatment for distant metastasis remains a dilemma.

The primary goals of treatment for metastatic hypopharyngeal cancer (MHPC) are palliation of symptoms, improvement of quality of life, and prolongation of survival. The treatment options include the best supportive care, locoregional treatment based on primary sites, systemic therapy, and the newly popular strategy immunotherapy. Locoregional treatment (LRT, surgery or/and radiotherapy) delivered in this setting is usually to reduce the tumor burden and alleviate symptoms such as pain, bleeding, ulceration, dyspnea and dysphagia. Multiple previously studies have shown that LRT effectively improve the quality of life in patients with metastatic head and neck cancers (7,8). However, Little attention has been paid to the survival outcomes associated with LRT. There is also a scarcity of literature regarding the prognosis of hypopharyngeal cancer with distant metastasis.

The incidence of hypopharyngeal cancer is very low, and cases with distant metastases are even scarce. Any single-center or multi-center study might fail to collect enough patients for the trial. Moreover, performing randomized trials in these patients may not be ethically appropriate. The Surveillance, Epidemiology and End Results (SEER) database covers approximately 28% of the United States population and has one of the largest cohorts of patients with hypopharyngeal cancer. Accordingly, the purpose of this study was to investigate the prognostic factors and the effect of LRT on survival in patients with MHPC using the SEER database. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-2953/rc).

Methods

Data collection

Data of hypopharyngeal cancer with distant metastasis were extracted from the SEER database. Patients diagnosed from 2010 to 2018 were selected since the information of metastatic sites was only available after 2010. The "Derived AJCC M6th ed" code was "M1" (n=588). The exclusion criteria were as follows: (I) not squamous cell cancer (n=12), (II) not the first tumor (n=63), (III) patient-related information such as pathological grade, T, and N stage, was unknown (n=50). The data extraction and analysis were performed in compliance with the relevant guidelines of the SEER database. Because SEER does not contain patient identity information, this study was exempt from review by the Institutional Ethic Committee of Peking University People's Hospital and individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Variables in the database consisting of age, sex, marital status, race, insurance, tumor location, pathologic grade, TNM classification (AJCC, 6th edition), treatment modality, survival time, and survival status were included in the analysis. Surgery for the primary tumor included local tumor excision (surgery codes 20-27) and pharyngectomy with or without laryngectomy (surgery codes 40-42). Information about radiotherapy and systemic therapy was also extracted from the database. LRT was defined as surgery for the primary tumor, radiotherapy for the primary tumor, and a combination of both. Patients were divided into four groups based on treatment modality: no treatment, LRT, systemic therapy alone, and LRT combined with systemic therapy. In our analysis, all LRT were performed in the setting of established metastatic hypopharyngeal cancer. Patients who were diagnosed with metastatic diseases later after LRT were excluded from our criteria.

Statistical analysis

Cox regression analysis was used to determine the independent risk factors for cancer-specific survival (CSS) and OS and estimate the hazard ratio (HR). The Kaplan-Meier method and log-rank test were used to compare survival curves between treatment modalities. In many situations in survival analysis, there are likely multiple endpoints competing with each other. For instance, patients dying from heart failure would not die from cancer. Therefore, competing risk analysis was performed when comparing survival outcomes between systemic therapy and combined treatment of LRT and systemic therapy. To assess the treatment effect on OS in various baseline subgroups, subgroup analysis was performed, and interactions between treatment modalities and patient characteristics were also tested. A P value <0.05 was considered statistically significant in these analyses. We performed the analyses using SPSS 22.0 software (IBM Corporation, Armonk, NY, USA) and the R language package (version 3.4.3, The R Foundation).

Results

Patient- and tumor-related characteristics

In total, 463 eligible patients with distant metastasis of hypopharyngeal cancer were included in the analysis. The incidence of distant metastasis was 8.3% (463/5,578) for hypopharyngeal squamous carcinoma. The clinical information of the study cohort is summarized in *Table 1*. The average age of this cohort of patients was 62.7±11.8 years. The majority of patients were male, white, and single, with proportions of 89.1%, 71.4%, and 58.4%, respectively. Three hundred and eighty-four patients (83.0%) had primary tumors located in the pyriform sinus. Two hundred and thirty-four patients (50.5%) presented with T4 disease. The most common (n=260, 56.2%) regional lymph node status was N2. The most common metastatic site was the lung, presenting in 55.1% of the patients, followed by the bone (20%) and the liver (12.5%). 280 (60.5%) and 68 (14.7%) patients presented with single organ metastasis and multiple organ metastases, respectively. Two hundred and ninety-five patients (63.8%) received systemic therapy. Two hundred and eighty-five patients (61.6%) received locoregional therapy, including surgery (n=17), radiotherapy (n=235), and surgery combined with radiotherapy (n=33). The types of surgery included local tumor excision (n=30) and pharyngectomy with or without laryngectomy (n=20). Neck dissection was performed in 18 of these patients. Systemic therapy combined with LRT was the most common treatment modality (n=217, 47.0%), followed by no therapy (n=100, 21.6%), systemic therapy alone (n=78, 16.7%), and LRT alone (n=68, 14.6%).

Survival analysis

Three hundred eighty-eight patients (83.8%) died of hypopharyngeal cancer. Forty-seven patients (10.2%) died of other causes such as lung and bronchus diseases, pneumonia and influenza, and heart diseases. Twenty-eight patients (6%) were still alive at the last follow-up. The median overall survival time was 7 (95% CI: 5.53–8.47) months, with a 1-year OS rate of 28.3% (95% CI: 21.8%–34.8%). In univariate analysis (*Table 1*), age, primary tumor site, bone metastasis, number of metastases, and treatment modality had significant influences on CSS. Patients with younger age (<65 years), pyriform sinus carcinoma, without bone metastasis, with solitary distant metastasis, and those who received systemic therapy plus LRT had better survival. Patients with higher age (>65 years), posterior wall cancer, bone metastasis, metastases involving two or more sites, and those without any treatment experienced poor prognosis. For overall survival, only bone metastasis, treatment modality, and the number of metastases were statistically significant. We further performed Kaplan-Meier analysis and log-rank test to examine OS stratified by different treatment modalities (*Figure 1*). LRT combined with systemic therapy showed the most favorable survival outcome compared with other treatment modalities (*vs.* no treatment, P<0.001; *vs.* systemic therapy, P=0.021; *vs.* LRT, P=0.021), followed by systemic therapy (*vs.* no treatment, P=0.021). The curves of OS between the LRT group and the no-treatment group were comparable (P=0.08). The no-treatment group was associated with a dismal prognosis, with a median OS of 2 months (95% CI: 1.25–2.75) and a 1-year OS rate of 8.8% (95% CI: 0.2%–17.0%). In comparison, the 1-year OS rates of the systemic therapy, LRT, and LRT plus systemic therapy group were 23.2%, 20.1%, and 41.4%, respectively (*Table 1*).

We next performed multivariable Cox analysis and patient-related variables in *Table 1* were included in the analysis. After adjusting confounding factors such as age, gender, insurance status, tumor characteristics (primary site and pathological grade), and disease burden (T and N stage, number of metastases), our results demonstrated that bone metastasis, liver metastasis, and treatment modality were independent prognostic factors for survival (*Table 2*). Patients with bone metastasis (OS, HR =2.01, 95% CI: 1.27–3.17) and liver metastasis (OS, HR =1.80, 95% CI: 1.10–2.95) had poor survival outcomes. Compared with systemic therapy, patients who received no therapy had a

Table 1 Characteristics and survival of patients with distantly metastatic hypopharyngeal cancer

Characteristics	No. of patients (%)	1-year CSS (95% CI)	P value	1-year OS (95% CI)	P value
Overall	463 (100.0)	31.6 (24.5–38.6)	NA	28.3 (21.8–34.8)	NA
Sex					
Male	413 (89.1)	33.7 (11.8–55.6)	0.245	28 (21.1–34.8)	0.437
Female	50 (10.9)	31.4 (23.9–33.8)		30 (10.1–49.9)	
Race					
Black	103 (22.2)	16.8 (4.9–28.7)	0.562	16 (4.6–27.6)	0.439
White	330 (71.4)	35.5 (26.9–44.1)		30.7 (23.9–38.5)	
Other	30 (6.5)	41.7 (13.9–69.5)		41.7 (13.9–69.5)	
Marital status					
Married	170 (36.8)	37.5 (25.6–49.5)	0.640	33.8 (22.5–44.9)	0.667
Single	270 (58.4)	27.8 (18.8–36.8)		24.3 (16.1–32.5)	
Unknown	23 (4.9)	33.3 (2.67–64.1)		33.3 (3.1–64)	
Insurance					
Uninsured/Medicaid	203 (43.8)	33.6 (22.8–44.6)	0.768	30.1 (19.9–40.3)	0.952
Insured	250 (54.1)	29.3 (20.1–38.5)		26 (17.4–34.6)	
Unknown	10 (2.2)	10 [5–92]		10 [5–92]	
Age (years)					
<65	295 (63.8)	34 [25–43]	0.047	30.5 (22.3–38.7)	0.057
≥65	168 (36.2)	27.7 (16.4–38.8)		24.4 (14.2–34.8)	
Primary site					
Pyriform sinus	384 (83.0)	33.3 (22.8–43.6)	0.041	29.5 (19.9–39.1)	0.107
Posterior wall of hypopharynx	61 (13.2)	23.1 (0.3–46)		21.4 (3.2–42.9)	
Postcricoid region	18 (3.8)	NA		NA	
Pathological grade					
Well/moderate	202 (43.6)	25.3 (12.6–38.0)	0.566	21.2 (10.2–32.4)	0.269
Poorly/undifferentiated	261 (56.4)	37.8 (22.1–45.3)		30.4 (19.6–41.2)	
T stage					
T1–T2	158 (34.2)	38.7 (24–52.6)	0.99	33.1 (21.8–44.4)	0.99
T3	71 (15.3)	30 (10.8–49.2)		24 (9.7–38.3)	
T4	234 (50.5)	27.4 (17.6–37.4)		25 (16.9–33.1)	
N stage					
N0	36 (7.7)	56.3 (29.8–82.7)	0.602	56.3 (33.5–79.1)	0.627
N1	99 (21.4)	30 (13.8–46.1)		23.7 (12.1–35.4)	
N2	260 (56.2)	34 (24.4–43.6)		30.9 (21.8–39.9)	
N3	68 (14.6)	12.8 (3–26.1)		11.5 (1–23.8)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	No. of patients (%)	1-year CSS (95% CI)	P value	1-year OS (95% CI)	P value
Metastasis site[a]					
Lung	255 (55.1)	31.3 (21.9–40.7)	0.983	28.9 (21.2–37.1)	0.906
Liver	58 (12.5)	17.4 (3–32.8)	0.093	17.4 (2–32.8)	0.247
Bone	93 (20.0)	11.2 (3–10.4)	<0.001	10.8 (1.2–21.7)	0.002
Brain	13 (2.7)	37.5 (0.3–93.5)	0.99	25.0 (0.6–54.9)	0.622
Treatment					
No therapy	100 (21.6)	10.1 (0.1–21.6)	<0.001	8.8 (0.2–17.0)	<0.001
Systemic therapy	78 (16.7)	23.4 (7.7–39.1)		23.2 (8.5–37.9)	
Locoregional treatment	68 (14.6)	24 (5.9–41.8)		20.1 (4.7–35.5)	
Locoregional treatment and systemic therapy	217 (47.0)	46 (35.1–56.8)		41.4 (31.0–51.8)	
Number of metastases[a]					
One site	280 (60.5)	35.4 (25.9–44.8)	0.003	32.9 (23.6–41.6)	0.018
Two or more sites	68 (14.7)	8.4 (0–19.6)		8.0 (0–18.6)	

The P value was calculated by the Kaplan-Meier method and log-rank test. [a], the SEER database only documented metastasis information of major organs such as lung, liver, bone, and brain. Accordingly, the total percentage of patients with the variable of "Metastasis site" and "Number of metastases" was not 100%. CSS, cancer-specific survival; OS, overall survival; 95% CI, 95% confidence interval; NA, not applicable.

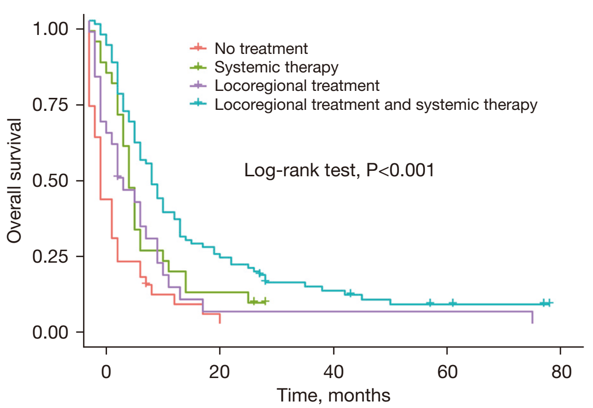

Figure 1 Overall survival curves of patients with distantly metastatic hypopharyngeal cancer undergoing different treatment modalities.

significantly increased risk of death (OS, HR =2.70, 95% CI: 1.51–4.84). Compared with systemic therapy, LRT and systemic therapy significantly reduced the risk of death (OS, HR =0.65, 95% CI: 0.39–0.92). In addition, the LRT alone strategy was likely to increase the risk of death compared with systemic therapy (OS, HR =1.41, 95% CI: 0.73–2.70), but the difference did not reach a significant level.

Since systemic therapy is the first choice for MHPC, we further performed survival analyses just between the systemic therapy group and LRT plus systemic therapy group. The clinicopathological features were summarized in *Table 3*. The Chi-square test was used for comparison. The patients with systemic therapy presented with a lower percentage of insurance (34.6% *vs.* 52.0%), higher age (patients >65 years of age 41% *vs.* 27.6%), a higher percentage of T3 diseases (32% *vs.* 12.9%), a higher percentage of lung metastasis (61.5% *vs.* 50.7%), bone metastasis (30.7% *vs.* 13.8%), and multiple metastases (30.7% *vs.* 11.5%) in comparison with patients received LRT plus systemic therapy. This reflects the fact that patients with systemic therapy alone had a more extensive burden of disease, higher age, and possibly poorer health status. After adjusting for confounding variables in *Table 3*, bone metastasis, liver metastasis, and treatment remained to be independent prognostic factors for survival (*Table 4*). LRT plus systemic therapy yielded a 37% decreased risk of death compared with systemic therapy alone (OS,

Table 2 Multivariate survival analysis of independent prognostic factors for patients with distantly metastatic hypopharyngeal cancer

Characteristics	CSS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Bone metastasis				
No	Reference	<0.001	Reference	0.003
Yes	2.34 (1.46–3.76)		2.01 (1.27–3.17)	
Liver metastasis				
No	Reference	0.003	Reference	0.019
Yes	2.14 (1.29–3.53)		1.80 (1.10–2.95)	
Treatment				
Systemic therapy	Reference		Reference	
No therapy	2.58 (1.40–4.75)	0.002	2.70 (1.51–4.84)	0.001
Locoregional treatment	1.26 (0.63–2.53)	0.509	1.41 (0.73–2.70)	0.306
Locoregional treatment and systemic therapy	0.60 (0.35–0.95)	0.044	0.65 (0.39–0.92)	0.028

CSS, cancer-specific survival; OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval.

Table 3 The distribution of patient characteristics in systemic therapy group and LRT + systemic therapy group

Characteristics	Systemic therapy, n=78 (%)	LRT + systemic therapy, n=217 (%)	P value
Sex			
Male	68 (87.2)	199 (91.7)	0.242
Female	10 (12.8)	18 (8.3)	
Race			
Black	14 (17.9)	40 (18.4)	0.982
White	59 (75.6)	162 (74.6)	
Other	5 (6.4)	15 (6.9)	
Marital status			
Married	30 (38.5)	87 (40.1)	0.849
Single	46 (58.9)	122 (56.2)	
Unknown	2 (2.5)	8 (3.7)	
Insurance			
Uninsured/Medicaid	49 (62.8)	100 (46.1)	0.03
Insured	27 (34.6)	113 (52.0)	
Unknown	2 (2.5)	4 (1.8)	
Age (years)			
<65	46 (58.9)	157 (72.4)	0.029
≥65	32 (41.0)	60 (27.6)	

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Systemic therapy, n=78 (%)	LRT + systemic therapy, n=217 (%)	P value
Primary site			
Pyriform sinus	65 (83.3)	186 (85.7)	0.417
Posterior wall of hypopharynx	10 (12.8)	28 (12.9)	
Postcricoid region	3 (3.8)	3 (1.4)	
Pathological grade			
Well/moderate	27 (34.6)	98 (45.2)	0.106
Poor/undifferentiated	51 (65.4)	119 (54.8)	
T stage			
T1–T2	21 (26.9)	75 (34.6)	0.001
T3	25 (32.0)	28 (12.9)	
T4	32 (41.0)	114 (52.5)	
N stage			
N0–N1	28 (35.8)	52 (23.9)	0.094
N2	42 (53.8)	130 (59.9)	
N3	8 (10.2)	35 (16.1)	
Metastasis site[a]			
Lung	48 (61.5)	110 (50.7)	0.046
Liver	16 (20.5)	30 (13.8)	0.163
Bone	24 (30.7)	30 (13.8)	0.001
Brain	0 (0)	5 (2.3)	0.176
Number of metastases[a]			
One site	40 (51.2)	110 (50.6)	0.004
Two or more sites	24 (30.7)	25 (11.5)	

P value was calculated by chi-square test. [a], the SEER database only documented metastasis information of the major organs such as lung, liver, bone, and brain in M1 patients. And patients may have multiple organ metastases at the time of diagnosis. Accordingly, the total percentage of patients with the variable of "Metastasis site" and "Number of metastases" was not 100%. LRT, locoregional treatment.

HR =0.63, 95% CI: 0.38–0.92). To reduce the impact of death from other causes, we performed competing risk analysis between the two treatment groups. Our results indicated that systemic therapy alone was associated with an increased risk of cancer-specific mortality compared with LRT plus systemic therapy (P<0.01, *Figure 2*). The risk of other causes of mortality was not significantly different among the two therapeutic methods (P=0.32). We further performed subgroup analysis in patients treated with the two methods and found that the survival benefit of LRT plus systemic therapy was significant in subgroups including younger age, single status, pyriform sinus originated, and lung metastasis (*Figures 3-5*, P<0.05). To explore the interaction between treatment effects and patient-related characteristics, we performed interaction analysis. However, the P value for interaction only showed a significant level for the age variable (P=0.01, *Figure 6*), indicating that younger patients (<65 years) were more likely to achieve survival benefit if they were treated with LRT and systemic therapy.

Table 4 Multivariate survival analyses for patients with systemic therapy and patients with locoregional treatment plus systemic therapy

Characteristics	CSS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Bone metastasis				
No	Reference	<0.001	Reference	<0.001
Yes	3.52 (1.97–6.29)		2.86 (1.62–5.06)	
Liver metastasis				
No	Reference	0.026	Reference	0.096
Yes	1.89 (1.08–3.31)		1.59 (0.92–2.76)	
Treatment				
Systemic therapy	Reference	0.037	Reference	0.043
Locoregional treatment and systemic therapy	0.57 (0.34–0.97)		0.63 (0.38–0.92)	

CSS, cancer-specific survival; OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval.

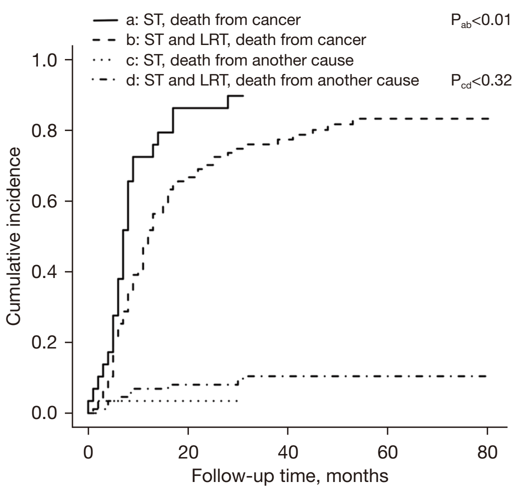

Figure 2 Competing risk analysis for patients with distantly metastatic hypopharyngeal cancer. ST, systemic therapy; LRT, locoregional treatment.

Discussion

Hypopharyngeal cancer with distant metastasis often heralds an incurable disease. According to a study of the National Cancer Database, LRT combined with systemic therapy was the most common (39.2%) treatment modality in M1 head and neck cancers (9). Other than in the setting of palliative intention, the role of LRT is controversial in metastatic HNSCC. The survival benefit of LRT for primary tumor and metastatic diseases has been demonstrated in many other cancers such as prostate cancer (10), lung cancer (11), and brain metastases (12). Although NCCN guidelines recommended LRT (surgery and radiotherapy) for selected patients with limited metastasis, the survival influence of LRT is poorly documented in the literature.

To our knowledge, we have explored the survival benefit of LRT and the prognostic factors for patients with MHPC for the first time. Multiple studies have reported factors associated with metastatic HNSCC and considered that T and N stages were associated with distant metastasis (13,14). And for laryngeal cancer with distant metastasis, Pan *et al.* found that the T stage was a significant risk factor for survival in their population-based retrospective study (15). In our work, the incidence of T4 or N2-N3 diseases in MHPC was 50.6% or 70.8%, respectively. Cox analysis indicated that bone and liver metastasis were independent predictors for survival, while T and N classifications were not. Perhaps T and N classifications are not important for prognosis once distant metastasis occurs. This is consistent with a retrospective single-institution study reported by Schulz *et al.* (16). They analyzed the outcomes of patients with metachronous distant metastasis of head and neck cancers after specific therapy and found relationships between survival and liver as well as bone metastasis. Although univariate survival analysis showed poorer survival outcomes in patients with multiple metastases, the multivariate analysis suggested the number of metastases was not an independent risk factor for survival. In our work, the site of metastasis (liver/bone) seems to have a greater influence than the number of metastases on survival. This was contrary to the results reported in laryngeal cancer and breast cancer (15,17).

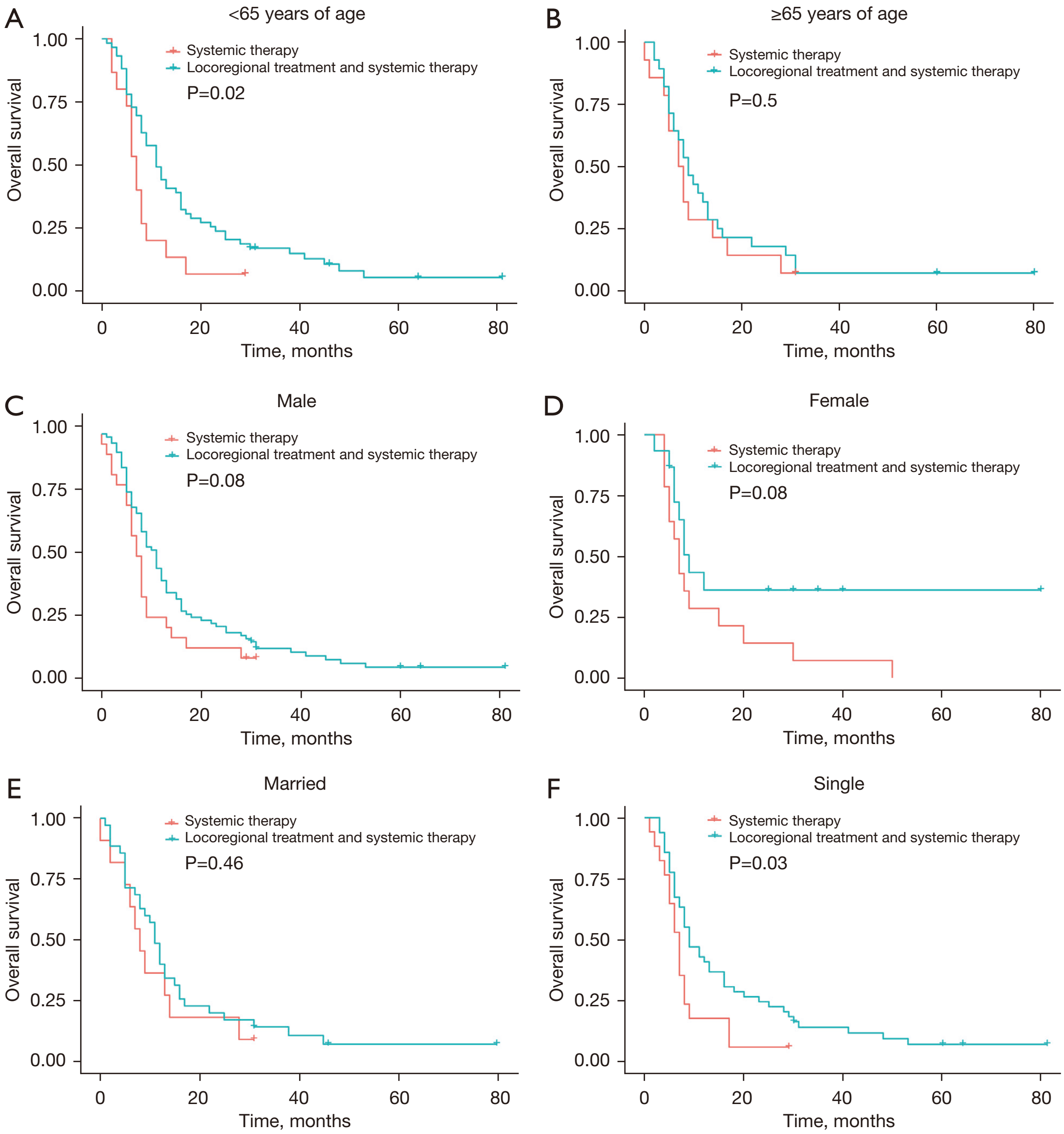

Figure 3 Overall survival curves for patients stratified by age, gender, and marital status.

LRT in our analysis includes surgery (17/285, 6%), radiotherapy (235/285, 82.4%), and surgery combined with radiotherapy (33/285, 11.6%). Surgery as a palliative intent in advanced head and neck cancers mainly includes nutritional support surgery (percutaneous gastrostomy and open jejunostomy), tumor debulking surgery, and tracheotomy, and so on. Types of surgery in the present study included 30 cases of local tumor excision and 20 cases of pharyngectomy with or without laryngectomy. Local excision in the SEER database requires specimens sent to pathology from this surgical event. However, we were unable to speculate about the extent of tumor excision and the situation at that time. Given the invasive nature of the procedure, the role of surgery in metastatic head and neck cancers has diminished. We believe that two types of local excision could be considered as effective local therapies. First, the primary tumor was quite small and able to be completely removed by surgery. Second, the primary lesion had severe complications such as respiratory obstruction and bleeding and had to be operated on. Considering that patients receiving radiotherapy accounted for 94% of all patients with locoregional treatment in our work, in

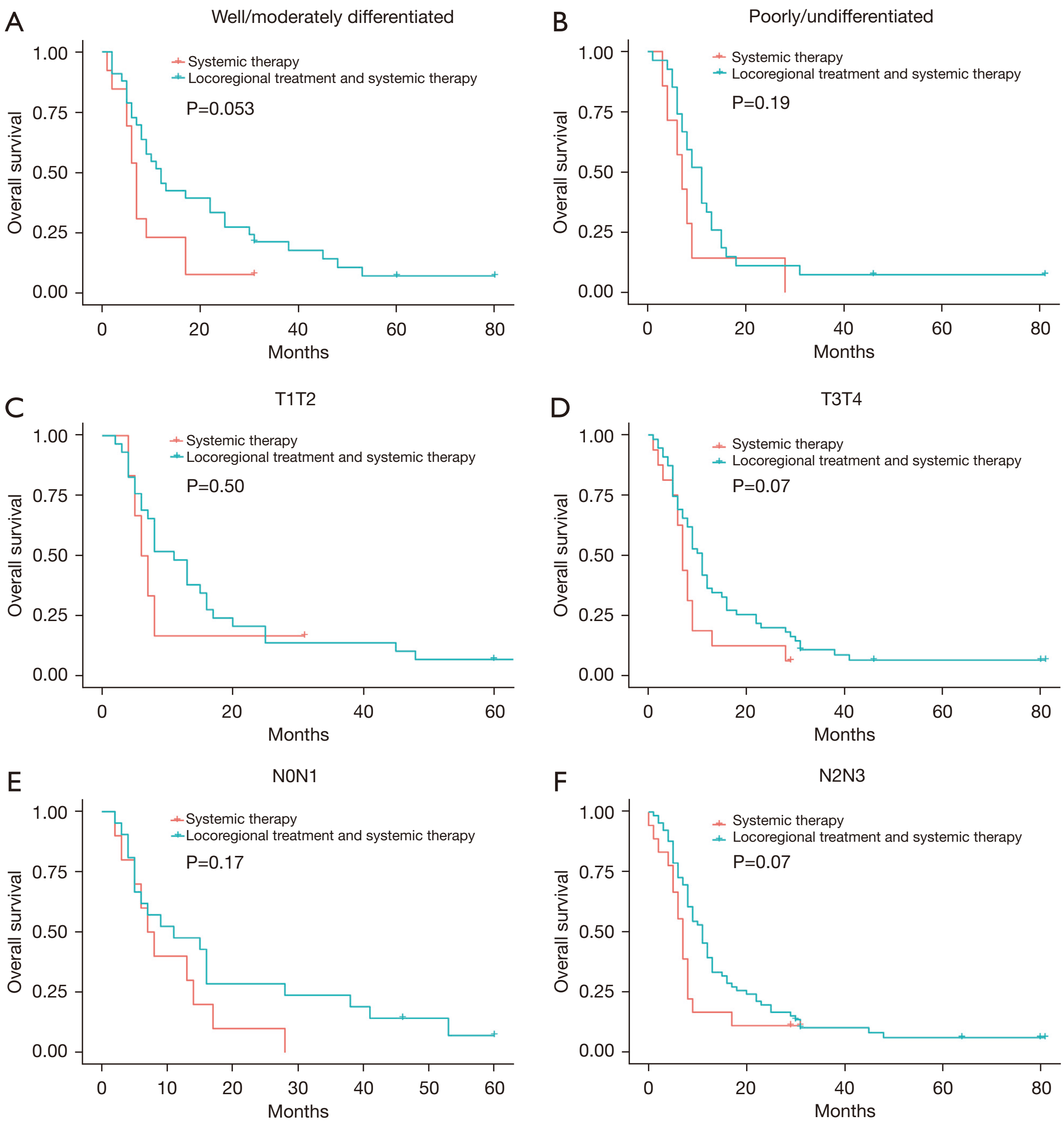

Figure 4 Overall survival curves for patients stratified by pathological grade, T and N stage.

fact, the results of this study are more instructive for local radiotherapy. This is also in line with the current status of locoregional treatment for metastatic hypopharyngeal cancer. Many patients received palliative radiotherapy with or without systemic therapy (18,19).

A recent study has demonstrated the safety and effectiveness of concurrent systemic therapy and palliative radiotherapy in advanced head and neck cancers, with an objective response rate up to 85.7% (19). Our results showed that systemic therapy and LRT yield a 37% decreased risk of death compared with systemic therapy alone (*Table 4*). Although the evidence of direct comparison is missing, patients with distantly metastatic HNSCC treated with palliative chemotherapy had a median survival of 7.4 months (20), which was evidently higher than 3.8 months reported for patients with no therapy (21). Our results showed that the risk of mortality in patients with systemic therapy was significantly lower than that of patients with no therapy (HR =2.70, *Table 2*). In Kaplan-Meier analysis, the survival curves of the LRT group and no treatment group were not significantly different. Besides, LRT was likely to increase the risk of mortality

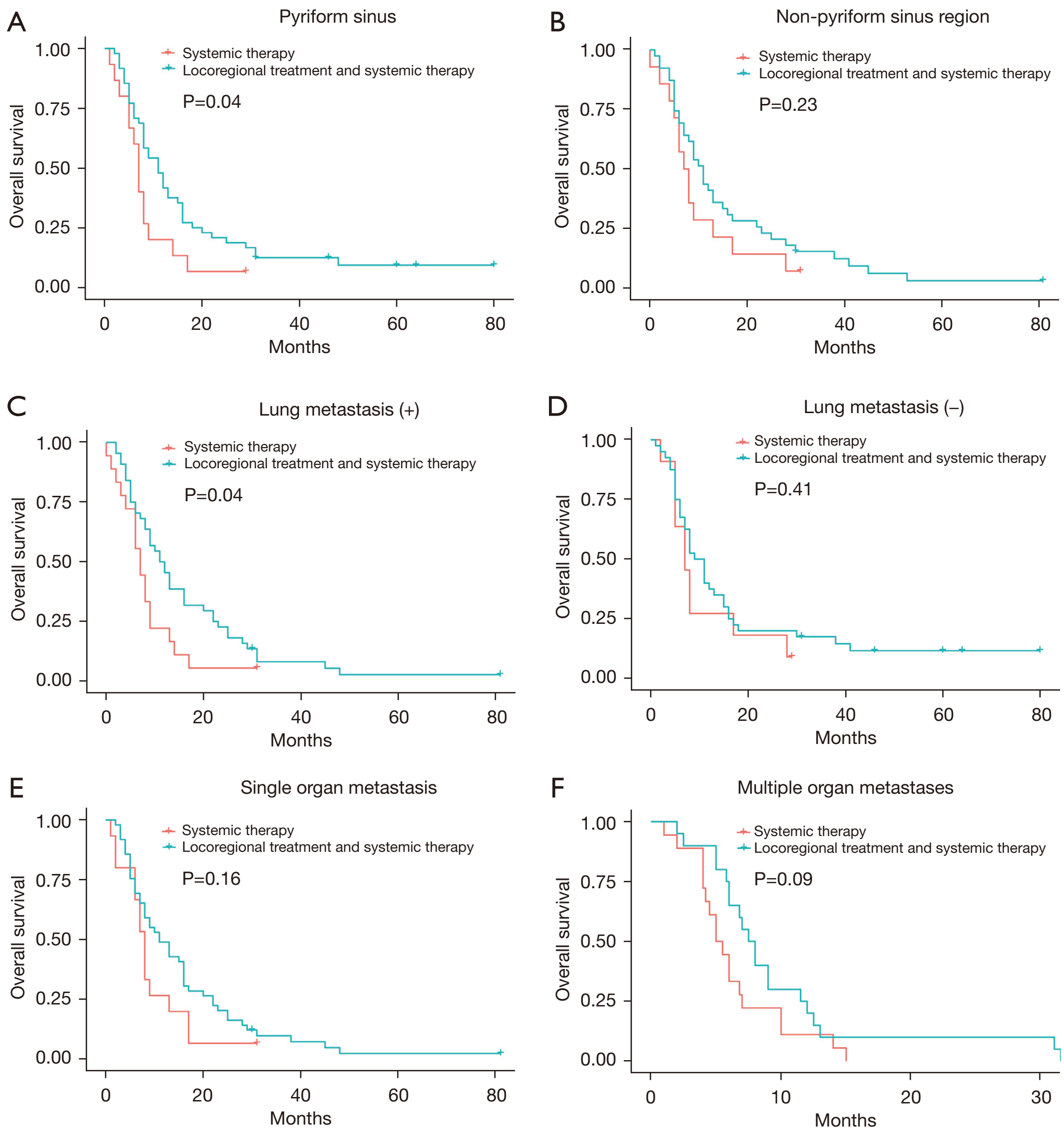

Figure 5 Overall survival curves for patients stratified by primary site, lung metastasis, and number of metastases.

than systemic therapy in cox regression analysis (OS, HR =1.41, 95% CI: 0.73–2.70). These results implied that only LRT would not benefit survival if a patient does not receive systemic therapy.

Patients with distant diseases often have advanced primary tumors, poor performance status, and other comorbidities. LRT may be correlated with a high risk of morbidity and mortality. Consequently, we performed competing risk analysis to determine whether different treatment modalities influenced multiple survival outcomes. Our results showed that LRT combined with systemic therapy was associated with improved cancer-specific mortality for patients with MHPC without affecting other-cause mortality compared to systemic therapy alone.

There are several reasons to explain the favorable effect of LRT. First, hypopharyngeal cancer is adjacent to the vital blood vessels and nerves in the head and neck region responsible for essential biological functions, such as respiration, swallowing, and phonation. Locoregional progression is often the primary cause of morbidity and mortality for head and neck cancers, even for those with distant metastasis (22). Second, LRT reduces the tumor

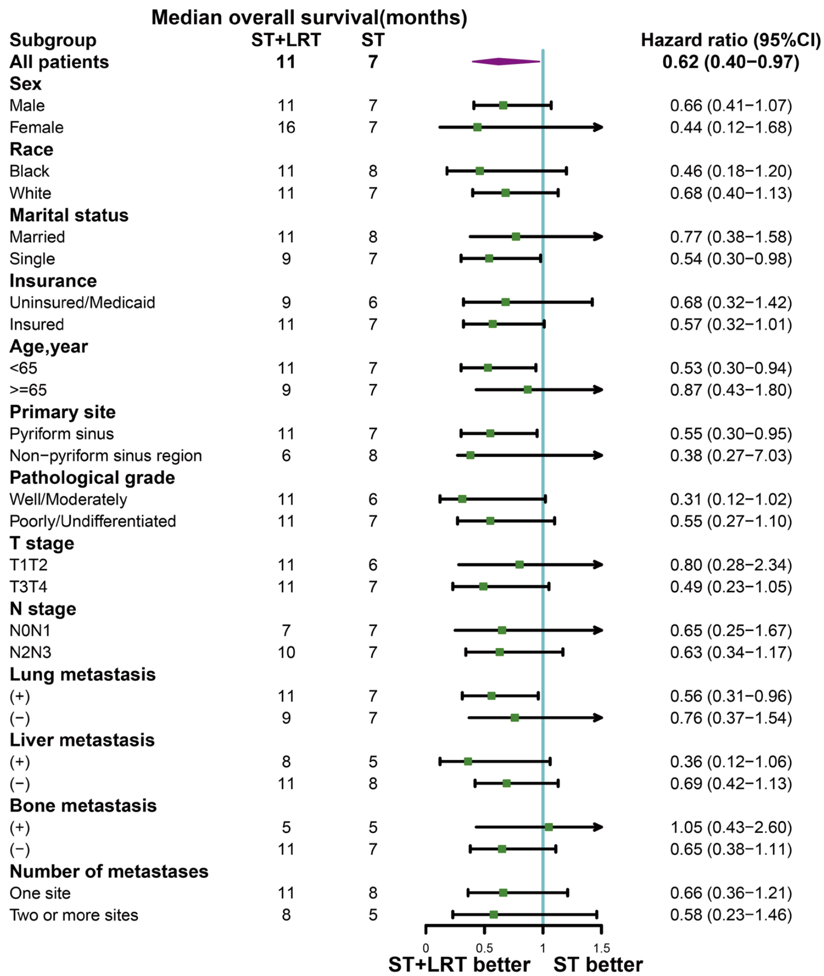

Figure 6 Forest plot of the treatment effect on overall survival by patient and tumor characteristics. ST, systemic therapy; LRT, locoregional treatment. A hazard ratio of less than 1 indicates a survival benefit of locoregional treatment combined with systemic therapy. There was an interaction between treatment effect and age variable (P for interaction =0.01).

burden and facilitates inhibiting tumor growth and distant metastasis. The abscopal effect is a phenomenon in which local radiotherapy is associated with the regression of metastatic cancer distant from the irradiated site (23). The effect is often mediated by the immunological mechanisms evoked by locally dead cancer cells (24). In addition, primary tumors have been reported to produce systemic signals, such as inflammatory cytokines and exosomes, affecting distant organs by constructing premetastatic niches (25). Consequently, the ablation of primary tumors may contribute to an abscopal effect on systemic diseases.

Not all patients achieved survival benefits from LRT. Although subgroup analysis demonstrated survival benefits of LRT and systemic therapy in many subgroups such as younger age, single status, pyriform sinus originated, and lung metastasis (*Figures 3-5*), the interaction analysis suggested that only the age variable significantly influenced the treatment effect, which suggested that younger patients were more likely to benefit from LRT with improved survival. Interaction analysis can examine a situation in which the effect of treatment on a survival outcome depends on another covariate. As shown in *Figure 6*, estimates of HR were indeed similar among subgroups defined by variables such as marital status, primary site, and lung metastasis. Young patients tend to have better tolerance to LRT than the elderly. Many palliative radiotherapy regimens will decide whether to deliver a higher dose of radiotherapy according to the patient's tolerance (18), while radiotherapy dose has been considered to be an independent factor affecting survival (26). However, we could not validate this hypothesis due to the limited information regarding radiotherapy regimens in the SEER database. Although NCCN guidelines recommended surgery and radiotherapy for patients with limited metastasis, we did not observe a survival benefit of LRT in patients with a single metastasis (*Figure 5E*).

The time of LRT might have an impact on the survival of patients. A study of metastatic head and neck cancers using the NCDB database suggested that the effect of early local treatment (<6 months) might be greater than that of later local treatment (>6 months) (27). However, the authors also acknowledged that such results may be due to the bias that patients with early response to chemotherapy were more likely to receive local treatment. Because no information about treatment time was available in the SEER database, we were unable to conduct further analyses. In another study using the NCDB database to evaluate the role of local radiotherapy in metastatic head and neck cancers (28), they reported that 46.7% of patients with radiotherapy and systemic therapy received concurrent chemoradiotherapy, 41.2% received chemotherapy after radiotherapy, and 12.1% received radiotherapy after chemotherapy. In our clinical practice, the timing of local radiotherapy is individualized. Generally speaking, patients with good performance status, limited distant metastases, and small primary tumors are preferred to give concurrent chemoradiotherapy. For patients with extensive primary tumors and severe lymphatic metastases, chemotherapy is preferred to be delivered first, and then local radiotherapy is decided according to therapeutic responses.

The lack of radiation dose is a major drawback of the present study. Because the survival benefit of radiotherapy may be dose-dependent. An NCDB database study suggested that high-intensity radiotherapy (>60 Gy) may be beneficial for survival of patients with M1 head and neck cancers (27). The commonly used dose of palliative radiotherapy in North America is of 4,400 cGy, and whether to give a higher dose was determined based on the patient's tolerance and therapeutic responses (8). Although patients in our analysis who were treated with local radiotherapy might have received palliative doses (<60 Gy), our results still showed a survival benefit for the locoregional treatment combined with systemic therapy group. For metastatic hypopharyngeal cancer with a median survival of only 7–8 months, the optimal radiotherapy dose should take full account of the performance status, life expectancy, quality of life, and patient's will. Whether the appropriate dose of radiotherapy is beneficial for survival in metastatic head and neck cancers remains to be tested in high-quality randomized control trials.

There are several limitations to keep in mind when interpreting our results. First, potential selection bias may exist among treatment groups. Patients treated with systemic therapy alone were older and had a more extensive tumor burden compared with patients with LRT plus systemic therapy. However, the Cox regression analysis still confirmed the survival benefit of LRT plus systemic therapy after adjusting the imbalance of these covariables. Second, there was no data on comorbidity and performance status of patients included in our analysis owing to the limitation of the data source. These variables may affect treatment choice and survival outcomes in patients with advanced head and neck cancer (29,30). Interestingly, our competing risk analysis suggested that LRT has mitigated cancer-related mortality. It is reasonable to speculate that the improved cancer-related mortality was due to the biological characteristics of tumor and treatment choice rather than well performance status or fewer comorbidities. Third, an immortal time bias, in which patients must have survived until fulfilling their LRT, could have contributed to results in favor of LRT. Consequently, it is insufficient to offer LRT as standard of care based on our work, and further clinical trials are still needed to validate our results. But our study suggests promising information that LRT, which is often used as palliative therapy in distantly metastatic cancers, was associated with improved survival in selected patients with MPHC.

Conclusions

Our results revealed that bone metastasis, liver metastasis, and treatment modality were independent factors affecting the survival of patients with distantly metastatic hypopharyngeal cancer. Locoregional treatment and systemic therapy was associated with prolonged survival compared with systemic therapy alone in selected patients. Furthermore, younger patients (<65 years) may be more likely to benefit from locoregional treatment with improved overall survival.

Acknowledgments

We thank Professor Yalin Chen from the Department of Radiotherapy of Peking University People's Hospital for his

excellent academic assistance.
Funding: This work was supported by the National Natural Science Foundation of China (No. 82071034).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-2953/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-2953/coif). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Garneau JC, Bakst RL, Miles BA. Hypopharyngeal cancer: A state of the art review. Oral Oncol 2018;86:244-50.
2. Gupta T, Chopra S, Agarwal JP, et al. Squamous cell carcinoma of the hypopharynx: single-institution outcome analysis of a large cohort of patients treated with primary non-surgical approaches. Acta Oncol 2009;48:541-8.
3. Spector JG, Sessions DG, Haughey BH, et al. Delayed regional metastases, distant metastases, and second primary malignancies in squamous cell carcinomas of the larynx and hypopharynx. Laryngoscope 2001;111:1079-87.
4. Spector GJ. Distant metastases from laryngeal and hypopharyngeal cancer. ORL J Otorhinolaryngol Relat Spec 2001;63:224-8.
5. Li W, Wei D, Qian Y, et al. A novel surgical approach for hypopharyngeal carcinoma resection via the paraglottic space. BMC Surg 2021;21:230.
6. Newman JR, Connolly TM, Illing EA, et al. Survival trends in hypopharyngeal cancer: a population-based review. Laryngoscope 2015;125:624-9.
7. Roland NJ, Bradley PJ. The role of surgery in the palliation of head and neck cancer. Curr Opin Otolaryngol Head Neck Surg 2014;22:101-8.
8. Grewal AS, Jones J, Lin A. Palliative Radiation Therapy for Head and Neck Cancers. Int J Radiat Oncol Biol Phys 2019;105:254-66.
9. Schwam ZG, Burtness B, Yarbrough WG, et al. National treatment patterns in patients presenting with Stage IVC head and neck cancer: analysis of the National Cancer Database. Cancer Med 2015;4:1828-35.
10. Yuan Y, Kishan AU, Nickols NG. Treatment of the primary tumor in metastatic prostate cancer. World J Urol 2019;37:2597-606.
11. Zhu H, Zhou Z, Wang Y, et al. Thoracic radiation therapy improves the overall survival of patients with extensive-stage small cell lung cancer with distant metastasis. Cancer 2011;117:5423-31.
12. Aoyama H, Tago M, Shirato H; Japanese Radiation Oncology Study Group 99-1 (JROSG 99-1) Investigators. Stereotactic Radiosurgery With or Without Whole-Brain Radiotherapy for Brain Metastases: Secondary Analysis of the JROSG 99-1 Randomized Clinical Trial. JAMA Oncol 2015;1:457-64.
13. Lee DH, Kim MJ, Roh JL, et al. Distant metastases and survival prediction in head and neck squamous cell carcinoma. Otolaryngol Head Neck Surg 2012;147:870-5.
14. Li X, Di B, Shang Y, et al. Clinicopathologic risk factors for distant metastases from head and neck squamous cell carcinomas. Eur J Surg Oncol 2009;35:1348-53.
15. Pan Y, Hong Y, Liang Z, et al. Survival analysis of distant metastasis of laryngeal carcinoma: analysis based on SEER database. Eur Arch Otorhinolaryngol 2019;276:193-201.
16. Schulz D, Wirth M, Piontek G, et al. Improved overall survival in head and neck cancer patients after specific therapy of distant metastases. Eur Arch Otorhinolaryngol 2018;275:1239-47.
17. Li X, Huang R, Ma L, et al. Locoregional surgical treatment improves the prognosis in primary metastatic breast cancer patients with a single distant metastasis except for brain metastasis. Breast 2019;45:104-12.
18. Lok BH, Jiang G, Gutiontov S, et al. Palliative head and neck radiotherapy with the RTOG 8502 regimen for incurable primary or metastatic cancers. Oral Oncol

2015;51:957-62.
19. Gamez ME, Agarwal M, Hu KS, et al. Hypofractionated Palliative Radiotherapy with Concurrent Radiosensitizing Chemotherapy for Advanced Head and Neck Cancer Using the "QUAD-SHOT Regimen". Anticancer Res 2017;37:685-91.
20. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-27.
21. Kowalski LP, Carvalho AL. Natural history of untreated head and neck cancer. Eur J Cancer 2000;36:1032-7.
22. Vengaloor Thomas T, Packianathan S, Bhanat E, et al. Oligometastatic head and neck cancer: Comprehensive review. Head Neck 2020;42:2194-201.
23. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med 2012;366:925-31.
24. Rodríguez-Ruiz ME, Vanpouille-Box C, Melero I, et al. Immunological Mechanisms Responsible for Radiation-Induced Abscopal Effect. Trends Immunol 2018;39:644-55.
25. Massagué J, Obenauf AC. Metastatic colonization by circulating tumour cells. Nature 2016;529:298-306.
26. Stevens CM, Huang SH, Fung S, et al. Retrospective study of palliative radiotherapy in newly diagnosed head and neck carcinoma. Int J Radiat Oncol Biol Phys 2011;81:958-63.
27. Zumsteg ZS, Luu M, Yoshida EJ, et al. Combined high-intensity local treatment and systemic therapy in metastatic head and neck squamous cell carcinoma: An analysis of the National Cancer Data Base. Cancer 2017;123:4583-93.
28. Kabarriti R, Baliga S, Ohri N, et al. Radiation therapy for patients with newly diagnosed metastatic head and neck squamous cell carcinoma. Head Neck 2019;41:130-8.
29. Schimansky S, Lang S, Beynon R, et al. Association between comorbidity and survival in head and neck cancer: Results from Head and Neck 5000. Head Neck 2019;41:1053-62.
30. Langius JA, Zandbergen MC, Eerenstein SE, et al. Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo)radiotherapy: a systematic review. Clin Nutr 2013;32:671-8.

Cite this article as: Wang W, Zheng H, Yu L, Zhang L. Prognostic factors and the role of locoregional treatment in patients with distantly metastatic hypopharyngeal cancer: a retrospective cohort study based on SEER database. Ann Palliat Med 2022;11(6):1925-1939. doi: 10.21037/apm-21-2953

