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ORIGINAL RESEARCH

The Pattern of Cervical Lymph Node Metastasis and Risk Factors of Retropharyngeal Lymph Node Metastasis Based on Magnetic Resonance Imaging in Different Sites of Hypopharyngeal Carcinoma

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Background: This study was to determine the patterns of regional lymph node (LN) spread and the risk factors of retropharyngeal lymph node (RPLN) metastasis based on magnetic resonance imaging (MRI) in hypopharyngeal squamous carcinoma (HPC) to improve clinical target volume (CTV) delineation.

Methods: A cohort of 326 consecutive patients of HPC in a single institute were retrospectively reviewed. All patients underwent MRI prior to initial treatment, and the diagnosis based on MRI of the LN metastasis was confirmed by all radiation oncologists in the head and neck group during twice weekly chat rounds. Statistical analysis of data was using chi-square test and multivariant logistic regression model in SPSS 22.0 software.

Results: The LN metastasis rate of all patients in this cohort was 90.5% (295/326). Level IIa/b and level III were the most frequently involved regions followed by level IV and retropharyngeal region. Skip metastasis only occurred in 6.4% (19/295). Univariate and multivariate analysis demonstrated that primary tumor subsites were located in the posterior pharyngeal wall (P=0.002), bilateral cervical LN metastasis (P=0.020), larger volume of primary gross target (GTVp, P=0.003), and larger volume of LN gross target (GTVnd, P=0.023) were significantly associated with RPLN metastasis.

Conclusion: The regional LN spread of HPC follows an ordered pattern as level II is the most frequently involved area followed by level III, level IV, and RPLN. RPLN metastasis is more likely to occur in patients with primary site of posterior pharyngeal wall, large tumor burden, or bilateral neck LN metastasis. Therefore, it is highly recommended that the RPLN should be included into CTV for patients who have these risk factors.

Keywords: hypopharyngeal carcinoma, lymph node metastasis, risk factors, retropharyngeal lymph node, metastasis

Introduction

HPC is an aggressive malignancy that can be treated by surgery combined with radiation and chemotherapy. However, overall results are still relatively poor compared with other head and neck carcinomas.[1] How to improve the prognosis and prolong the survival of these patients is the main direction of the current effort. Due to the abundant lymphatic network in the hypopharynx, more than 50% of patients diagnosed with clinically positive cervical lymph nodes and eventually 65% to 80% of patients will develop LN metastasis.[2] Levels II–IV, as well as RPLN region, all

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have high risk of LN metastases.[3,4] One of the dilemmas of clinical management is that most patients have difficulty obtaining a pathological diagnosis because the patient is not suitable for total laryngectomy due to advanced stage or the patient is unwilling to perform a total laryngectomy. Imaging diagnosis becomes critical under such circumstances. MRI has greater advantages than computed tomography (CT) in the diagnosis of LN metastasis, and it is easier to obtain than positron emission tomography–computed tomography (PET-CT), but previous studies on LM metastasis patterns were few and based on clinical examinations or CT. Amatsu et al found that 51 patients with hypopharyngeal and cervical esophageal cancer who had undergone previous surgery had uncontrolled lymph node metastasis in the retropharyngeal region after treatment, which meant that there was occult metastasis in this area. The study of MRI-based pattern of LN metastasis and risk factors of RPLN metastasis will help us to acquire more useful information. In clinical practice we have observed some possible patterns and risk factors of RPLN metastasis, which may be related to the anatomy of the primary cancer. Therefore, we retrospectively analyzed the clinical data of patients who underwent MRI prior to initial treatment in recent years to draw conclusions to guide the appropriate area of CTV delineation.

Methods and Materials

Patients diagnosed with hypopharyngeal squamous carcinoma who received radical radiotherapy or radiotherapy followed by surgery (postoperative radiation for patients with T3-4, N+, or other high-risk factors) were included in this study from January 2012 to September 2018 in a single institution. All patients underwent a clinical staging examination prior to initial treatment, including a complete patient history, mirror examination, serum biochemistry, electronic endoscope, and MRI of the head and neck, which included free water diffusion-weighted imaging (DWI) technique sequence (The type of MRI was GE SIGNA Pioneer 3.0T, with slice pitch of 5 mm, and the contrast was dimeglumine gadopentetate injection); computed tomography (CT) scans of the head and neck and chest; CT scan or ultrasound of abdomen; bone scan of whole body. Patients lack of MRI should be excluded. All patients were restaged according to the 7th edition of the American Joint Committee on Cancer staging system.

The diagnosis of LN metastasis was based on one or more of the following radiological criteria:[5] (a) lateral RPLN with a minimal axial diameter (MID) in the largest plane of an individual node at least 5 mm and any node seen in the median retropharyngeal group, LNs with a MID of at least 11 mm in the jugulodigastric region and 10 mm for all other cervical nodes, excluding the retropharyngeal group; (b) LNs of any size with central necrosis or a contrast-enhancing rim; (c) the presence of three or more contiguous and confluent LNs, each of which should have a MID of 8 mm or more; and (d) LNs of any size with extracapsular spread, including the presence of indistinct nodal margins, irregular nodal capsular enhancement or infiltration into the adjacent fat or muscle. The lymph nodal stations were assigned according to the DAHANCA, EORTC, GORTEC, NCIC, and RTOG consensus guideline.[6]

The data was statistically analyzed by the software of SPSS 22.0. Chi-square test was used for univariate analysis and logistic regression model for multivariate analysis of the relationship between RPLN metastasis and clinical tumor parameters. The level indicating statistical significance is 5% ($P<0.05$), 2-sides.

Results

We identified 334 consecutive patients with HPC diagnosed by histopathology, but eight patients were excluded for no available preoperative MRI. Of the 326 patients, 314 were males and 12 were females. Ages ranged from 36–83 years, with a median of 57 years. The characteristics of these patients are shown in Table 1.

Table 1 also presents the TNM staging, based on clinical and radiologic data. Most of the patients presented with T2–T4 disease. The incidence of LN metastasis at initial staging was 90.5% (295/326). In the initial staging, six patients developed distant lung metastases.

The distributions in different levels and in left or right sides of LNs metastasis are shown in Table 2. The most frequently involved regions were level IIa (222/326, 68.1%), level III (216/326, 66.3%), level IIb (160/326, 49.1%), and level IV (89/326, 27.3%). Other than these, the frequency of level VIIa (RPLN) LN involvement (70/326, 21.5%) was more than level Va and Vb (54/326, 16.6%). Involvement of level Ia and Ib was rather rare (3/326, 0.9%, and 19/326, 5.8%, respectively). There was no significant correlation between LN metastasis and the T stage because the metastasis rate of patients with T stage of T1 to T4 was 100.0%, 95.9%, 86.6%, and 89.0%, respectively ($P=0.106$). Ipsilateral LN metastasis rate was 56.1% (183/326), and bilateral LN metastasis rate was 34.6% (112/326)

Table 1 Clinical Characteristics of Patients with HPC

Characteristic	No. (Percentage of All Patients)
Sex	
Male	314 (96.3)
Female	12 (3.7)
Median Age (range)	57 (36–83)
T stage	
T1	16 (4.9)
T2	74 (22.7)
T3	82 (25.2)
T4	154 (47.2)
N stage	
N0	31 (9.5)
N1	33 (10.1)
N2a	12 (3.7)
N2b	111 (34.0)
N2c	91 (27.9)
N3	48 (14.7)
M stage	
M0	320 (98.2)
M1	6 (1.8)
Primary Site	
Piriform sinuses	260 (79.8)
Post-cricoid region	19 (5.8)
Posterior pharyngeal wall	47 (14.4)
Involved Site	
Piriform sinuses	273 (83.7)
Post-cricoid region	201 (61.7)
Posterior pharyngeal wall	150 (46.0)

Abbreviation: HPC, hypopharyngeal carcinoma.

This pattern of LN metastasis indicated that level II or level III LN metastasis may occur earlier than other cervical levels, representing the first station. There were 46 patients (46/326, 14.1%) who had metastasis first to level III instead of level IIa/b. Two patients had metastasis skipping over level IIa/b, nine skipping over level III, and seven skipping both level IIa/b and level III. In addition, 93.5% of patients (276/295) developed LN metastasis followed by orderly progression from the sentinel stations level IIa/b and level III. Level V nodes were involved only in cases with disease widely metastatic to the upper and middle neck nodes.

Among the 70 (21.5%) patients with RPLN metastases, three patients (0.9%) had isolated RPLN metastasis, 27 (37.5%) ipsilateral metastases, 25 (34.7%) contralateral metastases, and 18 (25.0%) bilateral metastases. Further univariate analysis demonstrated that RPLN metastasis was significantly correlated with the anatomic distribution of the primary sites. Patients whose primary site was located in the posterior pharyngeal wall were associated with a significantly higher RPLN metastasis rate compared with patients whose primary site was located in piriform sinus or post-cricoid region (26/49, 53.1%; 40/261, 15.3%; 0/9, 0.0%; respectively, P=0.000). Considering most patients have locally advanced disease, we also calculated that patients with posterior pharyngeal wall involvement were associated with a significantly higher RPLN metastasis rate compared with patients without posterior pharyngeal wall involvement (50/150, 33.3% vs 20/176, 11.4%; P<0.001), Patients with bilateral LN metastasis had a significantly higher rate than patients without bilateral LN metastasis (39/103, 37.9% vs 31/223, 13.9%, P=0.000). There was no statistically significant difference in patients with different T stage (T1–T4: 12.5%, 12.2%, 15.9%, and 28.6%, P=0.185), different N stage (N0–N3: 6.5%, 15.2%, 24.8%, and 20.8%, P=0.081). There was no statistically significant difference in patients with LN metastasis in the ipsilateral level II–IV and patients

Table 2 Distribution of Lymph Node Metastases in HPC

Level	Left	Right	Only Ipsilateral	Only Contralateral	Bilateral	Total
Level Ia	2	1	3	0	0	3
Level Ib	12	8	13	5	1	19
Level IIa	129	162	142	11	69	222
Level IIb	84	108	111	9	36	156
Level III	110	144	163	15	38	216
Level IV	49	50	67	12	10	89
Level V	25	33	44	6	4	54
Level VI	/	/	/	/	/	19
Level VIIa	48	40	14/13	12/13	18	70

Abbreviation: HPC, hypopharyngeal carcinoma.

without LN metastasis in the ipsilateral level II–IV (66/293, 22.5% vs 4/33, 12.1%, P=0.168). There was no statistically significant difference in patients with LN metastasis in level V and patients without LN metastasis in level V (11/45, 24.4% vs 59/281, 21.0%, P=0.0601).

The higher rate of RPLN metastasis rate appeared to be attributable to the tumor burden. Except 43 patients who were treated by surgery followed by radiotherapy, there are 283 patients available to GTVp data, range from 2.0–376.8 cc, with a median of 43.2 cc. The optimum cutoff value of 47.0 cc was determined based on the receiver operating characteristic curve (ROC). Patients with GTVp larger than 47.0 cc tended to have higher RPN spread compared with patients with GTVp smaller than 47.0 cc (43/283, 15.2% vs 15/283, 5.3%, P<0.001). Due to two patients having lymph excisional biopsy before treatment, there were 281 patients available to GTVnd (RPLN not included) data, ranging from 0.0–421.7 cc, with a median of 17.3 cc. The optimum cut-off value of 47.0 cc was determined based on the receiver operating characteristic curve (ROC). Patients with GTVnd larger than 22.0 cc were associated with a significantly higher RPLN metastases rate compared with patients with smaller than 22.0cc (35/281, 12.5% vs 23/281, 8.2%, P=0.005).

Multiple variables were analyzed by logistic regression, including the following factors: anatomic subsites, level II to IV metastasis, level V metastasis, bilateral cervical metastasis, GTVp, and GTVnd, and other parameters which potentially influence LN spread. The results demonstrated that the primary sites on the posterior pharyngeal wall (P=0.002), bilateral cervical LN metastasis (P=0.032), larger GTVp (P=0.000), and larger GTVnd (P=0.017) statistically significantly contributed to the occurrence of RPLN metastasis. The results are shown in Table 3.

Table 3 Results of Multivariate Analysis: Risk Factors for RPLN Metastasis in HPC

Variable	Hazard Ratio	95% Confidence Interval	*P*-value
Primary site	1.915	1.259–2.914	0.002
Level II to IV metastasis	2.041	0.420–9.925	0.377
Level V metastasis	0.716	0.279–1.842	0.489
Bilateral cervical lymph node metastasis	2.157	1.069–4.354	0.032
Lymph nodes with extracapsular spread	0.974	0.398–2.386	0.954
Lymph nodes with necrosis	0.781	0.388–1.573	0.490
GTVp	3.631	1.780–7.409	0.000
GTVnd	2.358	1.163–4.782	0.017

Abbreviations: RPLN, retropharyngeal lymph node; HPC, hypopharyngeal carcinoma; GTVp, primary gross target volume; GTVnd, lymph node gross target volume.

Discussion

To the best of our knowledge, this retrospective study is the first description base on MR imaging, with the largest cohort concerned about the patterns of LN spread, especially the RPLN metastasis in patients with HPC. Regional LN spread follows an orderly pattern, and LN skipping was unusual. The most commonly involved nodal regions were level II and level III, followed by Ievel IV, RPLN, and level V. RPLN metastasis is significantly associated with the primary tumor being located in the posterior pharyngeal wall, bilateral LN metastasis, larger GTVp, and larger GTVnd.

Due to its relatively uncommon incidence, previous studies have reported the patterns of lymphatic spread with a small sample size of HPC and always mixed with other head and neck squamous cell carcinomas. Only a few studies have focused on HPC. Otherwise, most of these studies were completed in the early years, based on CT imaging or X ray, which are not as accurate as MRI in terms of the diagnosis of LN metastasis. The pathways of LN spread related to target delineation have not been clearly addressed. Basically, it is recommended that RPLN should be included in the target of primary tumor located in the posterior pharyngeal wall. Our study not only confirmed many previous opinions, but also found other interesting results.

For the pattern of LN metastasis, previous studies showed that the rate of positive LN was 63–75% at the time of initial diagnosis, mainly occurring in ipsilateral level II (38–47%) and level III (30–37%), less common in level Ib (7%), and level IV (13%),[4,–7–9] which were basically consistent with our results. However, they demonstrated that contralateral neck metastases (1–6%) were rare, which was much higher in our study (34.6%). This is likely to be based on the high sensitivity of MRI for detecting LN metastasis so it can be more accurately assessed by our results.

RPLN receive lymphatic drainage from the posterior pharyngeal wall and to the deep cervical lymph nodes. Previous studies had indicated the incidence of RPLN of HPC was 20–62%. Su et al[10] found out the incidence of RPLN metastasis in HPC from 218 patients was 17.0%, and the highest rate of 36.4% was found in posterior

pharyngeal wall tumor, mainly based on CT. Our study had a higher rate of RPLN metastasis (21.5%) and primary tumor located in posterior pharyngeal wall (53.1%).

There is another controversy about the RPLN, which is whether there will be RPLN metastasis in patients with N0 classification. Su et al did not find patients with N0 exhibited RPLN metastasis. Other researchers have reported that some patients previously diagnosed with N0 stage disease in HPC do show positive RPLN, with an incidence ranging from 4–15%.[11–14] The rate is low (2/31, 6.45%) in the cohort of our study as well. Therefore, even if the probability of incidence is rare, patients with N0 may still have RPLN metastases. If MRI have shown it, further workup such as PET-CT may be needed.

There were a few studies in the early years showed that the risk factor of RPLN may be related to T stage, N stage, or the numbers of nodes.[12,15] Su et al[10] demonstrated that the primary tumor subsites, bilateral cervical LN metastasis, the number and size of cervical LNs, and level V metastasis were significantly associated with RPLN metastasis. The incidence of RPLN is higher in patients with LN metastasis in other cervical regions.[16–18] In our study, the RPLN metastases was associated with the primary site of the posterior pharyngeal wall, bilateral LN metastasis, larger GTVp, and larger GTVnd, but not with the T and N staging. Studies by Amatsu et al[12] showthat the metastasis rate of RPLN was 18% in T1, 14% in T2, 20% in T3, and 31% in T4. The metastasis rate of RPLN was 15% in N0, 13% in N1, 17% in N2a, 12% in N2b, 67% in N2, and 17% in N3. T4 and N2c showed a strong correlation with RPLN metastasis, respectively. Given the tendency for RPLN metastases in HPC, we would recommend the treatment volume include this high-risk area for patients for primary site located in the posterior pharyngeal wall, large tumor burden, or bilateral cervical LN metastasis.

Although our study was based on MRI with high sensitivity and specificity, this study has inherent limitations related to its retrospective nature. First of all, initial positron emission tomography–computed tomography (PET-CT) scan staging evaluation was not available for double validation. A recent large prospective study showed that PET-CT can detect metastatic or other diseases, significantly improving the staging of head and neck squamous cell carcinoma.[19] However, a meta-analysis concluding 1236 patients demonstrated that the accuracy of PET-CT was only marginally superior to that of CT or MRI. This study questioned the routine value of PET-CT for lymph node staging.[20] Currently, it is worth noticing that the DWI MR technique has made a definite breakthrough in clinical routine by yielding fast-to-acquire and easy-to-process accurate quantitative data that significantly add to pre-therapeutic nodal staging attempts.[21–23] Therefore, whether the addition of PET-CT can improve the diagnosis of LN metastasis in patients with HPC is still warranted. Second, RPLN metastasis was determined only based on MRI findings and lack of histological confirmation because the anatomical nature of the area has made it impossible to obtain a pathological diagnosis by imaging-guided fine-needle aspiration biopsy.

Conclusion

This study provides further understanding of patterns of lymphatic spread of HPC. Regional LN spread follows an orderly pattern, as level II was the most frequently involved and LN skipping was unusual. RPLN metastasis was more likely to occur in patients with primary tumor located in posterior pharyngeal wall, large tumor burden, and bilateral cervical LN metastasis. Therefore, it is reasonable for the CTV to routinely include this high-risk area for patients with these risk factors.

Abbreviations

LN, lymph node; RPLN, retropharyngeal lymph node; HPC, hypopharyngeal squamous carcinoma; CTV, clinical target volume; MRI, magnetic resonance imaging; GTVp, primary gross target volume; GTVnd, LN gross target volume; DWI, diffusion-weighted imaging; CT, computed tomography; PET-CT, positron emission tomography–computed tomography; MID, minimal axial diameter; ROC, receiver operating characteristic curve.

Data Sharing Statement

Unable to upload raw patient data due to patient-related private information.

Ethics Approval and Consent to Participate

This retrospective research has been reviewed, and approved to publish by the ethics committee of National Cancer Center/National Cancer Clinical Medical Research Center/Chinese Academy of Medical Sciences, Peking Union Medical College, Cancer Hospital, Beijing, China. The consents of all the patients was waived due to the retrospective nature of the review, and all the data was

anonymized to maintain confidentiality and in compliance with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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