Prognostic Factor of Severe Complications in Patients with Hypopharyngeal Cancer with Primary Concurrent Chemoradiotherapy

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Abstract. *Background/Aim: Organ-preservation treatment for hypopharyngeal cancer has recently become a popular treatment option. However, the severe complications and poor quality of life after non-surgical treatment should be avoided. We accessed the laryngeal or pharyngeal dysfunction-related complications after concurrent chemoradiotherapy (CCRT) as the primary treatment for hypopharyngeal cancer. Patients and Methods: Data concerning all patients treated for hypopharyngeal cancer with primary non-surgical treatment at the China Medical University Hospital from 2002 to 2012 were retrospectively reviewed. Results: A total of 161 patients were included with a median age of 56.6 years. The disease control rates (disease-free >12 months) and severe complication rates were correlated to the tumor (T) stage and nodal (N) stage. In the successful treatment group, the complication rate was related to the N stage. The overall pharyngeal dysfunction, laryngeal dysfunction and aspiration rates were 36%, 27% and 25%, respectively. For patients with T4a disease, hyoid bone invasion significantly increased the severe complication rate (p=0.0212). Conclusion: The treatment outcome was correlated to the T and N stage. A higher rate of laryngo-pharyngeal dysfunction occurred when treating hyoid bone invasion in T4a patients with primary non-surgical treatment. In advanced stage, but still resectable hypopharyngeal tumors, the poorer quality of life due to non-function larynx was noted after treating with CCRT.*

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Hypopharyngeal cancer has the poorest prognosis of all head and neck cancers. Almost 50% of patients with hypopharyngeal cancer experience recurrence, mostly within 12 months after completion of treatment (1). Laryngopharyngectomy with reconstruction of the pharynx is the preferred initial treatment modality for hypopharyngeal cancer. However, the morbidities associated with surgical treatment, such as loss of natural speech function and impairment of swallowing ability, have a negative impact on the quality of life, with cure rates being relatively low (2-5). Compared to radical surgery, chemoradiotherapy (organ preservation strategy) for the squamous cell carcinoma of the hypopharynx has been reported to result in similar local tumor control having a similar survival rate compared to non-organ preserving surgical therapy (6-8). The non-surgical treatment, such as radiotherapy or chemoradiotherapy, had been a main stream for treating the early stage of hypopharyngeal cancer. Otherwise, for patients at an advanced stage of hypopharyngeal cancer, recent studies have shown that organ preservation therapy has similar disease control to radical surgery but with high rates of treatment-related toxicity leading to the failure of organ preservation (9-11). Hence, disease status should be considered before organ preservation therapy to prevent further functional failure. Functional preservation with good disease control should be the goal of non-surgical treatment. This study evaluated early (during the first 6 months after therapy) and severe laryngeal/ pharyngeal dysfunctions after primary concurrent chemoradiotherapy (CCRT) and attempted to determine the presenting clinical factors that correlated with non-functional larynx and pharynx. Since it was difficult to accurately capture adverse outcomes in non-surgical treatment (9, 12) and tube-dependent naso-gastric (NG)/tracheostomy that massively influenced the quality of life of patients, we collected the durations of the placement the NG tube and tube-persistent tracheostomy after non-surgical therapy for the patients as

Table I. *Characteristics of all patients.*

Patients' characteristics	Number of patients (%)
Gender	161
Male	156 (96.9)
Female	5 (3.1)
Mean age	56.6
Male	56.2
Female	69.0
RT dose, Gy	
≤70.2	112 (69.6%)
>70.2	49 (30.4%)
Tumor classification	
T1	18 (11.2%)
T2	34 (21.1%)
T3	42 (26.1%)
T4a	46 (28.6%)
T4b	21 (13%)
Lymph node status	
N0	46 (26.6%)
N1	17 (11%)
N2a	5 (3%)
N2b	53 (32.9%)
N2c	28 (17.4%)
N3	12 (7.5%)

Table II. *Univariate analyses of the correlations of clinical tumor stage and the occurrence of severe complications.*

	Patient number (%)		Severe complications			*p*-Value
	No	Yes	Dysphagia	Tracheo-stomy	Severe infection	
cT						0.0003*
1	12 (19.1)	6 (6.1)	3	2	5	
2	19 (30.2)	15 (15.3)	10	4	6	
3	19 (30.2)	23 (23.5)	12	8	6	
4a	9 (14.3)	37 (37.8)	22	20	14	
4b	4 (6.4)	17 (17.4)	11	9	9	
cN						0.0001*
0	30 (47.6)	16 (16.4)	10	5	4	
1	9 (14.3)	8 (8.16)	6	3	3	
2a	3 (4.8)	2 (2.0)	1	1	1	
2b	14 (22.2)	38 (38.8)	23	16	17	
2c	6 (9.5)	22 (22.5)	9	12	9	
3	1 (1.6)	11 (11.2)	9	6	6	

Yes: severe complication occurred in six months after primary non-surgical treatment. No: no severe complication occurred in six months after primary non-surgical treatment. *By the Chi-square test.

Table III. *The classification of severe complication rate.*

Complication	Number of patients (%)
Dysphagia	58 (36)
Threatened airway	43 (27)
Severe infection	40 (25)
Massive tumor bleeding	15 (9)
Mortality	15 (9)
Osteoradionecrosis	4 (3)

an objective evaluation. Furthermore, we discuss the clinical outcomes and complication rates based on tumor stage, invasion and clinical presentation with the aim of providing suggestions for the best treatment modality for patients with hypopharyngeal cancer in order to enhance the cure rate while minimizing adverse effects and toxicity.

Patients and Methods

The medical records of patients who were diagnosed with hypopharyngeal cancer from January 2002 to December 2012 were reviewed retrospectively. The study was approved by the Institutional Review Board of China Medical University Hospital. In total, 529 patients with hypopharyngeal squamous cell carcinoma were identified at the China Medical University Hospital during this period. They all underwent tumor biopsy, tumor mapping and systemic survey at our hospital. Pretreatment evaluations consisted of a complete history and physical examination including flexible fibro-optic endoscopy and direct laryngoscopy tumor mapping. All patients had a complete blood count and biochemical profile, chest X-ray, head-and-neck computed tomography and, in some cases, magnetic resonance imaging. Staging was performed according to the TNM classification system of the American Joint Committee on Cancer (AJCC) at the time of diagnosis. All patients were treated by our multidisciplinary team, which included head-and-neck surgeons, medical oncologists and radiation oncologists. The treatment strategy was based on the preference of the oncologic team and/or patient. In our study, the enrollment criteria included patients who had received primary CCRT and had been followed up for a minimum of 1 year or until death. Patients who had undergone primary surgical treatment, those initially with distant metastasis, those with more than one kind of cancer, incomplete treatment course, had received induction chemotherapy before definite CCRT regimen and those lost to follow-up at our department after one-year treatment were excluded from this study. Furthermore, we only selected patients who had received cisplatin-based CCRT for primary treatment. According to the aforementioned inclusion-exclusion criteria, 161 patients were included in this study. Variables, including location of primary site tumor extent (T classification) and primary nodal classification (N classification) were analyzed. For T4 patients, the tumor was evaluated via direct laryngoscopy, tumor mapping and head and neck computed tomography. The main tumor of each hypopharyngeal tumor was confirmed as arising from the hypopharyngeal site by experienced radiologists and otolaryngologists. The disease control rate and severe complication rate were analyzed with the Chi-square test. Univariate analyses were performed to identify variables between disease control rate and occurrence of severe complications. In T4a patients (primary tumor invaded to thyroid/ cricoid cartilage, thyroid, neck soft tissue and/or hyoid bone), the categorical variables were analyzed with the Fisher's exact test. Variables with

Table IV. *Severe complications in patients who had successful treatment (disease-free >12 months).*

	Patient number (%)		Severe complications			*p*-Value
	No	Yes	Dysphagia	Tracheo-stomy	Severe infection	
cT						0.0870
1	7 (18.9)	1 (4.2)	1	1	0	
2	12 (32.4)	5 (20.8)	5	2	2	
3	11 (29.7)	6 (25)	4	4	2	
4a	5 (13.5)	10 (41.7)	9	7	5	
4b	2 (5.4)	2 (8.3)	2	1	1	
cN						0.0013*
0	21 (56.8)	6 (25)	5	3	2	
1	8 (21.6)	1 (4.2)	1	1	0	
2b	7 (18.9)	12 (50)	11	7	4	
2c	1 (2.7)	5 (20.8)	5	3	3	

Yes: severe complication occurred in six months after primary non-surgical treatment. No: no severe complication occurred in six months after primary non-surgical treatment. *By the Chi-square test.

$p<0.05$ were considered to be statistically significant. Statistical analyses were carried out using the Statistical Package of Social Sciences software, version 15.0 (SPSS, Inc., Chicago, IL, USA).

Treatment. All patients visited our outpatient department presenting a lump throat, mild short of breath or voice change. A minimal aspiration was found in some patients and there was no severe subjective pretreatment dysphagia recorded. Before the treatment, any patient with airway or gastrointestinal tract obstruction underwent the prophylatic tracheostomy or gastrostomy. Of the patients treated with an organ-preserving approach, cisplatin was typically administered intravenously at a dose of 100 mg/m^2 during week 1, 4 and 7. All of them received 1.8-2.0 Gy daily up to a total dose of 70 to 75.6 Gy. All patients underwent intensity modulation radiation therapy (IMRT) during their treatment. We only included patients who finished full dose chemoradiotherapy and had thorough follow-up and detailed medical records for at least one year.

Follow-up. At the start of treatment, all patients were followed up once a month over the first year. A physical examination and laryngoscopy was performed during each follow-up examination and a computed tomography scan of the neck was performed every 4 to 6 months over the first year. Successful treatment was defined as being disease-free for more than 12 months. We defined severe complications to include dysphagia, severe infections, threatening airway, osteoradionecrosis and mortality. Each patient was scored using the Swallowing Performance Scale as graded from 1 to 7 for dysphagia. The scores were following the categories: grade 1, normal; grade 2, within functional limits, abnormal oral or pharyngeal stage but able to eat a regular diet without modifications or swallowing precautions; grade 3, mild impairment, mild dysfunction in oral or pharyngeal stage requiring a modified diet without the need for therapeutic swallowing precautions; grade 4, mild-to-moderate impairment with the need for therapeutic precautions, mild dysfunction in oral or pharyngeal stage requiring a modified diet and therapeutic precautions to minimize aspiration risk; grade 5, moderate impairment, moderate dysfunction in oral or pharyngeal stage, aspiration noted on examination requiring a modified diet and swallowing precautions to minimize aspiration risk; grade 6, moderate-severe dysfunction, moderate dysfunction of oral or pharyngeal stage, aspiration noted on examination requiring a modified diet and swallowing precautions to minimize aspiration risk, needing supplemental enteral feeding support; and grade 7, severe impairment, severe dysfunction with significant aspiration or inadequate oropharyngeal transit to esophagus, nothing by mouth, requiring primary enteral feeding support. Dysphagia indicated that patients had a high grading dysphagia score as 5-7 and needed prolonged nasogastric or gastrostomy-dependent feeding and could not be weaned off after receiving the organ preserving treatment for 6 months. After completing the CCRT course, the tracheostomy tube weaning program and airway rehabilitation were encouraged at our outpatient department. However, if the patients needed to have prolonged tracheostomy tube placement to prevent aspiration or airway obstruction after a 6-month treatment, we defined this group of patients as patients with threatened airway. Severe infection was defined if the patients had significant leukocytosis, elevated C-reactive protein, obvious toxic signs or unstable vital signs requiring hospitalization during the 6 month period after completing treatment. Massive tumor bleeding was defined as the massive bleeding from the tumor site presenting unstable hemodynamic status and need for hospitalization during the first 6 months after completing treatment. The complication of osteoradionecrosis was defined by presenting bony necrotic lesions after radiotherapy and no biopsy-proven recurrence.

Results

Patient population. Out of the 161 patients (Table I), 156 were men and 5 were women with a median age of 56.6 years (range= 37-80 years). All patients were staged according to the AJCC staging system. The T and N distributions were as follows: T1: 18 (11.2%), T2: 34 (21.1%), T3: 42 (26.1%), T4a: 46 (28.6%) and T4b: 21 (13%); and N0: 46 (26.6%), N1: 17 (11%), N2a: 5 (3%), N2b: 53 (32.9%), N2c: 28 (17.4%), N3: 12 (7.5%). All patients were followed-up for at least one year or until death. The median follow-up time was 24.4 months.

Control population. We defined successful disease control as being disease-free for at least 12 months. Disease-free, in our study, was defined as the tumor in complete remission and no evidence of residual tumor, metastasis or tumor recurrence in clinical and image findings in regular follow-ups. There was a significant correlation between T (p=0.0081) and N (p=0.0025) stage and the treatment success rate when comparing the successful group (disease-free >12 months) and the no response to treatment group. There was also a significant correlation between the complication rate and T and N stage (Table II).

Table V. *Univariate analyses of the correlations of T4a tumor invasion with regards to disease control and complication rate.*

Tumor invasion	Patient numbers (%)		*p*-Value	Severe Complication		*p*-Value
	No	Yes		No	Yes	
T/C cartilage			0.6257			0.5664
Yes	14 (93.3)	18 (85.7)		9 (100)	32 (86.5)	
No	1 (6.7)	3 (14.3)		0 (0)	5 (13.5)	
Hyoid bone			0.7210			0.0212*
Yes	4 (26.7)	8 (38.1)		0 (0)	15 (40.5)	
No	11 (73.3)	13 (61.9)		9 (100)	22 (59.5)	
Thyroid gland			0.7050			0.1709
Yes	3 (20.0)	6 (28.6)		0 (0)	9 (24.3)	
No	12 (80.0)	15 (71.4)		9 (100)	28 (75.7)	
Neck soft tissue			0.5160			0.1506
Yes	9 (60.0)	10 (47.6)		2 (22.2)	19 (51.4)	
No	6 (40.0)	11 (52.4)		7 (77.8)	18 (48.7)	

For disease control, "Yes" means patients had successful disease-free at least 12 months and "No" means less than 12 months. For severe complication, "Yes" means severe complication occurred in six months after primary non-surgical treatment and "No" means no severe complication occurred in six months after primary non-surgical treatment. *By the Fisher's Exact Test.

Patient complications. Six months after treatment, still 58 patients (36%) were unable to be fed orally and required nasogastric feeding or gastrostomy. Forty-three patients (27%) could not be weaned from tracheostomy and 40 patients (25%) had suffered at least one severe infection requiring hospitalization. Thirty-two patients had episodes of aspiration pneumonia, 4 patients suffered neck abscess formation and 4 patients were hospitalized due to severe systemic sepsis. Fifteen patients had an episode of massive tumor bleeding and twelve of them died due to hypovolemia. Four patients presented with osteoradionecrosis over the radiation site. Overall, 15 patients died during 6 months after treatment. The most common complication was dysphagia (36%), followed by a threatened airway (27%) (Table III). In the successful-treatment group, the complication rate was significantly associated with the clinical N stage (p=0.0013); however, no significant association was noted with the tumor stage (Table IV). In the T4a patients, there was no significant difference in disease control between the types of tumor invasion (thyroid cartilage, cricoid cartilage, thyroid gland or neck soft tissue invasion); however, a higher complication rate was noted in patients who had hyoid bone invasion (Table V).

Discussion

The treatment strategy for a patient with hypopharyngeal cancer is complex and takes into consideration tumor stage, condition of the patient and individual preference. For the early stage of hypopharyngeal cancer, non-surgical treatment is a mainstream treatment strategy for organ preservation. For the resectable, advanced-stage hypopharyngeal cancer, non-surgical treatment has also been reported to have similar disease control and overall survival rates compared with surgery as the initial therapy; however, it has been reported to carry a high risk of non-functional larynx and hypopharynx (6). One study showed that significant acute and long-term toxic effects occur and organ preservation appears not necessarily equivalent to preservation of function and to have better quality of life (11). Therefore, we compared all the hypopharyngeal cancer patients at our hospital who received complete CCRT in order to investigate the risk factors for organ-preservation failure. For the objective evaluation, we recorded the duration of placement the feeding tube (persisted nasogastric tube or feeding gastrostomy) and persisted tracheostomy tube as prolonged tube placement significantly affects the quality of life. These objective data can exclude the different subjective evaluation on adverse symptoms, such as mucositis, dysphagia and pain. In our study, the 1-year disease control rate and severe complication rate were correlated to tumor stage and lymph node status, and were found comparable in a previous study (13). Interestingly, if we only analyzed patients who had successful disease control for at least one year, the severe complication rate would be associated with the N stage but not the tumor stage. Caudell *et al*. (14) have also demonstrated that N2 or N3 patients had poor function preservation and that T4 patients had a similar functional preservation compared with T2 and T3 patients.

With regards to treatment intended to preserve organ function, "function preservation" and "organ preservation" should be clearly defined. In hypopharyngeal cancer,

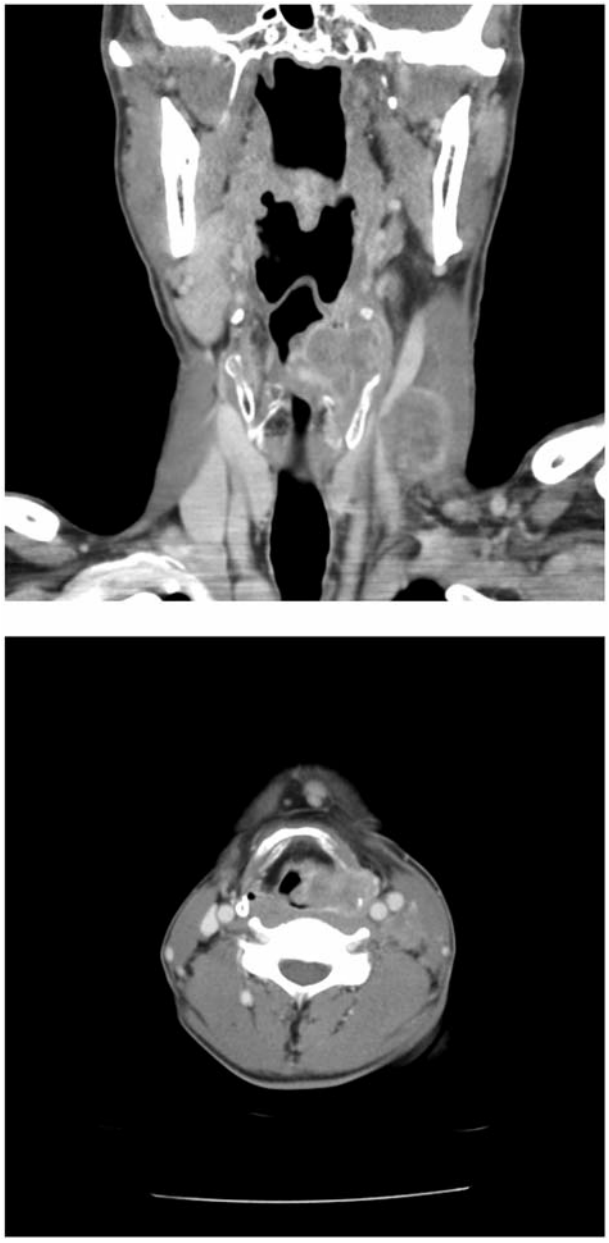

Figure 1. *Hypopharngeal cancer directly invading the hyoid bone.*

function includes both voice and swallowing and, in a broader sense, quality of life. This may even be better preserved after removal of the organ, permitting aspiration-free deglutition and a prosthetic voice rather than leaving intact a functionless larynx. Hence, we attempted to identify the patients who were at high risk of chemoradiotherapy (CRT) toxicity leading to a non-functional larynx or hypopharynx and who would have been better advised to receive surgical therapy, especially in patients who had an invasive advanced tumor stage that was still resectable. In our study, the most common complication was dysphagia, followed by a threatened airway. Dysphagia has been reported to be induced by the toxicity of CCRT (15, 16). Stijn *et al*. (11) reported that 78% of patients with hypopharyngeal cancer required tube feeding during and after treatment and that the acute toxicity resolved within 3 months, even though it was the most common long-term side effect. Thus, since acute toxicity could not be resolved in 3 months, we decided to use a 6-month interval after treatment for our evaluations.

According to the AJCC classification, T4a stage is defined as a tumor invading the adjacent structure, including the hyoid bone, thyroid/cricoid cartilage, thyroid gland and neck soft tissue. Compared with T4b tumors, T4a tumors are commonly considered to be invasive but are clinically resectable. However, the treatment outcomes and related quality of life for these patients are still controversial. In addition, to the best of our knowledge, only a few studies have evaluated the benefits of non-surgical treatment in T4a patients only. In the current study, there was no difference in the disease control rate among T4a patients who were treated either non-surgically or surgically. Hence, the quality of life and treatment-related complications should be considered. For the subsites of tumor invasion in T4a patients, Wagner *et al*. (17) reported that patients with thyroid or cricoid cartilage invasion were not associated with a reduced overall survival rate. Two separate studies have shown no difference in local control or overall survival in patients with hyoid bone and/or cartilage invasion (18, 19). However, in our study, there is no difference in disease-free rate compared to the subsite of tumor invasion. However, if there was hyoid bone invasion (Figure 1), the complication rate was significantly higher than for other sites. Wagner *et al*. (19) reported that thyroid or cricoid cartilage invasion did not affect laryngeal preservation; however, they did not report on the hyoid bone. The hyoid bone is suspended by musculature connecting the mandible, styloid process, thyroid cartilage, manubrium and scapulae and, in turn, contributes to support the base of tongue. It plays an important role in swallowing and airway protection, while adequate hyoid bone displacement is critical to swallowing safety (20). Many studies have reported that after radiation therapy, patients experience changes in swallowing and laryngeal function, including reduced tongue-base contact with the posterior pharyngeal wall, decreased laryngeal elevation, decreased anterior hyoid movement (21, 22) and decreased vestibular size and true vocal fold closure during swallowing (23). Displacement of the hyoid bone causes the epiglottis to tilt and the laryngeal vestibule to become sealed. It also helps to protect the larynx from the bolus and pulls the pharyngeal constrictor muscle to an open position (24). Hence, inadequate displacement of the hyoid bone may cause poor airway protection resulting in prolonged tracheostomy and tube feeding. Radiation can reduce hyoid bone movement (25) and

damage the pharyngeal constrictors, the glottic and the supraglottic larynx, causing dysphagia and aspiration (21, 26). The radiation dose to the pharyngeal constrictor and swallowing dysfunction has been reported to be significantly associated with the aspiration rate (27). If the cancer has invaded the hyoid bone, the radiation dose should be higher on the hyoid bone and constrictor muscle. The swallowing and larynx functions may have been destroyed by the tumor or by the toxicity of the radiotherapy. In our cases of hypopharyngeal tumor with hyoid cartilage invasion, the complication rate was higher when patients received organ-preserving therapies. Although we did not compare the results with the surgical group, surgical intervention -as the primary treatment for the patients with hyoid bone invasion- may be considered.

However, there are still some issues that need to be further identified. If the hypopharyngeal tumor has invaded the hyoid bone, the tumor volume would be usually large and pretreatment tumor-related dysfunction could be present. Therefore, larger tumor volume or hypopharyngeal tumor with hyoid destruction might correlate to the dysphagia, prolonged airway problems and threatening infection as aspiration pneumonia or deep neck infection after non-surgical organ preserving therapy (28). There are also study limitations due to the limited sample size as we could only find hyoid bone invasion from hypopharynx correlated to severe complications in univariate analysis. Larger sample sizes are required for multivariate analyses. However, the findings of our study indicated that hyoid invasion in patients with hypopharyngeal cancer results in significantly higher complication rates when considering non-surgical organ preservation as initial therapy.

Conclusion

The majority of hypopharyngeal cancer patients, in this study, presented at an advanced stage. If the tumor presented with hyoid bone invasion, the complication rate was higher when the patients underwent non-surgical treatment. We suggest that surgical intervention should be the first treatment strategy in patients with operable cases of a hypopharyngeal tumor with invasion of the hyoid bone.

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