Induction Chemotherapy for the Individualized Treatment of Hypopharyngeal Cancer with Oesophageal Invasion: A Retrospective Cohort Study

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Abstract

Background: This study aimed to evaluate the potential for induction chemotherapy to be an indicator for the management of advanced hypopharyngeal carcinoma with cervical oesophageal invasion.

Methods: Sixty-eight patients (admitted to our department between February 2003 and November 2016) with stage IVB hypopharyngeal cancer with cervical oesophageal invasion were retrospectively analysed. Patients were divided into two groups depending on the treatment they selected following an explanation they received on the different treatments. Group A patients received induction chemotherapy and had (1) complete or partial remission following chemotherapy combined with radiotherapy or concurrent chemoradiotherapy or (2) stable disease following chemotherapy combined with surgery. Group B patients underwent surgery and received adjuvant radiotherapy or concurrent chemoradiotherapy following surgery. Survival analyses were performed using the Kaplan–Meier method, differences between the two groups were tested using the log-rank test, and the laryngeal and oesophageal retention rates were compared using the cross-tabulation test.

Results: The 3- and 5-year overall survival rates of patients in Group A were 22.86% and 11.43%, respectively; in Group B, the rates were 24.25% and 6.06%, respectively ($P > 0.05$ for all). The laryngeal retention rates in Group A and B patients were 40% and 0%, respectively, whereas the oesophageal retention rates in Group A and B patients were 74.3% and 27.3%, respectively ($P < 0.01$ for all). There was no statistically significant difference in the incidence of postoperative complications between the two groups (Group A: 8.6%, Group B: 12.1%, $P > 0.05$).

Conclusions: For patients with advanced hypopharyngeal cancer with cervical oesophageal invasion, induction chemotherapy could be the appropriate first choice for individualized treatment to ensure laryngeal and oesophageal cancer preservation.

Background

Hypopharyngeal cancer is one of the most malignant head and neck tumours and has a poor prognosis. Although the survival of patients has improved over the past three decades, the 5-year overall survival (OS) rate is only approximately 40% (1–2). The National Comprehensive Cancer Network guidelines recommend surgical and non-surgical approaches as effective treatment strategies for advanced hypopharyngeal cancer. Recommended treatment methods include radiotherapy, concurrent chemoradiotherapy, or surgical treatment based on the curative effect after induction chemotherapy (3).

In the management of advanced hypopharyngeal cancer with cervical oesophageal invasion, the function of the pharynx, larynx, trachea, and oesophagus should be considered. Many studies have investigated the treatment of concomitant hypopharyngeal cancer and oesophageal cancer (4–5). However, there is little experience in the treatment of advanced hypopharyngeal cancer with cervical oesophageal invasion. Further, few studies have reported cases screened through induction chemotherapy that received individualized treatment. In this study, we retrospectively analysed the clinical data of patients with

advanced hypopharyngeal carcinoma with cervical oesophagus invasion. The therapeutic effects of two treatment modes were compared to provide a reference for selecting the appropriate treatment strategy for patients with advanced hypopharyngeal cancer with cervical oesophageal invasion.

Methods

Patients

A total of 68 patients with hypopharyngeal cancer with cervical oesophageal invasion admitted to our department between February 2003 and November 2016 were enrolled. Complete follow-up data were retrospectively reviewed after approval from the Institutional Review Board. This study was performed in accordance with the principles of the Declaration of Helsinki. The age of the patients ranged from 36 to 77 years, and the median age was 54.5 years; of the 68 patients, 63 were men and five were women. Among all patients, 14 had high pathological differentiation, 35 had moderate differentiation, and 19 had poor differentiation. The primary lesions were located in the piriform sinus in 27 patients, in the posterior wall of the pharynx in 23 patients, and in the postcricoid region in 18 patients. Gastroscopy and neck and chest enhanced computed tomography (CT; oesophageal barium meal) were used to identify invasion of the cervical oesophagus before treatment. According to the American Joint Committee on Cancer 7th edition (2010), clinical physical examination, and imaging before treatment, the clinical stage was identified as stage IVB for all patients.

Groups management

Sixty-eight patients were divided into two groups depending on the treatment mode they selected. The differences between the two treatment modes were explained to every patient. Thirty-five patients chose to receive induction chemotherapy (Group A). All Group A patients had a complete/partial response (CR/PR) after chemotherapy with radiotherapy/concurrent chemoradiotherapy or stable disease (SD) after chemotherapy with surgical treatment. Thirty-three patients chose to undergo surgery with postoperative adjuvant radiotherapy or concurrent chemoradiotherapy (Group B). There were no differences in baseline clinical characteristics between the two groups (Table 1).

Table 1
Patient characteristics

Variable	Classification	Total (N = 68)	Group A (N = 35)	Group B (N = 33)	χ^2-value	*P*-value
Sex	Male	63	33	30	0.2843	0.5939
	Female	5	2	3		
Age (years)	≤ 60	50	26	24	0.1675	0.8970
	> 60	18	9	9		
Subsite	Pyriform sinus	27	14	13	0.0217	0.9892
	Postcricoid region	23	12	11		
	Posterior wall	18	9	9		
Differentiation	High	14	8	6	0.3084	0.8571
	Moderate	35	18	17		
	Poor	19	9	10		
N classification	N0	19	8	11	0.4786	0.4890
	N1-3	49	27	22		
Drinking	Yes	42	22	20	0.0035	0.9532
	No	26	13	13		
Smoking	Yes	47	26	21	0.4725	0.4918
	No	21	9	12		

Treatment regimens

The scheme of induction chemotherapy in Group A was TPF (5–6) (paclitaxel + platinum + fluorouracil) for two cycles; each cycle was 21 days. Two weeks after the completion of chemotherapy, the outcomes were evaluated using neck-enhanced CT and stroboscopic laryngoscopy and biopsy in some of the cases. The corresponding responses and subsequent treatment plans were as follows: a complete remission of the primary tumour was considered CR, and a shrinkage of the primary tumour by 70% or more was considered PR. For such patients, we suggested concurrent chemoradiotherapy or radiotherapy after induction chemotherapy. If the primary tumours shrank by less than 70% or no change occurred, the condition was considered as SD and was treated surgically after the chemotherapy. A complete response was observed in four patients and PR in nine patients; all 13 patients were treated with radiotherapy or concurrent chemoradiotherapy after induction chemotherapy. Surgery was performed after chemotherapy in 22 patients who were considered to have SD. Among these, one patient underwent a trans-oral laser

resection of a hypopharyngeal tumour and retained the larynx, hypopharynx, and oesophagus. Twelve patients underwent total laryngectomy and partial hypopharynx resection, which preserved the oesophagus. Nine patients underwent total laryngectomy and oesophageal resection.

Group B had a total of 33 patients; of these patients, 19 patients underwent complete laryngeal and oesophageal resection and gastric pharyngostomy, six underwent partial pharyngeal and oesophageal resection and residual larynx stomach anastomosis, four underwent complete laryngeal resection combined with partial pharyngeal and oesophageal resection and pectoralis major musculocutaneous flap repair, and four underwent total laryngeal resection combined with oesophageal resection and repair with a free jejunum or ileum flap. All patients underwent neck dissection at the same time and postoperative radiotherapy or concurrent chemoradiotherapy within six weeks. The radiation dose was 65–70 Gy, and the chemotherapy scheme was platinum and paclitaxel. Ten patients underwent concurrent chemoradiotherapy, and 16 patients received radiotherapy alone.

Follow-up

Data for 68 patients were obtained by outpatient review and telephone follow-up. The last follow-up was conducted in November 2019. Three patients were alive at the last data collection date, and the rest of the patients had died.

Statistical analyses

OS was defined as the time from the date of surgery or treatment initiation to the date of death or last follow-up. The calculation of OS and survival analysis was performed using the Kaplan–Meier method, and the differences between groups were tested using the log-rank method. The laryngeal retention rate and oesophageal retention rate between Groups A and B were compared using the cross-tabulation method; the categorical variables were compared using the Chi-square test.

Results

Univariate analysis of prognosis

The median survival time in all 68 patients was 26 months, as calculated using the Kaplan–Meier method; the 3- and 5-year OS rates were 20.59% and 5.88%, respectively. Patient age, sex, anatomic sub-region, the degree of differentiation, cervical lymph node metastasis, smoking status, and alcohol consumption were included in the univariate analysis; there was no statistical difference in survival rates between the groups as examined using the log-rank test (Table 2).

Table 2
Results of the univariate analysis of patient prognosis

Variable	Classification	No.	3-year OS (%)	5-year OS (%)	Median	HR	95% CI	*P*-value
Sex	Male	63	23.81	7.47	24	1.142	0.4718 to 2.765	0.7682
	Female	5	20.00	0	32			
Age (years)	≤ 60	50	32.00	0	23.5	0.5572	0.2906 to 1.068	0.0782
	> 60	18	9.14	0	24.5			
Subsite	Pyriform sinus (Ps)	27	22.22	7.41	24	Ps:Pr: 1.1650 Ps:Pw: 0.8446 Pr:Pw: 0.7327	Ps:Pr: 0.6202 to 2.188 Ps:Pw: 0.4687 to 1.522 Pr:Pw: 0.3833 to 1.401	0.6417
	Postcricoid region (Pr)	18	22.22	5.56	26			
	Posterior wall (Pw)	23	26.09	8.70	19			
Differentiation	High (H)	14	21.43	7.14	27	H:M: 0.8906 H:P: 0.7915 M:P: 0.8499	H:M: 0.4698 to 1.688 H:P: 0.3869 to 1.619 M:P: 0.4690 to 1.540	0.7899
	Moderate (M)	35	28.57	11.43	23			
	Poor (P)	19	15.79	5.26	23			
N Classification	N0	19	26.32	10.53	24	1.004	0.5760 to 1.749	0.9899
	N1-3	49	22.45	8.16	24			
Drinking	Yes	42	23.81	7.14	23	1.151	0.6950 to 1.905	0.5855
	No	26	23.08	11.54	26			
Smoking	Yes	47	21.28	6.38	24	1.181	0.6991 to 1.994	0.0740
	No	21	28.57	14.29	27			

OS: overall survival; HR: hazard ratio; CI: confidence interval; Ps: pyriform sinus; Pr: postcricoid region; Pw: posterior wall; H: high; M: moderate; P: poor

Comparison of overall survival

Intra-group comparison

We divided the 35 patients in Group A into Groups A1 and A2 depending on their response to the induction chemotherapy. Those whose response was CR or PR were assigned to Group A1 (13 patients); whereas, those who had SD were assigned to Group A2 (22 patients). The 3-year OS rates in Groups A1 and A2 were 23.08% and 22.73%, respectively. The 5-year OS rates in Groups A1 and A2 were 7.69% and 13.64%, respectively; the difference in OS between the groups was not statistically significant (Fig. 1a).

Among the 33 patients in Group B, 21 who underwent surgery and postoperative radiotherapy were placed into Group B1, and 12 who underwent surgery and postoperative chemoradiotherapy were placed into Group B2. The 3-year OS rates in Groups B1 and B2 were 28.57% and 16.67%, respectively. The corresponding 5-year OS rates were 4.76% and 8.33%, respectively; the difference in OS between the groups was not statistically significant (Fig. 1b).

Comparison between groups

The 3- and 5-year OS rates in patients in Group A were 22.86% and 11.43%, respectively, and the median survival was 24 months. The 3- and 5-year OS rates in patients in Group B were 24.25% and 6.06%, respectively, and the median survival time was 29 months. The difference in survival rates between the groups was not statistically significant (Fig. 1c).

Comparison of laryngeal and oesophageal retention rates

The laryngeal retention rate in Group A was 40%, whereas that in Group B was 0%. The laryngeal retention rate in Group A was higher than that in Group B, and the difference was statistically significant (P = 0.0001). The oesophageal retention rate in Group A was 74.3%, and that in Group B was 27.3%. The oesophageal retention rate in Group A was higher than that in Group B, and the difference was statistically significant (P = 0.0002) (Fig. 2).

Comparison of postoperative complication rates

The most common postoperative complications of advanced hypopharyngeal cancer were anastomotic leakage and stricture. In Group A, anastomotic leakage occurred in two patients, and anastomotic stricture occurred in one patient, yielding a complication rate of 8.6%. Anastomotic leakage occurred in three patients, and anastomotic stricture occurred in one patient in Group B, yielding a complication rate of 12.1%. There was no statistical difference in the incidence of postoperative complications between the two groups (P = 0.9345) (Fig. 2).

Discussion

In this study, we evaluated the potential for induction chemotherapy to be used in the management of advanced hypopharyngeal carcinoma with cervical oesophageal invasion. Seventy percent of hypopharyngeal cancers are advanced at the time of diagnosis (6); advanced hypopharyngeal cancer can spread submucosally and tends to invade the cervical oesophagus (7). From February 2003 to November 2016, we treated approximately 800 patients diagnosed with hypopharyngeal cancer, and 75 patients had

lesions involving the cervical oesophagus, accounting for approximately 9.38% of all hypopharyngeal cancers. In this study, the 3- and 5-year OS rates were 20.59% and 5.88% in all patients, respectively, which was similar to that shown in the previously reported study on concomitant hypopharyngeal and oesophageal cancers (4).

Surgery is still the main treatment strategy for advanced hypopharyngeal cancer with cervical oesophageal invasion. Surgical treatment mainly includes three aspects: primary tumour excision; cervical lymph node dissection; and pharynx and digestive tract reconstruction, among which the reconstruction of the pharynx and digestive tract is the biggest challenge. In recent years, there have been many reports on the postoperative repair and reconstruction of advanced hypopharyngeal cancer (8–9). In this study, the reconstruction of the pharynx and digestive tract was performed mainly by one of the three different methods described in previous studies (8, 10, 11). For unilateral piriform sinus carcinoma, the lesion invaded the oesophageal inlet and did not reach the circumference of the oesophageal canal cavity but infiltrated downward for up to 2–3 cm, and it is feasible to repair the residual hypopharyngeal mucosa and the upper oesophageal mucosa with a pectoralis major myocutaneous flap. For pyriform sinus carcinoma or posterior pharyngeal wall carcinoma with a large range that has crossed the midline and has a 2–3 cm downward infiltration, the digestive tract can be repaired by residual laryngeal anastomosis instead of hypopharyngeal and oesophageal anastomosis. For annular tumours that infiltrated more than 2–3 cm from the inlet of the oesophagus, total esophagectomy can be performed, and the oesophagus can be replaced by a gastric lift or free jejunum or colon.

Induction chemotherapy, also known as neoadjuvant chemotherapy, refers to the chemotherapy administered before surgery or radiotherapy, which can reduce the tumour load in a short period of time. Induction chemotherapy has been widely used in clinical practice in recent years. Commonly used induction chemotherapy regimens in clinical practice include the TPF regimen and the PF (platinum + fluorouracil) regimen; TPF is significantly more effective than PF (12). Induction chemotherapy can increase the retention of organ function by shrinking the tumour (13). It also acts as a screening procedure to identify patients sensitive to treatment by either radiotherapy or concurrent chemoradiotherapy; for insensitive patients, surgical treatment is preferable. Induction chemotherapy is responsible for creating a more individualized, standardized, and precise treatment for advanced hypopharyngeal cancer (14).

According to our results, before 2010, patients were mainly treated surgically, and the treatment methods were relatively simple. With the increase in the volume of related studies and the advancements in treatment methods, treatment options after 2010 were no longer dominated by surgery, and adjuvant management methods such as chemotherapy and radiotherapy were added.

The differences in the 3- and 5-year OS rates between Groups A and B were not statistically significant, but the laryngeal and oesophageal retention rates in patients in Group A were significantly higher than those in Group B. The laryngeal and oesophageal retention rates are the important indicators of survival quality in patients with hypopharyngeal and oesophageal cancers. Using induction chemotherapy, we

could screen for sensitive patients, for whom radiotherapy or concurrent chemoradiotherapy regimens were administered. The survival rate of these patients was not affected, but their quality of life was improved. For patients insensitive to the induction chemotherapy, surgical treatment was not delayed, and in some cases, tumour size was reduced, which can improve the response to surgery and postoperative adjuvant therapy. This can also serve as an effective treatment. We found that there was no significant difference in the incidence of postoperative complications between the two groups, indicating that induction chemotherapy did not increase the incidence of surgical complications. Generally speaking, surgery is the main treatment method for advanced hypopharyngeal carcinoma, and patients who undergo surgery tend to have a longer OS; however, the surgical resection is large, the postoperative quality of life is poor, and the incidence of postoperative complications is high, which are the disadvantages of surgery.

This study does have limitations. When we performed the univariate analysis of survival, there was no significant difference between the two groups, regardless of age, sex, anatomic sub-region, the degree of differentiation, cervical lymph node metastasis, smoking status, and alcohol consumption. This could be due to the small number of cases included in this study. Further studies with larger sample sizes are needed to determine the relevance of the factors affecting survival.

Conclusions

The prognosis of patients with advanced hypopharyngeal cancer with cervical oesophageal invasion is poor; the appropriate treatment should be carefully selected according to the condition and preferences of the patient. Response to induction chemotherapy is an indicator for the preferred management of advanced hypopharyngeal carcinoma with cervical oesophageal invasion, making the treatment of patients more standardized and personalized. Questions on the choice of induction chemotherapy need to be addressed; for example, how to distinguish which patients would be sensitive to induction chemotherapy in advance, whether targeted drugs can be added to improve the efficacy of induction chemotherapy, and how to determine the cycle of induction chemotherapy. Problems such as these require multicentre collaboration, a large number of case studies, and fundamental research.

List Of Abbreviations

CP/CR; complete/partial response

CT; computed tomography

OS; overall survival

PF; platinum + fluorouracil

SD; stable disease

TPF; paclitaxel + platinum + fluorouracil

Declarations

Ethics approval and consent to participate:

Complete follow-up data were retrospectively reviewed after approval from the Institutional Review Board. This study was performed in accordance with the principles of the Declaration of Helsinki.

Consent for publication:

Not application.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

All authors have no potential competing interests.

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Authors' contributions:

JG F and SZ H: designed this reserach, reviewed and edited the manuscript, TQ H and R W prepared original draft and complete the manuscript, Q Z, LZ H, and HZ M made statistical analysis, XH C, XJn C, PD L, L F, Q S, and M L were in charge of data collection. All authors read and approved the final manuscript.

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Figures

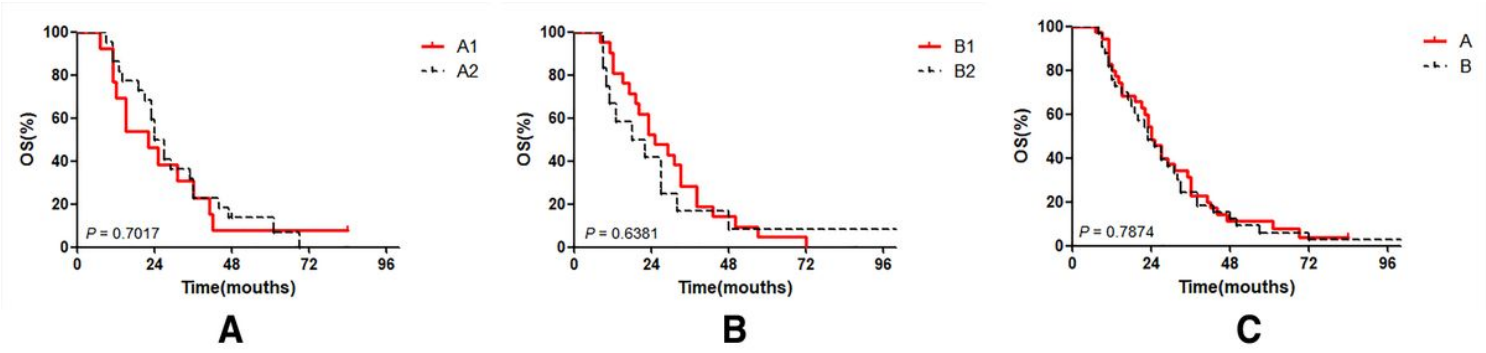

Figure 1

Kaplan–Meier survival curves a: The difference in survival rates between Groups A1 and A2 as examined using the log-rank test is not statistically significant (P = 0.7017). b: The difference in survival rates between Groups B1 and B2 as examined using the log-rank test is not statistically significant (P = 0.6381). c: The difference in survival rates between Groups A and B as examined using the log-rank test is not statistically significant (P = 0.7874).

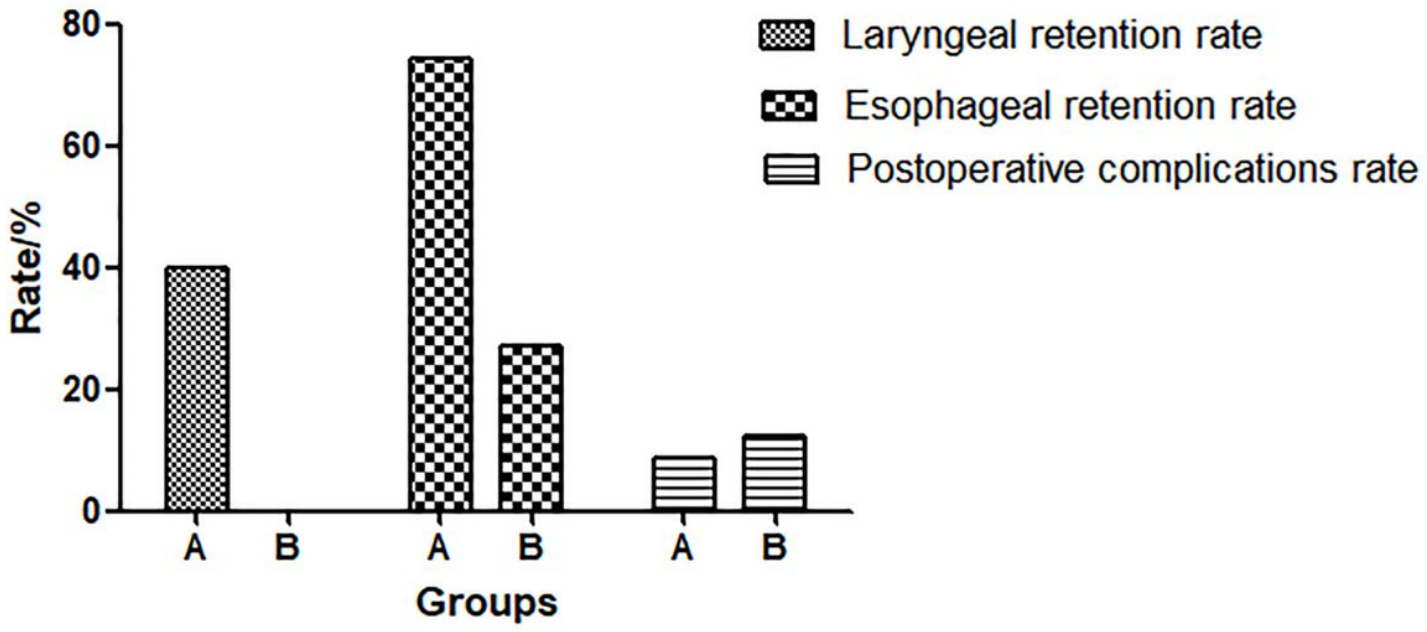

Figure 2

The difference in the laryngeal and the oesophageal retention rates between groups The difference in the laryngeal and the oesophageal retention rates between groups according to the degree of differentiation is statistically significant (log-rank: P = 0.0002 and P = 0003, respectively). The difference in postoperative complication rates between Groups A and B as examined using the log-rank test is not statistically significant (P = 0.9345).