Clinical study of poorly differentiated head and neck squamous cell carcinoma: a prospective cohort study in China

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Background: Although poorly differentiated is rare in head and neck squamous cell carcinoma (HNSCC), its prognosis are worse with high rate of local recurrence and distant metastasis (DS). Therefore, this study hopes to carry out prospective clinical research on different treatment options for poorly differentiated patients and explore the treatment scheme more suitable for these patients.

Methods: This study is a prospective cohort study. We selected patients with poorly differentiated carcinoma in larynx or hypopharynx (stage I–IV, T1–4a, N0–2, M0). The intervention treatment methods for stage I–II patients are as follows: surgery, induction chemotherapy (IC) + surgery, surgery + adjuvant therapy; The intervention treatment methods for stage III–IV patients are as follows: surgery, IC + surgery + adjuvant therapy, surgery + adjuvant therapy. The patients were followed up for at least 1 year, and the disease progression and survival were counted.

Results: From September 2016 to October 2020, 62 patients were included (29 patients in stage I/II and 33 patients in stage III/IV). We found that there was no significant difference in survival between treatment groups in stage I/II patients [overall survival (OS): P=0.447; progression free survival (PFS): P=0.504], but the surgery + adjuvant treatment group had a significant advantage in 3-year OS (100%). In stage III/IV patients, there were significant differences in DS, OS and PFS between different treatment groups (DS: P=0.013; OS: P=0.021; PFS: P=0.020). Among them, the survival rate of IC + surgery + adjuvant treatment group was the best, with 3-year OS of 78%.

Conclusions: Our study found that postoperative radiotherapy may improve the OS rate of patients with early (stage I/II) poorly differentiated HNSCC; For advanced patients (stage III/IV), surgery combined with IC and postoperative adjuvant radiotherapy may better control DS and improve the survival rate. However, our study draws the above conclusions based on small sample data, and we will continue to summarize and expand the sample size for verification.

Keywords: Squamous cell carcinoma of head and neck; clinical pathology; clinical protocols

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is the 6th most common cancer in the world (1), and the main pathological type of head and neck cancer, accounting for >90% of the total. In recent years, the incidence rate has been gradually increasing, and >500,000 new cases are diagnosed annually in the worldwide (2). According to the degree of differentiation of the tumor cells, SCC can be divided into three subtypes: well, medium and poorly differentiated, with the main subtype being well-differentiated SCC. Although poorly differentiated laryngeal SCC is rare among HNSCC, previous research indicates that survival and prognosis are worse than for the well-differentiated subtype, and the 5-year overall survival (OS) rate is 30% lower. Patients with the poorly differentiated subtype are more likely to have local recurrence or distant metastasis (DS), and this subtype has completely different characteristics to well-differentiated SCC (3). However, there is a general lack of treatment guidelines or consensus on the pathological differentiation of laryngeal SCC, so more clinical study is required to clarify the most favorable treatment options for this pathological subtype with poor prognosis.

The aims of this study were to clarify the current combinations of existing treatment methods, which treatment scheme is most suitable for patients with poorly differentiated HNSCC, and which treatment scheme could provide guidelines for the clinical treatment of patients. From this, it may be possible to improve the formulation of individualized treatment plans for patients with different pathological subtypes. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2630/rc).

Methods

Patient recruitment

This study was a prospective cohort study (clinical trial: ChiCTR-ONC-16009290), mainly for patients with poorly differentiated HNSCC (larynx or hypopharynx), to identify better treatment options for this subtype. Since September 2016, patients who met the following criteria were recruited: (I) primary lesion located in the larynx or hypopharynx; (II) T1–4a, N0–2, M0; (III) poorly differentiated SCC by pathological examination; (IV) newly treated patient (no history of surgery, radiotherapy or chemotherapy); (V) age 18–70 years; (VI) Karnofsky Performance Status >80; (VII) hemogram, heart, lung, liver, kidney and other major organs essentially normal; (VIII) CT, MRI and endoscopy completed before enrollment. The first patient was recruited in September 2016 and the last in October 2020.

Ethics and approvals

This study was approved by the Ethics Committee of Beijing Tongren Hospital, Capital Medical University (No. trecky2015-026/trecky2016-025). All patients were informed of the purpose of the study and signed informed consent before treatment. All information will be stored securely. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Treatment regimen

The flow diagram for this study is shown in *Figure 1*. According to disease stage, the patients in stage I/II were divided into surgery group, induction chemotherapy (IC) + surgery group, or surgery + adjuvant therapy group. Stage III/IV patients were divided into surgery group, IC + surgery + adjuvant therapy group, or surgery + adjuvant therapy group. In the surgery groups, the patients underwent laser resection or open surgery according to the location of the lesions. Two cycles of docetaxel/cisplatin/5-FU regimen comprised the IC. Postoperative adjuvant therapy was 30–35 doses of radiotherapy, to a total dose of 55–60 Gy. During radiotherapy and chemotherapy, if the patient could not complete the treatment, it was suspended and the patient was discharged from the study. After completion of the treatment plan, the patients were followed up regularly to observe disease progression as local recurrence, lymph node metastasis and DS, and the corresponding treatment was carried out according to existing treatment guidelines.

Statistical analysis

The Chi-squared test and non-parametric test were used to analyze the differences between groups. The Kaplan-Meier method was used to construct the OS rate curve and risk curve. Also, we performed univariate analysis on the factors that may affect local recurrence, DS, lymph node metastasis and survival rate, including gender, age, smoking history, drinking history, lesion location, surgical method, incision

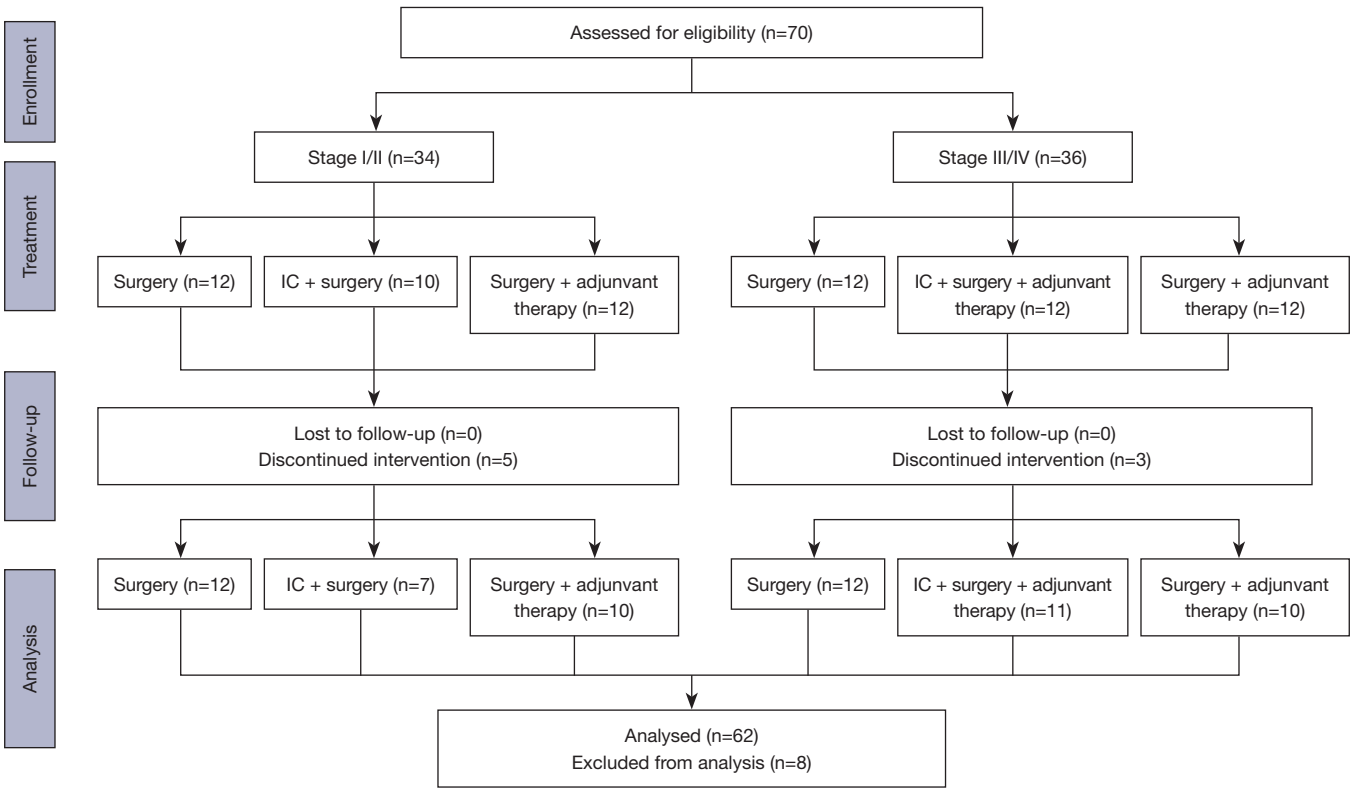

Figure 1 Flow diagram. IC, induction chemotherapy.

margin and comprehensive treatments. The meaningful possible factors are included in the multivariate analysis to obtain the independent influencing factors. SPSS 25.0 (IBM Corp., Armonk, NY, USA) was used, and the significance level was set as $P<0.05$ double-sided.

Results

Baseline information of the patients

In total, 70 patients were recruited and followed up to October 2021 (median follow-up, 19.5 months). Of them, 34 patients were in stage I/II: 12 were in the Surgery group, 10 in the IC + surgery group, and 12 in the Surgery + adjuvant therapy group. There were 36 patients in stage III/IV, with 12 patients in the Surgery group, 12 in the IC + surgery + adjuvant therapy group, and 12 in the surgery + adjuvant therapy group. We excluded 8 patients (5 patients in stage I/II, 3 patients in stage III/IV) who either did not wish to take part in the study or were intolerant to chemoradiotherapy. Therefore, 62 patients were finally included in the statistical analysis (*Table 1*). There were 29 patients with stage I/II disease (12 patients in the surgery group, 7 in the IC + surgery group, and 10 in the surgery + adjuvant therapy group), and 33 patients with stage III/IV disease (12 patients in the surgery group, 11 in the IC + surgery + adjuvant therapy group, and 10 in the surgery + adjuvant therapy group). The Chi-squared test and non-parametric test were used to analyze differences in the general clinical characteristics of patients with different disease stages and in the different treatment groups. There were no differences in age, sex, primary location of disease, smoking history, drinking history or surgery among the groups (*Table 1*). And the differences between different treatment groups are excluded.

Prognostic analysis of patients

The Kaplan-Meier univariate method was used to analyze the risk of local recurrence, lymph node metastasis and DS in patients with different stages and in different treatment groups. Among the stage I/II patients, there was no difference in prognosis for the three treatment groups. Among the stage III/IV patients, there were differences in

Table 1 Clinical characteristics of the 62 study patients

Characteristics	Stage I/II (n=29)				Stage III/IV (n=33)			
	Surgery (n=12)	IC + surgery (n=7)	Surgery + adjuvant therapy (n=10)	P	Surgery (n=12)	IC + surgery + adjuvant therapy (n=11)	Surgery + adjuvant therapy (n=10)	P
Mean age, years	62.5	57	61.5	0.210	62.5	59	58	0.220
Sex				0.130				0.406
Male	12	7	8		11	11	10	
Female	0	0	2		1	0	0	
Site				0.060				0.063
Larynx	9	2	8		10	4	5	
Hypopharynx	3	5	2		2	7	5	
Smoking				0.899				0.783
Yes	6	4	6		8	8	8	
No	6	3	4		4	3	2	
Drinking				0.283				0.672
Yes	4	4	2		7	6	4	
No	8	3	8		5	5	6	
Surgery				0.142				—
Laser	8	3	5		0	0	0	
Open	4	4	5		12	11	10	

IC, induction chemotherapy.

DS for the three treatment groups. Different treatment is an independent factor affecting DS, of which IC + surgery + adjuvant therapy had the best control of DS (*Table 2*, *Figure 2*).

Analysis of patient survival

To analyze the OS and progression-free survival (PFS) of patients with stage I/II and stage III/IV disease, the Kaplan-Meier method was used for univariate analysis of all factors that may be related to OS and PFS. Positive results were then selected for multivariate analysis using the Cox regression method to calculate the survival rate. There was no significant difference in OS or PFS among the treatment groups of stage I/II patients, but the long-term survival benefit in the surgery + adjuvant therapy group was better than the 1-, 2-, and 3-year OS of the other two groups. For the stage III/IV patients, there were significant differences in OS and PFS among the treatment groups: OS: 0.021 [hazard ratio (HR): 2.317, 95% confidence interval (CI): 1.133–4.741]; PFS: 0.020 (HR: 2.392, 95% CI: 1.150–4.973). As shown by the survival curves (*Figures 3*,*4*), the survival time of each group decreased in the order of: IC+ surgery + adjuvant therapy > surgery + adjuvant therapy > surgery. Based on the 1-, 2-, and 3-year OS for each group, the IC+ surgery + adjuvant therapy group showed a significant advantage in OS (*Table 3*).

Discussion

Because of the significant difference in survival among patients with different degrees of differentiation of SCC, research into poorly differentiated HNSCC is important clinically for improving the prognosis of patients through individualized treatment.

According to the degree of keratinization of tumor cells and the overall similarity between cancerous and normal squamous epithelium, tumors can be divided into three grades: well differentiated, medium differentiated and poorly differentiated. Well-differentiated tumor cells

Table 2 Summary of prognosis and survival of the 62 study patients

Prognosis and survival	Stage I/II (n=29)				Stage III/IV (n=33)			
	Surgery (n=12)	IC + surgery (n=7)	Surgery + adjuvant therapy (n=10)	P	Surgery (n=12)	IC + surgery + adjuvant therapy (n=11)	Surgery + adjuvant therapy (n=10)	P
Local recurrence				0.143				0.737
Yes	0	2	1		2	3	3	
No	12	5	9		10	8	7	
Distant metastasis				0.069				0.013
Yes	1	0	3		6	2	4	
No	11	7	7		6	9	6	
Lymph node metastasis				–				0.176
Yes	0	0	0		6	1	2	
No	0	0	0		6	10	8	
Survival				0.447				0.009
Yes	10	6	10		4	9	4	
No	2	1	0		8	2	6	

IC, induction chemotherapy.

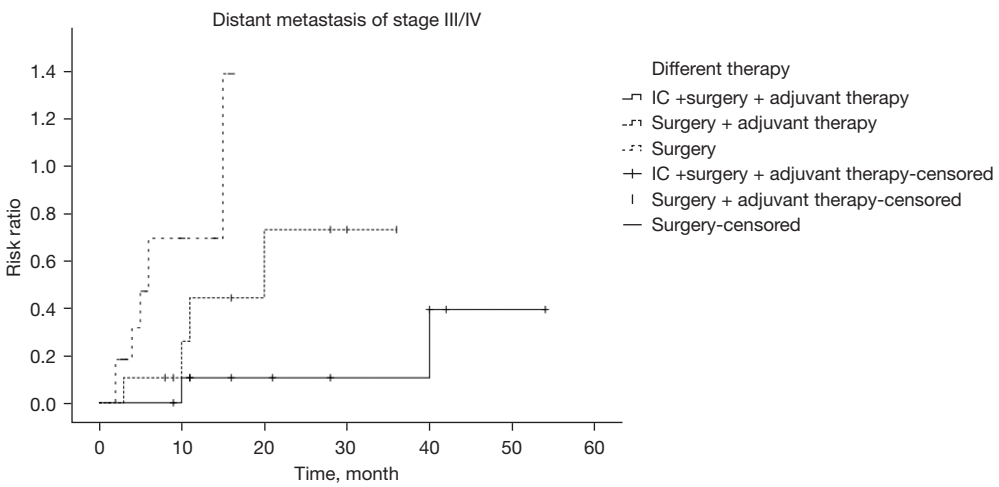

Figure 2 Distant metastasis of stage III/IV HNSCC with the different therapies. IC, induction chemotherapy; HNSCC, head and neck squamous cell carcinoma.

are similar to normal squamous cells, whereas poorly differentiated tumor cells are mainly immature cells with more mitotic figures, fewer interstitial bridges, and fewer or no keratinizing beads. Determination of cytokeratin, p63 and epithelial membrane protein is helpful to determine the pathology and degree of differentiation of laryngeal SCC (4). When the type of disease is confirmed pathologically, further knowledge of the pathological subtype is conducive to formulation of the treatment plan.

Despite multidisciplinary treatment, the 5-year survival rate has not improved significantly in the past 20 years, and is still only 40–50%, even though the quality of life of patients has continuously improved (5,6). Patients with poorly differentiated HNSCC showed significant differences

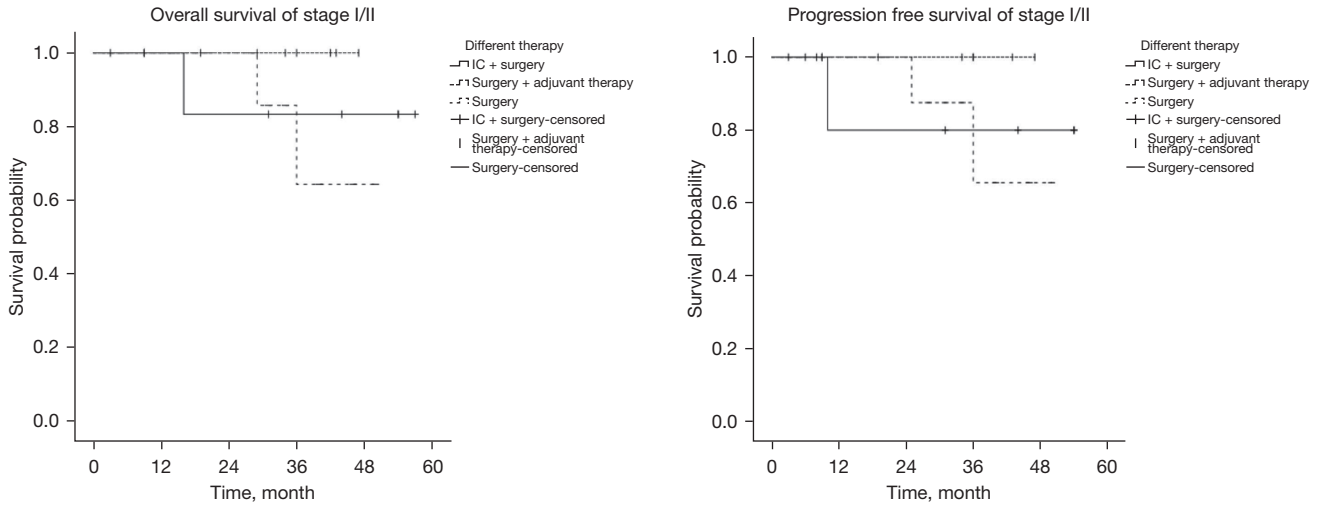

Figure 3 Overall survival and progression-free survival of stage I/II HNSCC patients. IC, induction chemotherapy; HNSCC, head and neck squamous cell carcinoma.

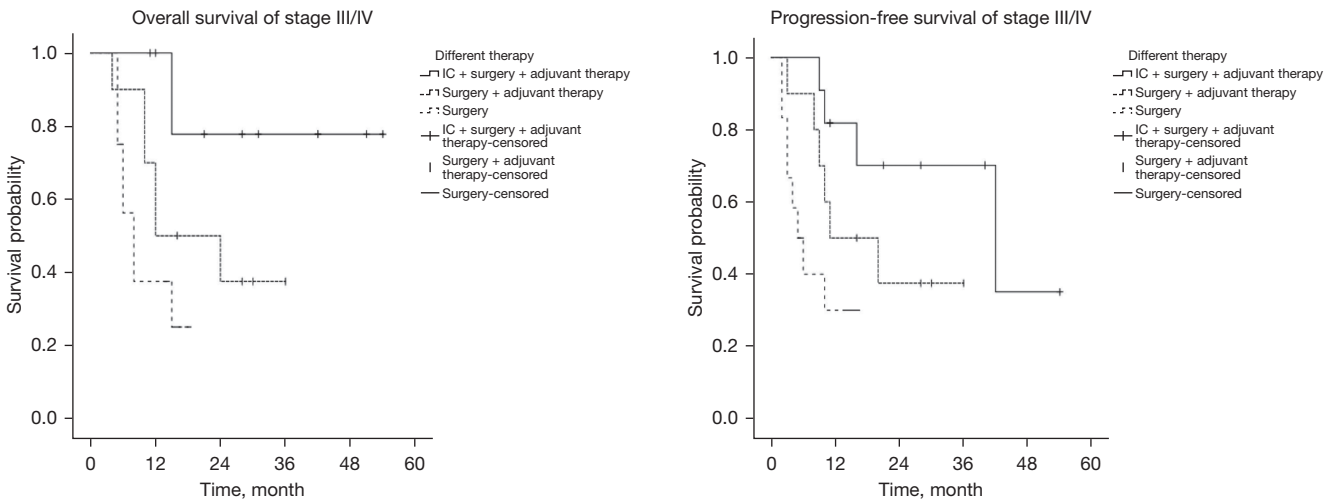

Figure 4 Overall survival and progression-free survival of stage III/IV HNSCC patients. IC, induction chemotherapy; HNSCC, head and neck squamous cell carcinoma.

in disease characteristics and survival compared with those with well-differentiated grades. In the past, there were few studies on poorly differentiated squamous cell carcinoma of head and neck. A study on 57 cases of poorly differentiated laryngeal carcinoma in China confirmed that the OS rate decreased with the increase of stage, and concluded that for patients without lymph node metastasis, there was no significant difference in survival between surgery and surgery with postoperative adjuvant radiotherapy (7). But patients with advanced stage should be combined with adjuvant radiotherapy, which is also consistent with the conclusion of tour study (7). However, this study is a retrospective cohort study, which may has a selection bias. Similarly, the study on the population of poorly differentiated oral and oropharyngeal cancer also found that the disease stage, lymph node metastasis and location of disease were the risk factors affecting the survival rate of poorly differentiated tumors, but the study showed that the 5-year OS of patients with different treatment methods was similar and maintained at about 60% (P=0.907) (8).

Table 3 One-, 2-, and 3-year overall survival rates

Survival rates	Stage I/II (n=29)			Stage III/IV (n=33)		
	Surgery (n=12)	IC + surgery (n=7)	Surgery + adjuvant therapy (n=10)	Surgery (n=12)	IC + surgery + adjuvant therapy (n=11)	Surgery + adjuvant therapy (n=10)
1-year OS	100%	83%	100%	23%	78%	48%
2-year OS	85%	83%	100%	–	78%	32%
3-year OS	56%	83%	100%	–	78%	32%
OS (P)	0.447			0.021 (HR: 2.317, 95% CI: 1.133–4.741)		
PFS (P)	0.504			0.020 (HR: 2.392, 95% CI: 1.150–4.973)		

IC, induction chemotherapy; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; P, P value of different treatment groups.

However, the study was also a retrospective analysis.

In our previous study, we found that the rate of positive surgical margins in patients with moderately and poorly differentiated laryngeal cancer (22.2%) was higher than in patients with well-differentiated laryngeal cancer (3.1%), and the difference between groups was statistically significant (P<0.01) (9), which indicates that poorly differentiated laryngeal SCC is highly invasive. We further matched 55 patients with poorly differentiated and 55 patients with well-differentiated glottic SCC (10), and found that the 5-year OS of the well-differentiated group and the poorly differentiated group were 90.2% and 50.9%, respectively, with a difference of nearly 30%. Moreover, the disease-specific survival (DSS) and disease-free survival (DFS) of patients in the well-differentiated group were significantly higher than those in the poorly differentiated group (10). Our center carried out a preliminary analysis of 93 patients with poorly differentiated hypopharyngeal cancer and the results also confirmed that OS (P=0.004), DSS (P=0.024) and DFS (P=0.019) of patients with poorly differentiated cancer were significantly lower than those of the patients with well-differentiated cancer (unpublished data). Therefore, independent study and analysis of this special group with poorly differentiated laryngeal SCC is desirable for the formulation of treatment plans for the different degrees of differentiation.

In 2019, we published a review of past medical records and clinical observations on poorly differentiated laryngeal SCC in the Chinese population (11). In it, we hypothesized that patients with early-stage poorly differentiated cancer should be given relatively active comprehensive treatment of combination radiotherapy and chemotherapy after surgery to improve the control rate and OS of the patients. Patients with advanced stage disease should be given systemic comprehensive treatment such as early intervention as adjuvant chemotherapy. Therefore, according to the different disease stages, we divided the study patients into I/II and III/IV stages, and different treatment groups. We found that for early-stage I/II patients, there was no significant difference in OS among the surgery, IC + surgery, and surgery + adjuvant therapy groups, but the long-term survival benefit in the group with surgery + postoperative adjuvant therapy was better than that of the other two treatment groups, with 3-year OS of 100%, 83% and 56%, respectively. This was consistent with our previous hypothesis.

Earlier a study showed that poorly differentiated disease was an independent factor for good prognosis of radiotherapy in patients with nasopharyngeal carcinoma (12), suggesting that poorly differentiated SCC is more sensitive to radiotherapy than the well-differentiated subtype. In the present study, for patients with advanced stage III/IV cancer, the incidence of DS differed among the treatment groups, and the OS and PFS were also significantly different. The IC + surgery + adjuvant therapy group had the lowest incidence of DS, followed by the surgery + adjuvant therapy group. Based on the 1-, 2-, and 3-year OS of each group, we observed that the IC + surgery + adjuvant therapy group had a significant advantage in OS compared with the other two treatments, which was also consistent with our previous hypothesis and the previous literature (13).

Some scholars have suggested that patients with poorly differentiated laryngeal cancer may be more sensitive to chemotherapy. The possible mechanism is that cytotoxic drugs are most effective in the cells undergoing active division, which is more common in poorly differentiated

tumors, suggesting that the degree of tissue differentiation may also be an important factor in determining the sensitivity of chemotherapy in patients with laryngeal cancer. Therefore, for patients with advanced disease, IC should be considered to improve the patient's condition and prognosis (14).

The differentiation grading system is considered to be an important prognostic tool for HNSCC. Some studies on oral cancer (15,16) have reported that poorly differentiated tumors have a higher recurrence rate and shorter survival time than well-differentiated and moderately differentiated tumors, but the prognostic benefits of this classification system are still controversial (17). There are few studies on poorly differentiated SCC of the larynx and pharynx. The results of the prospective trials carried out in this study will assist in determining the treatment of poorly differentiated SCC. Under the current medical model of individualized and hierarchical treatment, clinicians should explore better treatment schemes for poorly differentiated HNSCC to guide individualized precise treatment and comprehensively predict the prognosis of patients.

Conclusions

For patients with early poorly differentiated HNSCC, postoperative radiotherapy-based comprehensive treatment can improve the OS of patients. For patients with advanced disease, early intervention as adjuvant chemotherapy should be performed. Preoperative adjuvant chemotherapy combined with surgery and postoperative adjuvant radiotherapy should be carried out to control DS and improve the OS of patients. However, due to the relatively low incidence rate of poorly differentiated, our study draws the above conclusions based on small sample data. Our recommendations for this treatment model need to be verified by clinical trials using more patients' data.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2630/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2630/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2630/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. This study was approved by the Ethics Committee of Beijing Tongren Hospital, Capital Medical University (No. trecky2015-026/trecky2016-025). All patients were informed of the purpose of the study and signed informed consent before treatment. All information will be stored securely. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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