Complications and oncological outcomes after salvage surgery for recurrent and residual hypopharyngeal squamous cell carcinoma: a retrospective cohort study

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Background: Salvage surgery for hypopharyngeal squamous cell carcinoma (HPSCC) after radiotherapy may result in several postoperative complications and the oncological outcome is unsatisfying. Therefore, identifying the risk factors for postoperative complications and oncological outcome after salvage surgery is important. This study aimed to determine which HPSCC patients might benefit from salvage surgery following previous radiotherapy.

Methods: We retrospectively analyzed 91 HPSCC patients who underwent salvage surgery due to locoregional recurrence/residual disease after radiotherapy. The pre- and intraoperative characteristics with complications and oncological outcomes were collected through medical records and telephone follow-up. Risk factors for complications were analyzed by binary logistic regression. The oncological outcomes were assessed by overall survival (OS) after salvage surgery. Kaplan-Meier curves and Cox proportional hazard regression analysis were used for univariate and multivariate survival analyses.

Results: Postoperative complications occurred in 40.7% of patients, with pharyngo-cutaneous fistula (PCF) occurring in 29.7% of patients. Salvage surgery for local disease was the only independent risk factor for postoperative complications and PCF [complications: odds ratio (OR) =5.298, 95% confidence interval (CI): 1.163–24.130, P=0.031; PCF: OR =4.543, 95% CI: 1.187–17.387, P=0.027). In the subgroup of patients with local disease, time of curative treatment initiation >90 days (OR =7.331, 95% CI: 1.278–42.054, P=0.025) and preoperative hemoglobin <118 g/L (OR =10.101, 95% CI: 1.026–99.492, P=0.045) were independent risk factors for postoperative complications, while free flap reconstruction was an independent protective factor for PCF (OR =0.099, 95% CI: 0.010–0.934, P=0.043). The median OS time was 17 months, with 5-year OS rates of 30%. Age at salvage surgery <50 years [hazard ratio (HR) =2.047, 95% CI: 1.217–3.443, P=0.007] and recurrence or retreatment clinical T stage 3–4 (rcT3–4) (HR =2.051, 95% CI: 1.219–3.450, P=0.007) were identified as risk factors for OS. The 5-year OS rates of patients without and with both risk factors were 43% and 10% (P=0.001).

Conclusions: Salvage surgery for locoregional recurrence/residual disease after previous radiotherapy could improve survival in selected patients with HPSCC. Patients with local recurrence/residual disease had a higher complication rate. Efforts can be made to shorten the time of curative treatment initiation and treat anemia to reduce the risk of postoperative complications in this subgroup.

Keywords: Hypopharyngeal squamous cell carcinoma (HPSCC); salvage surgery; oncological prognosis; postoperative complication; risk factor

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Introduction

Head and neck cancer is the sixth most common cancer worldwide and the seventh most common cancer in China (1). Hypopharyngeal cancer is a subtype of head and neck cancer that accounted for 3–5% [84,254] of newly diagnosed cases and 38,599 deaths recorded worldwide in 2020 (2). Squamous cell carcinoma is the most prevalent pathological type, accounting for 95% of all cases. Hypopharyngeal squamous cell carcinoma (HPSCC) is usually diagnosed at an advanced stage and has a poor prognosis. With the advancement of radiotherapy technology, radiotherapy either alone or in combination with systemic therapy has become an increasingly essential component of HPSCC treatment. However, physicians must confront the difficult clinical challenge of recurrence/residual disease following radiotherapy. After radiotherapy, a limited number of therapeutic options are available, with salvage surgery being the most preferred and probable curative option after post-radiotherapy recurrence/residual disease. However, salvage surgery may result in several postoperative complications, significantly impairing patients' quality of life. Some of the complications such as flap loss, pharyngo-cutaneous fistula (PCF), and common carotid artery rupture may be fatal.

Previous studies have reported that risk factors for postoperative complications include (chemo)radiotherapy, types of surgery, types of reconstruction, neck dissection, positive tumor margins, presence of a preoperative tracheotomy, comorbidities, tumor stage, nutrition status, and hemoglobin levels (3-5). While, previous studies have suggested potential predictors for a worse survival are history of chemotherapy, residual disease, age, tumor stage, positive resection margins, and neck nodes with extranodal spread (4,6-8). However, results are not consistent across studies. And, the results were mainly obtained from American and European populations. Therefore, the purpose of this study was to determine the pre-salvage surgery characteristics that affect the oncological prognosis and risk of postoperative complications based on Asian population. This study presents recommendations to clinicians regarding which subgroup of patients with recurrent/residual HPSCC following previous radiotherapy is more likely to benefit from salvage surgery. We present the following article in accordance with the STROBE reporting checklist (https://atm.amegroups.com/article/view/10.21037/atm-22-1844/rc).

Methods

Patients

We conducted a retrospective assessment of patients with recurrent/residual HPSCC who underwent salvage surgery in the Department of Head and Neck Surgery at the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (China) between July 2008 and July 2018. The selection criteria were as follows: (I) squamous cell carcinoma of the hypopharynx; (II) received definitive/adjuvant radiotherapy with or without systemic therapy in the previous treatment with dose ≥50 Gy; (III) recurrent/residual hypopharyngeal cancer without distant metastasis; and (IV) successful salvage surgery with R0 resection. A total of 102 patients met the selection criteria. Then, patients with other advanced cancers were excluded from the study at the time of salvage surgery (n=7). Patients lost during follow-up (follow-up period less than 6 months without death detected) were also excluded (n=4). This study enrolled a total of 91 patients. The study was approved by the Independent Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. NCC2021C-512) and was conformed to the provisions of the Declaration of Helsinki (as revised in 2013). All patients signed an informed consent form before treatment.

Definition of variables, data collection, and follow-up

Before salvage surgery, all patients underwent imaging tests and fiberoptic endoscopy. The TNM classification was established using the American Joint Committee on Cancer (AJCC) 8th edition staging system during the preoperative examination, presented as recurrence or retreatment clinical T/N/M (rcT/N/M) stage. The medical records of patients

were evaluated for their general characteristics, clinical symptoms, treatments, and pathological data. Medical records and telephone follow-up were used to collect data on complications and oncological outcomes. Postoperative complications included PCF, hemorrhage, ruptures of the common carotid artery, wound infection, flap loss, tracheostoma necrosis, wound effusion, Horner syndrome, and lymphatic leakage. The oncological outcomes were evaluated by overall survival (OS). OS was defined as the date of salvage surgery to the date of death from any cause or the last follow-up. The patients were followed up every 3 months over the first 2 years, every 6 months for the next 3 years and then subsequently once a year. The follow-up examinations included imaging tests and fiberoptic endoscopy. The following indicators were also recorded for analyses, including salvage age, sex, smoking/alcohol history, previous radiotherapy dose (≤68 or >68 Gy), previous systemic treatment, the curative effect of radiotherapy [complete remission (CR) or not], time between salvage surgery and previous radiotherapy (≤12 or >12 months), recurrent/residual site (local, regional, or locoregional), lymphadenopathy (ipsilateral, contralateral, or bilateral), reconstruction techniques (pedicle flap or free flap), the time of curative treatment initiation (time interval between the clinical diagnosis of recurrence/residual disease and the date of salvage surgery), preoperative hemoglobin (<118 or ≥118 g/L), and preoperative albumin.

Statistical analysis

The continuous variables were presented as mean ± standard deviation for normally distributed variables and median (range) for abnormally distributed variables. Categorical variables were estimated using Chi-square tests or Fisher exact tests, and continuous variables were estimated using the Student's *t*-test the Wilcoxon rank-sum test. The survival curve was established using Kaplan-Meier analysis. Variables that were significant in the Kaplan-Meier analysis (log-rank test) were selected for multivariate survival outcomes analysis using the Cox model. Similarly, multivariate analysis was performed using a binary logistic regression model with variables that were significant in univariate analyses to identify potential risk factors for postoperative complications. All analyses were conducted using IBM-SPSS statistics (version 24.0). All reported P values were two-tailed, P<0.05 was considered statistically significant.

Results

Patient characteristics

There were 91 patients enrolled in this study. Of the 91 patients, 89 were males while 2 were females. The mean age of patients undergoing salvage surgery was 54.6 years, ranging from 39 to 81 years. Thirty patients were under 50 years old, while 61 patients were older. A total of 79 patients had a smoking history, while 77 patients had a history of alcohol consumption. Radiotherapy with or without systemic therapy was performed as an initial treatment in 82 patients, of whom the CR rates of the primary lesion alone and the whole disease were 68.1% (n=62) and 30.8% (n=28), respectively. The remaining 9 patients underwent primary surgery first, followed by adjuvant radiotherapy as an initial treatment. The radiation dose ranged between 50 and 76 Gy (67.8±5.3 Gy). There were 65 patients who received a radiotherapy dose >68 Gy. Furthermore, 55 patients received systemic therapy in previous treatment. Local recurrence/residual disease alone occurred in 32 patients, regional recurrence/residual disease alone occurred in 39 patients, and locoregional recurrence/residual disease occurred in 20 patients. A total of 32 patients were diagnosed with rcT3–4 disease, while 29 patients were diagnosed with rcN3 disease. Furthermore, 87.9% (n=80) of the patients received salvage surgery within 1 year after radiotherapy, and 62.6% (n=57) of the patients underwent salvage surgery in less than 90 days after their first clinical recurrence diagnosis. Additionally, 35.2% (n=32) of the patients received flap reconstructions, among which 62.5% (n=20) were free flap reconstructions (*Table 1*).

Complications

There was no perioperative death. A total of 37 (40.7%) out of 91 patients developed postoperative complications, 12 of whom developed more than 1 kind of complication. PCF occurred in 27 (29.7%) patients. In 25 patients, the time interval between salvage surgery and PCF occurrence was recorded, ranging from 6 to 90 days. Among them, 12 (48.0%) patients suffered from delayed PCF. Additionally, 9 (9.9%) patients experienced postoperative hemorrhage, including 4 (4.4%) ruptures of the common carotid artery. Other complications included wound infection (n=4), flap loss (n=2), tracheostoma necrosis (n=2), wound effusion (n=2), Horner syndrome (n=2), and lymphatic leakage (n=2).

In the univariate analysis, CR of the primary lesion at the

Table 1 General clinical factors of the patients

Factors	Numbers
Age (years), mean ± SD	54.6±8.4
Smoking history, n (%)	79 (86.8)
Alcohol history, n (%)	77 (84.6)
Radiation dose (Gy), mean ± SD	67.8±5.3
Combined systemic therapy, n (%)	55 (60.4)
Recurrence, n (%)	
Local recurrence/residual disease alone	32 (35.2)
Regional recurrence/residual disease alone	39 (42.9)
Locoregional recurrence/residual disease	20 (22.0)
rcT3–4 disease, n (%)	32 (35.2)
rcN3 disease, n (%)	29 (31.9)
Time of curative treatment initiation, n (%)	
<90 days	57 (62.6)
≥90 days	34 (37.4)

SD, standard deviation; rcT/N, recurrence or retreatment clinical T/N stage.

Table 2 Binary logistic regression of factors associated with complications and PCF

Factors	OR (95% CI)	P value
Complications		
Complete remission of the primary lesion		
No	Ref.	
Yes	1.426 (0.398–5.113)	0.568
Salvage surgery for local recurrence/residual disease		
No	Ref.	
Yes	5.298 (1.163–24.130)	0.031
rcN3		
No	Ref.	
Yes	1.465 (0.270–7.937)	0.658
Radiation dose		
≤68 Gy	Ref.	
>68 Gy	1.348 (0.278–6.531)	0.710
PCF		
Salvage lateral neck dissection		
No	Ref.	
Yes	2.112 (0.653–6.837)	0.212
Salvage surgery for local recurrence/residual disease		
No	Ref.	
Yes	4.543 (1.187–17.387)	0.027
rcN3		
No	Ref.	
Yes	1.530 (0.364–6.431)	0.561

CI, confidence interval; OR, odds ratio; PCF, pharyngo-cutaneous fistula; rcN, recurrence or retreatment clinical N stage.

end of radiotherapy, salvage surgery for local recurrence/residual disease, rcN3, and previous radiotherapy dose >68 Gy were associated with postoperative complications (P<0.05). In contrast, age, sex, smoking/alcohol history, previous systemic treatment, time between salvage surgery and previous radiotherapy, lymphadenopathy extent, reconstruction techniques, the time of curative treatment initiation, preoperative hemoglobin, and preoperative albumin had no significant effect on postoperative complications (P>0.05). Meanwhile, salvage surgery for local recurrence/residual disease, salvage lateral neck dissection, and rcN3 were associated with PCF (P<0.05).

Multivariate logistic regression was used to determine the independent factors associated with postoperative complications and PCF. Only salvage surgery for local recurrence/residual disease was an independent risk factor for postoperative complications [odds ratio (OR): 5.298, 95% confidence interval (CI): 1.163–24.130, P=0.031] and PCF (OR: 4.543, 95% CI: 1.187–17.387, P=0.027) (*Table 2*).

Subgroup analyses of patients who underwent salvage surgery for local recurrence were performed to identify the risk factors for postoperative complications and PCF in this group. This subgroup had a postoperative complication rate of 53.8% (28/52). PCF was detected in 23 (44.2%) out of 52 patients. Time of curative treatment initiation >90 days (OR: 7.331, 95% CI: 1.278–42.054, P=0.025) and preoperative hemoglobin <118 g/L (OR: 10.101, 95% CI: 1.026–99.492, P=0.045) were independently associated with postoperative complications. The complication rate was significantly higher in patients with both risk factors (time of curative treatment initiation >90 days and preoperative hemoglobin <118 g/L) than those without (100% *vs.* 40%, P=0.037). Additionally, free flap reconstruction served as an independent protective factor for PCF (OR: 0.099, 95% CI: 0.010–0.934, P=0.043). Patients undergoing free flap reconstruction had a lower rate of PCF than those

Table 3 Binary logistic regression of factors associated with complications and PCF in a subgroup of patients with local salvage

Factors	OR (95% CI)	P value
Complications		
Time of curative treatment initiation		
≤90 days	Ref.	
>90 days	7.331 (1.278–42.054)	0.025
Preoperative hemoglobin		
≥118 g/L	Ref.	
<118 g/L	10.101 (1.026–99.492)	0.045
PCF		
Reconstruction option		
Pedicle flaps	Ref.	
Free flaps	0.099 (0.010–0.934)	0.043
Preoperative hemoglobin		
≥118 g/L	Ref.	
<118 g/L	8.254 (0.885–76.937)	0.109

CI, confidence interval; OR, odds ratio; PCF, pharyngo-cutaneous fistula.

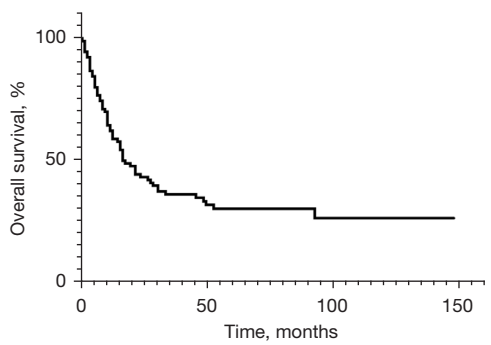

Figure 1 Overall survival in the entire cohort.

undergoing pedicle flap reconstruction (25.0% *vs.* 66.7%, P=0.031) (*Table 3*).

Oncological outcomes

The follow-up period ranged from 0 to 148 months, with an average follow-up period of 31 months. A total of 63 deaths were discovered during the follow-up period. The median OS time was 17 months, with 1-, 2-, 3-, and 5-year OS rates of 61.5%, 42.8%, 35.8%, and 30.0%, respectively (*Figure 1*).

Table 4 Univariate analysis of prognostic factors

Factors	Median survival (months)	P value
Previous radiotherapy		0.040
≤68 Gy	11	
>68 Gy	22	
Age at salvage surgery		0.018
<50 years	13	
≥50 years	27	
rcT3–4		0.001
No	29	
Yes	8	

rcT, recurrence or retreatment clinical T stage.

Table 5 Multivariate analysis of prognostic factors by Cox regression

Factors	HR (95% CI)	P value
Previous radiotherapy		
≤68 Gy	Ref.	
>68 Gy	0.593 (0.339–1.036)	0.066
Age at salvage surgery		
≥50 years	Ref.	
<50 years	2.047 (1.217–3.443)	0.007
rcT3–4		
No	Ref.	
Yes	2.051 (1.219–3.450)	0.007

CI, confidence interval; HR, hazard ratio; rcT, recurrence or retreatment clinical T stage.

In the univariate analysis, previous radiotherapy >68 Gy was found to be associated with a better prognosis. Age at salvage surgery <50 years and rcT3–4 were identified as factors associated with decreased OS (*Table 4*). Multivariate Cox regression analysis included components that were statistically significant in the univariate analysis. Age at salvage surgery <50 years [hazard ratio (HR) =2.047, 95% CI: 1.217–3.443, P=0.007] and rcT3–4 (HR =2.051, 95% CI: 1.219–3.450, P=0.007) were identified as independent risk factors for poor prognosis (*Table 5*). The 5-year OS rates of patients with both risk factors (n=10), patients with only 1 risk factor of age at salvage surgery <50 years (n=22), patients with only 1 risk factor of rcT3–4 (n=20), and

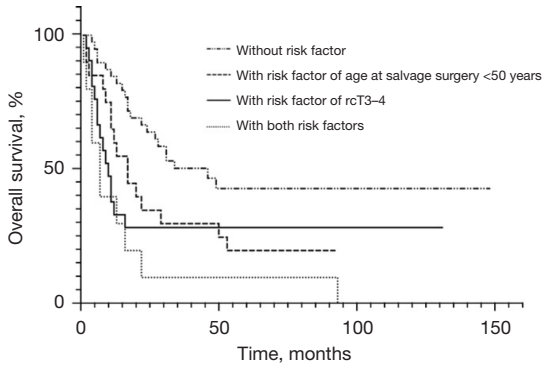

Figure 2 Survival rate of patients with and without risk factors. rcT, recurrence or retreatment clinical T stage.

patients without risk factors (n=39) were 10%, 20%, 27.3%, and 43%, respectively. The median survival of patients with both risk factors (7 months) was worse than patients with rcT3–4 (9 months) and patients with age at salvage surgery <50 years (17 months). On the other hand, patients without any risk factors had the best median survival of 46 months (P=0.001) (*Figure 2*).

Discussion

Among head and neck cancers, HPSCC has the poorest prognosis, with a 5-year OS rate of 25–40% (9,10). Radiotherapy, due to its high rate of organ preservation, has become an increasingly significant component of HPSCC treatment. However, 30–50% of patients experience recurrence following radiotherapy (8,11). Treatment of recurrent/residual HPSCC following radiotherapy remains challenging. Salvage surgery is considered initially in cases of recurrence. Re-irradiation is also an alternative option, however, as Spencer *et al.* (12) reported in a prospective multi-institutional trial, the efficacy is limited, with a 5-year survival rate of 3.8%. Patients who were not considered salvage surgery candidates and instead underwent palliative treatment died as a consequence of tumor after a median survival of 3.5 months (6).

In this study, the median OS time following salvage surgery was 17 months, with a 5-year OS rate of 30%. This finding was consistent with earlier studies in which the 5-year survival rates ranged from 20–40% (13-15). Given that survival outcomes following salvage surgery remain unsatisfactory, many researchers have concentrated on determining which pre-salvage surgical factors contribute to poor survival. Other studies revealed that a history of chemotherapy, concurrent local-regional failures, the time interval from radiation to salvage surgery <6 months, and N3 status were all potential predictors of poor survival (4,7,16). We discovered that pre-salvage surgery variables such as age at salvage surgery <50 years and rcT3–4 were associated with poor oncological prognosis. Putten *et al.* (8) noted that elderly patients frequently had several severe comorbidities, which resulted in a greater complication rate and poor survival. However, we discovered that younger patients are more likely to have poor survival. In this study, older patients had a significantly greater rate of comorbidity (salvage age ≥50 years *vs.* salvage age <50 years, 43.2% *vs.* 20%, P<0.05). Univariate analysis, on the other hand, revealed no correlation between comorbidity and survival. The association between younger age and poor survival outcomes could be explained in this study by the aggressive tumor biology of younger patients. Tan *et al.* (7) found a high correlation between TNM stage and survival outcomes, which corroborates our findings. Patients with rcT3–4 had a significantly shorter OS than other patients in this study. Furthermore, patients without any risk factors (salvage age <50 years or rcT3–4) could achieve a median OS of 46 months and a 5-year OS rate of 43%, which was comparable to that of patients who did not experience a recurrence.

Besides oncological prognosis, the most important concern is post-salvage surgery complications. The reported complication rate following salvage surgery for recurrent/residual hypopharyngeal carcinoma was relatively high, ranging from 33–92% (17-19). PCF was the primary cause of complications, with an incidence rate of 11–58% (14,20). In this study, 40.7% (37/91) of the patients developed post-salvage surgery complications, with a PCF rate of 29.7% (27/91). Given that postoperative complications lead to an increased length of hospital stay and higher cost of hospitalization, it is critical to identify potential risk factors for complications before performing salvage surgery. When all patients in this study were included in the analysis, univariate analysis revealed that CR of the primary lesion at the end of radiotherapy, salvage surgery for local recurrence, previous radiotherapy dose >68 Gy, salvage lateral neck dissection, and rcN3 were statistically significant predictors for complications and PCF. A possible explanation for these findings is the toxic effect of higher radiotherapy doses in tissue, particularly those associated with severe reactions. Additionally, advanced lymph node metastasis treated with aggressive neck dissection can affect the vasculature of the tissue. It is widely recognized that radiation has a significant

effect on the ability of the tissue to heal via direct cell and microvascular damage. Unsurprisingly, in the multivariate analysis, the only predictor associated with complications and PCF was salvage surgery for local recurrence/residual disease. Salvage surgery for local recurrence/residual disease must include destroying the integrity of the upper digestive tract mucosa, allowing clinical or subclinical salivary leakage to develop complications including PCFs. In this study, 12 patients (48% of the patients with PCF-detected-time recorded) developed delayed PCF, which frequently necessitated secondary hospital admissions, cessation of oral intake, and prolonged dressing changes. Therefore, attention for PCF should be paid to patients who have undergone salvage surgery, even if their short-term postoperative recovery was smooth.

Hemoglobin level was found to be associated with PCF formation in previous studies (5,21). In this study, preoperative hemoglobin <118 g/L was found to be an independent risk factor for postoperative complications. Surprisingly, multivariate analysis revealed that another risk factor for postoperative complications was the time of curative treatment initiation >90 days. A national database analysis in the United States of America revealed a correlation between the time of curative treatment initiation after diagnosis and survival in treatment-naïve patients (22). However, we observed differences in complications, not in survival, as a result of the time of curative treatment initiation. Patients with recurrent disease are typically in poor health. Additionally, such patients, particularly those with HPSCC, frequently experience eating constraints as a result of the tumor itself and previous invasive treatments. Therefore, it might be suggested that when patients with recurrent HPSCC undergo a delay in curative treatment initiation, the rapid tumor proliferation and stage progression affect general health and interact with hemoglobin levels, resulting in a high complication rate. Because of this, physicians should make efforts to expedite the commencement of curative treatment and to indicate intervention in patients with low hemoglobin to limit the risk of postoperative complications.

Typically, salvage surgery entails reconstruction. In comparison to primary closure, it is debatable whether reconstruction with flaps reduces the incidence of complications and PCF (5,23). In this study, patients undergoing free flap reconstruction suffered significantly less PCF than patients undergoing pedicle flap reconstruction. Because free flaps were typically harvested away from the irradiated field, they could provide non-irradiated tissue devoid of previous radiotherapy-induced cell and vascular damage. Individualized flap selection should take into account both the flaw defects as well as surgeon preferences and technical skills.

This study still has some limitations. The characteristics of retrospective studies include recall bias and investigation bias, which could not be completely avoided. Additionally, the case number was limited. A larger sample size is needed to provide stronger evidence.

Conclusions

The purpose of this study was to examine the relationship between pre-salvage surgery characteristics and postoperative outcomes to aid a multidisciplinary team in selecting suitable candidates for salvage surgery. Selected patients with HPSCC may benefit greatly from salvage surgery for locoregional recurrence/residual disease following previous radiotherapy. Adverse factors included salvage surgery <50 years old and rcT3–4. The only independent risk factor for postoperative complications and PCF was salvage surgery for local recurrence/residual disease. Patients with lymph node recurrence/residual alone had fewer complications and PCF. Since patients with local recurrence/residual disease had a high complication rate, efforts can be made to shorten the time of curative treatment initiation and include intervention in patients with low hemoglobin to reduce the risk of postoperative complications in this subgroup.

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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-22-1844/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1844/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1844/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). The study was approved by the Independent Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. NCC2021C-512) and informed consent was taken from all the patients.

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