

# Statistical Analysis of Post-operative Complications after Head and Neck Surgery

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**The risk factors for wound complications after surgery for head and neck cancers at Tokai University Hospital were evaluated. The medical records of 71 head and neck cancer patients who underwent surgery between January 2000 and December 2002 were reviewed. The overall incidence of postoperative complications was 39.4%. Uni- and multivariate analyses of the risk factors leading to complications demonstrated that free flap use was significant. Further, we analyzed the relationship between radiotherapy and postoperative complications.**

**There was no significant correlation between them. The prevention and treatment of postoperative complications were discussed.**

**Key words:** head and neck surgery, wound complications, risk factor, radiotherapy

## INTRODUCTION

Head and neck cancer and its treatment can have a profound impact on the most fundamental functions of life. After the treatment these patients are suffering from difficulties on eating, speech, mastication, and respiration. So, radiotherapy combined with chemotherapy has recently been increasingly applied to preserve organs, to achieve a better quality of life (QOL). Various postoperative complications, such as the necrosis of reconstructed flaps and skin fistula due to local circulatory failure, have been reported to occur more frequently after surgery following radiotherapy, compared to that without radiotherapy<sup>1)2)</sup>. Various factors other than radiotherapy, such as the influence of chemotherapy<sup>3)</sup>, operation time, and blood loss<sup>4)</sup>, may be involved in postoperative complications. Complications prolong hospitalization and reduce the patients' QOL. Prediction of the risk may help avoiding such complications. Several studies on risk factors of postoperative complications have been reported, but no consistent viewpoint has been reached, so far. In this study, we analyzed the risk factors in patients who underwent surgery at our hospital over the past 3 years, and investigated the relationship between radiotherapy and postoperative complications. Herein, we report the findings with a literature review.

## SUBJECTS

The subjects were 71 patients with head and neck cancers excluding tumors of the paranasal sinuses and thyroid who underwent surgery between January 2000 and December 2002. The primary lesion was epipharyngeal cancer in 2 patients, oro-pharyngeal cancer in 13, hypopharyngeal cancer in 16, laryngeal cancer

in 19, oral cancer in 18, and unknown in 3. There were 62 males and 9 females, with a mean age of 62.3 years. All patients underwent higher-grade surgeries than neck dissection (tumor excision accompanied by neck dissection, laryngectomy, and reconstruction).

## METHODS

### 1. Analysis of risk factors

All complications that developed after surgery were included (Table 1). As risk factors of complications, the following items were investigated and statistically analyzed.

### Univariate analysis

Disease stage, radiotherapy, chemotherapy, chemoradiotherapy, age, operation time, blood loss, and free flap were analyzed as risk factors. The cases were divided by the disease stage (I-III and IV), radiotherapy (with and without), chemotherapy (with and without), chemoradiotherapy (with and without), age (under 60 years and 60 years or older), operation time (shorter than 6 hours and 6 hours or longer), blood loss (less than 400 ml and 400 ml or more), and free flap (with and without), and the incidence of complications was calculated in each group. In addition, the relationship between the complications and risk factors was analyzed using the  $\chi^2$  test.

### Multivariate analysis

A significant association with the presence or absence of complications was detected in the operation time, blood loss, and presence or absence of a free flap on univariate analysis. These factors were adjusted using the age, disease stage, radiotherapy, and chemotherapy, and subjected to logistic regression

**Table 1** Complications

The incidence of wound complications in our department was 39.4%

Incidence of wound complications: 39.4% (28/71 cases)		
Complication	Number of cases	Incidence
Wound infection	10	14.1%
Fistula formation	7	9.9%
Hematoma	3	4.2%
Necrosis of free flap	3	4.2%
Skin necrosis	13	18.3%
Chylorrhea	1	1.4%
Serous retention	1	1.4%

analysis to investigate the relationship with the presence or absence of complications. But the problem of the multicollinearity was caused. The operation time and blood loss were strongly correlated (Spearman's correlation coefficient:  $r=0.831$ ,  $p<0.001$ ), and the presence or absence of a free flap was also related to the operation time and blood loss. So, each of these factors as independent variables adjusted with the age, disease stage, radiotherapy, and chemotherapy were analyzed to investigate the risk factors of post-operative complications in the logistic regression analysis.

## 2. Preoperative radiotherapy and postoperative complications

Preoperative radiotherapy was a risk factor in many reports. To closely investigate this point, the following 3 items were investigated:

(1) Preoperative radiotherapy and surgery-related factors (operation time, blood loss, and free flap) were investigated. The patients were divided into those with and without preoperative radiotherapy (17 and 54 patients, respectively). Each group was classified by the surgery-related factors, as in the univariate analysis, and the incidence of each factor was calculated.

(2) To investigate the relationship between preoperative radiotherapy and salvage surgery for complications, the presence or absence of radiotherapy and salvage surgery was investigated in 28 patients who developed complications. The frequency of salvage surgery was investigated and analyzed by the  $\chi^2$  test.

(3) To investigate the radiotherapeutic factors (pretreatment, dose, timing of surgery) and complications, 16 patients who underwent radiotherapy were classified based on pretreatment (radiotherapy alone and chemoradiotherapy), dose (lower than 70 Gy and 70 Gy or higher), and timing of surgery after radiotherapy (less than 1 year, 1 year or longer). The incidence of complications was investigated in each group, and the association was analyzed by the  $\chi^2$  test.

## RESULTS

The incidence of wound complications in our department was 39.4% (28/71) (Table 1). The complication was wound infection in 10 cases (14.1%), fistula formation in 7 (9.9%), hematoma in 3 (4.2%), necrosis of a free flap in 3 (4.2%), skin necrosis in 13 (18.3%), chylorrhea in 1 (1.4%), and serous retention in 1 (1.4%).

Complications occurred in 3 of 12 patients (25%) who underwent pretreatment with radiotherapy alone, and 3 of 5 patients (60%) who received pretreatment

with chemoradiotherapy.

### 1. Analysis of risk factors

Univariate analysis (Table 2)

Table 2 shows the  $\chi^2$  test results for each factor. Significant differences were detected in the operation time, blood loss, and free flap. The incidence of complications was significantly higher in cases with an operation time of 6 hours or longer ( $p=0.002$ ), blood loss of 400 ml or more ( $p=0.007$ ), and free flap ( $p=0.003$ ). Although the difference between the age groups was not significant ( $p=0.059$ ), the incidence tended to be higher in patients younger than 60 years of age. There were no significant differences between the groups divided based on the stage, radiotherapy, or chemoradiotherapy.

Multivariate analysis (Table 3)

The odds ratio of operation time was 1.005 ( $p<0.01$ ) (Table 3A), and that of blood loss was 1.001 ( $p<0.05$ ) (Table 3B), showing weak positive associations with complications. The presence of a free flap was significantly related to complications, at an odds ratio of 4.739 ( $p<0.01$ ) (Table 3C).

## 2. Preoperative radiotherapy and postoperative complications

(1) Preoperative radiotherapy and surgery-related factors (Table 4)

Operation time: The operation time was 6 hours or longer in 8 of the 17 patients with (47.1%) and 40 of the 54 patients without (74.1%) preoperative radiotherapy, showing that the operation time tended to prolong in the absence of preoperative radiotherapy.

Blood loss: The blood loss was 400 ml or more in 7 of the 17 patients with (41.2%) and 35 of the 54 patients without (64.8%) preoperative radiotherapy, showing a significantly higher incidence in the absence of preoperative radiotherapy.

Free flap: A free flap was used in 5 of the 17 patients with (29.4%) and 33 of the 54 patients without (61.1%) preoperative radiotherapy, showing that it was more frequently applied in the absence of preoperative radiotherapy.

Based on the above findings, less invasive surgical procedures were selected for the post-radiotherapy patients.

(2) Preoperative radiotherapy and salvage surgery (Table 5)

**Table 2** Univariate analysis

Significant differences were detected in the operation time, blood loss, and free flap. There were no significant differences between the groups divided based on the stage, radiotherapy, or chemoradiotherapy.

Factor		Number of cases	With complication	Incidence	$\chi^2$ test
Stage	I ~ III	29	11	37.9%	N.S.
	IV	42	17	40.5%	
Radiotherapy	Yes	17	6	35.3%	N.S.
	No	32	22	40.7%	
Chemotherapy	Yes	12	5	41.7%	N.S.
	No	59	23	39.0%	
Chemoradiotherapy	Yes	6	3	50.0%	N.S.
	No	65	25	38.5%	
Age	Under 60 years	26	14	53.8%	0.059
	60 years or older	45	14	31.1%	
Operation time	Shorter than 6 hours	23	3	13.0%	0.002
	6 hours or longer	48	25	52.1%	
Blood loss	Less than 400 ml	29	6	20.7%	0.007
	400 ml or more	42	22	52.4%	
Free flap	Yes	38	21	55.3%	0.003
	No	33	7	21.2%	

**Table 3** Multivariate analysis (logistic regression analysis)

The odds ratio of operation time was 1.005 ( $p < 0.01$ ) (Table 3A), and that of blood loss was 1.001 ( $p < 0.05$ ) (Table 3B), showing weak positive associations with complications. The presence of a free flap was significantly related to complications, at an odds ratio of 4.739 ( $p < 0.01$ ) (Table 3C).

Explanatory variable	Odds ratio	95% CI	P-value	
A	Age	0.953	0.890-1.021	0.173
	Disease stage	1.020	0.326-3.187	0.973
	Radiotherapy	1.632	0.398-6.694	0.496
	Chemotherapy	0.765	0.173-3.381	0.724
	Operation time	1.005	1.002-1.009	0.005
Explanatory variable	Odds ratio	95% CI	P-value	
B	Age	0.961	0.903-1.024	0.217
	Disease stage	1.037	0.336-3.198	0.950
	Radiotherapy	1.235	0.332-4.601	0.753
	Chemotherapy	1.027	0.241-4.384	0.971
	Blood loss	1.001	1.000-1.002	0.027
Explanatory variable	Odds ratio	95% CI	P-value	
C	Age	0.956	0.895-1.021	0.183
	Disease stage	1.338	0.428-4.186	0.617
	Radiotherapy	1.537	0.378-6.257	0.548
	Chemotherapy	0.848	0.195-3.689	0.826
	Free flap	4.739	1.497-15.002	0.008

**Table 4** Preoperative radiotherapy and surgery-related factors

Based on the above findings, less invasive surgical procedures were selected for the post-radiotherapy patients.

Factor		Number of cases	With radiotherapy (17 cases)	Without radiotherapy (54 cases)
Operation time	Shorter than 6 hours	23	9 (52.9%)	14 (25.9%)
	6 hours or longer	48	8 (47.1%)	40 (74.1%)
Blood loss	Less than 400 ml	29	10 (58.8%)	19 (35.2%)
	400 ml or more	42	7 (41.2%)	35 (64.8%)
Free flap	Yes	12	5 (29.4%)	33 (61.1%)
	No	59	12 (70.6%)	21 (38.9%)

**Table 5** Preoperative radiotherapy and salvage surgery

Salvage surgery was necessary for 4 of 6 post-radiotherapy patients (66.7%), and the rate was significantly higher than that in patients without preoperative radiotherapy (22.7%, 2/22) ( $p=0.007$ ).

	Number of cases	With surgery	Frequency	$\chi^2$ test
With radiotherapy	6	4	66.7%	p=0.007
Without radiotherapy	22	2	22.7%	

**Table 6** Radiotherapeutic factors and complications

There were no significant differences in the incidence of complications due to differences in the pretreatment, dose, or timing of surgery.

	Factor	Number of cases	With complication	Incidence
Pretreatment	Radiotherapy alone	11	3	27.3%
	With concomitant chemotherapy	5	3	60.0%
Dose	Lower than 70 Gy	6	2	33.3%
	70 Gy or higher	10	4	40.0%
Timing of surgery	Less than 1 year	11	4	36.4%
	1 year or longer	5	2	40.0%

Salvage surgery was necessary for 4 of 6 post-radiotherapy patients (66.7%), and the rate was significantly higher than that in patients without preoperative radiotherapy (22.7%, 2/22) ( $p=0.007$ ).

### (3) Radiotherapeutic factors and complications (Table 6)

There were no significant differences in the incidence of complications due to differences in the pretreatment, dose, or timing of surgery. Although the difference was not significant, the incidence was higher in patients with radiotherapy alone (27.3%) than in those with chemoradiotherapy (60.0%).

## DISCUSSION

The reported incidence of wound complications is 38–53%, and those after pretreatment with radiotherapy alone and in combination with chemotherapy were 37–74% and 46–100%, respectively<sup>5</sup>). Although the subjects and methods varied among reports, these findings indicated that the incidence of complications was higher when concomitant radiotherapy and chemotherapy was performed. In our study, the incidence of wound complications was 39% in all patients and 60% in those who underwent preoperative chemoradiotherapy, and these were similar to those in previous reports. However, the incidence was slightly lower (27%) in those who underwent preoperative treatment with radiotherapy alone, for which the cause is discussed below.

As risk factors of head and neck surgery for wound complications (including fistula), preoperative radiotherapy<sup>12)</sup>, preoperative chemoradiotherapy<sup>6)</sup>, preoperative chemotherapy<sup>3)</sup>, age<sup>7)</sup>, stage<sup>8)</sup>, internal medical complications<sup>9)</sup>, preoperative weight loss<sup>10)</sup>, positive stump<sup>10)</sup>, and a history of habitual alcohol drinking<sup>11)</sup> have been reported. The univariate analysis suggested that the operation time, free flap, and blood loss were

most strongly associated with wound complications. On multivariate analysis, free flap showed the strongest association, and the operation time and blood loss were also associated, although the correlations were weak, showing that surgery-related factors (operation time, blood loss, and free flap) were significantly correlated with wound complications. Griod *et al.*<sup>4)</sup> reported preoperative radiotherapy, flap reconstruction, blood transfusion, and operation time as factors related to all complications, similarly to our findings. Surgery-related factors cannot be simply described as risk factors because they involve various factors, such as the severity of cases, surgical procedure, and skill of operators. However, less complications occur when the operation time is shorter, blood loss is reduced when the same surgical procedure is employed, and various devices and countermeasures are necessary to perform such a surgery.

A significant difference due to radiotherapy was noted in many reports, but not in this study. Regarding this point, we investigated the relationship between preoperative radiotherapy and postoperative complications. It is generally considered that radiotherapy promotes vascular endothelial cell growth and causes fibrosis and thickening of the tunica intima, which narrows the vascular lumen and reduces blood flow, leading to fibrosis of the surrounding connective tissue<sup>12)</sup>. When surgery is performed under such conditions, circulatory disorder of the skin occurs, and causes skin necrosis and fistula formation.

First, we investigated the surgery-related factors (operation time, blood loss, and free flap) and the presence or absence of preoperative radiotherapy, and found that less invasive surgery was performed (the operation time was shorter than 6 hours, the blood loss was less than 400 ml, and no free flap reconstruction was employed) in cases with than in those without preoperative radiotherapy, which may have

been due to the fact that only lymph node dissection was performed in many cases (8 of 16 cases) in which the primary lesion was controlled by radiotherapy. Such a bias and the small number of cases may have been the reasons for the absence of a significant correlation between the postoperative complications and radiotherapy. In 8 patients treated with radiotherapy followed by neck dissection, the skin was incised (S or J-shape), avoiding producing a 3-point sutured site, and no complication occurred in 6. Intentionally performed preventive measures in post-radiotherapy cases may have been one reason for the low incidence of complications.

Once complications occur, some cases are resolved by conservative treatment, while others require salvage surgery. Preoperative radiotherapy and the necessity of salvage surgery were investigated in 28 patients who developed complications. The rate of requiring salvage surgery was higher in post-radiotherapy patients, and this was not contradictory to the fact known by experience that complications after radiotherapy are resistant to conservative treatment.

We also investigated the relationship between the radiotherapeutic factors and complications. Taler *et al.*<sup>13)</sup> investigated the relationship, and found that the total dose, single dose, and duration of treatment were correlated with wound complications. They also stated that the incidence of complications increased as the period between radiotherapy and surgery prolonged, although the difference was not significant. Terayama *et al.*<sup>14)</sup> also reported that the incidence of fistula was high in patients in whom surgery was performed more than 6 months after radiotherapy, being affected by delayed local disorder. Marcial *et al.*<sup>15)</sup> reported that surgery performed 4-6 weeks after 50 Gy radiotherapy did not affect postoperative complications. Various facilities evaluated preoperative radiotherapy at 40 Gy, and treatment is switched to surgery when the effect is insufficient, in which radiotherapy may not affect postoperative complications based on the above reports. However, the dose of radiotherapy for the neck and head region is 60-70 Gy or higher in many cases. Considering that the total dose was associated with the incidence of complications, and the incidence increased as the time after radiotherapy passed, the surgical risk may be high in cases that recur after radiotherapy. Neither the dose nor timing of surgery after radiotherapy was correlated with the incidence of complications, but the number of cases was only 16, and so reinvestigation in an increased number of cases may be necessary. The incidence of complications was higher in cases with concomitant chemotherapy, although the difference was not significant, suggesting that chemotherapy may also serve as a risk factor of complications.

The following methods to prevent complications have been reported<sup>11,14,16)</sup>: 1) Skin incision avoiding 3-point suture, 2) minimizing the use of electric cautery, 3) application and systemic administration of

PGE1 preparation, and 4) administration of Factor XIII (Fibrogammin). This study suggested the necessity of shortening the operation time and minimizing blood loss. Since post-radiotherapy cases are resistant to conservative treatment, as described above, when a complication occurs, particularly when infection and necrosis disseminate to a deep region or large blood vessels, it is better to perform reconstruction with a pedicle or free flap with abundant blood flow at the earliest possible time.

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