

Post-operative pharyngocutaneous fistula after laryngectomy

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TITLE; Post-Operative Pharyngocutaneous Fistulae after Salvage Laryngectomy

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ABSTRACT

Objectives: Although organ-preserving radiotherapy or chemoradiotherapy have offered good locoregional control, many patients still experience recurrent disease requiring salvage laryngectomy. The pharyngocutaneous fistulae (PCF) is a common and troublesome complication in the early postoperative period after laryngectomy. Here we evaluated the cause of PCF after laryngectomy, with special emphasis on radiotherapy and/or chemotherapy. **Study Design:** Retrospective chart review. **Methods:** A total of 66 consecutive patients undergoing salvage laryngectomy for squamous cell carcinoma of the larynx at Kanazawa University Hospital from 1990 to 2005 were reviewed. 40 of 66 had received primary total laryngectomy (PL). Eleven patients underwent radiotherapy alone (SL-RT) and 15 patients underwent concurrent chemoradiotherapy (SL-CRT) followed by salvage laryngectomy. **Results:** Overall, 20 of 66 patients (30.3%) developed PCF after laryngectomy. Fisher's exact test showed a statistically significant increase of PCF formation in the SL-CRT compared with PL (n=15, 60.0% vs. n=40, 17.5%, $p=0.0057$). There were non-significant increases of PCF formation both in SL-CRT compared with SL-RT (n=15, 60.0% vs. n=11, 36.4%,

$p=0.4495$), and also in SL-RT compared with PL (n=11, 36.4% vs. n=40, 17.5%, $p=0.2220$). Mann-Whitney U-test showed that the duration of PCF was significantly longer for SL-CRT PCF (100.9±89.3 days) compared with those for PL (39.0±55.3 days) ($p=0.0324$) or SL-RT (28.0±16.2 days) ($p=0.0406$). However, we did not find a significant difference in the duration of PCF with respect to PL (39.0±55.3 days) and SL-RT (28.0±16.2 days) ($p=0.2850$). **Conclusions:** Although radiotherapy or chemotherapy has only limited impact on PCF formation, concurrent chemoradiotherapy significantly pronounces the PCF formation. Addition of chemotherapy to irradiation delays the PCF closure.

Key Words: salvage laryngectomy, laryngeal carcinoma, pharyngocutaneous fistulae, radiotherapy, chemotherapy.

INTRODUCTION

Organ-preserving radiotherapy or chemoradiotherapy for laryngeal carcinoma produces good locoregional control and comparable survival outcomes to primary laryngectomy and post-operative radiotherapy with the benefit of preserving voice and swallowing in a significant number of patients (1, 2, 3). Despite these improvements, many patients still experience recurrent disease requiring salvage surgery, most frequently as a total laryngectomy. It has been reported that occurrence of post-operative wound complication is affected by the treatment prior to salvage surgery, mainly irradiation (4, 5, 6). Moreover, chemotherapy has also been reported to increase post-operative wound complications in patients with advanced-stage resectable head and neck carcinoma (7, 8). Looking at recent reports concerning chemoradiotherapy, the intensity of (chemo-) radiotherapy regimens has been increasing to improve disease control rate, which may result in more complications after salvage surgery.

Although the pharyngocutaneous fistula (PCF) is a common and troublesome complication in the early post-operative period after laryngectomy, no conclusive evidence has been gathered about the relative importance of predicted factors including

previous radiotherapy and chemotherapy. Several reports represent evidences incriminating some of these factors, while others do not arrive at similar conclusions (4, 5, 6, 11, 13, 14, 19).

Here we evaluated the post-operative PCF after laryngectomy at a single institution, with special emphasis on radiotherapy and/or chemotherapy that could contribute to post-operative fistulae.

PATIENTS AND METHODS

A total of 66 consecutive patients undergoing total or partial laryngectomy was identified from the existing database of 204 patients treated for squamous cell carcinoma (SCC) of the larynx at Kanazawa University Hospital between 1990 and 2005. Of the total sixty-six patients, total laryngectomy was performed in 63 patients. 40 of 66 had received primary total laryngectomy (PL) with 21 having surgery alone and 19 receiving surgery followed by post-operative RT. 26 of 66 underwent radiotherapy alone (SL-RT) or concurrent chemoradiotherapy (SL-CRT) followed by total or partial laryngectomy. Basically, patients with stage I disease were treated with conventional radiotherapy (2 Gy x 5/week, total 60 Gy). Those with stage II were treated with hyperfractionated radiotherapy (1.3 Gy/fraction, twice daily, 6h apart, 5 days/week to 72.8 Gy/56 fractions/5.6 weeks), or conventional radiotherapy (2 Gy x 5/week, total 66 Gy) concurrently with weekly carboplatin (with a target area under the concentration versus time curve of 1.5 mg/min/ml using the Calvert formula). PL was performed for locally advanced laryngeal SCC from 1990 to 1996. Since 1997, patients with advanced laryngeal cancer were basically treated with high-dose cisplatin-based

concurrent chemoradiotherapy. Those who were estimated to be intolerable to this treatment underwent primary total laryngectomy. Salvage laryngectomy (SL) was basically performed for persistent or locally recurrent disease within the larynx. SL was also indicated when the larynx was non-functional due to chondronecrosis or chronic aspiration. Initial therapy in the salvage patients included radiotherapy alone (SL-RT) (including pre-operative radiotherapy) in 11, and concurrent chemoradiotherapy (SL-CRT) in 15. Table 1 and Table 2 summarize patient and tumor variables for each laryngectomy group, respectively. Here we focused on the PCF formation and duration, thus, outcomes of the each treatment strategy were not analyzed in this study.

In this study, the following parameters other than radiotherapy and chemotherapy for PCF formation were analyzed: age, T classification, diabetes mellitus, dermatitis, mucositis, radiation dose, duration after radiotherapy, primary tumor location, albumin level, hemoglobin level, and smoking. Initial clinical staging was done according to UICC TNM classification 1987 at time of first visit. Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Sixty patients (90.9%) were men and 6 (9.1%) were women. Their mean age was 66.8 years

(range, 45-95 years). Diabetes mellitus was present in 18 (27.3%) patients. Fifty-seven cases (86.4%) were smokers. SCC of the supraglottic and glottic larynx was 32 cases (48.5%), respectively. Overall, 72.7% of patients presented with cT3 or cT4 tumors, and 39.4% were classified as cN-positive before initial therapy. In 44 (66.7%) patients, the laryngectomy was combined with neck dissection.

In all cases of total or partial laryngectomy, we performed a primary direct suture of the pharyngeal mucosa. Spontaneous closure of PCF was noted in 11 patients, whereas a surgical closure was necessary in nine patients. If the fistula did not close spontaneously within a month of laryngectomy, a surgical closure was usually planned. Two patients with longstanding PCF received reconstruction surgery with pectoralis myocutaneous flap, and 7 patients with a hinge flap.

To compare the statistical relationship between PCF formation and study criteria, we used Fisher's exact test or Chi-square test. We used Mann-Whitney U-test to compare the statistical relationship between PCF duration and study criteria. Statistical software used was SPSS for Windows (version 11.01; SPSS Inc., Chicago, IL). Only *p* value customary below the 0.05 was considered indicative of a significant effect.

RESULTS

Overall, 20 of 66 patients (30.3%) developed a post-operative PCF after salvage laryngectomy. On average, PCF occurred on post-operative day 8 (range, 4 to 22 days). Radiotherapy, prior to laryngectomy in a period ranging from 7 days to 6 years, had been performed in 26 out of 66 patients with a dosage varying from 20 to 77 Gy. Table 3 summarizes the relationship between the PCF formation and investigated parameters. Fisher's exact test showed significant difference in the frequency of PCF formation for SL compared with PL (n=26, 50.0% vs. n=40, 17.5%, $p=0.0068$). There also was a statistically significant increase in PCF formation in the SL-CRT group compared with PL (n=15, 60.0% vs. n=40, 17.5%, $p=0.0057$). There were tendencies that PCF formation were more frequent both in SL-CRT compared with SL-RT, and also in SL-RT compared with PL. However, there was no significant difference on both statistical analyses using Fisher's exact test. These results suggest that radiotherapy or chemotherapy has only limited impact on PCF formation, respectively. Thus, only chemoradiation significantly pronounced the PCF formation.

The median duration of PCF was 37 days, but with a wide range from 10 days to

240 days. The relationship between the PCF duration and investigated parameters are summarized in Table 4. The duration of PCF was significantly longer for SL (76.6 ± 80.2 days) compared with PL (39.0 ± 55.3 days) ($p=0.0436$). In addition, the duration of PCF was significantly longer for SL-CRT patients (100.9 ± 89.3 days) compared with those for PL (39.0 ± 55.3 days) ($p=0.0324$), and also for SL-CRT patients (100.9 ± 89.3 days) compared with SL-RT patients (28.0 ± 16.2 days) ($p=0.0406$). However, we did not find a significant difference in the duration of PCF between PL (39.0 ± 55.3 days) and SL-RT (28.0 ± 16.2 days) ($p=0.2850$). These results suggest that only the chemotherapy, when used concurrently with irradiation, delayed the PCF closure.

Finally, there were no statistically significant differences in PCF formation ratio and duration with regard to age, T classification, diabetes mellitus, dermatitis, mucositis, radiation dose, duration after radiotherapy, primary tumor location, albumin level, hemoglobin level, and smoking.

DISCUSSION

Some retrospective studies have reported an increased incidence of wound and systemic complications for salvage laryngectomy after RT or CRT (9, 10, 11, 12). However, the morbidity, including PCF, for SL is not well clarified, because a prospective randomized comparison with PL patients will be needed to clarify the important predictive factors to develop the post-operative complications. However, any randomized comparison of those groups is unlikely to happen, because CRT is currently accepted as a standard therapy for locally advanced laryngeal carcinoma. An example is the heterogeneity that might be introduced due to the lack of comparative details of chemotherapy considering the differences in the site and stage distribution.

There are conflicting reports on the relationship between previous radiotherapy and PCF formation (13). Sarkar et al. reported that prior irradiation significantly affected the incidence of PCF, 58% for irradiated patients and 21% for non-irradiated patients, respectively (12). A meta-analysis of post-laryngectomy PCF showed that pre-operative radiotherapy increased the risk of PCF formation, and the severity and duration of fistula were greater than those without pre-operative radiotherapy (14).

Johansen et al. reported an overall PCF rate of 32% in patients treated with primary radiation with an increase of fistula rate with RT dose (9). These data support that RT is an important predictor of PCF formation. High-dose radiation is supposed to promote a cascade of events in which the fibroblast population becomes dysfunctional and depleted resulting in hypovascularity and aggravation of atherosclerosis through the induction of myointimal fibrosis, followed by diminished healing capacity of irradiated tissue (15, 16, 17). In contrast, some other reports did not link the PCF formation with previous radiotherapy (13, 18, 19). In the present study, the incidence of PCF for SL-RT was 36.4%, which is nearly twice as much as that of PL, although statistically significant difference was not achieved.

More recently, patients with advanced laryngeal carcinoma have been treated with organ-preserving concurrent chemoradiotherapy (3). Although chemotherapy alone has been reported to increase wound complications in patients with advanced-stage resectable head and neck carcinoma (7, 8), wound complications were much increased when combined with radiotherapy (20, 21, 22). Weber et al. reported that the incidence of post-laryngectomy PCF was higher among patients who underwent

chemoradiotherapy (30%) compared with radiotherapy alone (15%) (23). In the current study, we report that the incidence and the duration of PCF was significantly greater in patients undergoing SL-CRT compared with PL. Furthermore, the duration of PCF was significantly greater in patients undergoing SL-CRT compared with SL-RT. These results suggest that the concurrent addition of chemotherapy enhances the damaging effects of RT on normal tissue, which results in PCF formation and continuous PCF after salvage laryngectomy. We conclude that both RT and chemotherapy produce adverse effects on PCF formation and healing with a synergistic or additive interaction when used together. Thus, chemotherapeutic agents combined with irradiation not only kill more tumor cells but also interferes with tissue repair (22). In addition to the direct damage to the pharyngeal tissue, a stricture of the cervical esophagus as a result of fibrosis due to concurrent chemoradiotherapy might be a cause of PCF. The stricture may cause an increased pharyngeal pressure, which results in PCF after starting oral intake.

In our study, the PCF occurrence ratio when laryngectomy was performed within 1 year after (chemo-) radiotherapy was more than twice as much as that of more than 1

year after (chemo-) radiotherapy, although we could not find a significant relationship between the PCF occurrence ratio and the duration after (chemo-) radiotherapy. Sassler et al. also found that major wound complications increased in salvage procedure performed less than 52 weeks from the completion of chemotherapy and radiation therapy (77%) vs. those performed after more than 52 weeks (23%) ($p = 0.047$) (20). This result might be, at least in part, because the patients usually experience fatigue, anorexia, and weight loss during the first year after chemoradiotherapy. Patients after chemoradiotherapy might be metabolically compromised and can be at greater risk of wound complications after salvage surgery. In contrast, for radiotherapy alone, Ganly et al. reported that wound complications including PCF after salvage surgery increases as the time interval from radiotherapy to salvage surgery increases, which is due to the radiotherapy-induced late injury increasing fibrosis and poor blood supply to the irradiated tissue (24). Thus, chemotherapy should have damaging effect on wound healing at relatively earlier period compared to radiotherapy. Further analysis of a larger number of patients, and a prospective study design if possible should be needed to elucidate underlying mechanisms for this observation.

Concerning the treatment, some authors refrain from waiting for spontaneous closure because it takes a long time, prolonging patient's stay in the hospital and resulting in swallowing difficulty due to fibrosis and stenosis (18). We agree that it is not wise to wait any longer than a month to plan surgery to close the PCF. In our study, there were several cases with longstanding PCF up to 240 days until the closure of PCF. We suppose that it is because of the frequent use of hinge flap. Well-vascularized musculocutaneous pedicled flaps are recommended for the management of PCF in previously chemoradiated patients.

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