Scientific Article

Risk factors for severe dysphagia after concurrent chemoradiotherapy for head and neck cancers

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Running head: Risk factor for dysphagia in combined therapy

Abstract

Purpose: To investigate the risk factors for dysphagia induced by chemoradiotherapy for head and neck cancers.

Materials and Methods: Forty-seven patients with head and neck cancers who underwent definitive chemoradiotherapy from December 1998 to March 2006 were reviewed retrospectively. Median age was 63 years (range, 16−81). The locations of the primary lesion were as follows: larynx in 18 patients, oropharynx in 11, nasopharynx in 7, hypopharynx in 7, and others in 4. Clinical stages were as follows: Stage II in 20 and III−IV in 27. Almost all patients underwent platinum-based concomitant chemoradiotherapy. The median cumulative dose of cisplatin was 100 mg/m^2 (range, 80−300) and median radiation dose was 70 Gy (range, 50−70).

Results: Severe dysphagia (grade 3−4) was observed in 22 patients (47%) as an acute toxic event. One patient required tube feeding even at 12-month follow-up. On univariate analysis, clinical stage (III−IV) (p = .017), primary site (oro-hypopharynx) (p = .041) and radiation portal size (>11 cm) (p < .001) were found to be associated with severe dysphagia. On multivariate analysis, only radiation portal size was found to have a significant relationship with severe dysphagia (p = .048).

Conclusion: Larger radiation portal field was associated with severe dysphagia induced by chemoradiotherapy.

Mini-abstract

Radiation portal size had a significant relationship with severe dysphagia in chemoradiotherapy for head and neck cancers. Age, smoking, and dose of cisplatin were not so related.

Keywords: toxicity, combined modality therapy, head and neck neoplasm, dysphagia, radiotherapy

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Conflict of Interest Notification

Any actual or potential conflicts of interest do not exist in this article.

Introduction

Prospective randomized clinical trials showed that chemoradiotherapy is superior to radiotherapy alone for patients with advanced nasopharyngeal carcinoma.(1) This combined therapy is now widely used in treatment of patients with head and neck cancers. A meta-analysis conducted by Pignon *et al.*(2) showed a significant benefit of concurrent chemoradiotherapy, which corresponded to an absolute 5-year overall survival benefit of 8% compared with radiotherapy alone in head and neck cancers. Indication of conventional radiation-alone therapy is confined to T1 and favorable T2, N0−1 tumors. Altered fractionation alone may be indicated for unfavorable T2, N0−1 tumors,(3) but more advanced and operative head and neck cancers are usually treated by surgery followed by radiotherapy or chemoradiotherapy. Patients in whom surgery is contraindicated are treated by chemoradiotherapy. This therapy is sometimes used for operative patients who wish to preserve their organs.

Concomitant addition of chemotherapy to radiotherapy not only improves the outcome but also increases toxicity of the treatment. Various toxic events, such as pain, dysgeusia, and dysphagia, are intensified. Rosenthal *et al.* reported that 40–70% of patients undergoing concomitant chemoradiotherapy for head and neck cancers experienced severe mucositis and 50–80% required feeding tube placement during the course of therapy.(4) Severe dysphagia arising during the course of therapy sometimes reduces the patients' quality of life and worsens their physical condition.

A retrospective review of patients with head and neck cancers who underwent definitive chemoradiotherapy in our facility was performed along with an investigation of the risk factors for dysphagia induced by chemoradiotherapy.

Materials and Methods

From December 1998 to March 2006, 47 patients with head and neck cancers underwent definitive chemoradiotherapy in our facility. The patients' characteristics are shown in Table 1. In our facility, definitive chemoradiotherapy had been usually eligible for the patients whose performance status was good, who had no distant metastasis, and who were not so old (75 years or less, basically).

All except two patients underwent platinum-based concomitant chemoradiotherapy; the two exceptions were treated by radiotherapy and docetaxel-alone chemotherapy, respectively. Various chemotherapy regimens were adopted in the treatment (Table 2). Since we had sought the optimal regimen of chemotherapy for years and had changed the way of the therapy, there had been heterogeneity as to chemotherapeutic agents in the present study. The cumulative dose of cis-diamminedichloroplatinum (cisplatin) ranged from 80 mg/m^2 to 300 mg/m^2 (median, 100 mg/m^2). 5-Fluorouracil (5-FU) was administered to 43 patients. The cumulative dose of 5-FU ranged from 2000 mg/m^2 to 12000 mg/m^2 (median, 4000 mg/m^2).

In radiation therapy, casts for immobilization and a photon beam of 4 MV were used in

all patients. The fraction size was 1.5−2.0 Gy. The total dose of radiation therapy ranged from 50–70 Gy, and median dose was 70 Gy. Since various treatment protocols with different fraction sizes and total doses had been used in our facility, we also calculated a biologic effective dose (BED) in a linearquadratic model(5). BED was defined as $nd(1+d/\alpha/\beta)$,with units of Gy, where n is the fractionation number, d is the daily dose, and α/β was assumed to be 10 for tumors. The BED ranged from 60 to 84 Gy (median, 84 Gy). Forty-one patients were treated by a once-daily fractionation schedule and 6 patients were treated by an accelerated hyperfractionation schedule. In this schedule, patients initially received 40 Gy in once-daily fractionation with a fraction size of 2 Gy. After that, radiation fields were shrinked down to avoid the spinal cord and 30 Gy was added in twice-daily fractionation with a fraction size of 1.5 Gy. Lateral opposing portals alone or lateral opposing and anterior portals (3-field approach) were used according to the individual tumor spread. Stage II disease was usually treated by locally confined portals. The whole neck was included in treatment of stage III−IV disease initially. Spinal cord was usually avoided by cone-down field reduction after the administration of 40 Gy. CT images for radiation dose distribution were attained in 14 patients. None of the patients underwent intensity-modulated radiation therapy. Overall treatment time ranged from 31 to 109 days (median, 50 days).

Toxicity was assessed using the Common Terminology Criteria for Adverse Events version 3.0 (National Cancer Institute, Rockville, MD, USA). In these criteria, grade 3

dysphagia is defined as symptomatic and severely altered eating and/or swallowing, which requires intravenous fluids, tube, feeding, or total parenteral nutrition for more than 24 hours. To evaluate radiation portal size, the length of the side of the equivalent square in each lateral opposing field was calculated; the median length was 11.3 cm (5.5−16.5 cm).

Statistical analyses were performed using Fisher's exact test for univariate analysis and the logistic regression model was used for multivariate analysis. Statistical significance for all analyses was set at $p < .05$. Survival rates were calculated from the start of treatment. Survival curves were calculated using the Kaplan-Meier method. These analyses were performed using the statistical software JMP version 5.1.1 (SAS Institute Inc., Cary, NC).

Results

Median follow-up time was 21 months (range, 3−85 months). Severe (grade ≥3) dysphagia was observed in 22 patients (47%) as an acute toxic event. Severe (grade ≥3) dermatitis occurred in 18 patients, and severe (grade ≥3) mucositis was observed in 18 patients.

On univariate analysis, the relationships between severe dysphagia and the following parameters were examined: age (<70 years old *vs*. ≥70 years old), performance status according to the Eastern Cooperative Oncology Group (0 *vs*. ≥1), pretreatment body

weight loss (<10% *vs*. ≥10%), smoking (<20 cigarettes per day *vs*. ≥20 cigarettes per day), primary site (oro-hypopharynx *vs*. others), clinical stage (II *vs*. III−IV), radiation portal size (length of the side of the equivalent square <11 cm *vs*. ≥11 cm), cumulative dose of cisplatin (<100 mg/m^2 *vs*. ≥100 mg/m^2), cumulative dose of 5-FU (<4000 mg/m^2 *vs*. ≥4000 mg/m^2), and radiation schedule (conventional fractionation *vs*. hyperfractionation). The results of univariate analysis are shown in Table 3. Primary site, clinical stage and radiation portal size were found to significantly influence the rate of severe dysphagia. Four parameters were chosen for multivariate analysis: primary site, clinical stage, radiation portal size, and cumulative dose of cisplatin. The results of multivariate analysis are shown in Table 4. In this analysis, only radiation portal size was found to have a significant effect on the outcome (p = .048).

Among the 22 patients who developed severe dysphagia, opioid analgesics were administered to 13 patients, and antibiotics were administered to 14 patients. As a measure for management of severe dysphagia, total parenteral nutrition was usually adopted in our facility. Percutaneous endoscopic gastrostomy tube and nasogastric tube were not usually placed. Seventeen patients required total parenteral nutrition. The median duration of severe dysphagia was 53 days (range, 21−142 days). Those patients also required prolonged hospitalization after termination of the treatment (15–117 days; median, 42). Ten patients presented some sort of dysphagia at the last follow up. One patient had been dependent on tube feeding for more than a year.

Discussion

Cisplatin-based chemoradiotherapy for locally advanced head and neck cancers is now recognized as a standard therapy for patients with inoperable disease because of its larger survival benefit than radiation therapy alone.(3) Sometimes, this non-surgical therapy can be adopted in operable patients to achieve better cosmetic outcome and organ preservation. There is still room for improvement of this therapy. Efforts to determine the optimal dosage of cytotoxic agents and optimal timing of chemotherapy and radiotherapy are still underway.(6) Despite using a non-surgical modality, this can be a rather toxic form of therapy.(7) Dysphagia caused by the therapy sometimes becomes severe and may last for a long time. This complication is thought to be one of the largest obstacles in conducting concomitant chemoradiotherapy for head and neck cancers. Few previous studies have addressed this issue,(8) but some reports mentioned that more than half of the cases required enteral feeding temporarily,(9) and about 20% required long-term enteral feeding.(4) Rademaker *et al.* reported that it took about one year for a patient whose eating ability was impaired by the therapy to recover to close to the normal level.(10) Nguyen *et al.* reported that aspiration was frequently observed during the course of therapy, sometimes leading to fatal aspiration pneumonia.(11, 12)

As mentioned above, it is becoming clear that concomitant chemoradiotherapy for head and neck cancers can be quite severe for patients. Therefore, care should be taken

in judging whether a patient really requires concomitant chemotherapy.(13) Administration of cisplatin at a dose of 100 mg/m^2 is the standard therapy, but only two thirds of patients can receive all cycles of treatment with such a regimen.(14) Improving compliance is one of the most pressing problems remaining to be resolved. Logeman *et al.* reported that alteration of chemotherapy protocols had minimal effect on swallowing function,(15) which may mean that arrangement of usual cytotoxic agents would not reduce the severity of this complication. Recently, use of biologically targeted therapy has been shown to improve the outcome without increasing the common toxic effects.(16) These newly emerging approaches represent promising means of improving treatment outcome in these patients.

Few studies have addressed risk factors for severe dysphagia in chemoradiotherapy for head and neck cancers. Manger *et al.* argued that clinical stage, general condition, and history of smoking could be risk factors for severe dysphagia.(9) In the present study, smoking was not found to be significant. This was assumed to be due to the strict prohibition against smoking by patients during the course of therapy in the present study. Regarding general condition, this type of therapy is usually confined to patients with good performance status, and this may cause selection bias. Machtay *et al.* reported that older age was a strong risk factor for severe late toxicity.(17) In the present study, which was aimed at early toxicity, older age was not identified as an independent risk factor. Almost all patients aged 70 or over had excellent performance status in the present study.

The adaptation of this therapy is rather selective in our facility, which may result in suppression of the risk of dysphagia in aged patients. Radiation portal size was found to be a risk factor for severe dysphagia in chemoradiotherapy for head and neck cancers in the present study. Clinical stage was also associated with severe dysphagia on univariate analysis, which was similar to the previous report by Manger, but not in multivariate analysis. This could be explained by a requirement of larger radiation portals for higher clinical stage, so there should be confounding factors between them. The results presented here suggest that radiotherapy plays a major role in the occurrence of dysphagia. It is supposed that broader mucous membranes and more anatomical parts important for swallowing would be affected to a greater degree by larger radiation portals, and these must be amplified by chemotherapy. Some reports suggested that primary site of disease could be important risk factors.(15, 17) We also identified that primary site was associated with severe dysphagia on univariate analysis, but not in multivariate analysis. These observations may also indicate the importance of radiotherapy in the occurrence of dysphagia, as higher radiation dose is usually administered to the primary site of disease.

Accordingly, improving radiotherapy might lead to relief of this complication. Intensity-modulated radiotherapy (IMRT) has been widely used for head and neck cancers.(18) Using this advanced technique, complications can be reduced without compromising therapeutic outcome. Good local control has been achieved in a number

of leading institutions. Xerostomia, which arises as an late toxic event, is less severe than with conventional radiotherapy.(18, 19) Chemo-IMRT may cause dysphagia to some extent, but it may be less severe than chemotherapy and altered fractionation schedule,(20) and requires less long-term tube feeding.(21) The further development of newly emerging approaches such as IMRT may result in a decrease in the severity of dysphagia.

Dysphagia is a complication for which clinicians should be prepared. It is important to take appropriate measures for this complication. Rosenthal *et al.* reported the importance of rehabilitation as a means of coping with dysphagia.(4) It would be useful to identify patients at high risk of severe dysphagia in advance so that clinicians could pay attention to this complication from the early stages of therapy.

Conclusions

Larger radiation portal size could be a risk factor for severe dysphagia after chemoradiotherapy for head and neck cancers. Patients treated with broad radiation portals should be managed carefully during the course of therapy.

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Table 1. Patient characteristics

Characteristics		Number of patients
Gender	Male	41
	Female	6
Age		16−81 (median: 63)
Performance status	0	44
	≥1	3
Stage	II	20
	III	6
	IV	21
Primary site	Larynx	18
	Oropharynx	11
	Nasopharynx	7
	Hypopharynx	7
	Nasal cavity	2
	Oral cavity	2
Histology	Squamous cell carcinoma	47
Cisplatin dosage*	80	5
	100	26
	300	11
	Docetaxel or nedaplatin	5
Radiation schedule	Conventional fractionation	41
	Hyperfractionation	6

* Cumulative doses are shown (mg/m^2).

Table 2. Chemotherapy regimens

Chemotherapy agents	Number of patients
Cisplatin (10 mg/m^2 on days 36−40, 43−47) + 5-FU (400 mg/m^2 on days 36−40, 43−47)	26
Cisplatin (50 mg/m^2 on days 6−7, 41−42, 71−72) + 5-FU (800 mg/m^2 on days 1−5, 36−40, 43−47)	9
Cisplatin (80 mg/m^2 on day 29) + 5-FU (400 mg/m^2 on days 29−33)	5
Others	7

Table 3. Univariate analysis to identify risk factors for severe dysphagia

Variable	Rate of patients with severe dysphagia	*P*-value
Age		
<70 years	43% (13/30)	
≥70 years	53% (9/17)	.56
Performance status		
0	48% (21/44)	
≥1	33% (1/3)	1.00
Pretreatment weight loss		
<10%	44% (16/36)	
≥10%	55% (6/11)	.73
Smoking		
<20 CPD	48% (12/25)	
≥20 CPD	45% (10/22)	1.00
Primary site		
Oro-hypopharynx	67% (12/18)	
Others	34% (10/29)	.041
Clinical stage		
II	25% (5/20)	
III−IV	63% (17/27)	.017
Radiation portal size*		
<11 cm	18% (4/22)	
≥11 cm	72% (18/25)	< .001
Cumulative dose of cisplatin		
<100 mg/m^2	39% (14/36)	
≥100 mg/m^2	73% (8/11)	.083
Cumulative dose of 5-FU		
<4000 mg/m^2	44% (4/9)	
≥4000 mg/m^2	47% (18/38)	1.00
Radiation schedule		
Conventional fractionation	47% (20/43)	
Hyperfractionation	50% (2/4)	1.00

Abbreviations: CPD, cigarettes per day.

* Length of the side of the equivalent square in each lateral opposing field was used as a surrogate for radiation portal size.

Table 4. Multivariate analysis to identify risk factors for severe dysphagia

Variable	Odds ratio (95% confidence interval)	*P*-value
Clinical stage		
II		
III–IV	1.41 (.23 to 7.48)	.69
Primary site		
Oro-hypopharynx	1.84 (.32 to 10.78)	.49
Others		
Radiation portal size*		
<11 cm		
≥11 cm	6.03 (1.08 to 42.06)	.048
Cumulative dose of cisplatin		
<100 mg/m^2		
≥100 mg/m^2	1.99 (0.29 to 15.80)	.49

* Length of the side of the equivalent square in each lateral opposing field was used as a surrogate for radiation portal size.