Scientific article

Validation of the Total Dysphagia Risk Score (TDRS) as a predictive measure for acute swallowing dysfunction induced by chemoradiotherapy for head and neck cancers

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Running head: Prediction of acute swallowing dysfunction

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Abstract

Background and Purpose: Methods for predicting acute swallowing dysfunction in patients with head and neck cancers undergoing definitive chemoradiotherapy have not been established. We investigated the validity of the Total Dysphagia Risk Score (TDRS) as a predictive measure for this morbidity.

Materials and Methods: Forty-seven patients with head and neck cancers who underwent definitive chemoradiotherapy between December 1998 and March 2006 were reviewed retrospectively. Median age was 63 years (range, 16 – 81). Almost all patients underwent platinum-based concomitant chemoradiotherapy. Factors of the TDRS were as follows: T-classification, neck irradiation, weight loss, primary tumour site and treatment modality. Patients were classified into three risk groups according to the TDRS.

Results: Swallowing dysfunction was observed in 27 patients (57%) as RTOG grade 2 or higher acute morbidity. This classification was significantly associated with grade 2 or higher acute swallowing function ($P < .001$). In ROC (receiver operator characteristic) analysis, the cut-off value of TDRS was set at 18 (sensitivity = .81; specificity = .85). Prediction of severe (grade ≥ 3) acute swallowing dysfunction was similarly obtained.

Conclusion: The TDRS is a useful tool to predict acute swallowing dysfunction induced by chemoradiotherapy for head and neck cancers.

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Conflict of Interest Statement

The authors report no actual or potential conflicts of interest.

Introduction

Definitive chemoradiotherapy is now a widely accepted treatment option for patients with head and neck cancers. In recent years, it has been revealed that addition of concomitant chemotherapy to radiotherapy not only improves the outcome but also increases toxicity of the treatment. 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 [1]. Severe swallowing dysfunction arising during the course of therapy reduces the patient's quality of life and adversely affects their physical condition. Prediction of this morbidity may facilitate prophylactic intervention and prevention of these adverse effects [2], but accurate predictive methods have not been established.

Recently, Langendijk *et al.* advocated a simple measure designated the Total Dysphagia Risk Score (TDRS) to predict swallowing dysfunction after curative radiotherapy for head and neck cancers [3]. They also reported that this predictive model could also be adapted for acute morbidity. Here, a retrospective review of patients with head and neck cancers who underwent definitive chemoradiotherapy in our facility was performed to investigate the validity of the TDRS as a predictive measure for acute swallowing dysfunction in these patients.

Materials and Methods

Between December 1998 and March 2006, 47 patients with head and neck cancers

underwent definitive chemoradiotherapy at our facility. The patients' characteristics are shown in Table 1. In our facility, definitive chemoradiotherapy is usually performed in patients with good performance status, with no distant metastasis and 75 years old or less.

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 (Table 2). As we had been searching for the optimal chemotherapy regimen for several years and the method of therapy had consequently changed over that time, the chemotherapeutic agents used in the cases included in the present study were heterogeneous. 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 2,000 mg/m^2 to 12,000 mg/m^2 (median 4,000 mg/m^2).

In radiation therapy, casts for immobilisation 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 the median dose was 70 Gy. As various treatment protocols with different fraction sizes and total doses had been used in our facility, we also calculated the biologically effective dose (BED) in a linear-quadratic model [4]. 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 tumours and acute toxicity. The

BED ranged from 60 to 84 Gy (median 84 Gy). Forty-one patients received a once-daily fractionation schedule and 6 patients were treated with a partially accelerated hyperfractionation schedule. In this schedule, patients initially received 40 Gy in once-daily fractionation with a fraction size of 2 Gy. Subsequently, radiation field size was reduced 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 tumour spread. Stage II disease was usually treated by locally confined portals. The whole (bilateral) neck was usually included in the treatment of stage III – IV disease initially. The spinal cord was usually avoided by cone-down field reduction after 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).

Morbidity was retrospectively assessed using medical records, and scored by the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria [5]. In these criteria, grade 2 swallowing dysfunction is defined as moderate dysphagia and/or odynophagia, which may require narcotic analgesics and/or pureed or liquid diet. Grade 3 is defined as severe dysphagia or odynophagia with dehydration or weight loss requiring naso-gastric feeding tube, intravenous fluids or hyperalimentation. The TDRS is a summation of the following risk points: T-classification (T3 = 4 points;

T4 = 4 points), neck irradiation (bilateral neck irradiation = 9 points), weight loss (1% – 10% = 5 points; > 10% = 7 points), primary tumour site (oropharynx = 7 points; nasopharynx = 9 points) and treatment modality (accelerated radiotherapy = 6 points; concomitant chemotherapy = 5 points). The definition used in this study was identical to that of Langendijk *et al.* [3]. In the present study, patients who underwent partially accelerated radiation therapy were not allocated to 6 points. Accordingly, the risk points of treatment modality were set at 5 in all patients. The patients were divided into a low risk group (TDRS = 0 – 9), intermediate risk group (TDRS = 10 – 18) and high risk group (TDRS > 18).

Statistical analyses were performed using the χ^2 test, and $P < .05$ was taken to indicate statistical significance. ROC (receiver operator characteristic) curves were also plotted to evaluate the predictive capability of TDRS for grade 2 or higher acute swallowing dysfunction.

These analyses were performed using the statistical software JMP version 5.1.1 (SAS Institute Inc., Cary, NC, USA).

Results

Grade 2 or higher swallowing dysfunction was observed in 27 patients (57%) as an acute morbidity. Of those, severe (grade ≥ 3) dysfunction occurred in 22 patients (81%). The results of classification into three risk groups according to TDRS and the relationship between the risk groups and RTOG grade are shown in Table 3. This

classification was significantly associated with both grade ≥ 2 and grade ≥ 3 acute swallowing function. The ROC curve was plotted to evaluate the prediction capability of TDRS for grade ≥ 2 acute swallowing dysfunction (Fig. 1). The cut-off value was set at 18 (sensitivity = .81; specificity = .85), which was consistent with the borderline between the intermediate and high risk groups. Accuracy for prediction was moderate (area under the curve = 0.80). Almost the same accuracy was obtained when grade ≥ 3 acute swallowing dysfunction was defined as positive (area under the curve = 0.83). The cut-off value was also set at 18 (sensitivity = .86; specificity = .76).

The median duration of severe (grade ≥ 3) swallowing dysfunction was 53 days (range, 21 – 142 days). To manage the severe swallowing function, total parenteral nutrition was usually adopted at our facility. Enteral feeding was not usually adopted. Seventeen patients required total parenteral nutrition. No patients in the low risk group and 3 patients (33%) in the intermediate risk group required this procedure. In contrast, 14 patients (64%) in the high risk group required this procedure. Median duration of hospitalization after termination of treatment in the low, intermediate, and high risk group was 15 days (range, 1 – 31), 26days (range, 7 – 117), and 41days (range, 17 – 77), respectively.

Discussion

Cisplatin-based chemoradiotherapy for locally advanced head and neck cancers is now widely recognised as a standard form of therapy for patients with locally advanced

disease, although considerable clinical problems remain to be resolved. This can be a rather toxic form of therapy despite using non-surgical modalities [6]. Swallowing dysfunction caused by the therapy sometimes becomes severe, and this is one of the largest obstacles in conducting concomitant chemoradiotherapy for head and neck cancers. Few previous studies have addressed this issue [7], but some reports mentioned that more than half of the cases required enteral feeding temporarily [8], and about 20% required long-term enteral feeding [1]. Nguyen *et al.* reported that aspiration was frequently observed during the course of therapy, sometimes leading to fatal aspiration pneumonia [9, 10]. Swallowing dysfunction leads to malnutrition, which causes body weight loss during the course of therapy. This results in not only physical damage for the patients, but also worsening of the clinical outcome [11]. Body weight loss also causes dosimetric problems. The risk of delivering an inadequate radiation dose to the target volume and critical structures may arise if coordinated replanning is not performed during the course of the therapy, especially when using highly conformal methods [12].

As mentioned above, care must be taken regarding swallowing dysfunction during concomitant chemoradiotherapy for head and neck cancers and appropriate measures should be taken to alleviate secondary averse effects, such as aspiration or body weight loss. Nutritional support is a high priority issue in the management of these patients. Enteral feeding is generally the preferred method [13]. However, total parenteral

nutrition was usually adopted in our facility. This might be due to preference of the attending physicians who were also in charge of the management of chemoradiotherapy for oesophageal cancers. Another part of the reason might be that healthcare system in our district has not strictly regulated this procedure.

As a measure for enteral feeding, percutaneous endoscopic gastrostomy (PEG) tube placement is one of the most effective interventions. Prophylactic PEG tube placement has been recognised as a beneficial approach for ameliorating the nutritional status of these patients [2]. Although a relatively safe procedure, PEG placement is invasive and this may leads to critical complications [14]. Therefore, it is not reasonable to place a PEG tube in all patients, and a selection index to identify patients requiring prophylactic PEG tube placement is urgently needed [2]. Several studies have addressed risk factors for severe swallowing dysfunction in radiotherapy for head and neck cancers. Manger *et al.* argued that clinical stage, general condition and history of smoking may be risk factors for severe dysphagia in chemoradiotherapy for head and neck cancers [8]. Poulsen *et al.* suggested that irradiated volume of the pharyngeal mucosa and musculature are strongly related to the swallowing toxicity in radiotherapy alone for head and neck cancers [15]. Other factors such as primary site or combined modality were also described as risk factors [2], but there is no comprehensive index in the literature. The Total Dysphagia Risk Score (TDRS) proposed by Langendijk *et al.* is a predictive model for swallowing dysfunction after curative treatment for head and neck

cancers [3]. As this model was derived from data regarding late radiation morbidity, it is intended for prediction of late swallowing dysfunction. However, this simple model may also be useful for predicting acute morbidity, as suggested by Langendijk *et al.* The results of the present study indicated that TDRS is a valid measure for predicting acute swallowing dysfunction in patients with head and neck cancers undergoing definitive chemoradiotherapy. The TDRS was applicable despite the differences in patient characters and method of therapy. Thus, the TDRS may become an international index to predict swallowing dysfunction. Initially, validity of the TDRS for predicting grade 2 or higher acute swallowing dysfunction was set as the endpoint of the present study. This was due to the fact that the TDRS was defined as a measure to predict RTOG grade 2 or higher swallowing dysfunction. However, more than 80% of the morbidity in patients with experienced grade 2 or higher swallowing dysfunction was severe (grade ≥ 3) in the present study. Then, we set validity of the TDRS for predicting severe acute swallowing dysfunction as another endpoint of this study. ROC analysis in our study suggested that severe acute swallowing dysfunction may be similarly predictive. These observations suggest that the TDRS could be a predictive tool for severe swallowing dysfunction. Thus, the TDRS would allow selection of the patients most likely to benefit from prophylactic PEG placement. Our previous study indicated that radiation portal size is a risk factor for severe swallowing dysfunction in chemoradiotherapy for head and neck cancers [16]. Of the five factors included in the TDRS, T-classification, neck

irradiation and primary tumour site are related to radiation portal size.

The annual number of the patients included in this study was relatively low (5 to 6 patients per year). This was the actual number of patients which we treated during this period. In our facility, definitive chemoradiotherapy has been strictly confined to patients with quite good condition. This might lead to scarcity of the number of patients.

It is obvious that radiotherapy plays a major role in the occurrence of swallowing dysfunction. Broader mucous membranes and more anatomical parts important for swallowing would be affected to a greater degree by larger radiation portals, and these would be amplified by chemotherapy. Therefore, improving radiotherapy may allow reduction of this complication. Intensity-modulated radiotherapy (IMRT) has been widely used for head and neck cancers [17]. Using this advanced technique, complications can now be reduced without compromising therapeutic outcome [18].

Determining whether a patient actually requires concomitant chemotherapy also must be considered [19]. Recently, use of biologically targeted therapy has been shown to improve the outcome without increasing the common toxic effects of radiotherapy plus chemotherapy [20]. These promising approaches combined with robust nutritional support may yield further improvement in the management of non-surgical therapy for head and neck cancers.

Conclusions

The TDRS has the potential to become a useful measure for predicting acute

swallowing dysfunction induced by chemoradiotherapy for head and neck cancers. This measure may serve as an index to enable selection of appropriate candidates for prophylactic PEG placement.

Figure legend

Figure 1. ROC (receiver operator characteristic) curve to evaluate the prediction capability of the TDRS for grade 2 or higher acute swallowing dysfunction.

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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
T-classification	T2	24
	T3–T4	23
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
Chemotherapy	Platinum-based	45
	Docetaxel alone	2
Radiation schedule	Conventional fractionation	41
	Hyperfractionation	6
Neck irradiation	Local or unilateral	20
	Bilateral	27
Weight loss (baseline)	No weight loss	36
	1–10%	10
	> 10%	1

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. Relationships between the three risk groups and grading of swallowing dysfunction in RTOG Acute Radiation Morbidity Scoring Criteria.

Risk groups	Total	RTOG grade		
		0-1	≥ 2	≥3
Low	16	13 (81%)	3 (19%)	1 (6%)
Intermediate	9	4 (44%)	5 (56%)	4 (44%)
High	22	3 (14%)	19 (86%)	17 (77%)
Total	47	20 (43%)	27 (57%)	22 (47%)

The differences were statistically significant ($P < .001$; degrees of freedom = 2) in both grade ≥ 2 and grade ≥ 3 acute swallowing dysfunction.

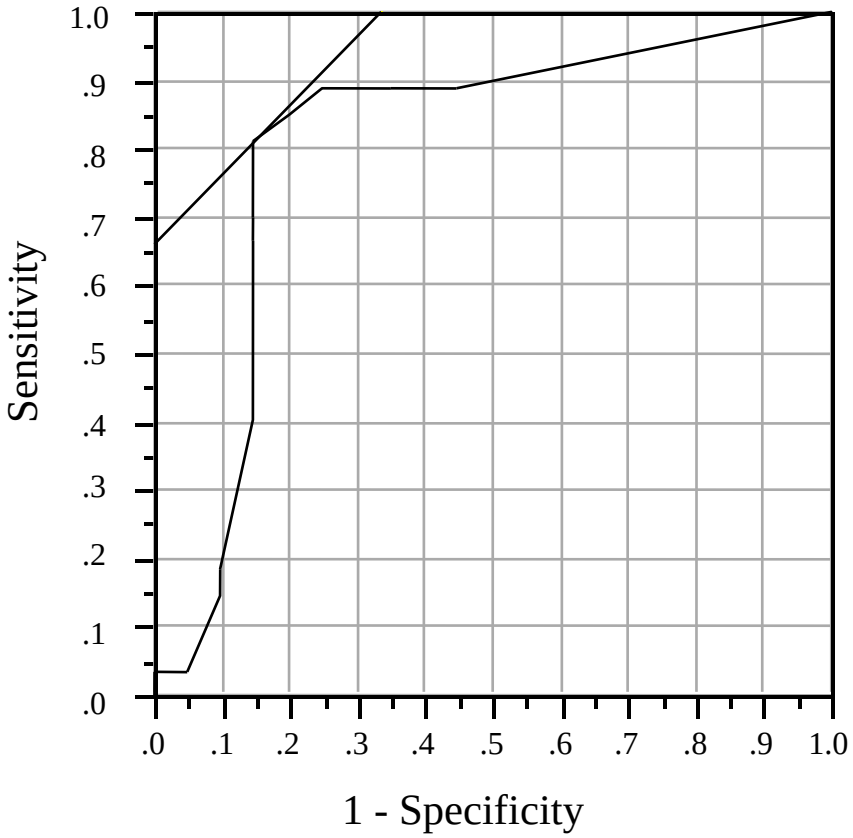

Figure 1