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Distinctive mucositis and feeding-tube dependency in cetuximab plus radiotherapy for head and neck cancer

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Abstract

Objective: Prophylactic percutaneous endoscopic gastrostomy may be considered before chemo-radiotherapy for patients with locally advanced head and neck squamous cell carcinoma, because severe mucositis is a common complication. We evaluated the mucosal findings and necessity of prophylactic percutaneous endoscopic gastrostomy in patients with head and neck squamous cell carcinoma receiving cetuximab and radiotherapy.

Methods: Fourteen consecutive patients with locally advanced head and neck squamous cell carcinoma receiving cetuximab and radiotherapy were analyzed.

Results: Patients' backgrounds were as follows: male/female, 8/6; median age, 64.5 years (range, 35–83 years); performance status, 0/1, 9/5. Primary tumor sites included the oropharynx, hypopharynx and larynx in four, seven and three patients, respectively. Patients completed a median of eight cetuximab cycles. All patients received three-dimensional conformal radiotherapy (median dose, 70 Gy). Thirteen patients were treated with elective neck irradiation at the ipsilateral ($n = 3$) or bilateral ($n = 10$) nodes. Grade ≥3 mucositis/stomatitis (clinical examination) occurred in 85.7% patients ($n = 12$). The median irradiation dose was 33 Gy at the Grade 3 mucositis onset. Eight patients showed mucositis with distinctive features, a wide range of white-coated lesions with a clear border; hypopharyngeal atresia was observed in two patients. Prophylactic percutaneous endoscopic gastrostomy was performed in 11 patients, and 11 patients (78.6%) actually required nutritional support because of Grade ≥3 mucositis/stomatitis (functional/symptomatic).

Conclusions: Prophylactic percutaneous endoscopic gastrostomy is recommended because most patients receiving cetuximab and radiotherapy for locally advanced head and neck squamous cell carcinoma have Grade ≥3 mucositis with distinctive features.

Key words: locally advanced squamous cell carcinoma of the head and neck, cetuximab, radiotherapy, mucositis, percutaneous endoscopic gastrostomy

Introduction

Head and neck cancers primarily involve the oral cavity, pharynx and larynx; more than 90% of such cancers are histologically squamous cell carcinomas (1). Most patients with head and neck squamous cell carcinoma (HNSCC) present with locally or regionally advanced disease (2). A number of treatment options are available for patients with locally advanced HNSCC, including concurrently administered chemoradiotherapy with or without surgery and the combination of the epidermal growth factor receptor (EGFR)-targeting immunoglobulin G1 monoclonal antibody cetuximab and radiotherapy (3,4). The use of cetuximab in combination with radiotherapy (BioRT) was implemented after the finding that EGFR is overexpressed in most cases of HNSCC (5,6), and the observation from *in vivo* models that this combination enhanced tumor regression compared with radiation or cetuximab alone (7). A large Phase III trial conducted by Bonner et al. (8,9) revealed that the addition of cetuximab to radiotherapy significantly improved the overall survival, progression-free survival and locoregional control compared with radiotherapy alone in patients with locally advanced HNSCC. The combination of cetuximab and radiotherapy has been approved for clinical use in the treatment of patients with HNSCC in the USA, Europe and Japan.

Because severe mucositis is a common complication induced by the chemoradiotherapy treatment of patients with HNSCC, prophylactic percutaneous endoscopic gastrostomy (PEG) may be considered at the initiation of chemoradiotherapy (10–12). The Bonner trial demonstrated that the incidence of adverse events commonly associated with radiotherapy of the head and neck, including mucositis, xerostomia and dysphagia, did not differ significantly between a cetuximab plus radiotherapy arm and a radiotherapy arm alone (8). However, little is known about the mucosal findings associated with cetuximab plus radiotherapy. Furthermore, the need for PEG for nutritional support remains unknown. The purpose of this study was to review the mucositis induced by BioRT and assess the need for prophylactic PEG for additional nutritional support in patients with HNSCC treated with radiotherapy and cetuximab.

Patients and methods

Patients

Patients with Stage III or IV (Union for International Cancer Control Tumor, Node, Metastasis classification, seventh Edition) pathologically proven SCC of the oropharynx, hypopharynx or larynx confirmed by using magnetic resonance imaging or computed tomography were eligible for this study. Criteria for eligibility also included medical suitability for definitive radiotherapy, performance status (ECOG) of at least one as well as normal hematopoietic, hepatic and renal function. Patients were ineligible if they underwent palliative BioRT for recurrent disease. This study was approved by the institutional review committee of the Shizuoka Cancer Center (Shizuoka, Japan), and met the standards set forth in the Declaration of Helsinki. Written informed consent was obtained from all patients.

Percutaneous endoscopic gastrostomy

The decision to perform PEG for nutritional support was made by each physician. We used the direct method, a modified version of the introducer method (Direct Ideal PEG kit; Olympus Corp., Tokyo, Japan) (13). After the stomach is secured to the anterior abdominal wall, the skin incision is dilated by passing a dilator percutaneously into the stomach over a guidewire, which is the same as the procedure performed in the introducer method. After the dilator is removed, the PEG tube is inserted by using an obturator (14).

Treatment of BioRT

All patients received a 7-week course of cetuximab concurrent with conventionally fractionated radiotherapy (2 Gy per fraction, five fractions per week). Cetuximab was administered at an initial dose of 400 mg/m^2 (over 120 min) with subsequent weekly doses of 250 mg/m^2 (over 60 min) as an intravenous infusion for 7 weeks. For radiation planning, all patients received three-dimensional conformal radiotherapy (3D-CRT) in the supine position with a thermoplastic mask fixing the head. The gross tumor volume (GTV) 1 was defined as the gross extent of the primary tumor shown by using imaging studies and physical examination as well as all grossly involved regional lymph nodes. The clinical target volume 1 (CTV1) was defined as the GTV plus a margin as a potential microscopic spread, while the planning target volume 1 (PTV1) was calculated as the addition of a 5 mm set-up margin to the CTV1. The total prescribed dose to the PTV1 was 70 Gy in 35 fractions for all patients. In the 3D-CRT protocol performed in our department, dynamic wedges or the field-in-field technique is applied to improve the dose homogeneity within the PTV and ensure adequate dose coverage for the PTV, while limiting the dose maximum to the treated volume to <110% of the prescription dose. The coverage for the elective nodal regions of the neck (CTV2) is dependent on the primary disease site as well as the extent of disease, and the PTV2 was calculated as the addition of a 5 mm set-up margin to the CTV2. Ten patients were treated with elective bilateral neck irradiation of 40 Gy in 20 fractions, and three patients received ipsilateral neck irradiation. The remaining patient with a glottic tumor (T3N0M0) was treated only for the primary tumor without elective neck irradiation. The mean irradiation dose of larynx in all patients was 65.1 Gy, with minimum dose of 32.1 Gy and maximum dose of 72.6 Gy, which was almost same as that of hypopharynx.

Evaluation

All clinical data were retrospectively obtained from medical records. Patients were evaluated by a dentist before starting radiotherapy, and any required dental treatment was performed. The mucosa of the lips, right and left buccal mucosa, left and right lateral tongue border, buccal floor, ventral tongue, oropharynx and hypopharynx were evaluated every week according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 mucositis scale by medical oncologists, radiation oncologists, head and neck surgeons or dentists who used a laryngoscope. Photographic images of representative mucosal findings were taken at least once a week per patient. The toxicities were surveyed until 2 months after the termination of BioRT.

Results

Patient characteristics

Sixteen patients were treated with radiotherapy in combination with cetuximab for head and neck cancer at the Shizuoka Cancer Center between December 2012 and September 2013. Of these, two patients who underwent palliative BioRT were excluded from the study. Therefore, the subjects of our study comprised 14 patients with locally advanced HNSCC. The baseline characteristics are summarized in Table 1. Docetaxel, cisplatin and 5-fluorouracil (TPF) induction chemotherapy was administered before BioRT in six patients. The patients completed a median of eight cetuximab cycles. Thirteen patients

Table 1. Patient characteristics

Characteristic	Number of patients
Sex	
Male	8
Female	6
Age (years) [median (range)]	64.5 (35–83)
PS (ECOG)	
0	9
1	5
Primary site	
Oropharynx	4
Hypopharynx	7
Larynx	3
T-stage	
T1	2
T2	4
T3	6
T4a	2
N-stage	
N0	3
N1	2
N2a	0
N2b	4
N2c	5
M-stage	
0	14
Induction TPF chemotherapy before BioRT	
−	8
+	6
Administration of cetuximab (times) [median (range)]	8 (6–8)

PS, performance status; ECOG, Eastern Cooperative Oncology Group; TPF, docetaxel, cisplatin and 5-fluorouracil; BioRT, cetuximab plus radiation.

had appropriate eating and swallowing abilities before the initiation of BioRT. In one patient, nutrition had to be administered through a transnasal feeding tube from the induction chemotherapy because oral intake was not possible owing to a bulky primary tumor. However, the transnasal feeding tube was removed and the PEG tube was inserted before BioRT was initiated.

Mucosal findings

Mucositis severity was assessed considering not only the functional disorder and symptomatic aspects but also the clinical examination according to the CTCAE v3.0 scale. Clinical examination revealed that 11 patients (78.6%) developed Grade 3 mucositis during BioRT, while one patient (7.1%) developed Grade 4 mucositis after completing BioRT. One patient with a glottic tumor (T3N0M0) who was treated without elective neck irradiation did not develop severe mucositis Grade ≥3. Overall, the rate of Grade ≥3 mucositis was 86% (Table 2). Grade ≥3 mucositis manifested ∼21.5 days (14–35 days) after the initiation of BioRT, with a median radiation dose of 33 Gy (20–48 Gy). Eight patients had mucositis with distinctive features, including a wide range of white-coated lesions with a clear border as shown in Fig. 1C. Furthermore, complete hypopharyngeal atresia was observed in two of these patients whose atresia were surgically treated directly under endoscopic assistance (endoscopic laryngopharyngeal surgery; ELPS).

Use of PEG and nutritional intervention

Prophylactic PEG for nutritional support was performed in 11 patients before BioRT was initiated according to each physician's decision. Of these, 10 patients who developed Grade 3 mucositis that interfered with sufficient oral intake needed PEG support. Prophylactic PEG was not performed in three patients, although whole-neck irradiation was planned for all three. Of these, one patient needed nutritional intervention owing to severe mucositis during BioRT, and a central vein catheter was inserted for total parenteral nutrition. However, the patient developed a catheter site infection. Overall, 11 patients (78.6%) developed Grade 3 mucositis (functional/symptomatic) that required nutritional intervention. The median onset of nutritional support was 23.0 days (0–31 days) (Table 3). Of these, one patient was unable to obtain sufficient nutrition via oral consumption before BioRT was performed, owing to primary disease. Her nutrition was dependent on the PEG support because of Grade 3 mucositis throughout the treatment regardless of a good tumor response to BioRT. Of the 11 patients who needed nutritional support, five were able to adequately eat or hydrate orally without PEG within 7 months after the completion of radiotherapy. The median PEG-dependent time after the completion of radiotherapy is 4.3 months in these five patients. Two patients died during PEG-dependent time, and remaining four patients are still unable to adequately eat or hydrate orally and are dependent on PEG even after 1 year.

Table 2. Summary of [a]mucositis/stomatitis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3 (%)
Mucositis/stomatitis (clinical examination)	1	1	11	1	86
The onset of Grade ≥3 mucositis/stomatitis (days) [median (range)] 21.5 (14–35)					
Radiation dose at the onset of Grade ≥3 mucositis/stomatitis (Gy) [median dose (range)] 33 (20–48)					
Mucositis/stomatitis (functional/symptomatic)	1	2	11	0	79
The onset of nutritional support (days) [median (range)] 23.0 ([b]0–31)					

CTCAE, National Cancer Institute Common Toxicity Criteria for Adverse Events; BioRT, cetuximab plus radiation; PEG, percutaneous endoscopic gastrostomy.

[a]CTCAE v3.0.

[b]One patient was unable to obtain sufficient nutrition via oral intake before BioRT owing to primary disease. Her nutrition was dependent upon PEG support because of mucositis throughout the treatment.

Case 1

A 58-year-old woman, a current smoker and non-drinker, complained of hoarseness. The primary tumor invaded the paralaryngeal space with immobility of left vocal cord, and it extended to the right side via the anterior commissure (Fig. 1A), suggesting laryngeal cancer (T3N0M0). BioRT was chosen as a larynx-preserving therapy. Prophylactic PEG was not performed. She completed a course of BioRT with a total irradiation dose of 70 Gy over 50 days, with elective bilateral neck irradiation of 40 Gy and boost irradiation of 30 Gy (Fig. 1B). Although she had no severe complaints of oral or pharyngeal pain and she was able to obtain sufficient nutrition via oral intake during and after treatment, the laryngoscope revealed diffuse white-coated lesions with clear borders around the pyriform sinus (Fig. 1C). The mucosal lesion

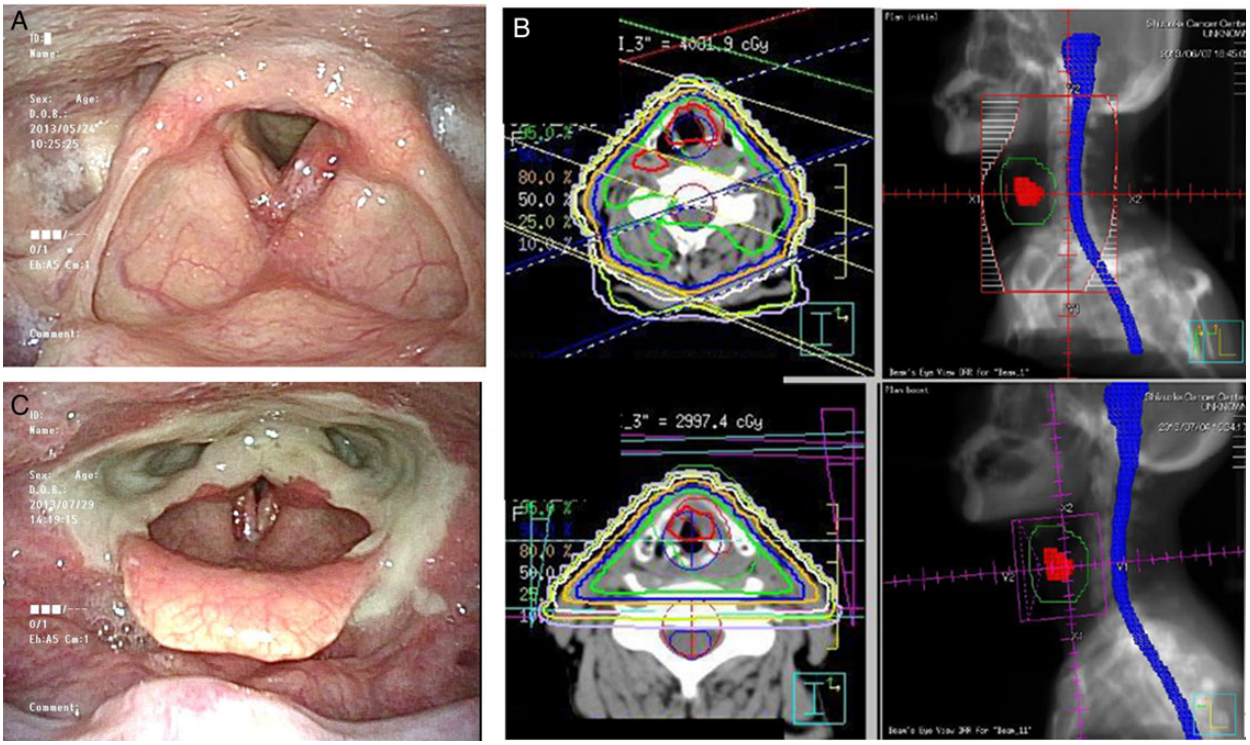

Figure 1. A case of laryngeal cancer (T3N0M0) in a 58-year-old woman. (A) Primary tumor before treatment. (B) Radiation field (elective bilateral neck irradiation of 40 Gy and boost irradiation of 30 Gy). (C) Mucosal finding around the pyriform sinus at Day 50 (70 Gy).

Table 3. Summary of nutritional intervention

Prophylactic PEG	–	+
Able to obtain adequate nutrition via oral intake	2	1
Unable to obtain adequate nutrition via oral intake	1	10

PEG, percutaneous endoscopic gastrostomy.

occurred 25 days after the initiation of irradiation, and it was not present 1 month after the BioRT was terminated. There were no treatment breaks or delays due to toxicity.

Case 2

A 69-year-old woman, who was a non-smoker and non-drinker, was diagnosed with hypopharyngeal cancer (T2N2cM0). She first received induction chemotherapy with TPF followed by concurrent BioRT. After prophylactic PEG was performed, she was treated with whole-neck irradiation during BioRT. The mean dose of larynx was 70.0 Gy. Diffuse, white-coated lesions around the pyriform sinus occurred, and nutritional support via the PEG tube was commenced 21 days after initiation of irradiation. Three months after the completion of radiation, a laryngoscope revealed complete obstruction of the lower hypopharynx despite the disappearance of the mucosal lesion (Fig. 2A). Videofluoroscopic examination of swallowing demonstrated that liquids did not pass through the esophagus at all despite repeated swallowing, and there were residual liquids in the pyriform sinuses (Fig. 2B). Although she then underwent ELPS, she was unable to obtain sufficient nutrition via oral intake, and she was dependent on PEG for more than 1 year.

Discussion

The Bonner trial demonstrated that the incidences of severe adverse events in the cetuximab plus radiotherapy arm were similar to those in the radiotherapy alone arm with the exception of an acneiform rash and infusion-related events (8). Indeed, the rate of Grade ≥3 mucositis in the cetuximab plus radiotherapy arm was 56%, whereas that in the radiotherapy alone arm was 52%, suggesting that cetuximab did not exacerbate mucositis associated with radiotherapy of the head and neck. However, our experience reveals that the combination of cetuximab with radiotherapy caused an unexpectedly high incidence of Grade ≥3 mucositis from the aspect of both functional/symptomatic and clinical examination.

Pharyngeal mucosa commonly represented distinctive features such as thick and white-coated lesions covering a wide area of the pyriform sinus. Interestingly, the margin between the involved and non-involved mucosal lesions was clear. Diffuse white-coated lesions were also frequently observed in the oral cavity (data not shown). These remarkable mucosal findings seem to be quite different from that observed in chemoradiotherapy, and its onset seems to be earlier after the initiation of BioRT than chemoradiotherapy. Even though the diffuse white-coated lesions had an appearance similar to those observed in severe mucositis, the patient describe in Case 1 was asymptomatic throughout the treatment period. On the other hand, in some cases, prolonged stricture of the lower hypopharynx leads to complete hypopharyngeal atresia, as was observed in the patient described in Case 2. Overall, all except one patient treated with elective neck irradiation developed Grade ≥3 mucositis as assessed via clinical examination, and most of them needed nutritional intervention.

Our findings suggest that mucosal complications should not be ignored but recorded when treating patients with BioRT, because they

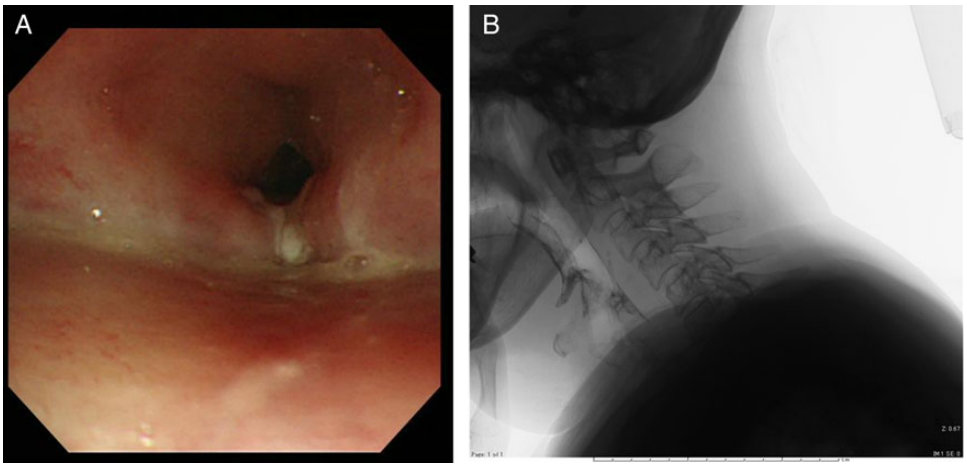

Figure 2. A case of hypopharyngeal cancer (T2N2cM0) at 3 months after the completion of radiation in a 69-year-old woman. (A) Endoscopic observation of the esophageal orifice observed from the oral side. (B) Videofluoroscopic examination of swallowing.

may significantly impair patients' oral intake and quality of life, especially if the irradiation field covers the pharyngeal cavity. Although so far there are no special methods to reduce radiotherapy-induced mucositis, we recommend the following points in the management of mucositis. First, prophylactic PEG is recommended before treatment with radiotherapy in combination with cetuximab. Second, physicians should continue to carefully monitor patients' oral and pharyngeal cavities by using a laryngoscope during and after BioRT. Because the median onset of Grade ≥3 mucositis is as early as 20 days after the initiation of BioRT, patients developing mucositis should be monitored closely throughout the treatment. Photographic documentation may be recommended depending on the mucosal reaction or infection severity as necessary. Furthermore, according to our post-treatment follow-up, four patients are still dependent on PEG due to swallowing dysfunction or hypopharyngeal atresia even after 1 year. Therefore, we raise dysphagia as one of the most important late complications induced by BioRT. Long-term follow-up and swallowing rehabilitation may also be recommended to improve swallowing function.

The continuation of treatment with BioRT should depend on the grade of observed radiation-associated mucositis. However, treatment interruption sometimes results in subsequent decreases in the treatment efficacy (15–17). Of the 14 patients we treated, 11 patients (78.6%) successfully completed a course of planned BioRT without radiation splitting, or treatment interruptions, despite a high rate of Grade ≥3 mucositis. Therefore, cetuximab and irradiation can continue to be administered to patients with up to Grade 3 mucositis. However, it is appropriate to consider briefly interrupting the treatment, if patients with severe mucositis are known to harbor an infection. Taken together, these results show that the decision of treatment continuation should be made on the basis of mucosal findings and patients' symptoms as well as the presence or absence of infection.

The concurrent use of chemotherapy also significantly enhances acute treatment-related toxicity and serious long-term morbidity induced by radiation (18–20). However, it is still unclear whether the severity or duration of mucositis induced by BioRT is comparable with that induced by chemoradiotherapy. Furthermore, the precise pathophysiological mechanism of thick and white-coated lesions in the pharynx remains unknown. It is likely that the concurrent administration of cetuximab and radiotherapy results in mucosal alterations through the interaction between the effects of radiation on the mucosa and EGFR inhibition caused by cetuximab. This interaction may manifest as a highly exacerbated inflammatory response in the oral and pharyngeal mucosa, as is proposed in skin reactions (21). It is quite difficult to define factors influencing mucosal reaction, such as smoking status and alcohol consumption, nutritional status, induction chemotherapy and radiation technique, in the small sample size of this study. Regarding radiation planning, all patients received 3D-CRT. Recently, intensity-modulated radiation therapy (IMRT) has emerged as a promising treatment for HNSCC. The advantage of IMRT is its highly conformal dose distribution to the primary tumor and involved lymph nodes with sufficiently low exposure to organs at risk. However, when confronted with laryngeal and hypopharyngeal cancers, the normal structures such as the pharyngeal constrictor muscles, supra-glottic larynx and glottis larynx are frequently overlapped with primary target, and the sparing of these structures is difficult in the IMRT technique. It is noteworthy that not just patients treated with elective bilateral neck irradiation, but also all three patients who received unilateral neck radiation, developed Grade ≥G3 mucositis. Furthermore, the mean irradiation dose in larynx of our patients was 65.1 Gy, which was almost identical dose distribution when compared with chemoradiotherapy. These findings suggest that severe mucositis is induced by BioRT regardless of radiation technique. In addition, of eight patients who did not receive TPF induction chemotherapy before BioRT, six patients (75%) developed Grade ≥3 mucositis/stomatitis (clinical examination), irrespective of 5-fluorouracil use. The correlation between mucositis and skin reaction seems to be also interesting. However, only five patients (35.7%) developed Grade 3 dermatitis radiation and no patient did Grade ≥3 skin rash during BioRT, while ~80% developed Grade 3 mucositis. Even though a patient has severe mucositis, the skin toxicity is not always severe. Although our sample size is too small to draw a conclusion, our findings may suggest that there is no significant correlation between mucositis and skin reaction, and the reaction in mucosa may be distinct from that in skin. Taken together, the rate of PEG requirement and mucosal changes might be less due to radiation technique, target volumes and 5-fluorouracil use prior to BioRT, more specific to BioRT. The identification of risk factors for mucositis may provide physicians with valuable pretreatment information regarding which patients may need more intense monitoring for mucosal reactions. A systematic way of preventing and managing radiation mucositis should also be established in the future.

In conclusion, this is the first report to evaluate mucosal findings associated with cetuximab plus radiotherapy and nutritional support in patients with locally advanced HNSCC treated with BioRT, although the current study has the limitation of being a retrospective case series at a single center. Our study findings suggest that extreme care should be taken for patients with mucositis and that prophylactic PEG may be required as a nutritional intervention for these patients.

Conflict of interest statement

Tomoya Yokota serves in an advisory role in AstraZeneca and Merck Serono, and has received lecture fees from Merck Serono and Bristol-Myers Squibb.

References

1. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. *Mayo Clin Proc* 2008;83:489–501.
2. Zbaeren P, Lehmann W. Frequency and sites of distant metastases in head and neck squamous cell carcinoma. *Arch Otalaryngol Head Neck Surg* 1987;113:762–4.
3. Budach V, Bernier J, Lefebvre J-L, et al. Trends in the treatment of locally advanced squamous cell carcinoma of the head and neck (LASCCHN) in Europe between 2006 and 2009. *Ann Oncol* 2010;21(suppl 8):viii321–2. Updated information presented at meeting.
4. Wong SJ, Harari PM, Garden AS, et al. Longitudinal Oncology Registry of Head and Neck Carcinoma (LORHAN): analysis of chemoradiation treatment approaches in the United States. *Cancer* 2011;117:1679–86.
5. Christensen ME, Therkildsen MH, Hansen BL, et al. Epidermal growth factor receptor expression on oral mucosa dysplastic epithelia and squamous cell carcinomas. *Eur Arch Otorhinolaryngol* 1992;249:243–7.
6. Rubin Grandis J, Melhem MF, Barnes EL, et al. Quantitative immunohistochemical analysis of transforming growth factor-alpha and epidermal growth factor receptor in patients with squamous cell carcinoma of the head and neck. *Cancer* 1996;78:1284–92.
7. Huang SM, Harari PM. Modulation of radiation response after epidermal growth factor receptor blockade in squamous cell carcinomas: inhibition of damage repair, cell cycle kinetics, and tumor angiogenesis. *Clin Cancer Res* 2000;6:2166–74.
8. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;354:567–78.
9. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol* 2010;11:21–8.
10. Chen AM, Li BQ, Lau DH, et al. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys* 2010;78:1026–32.
11. Lawson JD, Gaultney J, Saba N, et al. Percutaneous feeding tubes in patients with head and neck cancer: rethinking prophylactic placement for patients undergoing chemoradiation. *Am J Otolaryngol* 2009;30:244–9.
12. Silander E, Nyman J, Bove M, et al. Impact of prophylactic percutaneous endoscopic gastrostomy on malnutrition and quality of life in patients with head and neck cancer: a randomized study. *Head Neck* 2012;34:1–9.
13. Ogino H, Akiho H. Usefulness of percutaneous endoscopic gastrostomy for supportive therapy of advanced aerodigestive cancer. *World J Gastrointest Pathophysiol* 2013;4:119–25.
14. Horiuchi A, Nakayama Y, Tanaka N, et al. Prospective randomized trial comparing the direct method using a 24 Fr bumper-button-type device with the pull method for percutaneous endoscopic gastrostomy. *Endoscopy* 2008;40:722–6.
15. Tarnawski R, Fowler J, Skladowski K, et al. How fast is repopulation of tumor cells during the treatment gap? *Int J Radiat Oncol Biol Phys* 2002;54:229–36.
16. Van den Bogaert W, Van der Leest A, Rijnders A, et al. Does tumor control decrease by prolonging overall treatment time or interrupting treatment in laryngeal cancer? *Radiother Oncol* 1995;36:177–82.
17. McCloskey SA, Jaggernauth W, Rigual NR, et al. Radiation treatment interruptions greater than one week and low hemoglobin levels (12 g/dl) are predictors of local regional failure after definitive concurrent chemotherapy and intensity-modulated radiation therapy for squamous cell carcinoma of the head and neck. *Am J Clin Oncol* 2009;32:587–91.
18. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* 2003;349:2091–8.
19. Garden AS, Harris J, Trotti A, et al. Long-term results of concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: a phase II trial of the radiation therapy oncology group (RTOG 99–14). *Int J Radiat Oncol Biol Phys* 2008;71:1351–5.
20. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol* 2008;26:3582–9.
21. Bernier J, Russi EG, Homey B, et al. Management of radiation dermatitis in patients receiving cetuximab and radiotherapy for locally advanced squamous cell carcinoma of the head and neck: proposals for a revised grading system and consensus management guidelines. *Ann Oncol* 2011;22:2191–200.