ORIGINAL ARTICLE

Impact of prophylactic percutaneous endoscopic gastrostomy tube placement on treatment tolerance in head and neck cancer patients treated with cetuximab plus radiation

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Running head:

PEG during cetuximab plus RT for LA-SCCHN

Abstract

Objective: We conducted a retrospective analysis to evaluate the efficacy and safety of cetuximab plus radiation with or without prophylactic PEG in locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) patients who were not suitable to receive platinum.

Patients and Methods: We reviewed the case records of 27 LA-SCCHN patients treated with cetuximab plus RT between January 2013 and July 2014. No patient was able to receive platinum because of renal dysfunction or other contraindications. Patients received an initial dose of cetuximab of 400 mg/m^2, followed by weekly doses of 250 mg/m^2. The total dose of radiotherapy was 66-70 Gy in five daily fractions of 2-2.12 Gy per week.

Results: The incidence of leukopenia was significantly higher in patients without PEG placement than in those with (67.5 % vs. 7%, p=0.002). The incidence of grade 3 or 4 mucositis tended to be higher in patients without PEG placement than in those with (83% vs.47%, p=0.058). Five of 12 patients without PEG placement required interruption of treatment. More patients without PEG placement had significantly

greater than 10% weight loss than patients with (75% vs 27%, p=0.013). The overall response rate was 56% in all patients. The 1-year progression-free survival (PFS) rate was 30.6% in all patients.

Conclusions: Prophylactic PEG-feeding tube placement could reduce the incidence of severe toxicities, including mucositis and weight loss, and avoid RT interruption. These results require confirmation in a larger study.

244 words

Mini-Abstract

Patients with LA-SCCHN undergoing cetuximab plus radiation due to contraindication to platinum may require prophylactic PEG.

Key words: Locally advanced squamous cell carcinoma of the head and neck, platinum refractory, percutaneous endoscopic gastrostomy, cetuximab plus radiation, mucositis

Introduction

The standard treatment for unresectable locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) is platinum-based chemoradiotherapy (CRT) (1) (2). A standard regimen of CRT is high-dose cisplatin (CDDP 100 mg/m^2 on day1, 22, 43) plus RT. However(3), high cisplatin is not suitable for patients with certain risk factors, including old age, kidney and/or cardiac dysfunction, brain infarction and hearing loss. In the Bonner trial, a pivotal prospective randomized phase III trial which compared radiation with or without cetuximab for LA-SCCHN, the addition of cetuximab to radiotherapy significantly improved locoregional control, progression-free survival, and overall survival without increasing the incidence of radiation-related toxicities, including mucositis and dysphagia (4) (5). Although no direct comparison with CRT has appeared, cetuximab plus radiation is an alternative treatment option in LA-SCCHN.

A phase II study to confirm the feasibility of cetuximab plus radiotherapy for locally advanced head and neck cancer in Japanese patients (6) reported similar tolerability and efficacy with those reported in the Bonner trial, leading to the approval of cetuximab for head and neck cancer in Japan. However, the incidence of grade 3 or worse mucosal

inflammation was somewhat higher than that reported for mucositis in the cetuximab plus radiotherapy arm of the Bonner trial (73% vs 56%).

Investigators in the Bonner trial could select one of three radiotherapy-fractionation regimens - single daily, twice daily and concomitant boost. In the Japanese feasibility trial, in contrast, only concomitant boost radiotherapy was allowed when combined with cetuximab. Further, patients treated with concomitant boost in the Bonner trial experienced more high-grade mucositis than with standard fractionation (7). We therefore concluded that the higher incidence of mucositis in the Japanese trial was because of its use of concomitant boost radiotherapy only. Furthermore, we speculated that the addition of cetuximab to single daily radiotherapy for Japanese patients would not increase radiation-related toxicities, as in the Bonner trial. Therefore, we initially did not perform prophylactic percutaneous endoscopic gastrectomy (PEG) in patients who received cetuximab plus radiation, as is also not done in patients receiving radiation alone in our institution. However, most patients developed severe mucositis, dysphagia and radiation dermatitis, leading to treatment interruption. To avoid treatment interruption, prophylactic PEG placement is mandatory for patients with locally advanced head and neck cancer who receive concurrent CRT in our institute. The

previous studies demonstrated that treatment interruption were associated with increased local relapse, and worsening of local control (8). Accordingly, our institution mandated prophylactic PEG placement before the start of cetuximab plus radiation. However, the efficacy and safety of cetuximab plus radiation with or without prophylactic PEG in LA-SCCHN patients who are not suitable to receive platinum is unknown.

Here, we conducted a retrospective analysis to evaluate the tolerability of cetuximab plus radiation therapy for the LA-SCCHN patients with or without prophylactic PEG placement.

Patients and methods

We retrospectively reviewed the medical records of 27 patients with locally advanced SCCHN treated with radiotherapy in combination with cetuximab for head and neck cancer at the National Cancer Center Hospital East between January 2013 and July 2014. All patients were unable to receive cisplatin due to cardiac and kidney dysfunction, old age, and complications (poorly controlled diabetes, and alcoholic liver cirrhosis).

Patients had to meet the following inclusion criteria: pathologically proven SCC of the oropharynx, hypopharynx or larynx, stage III, IVA or IVB (Union for International Cancer Control Tumor, Node, Metastasis Classification, Seventh Edition), performance status of 0 to 2, and normal hematopoietic function. This study was approved by the institutional review committee of the National Cancer Center Hospital East.

Severe mucositis in locally advanced SCCHN patients receiving CRT frequently leads to dysphasia and weight loss. These patients may require adequate nutritional support to avoid treatment interruption, which can adversely impact treatment outcome. However, although the relative benefits of prophylactic versus therapeutic PEG feeding tube placement are controversial, we are convinced that prophylactic PEG feeding tube placement is indispensable to the completion of these high intensity treatments. Beginning in 2001, therefore, our institution now routinely performs prophylactic PEG placement in SCCHN patients with locally advanced disease who receive CRT and are accordingly at high risk of severe mucositis.

Because the Bonner trial demonstrated that the addition of cetuximab did not increase RT toxicities, including mucositis and dysphagia, we did not initially perform prophylactic PEG placement for patients who received cetuximab plus radiation

following the approval of cetuximab for head and neck cancer in December 2012. However, most of these patients developed severe mucositis requiring emergency hospitalization leading to treatment interruption. From this experience, we mandated prophylactic PEG placement for patients who scheduled to receive cetuximab plus RT.

Pretreatment evaluation consisted of complete history (including lifestyle) and physical examination, complete blood counts, liver and renal function tests, chest X-rays and ECGs. All patients underwent CT and MRI scan of the head and neck. Tumor staging was performed based on sections of the head and neck tumors using the TNM classification of the UICC 7^{th} edition.

Intravenous administration of cetuximab was initiated in the first week with a loading dose of 400 mg/m^2 (over 120 min.) infused over a period of 2 hours, followed by weekly 1 hour infusions of 250 mg/m^2 for the duration of cetuximab plus radiation treatment. Patients received a 7- to 8-week course of cetuximab concomitant with conventionally fractionated radiotherapy.

Radiation was administered in five 2-2.12 Gy single-daily fractions per week for a total dose of 66-70 Gy. Intensity modulated radiotherapy (IMRT) with the simultaneous integrated boost technique was routinely used.

Patients were immobilized using a custom-made mask. Target volumes and organs at risk were delineated in accordance with the ICRU-50/62 and 83 guidelines. Planning target volume 1 (PTV1) consisted of the primary site, and lymph node levels with macroscopic disease received 70 Gy in 33 or 35 fractions (Fr); PTV2, consisted of elective lymph node levels (60 Gy/33-35 Fr); and PTV3 consisted of prophylactic lymph node levels (54 Gy/33 Fr or 56Gy/35 fr). With regard to the prophylactic irradiated area, this was determined in accordance with DAHANCA, EORTC, GORTEC, NCIC, and RTOG consensus delineation (9). Three patients received 66 Gy in 33 fractions because of a national holiday. Chemotherapy- and chemoradiation-related toxicities were quantified using the National Cancer Institute Common Toxicity Criteria (version 4.0) (10).

Nutritional status was evaluated according the recommended diagnosis for malnutrition in adults by the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition (11). Weight change was assessed over time as 1-2% per week, 5% per month and 7.5% per 3 months.

Follow-up time for each patient was calculated as the time from the start of treatment to 31 January 2015.

Survival curves were generated using the Kaplan-Meier method. Safety and efficacy analyses were conducted on an intention-to-treat basis, defined as all patients who received at least one dose of cetuximab. Progression-free survival (PFS) was calculated from the date of the first administration of chemotherapy to the first documentation of disease progression, subsequent therapy (for example, salvage operation and chemotherapy), or death. Overall survival (OS) was determined from the date of the first administration of chemotherapy to the date of death or the last confirmed date of survival. Chi-square test, analysis of variance, and log-rank test were used for analysis. Statistical data were obtained using the SPSS software package (SPSS statistics 21®, SPSS Inc. Chicago IL, USA).

Results

Patient Characteristics

Patient characteristics are summarized in Table 1. Treatment details are described in Table 2. Fifteen patients received prophylactic PEG placement before cetuximab plus radiation while twelve patients did not. Reasons for administration of cetuximab were age > 75 years, renal dysfunction, and complications including poor control of diabetes

mellitus, cardiovascular disease and cirrhosis. There was no significant difference in patient characteristics between those receiving and not receiving PEG placement.

Adverse Events

There were no adverse events related with prophylactic PEG replacement. Hematologic and non-hematologic toxicities are listed in Table 3. Among hematological toxicities, the incidence of leukopenia was significantly higher in patients without PEG placement than in those with (67.5% vs. 7%, p=0.002). The incidence of grade 3 or 4 anemia (grade 3 to 5) tended to be higher in those without PEG placement (p=0.188). In contrast, the incidence of neutropenia, thrombocytopenia and hypomagnesemia (all grades) in the two groups was similar.

The most common non-hematological toxicities were mucositis and radiation dermatitis. The incidence of grade 3 or 4 mucositis tended toward be higher in patients without PEG placement (83% vs.47%, p=0.058). All patients received both mucosal care and education about gargling by a dentist, indicating that there was no difference in compliance with mucosal care between the two groups. No difference in the incidence

of other non-hematological toxicities was observed. No deaths due to treatment-related adverse events were seen.

Although all patients completed radiotherapy, five of 12 patients without PEG placement required interruption of treatment due to infected mucositis (three patients) and infection of the inserted central venous catheter (two patients) (Table 2). The median RT interruption was 4 (range 3-5) days.

Seventeen of 27 patients (63%) were required emergency hospitalization. Of these, eight had received prophylactic PEG and nine had not. The difference did not reach statistical significance (p=0.226). The most common reasons for emergency hospitalization were worsening nutrition, including due to the non-use of PEG, and infection due to mucositis. Most of these patients could not receive family support because they lived alone.

Clinical weight loss ≥ 10% during treatment was observed in 13 patients (48%). Incidence was higher in patients without PEG placement (75% vs. 27%, p=0.013). Further, the mean and percent rate reductions in body weight tended to be higher in those without PEG placement (5.5 kg vs 4.9kg (8.8 % vs 9.6%)) (Table 5).

Median duration of PEG placement was 10.3 months (range 5.2-15.3 months). Seven of 15 patients (46.6%) underwent removal within 1 year, while removal within 1 year was not possible in 8 patients due to persistent primary tumor (n=4) and dysphagia as a result of pharyngeal stenosis (n=4)

Median follow-up time was 13 months (range 6.0 - 22.0 months). Overall response rate by RECIST was 56% in all patients. The 1-year PFS, locoregional control rate, and OS in all patients were 30.6%, 30.2%, and 89.7%, respectively (Figure 1). The 1-year PFS and locoregional control rates for diseases of the oropharynx were 43.6%, 43.6%, and 25.0% and 28.1% for disease of the hypopharynx and larynx. The 1-year PFS of current smokers compared with former/never smokers was 24.7% and 45.0%, respectively. The 1-year PFS in the prophylactic PEG placement group compared with the PEG no placement group was 33.3% and 33.3%, respectively (p=0.934). The 1-year OS of prophylactic PEG placement group compared with the PEG no placement group was 93.3% and 73.3%, respectively (p=0.055) (Fig 2, Fig 3) . PFS and OS were not significantly different in patients without RT interruption, but tended to be better than in patients with RT interruption, albeit that the study population was small (1 year PFS, 31.8% versus 40%, p=0.606; 1 year OS, 90.5% versus 60%, p=0.362, respectively)

Local relapse developed in 13 patients (five with oropharyngeal disease, six patients with hypopharyngeal, and two patients with laryngeal disease). Regional relapse as lymph node recurrence or skin metastasis in the radiation field developed in four patients with hypopharyngeal and one patient with laryngeal disease. One patient had local and regional relapse. One patient developed distant metastasis to the lung. Eight patients underwent salvage surgery, included total pharyngo-laryngo-esophagectomy in six, neck dissection (ND) in one, and total laryngectomy plus ND in one. Five patients subsequently received palliative chemotherapy, while five received best supportive care.

Discussion

Optimal management of toxicities during cetuximab plus RT has not been established. Our retrospective study of patients receiving cetuximab plus RT demonstrated that prophylactic PEG placement reduced the incidence of severe toxicities, including mucositis and weight loss, leading to the avoidance of RT interruption, which has been associated with increased local relapse and worsening of local control (8)（12）.

Previous studies have demonstrated that malnutrition is associated with the increased severity of CRT-related toxicities, which in turn lead to treatment interruption (13) (14)

(15) (16). Appropriate nutrition control during definitive therapy is therefore essential for avoiding RT interruption.

Folllowing the results of Bonner' study, the addition of cetuximab has demonstrated significant improvement in both locoregional control and overall survival without worsening RT-related toxicities. However, several studies demonstrated that the incidence of RT-related toxicities was the same as that of CRT (17) (18) (19).

The TREMPLIN trial, which compared CRT with 3-weekly CDDP plus radiation vs. cetuximab plus radiation after induction chemotherapy, demonstrated that the incidence of grade 3 or 4 mucositis was similar between two arms (58% vs. 56%) (17).

Saleh et al. reported a randomised study which compared the use of cetuximab vs platinum-based chemotherapy (19). No significant difference in the incidence of grade 3 or 4 mucositis was observed between two arms (45.5 % in cetuximab plus radiation vs. 64.3% in CRT, p=0.43). Ghi et al. reported the results of the Head and Neck 07 trial, a randomized phase II-III study of CRT or cetuximab plus RT as definitive therapy with or without induction TPF. No significant difference in the incidence of grade 3 or 4 mucositis was observed between two arms (78% in CRT and 72% in cetuximab plus radiation, p = 0.670) (20).

Cetuximab plus radiation is widely used as an alternative to CRT for the patients who are not candidates for CDDP due to adverse organ function, such as renal dysfunction and comorbidities. These patients are at increased risk of toxicities than those who are fit to receive cisplatin. In fact, our experience revealed that the patients who did not undergo PEG placement developed severe mucositis and dysphagia, which lead to the interruption of RT radiation. Furthermore, they require nutrition from a central venous catheter during therapy, and several patients required it for several months after therapy, leading to increased risk of catherter-related infection due to skin colonization at the insertion site and the patient and hospital environment (21) (22).

Complications with a nasogastric tube include nasal irritation, mucosal ulceration, and aspiration pneumonia(23). These risks are reduced with PEG (24) (25) (26). Weight >10% loss during CRT is reported to reduce OS, PFS, performance status, and physical function with statistical significance (27). Early nutrition and the benefits of PEG placement have been reported, such as decreased weight loss, decreased hospitalization for nutrition or dehydration issues, and fewer treatment interruptions (28) (29). Enteral feeding through a pre-CRT-placed PEG is effective and safe (30) (31). Major complications related to the use of PEG by the direct method, such as pan-or localized

peritonitis and bleeding. Of the 421 patients who underwent PEG by the direct method in our institute, 9 (2.1%) developed peritonitis related to the PEG procedure. One patient with terminal stage lung cancer who needed PEG for palliative care required emergency surgical drainage while the remaining 8 recovered with conservative treatment, indicating that this method has an extremely low risk of adverse effects on treatment for locally advanced SCCHN (32). In fact, there was no adverse event related to prophylactic PEG placement

Although the relative benefits of prophylactic versus therapeutic PEG-feeding tube placement are controversial, we are convinced that prophylactic placement is indispensable to the completion of these high-intensity treatments. In fact, after prophylactic placement of PEG, all patients receiving cetuximab plus RT could complete their treatment without treatment interruption.

The impact of prophylactical PEG use on swallowing-related outcomes remains unclear. We therefore recommend that patients continue to take meals orally and undergo dysphagia rehabilitation during cetuximab plus radiation and CRT. If patients achieve CR and can take food orally after treatment, we recommend removing the PEG as soon as possible.

The incidence of leukopenia was significantly higher in patients without PEG placement than in those with PEG. Some articles have reported that malnutrition is associated with lymphopenia, anemia and weight loss (33) (34). Protein malnutrition decreases the production of blood cells, leading to bone marrow hypoplasia and inducing structural alterations which interfere with both innate and adaptive immunity. We hypothesized that malnutrition was associated with myelosuppression and immunosuppression, leading to the worsening of leukopenia and anemia.

Multiple scores are available for evaluating the nutritional status of cancer patients. However, no standard nutritional screening tool has been designed specifically for use in patients with cancer. One simple to use and objective tool is the Nutritional Risk Index (NRI), which has been validated in various clinical settings, including gastrointestinal cancers (3, 35, 36). The NRI can be calculated as (= 1.519 x serum albumin level [g/L] + 0.417 X current weight/usual weight X 100).(3) Based on the NRI, patients can be classified as having no malnutrition (NRI >97.5), moderate malnutrition ($97.5 \geq NRI \geq 83.5$), or severe malnutrition (NRI <83.5). In particular, both BW loss and albumin are good surrogate makers of nutritional status.

Prealbumin is used to monitor acute changes in the nutritional status of patients. Results may be influenced by the presence of infection and inflammation, however. For our present study population, a higher incidence of severe mucositis and dermatitis were observed, indicating that prealbumin is inappropriate for the evaluation of nutritional status.

Both response rate and PFS in the current study were lower than that in Bonner trial (response rate, 56% vs. 74%; 1 year PFS, 8.3 vs 17.1 months, respectively). The percentage of patients with oropharyngeal cancer was smaller in our present study than in the Bonner trial. Furthermore, all patients in the current study were unsuitable for platinum due to their older age (> 75 years), renal dysfunction and severe complications, leading to the poor outcomes compared with previous studies.

The present study has several limitations, including the small number of study subjects and retrospective study design.

In conclusion, our analysis reveals that prophylactic PEG-feeding tube placement reduces the incidence of severe toxicities, including mucositis and weight loss, and thereby helps avoiding RT interruption. Additional larger studies are required to confirm these results.

Conflict of interest statement

None declared

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Figure 1. Progression-free survival among all patients

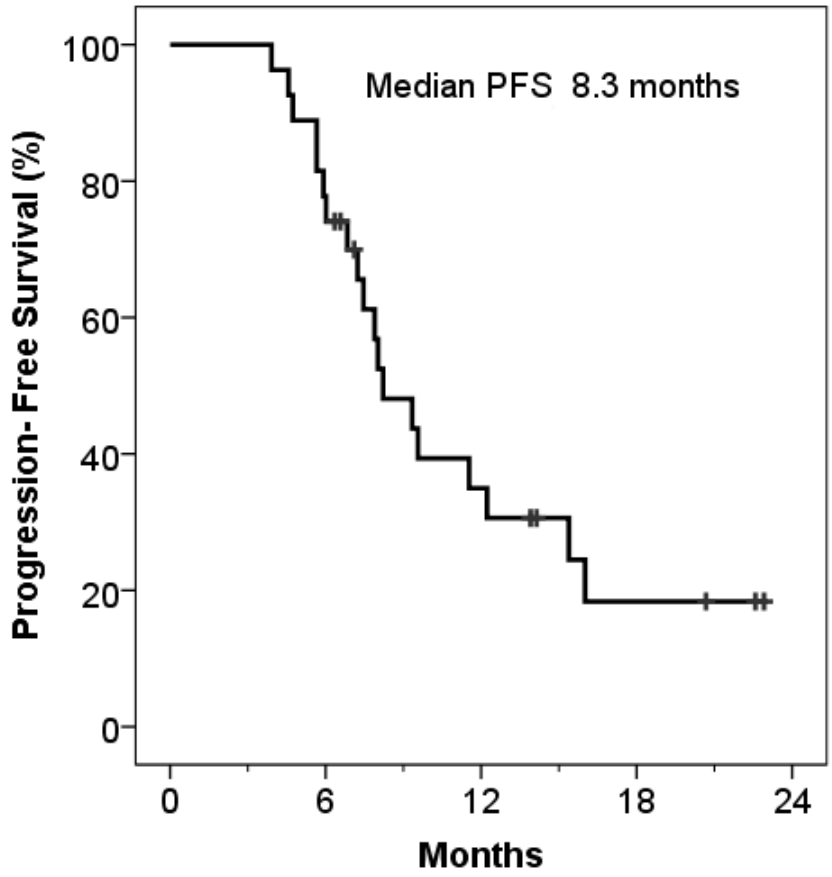

Figure 2. Progression-free survival compared PEG placement with PEG no placement

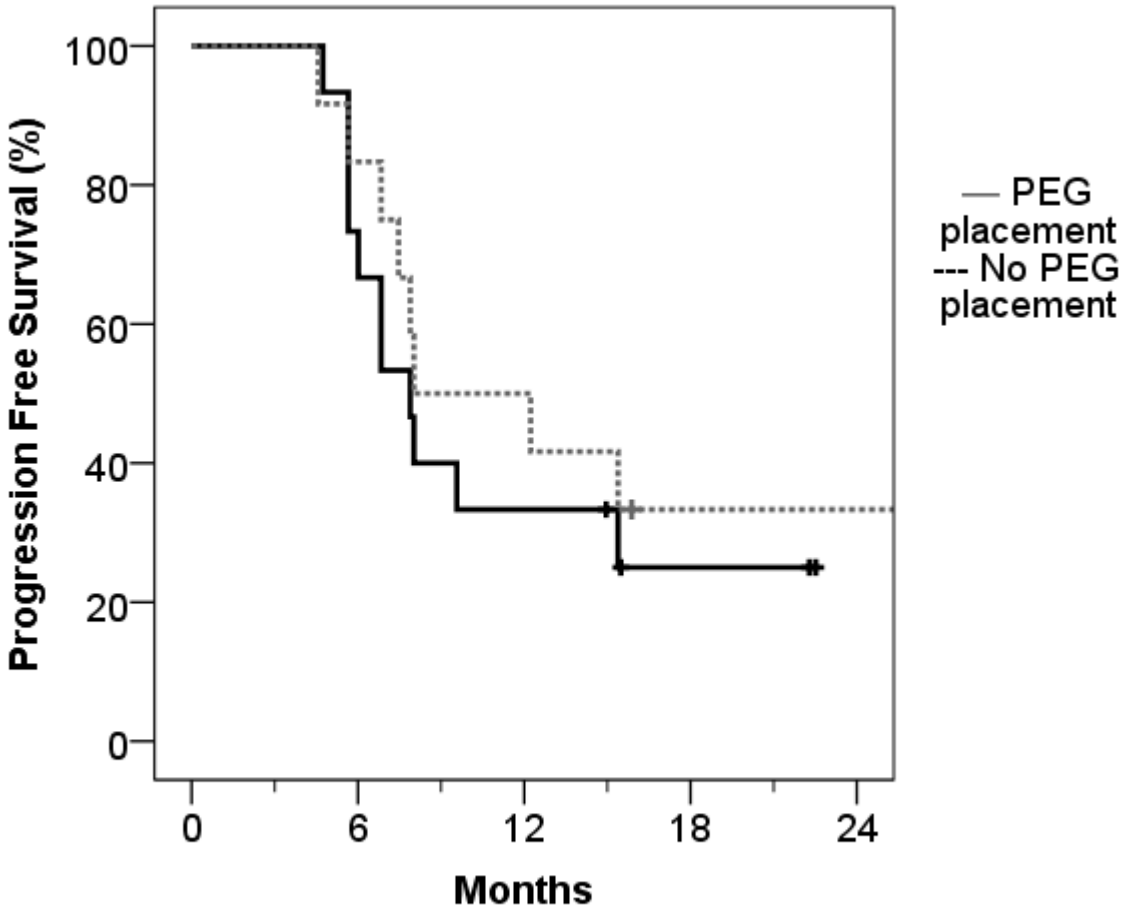

Figure 3. Overall survival compared PEG placement with PEG no placement

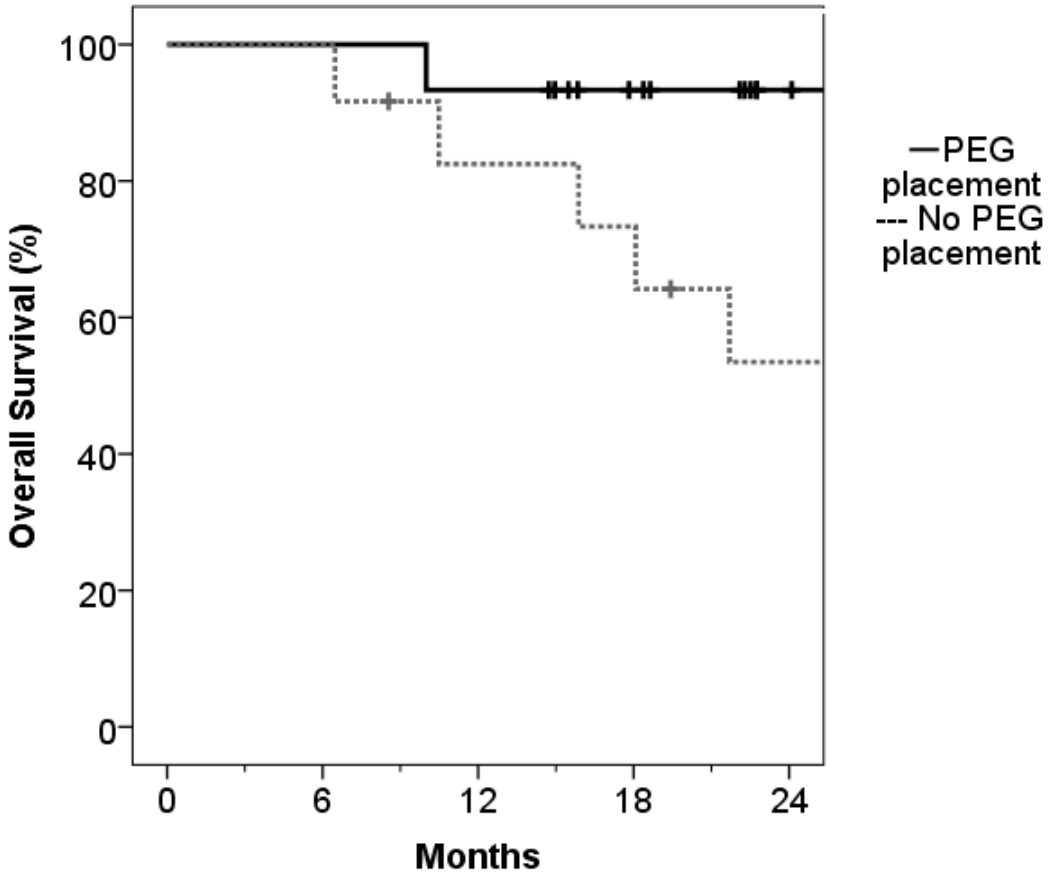

Table 1. Patient characteristics

Characteristic	No. of patients (n=27)	
	PEG placement (n=15)	No PEG placement (n=12)
Sex		
Male	15	10
Female	0	2
Age (years)		
Median	69	70
Range	44-77	45-80
ECOG performance score		
1	12	7
2	3	5
Primary Site		
Oropharynx	5	6
Hypopharynx	7	3
Larynx	3	3
Stage		
III	5	5
IVA	8	6
IVB	2	1
Reason for administration of cetuximab		
Age >75 years	7	2
Renal dysfunction	8	10
Complication*	5	1
Smoking history		
Current	12	7
Former	3	4
Never	0	1
Brinkman Index** [Mean (Range)]	1000 (200-1600)	1600 (0-1600)
Drinking history		
Current	7	8
Ex	4	2
Non	4	1

* Poorly controlled diabetes mellitus, cardiovascular disease and cirrhosis

** Number of cigarettes smoked per day × years of smoking

Table 2. Treatment exposure

	No. of patients (n=27)	
	PEG placement (n=15)	No PEG placement (n=12)
Number of cetuximab administrations		
Mean	7	7
Range	5-8	3-8
Radiation		
66-70 Gy (33-35 Fr)	15	12
Completed without interruption	15	7
Completed with interruption*	0	5
Reasons for interruption of radiation		
Mucosal infection, Grade 3	0	3
Central catheter-related infection, Grade 3	0	2

*: Long interval due to a national holiday.

Table 3. Adverse Events

Adverse Event	PEG placement （n=15)		No PEG placement (n=12)	
	All Grades	Grades 3-4 (%)	All Grades	Grades 3-4 (%)
	No. of patients (%)			
Hematological toxicity				
Leukopenia	1	0	8	0
Neutropenia	3	0	6	0
Febrile neutropenia	0	0	0	0
Anemia	13	0	9	2 (17)
Thrombocytopenia	1	0	2	0
Hypomagnesemia	4	0	4	0
Non-hematological toxicity				
Nausea	9	0	8	0
Vomiting	1	0	3	0
Mucositis	15	7 (47)	12	10 (83)
Radiation dermatitis	15	8 (53)	12	7 (58)
Acneform rash	13	0	11	1 (8)
Paronychia	9	0	10	0
Dry skin	12	0	11	0
Fissure	13	0	9	0

Table 4. Mucositis and radiation dermatitis.

	PEG placement (n=15)	No PEG placement (n=12)	P value
Adverse Event	No. of patients		
Mucositis			
Grade 2	8	2	p=0.058
Grade 3	7	10	
Radiation dermatitis			
Grade 2	6	5	p=0.632
Grade 3	8	7	

Table 5. Change in nutritional status.

	PEG placement (n=15)	No PEG placement (n=12)
Body weight loss (kg)		
Mean (range)	4.9 (2-6)	5.5 (1.6-16.2)
Percentage of weight loss during treatment		
Mean (range)	8.8 (3.1-11.5)	9.6 (3.1-28.5)
Decreased albumin (g/dL)		
Mean (range)	3.2 (0.2-1.8)	2.9 (0.3-1.5)