Research Article

Effectiveness of Prophylactic Gastrostomy in Head and Neck Cancer Patients Treated by Image-Guided Radiotherapy and Chemotherapy: Practice Proposal by the International Geriatric Radiotherapy Group

Nam P Nguyen[1*], Paul Vos[2], Jacqueline Vock[3], Juliette Thariat[4], Richard A Vo[5], Sarah Kratz[6], Michelle Bratton[7], Claire Lemanski[8], Vincent Vinh-Hung[9], Olena Gorobets[10], Alexander Chi[11], Juan Godinez[12], Michael Betz[13], Ulf Karlsson[14], Suresh Dutta[14], Fred Ampil[15]

[1]Department of Radiation Oncology, Howard University, Washington DC, USA
[2]Department of Biostatistics, East Carolina University, Greenville, NC, USA
[3]Department of Radiation Oncology, Lindenhofspital, Bern, Switzerland
[4]Department of Radiation Oncology, Centre Francois Baclesse, Caen, France
[5]School of Medicine, University of Galverston, Galverston, TX, USA
[6]Division of Hematology/Oncology, Mayo Clinic, Rochester, USA
[7]Department of Clinical Nutrition, University of Arizona, Tucson, AZ, USA
[8]Department of Radiation Oncology, Montpellier Cancer Institute, University of Montpellier, Montpellier, France
[9]Department of Radiation Oncology, University of Martinique Hospital, France
[10]Department of Oral Maxillofacial Surgery, Kyiv, Ukraine
[11]Department of Radiation Oncology, Capital Medical University, Beijing, China
[12]Department of Radiation Oncology, Waco Texas Oncology, Waco, TX, USA
[13]Department of Radiation Oncology, Hirslanden Radiation Oncology Institute, Lausanne, Switzerland
[14]Department of Radiation Oncology, International Geriatric Radiotherapy Group, Washington, DC, USA
[15]Department of Radiation Oncology, Louisiana State University, Shreveport, LA, USA

[*]**Corresponding Author:** Nam P Nguyen, MD, Professor of Radiation Oncology, Howard University Hospital, Department of Radiation Oncology, 2401 Georgia Avenue NW, Washington, DC 20060, USA, Tel: 202/865-1421; Fax: 202/806-7216; E-mail: NamPhong.Nguyen@yahoo.com

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Abstract

Objectives: To assess the effectiveness of prophylactic percutaneous endoscopic gastrostomy (PEG) tube feedings in locally advanced head and neck cancer patients undergoing image-guided radiotherapy (IGRT) and concurrent chemotherapy.

Materials and Methods: A retrospective review of 141 patients with locally advanced head and neck cancer who underwent concurrent chemoradiation using IGRT was performed. Prophylactic PEG placement was performed in 101 patients while 40 patients declined PEG. Grade 3-4 acute toxicities, treatment breaks, and weight loss were compared between the two groups.

Results: Mean weight loss was 11.4 and 15 pounds (p=0.06) for patients with and without PEG respectively. Mean treatment breaks was 8.1 and 7.4 days (p=0.6) for patients with and without PEG respectively. Both groups experienced significant grade 3-4 toxicity. Grade 3-4 hematologic toxicity and mucositis were 20% and 21% (p=0.8), and 75% and 80% (p=0.1) for the group with and without PEG respectively. Seven patients (4.8%) developed aspiration pneumonia (five with PEG and two without PEG). No patient had any complications related to PEG placement.

Conclusions: Grade 3-4 toxicity remains significant for head and neck cancer patients undergoing IGRT and chemotherapy leading to severe weight loss, treatment breaks, and aspiration pneumonia. Prophylactic PEG placement is safe to complement oral intake. Close patient monitoring and nutritional support should be provided regardless of the PEG status. Future prospective studies should be conducted to assess the impact of PEG on patient nutrition and quality of life in a larger number of patients with head and neck cancer.

Keywords: Head and neck cancer; Locally advanced; IGRT; Chemotherapy; PEG

1. Introduction

Standard of care for locally advanced head and neck cancer has been surgery followed by postoperative irradiation or concurrent chemoradiation for anatomic organ preservation [1]. Definitive chemoradiation with conventional radiotherapy techniques using two lateral and a supraclavicular field carries significant toxicity because of grade 3-4 mucositis and hematologic toxicity [2]. In severe cases, death may occur because of aspiration pneumonia [3]. Weight loss before and during radiotherapy is one of the major prognostic factors [4, 5]. Prophylactic percutaneous endoscopic gastrostomy (PEG) placement is often recommended [6, 7]. Intensity modulated radiotherapy (IMRT) has replaced the conventional radiotherapy technique because of the steep dose gradient allowing significant sparing of normal organs and improvement of patient quality of life [8, 9]. However, toxicity is still significant with IMRT resulting in severe weight loss and treatment breaks. Recently, image-guided radiotherapy (IGRT) has been introduced in an effort to minimize long-term treatment complications because of its ability to reduce radiation dose to the normal organs compared to IMRT and in particular radiation dose to the larynx and pharyngeal muscles if these organs are not invaded by the tumor [10, 11]. Preliminary results have been encouraging as aspiration risk is significantly reduced in patients undergoing IGRT and chemotherapy without compromising local control [12, 13]. As patients still experienced significant acute toxicity during IGRT, PEG tubes placement is frequently required, either prophylactically or during radiotherapy, to allow the patients to complete treatment. Because prophylactic PEG placement may lead to long-term feeding tubes dependence, its role in the management of locally advanced head and neck cancer remains controversial. As IGRT is a new treatment technique, the role of

prophylactic PEG placement in this setting has not been investigated so far and lead us to conduct this retrospective study. The results of this study may also help our international research group, the International Geriatric Radiotherapy Group (http://www.igrg.org), to design future prospective studies for head and neck cancer.

2. Materials and Methods

The medical records of 145 patients undergoing IGRT and concurrent chemotherapy from 2008 to 2012 for locally advanced head and neck cancer at the University of Arizona Radiation Oncology department were retrospectively reviewed. The University of Arizona institution review board approved and waived the consent for the study. Except for three patients, all patients were treated on the helical tomotherapy unit. The other three were treated on the Varian EX. Prior to treatment, each patient was simulated in a supine position with a head and neck aquaplast mask for treatment immobilization. A computed tomography (CT) scan with and without intravenous (IV) contrast for treatment planning was performed in the treatment position. The head and neck areas from the vertex to the mid thorax were outlined with a slice thickness of 3 mm. CT scan with IV contrast was employed to outline the tumor and grossly enlarged cervical lymph node for target volume delineation. Radiotherapy planning was performed on the CT scan without contrast to avoid possible interference of contrast density on radiotherapy isodose distributions. Diagnostic positron emission tomography (PET)-CT scan for tumor imaging was also incorporated into CT planning when available. A 0.5 cm bolus was placed on any area of the skin involved by the tumor and on any palpable cervical lymph nodes.

Normal organs at risk for complications were outlined for treatment planning (spinal cord, brain stem, cochlea, mandible, parotid glands, larynx, pharyngeal muscles, eyes, and oral cavity). Radiation therapy dose was similar for patients in both groups using the integrated boost technique to decrease treatment toxicity. The tumor and grossly enlarged lymph nodes on CT scan (CTV1) with a margin (PTV1) were treated to 70 Gy in 35 fractions (2 Gy/fraction). The margins were 5 mm to 1 cm all around CTV1 depending on anatomic location. The areas at high risk-PTV2 (at least 1 cm around gross tumor and pathologic cervical lymph nodes) and low risk -PTV3 (subclinical regional lymph nodes with 5 mm margins) for tumor spread were treated respectively to 63 Gy and 56 Gy in 35 fractions. Patients undergoing postoperative radiation were treated to 66 Gy, 59.4 Gy, and 54 Gy in 33 fractions to PTV1, PTV2, and PTV3 respectively. Indications for postoperative chemoradiation were positive margins, and/or extracapsular lymph node invasion. Minimal target coverage was 95% for all target volumes with at least 99% of the prescribed dose delivered to gross tumor and involved cervical lymph nodes. The lymph nodes in the ipsilateral neck including the retropharyngeal lymph nodes were treated to the base of skull in case of any cervical lymph node enlargement (or PET positive lymph nodes). Contralateral uninvolved lymph nodes were treated prophylactically with the C1 vertebrae as superior border. In case of bilateral cervical lymph nodes involvement, both necks were treated to the base of skull to avoid any marginal miss. Mean dose to the parotid was kept below 2600 cGy if there was no ipsilateral cervical lymph node enlargement. Dose constraints for other normal organs at risk (OAR) for complications were: spinal cord (45 Gy), brain stem (50 Gy), optic chiasm (45 Gy), mandible (70 Gy to less than 30% of the mandible). Doses to larynx and pharyngeal muscles for non-laryngeal and -hypopharyngeal cancers were kept between 20-40 Gy if feasible as it is our strict policy that all PTV should be covered by at least the 95% target dose. The larynx and pharyngeal muscles were contoured from the hyoid bone (superior border) to the cricoid cartilage (inferior border) following

consultation with a radiologist. The pharyngeal muscles outlined were the middle and inferior pharyngeal constrictors muscles.

Concurrent chemoradiation was recommended for all patients. The type of chemotherapy regimen was left to the discretion of the medical oncologists depending on the patient functional status and co-morbidities. Prophylactic PEG placement before treatment was recommended to all patients because of the expected severe mucositis and weight loss during treatment. However, if a patient declined PEG placement, his/her wish was respected. Patients with prophylactic tube placement were encouraged to continue with their oral feeding until dysphagia secondary to mucositis developed and impaired their oral intake. All patients in the study were monitored closely during treatment by a team of dietitians assessing patient caloric requirement and making treatment recommendations. Weekly complete blood count (CBC) and blood chemistry to assess renal function were performed during chemoradiation. Treatment breaks and weight loss during chemoradiation were recorded. Acute and long-term toxicities were recorded according to the Radiotherapy Oncology Group (RTOG) severity scale (http://ctep.cancer.gov). Statistical analysis was performed with the Welch's t test. A difference with p value <0.05 was considered statistically significant.

3. Results

We identified 145 patients with head and neck cancer treated with IGRT and concurrent chemotherapy at the University of Arizona Radiation Oncology department from 2008 to 2012. Four patients were excluded from the analysis because they had recurrent skin cancer leaving 141 patients with primary (n=139) or recurrent (n=2) squamous cell carcinoma of the head and neck for analysis. All except three patients had locally advanced disease. The three patients with stage II disease underwent postoperative chemoradiation because of positive margins. All patients had squamous cell carcinoma. The median age was 62 (range: 22-90). There were 16 females and 125 males. The anatomic disease site was: oropharynx (n=63), oral cavity (n=27), larynx (n=26), hypopharynx (n=5), unknown (n=11), nasopharynx (n=6), and paranasal sinus (n=3). The treatment setting was respectively postoperative (n=13) and definitive chemoradiation (n=128). A total of 40 patients declined prophylactic PEG placement. Table 1 summarizes patient characteristics. Chemotherapy consisted of the following: cisplatin 30 mg/m^2 intravenously (IV) weekly (n=56); cisplatin 100 mg/m^2 IV on day 1, 22, and 43 of chemotherapy (n=40), weekly carboplatin (CP) AUC 1.5 (n=33), CP AUC 6 weeks 1, 4 and 7 of radiotherapy (n=7), 5-fluorouracil (5-FU) 1,000 mg/m^2 and cisplatin 10 mg/m^2 on days 1-4 and days 22-24 (n=1) of radiotherapy, Taxol (T) 30 mg/m^2 (n=1). Three patients received cetuximab 250 mg/m^2 weekly during radiotherapy.

Six patients in the whole group did not complete the treatment because of death from aspiration pneumonia (n=1), stroke (n=1), severe vomiting (n=1) or grade 3-4 mucositis (n=2). Among the patients who did not complete treatment, two did not have a prophylactic PEG. Grade 3-4 hematologic and mucosal toxicity were 20 and 21% (p=0.8), and 75 and 80% (p=0.1) for the patients with and without PEG respectively. Mean weight loss and treatment breaks were 11.4 and 15 pounds (p=0.06) and 8.1 and 7.4 days (p=0.6) respectively for the group with and without PEG. No significant difference was found in term of weight loss and treatment breaks between the patients who had laryngeal and hypopharyngeal cancers and those with non-laryngeal/non-hypopharyngeal cancers. Mean weight loss and treatment breaks were 12.9 and 10.7 pounds (p=0.2), and 8.2 and 7 days (p=0.3) respectively, for patients with laryngeal and hypopharyngeal cancers and non-laryngeal/hypopharyngeal cancers.

Seven patients (4.8%) developed aspiration pneumonia during chemoradiation with resulting death in one patient. Five patients who had pneumonia also had neutropenia requiring granulocyte colony stimulating factors (GCSF) administration. Two of the patients who developed aspiration pneumonia did not have prophylactic PEG tubes. Table 3 summarizes characteristics of patients who developed aspiration pneumonia. Other grade 3-4 non-hematologic or mucosal toxicities included nausea and vomiting (n=9), skin reaction (n=9), neuropathy (n=1), psychosis (n=1), and pseudomembranous colitis (n=1). No patient developed complications related to PEG tube placement.

Characteristics	With PEG	Without PEG	Whole group
Patient No	101	40	141
Age (years)			
Median	64	71	62
Range	22-90	25-82	22-90
Sex			
Female	11	5	16
Male	90	35	125
Histology			
Squamous	101	40	141
Stage			
T stage			
Tx	5	6	11
T1	7	3	10
T2	32	11	43
T3	27	7	34
T4	34	7	41
Recurrence	2	0	2
N stage			
N0	19	6	25
N1	26	10	36
N2	42	18	60
N3	14	4	18
Recurrence	2	0	2
Stage			
II	1	2	3
III	23	12	35
IVA	50	20	70
IVB	22	5	27
IVC	4	0	4
Recurrence	2	0	2
Sites			

Oropharynx	41	22	63
Oral cavity	21	6	27
Larynx	22	4	26
Hypopharynx	4	1	5
Unknown	5	6	11
Nasopharynx	6	0	6
Paranasal sinus	2	1	3
Treatment			
Postoperative chemoradiation	7	6	13
Definitive chemoradiation	94	34	128

PEG: percutaneous endoscopic gastrostomy

Table 1: Patient characteristics.

	With PEG	**Without PEG**	**p-value**
Weight loss (pounds)			
Mean	11.4	15	0.06
Range	0-50	0-40	
Treatment breaks (days)			
Mean	8.1	7.4	0.6
Range	0-34	0-50	
Grade 3-4 toxicity (%)			
Hematologic	20	21	0.8
Mucositis	75	80	0.1

Table 2: Treatment toxicity.

Age	**Site**	**Stage**	**Treatment breaks**	**PEG tube**
80	oral cavity	T4N0M0	Died during treatment	yes
60	unknown	TxN2M0	19 days	no
66	larynx	T4N2M0	10 days	yes
66	oral cavity	T4N0M0	24 days	yes
64	nasopharynx	T4N0M0	14 days	yes
53	larynx	T4N3M0	10 days	yes
47	unknown	TxN1M0	10 days	no

PEG: percutaneous endoscopic gastrostomy

Table 3: Characteristics of patients who developed aspiration pneumonia during image-guided radiotherapy and chemotherapy for locally advanced head and neck cancer.

4. Discussion

To our knowledge, this is the first study looking at the effectiveness of prophylactic PEG placement in preventing weight loss and treatment breaks during concurrent chemoradiation with IGRT for locally advanced head and neck cancer. Patients with advanced stage head and neck cancer often had weight loss at diagnosis because of dysphagia. Patients with laryngeal and hypopharyngeal cancers may also have silent aspiration prior to treatment because of tumor invasion of the pharyngeal muscles and may involuntarily limit their oral intake as a result [14, 15]. PEG placement is indicated in the presence of aspiration to prevent aspiration pneumonia and in case of malnutrition to prevent further weight loss. Many institutions also advocate prophylactic PEG tube placement for patients undergoing chemoradiation for locally advanced head and neck cancer because the expected severe mucositis during the course of treatment which often lead to severe weight and treatment breaks which may compromise the cure rate [5]. Two randomized studies also support the use of prophylactic PEG tubes prior to chemoradiation [16, 17]. Silander et al. [16] reported on 134 patients who underwent chemoradiation or postoperative irradiation for advanced head and neck cancer. Among the patients who were randomized to prophylactic PEG, body mass index (BMI) and quality of life (QOL) were significantly better than those without PEG. Improvement of patient QOL with prophylactic PEG tubes placement was also corroborated in another study of head and neck cancer patients undergoing chemoradiation [17]. However, prophylactic PEG placement may also lead to prolonged tube feedings post treatment and prompt other institutions to advocate elective PEG placement only in case of severe dysphagia secondary to severe mucositis [18]. There were also possible complications related to PEG placement [19]. Thus, the controversial issue of prophylactic PEG tube placement for locally head and neck cancer remains unsettled in patients treated with 3D-CRT.

Further complicating the issue is the introduction of pharyngeal muscle-sparing IMRT to decrease the severity of dysphagia and possibly the need for PEG tube requirement during radiotherapy [20]. However, even with IMRT, grade 3-4 acute toxicity during chemoradiation and aspiration pneumonia remain significant, potentially leading to patient death which may be prevented with PEG [3, 21, 22]. As a result, we continue to recommend prophylactic PEG tubes placement for patients undergoing concurrent chemoradiation for head and neck cancer even though IGRT may minimize aspiration risk in non-laryngeal and non-hypopharyngeal head and neck cancer [11]. However, we will respect the patients' wish if they declined PEG placement. Grade 3-4 mucositis and hematologic toxicities remain significant for the whole group regardless of the anatomic sites of the cancer leading to severe weight loss and treatment breaks. We observe no statistically significant difference in terms of weight loss or treatment breaks between patients with and without PEG which highlight the importance of having nutritional support during treatment. All patients were closely monitored with a team of nutritionists who assessed the patient intake, weight, and nutritional parameters such as total protein, albumin and pre-albumin in order to make treatment recommendations. Nutritional counseling and oral nutritional supplements have been proven to be effective for the reduction of weight loss for patients undergoing chemoradiation for head and neck cancer [23]. Indeed, Kiss et al. reported that early intervention by a team of dietitians skilled in the management of head and neck cancer has led to a reduced need for hospital admission and unplanned nasogastric tube insertions for patients who had chemoradiation for head and neck cancer [24].

McLaughlin et al. also corroborated the role of aggressive supportive care in maintaining adequate

nutrition for patients who did not have prophylactic PEG placement prior to head and neck chemoradiation [25]. Paccagnella et al. illustrated the importance of early nutritional intervention to decrease treatment breaks, unnecessary hospitalizations and weight loss for head and neck cancer receiving chemotherapy and radiation [26]. On the other hand, if close monitoring with a nutritional support team is not available, placement of a PEG tube may prevent severe weight loss secondary to mucositis as tube feedings allows patients to maintain their body weight despite dysphagia [27-29]. Assenat et al. reported less treatment breaks and reduced weight loss among the patients who had prophylactic PEG placement prior to head and neck chemoradiation compared to those without feedings tube [28]. However, the patients who had feeding tubes also benefit from nutritional support during chemoradiation in the study. Atasoy et al. also illustrated the role of nutritional support among patients who had prophylactic PEG placement before their head and neck chemoradiation [29]. Nine out of 23 patients who were not compliant with their tubes feeding had significant weight loss during chemoradiation and four of these patients were not able to complete treatment.

We do not observe any significant difference in weight loss or treatment breaks among patients with laryngeal and hypopharyngeal cancers compared to other anatomic sites. As these tumors are located close to the middle and inferior pharyngeal muscles, the radiation dose to the pharyngeal muscles would have been higher compared to other anatomic sites. We do observe a high rate of aspiration pneumonia in the study as seven patients (4.9%) developed pneumonia during treatment. Five of these patients had severe neutropenia requiring GCSF administration. One died from pneumonia and the other six recovered after a long treatment break. The patient who died was 80 years old with multiple comorbidity factors. Thus, despite close monitoring, nutritional support, and PEG placement, aspiration pneumonia remains a life-threatening issue for patients undergoing concurrent chemotherapy and IGRT because of the severity of mucositis and associated neutropenia. As an illustration, Panghai et al. reported a high rate of oral infection and sepsis with Gram negative and positive bacteria which was associated with oral mucositis in patients with head and neck cancer undergoing radiotherapy alone or with chemotherapy [30]. Other studies also corroborated the high rate of aspiration pneumonia associated with head and neck cancer chemoradiation which may result in death [3, 18, 31, 32]. Chu et al. [31] reported that 776 (4.8%) out of 15,122 patients undergoing radiotherapy alone or combined with chemotherapy developed pneumonia within 90 days of the beginning of radiotherapy. Chen et al. [32] corroborated the high incidence of pneumonia (6.8%) during chemoradiation for 595 head and neck cancer patients resulting in termination of radiotherapy of 10 patients. As five of the seven patients who developed pneumonia in the study had prophylactic PEG placement, we do not know whether the pneumonia rate would have been higher without feeding tubes. As our treatment policy encouraged the patients to continue oral feeding until they developed dysphagia to avoid long-term feeding tubes dependence, this recommendation may have inadvertently exposed the patients to aspiration during treatment as PEG tubes have been shown effective to reduce aspiration pneumonia in patients with spinal cord injury [33].

We also argue that even though the patients who had prophylactic PEG placement had less weight loss compared to the ones without, this difference was not statistically significant. We postulate that if there were more patients in the non-PEG group, the statistical difference may have been significant. As an international research group devoted to the care of older cancer patients in 127 countries, we may be able to conduct prospective randomized studies among

head and neck cancer patients undergoing chemoradiation to evaluate the impact of PEG on patient nutrition and quality of life (QOL) [34-38]. The limitations of the study include its retrospective nature, the small number of patients, and the absence of information on long-term PEG dependence. Nevertheless, our study highlights the acute toxicity of concurrent chemotherapy and IGRT, the high rate of aspiration pneumonia most likely related to oral mucositis, and the importance of nutritional support during treatment regardless of prophylactic PEG placement.

5. Conclusion

Acute grade 3-4 toxicity during IGRT and chemotherapy for locally advanced head and neck cancer remains significant leading to severe weight loss, treatment breaks, and possible death secondary to aspiration pneumonia. PEG placement is safe procedure for providing nutritional supplements during treatment. Patients should be closely monitored and should receive nutritional support during treatment regardless of their PEG status. Future prospective randomized studies should be performed to assess the impact of prophylactic PEG tube placement on patient nutrition status and QOL.

Conflict of Interest

The authors have no conflict of interest and have no source of funding.

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