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Dysphagia following chemoradiation for locally advanced head and neck cancer

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Background: To assess the prevalence, severity and morbidity of dysphagia following concurrent chemoradiation for head and neck cancer.

Patients and methods: Patients who underwent chemotherapy and radiation for head and neck malignancies were evaluated for their ability to resume oral feeding following treatment. Modified barium swallow (MBS) studies were performed if the patients complained of dysphagia or if there was clinical suspicion of aspiration. The severity of dysphagia was graded on a scale of 1–7. If significant abnormalities were found, swallowing studies were repeated until resolution of dysphagia.

Results: Between March 1999 and May 2002, 55 patients with locally advanced head and neck cancer underwent concurrent chemotherapy and radiation. Aspiration pneumonia was observed in eight patients, three during treatment and five following treatment. Five patients died from pneumonia. Two patients developed respiratory failure requiring intubation as a complication of pneumonia. At a median follow-up of 17 months (range 6–48 months), 25 patients (45%) developed severe dysphagia requiring prolonged tube feedings for more than 3 months (22 patients) or repeated dilatations (three patients). Among 33 patients who underwent MBS following treatment, 12 patients (36%) had silent aspiration (grade 6–7 dysphagia). Thirteen patients (39%) developed grade 4–5 dysphagia which required prolonged enteral nutritional support to supplement their oral intake. Most patients had severe weight loss (0–21 kg) during treatment, likely due in part to mucositis in the orodigestive tube.

Conclusions: Dysphagia is a common, debilitating and potentially life-threatening sequela of concurrent chemoradiation for head and neck malignancy. Physicians should be aware that the clinical manifestations of aspiration may be unreliable and insidious, because of the depressed cough reflex. Modified and traditional barium swallows should be performed following treatment to assess the safety of oral feeding and the structural integrity of the pharynx and esophagus. Patients with severe dysphagia may benefit from rehabilitation. Tube feeding should be continued for those with aspiration.

Key words: aspiration, chemoradiation, dysphagia, head and neck cancer

Introduction

Locally advanced head and neck cancer carries a poor prognosis because of the high rate of loco-regional recurrences [1]. The combination of chemotherapy and radiation may improve the local control and survival rate because of the additive or synergistic effect of chemoradiation [2]. However, the radiosensitization effect of chemotherapy may also lead to increased acute toxicity and late complications [3]. The radiation therapy fields usually cover a large area of head and neck to ensure that tumor bed and regional lymph nodes receive an adequate dose.

Critical structures necessary for normal deglutition, such as tongue, larynx and pharyngeal muscles, may be treated to a high radiation dose. The increased radiation dose may lead to hyperactivation of transforming growth factor β1 (TGFβ1), a peptide involved in collagen deposition and degradation [4]. Excessive fibrosis may be responsible for abnormal motility of the deglutition muscles and may lead to the aspiration, dysphagia and stenosis observed following head and neck chemoradiation [5]. The patient's quality of life may be adversely affected [6]. For proper patient management, it is therefore important for the clinician to assess the prevalence and severity of dysphagia following the combined regimen.

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Patients and methods

Between March 1999 and May 2002, 55 patients with locally advanced head and neck cancer (stage III and IV) underwent concurrent chemotherapy and radiation. Patients were selected if they had T1–T4 primary tumor, N1–N3 metastatic neck nodes, Karnofsky performance status (PS) of >70%, and adequate end-organ function defined as an absolute neutrophil count >1500/mm^3, platelets >100 000/mm^3, serum creatinine <1.5 × normal, serum bilirubin <35 μmol/l, normal serum glutamic oxalacetic and pyruvic transaminase. All patients signed an informed consent.

Prior to treatment, the patients underwent dental extraction, nutritional assessment and placement of a gastrostomy tube for enteral feeding during treatment. Following enrolment, the patients received 5-fluorouracil (5-FU) 1000 mg/m^2 intravenously (i.v.) by continuous infusion on days 1–4 and 21–24, and cisplatin 100 mg/m^2 i.v. on days 1 and 21 of radiation. Patients with nasopharyngeal carcinoma received cisplatin 100 mg/m^2 i.v. on days 1, 22 and 43 of radiation.

Radiation therapy was delivered on a Cobalt Unit or a 6 mV linear accelerator using standard technique (two lateral and one supraclavicular field, off cord at 3960–4000 cGy, 180–200 cGy/fraction). The dose to the gross tumor was 6600–7200 cGy; lymph nodes at risk of subclinical metastasis received 5000–5400 cGy. Patients were evaluated weekly during treatment or more frequently if clinically indicated. Toxicity during treatment was assessed according to the Radiation Therapy Oncology Group (RTOG) toxicity scale. Degree of weight loss and any treatment delays were recorded at the end of treatment.

After completion of treatment, patients were followed monthly with repeated endoscopy by the Ear, Nose, and Throat service at each visit. Patients were instructed to continue with tube feeding until resolution of the acute mucositis enabled them to resume a normal diet. Modified barium swallow (MBS) studies were performed if the dysphagia persisted 3 months after treatment or if there was clinical suspicion of aspiration [7].

During the MBS procedure, the patients were either sitting or standing and viewed in frontal and lateral planes. The fluoroscopy tube was positioned to view the oral cavity anteriorly, the soft palate superiorly, the posterior pharyngeal wall posteriorly, and the seventh cervical vertebra inferiorly. In this way, the oral preparatory, oral, pharyngeal and cervical esophageal phases of deglutition could be assessed and viewed simultaneously. Seven consistencies of food and liquid were introduced by teaspoon to the patient. Water, liquid barium, applesauce, mashed potatoes, green beans, ground meat and sliced meat mixed with barium paste were used in the assessment. With each swallow, the patient was instructed to hold the material in his mouth until told to swallow. The fluoroscope remained focused on the oral cavity and pharynx during and after each swallow. A number of observations were made during each swallow. Residue on the tongue or in the pharynx after the swallow, laryngeal penetration or aspiration during or after the swallow, backflow, esophageal-pharyngeal reflux, and disordered peristalsis in the pharynx or esophagus were noted. The patient was then repositioned in the anterior–posterior position and presented with at least two additional consistencies, usually liquid barium and mashed potatoes introduced by teaspoon. Finally, at the completion of swallowing, the patient was instructed to vocalize on 'a' and count to five while being videotaped with fluoroscopy.

Each patient was scored using the Swallowing Performance Scale [8]. Grade 1: normal. Grade 2: within functional limits—abnormal oral or pharyngeal stage but able to eat a regular diet without modifications or swallowing precautions. Grade 3: mild impairment—mild dysfunction in oral or pharyngeal stage, requires a modified diet without need for therapeutic swallowing precautions. Grade 4: mild-to-moderate impairment with need for therapeutic precautions—mild dysfunction in oral or pharyngeal stage, requires a modified diet and therapeutic precautions to minimize aspiration risk. Grade 5: moderate impairment—moderate dysfunction in oral or pharyngeal stage, aspiration noted on exam, requires a modified diet, and swallowing precautions to minimize aspiration risk. Grade 6: moderate–severe dysfunction—moderate dysfunction of oral or pharyngeal stage, aspiration noted on exam; requires a modified diet and swallowing precautions to minimize aspiration risk; needs supplemental enteral feeding support. Grade 7: severe impairment—severe dysfunction with significant aspiration or inadequate oropharyngeal transit to esophagus; nothing by mouth; requires primary enteral feeding support.

In addition to a modified diet, patients were instructed about safe eating techniques, and the swallowing maneuvers designed to facilitate the safest swallow. The rehabilitation technique was individualized for each patient who was then followed at regular intervals by the speech pathologist. Modified barium swallow was repeated if deemed necessary by the team. Traditional barium swallow was also obtained to complement the MBS if abnormal structural integrity of pharynx and esophagus were suspected by the team. The patient's weight and nutritional status were also monitored by a dietitian who provided enteral nutritional support recommendations as needed.

Results

Fifty-five male patients were enrolled in the study. Their ages ranged from 34 to 86 years (median age 59 years). There were 43 Caucasians and 12 African Americans. The tumors were located in the oropharynx (29 patients), larynx (11 patients), hypopharynx (five patients), oral cavity (six patients) and nasopharynx (four patients). Seventeen patients had stage III disease (eight T3N0, three T2N1, three T3N1, two T1N2, one T2N2), and 38 had stage IV (seven T4N0, six T4N1, three T4N2, three T4N3, five T3N2, three T1N3, six T2N3, one T3N3, three T2N2, one T1N2). The histology was reported as 53 squamous and two basaloid with tumor grades: well differentiated (four patients), moderately differentiated (22 patients), poorly differentiated (12 patients) and unspecified (16 patients). Table 1 summarizes the patient characteristics.

Three patients received only one cycle of chemotherapy because of severe weight loss (one patient), renal failure (one patient) and death (one patient). The dose of 5-FU was reduced in one patient because of severe mucositis. Cisplatin was replaced by carboplatin in four patients because of increased creatinine at baseline (three patients), or after the first cycle of chemotherapy (one patient). Radiation therapy was discontinued in three patients at 2040 cGy, 4860 cGy and 5000 cGy because of death secondary to sepsis (two patients) and patient refusal to continue treatment (one patient).

Acute toxicity was primarily grade 3–4 mucositis (45 patients) and hematological. Grade 3–4 neutropenia, anemia and thrombocytopenia occurred in 27, 12 and three patients, respectively. Three patients developed aspiration pneumonia during treatment requiring artificial ventilation (one patient) or resulting in death (two patients). One patient had severe cellulitis which resolved with antibiotics. Six patients developed transient abnormal renal function (four patients), requiring replacement of cisplatin by carboplatin during the second cycle of chemotherapy (one patient) or discontinuation of chemotherapy (one patient). The amount of weight loss ranged from 0 to 21 kg (median 8 kg).

At a median follow-up of 17 months (range 6–48 months), 43 (78%) patients were alive. Late aspiration pneumonia developed in five patients and contributed to the death of three patients. Two patients required intubation because of respiratory failure resulting from the pneumonia, but they recovered. The causes of

Table 1. Patient characteristics

Characteristic	No. of patients (%)
Total	55 (100)
Gender (male)	55 (100)
Race	
Caucasian	43 (78)
African American	12 (22)
Histology	
Squamous	53 (96)
Basaloid	2 (4)
Grade	
Well differentiated	4 (7)
Moderately differentiated	23 (42)
Poorly differentiated	12 (22)
Not specified	16 (29)
Stage	
III	17 (31)
IV	38 (69)
Site	
Oropharynx	29 (53)
Larynx	11 (20)
Oral cavity	6 (11)
Hypopharynx	5 (9)
Nasopharynx	4 (7)

death in other patients were tumor recurrence (four patients), liver cirrhosis (one patient) and cardiovascular (two patients).

Twenty-five patients (45%) developed severe dysphagia requiring prolonged (>3 months) tube feeding (22 patients) or repeated dilatation because of pharyngeal or esophageal stenosis (three patients). The time dependence for tube feeding for these patients ranged from 4 to 21 months (median 9 months). Thirty-three patients underwent MBS studies. Twelve patients (36%) had grade 6–7 dysphagia. Three of them improved on repeated studies (grade 3, 4 and 5, respectively). The other nine patients still required tube feeding as the severity of the dysphagia did not improve on subsequent studies. Thirteen patients (39%) had grade 4–5 dysphagia that required prolonged tube feeding to supplement their oral intake, as they developed severe weight loss during treatment. The remaining eight patients had grade 2 (two patients) or grade 3 (six patients) dysphagia. Table 2 summarizes the degree of dysphagia for these patients.

Discussion

Locally advanced head and neck cancer is usually associated with a poor prognosis because of high recurrence rate, despite aggressive management with surgery followed by postoperative radiation [9]. In an attempt to improve the prognosis, concurrent chemo-

Table 2. Grade of dysphagia for patients who underwent swallowing study following chemotherapy and radiation for locally advanced head and neck cancer

Site	Grade		
	1–2	3–5	6–7
Oropharynx	1	6	8
Larynx		7	3
Hypopharynx		4	1
Nasopharynx	1	1	
Oral cavity	1		

radiation was introduced, chemotherapy acting as a radiosensitizer. The high rate of apoptosis from the combined modality was hypothesized to increase tumor cell killing while allowing organ preservation [10]. Preliminary studies were encouraging. A high rate of local control was observed even for inoperable tumors [11]. However, the acute toxicity of chemotherapy and radiation was significant. Grade 3–4 mucositis occurred frequently, thus preventing the patient from oral feeding and leading to severe weight loss [12]. A gastrostomy (G) tube was usually required, as patients were unable to swallow during treatment [12].

To monitor the treatment effects objectively, videofluoroscopic swallowing studies following chemoradiation were performed. There was severe dysfunction of the base of the tongue, larynx and pharyngeal muscles, leading to stasis of the bolus, vallecular residue, epiglottic dysmotility, and in severe cases, aspiration [5, 13]. If aspiration occurred during treatment, its combination with neutropenia resulting from the chemotherapy may lead to aspiration pneumonia, sepsis and respiratory failure. Eight of our patients (14%) developed aspiration pneumonia requiring artificial ventilation (three patients) or resulting in death during or shortly following treatment (four patients). The eighth patient recovered with conservative management.

Another factor that may have contributed to the high morbidity of the aspiration pneumonia was the severe weight loss that compromised the immune system, leading to a poor outcome. The median weight loss was 8 kg in our study (range 0–21 kg). This was consistent with other studies where the mean weight loss during chemoradiation was reported to be 10–12% of the initial body weight [10, 14, 15].

The high rate of aspiration pneumonia has also been observed in other studies with different chemotherapy regimen for organ preservation. In Machtay et al.'s [16] study, patients had induction chemotherapy with carboplatin and paclitaxel followed by concurrent chemoradiation. Two of the 53 patients (4%) died from respiratory failure during chemotherapy and radiation. Following treatment, 12% of their patients developed chronic severe dysphagia that persisted for >9 months. Eisbruch et al. [17] performed videofluoroscopic swallow studies following treatment for advanced head and neck cancer patients who had concurrent gemcitabine and radiation. One to three months post therapy, 65% of the patients showed evidence of aspiration which persisted for up to 1 year. Six patients developed aspiration pneumonia and two

Table 3. Rate of dysphagia and aspiration following chemoradiation for locally advanced head and neck cancer

Authors	No. of patients	Chemotherapy	Radiation (Gy)	Aspiration rate (%)	Chronic dysphagia (%)
Machtay et al. [16]	53	CP, P	70	4	12
Eisbruch et al. [17]	25	G	70	68	NS
Pauloski et al. [18]	132	NS	NS	22	NS
Present study	55	5-FU, Cs	66–72	36	45

CP, carboplatin; Cs, cisplatin; P, paclitaxel; 5-FU, 5-fluorouracil; G, gemcitabine; NS, non-specified.

Table 4. Time dependence on tube feeding following chemotherapy and radiation for locally advanced head and neck cancer

Authors	No. of patients	Chemotherapy	Radiation (Gy)	Time (months)	%
Staton et al. [23]	45	Cs	68–74	6	36
Kies et al. [24]	64	5-FU, HU, P	72–75	12	17
Ackerstaff et al. [25]	26	Cs	NS	12	19
Samant et al. [26]	25	Cs	68–74	12	30
Nguyen et al.	55	5-FU, Cs	66–72	3	40

Cs, cisplatin; 5-FU, 5-fluorouracil; HU, hydroxyurea; NS, non-specified; P, paclitaxel.

died. It was noteworthy that the aspiration was often unrecognized, dysphagia being the only complaint. The patients had suppressed cough reflex when they aspirated. Pauloski et al. [18] also corroborated the silent nature of the aspiration with videofluoroscopic swallow studies. Patients who complained of dysphagia during radiation treatment had larger residue and a higher rate of aspiration (22%) during the swallowing study compared to the ones with no dysphagia (3%). They subconsciously reduced their oral intake and lost weight. Wu et al. [19] also noticed that following radiation for nasopharyngeal tumors, 41% of their patients who complained of dysphagia revealed silent aspiration during the endoscopic swallowing exam. We therefore believe that aspiration is underreported in chemoradiation series, because it is often silent. Twelve of our patients with grade 6–7 dysphagia also had aspiration, discovered serendipitously following treatment, as we performed swallowing studies for all patients who complained of dysphagia and as a safety precaution, prior to the removal of their G-tube. Table 3 summarizes the aspiration rate and dysphagia described in the literature following chemoradiation for head and neck cancer.

Even without aspiration, the abnormal motility of the muscles controling the swallowing mechanism following chemoradiation may result in impaired oral feeding and prolonged dependence on tube feeding [20]. The excessive scarring which may be observed with the combined modality may lead to constriction of the hypopharynx or the cervical esophagus and may require dilatation. Thirteen patients in our study had grade 4–5 dysphagia which required a long period of rehabilitation. Their convalescence required continued use of the gastrostomy tube to supplement oral intake. It has been shown that a voluntary swallowing maneuver, such as the tongue-hold maneuver, may improve the patient's ability to eat, as it enhances the posterior motion of the tongue base [21]. Furthermore, increased use of tongue range-of-motion exercises after radiation may reduce the formation of fibrotic tissue in the oral cavity [22]. Three additional patients underwent repeated dilatation because of pharyngeal or esophageal stenosis. Although the procedure carried little morbidity, it created a lot of apprehension for the patients.

The long-term need for a G-tube following concurrent chemotherapy and radiation is also documented in other series. Staton et al. [23] treated locally advanced laryngeal carcinoma with intra-arterial cisplatin and radiation. Six months following treatment, 16 of 45 patients (36%) still required a G-tube because of an inability to swallow. Kies et al. [24] combined hyperfractionated radiation and chemotherapy for stage III and IV tumors of different sites. At 1 year, 17% of the patients were still unable to swallow adequately. Nineteen and 30% of the surviving patients in studies by Ackerstaff et al. [25] and Samant et al. [26], respectively, required tube feeding >12 months following concurrent intra-arterial cisplatin and radiation. Even at 18 months following completion of chemotherapy and radiation, 13% of the patients in the Newman et al. [27] study were still fed by G-tube. However, it is difficult to assess the prevalence of aspiration in these studies, as MBS studies were not performed. Table 4 summarizes the need for prolonged tube feeding described in the literature.

Since hyperactivation of TGFβ from hydroxyl radicals produced by radiation may induce excessive fibrosis responsible for the dysphagia, we postulated that neutralization of these radicals may reduce the occurrence of dysphagia following chemoradiation [4]. Amifostine, a thiol compound, was recently recognized as a radioprotector. Buntzel et al. [28] reported a significant reduction

of dysphagia and fibrosis in 313 patients with head and neck cancer who received amifostine during chemoradiation as compared to 218 patients who did not have amifostine. Further studies should be carried out to confirm this finding.

The limitations of our study include short follow-up, lack of baseline swallowing study, prior to treatment, and the retrospective nature of the study, as only patients who complained of dysphagia underwent swallowing studies. Patients with locally advanced carcinoma, particularly larynx and hypopharynx, may experience high-grade dysphagia because of the tumor extent and the destruction of normal tissue [29]. Some patients who complained of dysphagia did not undergo swallowing studies because of refusal, loss to follow-up, or physician reluctance to order the study. Nevertheless, we believe that physicians should be aware of the insidious nature of the aspiration complication and the debilitating effect of prolonged tube feeding that often result from effective therapy for advanced head and neck tumors.

The long-term toxicity of our study may be related to the chemotherapy regimen and the radiation therapy fractionation. Our chemotherapy regimen is similar to the intergroup study which reported 77% grade 3 or worse toxicity in patients with concurrent chemoradiation despite a split course of radiotherapy [30]. High dose of chemotherapy and conventional radiotherapy fractionation may explain high-grade toxicity as compared to the Brizel et al. study [31], where hyperfractionation and low-dose chemotherapy apparently did not lead to long-term dysphagia. Further studies should be carried out to investigate the toxicity and efficacy of different chemoradiation regimens. It is our current policy that all patients with locally advanced head and neck cancer undergo a MBS study before and following treatment to assess the safety of oral feeding. A traditional barium swallow may be obtained if deemed necessary (if structural damage of the pharynx and esophagus is suspected). If high-grade dysphagia is found, the patients are prescribed counseling and teaching of compensatory swallowing maneuvers to enhance the safety of oral feeding, while tube feeding continues to supplement their caloric intake based on nutritional assessment. We also use amifostine during chemoradiation to reduce the acute toxicity of the treatment and possibly lessen its long-term sequelae.

Conclusion

Dysphagia is a common, debilitating, and potentially life-threatening sequela of concurrent chemoradiation for head and neck malignancy. It may prolong patient recovery and rehabilitation and necessitate long-term G-tube feedings. Physicians should be aware that the dysphagia is often allied with silent, unrecognized tracheobronchial aspiration. Swallowing studies should be performed in the presence of dysphagia or clinical suspicion of aspiration pneumonia post-treatment. Modified barium swallow is often useful as it studies the pharyngeal motility which is often affected by chemoradiation. However, in the presence of structural damage linked to excessive scar formation, traditional barium swallow is indicated.

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