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Prevalence and trends of dysphagia following radiation therapy in patients with head and neck cancer

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PREVALENCE AND TRENDS OF DYSPHAGIA FOLLOWING RADIATION THERAPY IN PATIENTS WITH HEAD AND NECK CANCER

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Thank you Mom, Dad, & Brothers

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ABSTRACT

Head and neck cancer (HNC) accounts for 3-5% of all malignancies in the United States and is the sixth most common cancer worldwide. Over the past two decades, radiation therapy (RT) has become a frequent therapeutic strategy, however one of its side effects, dysphagia has had a huge impact on patients' quality of life. The value of determining the true prevalence of dysphagia is remarkable, which is what prompted us to carry out a study to determine the prevalence, trends, and risk factors for dysphagia following completion of RT over one year in patients diagnosed with HNC at Boston Medical Center over a 7-year period.

A retrospective cohort study was conducted that involved a chart review of the medical records of all patients who completed RT for HNC cancer from January 1, 2003 to December 31, 2009 at Boston University Medical Center. 113 eligible patients were who had comprehensive treatment and follow up data at 3, 6, 9 or 12

months post RT were analyzed. Outcome variables of interest included feeding tube status, diet status, subjective swallow status, and percent weight loss from end of RT.

113 patients were identified for this study, of which 31% (n=35) were female and 69% (n=78) were male. Average age was 58.6 years old (35 to 88). The most common cancer sites were oropharynx and nasopharynx (38.9%) as well as hypopharynx and larynx (31%). 71.7% of the cohort had chemotherapy (CT) in addition to RT, and about half the patients had some degree of surgery. Altogether, the most "clinically meaningful" indicator of dysphagia (diet level of moderate/severe diet restriction) showed that the prevalence or probability of dysphagia to be 49% at 3 months, 56% at 6 months, 45% at 9 months, and 31% at 12 months.

Our results suggest that about half the patients who undergo RT may be expected to develop a significant swallowing dysfunction in the first year following RT. This is extremely useful data for a health care provider to present to a patient after diagnosis of HNC and should complement counseling provided to them at the time of creating a treatment plan. Interestingly most of the patients who developed moderate/severe dysphagia did so within the first 6 months of completion of RT. Only oral cavity as cancer site was associated with moderate/severe dysphagia in our cohort of patients.

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LIST OF ABBREVIATIONS

ANOVA	Analyses of Variance
BMI	Body mass index
CRT	Chemotherapy and radiation therapy
CTCAE	Common Toxicity for Adverse Events
DNA	Deoxyribonucleic acid
DOSS	Dysphagia Outcome and Severity Scale
FDA	Food and Drug Administration
FEES	Flexible endoscopic evaluation of swallowing
GEE	Generalized Estimating Equations
HNC	Head and neck cancer
HPV	Human papilloma virus
ICD	International Classification of Diseases
IMRT	Intensity modulated radiation therapy
Kg	Kilogram
MBS	Modified barium swallow
PAS	Penetration-aspiration scale
PEG	Percutaneous endoscopic gastrostomy
QOL	Quality of life
ROS	Reactive oxygen species
RT	Radiation therapy
RTOG	Radiotherapy Oncology Group
SEER	Surveillance Epidemiology and End Results

SI	International system of units
SLP	Speech language pathologist
U.S.	United States

INTRODUCTION

Background

Head and neck cancer (HNC) refers to an array of malignant tumors that originate in the oral cavity, larynx, pharynx, nasal cavity, paranasal sinuses, and salivary glands. Over 80% of HNCs are squamous cell carcinomas, with adenocarcinomas, mucoepidermoid carcinomas, and adenoid cystic carcinomas making up the remaining histological types (1). HNC accounts for three to five percent of all malignancies in the United States (2), it is the sixth most common cancer worldwide (3), and was reported to be the eighth leading cause of cancer deaths in 2000 (4). The estimated number of new HNC cases in 2010 was 49,260 (35,530 in men and 13,730 in women) (5), and the estimated prevalence in 2007 was 339,000 cases (6). Primary risk factors for HNC development are tobacco and alcohol, especially when used concomitantly, and the human papilloma virus (HPV) (4, 5).

Over the past two decades, the use of Radiation Therapy (RT) has become a more prevalent therapeutic strategy. The increased use of chemotherapy + radiation therapy (CRT) is often attributed to the VA Laryngeal Cancer Study Group, which in 1991, concluded that there was no difference in 2 year survival rates between patients with advanced stage laryngeal cancer who received CRT vs. patients who received surgery and RT (7). Organ preservation, through surgery avoidance was then assumed to be the preferable treatment if outcomes were the same. In patients who undergo surgical resection for HNC, the cause of dysphagia is evident. Unfortunately, RT and/or CRT sometimes fail to preserve the functional integrity of the organ, which can lead to

compromised ability to eat and/or drink, and subsequently may adversely impact quality of life (QOL).

Long-term morbidities associated with RT or CRT (which, from this point on, will collectively be referred to as "RT") include dry mouth (xerostomia), altered taste, reduced sensory input, and swallowing impairment (dysphagia) (8) (see Table 1). Among these, dysphagia is often considered the most adverse complication. Knowledge of the specific molecular and biomechanical causes of RT-induced dysphagia remains limited. What has been recognized is that RT produces an acute and repeated inflammatory response, with substantial vascular damage and tissue remodeling in the area of soft tissue and mucosa exposed to RT (9).

Table 1: Radiation therapy-induced swallowing abnormalities[8]

Oral phase abnormalities • Reduced sensory input • Loss of muscles in the cheek • Drooling • Impaired oral opening • Limitations on food bolus positioning • Delayed initiation of swallowing
Pharyngeal phase abnormalities • Impaired transport of food through pharynx • Impairs clearance from pharynx • Increased risk of aspiration • Reduced epiglottis motion • Reduced pharyngeal constrictors' contraction • Reduced cricopharyngeal opening, resulting in increased pharyngeal residue

Health care providers including physicians, nurses, and therapists involved in the care of a patient with HNC should be familiar with the essentials of normal swallowing

function, the mechanism of RT-induced dysphagia, trends of dysphagia following completion of RT, and measures that may help to prevent and treat dysphagia.

Radiation Therapy (RT)

RT is frequently used as a therapeutic option in cancer treatment. Radiation is energy carried by a stream of particles or waves. The therapeutic agent in RT is ionizing radiation, which is divided into two groups; the corpuscular group and the electromagnetic group, also called photons (10). Protons, electrons, and neutrons represent corpuscular radiation, whereas X-rays and gamma rays represent electromagnetic radiation, the latter group being the most common form of RT in clinical practice (10). The unit used to express amount of absorbed radiation by tissues is the Gray (Gy), an international unit (SI unit), defined as 1 joule per kilogram (kg). The Gray replaced the traditional rad (radiation absorbed dose) unit in 1975, although the rad is often persistently used in the U.S. where 1 Gy is equal to 100 rad (10, 11, 12). RT regimens are administered on average over five to seven weeks with a total curative dose of 50-70 Gy. Pre-operative dosages are usually 45 Gy and post-operative dosages are 55-60 Gy.

Radiation targets and damages the deoxyribonucleic acid (DNA) in cancer cells, impairing their division and growth. To better comprehend the mechanism by which radiation works, it is important to understand the normal life cycle of a cell. The cell cycle runs through five phases; G0 (resting cell), G1 (cell starts to make proteins and material for DNA), S (chromosomes with DNA are duplicated), G2 (just before the

cell splits into two cells), and M (mitosis, when the cell divides into two identical cells). Radiation first kills cells that are actively or rapidly dividing while in the M phase of division. Malignant cells, which have a tendency to divide rapidly and grow out of control, are therefore preferentially killed by RT. Although RT kills malignant cells, it also affects dividing cells in normal tissues, which can result in undesired side effects. Rapid-growing tissues include skin, bone marrow, and intestinal lining, which may be affected immediately following RT. As a result, radiation oncologists always consider the fine balance between maximizing destruction of malignant cells and minimizing damage to normal cells.

Relative susceptibility to the effects of radiation varies by type of cancer cell, and is referred to as radiosensitivity (10). RT may be direct or indirect, depending on the wavelength of the incident photon. If administered directly, the DNA molecule is cleaved, thwarting duplication. During indirect administration, water is dissociated into its ionic state (H+ and OH-), permitting OH-, a reactive oxygen species (ROS) to react with DNA and interfering with its duplication (10). This is termed ionizing radiation. Interestingly most of a cell's content is water, and hence the effects of indirect (ionizing) RT are more significant compared to those of direct RT (13).

Normal Swallowing Function

Swallowing is an intricate process that involves multiple muscles in the oral cavity, esophagus, pharynx, and larynx. It is initiated by sensory stimuli that are transmitted to the brainstem and cortex where the presence of a bolus is recognized and a motor signal is sent to the peripheral muscles. The "swallowing center" lies within the brainstem but substantial supratentorial involvement is usually involved in the deglutition process. Normal swallowing is usually divided into three phases (14). Phase 1 (oral preparatory phase) consists of breakdown of food by chewing and salivary lubrication to form a bolus. Phase 2 (oral phase) transports the bolus from the anterior tongue back towards the oropharynx. Finally, Phase 3 (pharyngeal phase) results in the initiation of the swallow and propulsion of the bolus towards the cervical esophagus as the larynx closes to protect the airway (14). A disruption in the swallowing process is known as dysphagia.

Dysphagia can result in compromised nutritional status, depression, anxiety, aspiration pneumonia, and hence a compromised quality of life (15-18). Since dysphagia has such a profound affect on a patient's health and QoL, radiation oncologists have tried to employ radio protectors to mitigate dysphagia in head and neck cancer patients undergoing RT. Unfortunately such techniques have not been successful in reducing permanent dysphagia (19).

Dysphagia Induced by Radiation

Surgical resection and transection of muscles and nerves can result in tissue and structural loss, scar tissue formation, and loss of sensation, all of which can alter normal swallowing in a predictable manner. RT however, may cause a short- or long-term dysphagia of varying severities, and the etiology of the problem as well as the underlying mechanisms that drive the pathophysiology are poorly understood. One preliminary study identified the pharyngeal constrictor muscles and the larynx as the "crucial" structures associated with an increased risk of swallowing dysfunction based on videofluoroscopic evaluations following administration of Intensity Modulated Radiation Therapy (IMRT), which spared different muscle groups (20). However an alternative study suggested that the suprahyoid muscles are just as significant (21).

After completion of RT, the normal controlled healing process should continue until a patient is fully recovered (about 3 months post RT). However, some patients continue to react to the insult with an abnormal uncontrolled healing process. In these latter patients, an aberrant fibrotic response develops and continues for an undetermined period of time. Fibrosis has been described as a progressive problem related to an impaired wound healing process (22). Fibrosis and associated stiffness of tissues has been identified as the primary cause of dysphagia (8).

Damage to soft tissue and mucosa can begin within a few days of initiation of RT within the radiation field (23). This damage, along with a vigorous inflammatory reaction causes the acute effects of RT (during RT and up to 3mo post RT) (24). These acute effects can include pain, thickened, viscous mucous production, dry

mouth, erythema, and tissue swelling. Additionally, mucositis can be caused by environmental factors such as colonization of oral microflora (23).

Hypoxia caused by vascular damage and chronic oxidative stress during the course of RT may promote the fibrotic process and propagate further tissue injury after RT completion (25). This may partially explain why some patients develop dysphagia years after completion of RT. Long-term effect of RT-induced injury to neural structures has also been suggested as contributing to long term (greater than 3mo post RT) impairment of swallowing function (8). The variations in RT-related toxicities may in part be related to genetic predisposition (23).

Prevention and Treatment of Dysphagia

The mean dose and volume of intensity modulated radiation therapy (IMRT) to the pharyngeal constrictor muscles and larynx have been shown to highly correlate with the development of long term dysphagia (20, 26, 27). The implication is that sparing of the pharyngeal constrictor muscles and laryngeal structures from a significant radiation dose (50Gy or more) may prevent development of dysphagia in certain cases. However, specific dose or volume restrictions have not been established so optimal treatment entails minimizing the mean dose whenever possible (28).

Few prospective cohort studies or randomized trials evaluating therapeutic or preventive measures for dysphagia have been conducted in patients with HNC. Therapeutic options include a Food and Drug Administration (FDA) approved drug

called amifostine, a free radical scavenger that may be added to treatment regimens to minimize side effects. Randomized controlled trials have demonstrated its efficacy in prevention of xerostomia secondary to RT (29). A meta-analysis evaluating the efficacy and toxicity of amifostine also showed that the rate of dysphagia was significantly decreased in patients with HNC treated with amifostine during RT (30). A reduction in xerostomia may theoretically ameliorate dysphagia by improving mastication and preparation of food boluses. It would also help to propel the bolus through the pharynx without the need for supplementing every solid food bolus with a liquid. A reduction of free radicals may also decrease mucosal toxicity, which in turn may reduce the chance of developing fibrosis and an associated long term dysphagia.

Recent studies suggest that proactive swallowing therapy delivered early, during RT, may in fact prevent later problems (31-33). Some other studies, however, demonstrated no long-term benefit of swallowing exercises on dysphagia (34). A recent study by Carnaby-Mann et al (35) demonstrated a greater preservation of certain muscles during RT following active swallowing exercises (pharyngocise). Although there was no overall difference in clinical swallowing outcomes at 6 weeks post RT, the study found that muscle function, measured by T2 weighted MRI, deteriorated less in the exercise group as compared to the control group.

While preliminary evidence suggests that proactive interventions may be efficacious, it may be difficult to convince patients to perform proactive swallowing exercises for a “potential future problem”, especially when they are going through a taxing therapy

for their cancer. Predictive statistics for RT-induced dysphagia would be critical in helping clinicians and patients decide an appropriate course of therapy.

Assessment of Dysphagia

There are various methods for assessing swallowing function including clinical and instrumental methods. Clinical evaluation involves identification of swallowing abnormalities through evaluation of swallow function, collaboration with dieticians, patient education, potential swallow therapy, and identification of patients at a high risk of aspiration (8). Table 2 lists some triggers for evaluation of dysphagia.

Table 2: Triggers for evaluation of dysphagia[8]

- Incapacity to control saliva, food, or liquids in the oral cavity
- Food pocketing in cheek
- Coughing or choking before, during, or after swallowing
- Excessive chewing
- Subjective complaint of difficulty swallowing
- Subjective complaint of food "sticking" in throat
- Unusual voice quality after swallowing
- Weight loss

A medical history, oral and oropharyngeal examination, and swallow trials comprise a comprehensive clinical swallowing examination. A medical history includes complaints of swallowing by patients, avoidance of foods of specific consistencies, episodes of choking or coughing up food, poor nutrition, prior oral or oropharyngeal resection or CRT, presence of a feeding tube, and history of neurological issues. Patient perceptions of dysphagia are highly subjective and variable, an observation reported by a number of studies (36, 37). An oral or oropharyngeal examination consists of oral cavity inspection, and evaluation of oral health (including dental

status), dryness, and motion, strength, and symmetry of the lips, jaws, tongue, and soft palate. Additionally symptomatic dysphagia may be evaluated with a swallow test, which involves trials of different food and fluid consistencies of varying taste, temperature, and bolus sizes (38).

Standardized questionnaires that measure patients' QoL present an instrument to determine the impact of treatment. Questionnaires such as the M.D. Anderson Dysphagia Inventory (MDADI) have been designed to specifically assess the impact of dysphagia on the QoL of patients with HNC (39). QoL describes outcome measures of psychosocial well-being and functional status using two measures; general and disease-specific (39). Disease-specific measures evaluate specific patient populations or diagnostic groups and are more responsive to changes in status over time. Finally, diet scales can be used to objectively measure what patients can eat. An example is the Functional Oral Intake Scale (FOIS), a simple 7-point scale developed to rate the functional severity of dysphagia based on objective evaluations (40). The Performance Status Scale for Head and Neck Cancer (PSS-HNC) also has an 11 point objective diet scale domain that can be used to measure changes in a patient's ability to eat various consistencies over time. Efficient, easy, and clinically realistic diet scales can improve dysphagia screening and allow for rapid referrals to speech language pathologists for dysphagia therapy.

The most common instrumental method used to assess swallow function is the modified barium swallow (MBS), which uses videofluoroscopy to evaluate oral and pharyngeal function (24, 41). A second comprehensive method is the Fiberoptic

Endoscopic Evaluation of Swallowing (FEES) that can be performed bedside and permits direct visualization of swallowing structures including the nasopharynx, hypopharynx, larynx, and vocal cords (8). It also allows functional assessment including sensory deficits, movement of structures in view, handling of secretions, and ability to swallow food and liquid safely and effectively (8). Videofluoroscopy is often considered to be the gold standard since it was established before FEES and is available at most major medical institutions. However its use is limited due to high cost, lack of portability, and exposure to radiation. Objective swallowing assessment with either FEES or videofluoroscopy should be used to evaluate swallowing function over time in clinical trials involving RT.

The significance of objective swallowing function has been demonstrated by Agarwal et al (53) who looked at the patterns of objective swallowing dysfunction following CRT in patients with HNC (53). Their study demonstrated that at 6mo post RT, patients presented with higher rates of "significant" residue (bolus left in the pharynx after swallowing), aspiration (bolus entering the airway), and need for postural changes (changing head or body positioning during the swallow to prevent aspiration), as compared to pre-RT (baseline) rates. Using the same cohort, Agarwal et al found that patient-related factors including subjective dysphagia and tumor volume correlated with objective swallow function, even prior to RT (43). Since subjective reports of dysphagia are influenced by many factors, swallowing assessment using objective instrumental exams are critical in evaluating outcomes in future studies involving RT.

Patient-reported and clinician-reported scoring systems such as Radiotherapy Oncology Group (RTOG) late radiation toxicity scoring, and the Common Toxicity for Adverse Events (CTCAE) are the most common methods employed in radiation oncology research to assess patient health during and following RT. These scales however lack the specificity required to identify potentially detrimental swallowing dysfunction (42). Given that a recent systematic review concluded that evidence for swallowing outcomes in HNC patients is limited (42), the aforementioned objective outcome measures such as diet, QoL, and results of instrumental swallow studies should be incorporated in all future clinical trials to more accurately establish treatment efficacy and long term outcomes.

Prevalence of Dysphagia

The reported prevalence of dysphagia following RT varies tremendously, from as low as 15% (44) to as high as 85% (45). This huge discrepancy suggests that the true prevalence and incidence is unknown. There are numerous reasons for this. First, there are a multitude of known factors that may affect prevalence of dysphagia, including dosage of radiation delivered, cancer stage, the addition of surgery, and the site of the cancer. Other potential variables include age, body mass index (BMI), smoking/drinking history, and type of radiation used.

The terms incidence and prevalence should be used uniformly, but sometimes this is not the situation. An "incidence" study should identify the population to be studied and then identify all patients who develop the problem of interest in that population over a specified period of time (such as over one year). A "prevalence" study should

follow the same patients over time and report the frequency of the problem at different time points (such as at 12 months post RT). Some studies have reported a high prevalence or incidence of dysphagia, but on closer inspection, it is revealed that they have "selected" patients from that population that are at higher risk of having dysphagia; for example only looking at patients who complained of a swallowing problem (9). Other studies that have reported incidence of dysphagia have not kept the post-RT time constant; their figures have represented the frequency of dysphagia in patients who were anywhere from 3 months to 10 years post RT (20, 26, 37, 46). This is extremely important since the literature suggests that the severity of dysphagia may vary over time.

One major incidence study of dysphagia (47) looked at over 8000 patients from the Surveillance Epidemiology and End Results (SEER) registry and Medicare database over a 7-year period. Its objectives included determination of the overall and site-specific dysphagia and to calculate treatment-specific incidence rates. It reported the incidence of dysphagia to be 40% within 3 years of diagnosis of HNC. Furthermore patients who underwent CRT had more than 2.5 times greater odds of dysphagia compared to those who underwent solely surgery. Dysphagia in this study was identified using the ICD-9 code. This study represents our most systematic estimate of 'incidence' to date.

A noteworthy potential source of variance is the definition or indicator of dysphagia. Different sources have used definitions including "patient report or complaint of a swallowing problem", "diet restriction", "feeding tube in place", or findings from an

instrumental swallow study. These different indicators of dysphagia have yielded widely different incidence figures. Even using the same indicator, results have shown little agreement. For example, Agarwal et al (43) used diet restrictions as an indicator and reported 73.5% of their patients were on a semi solid or liquid diet at 6 months post- RT. Another study by Langendijk et al (44), using the RTOG /EORTC scale (48) reported that at 6 months post treatment, 23.1% of the patients were on a semi-solid or worse diet. Reasons for the disparities are not known. Perhaps the lower prevalence figure in the latter study may have been due to the fact that they pre-selected patients by excluding those with moderate dysphagia at baseline (pre-treatment).

Wilson et al (49) used the MD Anderson Dysphagia Index (patient-perceived Quality of Life (QOL) scale) (48) as an indicator of dysphagia. At 3 months post-RT, 85% of all their patients reported a swallowing problem, with patients receiving chemoradiation reporting the worst QOL scores. Over the course of the first year after treatment, there was no significant variation in QOL scores. QOL is a variable that may be vulnerable to many factors; one study suggested that patient-reported QOL varied tremendously by culture and time since the treatment for HNC (50). Studies that have used "presence of a feeding tube" as an indicator of dysphagia have reported a declining prevalence over the first year, but tremendous variation between studies; 4-55% (11, 51, 52). Early variance (3 months post-RT) may be related to the policy at some institutions of placing feeding tubes prophylactically in all patients prior to CRT. However, from 6 months post-RT or later, it is likely that "feeding tube" would be a mark of a "severe" dysphagia.

Very few studies have reported incidence or prevalence of dysphagia from clinical or instrumental swallowing studies, probably because these exams are rarely given to all patients, requiring clinical expertise, adequate SLP staffing, and easy access to equipment. Both Logemann (37) and Agarwal et al (53) have described the swallowing patterns using fluoroscopy procedures in relatively small groups of patients after RT, but neither specified how patients were selected, so accurate prevalence or incidence cannot be derived. A large cohort from four institutions was reported by Pauloski et al (46). Their results may reflect the "typical" patient although selection was not specified. However, about half the patients had "no complaints" of swallowing so they obviously did not select for patients with dysphagia. Their results indicated that patients with complaints did manifest worse swallowing as measured by MBS than patients without complaints, especially for findings of aspiration and pharyngeal residue, suggesting that patient complaint may be a reliable marker for a problem. On the other hand, Kendall et al (54), in a smaller study, reported on fluoroscopy findings from 20 patients who had not pursued treatment for a swallowing problem. They found that all of the patients had "abnormal swallowing" compared to their normal controls. Therefore it appears that this marker of dysphagia may vary between patients and that some patients may even "underreport" their problem.

Time since RT is also an important factor for understanding prevalence or incidence of dysphagia. In the acute stages of RT, including the weeks during the RT and the first 3 months after RT, patients may experience inflammation, pain, xerostomia, and

alterations in taste which all affect their ability to swallow. Consequently most patients will complain of some problem eating or swallowing up to 3 months post RT. As the acute effects subside, the trend of the problem is difficult to predict. Some patients recover while others continue to suffer from dysphagia. After the first year, swallowing function may stabilize or it may worsen. Some studies describe improvement over time (55, 32) while others report a worsening problem (56, 57) and still others have found no overall significant change over time (37, 49).

In summary, it appears that true incidence and prevalence of dysphagia are elusive and depend on numerous factors. Instrumental measurement appears to be the most sensitive marker and tube feeding is likely a marker for a severe dysphagia if present in the long term. Patient reports and diet restrictions likely fall somewhere between the other two markers. In the study mentioned above, Pauloski (46) found that patient complaint and diet restrictions were highly correlated. However a study comparing observer/clinicians vs. patient-reported symptoms found that observers tended to under-report the severity of symptoms compared to patients' self-report (58). Hence the two sources of report should not be deemed to be equivalent.

Aims

The value of determining the true incidence and prevalence of dysphagia is remarkable. Health care providers have little information regarding the probability of dysphagia development in when counseling their patients before treatment for their cancer. This also makes prescribing appropriate behavioral treatment for dysphagia difficult. It may be relatively easy to motivate a patient to perform intensive, daily exercises for an existing dysphagia, but it is nearly impossible to motivate a patient who is about to undergo RT to engage in daily exercises for a "possible swallowing problem that may affect them in the next year" or later.

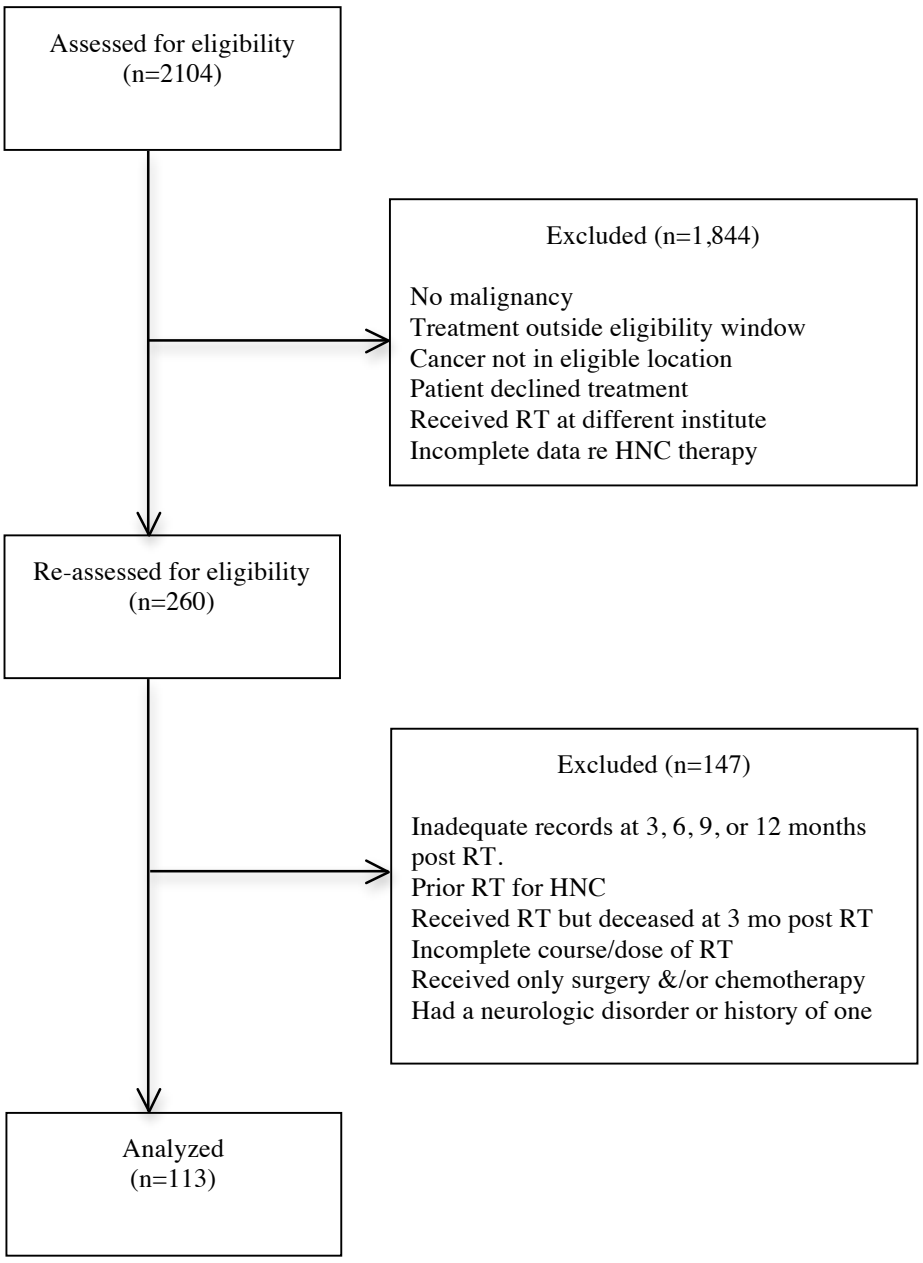
In response to this gap in knowledge, a retrospective cohort study was carried out to determine the prevalence of, trends in, and risk factors for, dysphagia following completion of radiation therapy at 3, 6, 9, and 12 months in patients diagnosed with head and neck cancer at Boston Medical Center over a 7-year period.

METHODS

A retrospective cohort study was conducted that involved a chart review of the medical records of all patients who completed radiation therapy for head and neck cancer from January 1, 2003 to December 31, 2009 at Boston University Medical Center. Approval was obtained from the Boston University Medical Center Intuitional Review Board prior to collecting and analyzing patient data. An initial search revealed 2104 patient records. Patients were excluded if they did not have a malignancy, their treatment fell outside the eligibility window, if their cancer was not in an eligible location (esophagus, thyroid, base of skull, other), if the patient declined treatment, if the patient received RT at a different hospital, or if there was incomplete information about their HNC therapy. This conferred a final list of 260 patients.

Next, patients were excluded from the list of 260 patients if they did not have adequate records at 3, 6, 9, or 12 months post RT, had previous RT for HNC, received RT but were deceased at 3 months post-RT, did not receive a full dose of RT (less than 50Gy), received only surgery and/or chemotherapy, if they received RT at another hospital, or had a neurologic disorder or history of one. Following these exclusions, 113 eligible patients were left who had comprehensive treatment and follow up data at 3, 6, 9 or 12 months post RT. Figure 1 illustrates the exclusion of patients.

Figure 1: CONSORT flow diagram of patients excluded



For each patient, age, gender, cancer stage, cancer site, treatment course (solely RT or with chemotherapy and/or surgery), radiation type, time of surgery in relation to RT, extent of surgery, previous treatment for HNC, cancer status at 3, 6, 9, and 12 months post RT, BMI at start of RT, HPV status (unavailable until 2009), tobacco use, alcohol consumption, clinic visits with SLP and PEG placement were all noted as predictor variables.

Outcome variables of interest included feeding tube status (regardless of use), diet status (Table 3), subjective swallow status, and percent weight loss from end of RT. All outcome data were acquired at 3, 6, 9, and 12 months post completion of RT (+/- 1 month to account for scheduling differences). If there were multiple reports of the same category (i.e. subjective diet status) within the time window, the most severe (worst) outcome was used.

Documentation of subjective swallow status data was only included if concrete statements on swallow status were made. Patient or clinician report of a problem with swallowing was categorized as "none", "mild/moderate", or "severe". Phrases such as "trouble swallowing" and "some dysphagia" were considered to be in the mild/moderate category. Severe dysphagia was categorized by "cannot swallow" or "significant problems eating". Normal swallowing was categorized as "no trouble swallowing" or "no dysphagia". Phrases such as "patient feels fine" or "doing well" were not specific enough to appropriately determine normal swallow status, and were categorized as "unknown" subjective swallow status.

Diet status determination and documentation was treated with the same methodology as subjective swallow status. It was defined by what the patient could eat (Table 3). A normal diet would be categorized by "eating full diet" or "can eat everything". Reports of "eating well", "tolerating diet well" or "strong appetite" were not specific enough to appropriately determine actual diet status, and therefore were categorized as unknown diet status.

Table 3: Diet Status Grading

	Grade	Diet Status
Any / Severe	1	No oral intake
Any / Severe	2	PEG use with some oral intake
Any / Moderate	3	Total oral intake but with limited consistencies
Any / Mild	4	Total oral intake with no special preparation but some food avoidance or liquid wash
Any	5	Total oral intake with no restrictions other than edentulous

Prevalence was studied according to three indicators or markers of dysphagia: current diet, report of swallowing difficulty, or use of a feeding tube. *Prevalence* was defined as the number of patients with dysphagia at 3, 6, 9, and 12 months, with each patient able to be counted multiple times. We also informally looked at when persons first developed dysphagia.

Statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc, Cary, NC, USA). Categorical variables were compared across risk groups using Fischer's exact test. Analyses of Variance (ANOVA) F-tests and T-tests were used to compare continuous variables.

Generalized Estimating Equations (GEE), a quasi-likelihood approach to modeling clustered or repeated data, was introduced by Zeger and Liang (1986). The cluster in our study was the individual and the repeated measure represented the multiple measures over time. The covariates in the model could be both categorical and continuous. The GEE modeling approach is able to accommodate various dependent variables including Gaussian, gamma (skewed distributions), binomial, or count. Using this approach, the user needs to make assumptions about the link function and the relationship between the first two moments. A logit link was used in modeling probability of dysphagia. The effects included in the model were risk factors, time, and the interaction between them. The same model was then used to test differences, in terms of association between risk factors and outcome, at each time point.

RESULTS

Population Demographics

113 patients were identified for this study, of which 31% (n=35) were female and 69% (n=78) were male. Average age was 58.6 years old (35 to 88). The most common cancer sites were oropharynx and nasopharynx (38.9%) as well as hypopharynx and larynx (31%). Fewer subjects had cancer of the oral cavity (18%) or "other" site (14.2%). The majority of the patients (60.2%) had Stage 4 cancer with the second most common stage being Stage 3 (22.2%). 71.7% of the cohort had chemotherapy (CT) in addition to RT, and about half the patients had some degree of surgery. The extent of surgery was most frequently limited to less than 50% of the oropharynx, hypopharynx, or larynx. IMRT was used in the majority of patients (74.5%) as opposed to conventional 3D RT (25.5%). Table 4 summarizes the demographics of this group. Some variables were not included in the final output if there was negligible or no recorded data for that variable.

Table 4: Patient Demographics

Characteristic	**Overall (N=113)**
Gender	
Female	35 (31%)
Male	78 (69%)
Age	
Mean ± SD	58.558±10.212
Median and Range	59 (35-88)
BMI	
Mean ± SD	26.88±7.011
Median and Range	26.2 (14.9-53.9)
Tobacco Use	
Never	18 (16.2%)
Prior only	53 (47.7%)
Prior and during	40 (36%)
Alcohol Use	
Never	59 (53.2%)
Prior only	32 (28.8%)
Prior and during	20 (18%)
Cancer Site	
OC	18 (15.9%)
NP/OP	44 (38.9%)
HP/Larynx	35 (31%)
Other	16 (14.2%)
Cancer Stage	
1	12 (11.1%)
2	7 (6.5%)
3	24 (22.2%)
4	65 (60.2%)
Chemotherapy	
Yes	81 (71.7%)
No	32 (28.3%)
Type of Radiotherapy	
IMRT	82 (74.5%)
Conventional 3D RT	28 (25.5%)
Surgery	
Yes	56 (49.6%)
No	57 (50.4%)
When Was Surgery Done	
Before RT	43 (38.1%)
After RT	5 (4.4%)
No surgery	57 (50.4%)
Both before and after RT	8 (7.1%)
Extent of Surgery	
None or Biopsy	57 (50.4%)
Neck Dissection or Tonsillectomy	12 (10.6%)
Resected<50% of OC, NP, OP, HP or Larynx	29 (25.7%)
Resected>50% of OC, NP, OP, HP or Larynx	15 (13.3%)
PEG Placed	
Never	56 (50%)
Before or during RT	47 (42%)
After RT completion	9 (8%)

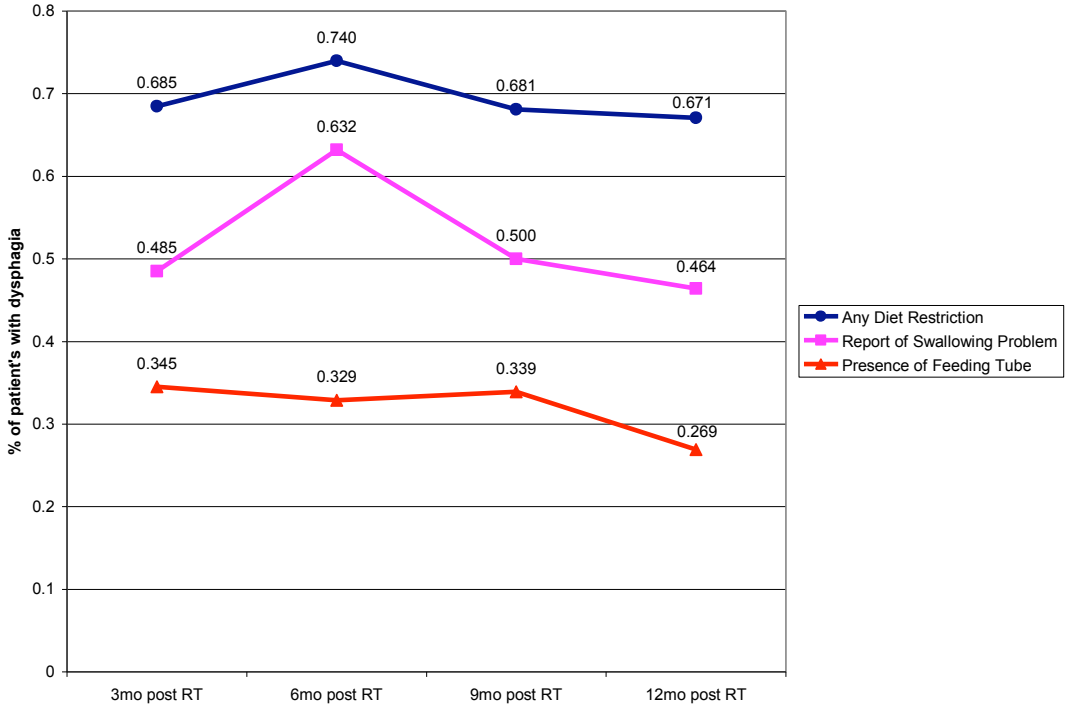
Prevalence of Dysphagia

The prevalence of dysphagia at 3, 6, 9, and 12 months was determined by the first set of analyses according to three indicators: any diet restriction (a diet score of 1-4 depicted in Table 1), feeding tube in place, and report of any swallowing problem (mild, moderate, or severe) by the patient/clinician. Prevalence varied by type of marker for dysphagia and ranged from 27% at 12 months post RT, indicated by use of a feeding tube to 74% at 6 months post RT, indicated by any diet restriction Table 5 and Figure 2 depict these results. Linear trends were not significant for the three measures.

Table 5: Prevalence of Dysphagia over Time and by Indicator of Dysphagia

Time Post RT	Any Diet Restriction		Report of Swallowing Problem		Feeding Tube	
	Probability of Dysphagia	**CI**	**Probability of Dysphagia**	**CI**	**Probability of Dysphagia**	**CI**
3mo	0.685	0.584-0.771	0.485	0.385-0.586	0.345	0.262-0.438
6mo	0.740	0.647-0.815	0.632	0.536-0.719	0.329	0.248-0.421
9mo	0.681	0.580-0.768	0.500	0.396-0.603	0.339	0.255-0.436
12mo	0.671	0.565-0.762	0.464	0.355-0.577	0.269	0.191-0.364

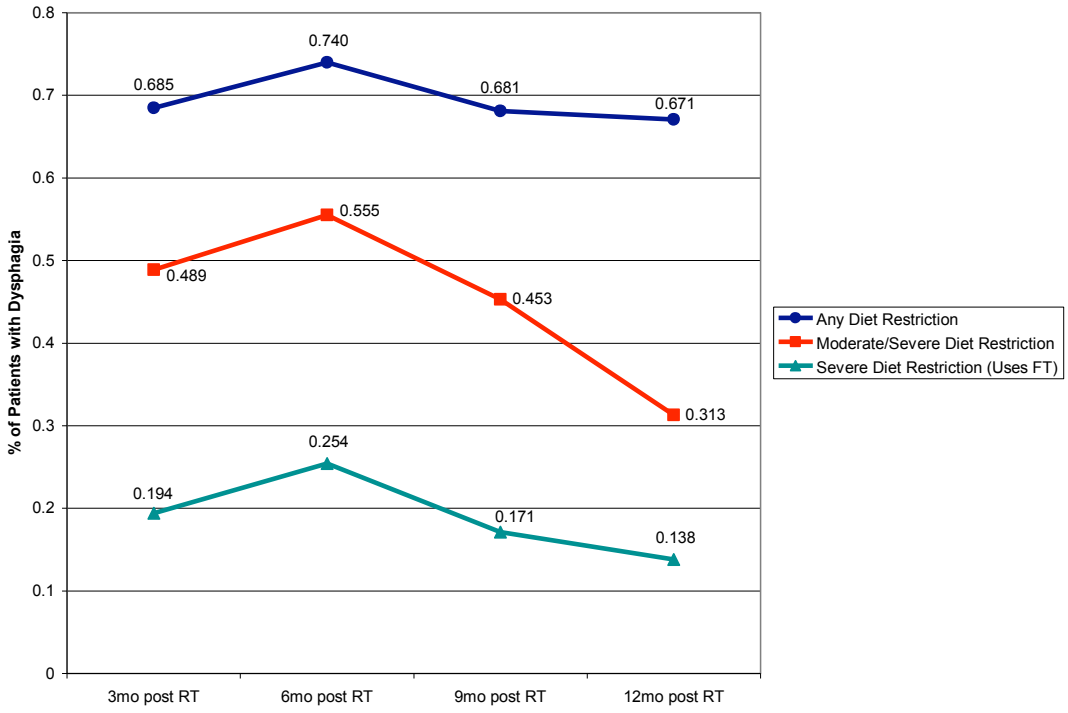
Figure 2: Prevalence of Dysphagia over Time and by Indicator of Dysphagia



In general, the presence of a feeding tube yielded the lowest estimates of dysphagia. The highest estimates of dysphagia were indicated by the presence of any diet restriction (defined as diet grades 1-4 in Table 3). Subjective reports of a swallow problem fell between these two estimates. The lowest estimate was 27% at 12 months as indicated by the presence of a feeding tube while the highest estimate was 74% at 6 months as indicated by any diet restriction. Over time, presence of a feeding tube remained fairly constant then declined between 9 and 12 months post RT. The restrictions in diet and report of swallowing problem peaked at 6 months post RT then declined.

Diet status was analyzed in three different ways; (a) Severe dysphagia (diet grade 1-2 which indicated people were using their PEG for some or all of their nutritional intake), (b) Moderate/Severe (diet grades 1-3 which indicate people were either using their PEG or having to significantly alter their diet), (c) any diet restriction (diet grades 1-4). Prevalence of dysphagia for 3 of these defined groups is delineated in Figure 3. The only indicator that showed a significant negative trend was moderate to severe diet restriction ($p = 0.005$).

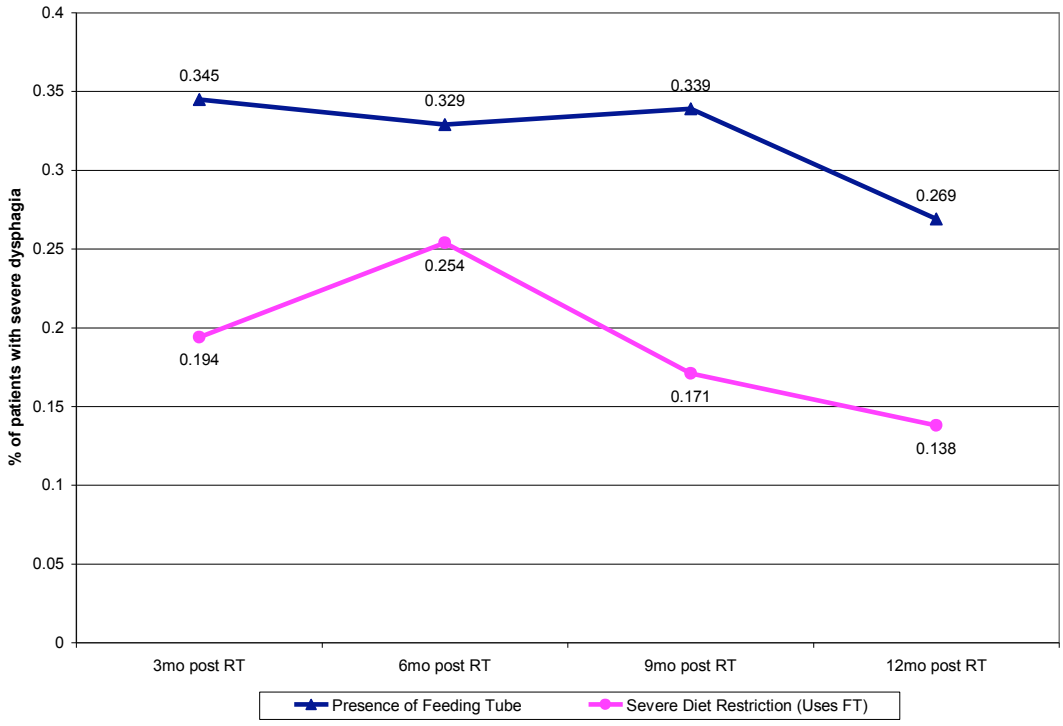
Figure 3: Prevalence of Dysphagia over Time by Diet Restriction Definition



The probability of having any diet restriction was more than 67% at all time points whereas the probability of having a severe diet restriction was less than 26% at all time points.

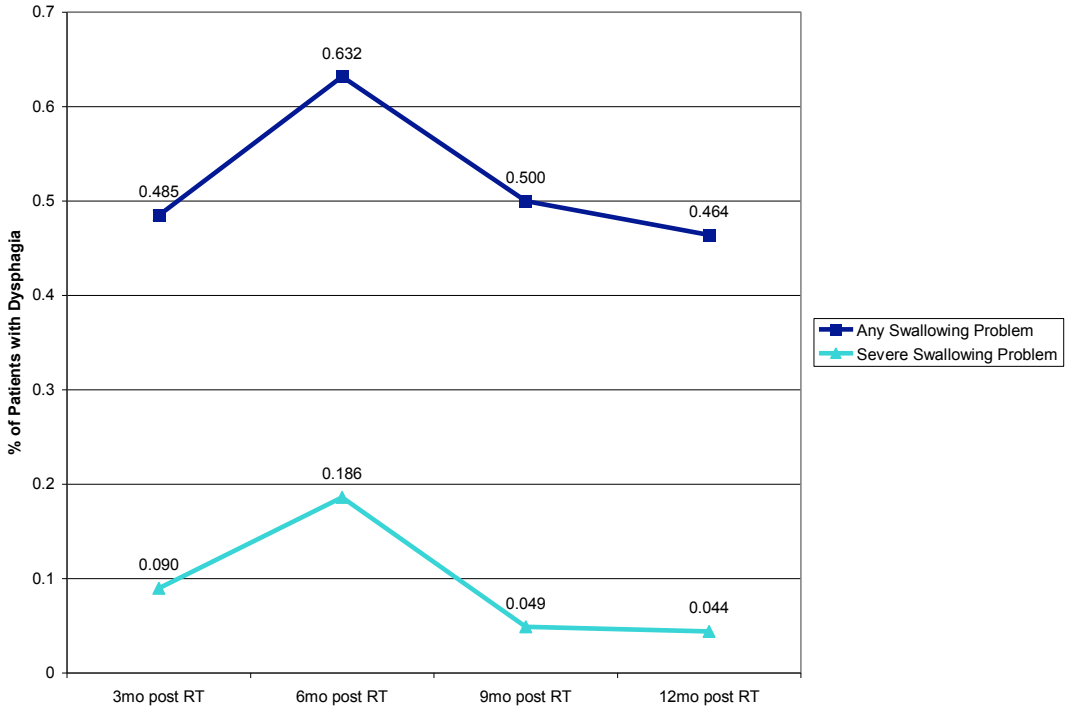
Severe dysphagia as defined by *presence of a PEG* ranged from approximately 27% to 34.5% (see Figure 2), but this differed from the results of severe dysphagia as defined by the *actual use* of a PEG (as defined by Diet levels 1+2 in Table 3). This discrepancy is shown in Figure 4 and suggests that presence of a PEG may not be a particularly accurate indicator of severe dysphagia.

Figure 4: Prevalence of Severe Dysphagia over Time – Presence of PEG vs. Use of PEG.



Subjective patient / clinician report of a swallowing problem was analyzed as two groups: any swallowing problem vs. report of a severe swallowing problem. At 6 months, 63% of patients reported having any swallowing problem but only 18% reported a severe swallowing problem (Figure 5).

Figure 5: Prevalence of Dysphagia over Time by Subjective Patient / Clinician Assessment



Since the three markers did not correlate highly with dysphagia, a decision was made to identify the most clinically meaningful marker. Presence of a feeding tube was eliminated first since it only represented a rough estimate of "severe dysphagia" and it did not seem to correlate with actual use of the feeding tube (ie what the patients were actually able to eat). Subjective patient / clinician report of dysphagia was eliminated next as it might have been unreliable, at least in this study which depended on written entries into the medical record. Inspection of our records indicated that reliability was highly influenced by the skill and care taken by the health care provider who needed to ask the right questions and report it accurately. Hence inter-provider reliability was poor and we did not have a gold standard for reliability. Reliability was also

influenced by how honest or forward the patient was about reporting this problem; clinicians are well aware that some patients do not complain to their cancer doctor even if they have a significant problem eating while others complain fervently about the slightest thing. Thus, the most clinically meaningful marker of dysphagia was deemed to be diet level, which is a more objective reflection of a person's true dysphagia status.

Since diet restriction had been categorized in several different ways (Figure 3), it was decided that the moderate / severe diet restriction group was the most meaningful (Diet levels 1-3) because it seemed to clinically impact the patient the most. This categorization did not include patients who altered their diet solely because they were edentulous, only needed to use a liquid wash, or had such mild problems that they would be unlikely to seek out therapy. Accordingly, the *moderate/severe* category included all patients who had to alter their diet to eliminate whole categories of food items, and their dysphagia was severe enough to impact their lives. This degree of diet restriction was considered meaningful not only clinically, but also personally for the patient. The remaining analyses were performed using this most "clinically meaningful" indicator of dysphagia.

Altogether, this most "clinically meaningful" indicator of dysphagia showed that the prevalence or probability of dysphagia to be 49% at 3 months, 56% at 6 months, 45% at 9 months, and 31% at 12 months.

Significant Predictors of Dysphagia

The second set of analyses attempted to determine the most accurate predictors of dysphagia, defined by moderate / severe diet restriction. Several variables were analyzed including cancer site, cancer stage, age, gender, BMI, surgery, CRT, prophylactic PEG placement, alcohol consumption, and tobacco use. Six and twelve months were chosen as the two most important time points post RT, beyond the acute toxicity stage and more likely representing a chronic swallowing problem that would be meaningful and concerning to patients and clinicians alike. Table 6 summarizes results of the univariate analyses showing the association of moderate-severe dysphagia at 6 months with the predictor variables and Table 7 shows these associations at 12 months.

Table 6: Univariate Results: Association of Independent Variables with Moderate-Severe Dysphagia at 6 months

Characteristic	Overall (N=88)	Dysphagia (N=55)	No Dysphagia (N=33)	p-value
Age, N (%)				
Less than 60	49 (55.7%)	34 (69.4%)	15 (30.6%)	0.184
60 and older	39 (44.3%)	21 (53.8%)	18 (46.2%)	
Gender, N (%)				
Male	60 (68.2%)	42 (70%)	18 (30%)	0.057
Female	28 (31.8%)	13 (46.4%)	15 (53.6%)	
BMI, N (%)				
Less than 25	44 (50%)	31 (70.5%)	13 (29.5%)	0.186
25 and higher	44 (50%)	24 (54.5%)	20 (45.5%)	
Excessive Tobacco Use, N (%)				
Yes	36 (41.9%)	25 (69.4%)	11 (30.6%)	0.263
No	50 (58.1%)	28 (56%)	22 (44%)	
Excessive Alcohol Use, N (%)				
Yes	17 (19.8%)	14 (82.4%)	3 (17.6%)	0.057
No	69 (80.2%)	39 (56.5%)	30 (43.5%)	
CRT, N (%)				
Yes	72 (81.8%)	47 (65.3%)	25 (34.7%)	0.268
No	16 (18.2%)	8 (50%)	8 (50%)	
Surgery, N (%)				
Yes	40 (45.5%)	24 (60%)	16 (40%)	0.666
No	48 (54.5%)	31 (64.6%)	17 (35.4%)	
Cancer Site, N (%)				
OC	15 (17%)	13 (86.7%)	2 (13.3%)	0.160
NP/OP	36 (40.9%)	22 (61.1%)	14 (38.9%)	
HP/Larynx	27 (30.7%)	15 (55.6%)	12 (44.4%)	
Other	10 (11.4%)	5 (50%)	5 (50%)	
Cancer Stage, N (%)				
Stage 1&2	11 (13.3%)	6 (54.5%)	5 (45.5%)	0.797
Stage 3	18 (21.7%)	11 (61.1%)	7 (38.9%)	
Stage 4	54 (65.1%)	35 (64.8%)	19 (35.2%)	

Table 7: Univariate Analyses: Association of Independent variables with Moderate-Severe Dysphagia at 12 months

Characteristic	Overall (N=66)	Dysphagia (N=23)	No Dysphagia (N=43)	p-value
Age, N (%)				
Less than 60	36 (54.5%)	12 (33.3%)	24 (66.7%)	0.801
60 and older	30 (45.5%)	11 (36.7%)	19 (63.3%)	
Gender, N (%)				
Male	45 (68.2%)	16 (35.6%)	29 (64.4%)	0.999
Female	21 (31.8%)	7 (33.3%)	14 (66.7%)	
BMI, N (%)				
Less than 25	27 (40.9%)	12 (44.4%)	15 (55.6%)	0.198
25 and higher	39 (59.1%)	11 (28.2%)	28 (71.8%)	
Excessive Tobacco Use, N (%)				
Yes	28 (42.4%)	10 (35.7%)	18 (64.3%)	0.999
No	38 (57.6%)	13 (34.2%)	25 (65.8%)	
Excessive Alcohol Use, N (%)				
Yes	12 (18.2%)	6 (50%)	6 (50%)	0.316
No	54 (81.8%)	17 (31.5%)	37 (68.5%)	
CRT, N (%)				
Yes	52 (78.8%)	20 (38.5%)	32 (61.5%)	0.346
No	14 (21.2%)	3 (21.4%)	11 (78.6%)	
Surgery, N (%)				
Yes	32 (48.5%)	9 (28.1%)	23 (71.9%)	0.309
No	34 (51.5%)	14 (41.2%)	20 (58.8%)	
Cancer Site, N (%)				
OC	10 (15.2%)	4 (40%)	6 (60%)	0.100
NP/OP	26 (39.4%)	12 (46.2%)	14 (53.8%)	
HP/Larynx	22 (33.3%)	7 (31.8%)	15 (68.2%)	
Other	8 (12.1%)	0 (0%)	8 (100%)	
Cancer Stage, N (%)				
Stage 1&2	9 (14.3%)	2 (22.2%)	7 (77.8%)	0.735
Stage 3	12 (19%)	5 (41.7%)	7 (58.3%)	
Stage 4	42 (66.7%)	16 (38.1%)	26 (61.9%)	

As can be seen in Tables 6 and 7, the only predictor variables that were (marginally) significantly associated with moderate-severe dysphagia at 6 months were: male

gender (p = 0.057) and alcohol history (p = 0.057). However these were no longer significant at 12 months and no other variables emerged at that time point.

Multivariate analyses were performed after accounting for correlations among the independent factors. The variables analyzed were age, gender, BMI, tobacco use, alcohol consumption, CRT, surgery, cancer site, and cancer stage. These analyses are shown in Table 8 and 9. From all the assumed predictors, only cancer site (oral vs. hypopharyngeal or laryngeal cancer) was a significant predictor at 6 months post RT– with oral cancer site having worse swallowing outcomes. At 12 months post RT, again, no significant predictors of moderate to severe dysphagia were identified in our cohort.

Table 8: Multivariate Analyses: Predictors of Moderate-Severe Diet Restrictions at 6 months (c=0.751)

	Adj. Odds Ratio	Lower Confidence Limit	Upper Confidence Limit	p value
Men vs. Women	1.7922	0.4776	6.7254	0.3872
Age <60 vs. >60	1.4084	0.4065	4.8800	0.5891
BMI <25 vs. >25	2.2471	0.7441	6.7863	0.1511
Tobacco Use	1.0266	0.2453	4.2968	0.9714
Alcohol Use	2.3243	0.3786	14.2676	0.3623
CRT	3.4368	0.4865	24.2775	0.2158
Surgery	0.5735	0.1718	1.9151	0.3661
Cancer Site: OC vs. HP/Larynx	17.2956	1.1635	257.1024	0.0385
Cancer Site: NP/OP vs. HP/Larynx	1.1891	0.3671	3.8521	0.7727
Cancer Stage: 1&2 vs. 4	1.5880	0.1836	13.7364	0.6744
Cancer Stage: 3 vs. 4	0.5942	0.1586	2.2258	0.4398

Table 9: Dysphagia: Multivariate Analyses: Predictors of Moderate Diet Restrictions at 12 months (c=0.729)

	Adj. Odds Ratio	Lower Confidence Limit	Upper Confidence Limit	p value
Men vs. Women	1.4912	0.3286	6.7661	0.6046
Age <60 vs. >60	0.7865	0.2289	2.7028	0.7029
BMI <25 vs. >25	1.6236	0.4254	6.1970	0.4782
Tobacco Use	1.1471	0.2206	5.9644	0.8704
Alcohol Use	2.8578	0.3726	21.9173	0.3124
CRT	2.2108	0.1620	30.1798	0.5519
Surgery	0.7110	0.1700	2.9733	0.6403
Cancer Site: OC vs. HP/Larynx	0.4906	0.0575	4.1836	0.5149
Cancer Site: NP/OP vs. HP/Larynx	2.3849	0.5141	11.0627	0.2669
Cancer Stage: 1&2 vs. 4	0.5749	0.0229	14.4277	0.7364
Cancer Stage: 3 vs. 4	2.5498	0.3714	17.5045	0.341

Trends in Dysphagia

A third analysis was performed to determine trends in dysphagia over the first year. It was determined that about 38% of our cohort developed, for the first time, a moderate to severe dysphagia by 3 months post RT. An additional 17-18% developed a newly diagnosed moderate to severe dysphagia by 6 months post RT. Only two patients developed a moderate to severe dysphagia after 6 months. This suggests that patients who develop a moderate to severe dysphagia tend to do so within the first 6 months following completion of RT. However, this must be interpreted with caution since many patients were missing data at 9 and 12 months post RT. As a result there may have been additional patients who developed moderate to severe dysphagia at some time after 6 months post RT. Table 10 summarizes the first onset of dysphagia over the first year.

Table 10: Trends in Dysphagia Development by Diet Restrictions

Outcome	Month	Cumulative	Quarterly	Percent of Cohort
Any diet restrictions	3	61	61	0.540
	6	80	19	0.708
	9	85	5	0.752
	12	86	1	0.761
Moderate/Severe diet restrictions	3	43	43	0.381
	6	63	20	0.558
	9	65	2	0.575
	12	65	0	0.575
Severe diet restrictions	3	19	19	0.168
	6	30	11	0.265
	9	32	2	0.283
	12	32	0	0.283

DISCUSSION

The purpose of this study was to determine the prevalence of dysphagia over the year following RT, any potential predictors of dysphagia, and any trends of dysphagia development in our retrospective study at Boston Medical Center.

The analysis of our prevalence data was conducted in various ways, using indicators of dysphagia and by severity of dysphagia within each indicator. The data were analyzed at four time points- 3, 6, 9, and 12 months post RT. A decision was made to use "moderate to severe" diet restriction as the measure of a moderate to severe dysphagia in order to bring some order to a data set that depicted widely different prevalence rates depending on indicator definition. This level of diet restriction was thought to be a substantial indicator that would impair quality of life and that would likely motivate a patient to seek treatment. With moderate or severe diet restriction as the indicator of dysphagia, the prevalence of dysphagia in the year following RT was 49% at 3 months, 56% at 6 months, 45% at 9 months, and 31% at 12 months. These results fell approximately mid-way between 2 previously cited studies that used diet as an indicator of dysphagia, which reported a prevalence at 6 months of 23.1% (42) and 73.5%, (59). The overall proportion of patients who developed dysphagia over the first year by moderate/severe diet marker, 56%, was higher than the 39.8% incidence reported to occur over the first three years using SEER and Medicare coding data (47). Our study calls into question whether coding/billing data underestimates the true incidence, as suggested by authors themselves. Second, the data collected for the study was in the 1990s, with a noted rise in incidence over the

decade from 33% to 44%. Our data were collected in the 2000s, which may reflect the a continuing trend since cancer treatments become more aggressive.

These results suggest that about fifty percent of patients who undergo RT may be expected to develop a significant swallowing dysfunction in the first year following RT. This is extremely useful data for a health care provider to present to a patient after diagnosis of HNC and should complement counseling provided to them at the time of molding a treatment plan.

Trends in dysphagia were also analyzed with moderate to severe diet restriction as the most "clinically meaningful" indicator of moderate/severe dysphagia. Interestingly all but two of the patients who developed moderate/severe dysphagia did so within the first 6 months of completion of RT. A similar observation was made when looking at "any" and "severe" diet outcomes. Due to missing data in the 9 and 12 month periods, analysis of the number of patients who showed a reversal in this pattern (those who developed dysphagia early on but recovered normal swallowing function during the first year after RT) was not conducted.

Analysis of subjective patient report and clinician report of swallowing problems revealed that at 6 months following RT completion, of the 63% of patients who reported having any swallowing impairment only 18% reported a severe swallowing issue (Figure 5). This is about 10% lower for both incidences than seen when using any and severe diet restriction as indicators, endorsing the assertion that patients tend to underreport their swallowing problems.

In patients with a severe dysphagia as defined as presence of feeding tube, prevalence of its use decreased only slightly over the first year but not as much as one would predict. Perhaps some patients who had feeding tubes placed prophylactically had them removed while others developed a worsening dysphagia eventually necessitating the insertion of a feeding tube, perhaps for the first time, during the year after completion of RT.

The two other markers for dysphagia ("any" diet restriction and any patient/clinician report of a swallowing problem) showed a worsening dysphagia at 6 months post RT but no significant negative linear trend from 3 to 12 months post RT. The prevalence of dysphagia did not change substantially over the first year overall. This agrees with Wilson et al (49) who used QOL scores as their indicator of dysphagia and suggested that the problem seen at 3 months is likely to continue over the first 12 months. There are no studies that have followed patients beyond one year for prevalence statistics, however clinicians are cognizant of the fact that some patients continue to have swallowing abnormalities for many years. Surprisingly some patients get worse, sometimes after several years of reportedly doing "ok". Evidently the long-term course of dysphagia after RT needs to be better understood.

Awareness that the odds of developing dysphagia are approximately 50% may be a motivating factor for some patients to begin exercises. Unfortunately our data did not identify any variables that could help predict who is at greater risk of developing such a long term dysphagia. This study identified only oral malignancy as a significant risk factor at 6 months post RT. As a result, it may be difficult for clinicians to motivate

their patients to undergo intensive, daily exercises for an issue that "might appear at some point in the next year" or later.

Our study left some critical questions unanswered. Who and why do some patients develop a dysphagia while others remained untouched? Attempts to identify significant predictors of dysphagia in our cohort were surprising. BMI, age, cancer stage, and smoking history were not found to be significantly associated with dysphagia, even though the literature suggested otherwise (60-62). Only oral cavity as cancer site was associated with moderate/severe dysphagia in our cohort of patients. Interestingly, while 75% of our cohort received IMRT, our prevalence figures are not much different from studies that did not use IMRT or only had a minority of patients that received IMRT therapy (23, 32, 34).

The outcome may have been altered by one final variable, which is delivery of swallowing therapy. Few of the patients received therapy for a dysphagia in this study so it could not be factored into the results. None of the above cited incidence or prevalence studies included this as a factor, either.

There have been several published small-scale clinical trials to determine the efficacy of exercise therapy to date, but with mixed results (34, 44, 55, 63-65). A few studies suggest that delivery of early swallowing therapy during RT may help prevent later swallowing problems (34, 35). With the results of the current study showing a prevalence of 50%, physicians may be encouraged to enroll patients into early therapy

i.e., during or end of RT. However the real effect of intervention is still to be determined.

Limitations

Limitations of this study were a retrospective research design, relatively small sample size, no instrumental swallowing studies, no quality of life scale, lack of standardized scales for identifying diet or patient report, and single-center study. Complaints of swallowing were evaluated using subjective accounts rather than objective instrumental measurements hence the degree of correlation between subjective reports by patients and objective measurements could not be established. Additionally, the retrospective design of the study resulted in a few potentially significant clinical parameters to be excluded from collection. For example, post RT alcohol and tobacco consumption was not collected. Many subjects were excluded from the analysis due to lack of outcome data, hence our results may possibly be a slight over estimate of the actual global prevalence rate. This is because it is possible that a greater proportion of patients with minimal or no swallowing troubles may not have had dysphagia status notes in the medical records since lack of dysphagia is not considered to be a documentation priority. Furthermore we may have had a biased sample due to the exclusion of a huge proportion of the initial sample. The chance of under documentation of no dysphagia may be higher than the lack of documentation of a mild or moderate dysphagia. In spite of these limitations, it is, to our knowledge, the most systematic and comprehensive reflection of the true prevalence of dysphagia in HNC patients in the first year after RT available to the scientific and clinical

communities at this time. Prospective studies that address the limitations of this one will add significant insight to this critical issue.

Future Directions

Future research efforts must be made to address several issues despite the limitations of our study. A number of ideas for future projects arose from our study. Randomized clinical trials should be conducted to establish the clinical benefits of diagnosing dysphagia during and after RT. This can be approached systematically if physicians and staff were to document dysphagia consistently using validated QoL and/or diet scales. Institutions with sufficient SLP coverage could use standard protocols to evaluate patients with objective measurements including FEES, MBS, QoL, or diet scales. These outcome measures should be collected at specific time points before, during and after therapy for head and neck cancer. Future studies should evaluate the degree of correlation between subjective reports by patients and objective measures of swallowing in the setting of a prevalence or incidence study.

Collecting accurate prevalence data to compare patients who did not undergo exercise therapy with those who did would be useful to future studies as well. Future prospective studies could perform regular "screening" assessments to determine whether the assessments and subsequent therapeutic strategies have an impact on QoL. Similarly, prospective studies could also determine whether regular instrumental swallow assessment during and/or after RT would alter the management of dysphagia. This could potentially translate into modified standards of care during

or after radiation therapy to either prevent or treat any RT associated dysphagia. A standardized practice could guide improved patient care and result in collection of comprehensive data for future research.

Conclusion

The results of our retrospective cohort study suggest that about half of patients who undergo RT may be expected to develop a major swallowing dysfunction within the first year of RT. The majority of those who develop dysphagia are likely to do so within the first 6 months of completion of RT. The only significant predictor of dysphagia was oral cavity as a cancer site. Male gender and alcohol consumption at 6 months post RT completion were marginally significant. Altogether this is exceptionally valuable data for a health care provider to present to a patient following a diagnosis of HNC and should complement counseling provided to them at the time of fashioning a treatment plan.

LIST OF JOURNAL ABBREVIATIONS

Ann Oncol	Annals of Oncology
Ann Otol Rhinol Laryngol	Annals of Otology, Rhinology, and Laryngology
Arch Otolaryngol Head Neck Surg	Archives of Otolaryngology Head and Neck Surgery
Biochem Society Transactions	Biochemical Society Transactions
CA Cancer J Clin	A Cancer Journal for Clinicians
JADA	The Journal of the American Dental Association
J Cancer Res Ther	Journal of Cancer Research and Therapeutics
J Clin Oncol	Journal of Clinical Oncology
J Dent Res	Journal of Dental Research
J Support Oncol	The Journal of Supportive Oncology
Int J of Phoniatrics	International Journal of Phoniatrics
Int J Radiat Oncol Biol Phys	International Journal of Radiation Oncology*Biology*Physic
N Engl J Med	TheNew England Journal of Medicine
Otolaryngol Head Neck Surg	Otolaryngology Head and Neck Surgery
Radiother Oncol	Radiotherapy and Oncology

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CURRICULUM VITAE

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Education

2010-2012	Boston University School of Medicine Expected Graduation Date: January 2013 Degree: M.A. in Clinical Investigation	Boston, MA, USA
2002-2008	The Royal College of Surgeons in Ireland (RCSI) Graduation Date: 06/05/08 Degree: M.B, B.Ch, BAO (NUI)-Honors	Dublin, Ireland
1998-2002	The International School of Choueifat (ISC) Degree: High School Diploma	Dubai, UAE

Employment Experience

Baystate Medical Center Department of Internal Medicine 07/12-present
Program Director: Dr. Michael Rosenblum
I am currently in my second postgraduate year of my internal medicine residency training.

Berkshire Medical Center Department of Internal Medicine 07/11-06/12
Program Director: Dr. David Albert
My first year of postgraduate training in internal medicine was completed at Berkshire Medical Center.

Boston Medical Center Department of Otolaryngology 09/10 – 06/11
Mentor: Dr. Susan Langmore
Volunteered as a research associate
-*Study:* A retrospective cohort study, titled "Prevalence and Trends of Dysphagia Following Radiation Therapy in Patients With Head and Neck Cancer".

Beaumont Hospital Department of Medicine & Surgery 07/08 – 12/09
Undertook postgraduate training in Dublin, Ireland in Medicine and Surgery for 18 months.

Academic Honors

2008	Medicine & Surgery, Pediatrics, Psychiatry
2007	Otolaryngology, Pediatrics, Tropical Medicine, Psychiatry
2004/05	Anatomy, Physiology, Biochemistry, Pharmacology, Behavioral Science
2002/03	Pre-Medical: Physics, Chemistry, Biology

Research/Case Reports

Diagnostic accuracy of ultrasound-guided fine needle aspirate (FNA) in thyroid malignancy.
L Rahmat, D Al Azawi, ADK Hill, Dublin, Ireland

Factors influencing the length of stay for the appendicectomy in a university teaching hospital
G Falk, Y Doyle, L Rahmat, N O'Farrell, C Collins, P Broe, Dublin, Ireland

A rare cause of acromegaly: ectopic growth hormone releasing hormone (GHRH) secretion from lung carcinoid tumour.
L Rahmat, C McCarthy, C Collins, P Broe, Dublin, Ireland

Presentations/Meetings

CHEST Conference 2012 Oct 2012
Invited to present a clinical case about an incidental finding of pulmonary alveolar proteinosis.

200th Anniversary New England Journal of Medicine (NEJM) Meeting June 2012
An essay contest was held regarding internet/social media and healthcare, where out of 600 entries I was awarded one of the 120 winning invitations to the meeting as a scholar.

Royal Academy of Medicine in Ireland Meeting (Dublin, Ireland) Oct 2009
A case presentation of a rare case of a patient with heart failure, liver failure and renal failure surviving an open repair of an aortocaval fistula.

Charter Day: Intercollegiate Case Competition (Dublin, Ireland) Feb 2008
I was given the opportunity to represent RCSI on Charter day by presenting "A rare cause of acromegaly- ectopic growth hormone releasing hormone (GHRH) secretion from lung carcinoid tumor".

Surgical Oncology Conference (Baltimore, MD) Jan 2008
Title: "Chromogranin A (CgA)-a useful tumour marker?" A case presentation of carcinoid syndrome & the utilization of CgA as a tumour marker. Presented at Johns Hopkins Hospital.

RCSI Senior Poster Presentation (Dublin, Ireland) March 2007
Conducted a study to explore the concept of medical humanities within the RCSI syllabus. It was part of six-week elective called "Medicine, Film, & Literature".

Awards

RCSI Surgical Case Competition (Dublin, Ireland) 2008
Awarded first prize for presentation of "A rare cause of acromegaly- ectopic growth hormone releasing hormone (GHRH) secretion from lung carcinoid tumor".

"Early Patient Contact"Case Presentation (Dublin, Ireland) 2003
As part of an curriculum, I had the privilege of interviewing a lady (only lady in Ireland at the time) with an extremely rare neurological disorder characterized by muscle spasms & rigidity, called "Stiff Person Syndrome". Awarded first prize for presentation.

Physics 2nd Prize, Chemistry 2nd (Dublin, Ireland) 2003
Awarded 2ndprize out of class of 209.