# Effect of Regularly Scheduled Artificial Hydration on Treatment Outcomes in Head and Neck Cancer Patients Undergoing Radiotherapy

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CERTIFICATE OF APPROVAL

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**LIST OF ABBREVATIONS AND ACRONYMS**

| | |
|---|---|
| CT | Computed Tomography |
| DNA | Deoxyribonucleic Acid |
| EPIC | Electronic Privacy Information Center |
| G1 | Gap 1 |
| G2 | Gap 2 |
| HNC | Head and Neck Cancer |
| HPV | Human Papilloma Virus |
| IMRT | Intensity-Modulated Radiation Therapy |
| M | Mitosis |
| OHSU | Oregon Health & Sciences University |
| PICC | Peripherally Inserted Central Catheter |
| S | Synthesis |
| SPSS | Statistical Product and Service Solution |

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## Abstract

**Background:**

Head and neck cancer is one of the top ten cancers diagnosed in the United States, accounting for 53,640 new cases in 2013. Patients suffering from head and neck cancer are at higher risk for dehydration due to the site of the tumor and negative effects of cancer treatment on the ability to swallow. Clinical dehydration is believed to: negatively impact the efficacy of cancer treatment, increase frequency and severity of side effects, and increase the number of unplanned hospital admissions and treatment breaks and unplanned hospital admissions. Improved hydration status may decrease some of these adverse effects and reduce the number of unplanned treatment breaks. Artificial hydration, the intravenous administration of normal saline, is an intervention used to treat clinical dehydration.

**Objective:**

The goal of this study was to determine if regularly scheduled artificial hydration decreased the number of unplanned hospital admissions and treatment breaks, protected renal function and improved hydration status among head and neck cancer patients undergoing radiotherapy-based treatment.

**Methods:**

A retrospective chart review was performed to determine if frequency of regularly scheduled artificial hydration administration affected treatment outcomes of head and neck cancer patients treated with radiotherapy at Oregon Health & Science University

(OHSU). Sixty patients who received regularly scheduled artificial hydration and were treated before August 2011 were compared with 45 patients who did not receive regularly scheduled artificial hydration and were treated after August 2011. The electronic medical records, Electronic Privacy Information Center (EPIC), were queried to obtain the following information: date of birth, treatment initiation and completion dates, cancer diagnosis, treatment type, feeding tube placement and location, renal function values (blood urea nitrogen and plasma creatinine), hydration status values (hemoglobin, hematocrit), number of unplanned hospital admissions, number of treatment breaks, number of times and volume of artificial hydration administered, registered dietitian exposure, height, and weight throughout treatment. The number of unplanned hospital admissions, number of treatment breaks, and number of times artificial hydration administered throughout treatment were compared between groups. Patients who were under the age of eighteen, had a diagnosis other than head and neck cancer, were treated at any facility other than OHSU, or were treated with only one treatment modality such as only surgery, only chemotherapy, or only radiation were excluded.

The data were analyzed using a Poisson regression model comparing the two group's number of unplanned hospital admissions and number of unplanned treatment breaks between groups. Paired t-tests were used to determine differences in mean lab values at the beginning, middle and end of treatment within groups. Unpaired t-tests were used to compare, the mean number of times artificial hydration was administered, registered dietitian exposure, and weight change, between groups. Chi square analysis

was used to compare the proportion of patients that were outside the established normal reference ranges.

**Results:**

1) There were no significant differences in mean number of unplanned hospital admissions and mean number of treatment breaks between those receiving regularly scheduled artificial hydration and those not receiving regularly scheduled artificial hydration.

2) Mean change in renal function values were not significantly different between groups. Blood urea nitrogen and plasma creatinine concentrations increased and hemoglobin and hematocrit decreased similarly throughout treatment in both groups.

3) Both groups had a mean weight loss of greater than 1.5% of pre-treatment weight per month. This rate of weight loss is considered excessive by OHSU nutritional care standards because, if weight loss continued at this rate, it would result in a total weight loss of greater than 10% of pre-treatment body weight in six months.

4) Patients who saw or who did not see a dietitian had no differences in number of unplanned hospital admissions, number of unplanned treatment breaks, or percent of body weight lost. This subsample of patients was difficult to compare because there were registered dietitian staffing changes in the middle of the dates of data collection.

**Conclusions:**

1) Treatment outcomes were similar for those who received regularly scheduled artificial hydration and those who did not receive regularly scheduled artificial

hydration. The use of regularly scheduled artificial hydration did not result in fewer unplanned hospital admissions or unplanned treatment breaks compared to those who did not receive regularly scheduled artificial hydration.

2) Similar to previously reported research, treatment modality appeared to play the largest role in the number of unplanned hospital admissions and treatment breaks. Those who received chemoradiation had the highest rates of unplanned hospital admissions and treatment breaks.

# Chapter 1
# Introduction

Head and neck cancer accounts for three percent of all cancer occurrences in the United States with over 40,000 new cases diagnosed in 2011[1]. Head and neck cancer patients are at high risk for clinical dehydration because the site of the tumor and the cancer treatment can synergistically decrease the patient's ability to effectively swallow. Clinical dehydration in cancer patients can negatively impact the efficacy of cancer treatment[2]. Artificial hydration is an intervention that treats clinical dehydration and may improve overall treatment outcomes. Artificial hydration is defined as the provision of fluid or electrolyte solutions (e.g., normal saline) either intravenously or enterally. No consensus exists on the role of regularly scheduled intravenous artificial hydration on treatment outcomes in head and neck cancer patients.

The goal of this study was to determine if regularly scheduled artificial hydration decreased the number of unplanned hospital admissions and, treatment breaks, improved renal function as measured by blood urea nitrogen and plasma creatinine concentration, and, improved hydration status as measured by hematocrit and hemoglobin.

Often head and neck cancer patients undergo a combination of chemotherapy, surgery, and radiation. Both of these treatments can cause distortion of sense of taste (dysguesia), olfactory dysfunction (dysomia), and changes in the thirst mechanism.

These factors can result in a decrease in fluid intake, which in turn can lead to clinical dehydration. One approach to prevent dehydration is to deliver fluids enterally via a gastrostomy tube.

Previous research has shown that patients who have gastrostomy tubes placed prior to treatment have significantly fewer nutrition-related (e.g., clinical dehydration or malnutrition) hospitalizations compared with those who had either no gastrostomy tube placed or had the gastrostomy tube placed after treatment initiation[3,6,27,30,35]. Despite these advantages of early gastrostomy tube placement, chemotherapy and radiation treatment decrease tolerance to gastrostomy tube feedings and fluid flushes, thereby potentially decreasing the nutritional and hydration status of the patient and limiting the utility of gastrostomy tubes[3]. An alternative option for replenishing fluids is through artificial hydration.

Artificial hydration is an efficient way to replenish fluid deficits caused by poor oral fluid intake related to head and neck cancers and their treatments. OHSU head and neck cancer patients currently only receive artificial hydration when diagnosed with clinical dehydration. In contrast, prior to August 2011, OHSU head and neck cancer patients received regularly scheduled artificial hydration for prophylaxis or prevention of dehydration, but the benefits of this practice have not been documented. Preventive artificial hydration may reduce the number of unplanned hospital admission, decrease the number of breaks in chemoradiation, and improve overall outcomes as

demonstrated by laboratory markers of renal status and hydration status in head and neck cancer patients.

Specific Aims:

To determine the effect of regularly scheduled artificial hydration treatments on the number of unplanned hospital admissions and unplanned treatment breaks, markers of renal status and hydration status in head and neck cancer patients.

Hypothesis: Head and neck cancer patients who receive regularly scheduled artificial hydration treatments have fewer unplanned hospital admissions and unplanned treatment breaks and larger proportion of patients whose blood urea nitrogen, plasma creatinine, hemoglobin, and hematocrit concentrations are within the established normal reference ranges compared to those who did not receive regularly scheduled artificial hydration treatments.

# Chapter 2
# Background and Significance

## Head and Neck Cancer

By 2020 it is estimated that over 18.7 million people will be diagnosed with cancer worldwide. Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. If this spread of cells is not controlled, the result could be death. Specifically, head and neck cancer (HNC) is a broad category of cancers that occur in the oral, pharyngeal, laryngeal, and nasal cavities. Death rates from HNC have decreased over the past twenty years from 5.61 to 3.81 deaths per 100,000 people. HNC is more common in men than women and in adults who are 50 years and older[4]. Factors that increase a person's risk for developing HNC include smoking, chewing tobacco, consuming alcohol, or infection with the human papilloma virus (HPV)[1]. Patients who have HNC caused by HPV infection have a less severe form which decreases the treatment needed to eradicate the tumor from the body. Seventy-five percent of all HNC occurrences are due to tobacco use; either from smoking or chewing tobacco[5]. HNC patients are prone to developing difficulties eating and drinking due to the treatment related irradiation of a large area of mucus membranes and salivary glands[3]. Side effects of HNC, or the treatment of HNC, include: nausea, vomiting, pain, fever, febrile neutropenia, shortness of breath, dehydration, anemia, fatigue, diarrhea, and psychological issues. Twenty-five to fifty percent of HNC patients are classified as nutritionally-compromised prior to initiation of treatment making them at higher risk for

side effects and suboptimal treatment tolerance[4]. Many of the side-effects of HNC, or treatments of HNC, impede the patient's oral fluid and food intake. Research has shown that malnutrition and dehydration are associated with shorter survival time, decreased quality of life, decreased efficacy of treatment, increased health care costs, and increased unplanned treatment breaks[6]. Treatment breaks that are planned are not detrimental to treatment efficacy because patients still receive the needed doses of radiation or chemotherapy. But when treatment breaks are not planned and the patient does not receive the necessary treatment dose, cancer treatment can lose its efficacy on tumors.

## Treatment of Head and Neck Cancer

Various treatments are used to combat HNC including: surgery, radiation, chemotherapy, hormone therapy, biological therapy, or targeted therapy. Recently there has been a tendency to combine treatments to create a personalized treatment plan. Treatment regimens are usually dependent on the tumor site and stage of cancer[6]. Combined treatments have dramatically improved throughout the years resulting in improved outcomes but the combination of treatments also presents new clusters of complications for patients that must be addressed by healthcare providers.

### *Radiation Treatment for Head and Neck Cancer*

At least 50% of all cancer patients receive radiation treatment at some point during cancer treatment. Radiation damages the cancer cell and inhibits its growth. Radiation damages DNA within the tumor cell rendering the cell incapable of dividing and growing;

it significantly effects cells that are rapidly dividing. Cancer cells are damaged or killed in the process as are other normal, non-cancerous, rapidly-dividing cells. Non-cancerous cells that divide rapidly which are often affected by radiation treatment include: bone marrow cells, gastrointestinal cells, mucosal surface cells, and skin cells. The goal of radiation therapy is to maximize the dosage given to the cancer cells while minimizing exposure to healthy cells. Radiation therapy initially affects quickly dividing cells; with repeated exposure, radiation treatment also affects cells that divide more slowly.

Intensity-modulated radiation therapy (IMRT) is a treatment approach that limits the frequency of toxicities by avoiding high doses of radiation directed toward critical non-cancerous nerve cells and salivary cells when possible[7]. IMRT lessens the impact and severity of bleeding, neural toxicities, oral toxicities, and skin sensitivity induced by radiation treatment, depending on the location of the cancer site. IMRT is a mode of high-precision radiotherapy that employs computer-controlled linear accelerators to deliver precise radiation doses to a malignant tumor. This type of radiation therapy has the ability to conform more precisely to the three-dimensional shape of the tumor by delivering the radiation in various small doses. IMRT uses three-dimensional computed tomography (CT) to calculate the dose and intensity of radiation, as well as to target the location and shape of the radiation profile to conform to the tumor volume.

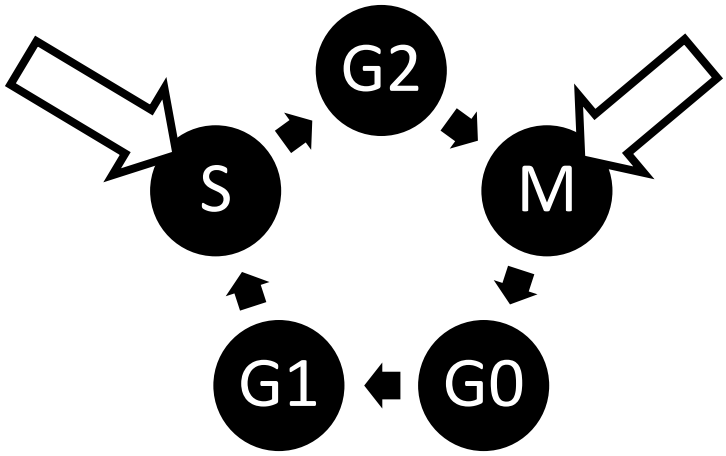
Even with focused radiation treatment, 58% of patients receiving radiation still suffer from severe dehydration due to damage to critical portions of the mouth[8]. This is due

to the large amount of submandibular and/or sublingual gland tissue in close proximity to many HNC locations. Damage to these critical portions not only decreases saliva production but also causes pain and inflammation which can cause a patient to consume less fluids. Severe dehydration, from radiation treatment, can lead to renal deficiencies because of the increased solute load on the kidneys which then must work harder to filter harmful substances from the body. Despite the negative impact on renal status, of the post-surgical treatment methods for HNC, radiation has been found to be the most cost effective treatment plan to eliminate cancer[9]. Optimal use of artificial hydration to address side effects such as clinical dehydration have not been fully evaluated or reported in the literature.

***Chemotherapy***

Chemotherapy, like radiation, damages or targets cells that are rapidly dividing. Oncologists determine when chemotherapy drugs should be administered in relation to the cancer cell cycle. There are four main stages in the cell cycle: Gap 1 Stage (G1), Synthesis Stage (S), Gap 2 Stage (G2), and Mitosis Stage (M). Chemotherapy drugs attack cells that are in a specific cell cycle phase, usually the M or S phase. The M and S phases are critical for cell survival: during the S stage, DNA replication occurs; during the M phase, nuclear and cytoplasmic division occurs. Inhibiting the cell cycle prevents cancer cells from growing, dividing, and may induce cell death. Figure 1 shows the cell cycle with arrows pointing to the M and S phases targeted by chemotherapy drugs.

**Figure 1: Target Phase of Chemotherapy in the Cell Cycle**




One non-cancerous tissue that rapidly divides and can be negatively affected by chemotherapy is bone marrow. As a result, chemotherapy has a large impact on hematopoesis because bone marrow cells are critical for the production of red blood cells. Without proper hematopoesis there is a significant increase in the presence of disorders in the blood, hematologic toxicity, due to slow red blood cell synthesis[7]. A study by Givens et al,, (2009) found that chemotherapy treatments, consisting of one dose (20-30 mg/$m^2$) of cisplatin or carboplatin with paclitaxel, administered every week for six to seven weeks, reduced the rate of hematologic toxicities and prevented the occurrence of unplanned hospital visits compared with conventional chemotherapy treatment[7].

### *Chemoradiation Combination Therapy for Head and Neck Cancer*

The goal of combined radiation and chemotherapy (chemoradiation) is to enhance the elimination of cancer cells while minimizing damage to the surrounding normal cells. Chemoradiation has been proven to have good disease-specific survival rates, and loco-

regional control. Loco-regional control is when a patient does not have progression of a tumor into other areas and when the tumor positively responds to cancer treatment. Chemoradiation has superior three to five year survival rates, disease-free survival, and loco-regional control rates compared to either chemotherapy or radiation therapy alone[7,10]. However, the enhanced treatment required to eliminate cancer tissue comes at the cost of greater occurrence of both short-term and long-term adverse effects of treatment[7,11]. For example, a greater percentage of patients receiving both chemotherapy and radiation therapy were found to have problems with global functioning, and normalcy of diet and speech during and after treatment compared to patients either receiving chemotherapy or radiation therapy alone[9]. Managing the more significant side effects of combination therapy for HNC is an important aspect of patient care that may enhances the patient's quality of life and improve treatment outcomes.

**Effect of Hydration Status on Head and Neck Cancer Treatment Outcomes**

The efficacy of HNC treatment is dependent on multiple variables. Hydration and nutritional status before, during, and after treatment has a significant impact on the efficacy of treatment and recovery time[6]. Dehydration can cause fatigue, lethargy, nausea, vomiting, confusion, muscle cramps, and result in increased mortality rates[12]. To determine which patients are dehydrated can often be difficult since physical signs of dehydration are unreliable, particularly among malnourished cancer patients. Physical signs of dehydration, like physical signs of malnutrition, include: decreased skin turgor, tachycardia (rapid heart rate), orthostasis or hypotension, dry oral mucosa, and

delirium. The similarities between dehydration and other cancer-related side effects make diagnosing and treating dehydration extremely difficult. Weight loss, vital signs including sitting blood pressure, electrolyte balance, urine excretion, and bioelectrical impedance are the primary methods used to assess hydration status. In one research study, severe weight loss accurately predicted future visits to the emergency department to treat dehydration[8]. Weight that is recorded and measured frequently throughout the day is one way to track a patient's hydration status. A weight loss as low as 1.5-2% loss of body weight over 12 to 24 hours is classified as mild dehydration. Pulse rate and blood pressure are more accurate measurements that are commonly used to determine hydration status. Biochemical markers, along with physical signs, can be unreliable markers of hydration status in certain conditions. For example, plasma osmolality and sodium concentrations are often used to assess hydration status but it has been shown that these markers become elevated with dehydration. Change in plasma osmolality is a good marker of chronic hydration status but a poor marker of acute dehydration. Malecka-Massalska et al, (2012) found that using bioelectrical impedance vector analysis in HNC patients reliably and accurately determined hydration status[11]. Bioelectric impedance sends a harmless electric current through the body. The resistance this current experiences through the body is used to determine the body composition; the electrical current flows with less resistance through tissues with higher water content[13]. Combining physical signs and biochemical markers improves the clinician's ability to determine a patient's hydration status, to intervene when necessary, and to avoid hospitalizations to treat dehydration[12].

### *Unplanned Hospital Admissions during Head and Neck Cancer*

When severe dehydration develops, it can result in unplanned hospital admissions or severe delays in treatment that can compromise treatment efficacy[14]. Many HNC patients are malnourished prior to treatment making it difficult for the patient to meet their current nutrient and fluid needs and ameliorate previous energy losses[15].

Causes for HNC-related hospital admissions vary depending on the location of the tumor and the type of treatment. Mucositis, hematologic toxicity and toxicity-related treatment delays, such as neural toxicities and oral toxicities, were the most common causes of unplanned hospital admissions[7]. Patients who had the highest rates of hospital admissions for dehydration were those with tumors located in the nasopharynx[8]. Patients with tumors in the oral cavity or oropharynx had lower rates of unplanned hospital admissions. Along with tumor location, treatment type affects hospitalization rates. Capuano et al,, (2010) found that patients treated with concomitant chemotherapy and radiation therapy had higher rates of unplanned hospital admissions compared with patients who received other treatments[15]. Of these hospital admissions, severe mucositis accounted for 10% of unplanned hospital admissions, intravenous fluid replacement accounted for 27% of admissions, and dehydration or malnutrition accounted for 26% of admissions among HNC patients[7]. Improved approaches to cope with these side effects may decrease the number of unplanned hospital admissions of HNC patients.

### *Delays in Treatment for Head and Neck Cancer*

It is reported that half of head and neck cancer patients experience toxicity-related delays in treatment[7]. Around 90% of patients have unplanned radiation treatment breaks. On average about 50% of patients do not receive the planned number of chemotherapy cycles due to unplanned delays or hospitalization[7]. An unplanned break can cause decreased control over tumor growth. A break of one day can lower control over tumor growth by up to 1% per day of radiation therapy interruptions[11]. This decrease in control can cause significant loss of loco-regional control and lower survival rates[7]. Unplanned treatment breaks for several days or more can result in shorter overall survival and relapse-free survival[11].

Delays during treatment are becoming more common due to many factors such as an increase in the total amount of radiation or chemotherapy given, and the increase in outpatient treatment[7]. Many treatment centers follow patients on an outpatient basis, which may decrease the time and interaction between patients and health care providers as well as decrease information obtained by health care providers due to patient lack of recall. In addition to reduced interaction with the patient, treatment in the outpatient setting may interfere with collaboration between primary health care professionals and other oncology experts[6].

Some research on the effects of nutrition interventions have shown that dietitian-led services can reduce the frequency of unplanned hospital admissionss[6]. Unplanned hospital visits are a frequent cause of unplanned treatment breaks. Many patients may

lose an additional 10% of their pretherapy body weight during treatment. Nutrition counseling to improve nutrient and fluid intake may help decrease weight loss among cancer patients. A weight reduction of greater than 20% is correlated with treatment interruptions, infection, hospital readmissions and decreased survival rates[15]. Patients who participated in a dietitian-led clinic transitioned back to oral diet quicker, had a fewer nutrition-related hospital admissions, and fewer unplanned nasogastric tube placements, than those who did not receive extra health care follow up[6].

A major underlying factor resulting in unplanned hospital visits among HNC patients is a decline in salivary flow. Improved radiation targeting can lower the dose and decrease damage done to critical cells in the mouth, but some damage does occur. The parotid gland, which consists of serous acini cells, produces watery and albuminous secretions and is extremely sensitive to radiotherapy[16]. Absence of watery secretions in the mouth, results in thicker secretions and can lead to gagging, nausea, and vomiting[4]. This damage to the salivary glands can cause dry mouth, difficulty swallowing, and difficulty manipulating foods. The most significant decline in salivary flow occurs 3 to 6 months after initiation of radiation treatment. Partial recovery occurs around 12 months after radiation termination[16]. Proper hydration, either orally or by artificial hydration, and mouth care is crucial to ameliorate the effects of salivary gland damage[4].

Renal function also has a significant impact on the efficacy of chemotherapy treatment. It has been found that ethnicity, age, and creatinine clearance rate are all factors that should be considered when determining the dose of chemotherapy treatment and how

the patient's kidneys will handle the treatment. The treatment effect on quickly dividing cells in the kidneys as well as decreased fluid intake can put greater pressure on the kidneys leading to decreased renal function. Nishimura et al, (2007) found that Japanese patients had a significantly lower creatinine clearance rate than other ethnicities, thereby decreasing the tolerance of doses that are typical for the general United States population[17]. Many elderly patients have decreased renal function making it more difficult for them to clear the medications and treatments out of their system and to deal with the side effects[18]. For patients who are elderly, of Asian descent, or who have lower creatinine clearance rates, treatment doses might need to be lowered for better tolerance. Renal function must be routinely monitored during chemotherapy to assess tolerance and to adjust the dose and minimize adverse complications[17].

### *Mucositis*

Mucositis is a painful inflammation and ulceration of the mucous membranes and is a primary cause of inadequate nutrition or hydration, mental status, and treatment delays in HNC patients[5]. Mucositis is one of the most debilitating acute complications of HNC treatment[19]. Sixteen to forty-seven percent of unplanned treatment breaks are due to moderate to severe mucositis[19]. The mechanism through which mucositis occurs is based on the fact that the oral mucosa has continuous cell turnover. Tissues that are rapidly dividing are often negatively affected by cancer treatment, which makes the mucosa extremely sensitive to the action of chemotherapy and radiation.

The first occurrence of mucositis often emerges during the first two weeks after initiation of radiotherapy and persists for an average of five weeks [19]. Risk factors for mucositis, aside from HNC treatment, are smoking, presence of chronic illness, and age. Smoking irritates the mucosal cells making these cells much more prone to mucositis. Santos et al, (2011) found that patients with diabetes had a higher prevalence of mucositis compared with patients who did not have diabetes[19]. Young patients were at a lower risk for developing mucositis than elderly patients because of the high mitotic activity (the target phase for treatment) of the oral epithelial cells[17, 18,20,21,].

Severe mucositis may delay radiation treatments and decrease oral intake leading to weight loss[22]. Along with functional complications, mucositis can alter in the oral environment thereby predisposing HNC patients to opportunistic infections such as candidiasis[23]. Planned radiation treatment breaks can be beneficial to tolerability of treatment and quality of life. If tumor control declines during these breaks, the treatment can be adjusted by adding additional treatments[11]. However, additional treatments after a break due to adverse side effects can also increase the risk of further complications of the treatment[24]. Machon et al, (2012) found that good nutritional support can lower inflammatory markers and prevent severe mucositis[25]. Mucositis is one side effect that can cause dehydration, lower quality of life and lead to unplanned treatment breaks if not addressed in HNC patients undergoing radiation therapy.

### *Cost of Side Effects Associated with Treating Head and Neck Cancer*

Treatment of cancer is costly. The unplanned hospital admissions and unplanned treatment breaks associated with side effects can be just as, or even more, costly. Hospital admissions account for the largest amount of the average total incremental cost of cancer treatment, compared to outpatient support and prescription medication which is less costly[9]. These costs cause financial burdens for both the patient and the healthcare facility.

Various research studies have investigated potential areas of cost savings. Kiss et al, (2012) reported that the use of non-medical related clinics in Australia, which are easily accessible for patients, can provide savings of up to $95,000 per year for cancer treatment while preventing severe side effects[6]. Incorporating a dietitian into outpatient clinics has been shown to improve communication with health professionals on the cancer treatment team and decreases costs[6]. Elting et al, (2007) reported that the average incremental cost of all grades of oral mucositis is about $6,000 per patient[22]. On average, the cost of grade one or two oral mucositis is around $1,700. The cost of grade three or four mucositis is around $3,600 per patient per visit. Many patients require more than one hospital visit for mucositis.

Along with symptom management and prevention, the type of treatment for HNC can impact the total cost of cancer therapy. The most cost efficient method or treatment for HNC is surgery, alone, followed by radiation and chemotherapy. Radiation therapy has been shown to provide the best value for efficacy of treatment[9]. Through better

coordination of care, management of side effects, and promotion of more cost effective treatments, the patient and hospital could save a significant amount of money[14].

**Artificial Hydration Administration throughout Head and Neck Cancer Treatment**

Artificial hydration can be used as either a supplemental or as a primary source of fluids, when there is a decrease in oral intake of fluids over the course of treatment. For the most part, artificial hydration is used to manage the side effects of treatment. Factors such as family support, physician preference, and location of a medical facility all determine the frequency of using artificial hydration as a key part of HNC treatment. Studies are conflicting as to whether nutritional and hydration status can impact tumor response, toxicity or survival. Nutrition and hydration status may have no direct effect on tumor response to therapy[26]. Ethical dilemmas can hinder the usage of artificial hydration when it comes to end of life care. If and when artificial hydration should be used during end of life care is frequently debated[27].

Once a patient is dehydrated, artificial hydration can efficiently improve fluid status and correct dehydration. Paradoxically, sometimes with an improvement in fluid status there is an increase in thirst. Extremely dehydrated patients might not respond to normal thirst signals and in turn may drink less, which compounds the dehydrated. Adequate hydration may improve the patient's oral fluid intake by improving thirst signals. For patients who are not allowed to consume food or fluids by mouth, consuming sips of water on occasion can help with the physical desire to drink fluids whether or not they are dehydration[12]. There are several options available to treat

dehydration but deciding whether artificial hydration is needed, and which type of fluid replacement should be used, can be a challenging decision made by the patient, family, and health care provider.

### *Effect of Intravenous Fluid Administration on the Treatment of Head and Neck Cancer*

Intravenous fluid hydration is the process whereby fluids are administered into blood vessels. For long term or frequent intravenous fluid administration a centrally located port, or small device that is inserted into a larger blood vessel is used to avoid frequent punctures with a needle. For infrequent fluid administration, peripheral vessels, e.g. veins in the arms, are used. Intravenous hydration decreases the symptoms and occurrence of dehydration in cancer patients[28]. The volume of fluid supplied intravenously to dehydrated HNC patients averages one and a half liters a day[27]. The fluid given to the patient is typically normal saline, consisting of water, sodium, chloride, and other electrolytes can be added if required for patient health. Intravenous fluids are quick and easy to administer. The main concerns with intravenous fluid administration are the repetitive venipunctures, decreased mobility, possible congestive heart failure, edema, and skin breakdown[12]. A peripherally inserted central catheter (PICC) can be used to avoid repeated venipunctures. Yet even for those patients with gastrostomy tubes that could be used for rehydration, many still require intravenous administration of fluids. Additional fluids needed by HNC patients is because oral fluid intake often decreases throughout treatment. Research has shown that 17% of patients

with HNC with gastrostomy tubes required intravenous fluids during treatment while 54% of those without gastrostomy tubes needed intravenous hydration[3].

### *Enteral Fluid Administration with Feeding Tubes*

Use of feeding tubes to deliver fluids can improve treatment and help avoid unplanned hospital admissions. Giving all cancer patients feeding tubes, though, is not cost effective or necessary. The tumor site, recent change in body weight, previous hospital admissions for dehydration, treatment type, and physician practice are some of the factors that determine whether a patient will attain a feeding tube. Currently around 57% of all cancer patients have enteral feeding tubes placed[6]. However, several studies suggest placement of prophylactic gastrostomy tubes before cancer treatment decreases the incidence of weight loss and dehydration in high risk HNC patients[8].

There are multiple sites for enteral feeding tube placement: nasogastric, gastric, and small intestine. Patients fed by nasogastric tubes have superior functional outcomes with respect to swallowing compared to those with gastrostomy tubes[29]. But dislodgement of nasogastric tubes can cause serious side effects and should be closely monitored[2]. Nasogastric tubes are used for short term hydration and feeding purposes, while gastrostomy tubes are the primary tool used for long term hydration and feeding purposes. Percutaneous endoscopic gastrostomy placement has been shown to decrease the number of treatment interruptions and to hasten delivery of complete radiation therapy. The use of percutaneous gastrostomy tubes is one of the most commonly used strategies to avoid unplanned treatment breaks. Uninterrupted

radiation therapy results in better tumor control but can in turn lead to more severe toxicity affects[3]. Gastrostomy feedings can improve the quality and quantity of feedings which in turn improves the well being of the patient[30]. The average weight loss for patients with gastrostomy tubes was nineteen pounds while those without prophylactic gastrostomy tubes lost forty-three pounds[3]. Increased weight loss during treatment means the patient is in much poorer nutritional and hydration status to tolerate the treatment regimen. Raykher et a (2009) found that enteral feeding through a percutaneous endoscopic gastrostomy tube was an adequate way to manage nutritional and hydration status, with only 10% of patients admitted to the hospital for dehydration[31].

One concern with use of tube feedings is that patients will become dependent on tube feedings and not use the muscles required for eating; thereby making the transition back to oral intake more complicated. A study by Kiss et al, (2012) found that most patients were not tube dependent and transitioned back to regular diets within eight weeks after treatment[6]. Other studies have found that patients with feeding tubes can require enteral feeding for up to three and a half years after treatment due to lingering poor oral functioning[7]. Patients without feeding tubes may have restrictions to their diet, like softer or moister foods, due to side effects from radiation treatment. The intensity of the treatment regimen can increase the degree of dysphagia which directly correlates with the amount of gastric tube dependence[32]. Patients may also not understand how to use feeding tubes which can cause confusion and issues with proper enteral feeding techniques. While the majority of patients with gastrostomy tubes

understood that the main purpose of the tube was to prevent or minimize weight loss, they also reported that the instructions and procedures to use the tube were difficult to understand. For optimum gastrointestinal fluid intake timely dietetic management (e.g. nutritional assessment, nutritional supplementation, nutritional requirements) is needed for the patient to feel more confident about weaning off of tube feedings[30]. Mayre-Chilton et al, (2011) showed that four out of six caregivers and patients found dietetic management helpful when weaning off the tube. Reasons for extended enteral feedings could be due to lack of insurance to pay for oral rehabilitation or speech therapy, complications presented during treatment, stage of cancer, increase treatment intensity, and severity of side effects.

### *Alternative Methods of Hydration to promote Adequate Hydration*

Hypodermoclysis is a method of subcutaneous hydration used to replace fluids. For patients receiving palliative care, health professionals will occasionally use subcutaneous fluid infusion because it is less invasive then other forms of hydration[27]. Hypodermoclysis is mainly used for rehydration rather than symptom management. This method is advantageous because it can be started and stopped with no risk of thrombosis or bleeding, is easily managed in the home setting, does not need a health professional to administer, and does not require use of an infusion pump[28]. This type of hydration is administered in the chest, abdomen, thighs, and upper arms. Fluids are administered directly into the subcutaneous tissues and sites may be used for up to four to five days. Hypodermoclysis is a useful and safe method for maintaining hydration in

terminally ill patients[24]. This is an alternative method of hydration for families and patients who object to artificial hydration through feeding tubes or intravenously.

**Quality of Life among Patients with Head and Neck Cancer**

Patients with HNC can have many complications associated with the disease in general and with its treatment. The overall goal of treatment is to destroy the cancerous cells while limiting the negative impact of therapy on the patient's quality of life. Quality of life refers to the extent to which a patient's usual physical, emotional, and social well being are affected by a disease or its treatment[9]. The diagnosis, place of tumor, and treatment regimen can have a large impact on a patient's quality of life.

HNC patients deal with a variety of difficulties that are both physical and psychological. Research has shown that even with increased side effects of more aggressive treatment, the majority of patients will choose the more aggressive treatment over the non aggressive treatment; even when the more aggressive treatments are not necessarily superior[33]. The disabilities caused by HNC treatment can be life-altering but at the same time can kill the cancer and decrease cancer-related mortality. Physical disabilities are dealt with much more successfully than psychological difficulties. Patients deal with physical impairments well; only 25% of patients report low physical health scores. In contrast 43% of patients rate their mental health as low or poor with 4% of those people experiencing moderate to severe depression[7]. Along with depression, pain scores and measures of psychological distress were the only specific symptoms that directly affected the overall quality of life[33].

One physical symptom that does have a significant impact on quality of life is oral mucositis. By reducing mucositis, tolerability of radiation and quality of life can be improved[11]. Mucositis can cause lasting residual pain and eating difficulties, even one year after treatment is concluded. Oral mucositis is a severe physical impairment, but physical impairment has an even greater effect on quality of life because of the psychological aspects of dealing with oral mucositis.

Due to many contributing factors, HNC patients often have poor oral function which can cause a decrease their ability to eat and drink. Throughout the world eating is a social event. When a person is unable to eat, the social event changes or is taken away from them, often causing detrimental psychological issues[9]. Poor oral function can be a persistent long term complication for a majority of HNC patients[7]. Thus, patients have to deal with complications long after treatment subsides. To improve quality of life in patients it is important to address oral intake, nutrition, and swallowing functions even before treatment begins. For quality of life purposes it is important to have patients continue to use oral feeding as long as possible to maintain swallow function[29]. The complications of aggressive treatments can linger for long periods of time; patients will sacrifice their quality of life in hopes of a better future, but improved symptom management may alleviate some side effects associated with these treatments.

HNC patients deal with a variety of difficulties when it comes to treatment, diagnosis, and all the side effects associated with this disease. In order to better manage these symptoms and improve the patient's quality of life certain side effects should be

addressed. The hydration status of HNC patients significantly contributes to the quality of life and severity of symptoms of treatment and diagnosis. Better management of hydration status in HNC patients could potentially diminish side effects and significantly improve their quality of life.

# Chapter 3
# Methods

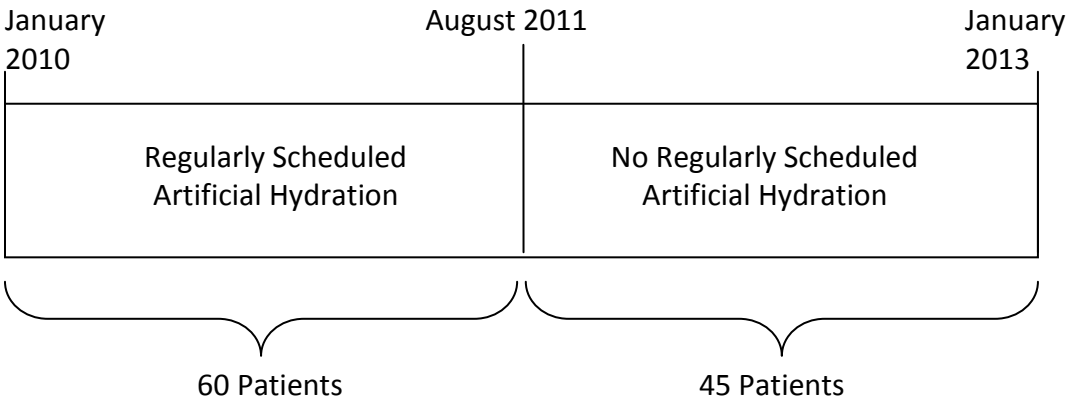
## General Design

A retrospective study design was used to determine the relationship between regularly scheduled artificial hydration and the number of unplanned hospital admissions, unplanned treatment breaks, renal function and hydration status during treatment of patients with HNC. Patients treated at OHSU for HNC typically undergo seven weeks of combined radiation and chemotherapy. Prior to August 2011, patients received regularly scheduled artificial hydration to prevent dehydration. After August 2011, because of a change in the standard treatment protocol, patients were only provided artificial hydration when they presented to the emergency department or when severely dehydrated, or orthostatic, due to decreased consumption of fluids. The protocol was reviewed and approved by the OHSU Institutional Review Board (IRB) and did not require collection of consent for this study.

Medical records of 105 adults who received radiation treatment for HNC at OHSU between January 2010 to January 2013 were reviewed. Patients who met the inclusion of being 18 years or older, who were diagnosed with head and neck cancer, treated with radiation plus either surgery or chemotherapy, and who were patients at OHSU between January 2010 and January 2013 were included in this study. Among HNC patients who received treatment at OHSU between August 2011 and January 2013, 45 did not receive regularly scheduled artificial hydration. While 60 HNC patients treated

at OHSU received regularly scheduled artificial hydration and were treated between January 2010 and August 2011

**Figure 2: General Study Design**




**Data Collection**

Data collected from medical records of patients with HNC who received cancer treatment were included in this retrospective review. A list of patients who received radiation therapy was obtained from the OHSU tumor registry. Data collected included date of birth, treatment initiation and completion dates, cancer diagnosis, treatment type, gastrostomy tube placement and site of access, renal function values (blood urea nitrogen and plasma creatinine), hydration status values (hemoglobin, hematocrit), number of unplanned hospital admissions, number of unplanned treatment breaks, number of times and volume of artificial hydration that was administered, registered dietitian exposure, and the patient's height and weight throughout treatment. Nurse's notes were queried to see if patients reported use of gastrostomy tubes and, if so, how frequently. All individuals' data were compared to established normal reference values

for OHSU. Values outside of the acceptable reference ranges were considered detrimental for HNC treatment (Table 1).

**Table 1: Acceptable Values or Ranges for Outcome Variables**

| Variable | Acceptable Values or Ranges |
|---|---|
| Blood Urea Nitrogen | 7-25 mg/dL |
| Plasma Creatinine | 0.7-1.4 mg/dL |
| Hemoglobin | Male: 13.8-17.2 g/dL<br>Female: 12.1-15.1 g/dL |
| Hematocrit | Male: 40.7-50.3%<br>Female: 36.1-44.3% |
| Unplanned Hospital Admissions | 0 Admissions |
| Weight Loss Throughout Treatment | Weight loss less than 10% in 6 months |
| Number of Unplanned treatment breaks | 0 Breaks |

**Data Management**

Data for each patient were de-identified, recorded on a data collection sheet, transferred to an Excel database, and imported into SPSS (Statistical Package for the Social Sciences) Version 20 for statistical analysis (Armonk, New York). Until transferred to the electronic database, information was kept in a locked cabinet. Data were maintained electronically on an OHSU internal server which was backed up daily and archived off-line on a daily, weekly, monthly and yearly basis.

**Confidentiality**

Participant's confidentiality was protected by using a unique study identifier on all forms and in all data sets. Information was kept in locked storage in Gaines Hall Room 212 on the OHSU campus. When not in use access to participant data and information was restricted to authorized personnel only.

**Power calculations**

Sample size and power were estimated for the primary outcomes of interest, only. All tests employed a (two-sided) significance level of 0.05. The mean number of unplanned hospital admissions was anticipated to be less than one and expected to average near 0.6 visits per patient over the course of treatment (about seven weeks, presumed equal between groups for purposes of power calculations). This estimated mean was supported by Elting et al, (2007) who reported an average of 0.62 visits per patient over the treatment cycle for HNC. Our sample of 60 patients under the regularly scheduled artificial hydration protocol and 45 patients under the newer (no routine hydration) protocol provided an 80% chance of detecting at least an 85% increase in the mean number of admissions by the group who did not receive regularly scheduled artificial hydration (Wald test; increase from an average of 0.6 to 1.1 visits). For blood urea nitrogen we expected initial lab values for both groups to be near the middle of the normal reference range (about 15 mg/dL) and assumed the standard deviation to be approximately one-fourth the range (about 4.5 mg/dL). Typically blood urea nitrogen concentrations range from 6-32 mg/dL. Correlation between initial and final blood urea

nitrogen was expected to be fairly weak (about 0.20). Under these assumptions, we would have 80% power to detect a mean change of at least 2.4 mg/dL relative to baseline within either group, with the minimal effect being even smaller for the sample of 60 patients under the regularly scheduled artificial hydration treatment protocol. Similarly, if the mean change over time between the two groups differed by at least 3.2 mg/dL, the power would still be 80% to detect this effect with the sample sizes specified. Similar assumptions for plasma creatinine concentration indicated there would be an 80% chance to detect changes (from start to end of treatment) of at least 0.10 mg/dL within either group, and that a difference in the mean change of at least 0.13 mg/dL between the groups could be identified.

## Statistical Methods

### *Descriptive Statistics*

Means and standard deviations were calculated for all outcome variables. Primary outcomes were the number of unplanned hospital admissions during treatment (not including regularly scheduled artificial hydration appointments), and blood urea nitrogen and plasma creatinine concentrations during treatment. Secondary outcomes included the number of breaks in treatment, weight loss during treatment, concentration of hemoglobin and hematocrit percentage (Table 2).

**Table 2: Primary and Secondary Outcomes**

| **Primary Outcomes** | |
|---|---|
| Number of Unplanned Hospital Admissions<br><br>Number of Unplanned Breaks in Treatment | Renal Function (Blood Urea Nitrogen/Plasma Creatinine Values) |
| **Secondary Outcomes** | |
| Hemoglobin | Weight loss throughout treatment<br><br>Hematocrit |

***Analytical Methods***

Poisson regression was used to compare the two groups with respect to the number of unplanned hospital admissions and the number of breaks in treatment. An offset variable [log (treatment duration)] was included in these models to account for patients having varying durations of treatment. Paired t-tests were used to compare differences in means within groups from start to end of treatment with respect to continuous outcomes (e.g. blood urea nitrogen, creatinine, hematocrit, hemoglobin). Chi square tests were used to determine differences in the proportion of outlying values for the same continuous outcomes between groups. Chi square analysis was done to compare similarities in biochemical values in three ways including: comparison between groups, comparison within groups over time, and comparison between groups over time. Unpaired t-tests, were used to compare differences in mean change overtime (beginning to middle of treatment, middle to end of treatment, and beginning to end of treatment) in the continuous outcomes between the two groups.

### *Exploratory Studies*

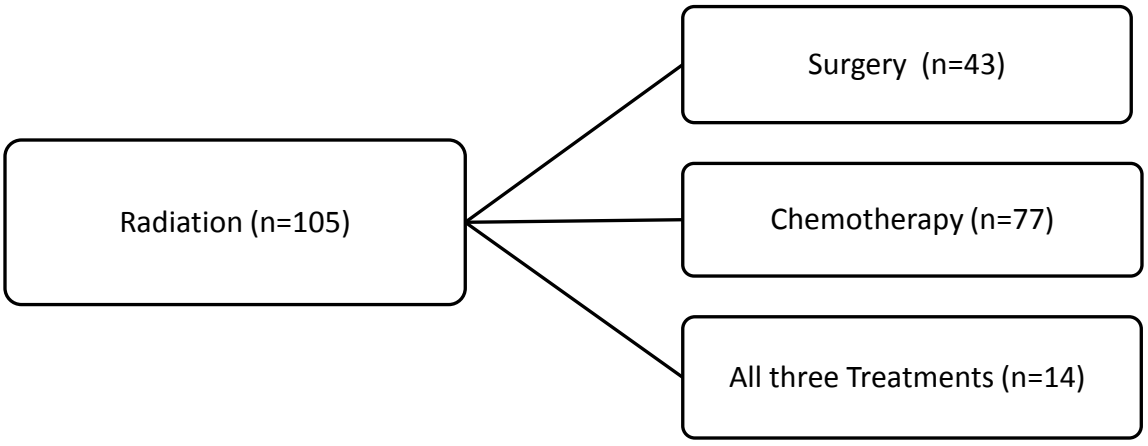
Studies were conducted to explore the correlation between weight loss and artificial hydration treatment, renal function markers, and other treatment outcomes. The goal of these studies was to evaluate if minimizing weight loss or providing regular hydration treatment was associated with fewer unplanned hospital admissions or unplanned treatment breaks during treatment for HNC patients.

# Chapter 4
# Results

## Patient Characteristics

One hundred and eight medical records were reviewed. One hundred and five patients fulfilled all inclusion criteria. All patients received radiation with the majority of each group also receiving chemotherapy (Figure 3). Sixty patients received regularly scheduled artificial hydration. Forty five patients received no regularly scheduled artificial hydration. Half of the patients who did not receive regularly scheduled artificial hydration underwent surgery compared to about one-third of those who received regularly scheduled artificial hydration.

**Figure 3: Treatment Distribution of Patients with Head and Neck Cancer**



Descriptive characteristics of our study sample are presented in Table 3. There were more males (n=83) than females (n=22) in the total sample. The average age for both groups was about 60 years. Forty-four patients had oropharyngeal cancer with similar numbers between those who did and did not receive regularly scheduled artificial hydration. The average treatment completion time was 48 days (± 20 days). Typical treatment duration without breaks was about 49 days or 7 weeks. Some patients did not complete treatment, or had accelerated treatment, causing our average completion time to be lower than expected. The average treatment time differed between the two groups by 4 days but this difference was not significant. Patients who received regularly scheduled artificial hydration received on average of 17 ± 10 hydration administrations while those not receiving regularly scheduled artificial hydration received on average 3 ±3 hydration administrations.

**Table 3: Descriptive Characteristics***

| | Regularly Scheduled Artificial Hydration | No Regularly Scheduled Artificial Hydration | Total |
|---|---|---|---|
| Number of Patients | 60 | 45 | 105 |
| Male | 50 (83%) | 33 (73%) | 83 (79%) |
| Female | 10 (17%) | 12 (27%) | 22 (21%) |
| Age (Youngest-Oldest) | 61 ± 12 (26-90) | 60 ± 10 (40-92) | 60 ± 11 (26-92) |
| Location of Cancer | | | |
| Nasopharynx | 8 (14%) | 5 (11%) | 13 (12%) |
| Oral Cavity | 5 (8%) | 5 (11%) | 10 (9%) |
| Oropharynx | 23 (38%) | 21 (47%) | 44 (42%) |
| Salivary Gland | 1 (2%) | 1 (2%) | 2 (2%) |
| Thyroid | 0 | 5 (11%) | 5 (5%) |
| Hypopharynx | 1 (2%) | 3 (7%) | 4 (4%) |
| Nasal Cavity | 5 (8%) | 2 (4%) | 7 (7%) |
| Larynx | 17 (28%) | 3 (7%) | 20 (19%) |
| Treatment Type | | | |
| Radiation | 60 | 45 | 105 |
| Chemotherapy | 48 (80%) | 29 (64%) | 77 (73%) |
| Surgery | 16 (20%) | 27 (36%) | 43 (27%) |
| Treatment Duration (Days) | 46 ± 17 (9-158) | 50 ± 21.5 (14-134) | 48 ± 20 (9-158) |
| Registered Dietitian Exposure (Number of patients) | 14 (23%) | 29 (67%) | 43 (42%) |
| Unplanned Hospital Admissions Per Person | 0.48 ± 0.79 (0-3) | 0.42 ± 0.75 (0-3) | 0.46 ± 0.77 (0-3) |
| Unplanned treatment breaks per person | 1.7 ± 1.6 (0-7) | 1.6 ± 1.4 (0-6) | 1.6 ± 1.5 (0-7) |
| Number of Artificial Hydration Administrations Per Person | 17.1 ± 10.4 (0-42) | 3.4 ± 3.8 (0-16) | 11.4 ± 10.8(0-42) |

*Data is presented as the number per group (percent of total) or the mean ±SD
Minimum and Maximum values are represented in parenthesis

**Unplanned Hospital Admissions**

On average both groups had less than one unplanned hospital admission per person. A total of 29 unplanned hospital admissions occurred in the regularly scheduled artificial hydration group; 22 of the 60 patients (37%) were hospitalized at least once of whom 5 patients were hospitalized more than once. A total of 18 unplanned hospital admissions occurred among those receiving no regularly scheduled artificial hydration; 13 of the 45 patients (29%) were hospitalized at least once of whom 5 patients who were hospitalized more than once (Table 4). Patients who received regularly scheduled artificial hydration were admitted to the hospital most often for fevers, aside from other causes, which consisted of toe pains, hypomagnesium, and other diagnoses. Patients not receiving artificial hydration were also hospitalized for fever most often, but dehydration was the second most common reason for hospitalization in this group.

**Table 4: Reasons for Unplanned Hospital Admissions**

| Reasons for Hospital Admissions | Regularly Scheduled Artificial Hydration* | No Regularly Scheduled Artificial Hydration** |
|---|---|---|
| Fever | 7 (24%) | 6 (33%) |
| Infection | 5 (17%) | 2 (11%) |
| Nausea/Vomiting | 4 (14%) | 0 |
| Dehydration | 3 (10%) | 5 (28%) |
| Other | 10 (35%) | 5 (28%) |

*Of the 29 unplanned hospital admissions, 22 patients were admitted at least once and 5 patients were admitted more than once.
**Of the 18 unplanned hospital admissions, 15 patients were admitted at least once and 5 patients were admitted more than once.

The relationship between regularly scheduled artificial hydration administration and number of unplanned hospital admissions during the course of treatment was explored using Poisson regression. Initially a baseline model including patient characteristics (age, gender, treatment type, placement and use of gastrostomy tube) was created which was then altered to include only those characteristics that were significantly associated with number of unplanned hospital admissions. This baseline model was then supplemented to include the hydration regimen (regularly scheduled artificial hydration versus no regularly scheduled artificial hydration). All models included treatment duration as an offset variable so the model estimates the mean number of unplanned hospital admissions expected during a 49-day treatment cycle (the typical duration of treatment).

In the baseline model, the mean number of unplanned hospital admissions was not significantly associated with age, gender, or use of a gastrostomy tube [$X^2$(4df)= 5.84, p= 0.21] but was associated with surgical intervention and chemotherapy [$X^2$ (2df)= 8.62, p= 0.01]. After controlling for these two treatment factors, the effect of hydration regimen (regularly scheduled artificial hydration versus no regularly scheduled artificial hydration) was not significant [$X^2$ (1df)= 0.42. p= 0.52]. After controlling for chemotherapy and hydration regimen, the mean number (0.41 per person) of unplanned hospital admissions (per 49 day treatment cycle) for those who had surgery was estimated to be 2.22 (95% CI: 1.08-4.53; p= 0.029) times higher than the mean number of unplanned hospital admissions for those who did not have surgery. Among individuals with similar surgical interventions and hydration regimens, those who

received chemotherapy had a mean number of unplanned hospital admissions (0.57 per person) that was 4.32 (95% CI: 1.53-12.1; p= 0.006) times higher than the corresponding mean number of unplanned hospital admissions for those who did not have chemotherapy. As noted, the effect of hydration regimen (after controlling for surgery and chemotherapy) was not significant (p=0.52), with those who received artificial hydration having a mean number of unplanned hospital admissions per 49-day cycle that was 23.5% higher than the corresponding mean for those who did not receive regularly scheduled artificial hydration (95% CI: 35% lower to 134% higher). It should be noted that the unadjusted effect associated with hydration regimen was also not statistically significant (p= 0.75), with the mean number of unplanned hospital admissions 9.6% higher for those who received regularly scheduled artificial hydration than those who did not receive regularly scheduled artificial hydration (95% confidence interval (CI): 35% lower up to 95% higher).

**Renal Function throughout Head and Neck Cancer Treatment**

Renal function was measured using blood urea nitrogen and plasma creatinine concentrations. Elevated blood urea nitrogen and plasma creatinine levels may indicate decreased renal function or decreased hydration status. The normal reference range for blood urea nitrogen concentrations is between 6-20 mg/dL. The mean blood urea nitrogen concentrations were within normal limits for both treatment groups however standard deviations showed a large variance and suggest that some patients in each group had blood urea nitrogen concentrations above the normal reference ranges (Table 5).

To compare changes in blood urea nitrogen and plasma creatinine concentrations throughout treatment, a value obtained during the middle of treatment was selected for each patient. This middle point was determined to be the closest date, but not over, to the exact mid-point of treatment. All data used for beginning, middle, and end of treatment was within seven days of the actual date either calculated for midpoint of treatment, or recorded as beginning or end of treatment. If there was no value in a particular range, the data were left blank. The changes in blood urea nitrogen concentrations throughout treatment are illustrated in Figure 4 and Table 5. Changes in blood urea nitrogen and creatinine concentrations in the following segments of treatment were compared: beginning to middle, middle to end, and beginning to end of treatment. Many of our patients had some or all of their values missing for blood urea nitrogen and plasma creatinine. This was taken into consideration when analyzing the total sample.

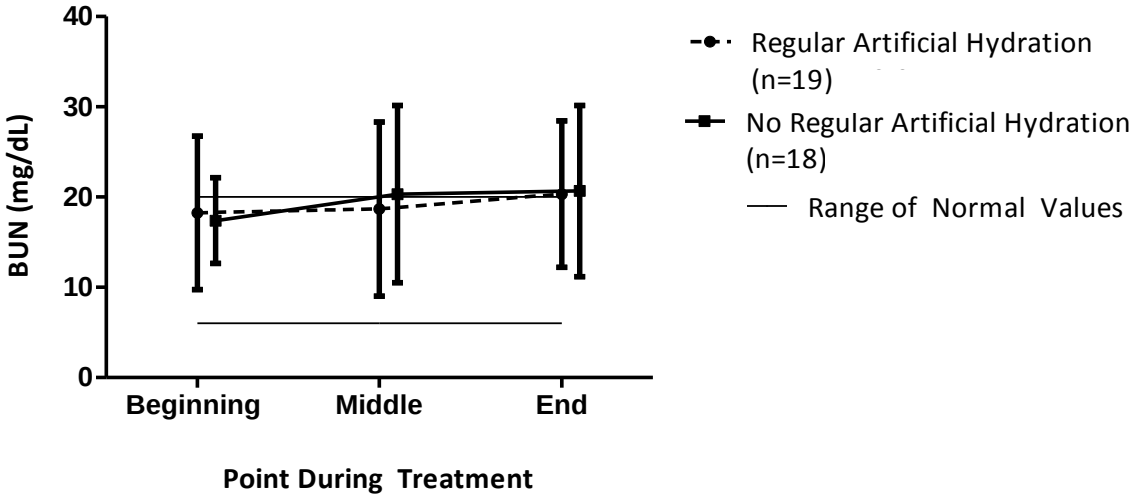
**Table 5: Change in Blood Urea Nitrogen Concentrations throughout Head and Neck Cancer Treatment and in Response to Receiving or Not Receiving Regularly Scheduled Hydration**

| Blood Urea Nitrogen (mg/dL) | Beginning of Treatment | Middle of Treatment | End of Treatment | Beginning of Treatment Compared to Middle of Treatment | Middle of Treatment Compared to End of Treatment | Beginning of Treatment Compared to End of Treatment |
|---|---|---|---|---|---|---|
| Mean ± SD Analysis Within Group Comparison | | | | Mean Difference Within Groups Comparison Over Time | | |
| Regularly Scheduled Artificial Hydration | n= 22<br>18.2 ± 8.5 | n= 19<br>18.7 ± 9.6 | n= 19<br>20.3 ± 8.1 | n= 22<br>0.4 ± 9.8 | n= 19<br>2.3 ± 9.0 | n= 19<br>3.3 ± 10.5 |
| No Regularly Scheduled Artificial Hydration | n:22<br>16.4 ± 4.8 | n: 21<br>19.3 ± 9.8 | n: 18<br>19.7 ± 9.5 | n= 22<br>4.1 ± 10.4 | n=21<br>-0.1 ± 7.7 | n= 18<br>5.0 ± 11.8 |
| Between Group Comparison of Mean Differences ± 95% CI | | | | Between Group Comparison Over Time | | |
| Comparisons Between Treatment Groups | -1.9 ± (-5.9 – 2.2)<br>p= 0.36 | 1.9 ± (-5.8 – 2.1)<br>p= 0.35 | 0.67 ± (-4.6 – 5.9)<br>p= 0.79 | p= 0.31 | p= 0.52 | p= 0.64 |

Mean difference of zero shows no difference between those who did and did not receive regularly scheduled artificial hydration
No statistical significant differences or changes throughout treatment were found

The change in blood urea nitrogen concentration between any two time points during treatment was not different when comparing within groups. The results showed that blood urea nitrogen concentrations increased slightly, though not significantly, throughout cancer treatment despite type of hydration treatment administered. Standard deviations for both groups were large indicating a great variation in blood urea nitrogen concentrations among head and neck cancer patients.

**Figure 4: Mean Blood Urea Nitrogen Concentration Before, During, and at the End of Head and Neck Cancer Treatment**




Data are mean ± SD for all patients with blood urea nitrogen measured at each time point
No statistical differences were found between groups at each time point or within groups over time.

Chi square analysis were used to characterize how the odds of being within the normal range (for blood urea nitrogen, serum creatinine, hemoglobin, and hematocrit) changed over time or differed between those who did and did not receive regularly scheduled artificial hydration, and whether changes over time differed by treatment group. To do the analysis, proportions were converted to odds because of the small sub-population that had consistent biochemical values collected throughout treatment. An initial chi square analysis was conducted to determine if any of the effects (changes over time, changes between groups, or differences in changes over time between groups) were significant for blood urea nitrogen. If the overall odds comparison was significant (overall p-value <0.10), the individual effects were estimated and tested. Additional analysis determined if there was a difference between the odds of having a blood urea nitrogen concentration above normal between those who did and did not receive regularly scheduled artificial hydration (Between Treatment Comparison). If the change in odds throughout treatment was not significantly different (p>0.10) between groups who received and did not receive regularly scheduled artificial hydration (Change Over Time Between Treatment Comparison) this interaction implied that the profiles over time were parallel for the two groups and therefore the difference between groups was constant throughout treatment. Parallel profiles also imply that both groups experienced the same pattern of change over time. Additionally, chi square analysis was used to determine the odds of developing elevated blood urea nitrogen concentrations over time within an individual's treatment (Change Over Time Within Patient). Models used an exchangeable correlation structure to maximize sample size

when data was missing. Tests for whether a patient was within the normal reference range for blood urea nitrogen are shown in Table 6.

**Table 6: Tests to Determine Whether a Patient was Within the Normal Reference Range for Blood Urea Nitrogen**

| Effect | Blood Urea Nitrogen |
|---|---|
| Change Over Time Within Patients | $X^2_2$= 8.18 (p=0.017) |
| Between Treatment | $X^2_1$=0.60 (p=0.44) |
| Change Over Time Between Treatment* | $X^2_2$=0.43 (p=0.81) |
| Overall Comparison** | $X^2_5$= 9.71 (p=0.08) |

*Changes over time differ by artificial hydration treatment.
**Significance of any of the three effects

For blood urea nitrogen concentration there were no changes in the odds of a patient being above the normal reference range when comparing those who did and did not receive regularly scheduled artificial hydration (p=0.44). But both groups had a significant increase in the odds of developing blood urea nitrogen concentrations above the normal reference range when comparing concentrations obtained at the beginning, the middle, and the end of treatment. Both groups experienced the same profile of change over the three sampling periods and, relative to the beginning of treatment, the middle of the treatment sampling period showed a non-significant (p=0.15) reduction in the odds of being within the normal range. By the end of the study, the odds of being within the normal reference range were estimated to be 73% (95% CI: 32-89%; p=0.01) less than the corresponding odds of being within the normal reference range at the beginning of treatment. Those receiving and not receiving regularly scheduled artificial

hydration did not have different odds of having blood urea nitrogen concentrations above the normal reference range.

### *Creatinine Concentrations throughout Treatment*

The normal reference range for plasma creatinine concentrations is 0.7-1.3 mg/dL. The mean plasma creatinine concentrations were within the acceptable range for both groups. Mean plasma creatinine concentrations were not statistically different between the two groups. The same statistical methods used to analyze blood urea nitrogen concentrations throughout treatment were used to analyze creatinine concentrations throughout treatment. Creatinine concentrations throughout treatment, comparisons between those who did and did not receive regularly scheduled artificial hydration, as well as comparisons between groups throughout treatment are shown in Table 7.

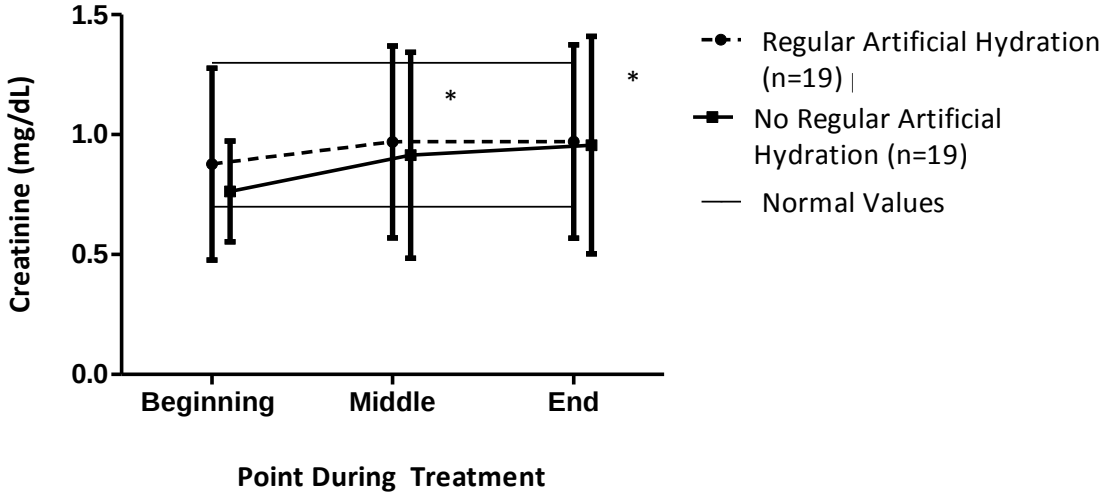
**Table 7: Change in Creatinine Concentrations throughout Head and Neck Cancer Treatment and in Response to Receiving or Not Receiving Regularly Scheduled Hydration**

| Creatinine Concentration (mg/dL) | Beginning of Treatment | Middle of Treatment | End of Treatment | Beginning of Treatment Compared to Middle of Treatment | Middle of Treatment Compared to End of Treatment | Beginning of Treatment Compared to End of Treatment |
|---|---|---|---|---|---|---|
| Mean ± SD Analysis Within Group Comparison | | | | Mean Difference Within Groups Comparison Over Time | | |
| Regularly Scheduled Artificial Hydration | n= 25<br>0.9 ± 0.4 | n=27<br>1.0 ± 0.4 | n= 17<br>1.0 ± 0.4 | n= 22<br>0.1 ± 0.3 | n= 19<br>0.0 ± 0.0 | n= 19<br>0.1 ± 0.1 |
| No Regularly Scheduled Artificial Hydration | n= 24<br>0.8 ± 0.2 | n= 28<br>0.9 ± 0.4 | n= 20<br>1.0 ± 0.5 | n= 23<br>0.2 ± 0.5** | n= 21<br>0.00 ± 0.5** | n= 19<br>0.2 ± 0.5** |
| Between Group Comparison of Mean Differences ± 95% CI | | | | Between Group Comparison Over Time | | |
| Comparisons Between Treatment Groups | -0.1 ± (-0.3 – 0.1)<br>p= 0.21 | -0.1 ±( -0.3 –0.2)<br>p= 0.63 | -0.0 ± (-0.3– 0.2)<br>p= 0.73 | p= 0.47 | p= 0.93 | p= 0.62 |

Mean difference of zero shows no difference between those who did and did not receive regularly scheduled artificial hydration
Both groups had creatinine concentrations which increased from baseline indicated by these symbols: *p<0.05 **p<0.01

Mean plasma creatinine concentrations increased significantly from beginning to middle of treatment (Mean difference: 0.18 ± 0.5, $p<0.01$), from middle to end of treatment (Mean difference: 0.00 ± 0.52, $p<0.01$), and from beginning to end of treatment (Mean difference: 0.19 ± 0.47, $p<0.01$) for those patients not receiving regularly scheduled artificial hydration (Table 7). There was no significant change in mean plasma creatinine concentration throughout treatment for those receiving artificial hydration (Table 7). Patients who did not receive artificial hydration had a greater increase in plasma creatinine concentrations than those receiving regularly scheduled artificial hydration from the beginning to the end of treatment (0.88 vs. 0.76), from the beginning to the middle of treatment (0.97 vs. 0.91), and from the middle to the end of treatment (0.97 vs. 0.96). Changes in plasma creatinine concentrations throughout treatment are illustrated in Figure 5 and Table 7.

**Figure 5: Mean Plasma Creatinine Concentration Before, During, and at the End of Head and Neck Cancer Treatment**




Data are mean ± SD for all patients who had creatinine concentrations measured
No significant difference in means was found between groups at any point in time.
*Statistical differences was found between beginning and middle of treatment for those not receiving regularly scheduled artificial hydration (1.2 ± 1.2, $p<0.01$), middle to end of treatment (1.0 ± 1.3, $p<0.01$), and beginning to end of treatment (2.4 ± 1.8, $p<0.01$)

Chi square analysis, similar to that described for blood urea nitrogen, was used to determine the odds of having a plasma creatinine concentration was above the normal reference range. The overall chi square comparison of plasma creatinine concentrations was not significant ($p>0.05$). Since overall comparison showed no significant differences when comparing odds between groups, within groups, and over time, no additional analysis was performed.

**Unplanned Treatment Breaks during Head and Neck Cancer Treatment**

Both groups had an average of 1.6 ± 1.5 unplanned treatment breaks per person during treatment for HNC, with no significant difference between the regularly scheduled artificial hydration group and the no artificial hydration group (Table 8).

**Table 8: Number of Unplanned Treatment Breaks during Treatment for Head and Neck Cancer**

| Treatment Breaks | Regularly Scheduled Artificial Hydration (n=60) | No Regularly Scheduled Artificial Hydration (n=45) |
|---|---|---|
| Total Treatment Breaks | 102 | 72 |
| Number of Patients with Treatment Breaks | 43 (72%) | 33 (73%) |
| Number of Patients with More than One Treatment Break | 32 (53%) | 21 (47%) |

Data presented as number (% of total)

We applied the same Poisson regression analysis methodology described above for unplanned hospital admissions to analyze distribution of treatment breaks. The initial Poisson model displayed evidence of large variation in the number of treatment breaks (sum of squared Pearson residuals was 37% higher than justified from a standard Poisson model); consequently, the number of unplanned treatment breaks was modeled by following a negative binomial distribution, which is a generalization of the Poisson regression analysis with an additional parameter to account for large variation.

There was no statistically significant association between number of unplanned treatment breaks and any characteristic considered as part of the baseline model (age, gender, treatment, placement/use of gastrostomy tube; p= 0.58). There was no significant association with the number of unplanned treatment breaks and regularly scheduled artificial hydration (p= 0.98). Patients who had surgery had an estimated 28% fewer unplanned treatment breaks compared to those who did not have surgery (p=0.087), however, these findings were not statistically significant.

**Weight Changes during Head and Neck Cancer Treatment**

The average weight loss for both groups was approximately 5 kg which reflects a loss of 5 to 6 percent of pre-treatment body weight (Table 9). There were 7 patients in the regularly scheduled artificial hydration group who had no weight measurements recorded and 3 patients in the no regularly scheduled artificial hydration group who had no weight measurements recorded. Typically, in patients with head and neck cancer, there is significant weight loss between the time of diagnosis and the time that treatment begins. Therefore, overall weight loss could be even greater than what occurred during the treatment period.

**Table 9: Change in Weight during Head and Neck Cancer Treatment***

| Weight Change | Regularly Scheduled Artificial Hydration (n= 53) | No Regularly Scheduled Artificial Hydration (n= 42) | Total (n=95) |
|---|---|---|---|
| Weight Loss Throughout Treatment (kg) | -4.6 ± 5.1 | -5.9 ± 4.8 | -4.8 ± 5.0 |
| % Pre-Treatment Body Weight | -5.3 ± 5.4 | -5.8 ± 5.6 | -5.6 ± 5.5 |

*Data presented as means ± Standard Deviations for all patients with weight measured

Both groups lost similar amounts of weight over the course of treatment for HNC (p=0.61). Based on our hospital's weight loss criteria it is acceptable to lose up to 3% of pre-treatment body weight over the 7 week course of HNC treatment. Both groups lost an average of 5% of their initial body weight which exceeds the standard criteria for acceptable treatment-related weight loss. The differences in body weight between beginning to middle of treatment, middle to end of treatment, and beginning to end of

treatment, and the significance levels associated with each comparison are presented in Figure 6 and Table 10.

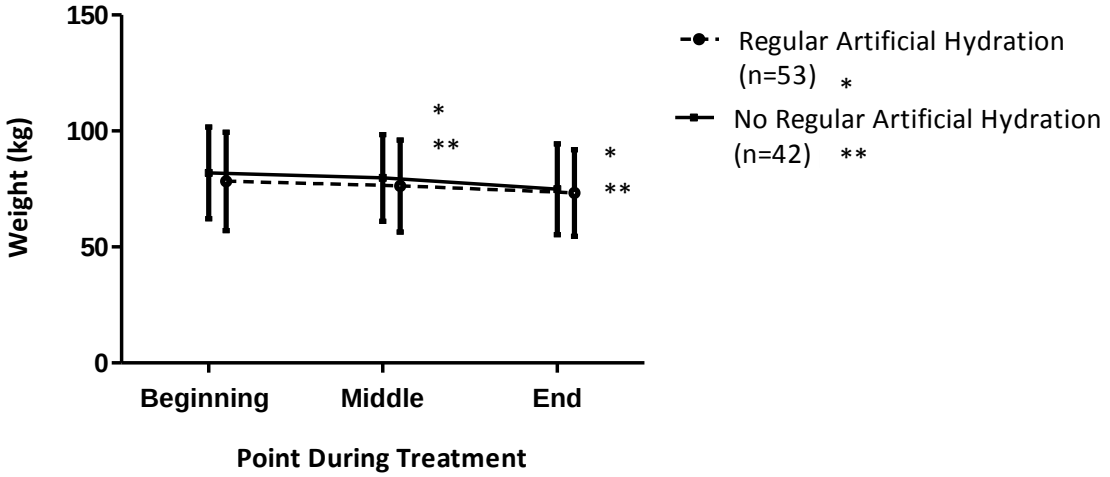
**Table 10: Change in Weight throughout Head and Neck Cancer Treatment and in Response to Receiving or Not Receiving Regularly Scheduled Hydration**

| Weight Change (kg) | Beginning of Treatment | Middle of Treatment | End of Treatment | Beginning of Treatment Compared to Middle of Treatment | Middle of Treatment Compared to End of Treatment | Beginning of Treatment Compared to End of Treatment |
|---|---|---|---|---|---|---|
| Mean ± SD Analysis Within Group Comparison | | | | Mean Difference Within Groups Comparison Over Time | | |
| Regularly Scheduled Artificial Hydration | n= 51<br>78.3 ± 21.2 | n= 51<br>76.3 ± 19.8 | n= 51<br>73.3 ± 18.7 | n= 54<br>-1.9 ± 2.9** | n= 51<br>-3.0 ± 3.0** | n= 51<br>-5.1 ± 4.8** |
| No Regularly Scheduled Artificial Hydration | n= 43<br>81.9 ± 19.8 | n= 43<br>79.8 ±8.7 | n= 43<br>75.0 ± 19.6 | n= 43<br>-2.1 ± 3.2* | n= 43<br>-4.9 ± 17.3 | n= 42<br>-7.1 ± 17.4** |
| Between Group Comparison of Mean Differences ± 95% CI | | | | Between Group Comparison Over Time | | |
| Comparisons Between Treatment Groups | 2.6 ± (-5.5 –10.8)<br>p= 0.52 | 2.5 ± (-5.3 –10.3)<br>p= 0.52 | 1.7 ± (-6.0 -9.3)<br>p= 0.67 | p= 0.71 | p= 0.40 | p= 0.61 |

Mean difference of zero shows no difference between those who did and did not receive regularly scheduled artificial hydration

Both groups had decreased weight from baseline indicated by these symbols: *p<0.05 **p<0.01

**Figure 6: Mean Weight Changes Before, During, and at the End of Head and Neck Cancer Treatment**




Data are mean ± SD for all patients who had weight recorded.
No significant differences were found between groups at any point in time.
*Statistical significance between beginning and middle of treatment for those receiving regularly scheduled artificial hydration (-1.9 ± 2.9, p<0.01), middle to end of treatment (-3.0 ± 3.0, p<0.01), and beginning to end of treatment (-5.1 ± 4.8, p<0.01)
** Statistical significant difference between beginning and middle of treatment for those receiving no regularly scheduled artificial hydration (-2.1 ± 3.2, p<0.01), and beginning to end of treatment (-7.1 ± 17.4, p<0.05)

**Effect of Gastrostomy Tube Placement on Head and Neck Treatment Outcomes**

Among patients who did not receive regularly scheduled artificial hydration, 42% had gastrostomy tubes placed at the beginning of treatment; 79% of whom used their gastrostomy tubes on a regular basis during treatment (Table 11). Seventy five percent of those who received regularly scheduled artificial hydration throughout treatment received gastrostomy tubes at the beginning of treatment; of whom 89% of the patients used their tubes regularly throughout treatment (Table 11).

**Table 11: Gastrostomy Placement and Use among Head and Neck Cancer Patients**

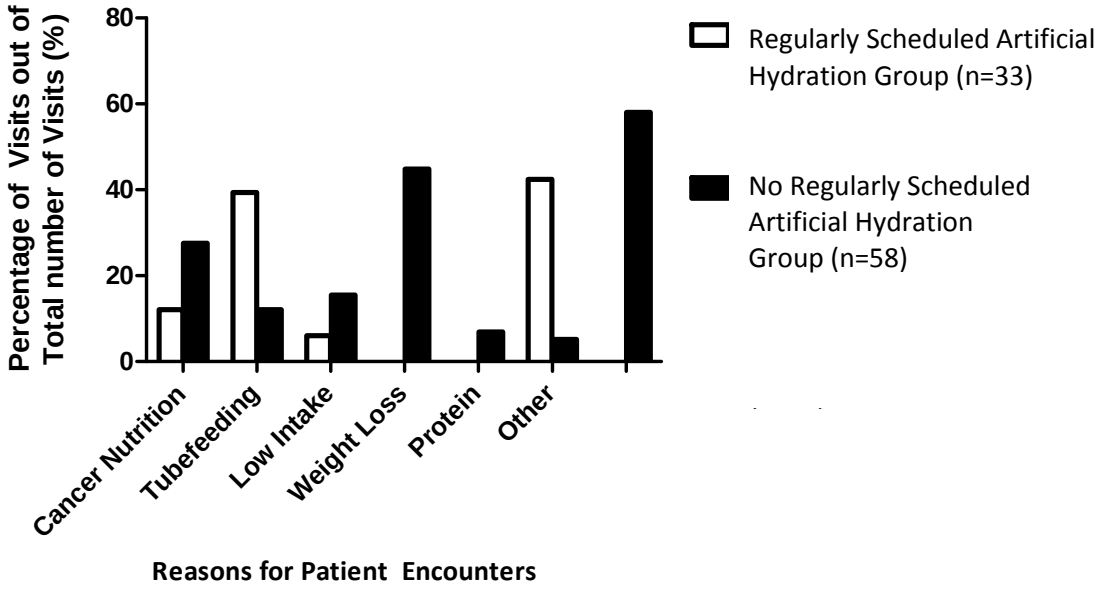
| | Regularly Scheduled Artificial Hydration | No Regularly Scheduled Artificial Hydration | Total Sample |
|---|---|---|---|
| Gastrostomy Tube Placement, % | 45 (75%) | 19 (42)% | 64 (61%) |
| Number of Patients Who Used their Gastrostomy Tube | 40 (89%) | 15 (79%) | 55 (86%) |

Data presented as number of individuals (% of total)

**Registered Dietitian Exposure During Head and Neck Cancer Treatment**

One fourth of those who received regularly scheduled artificial hydration met with an OHSU dietitian at least once during their treatment for HNC (n=14, 23.3%). Reasons that HNC patients met with a dietitian are reported in Figure 7. Of those receiving regularly scheduled artificial hydration, tube feeding instruction and trouble shooting were the major reasons patients met with a registered dietitian. Fourteen patients who received regularly scheduled artificial hydration were exposed to a registered dietitian (n=14, 23%). A total of 20 appointments, in those receiving regularly scheduled artificial hydration, with a registered dietitian occurred and 6 patients saw a registered dietitian more than once (ranged from 0-4 visits with a registered dietitian). Two thirds of patients who did not receive regularly scheduled artificial hydration met with a dietitian at least once during their treatment (n=30, 66.7%). A total of 69 registered dietitian appointments were made with 19 patients who saw a registered dietitian more than once (ranged from 0-5 visits with a registered dietitian). Weight loss was the most frequent reason for seeing a dietitian for those who did not receive regularly scheduled artificial hydration.

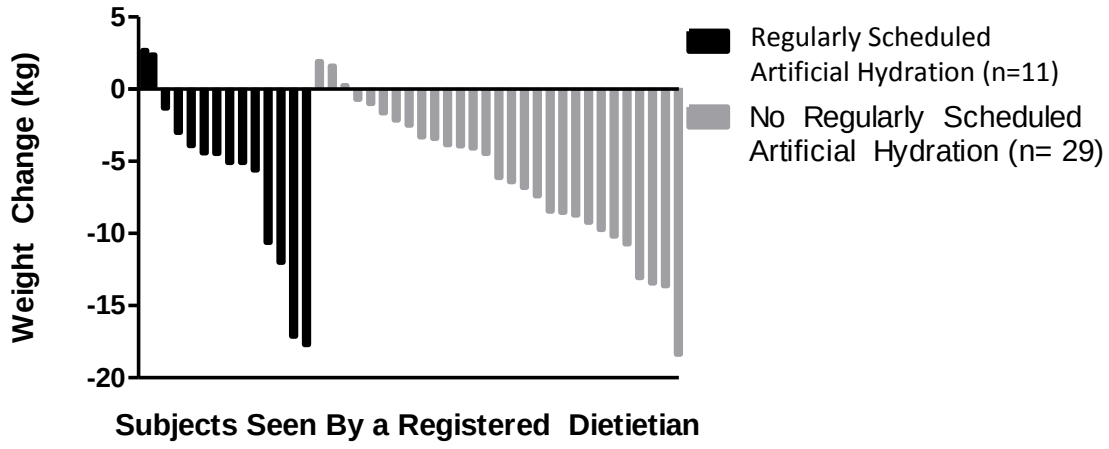
**Figure 7: Reasons for Registered Dietitian Visits during Head and Neck Cancer Treatment**




The percentage of patients who had weight loss and saw a registered dietitian was similar for both groups as illustrated in Figure 8. A majority of patients lost between zero and five kilograms of weight, the next largest category lost between five to ten kilograms of weight. Patients who saw a registered dietitian lost a mean of -5.6 ± 15.3 kg. While those who did not see a dietitian lost a mean of -11.3 ± 26.0 kg. The difference in mean weight loss between those who saw and those who did not see a registered dietitian were not significant. There were also no significant differences in mean number of hospital admissions, number of unplanned treatment breaks, and renal function marker values between those who did and did not see a dietitian.

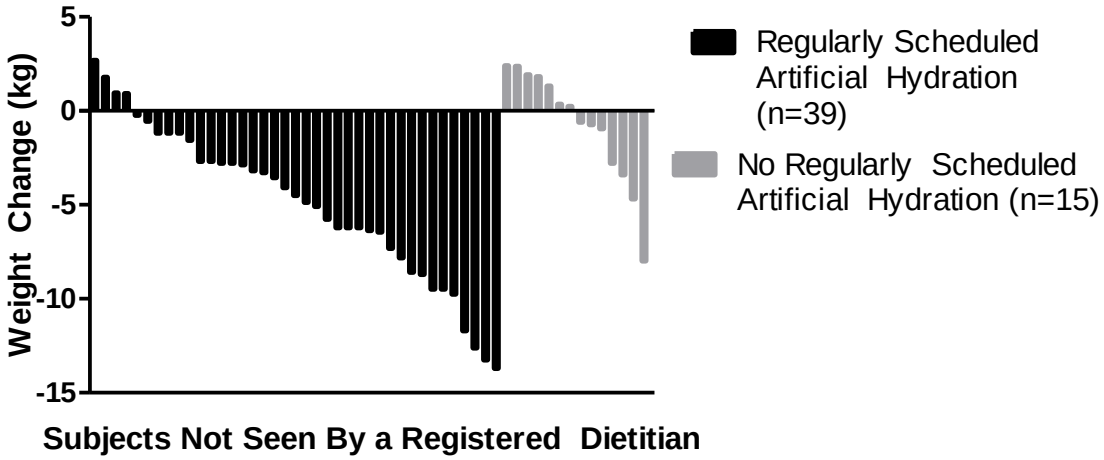
Weight loss among HNC patients did not decrease after seeing a dietitian. No obvious pattern was identified as to why one participant was referred to a registered dietitian and another participant was not. There were few consistent referrals to dietitians; patients saw a registered dietitian on average one to two times during the seven weeks of HNC treatment. Patients who did not see a registered dietitian had similar rates of weight loss regardless of hydration group (see Figure 9). The majority of patients who saw a registered dietitian lost weight but two people who received regularly scheduled artificial hydration and three people who did not have regularly scheduled artificial hydration gained between 0 and 5 kilograms. Of those who did not see a registered dietitian, 5 people who received regularly scheduled artificial hydration and 6 people who did not receive regularly scheduled artificial hydration gained between 0 and 5 kilograms.

**Figure 8: Weight Loss among Patients seen by a Registered Dietitian during Treatment for Head and Neck Cancer**




*Patients were included if they had weight recorded and saw a registered dietitian

**Figure 9: Weight Loss among Patients Not Seen by a Registered Dietitian during Treatment for Head and Neck Cancer**




*All patients were included if they had weight recorded and did not see a registered dietitian

**<u>Assessment of Hydration Status during Head and Neck Cancer Treatment</u>**

Hydration status was assessed by examining hematocrit and hemoglobin concentrations. Mean hematocrit values and hemoglobin concentrations were similar between groups. Hemoglobin concentrations were considered to be within the normal reference range if they were between 13.5-17.5 g/dL. Hematocrit values between 41-53% were considered to be within the normal reference range (Table 12).

**Table 12: Mean Hemoglobin Concentrations and Hematocrit Values throughout Head and Neck Cancer Treatment**

| Markers of Hydration Status | Regularly Scheduled Artificial Hydration (n=19) | Not Regularly Scheduled Artificial Hydration (n=19) | Total |
|---|---|---|---|
| Hemoglobin (g/dL) | 11.6 ± 1.0 | 11.4 ± 1.9 | 11.5 ± 2.3 |
| Hematocrit (%) | 34.7 ± 5.5 | 34.6 ± 5.9 | 34.6 ± 5.7 |

Data are presented as mean ± standard deviation of the mean (SD) for all patients who had hemoglobin and hematocrit measured

Those who are dehydrated may have elevated hemoglobin concentrations and hematocrit values. While these values alone are not indicative of hydration status they can be used in conjunction with plasma creatinine, blood urea nitrogen concentrations, and weight changes to assess relative hydration status.

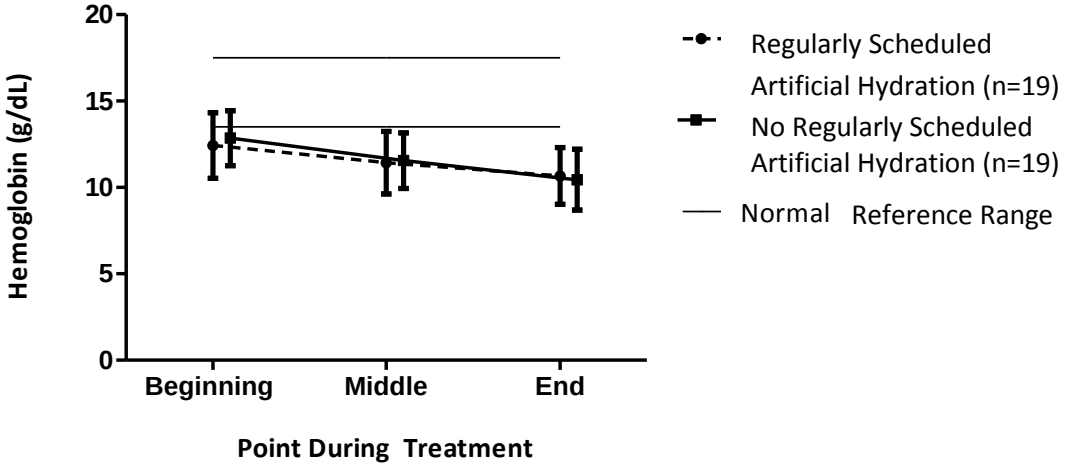
Hemoglobin concentrations decreased throughout HNC treatment and the means for both groups were below the lower limit of the normal reference range at baseline, middle, and end of treatment. Changes in hemoglobin concentrations throughout HNC treatment are illustrated in Figure 10 while statistical analysis of significance can be seen in Table 13.

**Table 13: Change in Hemoglobin Concentrations throughout Head and Neck Cancer Treatment and in Response to Receiving or Not Receiving Regularly Scheduled Hydration**

| Hemoglobin Concentrations (g/dL) | Beginning of Treatment | Middle of Treatment | End of Treatment | Beginning of Treatment Compared to Middle of Treatment | Middle of Treatment Compared to End of Treatment | Beginning of Treatment Compared to End of Treatment |
|---|---|---|---|---|---|---|
| Mean ± SD Analysis Within Group Comparison | | | | Mean Difference Within Groups Comparison Over Time | | |
| Regularly Scheduled Artificial Hydration | n= 17<br>12.4 ± 1.9 | n= 17<br>11.4 ± 1.8 | n= 17<br>10.7 ± 1.6 | n= 23<br>-0.9 ± 1.3* | n= 21<br>-0.7 ± 1.2 | n=19<br>-1.7 ± 1.5** |
| No Regularly Scheduled Artificial Hydration | n= 20<br>12.9 ± 1.6 | n= 20<br>11.6 ± 1.6 | n= 20<br>10.5 ± 1.8 | n= 23<br>-1.2 ± 1.2** | n= 21<br>-1.0 ± 1.3** | n= 19<br>-1.4 ± 1.8** |
| Between Group Comparison of Mean Differences ± 95% CI | | | | Between Group Comparison Over Time | | |
| Comparisons Between Treatment Groups | -0.1 ± (1.0 -0.9)<br>p: 09 | -0.2 ± (-1.0 – 0.7)<br>p: 0.69 | -0.2 ± (-1.1 – 0.8)<br>p= 0.74 | p= 0.38 | p= 0.39 | p= 0.18 |

Mean difference of zero shows no difference between those who did and did not receive regularly scheduled artificial hydration
Both groups had decreased hemoglobin concentrations from baseline indicated by these symbols: *p<0.05 **p<0.01

**Figure 10: Mean Hemoglobin Concentrations Before, During and at the End of Head and Neck Cancer Treatment**




Data presented as mean ± SD for all patients who had hemoglobin measured
No significant differences were found between groups at any point in time.
*Statistical significance between beginning and middle of treatment for those receiving regularly scheduled artificial hydration (-0.9±1.3, $p<0.05$), and beginning to end of treatment (-1.7±1.5, $p<0.01$)
** Statistical significance between beginning and middle of treatment for those receiving no regularly scheduled artificial hydration (-1.2±1.2, $p<0.01$), middle to end of treatment (-1.0±1.3, $p<0.01$), and beginning to end of treatment (-2.4.1±1.8, $p<0.01$)

Chi square analysis was done to determine whether a patient was within normal limits for hemoglobin. Similar to the analysis done for blood urea nitrogen, chi square analyses were done to first determine overall significance, the parallel profiles over time, a comparison between the proportion of patients outside of normal reference range, and the changes over time within patients. Tests for whether patients were within normal limits for hemoglobin can be seen in Table 14.

**Table 14: Test to Determine Whether a Patient's Hemoglobin Concentrations was Within Normal Limits**

| Effect | Hemoglobin |
|---|---|
| Change Over Time Within Patients | $X^2_2$= 20.15 (p<0.001) |
| Between Treatment | $X^2_1$=0.52 (p=0.47) |
| Change Over Time Between Treatment* | $X^2_2$= 1.00 (p=0.61) |
| Overall Comparison** | $X^2_5$=22.2 (p<0.001) |

*Changes over time differ by artificial hydration treatment. Lack of significance indicates parallel profiles over time
**Significance of any of the three effects

For hemoglobin there was no differences in the odds of being within the normal reference range between those who did and did not receive regularly scheduled artificial hydration (p=0.47). The odds of having hemoglobin concentrations below the normal reference range during treatment was the same when comparing the two treatment groups (p=0.61). Both groups had a significant decrease in the odds of having a hemoglobin concentrations below the normal reference range when comparing between the beginning, the middle, and the end of treatment (beginning to middle of treatment: 95% CI: 0.14-0.63; p=0.002, middle to end of treatment: 95% CI: 0.03-0.31; p<0.001). Those patients receiving and not receiving regularly scheduled artificial hydration did not have different odds of having a hemoglobin concentration below the normal reference range.

### *Hematocrit Values*

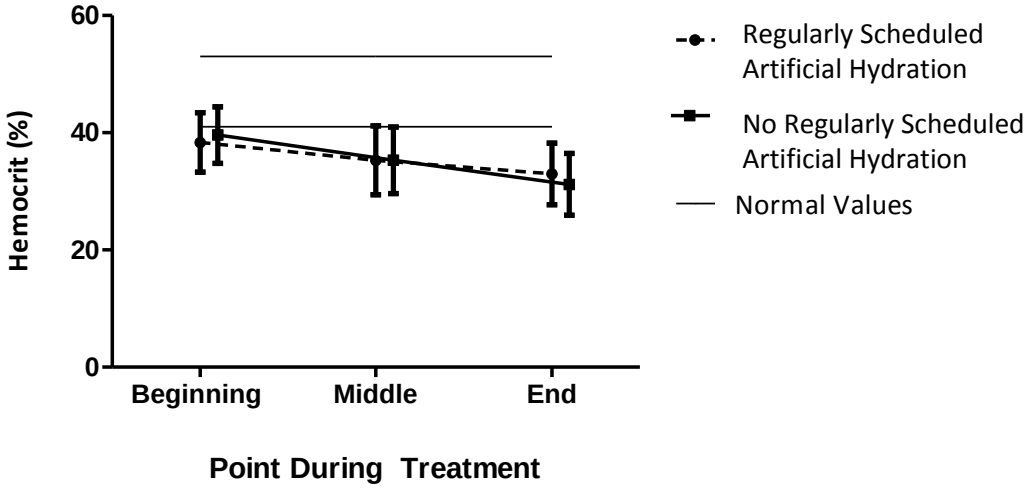
Changes in hematocrit can be seen in Table 15 and Figure 11 with statistical analysis of changes displayed in Table 16. Hematocrit changes throughout treatment were similar to hemoglobin. Both group's mean values were below normal throughout the entirety of treatment, with no statistical differences in means between the groups at any time during treatment. Mean hematocrit values decreased significantly in both groups from the beginning of treatment to the middle of treatment, from the beginning of treatment to the end of treatment, and from the middle of treatment to the end of treatment.

**Table 15: Change in Hematocrit Values throughout Head and Neck Cancer Treatment and in Response to Receiving or Not Receiving Regularly Scheduled Hydration**

| Hematocrit Values (%) | Beginning of Treatment | Middle of Treatment | End of Treatment | Beginning of Treatment Compared to Middle of Treatment | Middle of Treatment Compared to End of Treatment | Beginning of Treatment Compared to End of Treatment |
|---|---|---|---|---|---|---|
| Mean ± SD Analysis Within Group Comparison | | | | Mean Difference Within Groups Comparison Over Time | | |
| Regularly Scheduled Artificial Hydration | n= 18<br>38.3 ± 5.1 | n: 18<br>35.3 ± 5.9 | n= 18<br>33.0 ± 5.2 | n= 24<br>-3.4 ±0.9 | n= 21<br>-2.1 ± 0.9 | n= 19<br>-5.3 ± 4.7 |
| No Regularly Scheduled Artificial Hydration | n= 20<br>39.6 ± 4.8 | n= 20<br>35.3 ± 5.7 | n= 20<br>31.2 ± 5.3 | n= 23<br>5.3 ± 6.9 | n= 21<br>3.8 ± 4.9 | n= 19<br>8.6 ± 5.7 |
| Between Group Comparison of Mean Differences ± 95% CI | | | | Between Group Comparison Over Time | | |
| Comparisons Between Treatment Groups | 0.5 ± (-2.2 - 3.3)<br>p= 0.52 | -0.7 ± ( -3.9 - 2.5)<br>p= 0.67 | -0.8 ± ( -3.7 - 2.1)<br>p= 0.57 | p= 0.33 | p= 0.23 | p= 0.07 |

Mean difference of zero shows no difference between those who did and did not receive regularly scheduled artificial hydration
Both groups had decreased Hematocrit Values from baseline indicated by these symbols: *p<0.05 **p<0.01

**Figure 11: Mean Hematocrit Values Before, During, and at the End of Head and Neck Cancer Treatment**




Data presented as mean ± SD for all patients who had hematocrit measured

Chi square analysis was done to determine whether a patient was within normal limits for hematocrit. Similar to blood urea nitrogen, chi square analysis was done to first determine overall significance of the parallel profiles over time, a comparison between the proportion of patients outside of normal limits, and the changes over time within patients. The model for hematocrit had insufficient data to test interaction that those who received and did not receive regularly scheduled artificial hydration followed similar profiles throughout radiation treatment, so the interaction was assumed to be 0. Tests for whether a patient was within the normal reference range for hematocrit is shown in Table 16.

**Table 16: Tests to Determine Whether a Patient's Hematocrit Values were Within Normal Limits for Hematocrit**

| Effect | Hematocrit |
|---|---|
| Change Over Time Within Patients | $X^2_2$= 14.96 (p<0.001) |
| Between Treatment | $X^2_1$=2.14 (p=0.14) |
| Change Over Time Between Treatment* | # |
| Overall Comparison** | $X^2_5$=15.82 (p=0.001) |

*Changes over time differ by artificial hydration treatment. Lack of significance indicates parallel profiles over time
**Significance of any of the three effects
# Model with interaction had insufficient data for fitting the model

Hematocrit values showed no difference in odds of being below the normal reference range between those who did and did not receive regularly scheduled artificial hydration (p=0.14). But when comparing hematocrit values the odds of being below the normal reference range increased throughout treatment. The odds of a patient being within the normal reference range at the middle point during treatment were estimated to be 73% (95% CI: 0.12-0.63; p=0.002). The odds of a patient to be within the normal reference range at the end of treatment was 95% lower than their odds at the beginning of treatment (95% CI: 0.01-0.28; p=0.001). Those receiving and not receiving regularly scheduled artificial hydration did not have any significant differences in the proportion of patients who were within the normal reference range throughout treatment.

Both mean hemoglobin concentrations and hematocrit values were below the normal reference range throughout treatment. This could be indicative of decreased hematopoesis from bone marrow from chemotherapy and radiation therapy. To better

determine hydration status, previous research has shown that if hematocrit values are three times greater than hemoglobin concentrations this can indicate hemoconcentration or dehydration (Table 17). Hematocrit to hemoglobin ratio around three at all time points did not increase over the course of treatment suggesting the decrease in both hematocrit and hemoglobin may be related to decrease hematopoiesis rather than hemoconcentration and dehydration. There were no differences when comparing hematocrit to hemoglobin rations between those who received and did not receive regularly scheduled artificial hydration (Table 17).

**Table 17: Hematocrit to Hemoglobin Ratio to Determine Hydration Status**

| | Beginning of Radiation Treatment | Middle of Radiation Treatment | End of Radiation Treatment |
|---|---|---|---|
| Regularly Scheduled Artificial Hydration | 3.1 ± 0.2 | 3.0 ± 0.2 | 3.0 ± 0.2 |
| No Regularly Scheduled Artificial Hydration | 3.1 ± 0.2 | 3.0 ± 0.4 | 3.0 ± 0.1 |
| Both Groups | 3.1 ± 0.2 | 3.0 ± 0.3 | 3.0 ± 0.2 |

# Chapter 5
# Discussion

This retrospective study examined the effect of regularly scheduled artificial hydration administration on treatment outcomes in patients with head and neck cancer. We investigated whether treatment outcomes (number of unplanned hospital admissions, number of unplanned treatment breaks, renal markers of function, and hydration status markers) differed between patients receiving regularly scheduled artificial hydration compared with those not receiving regularly scheduled artificial hydration. The results suggest that the number of unplanned hospital admissions, the number of unplanned treatment breaks, and changes in hydration status were similar regardless of the use of artificially administered hydration. Thus we reject our hypothesis, that those receiving artificial hydration would have fewer unplanned hospital admissions, and treatment breaks. We also reject the hypothesis that those receiving regularly scheduled artificial hydration would maintain renal function markers and hydration markers within the normal reference range.

This is a unique study in that it examined use of artificial hydration administration on hydration status as a significant variable affecting treatment outcomes. There are many studies that focus on other side effects that could alter treatment outcomes, such as mucositis, treatment type, registered dietitian exposure, and location of cancer.

## Patient Characteristics

### *Age*

Head and neck cancer generally impacts the elderly, with 43% of all incidents of cancer being those over 65 years old[18]. Our study had a similar age distribution to previous studies. In other studies, age increased the risk and severity of side effects, causing an increase in unplanned treatment breaks. Diminished renal function allows chemotherapy drugs to stay in the system longer creating a greater impact on tumors but may also damage normal cells. Michal et al, (2012) found that elderly patients treated for HNC experienced more myelosuppression, required more unplanned hospital admissions and were feeding tube dependent longer than younger patients[18]. Renal function could play a large factor in the increased hospitalizations found in elderly patients.

Age was considered a confounding factor during our data analysis. However, there were no differences in number of unplanned treatment breaks, unplanned hospital admissions, and renal function between treatment groups when age was included as a confounding factor. For our study age did not significantly change the results but was kept as a confounding factor to be consistent with previous research.

### *Gender*

Generally there are significantly more men diagnosed with HNC than women. In our study we had 20% women and 80% men (83% men among those receiving regularly scheduled artificial hydration and 73% men among those not receiving regularly scheduled artificial hydration). Our proportion of male to females was similar to those

reported in previous HNC studies. This sex disparity is expected from the prediction that men are more likely to drink alcohol excessively and to use tobacco more frequently than women[5]. Males have a higher incidence of HNC but women who do develop HNC have higher rates of acute and long term toxicities[34]. There were no significant differences in treatment outcomes between those who received regularly scheduled artificial hydration and those that did not when gender was included as a confounder in the analysis. When gender was excluded from the model, the results were the same.

***Location of Cancer***

Sites of cancer varied between groups as illustrated by the large disparity between the number of thyroid and larynx cancers. Other studies found the most prominent cancer in their study to be oropharnygeal cancer. This was similar to our patients. Other research has shown that those with cancer in the oral cavity or oropharynx had significantly less weight loss as well as fewer unplanned hospital admissions for dehydration than those with nasopharyngeal cancer[6]. Both groups in our study had similar percentages of patients with nasopharyngeal cancer. Similar numbers of oropharynx cancer were reported for both groups. There were discrepancies between the types of oropharynx cancer, individuals with bottom of the tongue cancers often have larger weight loss than those with other oropharyngeal cancer locations[8]. Elting et al, (2007) also found an increase in oral mucositis in those with oropharyngeal cancer compared with cancer of the larynx and hypopharynx (99% vs. 64%; $p<0.001$)[22]. While our data did not focus on location of cancer, we did take into consideration that

different sites of cancer would be correlated with different frequency and severity of side effects. In this data set, we did not observe location of cancer to be a significant confounding factor.

### *Type of Treatment*

In our data, all patients received radiation therapy and the majority also received chemotherapy. Some patients were treated with surgery. In a previous study the primary treatment was surgery[35]. This difference between our sample and those of previous studies should be considered when interpreting our data.

Previous studies found chemoradiation had the highest rates of complications and hospitalizations[3,6,7,8]. Our study supported the findings of other studies; patients undergoing chemoradiation had the highest rates of unplanned hospital admissions and unplanned treatment breaks compared with those undergoing radiation therapies with surgery. Elting et al, (2007) found that patients receiving chemoradiation had a 98% chance of developing oral mucositis compared with those who received radiation only who had an 85% chance of developing oral mucositis[22]. Previous studies have also demonstrated that chemoradiation has better long term survival but often has more toxicity-related delays[7]. Some of these late toxicities, including dysphagia, require some patients to be dependent on gastrostomy tubes much longer than desired[29]. Based on the current scientific literature, chemoradiation has the greatest tumor control and patient survival time but often comes at the cost of debilitating long and short term side

effects. Better control of side effects can decrease unplanned hospital admissions and unplanned treatment breaks.

Treatment types were taken into account when calculating differences in outcomes for those receiving and not receiving regularly scheduled artificial hydration. Results from our data show that hydration status does not alter treatment outcomes when cancer treatment type is considered as a confounding factor altered treatment outcomes.

**Unplanned Hospital Admissions**

Many factors play a role in the number of unplanned hospital admissions typically seen in patients with HNC including: weight changes, renal function, treatment type, cancer location, and severity of side effects. Unplanned hospital admissions often decrease the efficacy of treatment and decreased tumor control. Any unplanned hospital admissions were considered unacceptable by OHSU current standards of care.

Previous research suggests that there are delayed side effects of chemotherapy including nausea and vomiting that affect up to 75% of all chemotherapy patients and that can be linked to poor treatment outcomes due to delay, reduction or refusal of chemotherapy[14]. We found that 3.8% (n=4) of our patients were hospitalized for nausea and vomiting. Each of these patients was in the group that received regularly scheduled artificial hydration. This number greatly underestimates the number of patients who might have had severe nausea and vomiting but were not hospitalized.

Different locations of tumors can cause more severe side effects or require more intense treatment regimens. Patients who had tumors in the nasopharynx had significantly higher rates of hospital admissions for dehydration during radiation in previous research[8]. Our study had at total of 13 patients with nasopharyngeal cancer with only 4 of those who were hospitalized (3 out of 4 received regularly scheduled artificial hydration, 1 out of 4 did not receive regularly scheduled artificial hydration). Cancer location was considered a cofounding factor when doing analysis, but our results found that the location of cancer did not significantly alter treatment outcomes for either group.

Our patients were hospitalized most frequently for infection, dehydration, nausea and vomiting, and fever. Previous literature found that these are common reasons for hospital admissions because of the typical side effects of HNC treatment[2,7].

There are many factors that affect the frequency and length of stay in the hospital. Our study did not find a difference in unplanned hospital admissions between those who received regularly scheduled artificial hydration and those who did not receive regularly scheduled artificial hydration. The incidence of hospitalization in our study is significantly lower than those from previous studies. Previous studies reported up to 50% of patients with at least one hospitalization and in our study, only 30% of our patients had unscheduled admissions to the hospital[14]. With so many factors affecting unplanned hospital admissions it is difficult to determine which factor has the greatest effect. Our sample could have been diagnosed earlier, been younger, had a milder type

of cancer, or our hospital might have lower hospital admissions rates compared to national standards. Because our patient sample had a lower incidence of unplanned hospital admissions than has been published in the literature, it is possible we are unable to detect a difference between the group who received artificial hydration and the group who did not when, in fact, a difference does exist. The lower than expected rate of unplanned hospital admissions may result in a type 2 statistical error.

**Renal Function throughout Head and Neck Cancer Treatment**

Maintaining renal function during chemotherapy is an important part of managing potential side effects during cancer treatment. Nishimura et al, (2007) found decreased creatinine clearance is often associated with age and can be a warning sign for decreased renal function. Twenty-seven percent of those in their fifties, 37% of those in their sixties, 62% of those in their seventies, and 87% of those in their eighties have below normal creatinine clearance rates increasing their risk for treatment delays[17]. Nishimura et al, (2007) also found that sufficient hydration prior to and after chemotherapy dosage helped to protect renal function. It has been reported that fluid administration 24 hours before and in the weeks following chemotherapy treatment has a positive impact on renal function. Many of our patients who received regularly scheduled artificial hydration did continue to obtain hydration after treatment, but were not followed closely.

Our study showed a significant increase in plasma creatinine concentrations and an increase, though not significant, in blood urea nitrogen concentrations throughout

treatment, with no significant differences between those receiving regularly scheduled hydration compared with those not receiving regularly scheduled artificial hydration. Frequency of hydration administration was not a predictive factor for increased plasma creatinine or, blood urea nitrogen concentrations, or decreased overall renal functioning. There was no difference in proportion of patients who were within the normal reference range for blood urea nitrogen or plasma creatinine during radiation therapy when comparing those who did and did not receive regularly scheduled artificial hydration. The odds of blood urea nitrogen concentrations being out of normal reference range were 75% higher at the end of treatment then at the beginning of treatment. There were no significant alterations in number of patients who were out of normal reference range for plasma creatinine. Increased plasma creatinine and blood urea nitrogen concentrations were not dependent on artificial hydration status suggesting an alternative reason for decreased renal function in our study sample.

**Unplanned Treatment Breaks during Head and Neck Cancer Treatment**

Treatment breaks can be severely detrimental to treatment outcomes. Avoiding severe side effects and controlling nutrition and hydration status should decrease the number of treatment breaks. There was no difference in the number of unplanned treatment breaks between those receiving and those not receiving regularly scheduled artificial hydration in our study. The average number of unplanned treatment breaks was 1.6 per person in both groups. The majority of our patients (72%) had some sort of treatment break ranging from a day to a couple months. This percentage is greater than reported

in previous research that estimated that 50% of patients had toxicity related treatment delays[7] Differences between our patients and those in previous research could be that we had more planned treatment breaks that were counted as unplanned treatment breaks.

We are not aware of previous research looking at hydration as a cause of unplanned treatment breaks. Treatment breaks are often caused by similar reasons as unplanned hospital admissions. We were unable to determine reasons for unplanned treatment breaks due to the retrospective nature of our study. Knowing the reason for unplanned treatment breaks might suggest what can be done to decrease the number of treatment breaks in future management of HNC patients.

**Weight Changes during Head and Neck Cancer Treatment**

Weight changes in our study were consistent with previous studies that showed significant weight loss throughout cancer treatment. While our results on the presence of weight loss are consistent with other studies, we did not find a correlation between the administration of regularly scheduled artificial hydration and the occurrence or severity of weight loss. Patients in both hydration groups had the same mean weight loss whether absolute weight loss or percentage of pre-treatment weight was considered. Weight loss in our patients was greater than the hospital's acceptable ranges; patients lost more than 3% of their initial body weight during the treatment period of 49 days or about one and a half months. It is difficult to tell if this rate of weight loss is similar or greater than previously reported because it has been shown

that many patients lose a significant amount of weight before treatment for HNC begins. Elting et al, (2007) found that patients with gastrostomy tubes lost on average 8% of their initial body weight compared to those without gastrostomy tubes who lost on average 14% of their pre-treatment body weight throughout treatment. Our patients demonstrated much lower weight loss during treatment than reported in previous literature. Patients who had significant pre-treatment weight loss, despite receiving gastrostomy tube feedings, still had a greater incidence of hospitalizations for dehydration[8].

Previous weight loss, location of tumor, and type of treatment are all factors that affect the amount and rate of weight loss. Our patients experienced similar weight loss to that reported in previous research; patients with nasopharyngeal cancer lost 6.9 kg compared to the total group average of 4.8 kg. Those receiving combined chemoradiation were more likely to have severe weight loss, defined as greater than 10% in 6 months, than those receiving radiation only (56% vs. 37%, p=0.006) primarily related to grade 3-4 mucositis[22]. Chemoradiation patients in our study lost an average of 5.3 kg. Weight loss has been shown to be a significant factor contributing to greater side effects and decreased efficacy of treatment. Preventing or decreasing weight loss is one strategy to avoid or minimize adverse effects of HNC treatment.

**Effect of Gastrostomy Tube Placement on Head and Neck Cancer Treatment Outcomes**

Nutritional supplementation is required by a majority of patients undergoing HNC treatment[29]. Use of gastrostomy tubes has been reported to decrease weight loss, decrease the number of unplanned hospital admissions, and decrease the number of treatment breaks in this population[36]. The majority of our patients who received gastrostomy tubes had the feeding tubes placed prior to treatment. Surprisingly a greater percentage of patients received gastrostomy tubes in the group that also received artificial hydration. This is surprising because we had assumed that patients receiving regularly scheduled hydration would be less likely to need a gastrostomy tube but that patients not receiving hydration may need a gastrostomy tube for both hydration and nutrition. In previous research, about half of all patients received gastrostomy tubes. It is possible those who received hydration and a gastrostomy tube were at higher risk for nutritional deficiencies but we found no differences to support that hypothesis.

Previous research found gastrostomy tubes placed prior to treatment decreased weight loss and minimized nutritional deterioration that often occurs during HNC treatment [8,36]. The majority of patients in our study who had gastrostomy tubes placed did not use their gastrostomy tubes prior to treatment. Our results did not support the findings of previous research; the amount of weight loss was greater in those with gastrostomy tubes than the group average (gastrostomy tubes weight loss 5.6 kg compared with group average 4.8 kg). Some differences that might explain this discrepancy between

our population and previous studies might be, our patients were using gastrostomy tubes incorrectly or our population characteristics varied from previous research patients. One potential treatment strategy in the future, to decrease weight loss during treatment in those who have gastrostomy tubes, could be to educate patients to begin using the gastrostomy tube prior to the beginning of treatment.

Similar to many other feeding tube studies, use of feeding tubes is based on patient self report resulting in questionable accuracy of data collected[29]. In our study, gastrostomy tube usage was determined from patient report to the nurse of how often they used the gastrostomy tube. While feeding tubes should be used to supplement the oral diet before, during and after treatment, oral intake should be sustained as long as possible for the best swallowing outcomes[36]. The majority of our patients who received gastrostomy tubes used them at least for a short period during their treatment (86.5% patients using gastrostomy tubes). There was no observable pattern to suggest that use of gastrostomy tubes decreased weight loss in our population.

**Registered Dietitian Exposure During Head and Neck Cancer Treatment**

There is a significant influence of nutritional status on therapeutic outcomes including surgical morbidity, tolerance of therapy, and overall mortality in cancer patients[37]. Poor nutrition can cause poor wound healing, increased postoperative complications, decrease immune function and increased length of stay[25,30]. Nutritional deterioration is reported in 25% to 50% of HNC patients before treatment initiation[16]. Nutrition

monitoring and intervention by a registered dietitian may improve the nutritional status of patients with HNC during and after treatment.

However, we observed no significant differences in weight loss, unplanned hospital admissions, and number of unplanned treatment breaks in those who had seen a registered dietitian and those who did not see a registered dietitian in our study. The majority of patients in our study did not see a dietitian until the beginning of treatment or during treatment. When patients did see a dietitian, visits were sporadic and not consistent. Early and regular nutritional intervention has been show to be important to decrease weight loss throughout the cancer treatment process[36]. It is possible we did not observe a difference between patients who saw the registered dietitian and those who did not because the registered dietitian intervention was initiated too late in the treatment and was not consistent enough to significantly influence the nutritional status of the patient. Also our hospital had a staffing change with the registered dietitian making it difficult to determine effect on treatment outcomes.

Previous studies reported that dietitians are pivotal members of the health care team who can help in explaining the importance of nutritional care during cancer treatment. Chiu et al, (2002) found that 25% of patients reported feeling conflicts about using artificial hydration and nutrition[26]. Patients in this same study also found confidence in weaning off feeding tube when regular and consistent registered dietitian appointments were provided[30]. We hypothesize, that the dietitian's roles in our study was not

consistent enough to make an impact. With greater dietitian involvement there could be a decrease in unplanned treatment breaks and unplanned hospital admissions.

**Assessment of Hydration Status during Head and Neck Cancer Treatment**

Hematocrit and hemoglobin are typically used to determine iron status or hydration status. For this study hemoglobin and hematocrit were used as an additional value to determine hydration status. Previous research has shown that when hematocrit is significantly higher than hemoglobin (three times greater than hemoglobin) hemoconcentration or dehydration is present. Additionally if the total blood count (hemoglobin concentration) remains the same with a decreased blood volume (plasma) we can assume dehydration. Our patients had hematocrit values three time greater than hemoglobin concentrations for both those who received and those who did not receive regularly scheduled artificial hydration. The average ratio of three or greater is indicative of dehydration throughout radiation treatment among our sample.

Other studies did not monitor hemoglobin concentration and hematocrit values during cancer treatment. Hemoglobin concentrations and hematocrit values in our study were found to be low from the beginning of treatment and continued to be below the normal reference range throughout treatment. The proportion of patients who had were not within the normal reference range considering change over time but there was no significant difference in proportion of patients being out of normal limits when comparing those who received and did not receive artificial hydration. Patients had 90% higher odds of being out of the normal reference range at the end of treatment

compared with the beginning for both hemoglobin and hematocrit. Depressed hemoglobin concentration and hematocrit values could be due to the cancer treatment's effect on hematopoiesis. But these depressed values along with increasing plasma creatinine and blood urea nitrogen values could suggest a decreased hydration status, and possibly malnutrition when coupled with large weight changes.

**Study Limitations**

Our study had multiple limitations that could not be controlled. The first limitation of our study was that it was a retrospective chart review, which limits the amount and consistency of information that can be obtained. Some patients had more information in their charts than others. Since this study was retrospective we do not know the manner in which each patient was weighed or how consistent these measurements were. Patients might have been weighed one time with winter clothes and another time wearing summer clothes, which could have influenced the change in weight observed. Lastly we were unable to obtain information about the volume of enteral fluids ordered, or the amount of fluid administered per day by the patient to better understand the frequency of gastrostomy tube usage. Future research controlling for those limitations would allow for better understanding of the effects of regularly scheduled artificial hydration on HNC treatment outcomes.

**Future Research**

The data presented here suggests that regularly scheduled artificial hydration does not significantly improve treatment outcomes among HNC patients. Future research using a

prospective study design comparing treatment outcomes between those receiving regularly scheduled artificial hydration and those not receiving regularly scheduled hydration would provide a more definitive conclusion about the effects of hydration status on clinical outcomes in this patient population. Other future research might focus on nutritional status of patients undergoing treatment for HNC rather than focusing on hydration status alone.

## Conclusion

Patients living with HNC suffer from many side effects of treatment and cancer diagnosis. We found no association between the administration of regularly scheduled artificial hydration and its effect on treatment outcomes such as unplanned treatment breaks, unplanned hospital admissions, and renal function. Artificial hydration is essential for patients presenting with acute dehydration but may not to prevent subsequent episodes of dehydration. Our data does not support the hypothesis that regularly scheduled artificial hydration decreases the number of unplanned hospital admissions, the number of unplanned treatment breaks, or improves treatment outcomes.

## Appendix 1

| | Study Identification | Patients | Duration | Design | Outcomes |
|---|---|---|---|---|---|
| 1 | Atasoy, Beste M.; Yonal, Oya; Demirel, Birsen; Dane, Faysal; Yilmaz, Yusuf; Kalayci, Cem; Abacioglu, Ufuk; Imeryuz, Nese (2012). The impact of early percutaneous endoscopic gastrostomy placement on treatment completeness and nutritional status in locally advanced head and neck cancer patients receiving chemoradiotherapy. European Academy of Otorhinolarngeal Journal | 23 patients with head and neck cancer who participated in weekly dietary visits and dental and oral hygiene evaluation before concurrent chemotherapy and radiation | Pre, During, and Post radiation treatment | Had dietary education at the beginning of concurrent chemoradiotherapy and weekly during treatment. All energy requirements were calculated weekly for weight maintenance. With any toxicities or PEG tube changes being recorded | Providing adequate enteral nutrition allows for an increase in the completeness rate of concurrent chemotherapy. Toxicities require aggressive supportive care to alleviate symptoms and limit the number of treatment breaks. |
| 2 | Beaver ME, Matheny KE, Roberts, Dianna B., PhD; Myers JN. Predictors of weight loss during radiation therapy. Otolaryngology-Head and Neck Surg. 2001 Dec; 125(6): 645-8. | 249 head and neck cancer patients form 1985-1996 | 1985-1996 | Used medical records to retrospectively review and determine the risk factors for weight loss and dehydration during radiation therapy. | Placement of prophylactic gastrostomy tubes before treatment significantly decreased the occurrence of severe weight loss. Greatest predictors of severe weight loss was lost weight before treatment, tumor site of nasopharynx or base of tongue and undergoing concomitant chemo radiation. |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 3 | Bruera E, Sala R, Rico MA, Moyano J, Centeno C, Willey J, Palmer JL. Effects of Parenteral Hydration in Terminally Ill Cancer Patients: A Preliminary Study. J Clin Oncol. 2005 Apr 1;23(10): 2366-71. | 27 cancer patients at the University of Texas M.D. Anderson Cancer Center in Houston, Texas | 4 hours for 2 days for infusion | Double blind, randomized controlled study. Patients were randomly assigned to receive either 1000 ml of normal saline or 100 ml of saline | Parental hydration decreased symptoms of dehydration in cancer patients who had decreased fluid intake. Placebo affect was observed. Would need larger sample size to validate the results found. |
| 4 | Burge FI. Dehydration Symptoms in Palliative Care Cancer Patients. J Pain Symptom Manage. 1993 Oct; 8(7): 454-64. | 52 inpatient palliative care patients in terminally ill cancer patients | | Questionnaire was given out to evaluate experience of seven symptoms. Then the questionnaire was given out 24 hours later. Chart review to determine other clinical states, and a venous blood sample was taken. | Physical signs of dehydration are unreliable when dealing with malnourished patients. Biochemical markers are also unreliable markers for dehydration. Combining all assessment tools a complete picture of hydration status |
| 5 | Capuano G, Gentile PC, Bianciardi F, Tosti M, Palladino A, Di Palma M. Prevalence and influence of malnutrition on quality of life and performance status in patients with locally advanced head and neck cancer before treatment. Support Care Cancer. 2010 Apr; 18(4):433-7. | 61 patients with locally advance head and neck cancer at Roma Saint Peter Hospital oncology department. | 1 day of surveys | All patients were evaluated for malnutrition, nutrition intake ,nutrition status, serum prealbumin, hemoglobin levels, c-reactive protein, quality of life, and performance status. | 30% of patients already were malnourished before study implementation. 13% patients had CPR levels <10 mg/dL due to reduced food intake. CPR $\geq$10 mg/dL malnourished patients because of decreased food intake. Patients may lose an additional 10% pretherapy body weight, during treatment $\geq$20% weight reduction has a significant correlation with treatment interruptions, infection, hospital readmissions and increased mortality. |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 6 | Chaukar DA, Walvekar RR, Das AK, Deshpande MS, Pai PS, Chaturvedi P, Kakade A, D'Cruz AK. Quality of Life in Head and Neck Cancer Survivors: a Cross Sectional Survey. Am J Otolaryngol. 2009 May-Jun;30:176–180. | 212 HNC 1 year survivors in India | 1 year treatment | 1 year after treatment patient filled out EROTC QOLC-30 and EROTC QOL H&N | Patient like QOL surveys before is a great way to talk with doctor about financial situation, decreased appetite, and fatigue and other big issues. |
| 7 | Chen AM, Li BQ, Lau DH, Farwell DG, Luu Q, Stuart K, Newman K, Purdy JA, Vijayakumar S. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemo radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2010 Nov 15; 78(4):1026-32. | 129 treated with radiation and current chemotherapy between January 2002-March 2009 | January 2002-March 2009 | Medical records of patients that were treated with definitive radiation therapy with concurrent chemotherapy were retrospectively reviewed. Compared the outcomes of patients who had g-tubes placed before and after HNC treatment initiation | GT placement before HNC treatment is a huge benefit to preventing weight loss, potential delays in radiation therapy. Further studies in quality of life will be needed to determine the benefit. |
| 8 | Chiu TY, Hu WY, Chuang RB, Chen CY. Nutrition and hydration for terminal cancer patients in Taiwan. Support Care Cancer. 2002 Nov; 10(8):630-6. | 344 patients with advanced cancer admitted to the hospice and palliative care unit of National Taiwan University Hospital | January 2000-February 2001 | Recorded information to determine conditions of water and nutrition intake. Things recorded were oncological conditions, hydration and nutrition status, causes of any inability to eat or drink, and use of artificial nutrition and hydration | Artificial nutrition and hydration given did not lengthen the survival of cancer patients. Focusing on quality of life for care can be more beneficial when treating terminally ill cancer patients. |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 9 | Doeer, Timothy D. MD; Marks, Steven C. MD; Shamsa, Falah H. PhD; Mathog, Robert H. MD; Prasad, Anada S. MD, PhD (1998), Effects of Zinc and Nutritional Status on Clinical Outcomes in Head and Neck Cancer. The International Journal of Applied and Basic Nutritional Sciences | 52 zinc supplemental and 47 nutritional evaluations. All patients were newly diagnosed head and neck cancer patients | June 1987-June 1995 | Patient prognostic nutritional index was calculated to determine baseline nutritional status using; triceps skin fold, albumin, transferring, and zinc assays along with a general chart review | The assessment and treatment of malnutrition and zinc deficiencies correlates with treatment morbidity, unplanned hospital stays, and delay in treatment |
| 10 | Elting LS, Cooksley CD, Chambers MS, Gerden AS. Risk, Outcomes, and Cost of Radiation-Induced Oral Mucositis Among Patients with Head-And-Neck Malignancies. Int J Radiat Oncol Biol Phys. 2007 July 15; 68(4): 1110-20 | 204 newly diagnosed with head and neck cancer receiving radiation therapy and completed all follow up visits during study. | During radiation and 6 weeks after radiation | Records were reviewed for the patients looking at treatment, outcome, and resources used. Also cost information was obtained from the hospital accounting system. | 91% of patients developed oral mucositis with 66% having a severe case. Oral mucositis occurred for an average of 5 weeks. Mucositis can cause radiation delays, significant weight loss, and inability to eat. The incremental cost of oral mucositis is about $6000 per patient. |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 11 | Elting, Linda S.; Keefe, Dorothy M.; Sonis, Stephen T.; Garden, Adam S.; Spijkervet, F.K.L.; Barasch, Andrel; Tishler, Roy B.; Canty, Thomas P.; Kudrimoti, Mahesh K.; Vera-Llonch, Montserrat. (2008). Patient-reported Measurements of Oral Mucositis in Head and Neck Cancer Patients Treated with Radiotherapy with or without Chemotherapy, Demonstration of Increased Frequency, Severity, Resistance to Palliation and Impact on Quality of Life. American Cancer Society | 126 patients with oral cavity or oropharynx tumors compared with 65 patients with tumors of the larynx or hypopharynx | Followed throughout treatment | Pt are given survey before radiotherapy, daily during radiotherapy, an d4 weeks after radiotherapy. The FACT-G, ECS, and FACIT questionnaires were used to assess the patient's quality of life. | Risks for mucositis were virtually the same to oral cavity and oropharynx tumors compared with larynx or hypopharynx tumors. QOL decreased significantly after the initiation of radiation. The impact on mucositis on QOL was proportional to the severity of mucositis. |
| 12 | Fainsinder RL, MacEachern T, Miller MJ, Breuera E, Spachynski K, Kuehn N, Hanson J. The Use of Hypodermoclysis for Rehydration in Terminally Ill Cancer Patients. J Pain Symptom Manage. 1994 Jul; 9(5):298-302. | 100 patients who died while admitted to the palliative care unit and were monitored on a daily basis. | December 1990 to November 1991. | Patients were assessed clinically by looking at indication for starting hypodermoclysis, history of oral fluid intake, clinical signs of dehydration, changes in blood tests. | Dehydration was found to have significant affects on confusion, restlessness, renal failure, increased risk of bed sores and constipation. Hypodermoclysis is mainly used for rehydration rather than symptom management. Is a useful and safe method for maintain hydration in terminally ill patients. |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 13 | Funk GF, Karnell LH, Smith RB, Christensen AJ. Clinical Significance of Health Status Assessment Measures in Head and Neck Cancer. Arch Otolaryngol Head Neck Surg. 2004 Jul; 130(7):825-9. | 421 Patients with head and neck cancer | August 1997-August 2002 | Anchor and distribution based techniques in determining clinical significance in health-related quality of life scores. | Observed intra-group changes differences in reported scores should be clearly defined in order to quantify quality of life. Reporting just a quality of life score is not sufficient. |
| 14 | Givens DJ, Karnell L, Gupta A, Clamon, Gerald GH, Pagedar NA, Chang KE,Van Daele DJ, Funk GF. Adverse events associated with concurrent chemo radiation therapy in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg. 2009; 135: 1209-17. | 104 patients. Mostly oropharyngeal tumors and stave IV disease | 12 months | Data was gathered from patient self-report about quality of life. Background information from medical records. Toxicities were recorded as present or not. Type of diet and adverse clinical outcomes were recorded | About half the patients experienced toxicity related delay in chemotherapy or radiation therapy. Patients had poor oral function occurring a long time after diagnosis and treatment (one patient still has persistent poor oral function at 3.4 years after diagnosis). |
| 15 | Kiss NK, Krishnasamy M, Loeliger J, Granados A, Dutu G, Corry J. A dietitian-led clinic for patients receiving (chemo)radiotherapy for head and neck cancer. Support Care Cancer. 2012; 9:2111-20. | 198 patients Primary diagnosis of head and neck cancer, $\geq$ 18 years old, at least 15 fractions of RT or chemotherapy | 8+ weeks depending on treatment. After 8 weeks there was a review every 2-8 weeks | Two independent cohort studies with a pre-post test. Cohort 1 was identified ahead of introduction of dietitian led clinic and cohort 2 was recruited for dietitian led clinic. Set up to operate twice weekly next to radiation oncologist | Patients who received dietitian led clinic transitioned back to oral diet quicker, reduction in nutrition related hospital admissions, unplanned nasogastric tube placements, than those who did not. |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 16 | Lal P, Bajpai R, Khurana R, Das K.J, Kumar P, Tiwari A, Gupta N, Kumar S. Changes in salivary flow rates in head and neck cancer after chemoradiotherapy. J Cancer Res Ther. 2010;6(4):458–463. | 36 Squamous cell carcinoma head and neck cancer stage III and IV patients were followed and had to be disease free for at least a year. | 1 year from July 2003-July 2005 | Salivary gland function was assessed baseline and 3, 6, and 12 months following radiation. To do this the patient would allow saliva to accumulate in mouth for 60 seconds before test and then would collect all specimens in a container. This occurred 4 times. Then they would repeat this but stimulate saliva using lemon juice. | It was found that there was a sharp decline in saliva production 3-6 months after ending treatment and there was a partial recovery at 12 months post treatment. |
| 17 | Li B, Li D, Lau DH, Farwell DG, Luu Q, Rocke DM, Newman K, Courquin J, Purdy JA, Chen AM. Clinical-dosimetric analysis of measures of dysphagia including gastrostomy-tube dependence among head and neck cancer patients treated definitively by intensity-modulated radiotherapy with concurrent chemotherapy. Radiat Oncol. 2009 Nov 12;4:52. | 39 patients with squamous HNC. Treated by concurrent chemotherapy and IMRD with gastric tubes | 6 months to 4 years after treatment | Treatment intensity, gastric tube dependence, and degree of dysphagia were recorded and scored from participant interviews | 3-6 months after treatment 87%, and 44% were g-tube depended. Intensity of treatment determines the degree of dysphasia which in turn correlates to the time of g-tube dependence. |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 18 | Machon C, Thezenas S, Dupuy AM, Assenat E, Michel F, Mas E, Senesse R, Cristol JP. Immunonutrition before and during radiochemotherapy improvement of inflammatory parameters in head and neck cancer. Support Care Cancer. 2012 Mar 28. | 46 patients with stage II or IV HNC according to TNM classifications | 5 days before treatment and 2 months post radiation | For 5 days before each cycle of chemotherapy patients received three sachets per day of an enriched formula. Then they followed up with a dietitian and radiotherapist once a week during radiation for the following 2 months | HNC patients already have an increased prevalence of inflammation. CRP levels were lower in patients receiving nutritional support containing arginine ω-3 fatty acids, and ribonucleic acids |
| 19 | Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, Forastiere A, Ang KK. Factors Associated with Severe Late Toxicity After Concurrent Chemoradiation for Locally Advanced Head and Neck Cancer: An RTOG Analysis. J Clin Oncol. 2011;26(21):3582–3589. | 230 patients from previous studies. 99 had severe toxicity while 131 were controls. About 3 years after treatment | 1991-2011 | Retrospective analysis of several prospective trials. | 43% had severe late toxicity. Severe late toxicity was more common in patients treated with concurrent chemoradiotherapy. The older age made increase risk factors for post treatment survival time. |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 20 | Maida, Vincent; Peck, Jonathan; Ennis, Marguerite; Brar, Navjot; Maida, Alexandria R. (2010). Preferences for active and aggressive intervention among patients with advanced cancer. BioMed Central | 380 patients with advanced cancer who were participating in palliative care approach | Between May 1, 2005-June 30,2006 | Patients completed questionnaire at baseline that assessed their preferences about active and aggressive medical management to conservative palliative management. | Elderly were more likely to go for CPM, while about 20% of people were interested in potentially life-prolonging drugs that could cause them to feel worse at times. |
| 21 | Malecka-Massalska T, Smolen A, Zubrzycki J, Lupa-Zatwarnicka K, Morshed K, Bioimpedance Vector Pattern in Head and Neck Squamous Cell Carcinoma. J Physiol Pharmacol. 2012;63(1):101–104. | 28 HNC patients compared to 28 healthy individuals | October 2009-May 2010 | Bioelectrical impedance analysis (BIVA) and attentive global assessments were given to both groups. HNC patients got a nutritional assessment, albumin, transferring, and total protein labs drawn. | BIVA can be used as an early detector for dehydration in HNC patients |
| 22 | Mayre-Chilton KM, Talwart BP, Goff LM. Different experiences and perspectives between head and neck cancer patients and their care-givers on their daily impact of a gastrostomy tube. J Hum Nutr Diet. 2011 Oct;24(5):449-59. | 21 head and neck cancer patients from a dietetic led gastrostomy database at Hospitals Head and Neck centre were invited, 6 patients and 3 care-givers participated | focus groups during the 3 month long treatment | Qualitative focus group interview sampling head and neck cancer patients, and a separate focus group interview for the care-givers to explore their views and experiences with living with a gastrostomy tube | Patients found that there was a negative impact of knowledge deficit about gastrostomy tubes. But understood the main purpose of the tube; for weight loss avoidance. Timely dietetic management was needed for the patient to feel more confident about weaning off of tube feedings. |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 23 | McKenzie H, Hayes L, White K, Cox K, Fethney J, Boughton M, Dunn J. Chemotherapy outpatients' unplanned presentations to hospital: a retrospective study. Support Care Cancer. 2011 July; 19(7):963-9. | 233 cancer patients | between July and October 2008, patients also reported 6 months retrospecti ve health | Unplanned hospital admissions to emergency department and/or cancer center were identified and reason for presentation, cancer diagnosis, chemotherapy regimen, position in chemotherapy trajectory, actions taken and outcome of visit were recorded. | Unnecessary suffering of chemotherapy outpatients occurs due to patient's confidence in caring for symptoms or lack of reporting symptoms till adverse events occur. Better coordination of care to help with coping would save the patient and hospital lots of money |
| 24 | Meyer, Francois, MD, D.Sc; Fortin, Andre, MD; Wang, Chang Shu MD, PhD; Lui, Geoffrey, MD; Bairati, Isabelle MD, PhD. (2010). Predictors of Severe Acute and Late Toxicities in Patients with Localized Head-and-Neck Cancer Treated with Radiation Therapy. International Journal of Radiation Oncology. | 540 patients who have been treated with RD for localized HNC | During radiation, one month after radiation, and 12 months after radiation. From October 1, 1994 to June 6, 2000 | Randomized trial of patients with Stage I or II HNC patients. Patients were given several questionnaires on patient's characteristics, received baseline blood samples and were asked to fill out a dietary intake and food frequency questionnaire. Average daily intakes were calculated. EORTC-QLQC-30 was administered at baseline, on the last day of radiation and one month after the end of radiation. | 24% of patients suffered from Grade 3 mucositis toxicity while 4% suffered from Grade 4 mucositis toxicity. Independent predictors of severe acute toxicity were sex, Karnofsky Performance Status, body mass index, TNM stage. With the female sex and weight loss during radiation being strong predictors of toxicities. |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 25 | Michal SA, Adelstein DJ, Rybicki LA, Rodriguez CP, Saxton JP, Wood BG, Scharpf J, Ives DI. Multi-Agent Concurrent Chemoradiotherapy for Locally Advanced Head and Neck Squamous Cell Cancer in the Elderly. Head Neck. 2012 Aug; 34(8): 1147-52. | 44 patients $\geq$ 70 years old and 137 patients < 70 years old. All newly diagnosed HNC patients stage III-IV | November 1989-September 2007 | Medical records were reviewed on those who were treated with MCCRT. Each patient was treated according to stage of cancer and patient needs. All patients were monitored at least weekly for antibiotic and feeding tube placement | Age alone should not determine the aggressiveness of treatment. Elderly patients were found to have greater toxicities but projected 5 year survival was similar between the elderly and young group. |
| 26 | Morton RP. Studies in the Quality of Life of Head and Neck Cancer Patients: Results of a Two-Year Longitudinal Study and a Comparative Cross-Sectional Cross-Cultural Survey. The Laryngoscope. 2003 Jul; 113(7): 1091-103.. | 201 patients attending the Head and Neck Cancer clinic at Green Lane Hospital, Auckland, New Zealand | August 22, 1989-February 5, 1993 | Longitudinal Study where people were given a questionnaire that rated twelve items of general health questions. This questionnaire was given at 3,12, and 24 months. | Patients could learn to cope with a disability so that their overall quality of life was not related to the treatment received. Pain scores and measures of psychological distress were the only specific symptom that directly correlated with overall quality of life. |
| 27 | Nishimura G, Tsukuda M, Horiuchi C, Yoshida T, Taguchi T, Nagao J, Kawakami M, Kondo N, Matsuda H, Mikami Y. Decrease of creatinine clearance rate with aging in patients with head and neck cancer in Japan. Int J Clin Oncol.2007 Apr; 12(2): 120-4. | 375 HNC patients who had been hospitalized for evaluation and treatment of disease | January 1998 to October 2005 | The creatinine clearance rate (Ccr) was calculated at least 3 times to find patients average before beginning of treatments. This was used to estimate renal function. | Ccr decreased with aging with Japanese population renal function decreasing much more rapidly. Poor renal function (anything below 65 ml/min per 1.73 $m^2$ should have alternative cancer treatment given until their Ccr raises to above desired rate. |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 28 | Oozeer NB, Corsar K, Glore RJ, Penney S, Patterson J, Paleri V. The impact of enteral feeding route on patient-reported long term swallow outcome after chemo radiation for head and neck cancer. Oral Oncol. 2011 Oct; 47(10):980-3. | Patients who underwent concurrent chemo radiation as primary treatment for HNC from February 2005-October 2007 | February 2005-October 2007 | Patients with g-tubes were followed during HNC and were compared with those who did not have g-tubes. Each group MD Anderson Dysphagia Inventory questionnaire to assess emotion, function physical and one global score for swallowing outcomes. | Nasogastric tubes fed patients have superior functional outcomes with respect to swallowing compared to those with g-tubes |
| 29 | Paccagnella, Agostino; Morello, Michela; Mosto, Maria C. Da; Baruffi, Carla; Marcon, Maria L.; Gava, Alessandro, Baggio, Vittorio; Lamon, Stefano; Babare, Roberta; Rosti, Giovanni; Giometto, Marta; Boscolo-Rizzo, Paolo; Kiwanuka, Edward; Tessarin, Michele; Caregaro, Lorenza; Marchiori, Carlo. (2009). Early nutritional intervention improves treatment tolerance and outcomes in head and neck cancer patients undergoing concurrent chemoradiotherapy. J of Support Care Cancer | 33 HNC patients who were referred for early nutritional intervention before they initiated chemoradiotherapy and 33 HNC patients who did not receive early nutritional intervention. | 2005-2007 | Patients who were weight stable received therapeutic diet education with regular foods or texture-modified diets. PEG was used when EN was indicated in early concurrent chemoradiation therapy. | Nutrition intervention should be initiated before chemoradiotherapy for the best treatment completion. Patients who had early EN had less unplanned hospitalizations then those who did not have early EN intervention. |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 30 | Page RD, Oo AY, Russell GN, Pennefather SH. Intravenous hydration versus naso-jejunal enteral feeding after esophagetomy: a randomized study. Eur J Cardiothorac Surg. 2002 Nov;22(5):666-72. | 40 patients undergoing esophageal resection | 12 months; 7 day study after surgery | Each group was placed in either control or feeding group. Compared standard of hydration only with crystalloid via peripheral vein with post-operational nutritional supplement using naso-jejunal tube. | No difference was found in hospital stays and oral reuptake with crystalloid hydration and naso-jejunal tube feeding. Hospitals continue to support patient with intravenous crystalloid until normal swallowing |
| 31 | Peterman A, Cella D, Glandon G, Dobrez D, Yount S. Mucositis in head and neck cancer: economic and quality-of-life outcomes. J Natl Cancer Inst Monogr. 2001;(29):45-51. | 45 head and neck cancer patients | May 1994-December 1996 | Retrospective chart review of patients treated with radiation or chemo-radiotherapy. Examined G-tube placement, hospitalizations, outpatient support, and nutritional supplements | 70% of population experienced mucositis still had lasting residual pain and eating difficulties 1 year later. More intensive treatment was associated with decreased performance status which was good predictors of quality of life. |
| 32 | Pow, Edmond H.N. PhD; Kwong, Dora L.W. MD, FRCR; Sham, Jonathan S.T. MD, FRCR; Lee, Victor H.F. MBBS FRCR; Ng, Sherry C.Y. Phd. (2011). Can Intensity-Modulated Radiotherapy Preserve Oral Health-Related Quality of Life of Nasopharyngeal Carcinoma Patients? International Journal of Radiation Oncology | 57 early stage nasopharyngeal carcinoma patients who had received IMRT | Followed from last IMRT treatment to two years after | All patients were given Medical Outcomes short form 36-item questionnaire, the European Organization for Research and Treatment of Cancer QOL core questionnaire, the EORTC head and neck module, and the oral healthy impact profile. 2,6,12,18,and 24 months after treatment | Parotid saliva flow recovered fully within one year after treatment while whole saliva flow only recovered 40% of baseline by 2 years. Revealing that persistent oral-related symptoms were found 2 years post treatment which still continued to affect the participant's quality of life. |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 33 | Psoter WJ, Aguilar ML, Levy A, Baek LS, Morse DE. A Preliminary Study on the Relationships between Global Health/Quality of Life and Specific Head and Neck Cancer Quality of Life Domains in Puerto Rico. Jl of Prostodont. 2012; 6:460-71. | 46 Spanish speaking HNC patients were recruited | Between July and October 2007 | Each participant was asked to fill out each survey (EORTC QLQ-C30, and QLQ-H&N35). Used the validated method of analyzing these questionnaires from the EORTC | Pain, social eating, social interactions, and loss of sexuality were the critical factors that impacted HNC patients most drastically. |
| 34 | Raykher A, Correa L, Russo L, Brown P, Lee N, Pfister D, Gerdes H, Shah J, Kraus D, Schattner M, Shike M. The Role of Pretreatment Percutaneous Endoscopic Gastrostomy in Facilitating Therapy of Head and Neck Cancer and Optimizing the Body Mass Index of Obese Patient. JPEN J Parenter Enteral Nutr. 2009Jul-Aug;33(4):404–410. | 161 patients treated for HNC who had PEGS placed prior to chemoradiation | 1999-2003 | Retrospective review of patients over 4-year period. Attained date of PEG placement throughout treatment PEG utilization, PEG removal, age, diagnosis, treatment history, complications, BMI, and hospitalizations | Enteral feeding is a safe and effective way to feed patients undergoing chemoradiation. Also helped with weight management throughout and after treatment. |
| 35 | Russo G, Haddad R, Posner M, Machtay M. Radiation Treatment Breaks and Ulcerative Mucositis in Head and Neck Cancer. Oncologist. 2008 Aug; 13(8):886-9 | Literature search | Published before the year 2000 | Literature review based on their relevance to current clinical practice for treatment for head and neck cancer patients. | 90% of all patients have unplanned radiation treatment breaks. Unplanned breaks can cause a lower tumor control rate. By reducing mucositis, tolerability of radiation and quality of life can be improved. |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 36 | Santos RC, Dias RS, Giordani AJ, Segreto RA, Segreto HR. Mucositis in head and neck cancer patients undergoing radiochemotherapy. Rev Escola de Enfermagem da USP. 2011;45(6):1336–1342. | 50 HNC patients who were receiving concomitant radiotherapy and chemotherapy | January to December 2006 | The nurse interview patients on treatment planning day then repeated every week during the entire treatment. During the treatment visits radiotherapists assess the degree of mucositis | Most patients showed symptoms of grade 1 or 2 mucositis between the third and sixth week of treatment. Diabetes was found to enhance the development of severe mucositis |
| 37 | Stevens CS, Lemon B, Lockwood GA, Waldron JN, Bezjak A, Ringash J. The development and validation of a quality-of-life questionnaire for head and neck cancer patients with enteral feeding tubes: the QOL-EF. Support Care Cancer. 2011 Aug; 19(8):1175-82. | Phase 1: Outpatient nurses, Cancer center and home care dietitians, Radiation oncologist, and HNC surgeon surveyed. Phase 2: 12 HNC patients treated with radiotherapy. Phase 3: 36 patients. Phase 4: 40 patients | 4 years | 4 phases: 1 literature review, 2 pilot testing, 3 judgmental item reduction, and 4 QOL-EF, FACT-H&N, and UW-QOL were administered in a cross-sectional group of HNC patients on active enteral tube feedings to test reliability and validity | The FACT-H&N was selected most frequently for the best reflection of QOL then QOL-EF then UW-QOL. QOL surveys are important in evaluating treatment outcomes and complications with HNC patients. |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 38 | Suryawanshi H, Ganvir SM, Hazarey VK, Wanjare VS. Oropharyngeal candidosis relative frequency in radiotherapy patient for head and neck cancer. J Oral Maxillofac Pathol. 2012 Jan; 16(1): 31-7. | 107 patients with oral and/or pharyngeal area carcinoma undergoing radiotherapy | At the beginning of radiation treatment to fifteen days after the last treatment | First visit a complete history and thorough clinical examination with sample collected by oral rinse method for candidosa cultures. Then every visit/treatment day | Radiation increase the frequency of occurrence of oral candidosis. Those patients that are healthy carriers of candidosis should be closely followed due to increased chances of getting a candidosis infection |
| 39 | Van Herper CM, Mauer ME, Mesia R, Degardin M, Jelic S, Coens C, Betka J, Bernier J, Remenar E, Stewart JS, Preiss JH, Van den Weyngaert D, Bottomley A, Vermokern JB, EORTC Head and Neck Group. Short-term health-related quality of life and symptom control with docetaxel, cisplatin, 5-fluorouracil and cisplatin (TPF), 5-fluorouracil (PF) for induction in unresectable locoregionally advanced head and neck patients (EORTC 2497I/TAX 323). Br J Cancer. 2010 Oct 12;103(8):1173–1181. | 358 patients with HNC | 32.5 months from April 1999 to March 2002 | Patients were assessed at end of cycle 2,4,6, and 9. Patient either received TPF or PF treatments | Induction chemotherapy with TPF before radiotherapy increases survival rate and decreases toxicity prevalence. Also slightly improves HRQOL |

| | Study Identification | Patients | Duration | Design | Outcomes |
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| 40 | Vera-Llonch M, Oster G, Hagiwara M, Sonis S. Oral Mucositis in Patients Undergoing Radiation Treatment for Head and Neck Carcinoma: Risk Factors and Clinical Consequences. Cancer. 2006 Jan 15;106(2):329–336. | 154 oncologists participated with 450 head and neck cancer patients | November 2004-August 2005 | Oncologists asked to collect data for up to six patients through chart review. Obtain age, gender, body weight, prior and/or current alcohol or tobacco use, tumor location, status of tumor, stage of disease, oral mucositis experience, outcomes, and type of insurance | Nasopharyngeal/oropharyngeal tumor locations with a cumulative radiation dose >5000 cGy and recipients of concomitant chemotherapy were at the greatest risk of having oral mucositis. Younger patients were at higher risk of getting oral mucositis. And the degree and duration of oral mucositis varied depending on total does, volume of tissue treated, and overall treatment time |
| 41 | Youn Oh, Do; Hyun Kim, Jee; Hoon Lee, See; Wan Kim, Dong; Ah Im, Seock; You Kim, Tae; Seog Heo, Dae; Jue Bang, Yung; Kyeogn Kim, Noe. (2007). Artificial nutrition and hydration in terminal cancer patients: the real and the ideal. Journal of Support Care Cancer | 165 terminal cancer patients | ~ 5 weeks | Recorded ability of oral intake on admission, 1 week after admission, and 2 days before death. Calculated calories by oral intake. Looked into the status of artificial nutrition and hydration. | Oral intake was possible for 50% on admission, 47% 1 week after admission, and only 17% 2 days before death. Average volume supplied with 1.51 L daily intravenously. |

## References


1. Siegel R, Ward E, Brawley O, Jemal A. Cancer Statistics, 2011. The Impact of Eliminating Socioeconomica and Racial Disparities on Premature Cancer Deaths. 2011.

2. Page, Richard; Oo, Aung Y; Russell, Glen; Pennefather, Stephen. Intravenous hydration versus naso-jejunal enteral feeding after esophagetomy: a randomized study. *European Journal of Cardio-thoracic Surgery*. 2002.

3. Chen, Allen M. MD; Li, Bao-Qing, MD, PhD; Lau, Derick H. MD, PhD; Farwell, D. Gregory MD; Luu, Quang MD; Stuart, Kerri RN; Newman, Kathleen RD; Purdy, James A. PhD; Vijayakumar, Srinivasan, MD. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemo radiotherapy for head and neck cancer. *Radiation Oncology*. 2009.

4. Nguyen, Adnreea, RD, LD, CNSD; Nadler, Eric, MD, MPP. Head and Neck Cancer: Defining Effective Medical Nutrition Therapy for Nutritional Phases Observed During Chemoradiation. *Journal of Oncology Nutrition Connection*. 2012;20(1):3–16.

5. Morse, Douglas, E.; Psoter, Walter J.; Cleveland, Deborah; Cohen, Donald; Mohit-Tabatabai, Mireseyed; Kosis, Diane; Eisenberg Ellen. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Research*. 1998.

6. Kiss, Nicole K.; Krishnasamy, Meinir; Loeliger, Jenelle; Granados, Alba; Dutu, Gaelle; Corry, June. A dietitian-led clinic for patients receiving (chemo)radiotherapy for head and neck cancer. *Journal of Support Care Cancer*. 2011.

7. Givens, Daniel J. BS; Hynds Karnell, Lucy PhD; Gupta, Anjali K. MD; Clamon, Gerald H. MD; Pagedar, Nitin A. MD; Chang, Kristi E. MD; Van Daele, Douglas J. MD; Funk, Gerry F. MD. Adverse events associated with concurrent chemo radiation therapy in patients with head and neck cancer. *Archives of Otolaryngology-Head & Neck Surgery*. 2009.

8. Beaver, Mary ES, MD; Matheny, Keith E., MD; Roberts, Dianna B., PhD; Myers, Jeffrey N., MD, PhD. Predictors of weight loss during radiation therapy. *American Academy of Otolaryngology-Head and Neck Surgery*. 1998.

9. Peterman, Amy; Cella, David; Glandon, Gerald; Dobrez, Deborah; Yount, Susan. Mucositis in head and neck cancer: economic and quality-of-life outcomes. *Journal of National Cancer Institute*. 2001.

10. Van Herper, CML; Mauer, ME; Mesia, R; Degardin, M.; Jelic, S.; Coens, C; Betka, J; Bernier, J; Remenar, E; Stewart, JS; Preiss, JH; Van den Weyngaert, D; Bottomley, A; Vermokern JB. Short-term health-related quality of life and symptom control with docetaxel, cisplatin, 5-fluorouracil and cisplatin (TPF), 5-fluorouracil (PF) for induction in unresectable locoregionally advanced head and neck patients (EORTC 2497I/TAX 323). *British Journal of Cancer*. 2010;103(8):1173–1181.

11. Russo, Gregory; Haddad, Robert; Posner, Marshall; Machtay, Mitchell. Radiation Treatment Breaks and Ulcerative Mucositis in Head and Neck Cancer. *The Oncologist, Head and Neck Cancers*. 2008.

12. Burge, Frederick I. MD. Dehydration Symptoms in Palliative Care Cancer Patients. *Journal of Pain and Symptom Management*. 1993.

13. Malecka-Massalska, T.; Smolen, A.; Zubrzycki, J.; Lupa-Zatwarnicka, K.; Morshed, K; Bioimpedance Vector Pattern in Head and Neck Squamous Cell Carcinoma. *Journal of Physiology and Pharmacology*. 2012;63(1):101–104.

14. Mckenzie, Heather; Hayes, Lillian; White, Kathryn; Cox, Keith; Fethney, Judith; Boughton, Maureen; Dunn, Jo. Chemotherapy outpatients' unplanned presentations to hospital: a retrospective study. *Support Care Cancer*. 2011.

15. Capuano, Giorgio; Gentile, Pier Carlo; Bianciardi, Federico; Tosti, Michela; Palladino, Anna; Palma, Mario. Prevalence and influence of malnutrition on quality of life and performance status in patients with locally advanced head and neck cancer before treatment. *Support Care Cancer*. 2010.

16. Lal, Punita; Bajpai, Renjeet; Khurana, Rohini; Das, K.J. Maria; Kumar, Prabhat; Tiwari, Anu; Gupta, Neha; Kumar, Shaleen. Changes in salviary flow rates in head and neck cancer after chemoradiotherapy. *Jounral of Cancer REsearch and Therapeutics*. 2010;6(4):458–463.

17. Nishimura, Goshi; Tsukuda, Mamoru; Horiuchi, Choioshida, Takafumi; Taguchi; Takahide; Nagao, Junichi; Kawakami, Mariko; Kondo, Norio; Matsuda, Hideki; Mikami, Yasukazu. Decrease of creatinine clearance rate with aging in patients with head and neck cancer in Japan. *International Journal of Clinical Oncology*.2007.

18. Michal, Stephani A. BA; Adelstein, David J. MD; Rybicki, Lisa A. MS; Rodriguez, Cristina P. MD; Saxton, Jerrold, P. MD; Wood, Benjamin G. MD; Scharpf, Joseph MD; Ives, Denise I. BSN. Multi-Agent Concuurent Chemoradiotherapy for Locally Advanced Head and Neck Squamous Cell Cancer in the Elderly. *Wiley Online Library*. 2011.

19. Santos, Renata Cristina Schmidt; Dias, Rodrigo Souza; Giordani, Adelmo Jose; Segreto, Roberto Araujo; Segreto, Helena Regina Comodo. Mucositis in head and neck cancer patients undergoing radiochemotherapy. *Revista da Escola de Enfermagem da USP*. 2011;45(6):1336–1342.

20. Machtay, Mitchell; Moughan, Jennifer; Trotti, Andrew; Garden, Adam S.; Weber, Randal S.; Cooper, Jay S.; Forastiere, Arlene; Ang, K. Kian. Factors Associated with Severe Late Toxicity After Concurrent Chemoradiation for Locally Advanced Head and Neck Cancer: An RTOG Analysis. *Journal of Clinical Oncology*. 2011;26(21):3582–3589.

21. Vera-Llonch, Montserrat MD, MPH; Oster, Gerry, PhD; Hagiwara, May PhD; Sonis, Stephen, DMD, DMSc. Oral Mucositis in Patients Undergoing Radiation Treatment for Head and Neck Carcinoma: Risk Factors and Clinical Consequnces. *American Cancer Society*. 2005:329–336.

22. Elting, Linda S.; Cooksley, Cahterine D.; Chambers, Mark S.; Gerden, Adam S. Risk, Outcomes, and Cost of Radiation-Induced Oral Mucositis Among Patients with Head-And-Neck Malignancies. *International Journal of Radiation Oncology Biology Physiology*. 2007.

23. Suryawanshi, Hema; Ganvir, Sindhu M.; Hazarey, Vinay K.; Wanjare, Varsha S. Oropharyngeal candidosis relative frequency in radiotherapy patient for head and neck cancer. *Journal of Oral and Maxillofacial Pathology*. 2012.

24. Fainsinder, Robin L.; MacEachern, Tara; Miller, Melvin J.; Breuera, Eduardo; Spachynski, Kathy; Kuehn, Norma; Hanson, John. The Use of Hypodermoclysis for Rehydration in Terminally Ill Cancer Patients. *Journal of Pain and Symptom Management*. 1994.

25. Machon, Christell; Thezenas, Simon; Dupuy, Anne-Marie; Assenat, Eric; Michel, Francoise; Mas, Emilie; Senesse, Pierre; Cristol, Jean-Paul. Immunonutrition before and during radiochemotherapy improvement of inflammatory parameters in head and neck cancer. *Support Care Cancer*. 2012.

26. Chiu, T.Y.;Hu, W.Y.; Chuang, R.B.; Chen, C.Y. Nutrition and hydration for terminal cancer patients in Taiwan. *Support Care Cancer*. 2002.

27. Youn Oh, Do; Hyun Kim, Jee; Hoon Lee, See; Wan Kim, Dong; Ah Im, Seock; You Kim, Tae; Seog Heo, Dae; Jue Bang, Yung; Kyeogn Kim, Noe. Artificial nutrition and hydration in terminal cancer patients: the real and the ideal. *Journal of Support Care Cancer*. 2007.

28. Bruera, Eduardo; Sala, Raul; Rico, Maria Antonieta; Moyano, Jairo; Centeno, Carlos; Willey, Jie; Palmer, J. Lynn. Effects of Parenteral Hydration in Terminally Ill Cancer Patients: A Preliminary Study. *Journal of Clinical Oncology*. 2005.

29. Oozeer, Nashreen B.; Corsar, Kenneth; Glore, Raad John; Penney, Susannah; Patterson, Joanne; Paleri, Vinidh. The impact of eneteral feeding route on patient-reported long term swallow outcome after chemo radiation for head and neck cancer. *Oral Oncology*. 2011.

30. Mayre-Chilton, K. M,; Talwart, B.P.; Goff, L.M. Different experiences and perspectives between head and neck cancer patients and their care-givers on their daily impact of a gastrostomy tube. *Journal of Human Nutrition and Dietetics*. 2011.

31. Raykher, Aleksandra, MD; Correa, Lilia, MD; Russo, Lianne, MS; Browht, Pat, RN; Lee, Nancy, MD; Pfister, David, MD; Gerdes, Hans, MD; Shah, Jatin, MD; Kraus, Dennis, MD; Schattner, Mark, MD; Shike, Moshe, MD. The Role of Pretreatment Percutaneous Endoscopic Gastrostomy in Facilitating Therapy of Head and Neck Cancer and Optimizing th eBody Mass Index of the Obese Patient. *Journal of Parenteral and Enteral Nutrition*. 2009;33(4):404–409.

32. Li, Baoqing; Li, Dan; Lau, Derick H.; Farwell, Gregory D.; Luu, Quang; Rocke, David M.; Newman, Kathleen; Courquin, Jean; Purdy, James A.; Chen, Allen M. Clinical-dosimetric analysis of measures of dysphagia including gastrostomy-tube dependence among head and neck cancer patients treated definitively by intensity-modulated radiotherapy with concurrent chemotherapy. *Radiation Oncology*. 2009;4(52). Available at: http://www.ro-journal.com/content/pdf/1748-717X-4-52.pdf.

33. Morton, Randall. Studies in the Quality of Life of Head and Neck Cancer Patients: Results of a Two-Year Longitudinal Study and a Comparative Cross-Sectional Cross-Cultural Survey. *The Laryngoscope*. 2003.

34. Meyer, Francois, MD, D.Sc; Fortin, Andre, MD; Wang, Chang Shu MD, PhD; Lui, Geoffrey, MD; Bairati, Isabelle MD, PhD. Predictors of Severe Acute and Late Toxicities in Patients with Localized Head-and-Neck Cancer Treated with Radiation Therapy. *International Journal of Radiation Oncology Biology Physiology*. 2011;82(4):1454–1462.

35. Psoter, Walter J. DDS PhD; Aguilar, Maria L. DDS, MSD, MSc; Levy, Adrea MS, MPH; Baek, Linda S. BS; Morse, Douglas E. DDS, PhD. A Preliminary Study on the Relationships between Global Health/Quality of Life and Specific Head and Neck Cancer Quality of Life Domains in Puertor Rico. *Journal of Prosthodontics*. 2012.

36. Paccagnella, Agostino; Morello, Michela; Mosto, Maria C. Da; Baruffi, Carla; Marcon, Maria L.; Gava, Alessandro, Baggio, Vittorio; Lamon, Stefano; Babare, Roberta; Rosti, Giovanni; Giometto, Marta; Boscolo-Rizzo, Paolo; Kiwanuka, Edward; Tessarin, Michele; Caregaro, Lorenza; Marchiori, Carlo. Early nutritional intervention improves treatmetn tolerance and outcomes in head and neck cancer patients undergoing concurrent chemoradiotherapy. *Journal of Support Care Cancer*. 2010;18:837–845.

37. Doeer, Timothy D. MD; Marks, Steven C. MD; Shamsa, Falah H. PhD; Mathog, Robert H. MD; Prasad, Anada S. MD, PhD. Effects of Zinc and Nutritional Stuatus on Clinical Outcomes in Head and Neck Cancer. *The International Journal of Applied and Basic Nutritional Science*. 1998;14(6):489–495.