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Predictors of Nonadherence to Radiation Therapy Schedules
Among Head and Neck Cancer Patients

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Predictors of Nonadherence to Radiation Therapy Schedules
Among Head and Neck Cancer Patients

by

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy
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Keywords: oncology, nursing, symptoms, treatment, compliance

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Dedication

I would like to dedicate this dissertation first to my husband, Brent Miller, who has never doubted I would achieve anything I set my mind to since the day we met. During this program, I was blessed with my son Blake, who inspired me every day to finish what I started for our family. Finally, I’d like to dedicate this work to my late grandmother, Faye, who was always one of my biggest supporters, starting by funding my education to become a certified nurse’s assistant and setting me on this journey neither one of us knew was in my future.
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Dr. Laura Szalacha, your guidance in designing and analyzing my study was exactly what I was looking for and needed. You always showed excitement for the topic and would provide me with the direction I needed to go and learn a little bit more, one step at a time. You were always smiling and giving me positive words of encouragement. I truly felt proud of my work every time we talked.

Dr. Paula Cairns, thank you for agreeing to join my committee late in the process, but still showing great interest in my topic, providing pointed feedback and positive words in the most stressful of times.

Dr. Susan Hartranft, thank you for helping me navigate through many important processes at my study site, providing valuable feedback on my work, and always believing in me. I would not have accomplished this in such a timely manner without your assistance.
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Abstract

Nonadherence to radiation therapy schedules is a documented problem among head and neck cancer patients. This retrospective dissertation study examined whether demographics, clinical characteristics, or physical and psychological symptoms were related to nonadherence in head and neck cancer patients. The electronic medical records of 262 head and neck cancer patients at a southeastern U.S. cancer center were reviewed to determine whether nonadherence was related to symptom scores and other patient and clinical-related factors. Nonadherent patients were more likely to be female, be admitted to the cancer center as inpatients during treatment and receive outpatient IV fluids during treatment. Nonadherent patients reported higher mean symptom scores on 9 out of 12 symptoms measured during treatment, illustrating that this group had a higher symptom burden. The logistic regression modeling contained significant predictors of treatment nonadherence: concurrent chemotherapy and radiation treatment regimens as well as the symptoms of tiredness and depression predicted patients were more likely to be nonadherent. Tumor location at the tongue, spiritual well-being, and constipation predicted patients were less likely to be nonadherent. Findings support routine screening for symptoms and distress in this population, as well as future research to confirm and build on the results.
Chapter One: Introduction

Head and neck cancer (HNC) is the sixth most common type of cancer in the United States with nearly 53,000 new cases and over 10,000 deaths anticipated in 2020 (American Cancer Society, 2020). The five-year relative survival is 60.8% (Centers for Disease Control and Prevention, 2018).

The increasing prevalence of human papillomavirus (HPV) has been changing the clinical picture of HNC in the past 10 years. HNC used to primarily affect older adults with strong tobacco use history and in the 1980s, the incidence of HNC was decreasing, paralleling trends in smoking (Westra, 2009). HPV-negative HNCs are continuing to decrease in incidence, while HPV-positive HNCs are increasing. HPV is associated with sexual practice risk factors, including a high number of sexual partners, history of oral-genital sex, and history of oral-anal sex (Westra, 2009). This type of HNC is often found in patients who have never smoked cigarettes or drank alcohol (Westra, 2009). There has been a greater than 25% increase in HPV-related HNC in the U.S. in the past decade, especially affecting middle-aged men (American Cancer Society, 2017a). Despite this trend, HNC research is reported to be underfunded and understudied (Svider et al., 2016).

Treatment for HNCs may include one or a combination of the following: radiation therapy, chemotherapy, and surgery. Early-stage HNCs that have not spread to other sites are commonly treated with radiation or surgery, while more extensive head and neck cancers may be addressed by using radiation combined with chemotherapy (Ratko, 2014). Radiation therapy is offered to nearly 75% of all HNC patients with curative or palliative intent (Ratko, 2014).
Radiation therapy (RT) is a demanding course of treatment that usually requires daily (Monday-Friday) treatments and weekly doctor visits. HNC treatment regimens vary from six to seven and a half weeks of Monday-Friday treatments, depending on the classification of the tumor and the treatment plan (National Comprehensive Cancer Network, 2018). Research suggests that patients who missed RT visits were more likely to experience tumor recurrence and worse outcomes in the future (Ferreira, Sa-Couto, Lopes, & Khouri, 2016; Ohri, Rapkin, Guha, Kalnicki, & Garg, 2016; Thomas et al., 2017). Nonadherence to RT is a documented problem in HNC patients (Naghavi et al., 2016; Ohri et al., 2016; Pujari, Padhi, Meher, & Tripathy, 2017; Rangarajan & Jayaraman, 2017). The literature reports a range of 20% - 57% nonadherence rates to RT schedules in HNC patients in both the United States and India (Naghavi et al., 2016; Ohri et al., 2015; Pujari et al., 2017; Rangarajan & Jayaraman, 2017).

**Statement of the Problem**

HNC treatment causes symptom burden in patients to include fatigue, nausea, pain, dysphagia, and respiratory problems (American Cancer Society, 2017b). These symptoms can affect the HNC patient’s actual and perceived abilities to complete RT (Edmonds & McGuire, 2007). Nonadherence with RT schedules can negatively affect patient outcomes and the chance of tumor recurrence in the future (Bese, Hendry, & Jeremic, 2007; Ohri et al., 2016). However, the current research examining nonadherence to RT has been limited to physicians examining demographic and clinical factors (Naghavi et al., 2016; Ohri et al., 2015, 2016; Pujari et al., 2017).

There was a gap in the literature examining the association between HNC patients, their symptoms, and their adherence to RT schedules. This is important to address because nurses can intervene early to recognize patients at risk for treatment nonadherence and provide education as
well as interdisciplinary treatment to provide symptom management (Edmonds & McGuire, 2007). The purpose of this retrospective study was to examine if demographic characteristics, clinical characteristics, or symptoms were associated with nonadherence to RT schedules among HNC patients.

**Specific Aims**

The aims that guided this retrospective study were:

1. **Demographic characteristics:** To evaluate if variables such as age, biological sex, race, marital status, distance traveled to treatment, smoking history, and education level were correlated to nonadherence to RT schedules among HNC patients.

2. **Clinical characteristics:** To evaluate if clinical characteristics of the cancer and treatment, including the number of RT treatments prescribed, tumor location, cancer stage, placement of percutaneous endoscopic gastrostomy (PEG) tube, inpatient admission during treatment, outpatient IV fluid administration during treatment, and concurrent chemoradiation status, were correlated to nonadherence to RT schedules among HNC cancer patients.

3. **Physical and Psychological Symptoms:** To evaluate whether the presence of physical and psychological symptoms, including pain, tiredness, drowsiness, nausea, shortness of breath, depression, anxiety, constipation, and well-being were predictors of nonadherence to RT schedules among HNC patients.

**Limitations**

This study presented the prevalence and severity of symptoms and other factors in relation to radiation therapy adherence. Limitations of the study were as follows:
1. The data was collected using a retrospective chart review; therefore, the data was limited to what was already present in the electronic medical record (EMR). For symptom assessment, the Edmonton Symptom Assessment Scale-revised (ESAS-r) was utilized as it was already collected on every patient in the Radiation Oncology Clinic. However, for many of the symptoms of interest, there are other tools available that may have provided better data for this population.

2. Treatment nonadherence was broadly defined as an unplanned treatment break. This information was discerned from notes entered by the radiation therapists in the EMR and relied on the accuracy and detail of the notes. There were not opportunities to talk to patients and confirm the reasons they missed appointments.

**Assumptions**

1. Patients understood the ESAS-r system of scoring and answered questions accurately and honestly.

2. Demographics, clinical data, and record-keeping of appointments were entered in the EMR accurately by the health care team.

**Significance to Nursing**

Oncology nurses are responsible for educating patients on how to manage their treatment-related symptoms with the healthcare team. If nurses are aware of factors that predict nonadherence, they can identify at-risk patients early and intervene to help patients lessen symptoms, improve quality of life and ultimately improve outcomes by encouraging patients to adhere to treatment (Edmonds & McGuire, 2007). This dissertation study will provide nurses with information on what factors are most relevant to nonadherence and therefore inform clinical practice and future research, including prospective and intervention studies.
Definitions of Relevant Terms

1. Head and neck cancer: cancer that arises in the head and neck region (in the nasal cavity, sinuses, lips, mouth, salivary glands, throat or larynx [voice box]) (National Cancer Institute, 2019).

2. Radiation therapy (RT): a cancer treatment that uses high doses of radiation to kill cancer cells and shrink tumors (National Cancer Institute, 2016).

3. External beam radiation therapy (EBRT): radiation therapy that is applied externally through directed beams of radiation to treat the cancer deep within the body (Jaffray, 2015).

4. Treatment adherence: the extent to which a person’s behavior, e.g., taking medications, following a diet, and/or executing lifestyle, corresponds with agreed recommendations from a health care provider (World Health Organization, 2003).

5. Nonadherence: In this study, nonadherence is defined as a self-cancellation or did not show status for three or more RT appointments in the prescribed treatment regimen.

6. Locoregional control: local control of cancer without any recurrence in the lymph nodes (Buffa et al., 2004).
Chapter Two: Review of Literature

This chapter presents a review of the literature related to the topic. First, a review of the Five Dimensions of Adherence conceptual framework is presented, followed by a discussion about adherence to cancer treatments among head and neck cancer (HNC) patients and how adherence is related to symptoms. Following, a review is provided about demographic characteristics and clinical characteristics that affect adherence in this population.

Conceptual Framework

The Five Dimensions of Adherence conceptual framework, depicted in Figure 1, from the World Health Organization (2003), suggests that adherence is a multidimensional phenomenon, influenced by five sets of factors or “dimensions:” social and economic factors, healthcare team (HCT) and system-related factors, condition-related factors, therapy-related factors, and patient-related factors. This framework challenges the common conception in healthcare that patients are solely responsible for adhering to agreed-upon treatment plans (World Health Organization, 2003). This study included variables from four dimensions (See Table 1). Each dimension will be described, and literature related to each factor will be reviewed.

Figure 1. The Five Dimensions of Adherence (World Health Organization, 2003a)
*Figure used with permission (Appendix 1)
Table 1.

Examples of factors in each of the Five Dimensions of Adherence

<table>
<thead>
<tr>
<th>Health care team factors</th>
<th>Patient-related factors</th>
<th>Condition-related factors</th>
<th>Therapy-related factors</th>
<th>Socioeconomic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment facility</td>
<td>Previous experiences</td>
<td>Cancer stage*</td>
<td>Duration of treatment*</td>
<td>Education level*</td>
</tr>
<tr>
<td>Team expertise</td>
<td>Personal beliefs and expectations</td>
<td>Location of tumor*</td>
<td>Medical interventions*</td>
<td>Living situation*</td>
</tr>
<tr>
<td>Patient education provided</td>
<td>Spirituality*</td>
<td>Symptoms*</td>
<td>Side effects*</td>
<td>Support system*</td>
</tr>
<tr>
<td>Medical insurance</td>
<td>Distress*</td>
<td>Co-morbidities</td>
<td>Complexity of treatment*</td>
<td>Social histories*</td>
</tr>
<tr>
<td>Relationship between patient and team</td>
<td>Knowledge deficit</td>
<td>Availability of treatments</td>
<td>How long to see results</td>
<td>Employment</td>
</tr>
</tbody>
</table>

Note. * variables measured in this study

Social and Economic Factors

Socioeconomic status has not been found to be an independent predictor of adherence, but several factors have been reported to have a significant effect on adherence, including poor socioeconomic status, poverty, illiteracy, low level of education, unemployment, poor social support, unstable living conditions, transportation barriers, and family dysfunction (World Health Organization, 2003). This is a complex factor to assess. Factors may range from transportation issues to competing priorities such as a single working mother who is trying to care for her family while also receiving cancer treatment. Nursing interventions to address these factors include coordinating interdisciplinary care, referrals to social work, and community-based organizations (World Health Organization, 2003) and telephone navigation to check in with patients and help resolve issues to avoid adherence problems (Percac-Lima et al., 2015).

Health Care Team (HCT) and System-Related Factors

Factors that fall under this dimension include systems issues such as medical insurance difficulties, overworked healthcare providers, medication shortages, as well as HCT issues including lack of education by the team and poor follow-through (World Health Organization,
Nursing interventions include training healthcare workers on adherence, educating patients on treatments, supporting caregivers, identifying patient goals and individualized strategies to achieve the goals (World Health Organization, 2003).

**Condition-Related Factors**

Condition-related factors encompass illness-related demands. Adherence depends on factors related to the disability of the patient (including physical, psychological, social, and vocational considerations), prevalence and severity of symptoms, severity of the disease, and availability of effective treatments (World Health Organization, 2003). Co-morbidities have also been found to be modifiers of adherence behavior (World Health Organization, 2003). Nurses are well-positioned to assess for and intervene regarding symptom management.

**Therapy-Related Factors**

Therapy-related factors are specific to the unique characteristics of the patient’s treatment plan. Complex treatments, long duration of treatment, previous experiences with the treatment, frequent changes in the plan, how long it takes to see improvement, side effects, and medical support are all examples of therapy-related factors (World Health Organization, 2003). Nurses can help patients navigate complex health care plans and coordinate care with other disciplines. Nurses also are the front-line educators and can educate patients on the importance of receiving treatments, what side effects to expect, and how to manage them.

**Patient-Related Factors**

Patient-related factors include the patient’s resources, expectations, perceptions, knowledge, attitudes, and beliefs (World Health Organization, 2003). Examples of patient-related factors that negatively affect adherence include forgetfulness, anxiety, stress, low motivation, lack of knowledge, not perceiving the need for treatment, low treatment attendance,
and feeling stigmatized by the disease (World Health Organization, 2003). Nurses can provide education, explore beliefs and conceptions with the patient, promote good patient-provider relationships, teach behavioral interventions, and teach and encourage self-management of disease (World Health Organization, 2003).

**Radiation Therapy Adherence**

The limited research studies exploring nonadherence in RT patients suggest that patients who missed RT visits were more likely to experience tumor recurrence and worse outcomes in the future (Ferreira et al., 2016; Ohri et al., 2016; Thomas et al., 2017). In a study of 2184 cancer patients, HNC predicted nonadherence to RT treatment regimens, compared with cancers of other sites (Ohri et al., 2015). Missing even one RT appointment can have detrimental negative outcomes in HNC treatment (Bese et al., 2007). When an RT dose is missed, the tumor cells have the opportunity to repopulate rapidly and can decrease the local control rate of the tumor by 1.4% daily or 10-12% for a break lasting a week (Bese et al., 2007). Naghavi and colleagues (2016) found that in a cohort study of 1802 HNC RT patients, 50% experienced treatment interruptions which predicted worse locoregional control of cancer and overall survival.

Nonadherence to RT is a documented problem in HNC patients (Naghavi et al., 2016; Ohri et al., 2016; Pujari et al., 2017; Rangarajan & Jayaraman, 2017). The literature available regarding RT nonadherence in the HNC population has reported a range of 20% - 57% of HNC patients were nonadherent to their RT schedules in both the United States (Naghavi et al., 2016; Ohri et al., 2015) and India (Pujari et al., 2017; Rangarajan & Jayaraman, 2017).

**Demographic Characteristics**

Demographics may be used to describe the patient population and may reflect some of the social and economic factors that affect adherence to treatment. Age, biological sex, race,
distance traveled to treatment, education level, marital status and smoking history will be reviewed in relationship to HNC patients’ adherence to RT treatment. The literature available that considers each demographic and its relationship to adherence to cancer treatments and the HNC population is described in the following sections.

**Age**

Ohri and colleagues (2015) did not find that age was a significant predictor of nonadherence to RT schedules among all cancer populations. The limited literature in the HNC population reported that patients who declined standard RT treatment plans proposed by physicians were more likely to be older (Dronkers, Mes, Wieringa, van der Schroeff, & Baatenburg de Jong, 2015). No known literature has reported if age predicted RT adherence in the HNC population.

**Biological Sex**

Similar to the reports available on age, biological sex was not a predictor of nonadherence to RT schedules among all cancer populations (Ohri et al., 2015). In a related study, HNC patients who declined standard treatment plans proposed by physicians were more likely to be female (Dronkers et al., 2015).

**Race**

RT treatment adherence was not predicted by race in two studies (Naghavi et al., 2016; Ohri et al., 2015). However, race has been reported to be a factor for overall survival and tumor recurrence. Naghavi et al. (2016) identified that black HNC patients were found to present with delays in diagnosis or advanced disease and also had worse outcomes in terms of recurrence and survival. Another study reported that white female, male and married HNC patients had better locoregional control compared to their non-white counterparts, respectively (Dilling et al., 2011).
Distance Traveled to Treatment

There are contradictory findings related to distance from the patient’s home to the treatment site and adherence to RT. Ohri and colleagues (2015) did not find that distances from patient homes to treatment facilities were predictive of cancer patients missing appointments. However, several related studies found the opposite. In the HNC population, distance traveled was a predictive factor for HNC patients refusing recommended RT treatment post-operatively (Schwam, Husain, & Judson, 2015). In a rural study of 33 HNC patients, 87% stated that distance was the main barrier of access to RT treatment and that it affected treatment decisions (Cosway, Douglas, Armstrong, & Robson, 2017).

The following results also suggest that distance from the treatment site may also influence adherence. In a study of all cancer populations, cancer patients having to travel 50 miles or 1 hour to the treatment site were noted to present with more advanced disease (Ambroggi, Biasini, Del Giovane, Fornari, & Cavanna, 2015). Two prospective studies in Texas, US, reported that most patients who missed appointments did so due to nonmedical or logistical reasons including transportation (Guidry, Aday, Zhang, & Winn, 1997; Thomas et al., 2017). The need for housing assistance was a significant predictor of minority patients missing chemotherapy or radiation appointments (Costas-Muniz et al., 2016).

Marital Status

Naghavi et al. (2016) identified that married HNC patients were less likely to experience delays in initiation of treatment, but did not find a relationship between marital status and delays in completion of RT. There are no other known studies regarding HNC marital status and RT treatment adherence.
In related studies, there are contradictory findings on the relationship between marital status and HNC treatment decisions and survival. While one study reported that widowed or single female HNC patients were more likely to decline treatment (Dronkers et al., 2015); another study reported that HNC patients who were married were more likely to receive definitive treatment and less likely to die from HNC (Inverso et al., 2015). Unpartnered males had the worse overall survival compared to other groups of unpartnered females, partnered females, and partnered males in a study of 1736 HNC patients who completed RT (Dilling et al., 2011). A third study reported that marital status was not a significant predictor in survival in a cohort of HNC patients with HPV+ oropharyngeal cancer (Rubin et al., 2017).

**Education**

One study identified that HNC patients who were estimated to have graduated high school were more likely to adhere to the treatment timeline (Graboyes, Garrett-Mayer, Sharma, Lentsch, & Day, 2017). However, this study is limited because the education level was estimated solely based on zip codes. Another study from India that included all cancer populations reported that among 61 nonadherent patients, 51% had only a primary school education and 44% were illiterate (Rangarajan & Jayaraman, 2017).

**Clinical Characteristics**

Clinical characteristics are condition-related and therapy-related factors in the conceptual framework (World Health Organization, 2003) previously introduced. Treatment plan recommendations for HNC depend on the size, location, and grade of the primary tumor (National Comprehensive Cancer Network, 2018; Ratko, 2014). For this study, the relationship between adherence to treatment and the following characteristics will be reviewed: tumor location, cancer stage, and concurrent chemotherapy status.
**Tumor Location**

The different sites of head and neck cancer defined by the American Joint Commission on Cancer are oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, and nasal cavity/paranasal sinuses (American Academy of Otolaryngology, 2014). No studies are known to examine if the location of the HNC tumor site is related to RT treatment adherence.

**Cancer Stage**

A study of all cancer populations in India with 61 nonadherent patients reported that 69% were Stage III at presentation and 18% were at Stage IV at presentation, suggesting that more advanced cancer presentation may be a predictor of treatment nonadherence (Rangarajan & Jayaraman, 2017). However, there is no known literature looking specifically at cancer stage, HNC, and treatment adherence. One study reported that advanced tumor stage was a predictor of HNC male patients’ decision to decline treatment recommendations altogether (Dronkers et al., 2015).

**Concurrent Chemotherapy Status**

Certain clinical situations such as advanced stage and metastasis require that HNC patients receive both RT and chemotherapy to provide the best chance for disease control (John Hopkins University, 2019; Ratko, 2014). Receiving both treatment modalities predicted worse symptom burden in HNC patients (Rosenthal et al., 2014). Trotti and colleagues (2003) identified that patients receiving both chemotherapy and radiation experienced one particular side effect, mucositis, more frequently than patients receiving radiation alone. Concurrent chemoradiation was reported in 58% of HNC patients in a cohort study conducted by radiation oncologists in the Southeastern United States (Naghavi et al., 2016).
Two studies in India are known to have examined if concurrently receiving chemotherapy and radiation affects RT adherence. One study that includes reports that 71% of 61 nonadherent RT patients with any type of cancer were receiving concurrent chemoradiation (Rangarajan & Jayaraman, 2017). The other retrospective study of 378 HNC patients in India reported that 66% of HNC patients receiving concurrent chemoradiation experience treatment prolongation of at least two days and 14% did not complete their RT treatment course (Sharma et al., 2016).

**Physical and Psychological Symptoms**

Symptoms that interfere with treatment adherence may be condition or therapy-related factors. HNC treatment causes symptom burden in patients including fatigue, nausea, pain, dysphagia, and respiratory problems (American Cancer Society, 2017b).

Symptom clusters have been identified in the RT population. Results from symptom distress screening using the Edmonton Symptom Assessment Scale identified the following symptom clusters among cancer patients receiving RT: tiredness (tiredness and drowsiness), low well-being (overall and spiritual well-being), loss of appetite (nausea and loss of appetite), and depression (depression and anxiety), though this is among all cancer populations (Johnstone et al., 2017). A study in China identified two clusters among HNC patients: cluster number one consisted of the symptoms of pain, dry mouth, lack of appetite, sleep disturbance, fatigue, drowsiness, distress, and sadness; cluster number two encompassed nausea, vomiting, numbness, shortness of breath and difficulty remembering (Chiang, Ho, Wang, & Lin, 2018).

**Fatigue and Sleep Disturbance**

Several studies have reported on the burden of sleep disturbance, tiredness, and fatigue among HNC patients receiving RT. Fatigue is known to increase throughout the RT course (Sawada et al., 2012). HNC patients had a greater risk of disturbance to their daily functioning
due to fatigue, compared to other cancers (Poirier, 2011; Sawada et al., 2012). HNC patients have also reported sleep and fatigue to be among the top causes of distress during RT (Badr, Gupta, Sikora, & Posner, 2014). Though evidence shows that fatigue and sleep disturbances have negative effects on HNC patients, no known literature assesses for correlation between these sleep-related symptoms and RT adherence. Nurses can intervene by assessing patients’ sleep patterns and activity levels, educating the patient on getting frequent rest periods and light exercises, reducing activity when tired, limiting naps to avoid losing sleep at night, and eating a high-protein, high-calorie diet to improve energy levels (Edmonds & McGuire, 2007).

**Mucositis**

RT toxicity is a major cause of treatment interruption (Ferreira et al., 2016). Mucositis is one such side effect of toxicity, characterized by inflammation of the oral mucosa which may cause pain and burning sensations, consequently compromising oral intake in the HNC population while undergoing RT (Siddiqui & Movsas, 2017). A qualitative study of HNC patients receiving radiotherapy described pain on swallowing as the main feature, describing the pain as “…to drink a drop of water it was like swallowing barbed wire…” and “…nagging, dull pain around the throat, and it seemed to get worse when I tried to eat” (Pattison et al., 2016). The patients of this qualitative study also described that mucositis led to worsening oral intake, fatigue, and well-being (Pattison et al., 2016).

In a systematic review of the literature, mucositis was found among 90-100% of HNC patients (n = 6181) and 11% of these patients experienced RT treatment interruptions or modifications due to mucositis (Trotti et al., 2003). Badr and colleagues (2014) also reported that mucositis is a documented problem among HNC patients receiving RT and that mouth sores and
eating difficulties were reported as sources of distress by HNC patients during RT (Badr et al., 2014).

Nursing interventions to help reduce or mitigate mucositis include coordinating dental evaluations before the start of treatment, educating the patient against smoking, drinking alcohol, or consuming acidic or spicy foods during treatment (Edmonds & McGuire, 2007; Siddiqui & Movsas, 2017). Medications may also be prescribed to minimize pain and nurses can provide education on daily oral inspection and use of soft toothbrushes and swabs, and following up to ensure the medications are effective (Edmonds & McGuire, 2007; Siddiqui & Movsas, 2017).

**Xerostomia**

Xerostomia, or dry mouth, is another significant side effect of RT in HNC patients (Ratko, 2014; Siddiqui & Movsas, 2017). Xerostomia can cause patients to experience discomfort and become nauseous when they are unable to manage their saliva effectively due to dry mouth (Siddiqui & Movsas, 2017). This side effect may be associated with dysgeusia (altered or lack of taste) and either or both side effects may alter oral intake, leading to the need for parenteral or enteral nutrition in moderate to severe cases (Siddiqui & Movsas, 2017). Dysgeusia is usually an early side effect of RT (Schoeff, Barrett, Gress, & Jameson, 2013).

Nurses can intervene by educating the patients about saliva substitutes such as sprays and lozenges, encouraging oral intake, monitoring patient’s nutritional status, and coordinating care with physicians, dieticians, and social workers as needed (Edmonds & McGuire, 2007). No known literature describes the effect of this symptom on adherence to RT.

**Dysphagia**

Dysphagia refers to difficulty swallowing and is known to be a side effect of RT to the head and neck (Ratko, 2014). Nurses can intervene by coordinating consults for speech therapy
and feeding tube evaluation, educating the patient on daily weights to assess nutritional status, encouraging soft, moist foods, encouraging the use of prescribed pain medications before eating, and how to minimize irritation (Edmonds & McGuire, 2007). No known literature describes the effect of this symptom on adherence to RT.

Malnutrition is present in nearly all HNC patients at the time of diagnosis due to metabolic changes, dysphagia, or a history of chronic malnutrition secondary to alcohol and tobacco abuse (Schoeff et al., 2013). Weight loss also affects 75% - 80% of HNC patients undergoing treatment (Schoeff et al., 2013).

*Psychosocial Distress*

Psychosocial distress is known to appear or increase in the HNC population over the RT course (Chen et al., 2009; Sawada et al., 2012). Increased depression scores were related to worse rates of completion of adjuvant therapy in HNC patients undergoing surgery (Barber et al., 2015) and also related to worse RT adherence among HNC patients in China (Chen, Hsu, Felix, Garst, & Yoshizaki, 2018). Another study examining all cancer populations undergoing RT found a significant association between missing at least one appointment and distress scores between 7 and 10 out of 10 (Anderson, Slade, McDonagh, Burton, & Fields, 2018).

*Summary*

The goal of this research study was to describe the characteristics of the HNC population that did not adhere to RT schedules. The goal of this program of research is to intervene with early education and ultimately improve the quality of life and outcomes of HNC patients. Nonadherence to RT treatment is a documented problem among HNC patients, however, the
studies about the relationship between treatment-related symptoms and RT nonadherence are scarce. This study addressed a gap in the literature and established a scientific premise for further research in this field.
Chapter Three: Methods

This chapter describes the research methods and procedures for the study by providing detailed information about the study design, setting, sample, instruments, procedures, and data analysis for the specific aims of the study.

Design

This retrospective descriptive study explored if demographic characteristics, clinical characteristics, and symptoms among HNC patients were correlated with nonadherence to their radiation therapy treatment schedules.

Setting

The study is a retrospective chart review from a Cancer Center (CC) in the southeast region of the United States. More than 9,000 new patients are seen annually at the CC, including more than 680 patients with HNC. There were 1308 RT treatment plans administered for HNC over 4 years between July 2015 and July 2019 at the CC.

Population and Sample

The population for this study included HNC patients that started the RT treatment course at the CC between July 3, 2017 and June 29, 2018. This sample included all patients that met the inclusion criteria for that year-long period (n = 262). The inclusion criteria were as follows: adult patients diagnosed with HNC that were prescribed to receive curative external beam radiation therapy (EBRT) at the CC and had completed ESAS questionnaires in the EMR. HNC patients receiving palliative RT were excluded because the treatment course is limited to 1 to 4 weeks.
which is substantially different from the curative external beam course that typically lasts 6 to 7 weeks (35 - 40 fractions) (National Comprehensive Cancer Network, 2018).

A target sample size of at least 250 patients was desired to achieve a power of 90% to perform analysis with a small effect size and an alpha of .05. A sample of 300 electronic medical records of patients meeting the inclusion criteria was requested from the CC in anticipation that some of the records may be incomplete. To capture data for a whole calendar year, data collection of 262 patients was performed.

**Measurement of Nonadherence**

The primary outcome, nonadherence, was a nominal variable and patients were classified as adherent (0) or nonadherent (1). Nonadherence was operationalized as a patient who canceled or did not show for three or more scheduled RT appointments during their treatment plan. If a patient met this criterion, the patient was placed in the nonadherent group. If the patient attended all scheduled RT treatments or missed one or two appointments only, the patient was placed in the adherent group.

**Measurement of Demographic Characteristics**

Demographic characteristics of the sample included age, biological sex, marital status, distance traveled to the treatment site, education level, and smoking history. These were collected from the electronic medical record (EMR) and entered into an SPSS database by the PI to address aim number one.

All of the demographic characteristics were categorical variables and classified as available in the EMR, except for distance from CC. For this variable, the distance was calculated based on the zip code of the patient’s home address and the CC address, and then was classified as less than 50 miles from the CC, or equal to or greater than 50 miles to the CC.
Measurement of Clinical Characteristics

The number of RT treatments prescribed, location of tumor, cancer stage, placement of percutaneous endoscopic gastrostomy (PEG) tube, inpatient admission during treatment, outpatient intravenous (IV) fluid administration and concurrent chemoradiation status, were extracted by the PI and recorded into an SPSS data spreadsheet to address aim number two. For the number of treatments prescribed, tumor location, and cancer stage, the data were classified in categories noted in the record. For the other clinical characteristics, the data were classified as binary yes or no categorical variables dependent on if the patient’s medical record reflected that they received the intervention.

Measurement of Symptoms

Physical and psychological symptoms were collected by the PI from the EMR and entered directly into an SPSS database. The operationalization of the symptoms collected are described below.

ESAS-r

The retrospective study was limited to analyzing data that was already available in the chart. Consequently, there wasn’t data available for every symptom that is known to affect HNC patients. Distress screening is conducted weekly on every RT patient by using the ESAS-r. These symptom scores were collected and may broadly represent some of the symptoms not measured. For example, there wasn’t a mucositis score to analyze, but pain was measured and is a symptom of mucositis.

The ESAS-r is a 10-item measure developed to assess pain, activity, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath, and distress in palliative care patients (Watanabe et al., 2011). Patients are instructed to rate with a number from 0 – 10 for
each symptom to describe how they are feeling at present, with 0 being no symptom and 10 being the worst possible symptom. There is one single score reported per item.

The instrument has evidence of validity in cancer patients cared for by a medical oncology service. An overall Cronbach alpha of .79 suggests internal reliability (Chang, Hwang, & Feuerman, 2000). Criteria validity was demonstrated by comparison with the Karnofsky Performance Scale, Functional Assessment of Cancer Tool, and Memorial Symptom Assessment Scale (Chang et al., 2000). The original ESAS was revised in 2011 to improve interpretation and clarification of symptom intensity assessment and was preferred by cancer patients (Watanabe et al., 2011). An updated version, the ESAS-r-CSS, added the dimensions of spiritual well-being and constipation, and is the form that was used for this study (Johnstone et al., 2017).

The ESAS-r was collected at every physician visit in the RT department at the Cancer Center, which includes the initial consult and weekly on-treatment visits. The ESAS-r was completed on an iPad by the patient and uploaded directly into the EMR. An alternative paper assessment was available if a patient was unable to use an iPad. Electronic self-reporting is a suitable collection technique for routine screening in HNC patients (Goncalves & Rocha, 2012). In this study, the ESAS-r was used to collect data related to physical and psychological symptoms for aim number three. Each symptom and the total scores were averaged for the RT treatment period and these means were used as independent variables to address aim number three.

**Weight Loss**

Common symptoms among HNC patients that can affect nutrition are dysphagia, xerostomia, and mucositis. There were no measures available in the EMR to directly assess these problems in the retrospective review. Weight loss, along with PEG tube placement and ESAS-r
reporting of GI symptoms, was used to reflect nutritional changes. Weight loss was measured as a percentage of weight lost between the first week of RT and the cessation of RT treatment. Weight in kilograms was extracted from the EMR for the first and the last weeks of the RT treatment. The percentage of weight lost was calculated and recorded as an independent variable used to address aim number three.

**Procedures**

**IRB Approval (Including Study Site Requirements)**

The study protocol (IRB# Pro00041176) was reviewed, approved, and implemented per the ethical standards and requirements of the University of South Florida (USF) institutional review board (IRB) (Appendix 2) and the Cancer Center (Appendix 3).

**Data Collection**

The data were collected in a retrospective chart review of the EMR of patients who completed radiation treatment at the Cancer Center. The PI received the MRNs of eligible patients from the HNC physician program leader. The PI reviewed and extracted data from each EMR and entered into an SPSS database for patients who met inclusion criteria. Once the sample size was met, the PI ceased record review and data collection.

**Data Management**

The data was de-identified and managed by the PI on a spreadsheet using SPSS Version 25.0.0. An electronic, password-protected spreadsheet key was created with the patient’s medical record number and accompanying study reference number. The data was stored on a laptop computer dedicated to the research project secured with a password and firewall. Study data was backed up to an encrypted, password-protected external hard drive stored in a locked file cabinet in a locked office of the PI. The files were only accessible to the PI and personnel involved in the
study’s analysis, including the study statistician and co-investigator committee members. The key containing PHI was deleted after data collection and analysis were complete. No patient information was recorded on paper. All measures were taken to ensure the privacy and security of patient data.

**Data Analysis**

After the data was screened for data anomalies (e.g., outliers, non-normality), an analytic dataset of 262 individuals was created. Descriptive statistics were used to summarize the sample demographic characteristics, clinical factors, symptoms, and adherence. Bivariate tests were conducted to test for differences in all independent variables by adherence. Contingency table analyses were used to estimate the odds of adherence by all independent variables. Independent t-tests were used to detect significant differences within the independent variables.

Logistic regression was used to model nonadherence. The goal of the logistic regression was to determine which clinical factors, demographics, and symptoms significantly predicted the probability of nonadherence to RT schedules (McDonald, 2014). A series of logistic regression models were fit to determine the significant predictors of nonadherence to RT.

**Sample Size and Statistical Power**

Taken individually, a logistic regression model of nonadherence to RT on a binary independent variable, such as biological sex, with a sample size of 250 observations (of which 70% were adherent and 30% were nonadherent) achieves 90% power at alpha= 0.05 to detect a small effect, an Odds Ratio of 1.5 (Demidenko, 2007; Hsieh, 1998; PASS 16 Power Analysis and Sample Size Software, 2018).
Summary

This study aimed to identify risk factors for treatment nonadherence among HNC patients undergoing radiation therapy. Using a retrospective chart review to collect data, the demographics, clinical factors, and symptoms related to head and neck cancer were examined to determine significant predictors of treatment nonadherence.
Chapter Four: Results

This chapter presents the results of the study. The process of analysis as it relates to the aims of the study is presented through univariate tests, bivariate tests, and individual and logistic regressions.

Outcome Variable: Nonadherence

The sample consisted of 262 participants with a diagnosis of HNC who received RT at the Cancer Center (CC). Three-quarters of the sample (n=198, 75.6%) attended all their RT appointments as scheduled without any unplanned breaks. 64 participants (24.4%) canceled or did not show for at least one scheduled appointment. Of these 64 participants, the distribution of the number of missed appointments was: 23 participants (35.9%) missed one appointment, 31 participants (48.4%) missed two appointments, and the remaining 33 participants (51.6%) missed between 3 and 41 appointments. Nonadherence was operationalized as missing three or more appointments in this study (n = 33).

Aim One: Demographic Characteristics

The sample consisted of 262 participants with a diagnosis of HNC who received RT at the CC. The majority of the patients were male (n=202, 77.1%) and the average age was 62.42 years (SD= 10.08) (See Table 2). The majority were white (n=242, 92.4%), married (n=184, 70.2%), and approximately half of the sample lived within 50 miles of the cancer center (n=134, 51.1%). Just under half of the participants (n=130, 49.6%) had a high school diploma or equivalent education, while 40.5% (n=106) reported graduating from college. Nearly half
Table 2.

Demographic characteristics of head and neck cancer dataset comparing groups based on adherence to radiation therapy appointment schedules

<table>
<thead>
<tr>
<th>Variable</th>
<th>All participants mean ± SD</th>
<th>Adherent: Yes mean ± SD</th>
<th>Adherent: No mean ± SD</th>
<th>Test Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>p-value</td>
</tr>
<tr>
<td>N = 262</td>
<td>n = 229 (87.4%)</td>
<td>n = 33 (12.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>62.42 ± 10.08</td>
<td>61.98 ± 9.96</td>
<td>65.52 ± 10.49</td>
<td>t = 1.894, df = 260</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>60 (22.9)</td>
<td>47 (20.5)</td>
<td>13 (39.4)</td>
<td>χ² = 4.797, df = 1*</td>
</tr>
<tr>
<td>Male</td>
<td>202 (77.1)</td>
<td>182 (79.5)</td>
<td>20 (60.6)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>242 (92.4)</td>
<td>212 (92.6)</td>
<td>30 (90.9)</td>
<td>χ² = 2.082, df = 4</td>
</tr>
<tr>
<td>Black</td>
<td>6 (2.3)</td>
<td>5 (2.2)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>3 (1.1)</td>
<td>3 (1.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Asian Indian</td>
<td>3 (1.1)</td>
<td>3 (1.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (3.1)</td>
<td>6 (2.6)</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Distance from Cancer Center</td>
<td></td>
<td></td>
<td></td>
<td>χ² = .000, df = 1</td>
</tr>
<tr>
<td>Less than 50 miles</td>
<td>134 (51.1)</td>
<td>117 (51.1)</td>
<td>17 (51.5)</td>
<td></td>
</tr>
<tr>
<td>More than 50 miles</td>
<td>128 (48.9)</td>
<td>112 (48.9)</td>
<td>16 (48.5)</td>
<td></td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
<td></td>
<td>χ² = 3.625, df = 1</td>
</tr>
<tr>
<td>Married</td>
<td>184 (70.2)</td>
<td>166 (72.5)</td>
<td>18 (54.5)</td>
<td></td>
</tr>
<tr>
<td>Not married</td>
<td>78 (29.8)</td>
<td>63 (27.5)</td>
<td>15 (45.5)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td>χ² = 4.518, df = 3</td>
</tr>
<tr>
<td>Less than HS</td>
<td>2 (.8)</td>
<td>2 (.9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>HS graduate/GED</td>
<td>130 (49.6)</td>
<td>108 (47.9)</td>
<td>22 (66.7)</td>
<td></td>
</tr>
<tr>
<td>College graduate</td>
<td>106 (40.5)</td>
<td>97 (42.4)</td>
<td>9 (27.3)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>24 (9.2)</td>
<td>22 (9.6)</td>
<td>2 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
<td>χ² = 2.451, df = 2</td>
</tr>
<tr>
<td>Never smoker</td>
<td>95 (36.3)</td>
<td>87 (38)</td>
<td>8 (24.2)</td>
<td></td>
</tr>
<tr>
<td>Previous smoker</td>
<td>130 (49.6)</td>
<td>110 (48)</td>
<td>20 (60.6)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>37 (14.1)</td>
<td>32 (14)</td>
<td>5 (15.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Note. *p < 0.05
(n=130, 49.6%) reported having been a smoker, 36.3% reported never smoking and 14.1% reported currently smoking cigarettes during treatment.

**Differences Between Groups**

Demographic characteristics were compared for adherent and nonadherent groups. The nonadherent group (n=33) was made up of a higher percentage of females (39.4%) compared to the adherent group (20.5%) ($\chi^2 = 4.797, p = .016$). There were no other statistically significant differences in adherence by demographic characteristics.

**Aim Two: Clinical Characteristics**

The participants’ stages of cancer ranged from Tumor-in-situ (Tis) to Tumor-Node-Metastasis (TNM) stage IV. The majority of the sample was diagnosed with Stages I-IV cancer; the largest number was Stage II (n=87, 33.2%), followed by Stage IV (n=59, 22.5%), Stage I (n=58, 22.1%), and Stage III (n=41 15.6%) (See Table 3). There were thirteen different tumor locations described by the treating physicians. The most common tumor location was the tongue (n=81, 30.9%) (See Table 3). Chemotherapy and radiation therapy were prescribed concurrently for 62.2% (n=163) of the sample. The average number of radiation therapy treatments prescribed by the physician was 31.86 (SD = 3.34).

Other clinical characteristics were examined that could have indicated the participant’s health status during treatment including inpatient admissions, outpatient intravenous (IV) fluid administration, percutaneous endoscopic gastronomy (PEG) feeding tube placement, and percentage of weight lost during RT. Inpatient admission to the CC was noted in 12.2% (n=32) of the sample, while a third of participants were given outpatient IV fluids (n=87, 33.2%). PEG feeding tubes were placed in one-fourth of the sample (n=66, 25.2%). The mean amount of weight lost during treatment was 5.64% (SD = 6.88) of body weight from their baseline weight.
Table 3.

Clinical characteristics of head and neck cancer dataset comparing groups based on adherence to radiation therapy appointment schedules

<table>
<thead>
<tr>
<th>Variable</th>
<th>All participants mean ± SD n (%)</th>
<th>Adherent: Yes mean ± SD n (%)</th>
<th>Adherent: No mean ± SD n (%)</th>
<th>Test Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of RT</td>
<td>31.86 ± 3.34 N = 262</td>
<td>31.92 ± 2.80 n = 229 (87.4%)</td>
<td>31.42 ± 5.92 n = 33 (12.6%)</td>
<td>t = .799, df = 260</td>
</tr>
<tr>
<td>Tumor Location</td>
<td></td>
<td></td>
<td></td>
<td>χ² = 14.165, df = 12</td>
</tr>
<tr>
<td>Palate</td>
<td>3 (1.1)</td>
<td>2 (.9)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>32 (12.2)</td>
<td>29 (12.6)</td>
<td>3 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>27 (10.3)</td>
<td>23 (10)</td>
<td>4 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>7 (2.7)</td>
<td>5 (2.2)</td>
<td>2 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Tongue</td>
<td>81 (30.9)</td>
<td>76 (33.2)</td>
<td>5 (15.2)</td>
<td></td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>6 (2.3)</td>
<td>4 (1.7)</td>
<td>2 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Gum</td>
<td>14 (5.3)</td>
<td>13 (5.7)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Lip</td>
<td>1 (.4)</td>
<td>1 (.4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mouth Floor</td>
<td>4 (1.5)</td>
<td>4 (1.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tonsil</td>
<td>68 (26.0)</td>
<td>57 (24.9)</td>
<td>11 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Salivary gland</td>
<td>9 (3.4)</td>
<td>8 (3.5)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Neck</td>
<td>5 (1.9)</td>
<td>4 (1.7)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Lymph node</td>
<td>5 (1.9)</td>
<td>3 (1.3)</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>TNM Stage</td>
<td></td>
<td></td>
<td></td>
<td>χ² = 5.364, df = 6</td>
</tr>
<tr>
<td>0</td>
<td>7 (2.7)</td>
<td>6 (2.6)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>58 (22.1)</td>
<td>53 (23.1)</td>
<td>5 (15.2)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>87 (33.2)</td>
<td>78 (34.1)</td>
<td>9 (27.3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>41 (15.6)</td>
<td>37 (16.2)</td>
<td>4 (12.1)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>59 (22.5)</td>
<td>48 (20.9)</td>
<td>11 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>9 (3.5)</td>
<td>5 (2.2)</td>
<td>2 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Concurrent Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td>χ² = 3.642, df = 1</td>
</tr>
<tr>
<td>Yes</td>
<td>163 (62.2)</td>
<td>137 (59.8)</td>
<td>26 (78.8)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>99 (37.8)</td>
<td>92 (40.2)</td>
<td>7 (21.2)</td>
<td></td>
</tr>
<tr>
<td>Inpatient Admission</td>
<td></td>
<td></td>
<td></td>
<td>χ² = 9.673, df = 1*</td>
</tr>
<tr>
<td>Yes</td>
<td>32 (12.2)</td>
<td>22 (9.6)</td>
<td>10 (30.3)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>230 (87.8)</td>
<td>207 (90.4)</td>
<td>23 (69.7)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3 Continued.

<table>
<thead>
<tr>
<th>Outpatient IV administration</th>
<th>$\chi^2$ = 4.801, df = 1*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>87 (33.2)</td>
</tr>
<tr>
<td>No</td>
<td>175 (66.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PEG Tube</th>
<th>$\chi^2$ = 1.869, df = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>66 (25.2)</td>
</tr>
<tr>
<td>No</td>
<td>196 (74.8)</td>
</tr>
</tbody>
</table>

| Weight Lost (%) | 5.64 ± 6.88 | 5.63 ± 7.081 | 5.7 ± 5.3 | $t = .051$, df = 260 |

Note. * $p < 0.05$

Abbreviations. RT, Radiation therapy, TNM, Tumor Node Metastasis Staging System, IV, intravenous, PEG, percutaneous endoscopic gastrostomy.

**Differences Between Groups**

Clinical characteristics were compared for adherent and nonadherent groups. The nonadherent group (n=33) was more likely to have inpatient admission(s) ($\chi^2 = 9.673$, p = .002) and outpatient IV administration during treatment ($\chi^2 = 4.801$, p = .028). There were no other statistically significant differences between the two groups’ clinical characteristics and adherence.

**Aim Three: Physical and Psychological Symptoms**

The means and standard deviations of the ESAS-r symptom scores are presented in Table 4. The scores are based on a 0-10 scale, in which 0 indicates no symptom at present and 10 is the worst possible symptom at the time of completing the instrument. The symptoms with the highest scores overall were tiredness (3.85, SD= 2.19), pain (3.61, SD= 2.19), and lack of appetite (3.55, SD= 2.38).

**Differences Between Groups**

The nonadherent group reported higher mean scores for every individual symptom as well as with the overall mean total of all scores. There were statistically significant differences
with the mean scores in: pain ($t = 2.943, p = .03$), tiredness ($t = 3.961, p < .001$), drowsiness ($t = 3.399, p < .01$), lack of appetite ($t = 4.021, p < .001$), shortness of breath ($t = 2.608, p < .05$), depression ($t = 2.864, p = .02$), anxiety ($t = 2.325, p = .02$), overall well-being ($t = 4.913, p < .001$), difficulty sleeping ($t = 3.058, p = .02$), and the total score ($t = 3.710, p < .001$).

Table 4.

Mean ESAS-r scores of head and neck cancer patients reported during radiation therapy regimen comparing groups based on adherence to radiation therapy appointment schedule

| Variable               | All participants | Adherent: Yes  
|                       | N = 262 | n = 229 (87.4%) | Adherent: No  
|                       | mean ± SD | mean ± SD | mean ± SD | Test Statistic |
|-----------------------|---------|-------------|------------|--------|----------------|
| Pain                  | 3.61 ± 2.19 | 3.46 ± 2.02 | 4.64 ± 2.95 | $t = 2.943^*$ |
| Tiredness             | 3.85 ± 2.19 | 3.65 ± 2.11 | 5.22 ± 2.25 | $t = 3.961^{***}$ |
| Drowsiness            | 2.61 ± 1.98 | 2.46 ± 1.86 | 3.69 ± 2.48 | $t = 3.399^*$ |
| Nausea                | 1.80 ± 1.97 | 1.74 ± 1.93 | 2.17 ± 2.23 | $t = 1.193260$ |
| Lack of Appetite      | 3.55 ± 2.38 | 3.34 ± 2.29 | 5.07 ± 2.46 | $t = 4.021^{***}$ |
| Shortness of Breath   | 1.03 ± 1.58 | 0.93 ± 1.48 | 1.69 ± 2.06 | $t = 2.608^*$ |
| Depression            | 1.57 ± 1.98 | 1.44 ± 1.88 | 2.48 ± 2.43 | $t = 2.864^*$ |
| Anxiety               | 1.87 ± 2.06 | 1.76 ± 1.97 | 2.64 ± 2.51 | $t = 2.325^*$ |
| Overall Well-being    | 2.75 ± 2.04 | 2.53 ± 1.93 | 4.32 ± 2.18 | $t = 4.913^{***}$ |
| Spiritual Well-being  | 1.10 ± 1.53 | 1.10 ± 1.55 | 1.09 ± 1.43 | $t = .038$ |
| Constipation          | 2.09 ± 1.87 | 2.13 ± 1.86 | 1.81 ± 1.95 | $t = .910$ |
| Difficulty Sleeping   | 2.72 ± 2.37 | 2.55 ± 2.22 | 3.88 ± 3.02 | $t = 3.058^*$ |
| Total Score           | 28.44 ± 17.33 | 26.97 ± 17.01 | 38.65 ± 16.25 | $t = 3.710^{***}$ |

Note. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$.
Abbreviations. ESAS-r, Edmonton System Assessment Scale-revised

The ESAS-r scores were also analyzed based on concurrent chemotherapy status to establish if concurrent chemoradiation was correlated with higher symptom burden as is suggested in the literature; however, the only significant finding was depression ($t=2.287, p = .024$). Patients not receiving concurrent chemotherapy ($n=99; 37.8\%$) reported a mean depression
score of 1.95, higher than the mean depression score of 1.36 reported from those receiving concurrent chemotherapy (n=162, 62.2%).

**Influence of Demographics, Clinical Characteristics, and Symptoms on Nonadherence**

Logistic regression models were fit to the data to assess the impact of demographic, clinical, and ESAS-r symptom scores on the likelihood that participants would be nonadherent to their RT schedules. After establishing the relationships by individual predictors, the final model contained ten predictors (age, biological sex, race, concurrent chemotherapy status, tumor location, inpatient admission, and the ESAS-r scores of tired, depression, spiritual well-being, and constipation). Sensitivity analyses were performed, and one outlier was excluded from the final regression model. The outlier was different from the rest of the sample because the participant missed 41 appointments, which is 20 more appointments than any other participant in the sample. The outlier’s spiritual well-being score was 5.40, more than two standard deviations from the mean spiritual well-being score of the sample (1.10, SD=1.53). With the outlier in the analysis, spiritual well-being was not a significant predictor in the model.

**Logistic Regression**

The full model containing all the predictors was statistically significant, $x^2 = 24.523$, N = 262, $df = 8$, $p = .002$. The model, as a whole, explained between 18.6% (Cox and Snell R squared) and 35.4% (Nagelkerke R squared) of the variance in adherence and correctly classified 90.4% of all cases.

After controlling for age, biological sex, and race, the significant predictors of nonadherence were tumor location, concurrent chemotherapy status, tiredness, depression, spiritual well-being, and constipation (See Table 5). The strongest predictor of nonadherence was concurrent chemotherapy status with an odds ratio of 4.894 (95% CI 1.330, 12.790).
This indicated that participants who were receiving chemotherapy and radiation treatments concurrently were almost five times more likely to miss more than two RT appointments than were those without concurrent chemoradiation. For every point positive difference in the ESAS-r tired and depression scores, the participants were 1.343 and 1.563 times more likely to be nonadherent, respectively. However, the tumor location tongue, spiritual well-being, and constipation demonstrated significant negative relationships. For every positive point difference in spiritual well-being and constipation, the patient was .643 and .684 less likely to be nonadherent, respectively. Participants being treated for tongue tumors, the most common tumor location in this dataset, were .197 less likely to be nonadherent.

Table 5.

*Logistic regression model of demographics, clinical characteristics, and ESAS-r symptoms on nonadherence*

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>Standard Error of B</th>
<th>Odds Ratio (Exp(B))</th>
<th>Lower CI (95% for Exp(B))</th>
<th>Upper CI (95% for Exp(B))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.042</td>
<td>.024</td>
<td>1.043</td>
<td>.995</td>
<td>1.092</td>
</tr>
<tr>
<td>Biological sex</td>
<td>-.604</td>
<td>.506</td>
<td>.547</td>
<td>.203</td>
<td>1.473</td>
</tr>
<tr>
<td>Race</td>
<td>-.558</td>
<td>.848</td>
<td>.572</td>
<td>.109</td>
<td>3.019</td>
</tr>
<tr>
<td>Concurrent Chemo</td>
<td>1.588</td>
<td>.587</td>
<td>4.894</td>
<td>1.548</td>
<td>15.466*</td>
</tr>
<tr>
<td>Tumor Location (Tongue)</td>
<td>-1.627</td>
<td>.612</td>
<td>.197</td>
<td>.059</td>
<td>.653*</td>
</tr>
<tr>
<td>Inpatient Admission</td>
<td>.598</td>
<td>.574</td>
<td>1.819</td>
<td>.591</td>
<td>5.598</td>
</tr>
<tr>
<td>Tired (ESAS-r)</td>
<td>.295</td>
<td>.124</td>
<td>1.343</td>
<td>1.053</td>
<td>1.712*</td>
</tr>
<tr>
<td>Depression (ESAS-r)</td>
<td>.446</td>
<td>.150</td>
<td>1.563</td>
<td>1.165</td>
<td>2.096**</td>
</tr>
<tr>
<td>Spiritual Well-being (ESAS-r)</td>
<td>-.442</td>
<td>.204</td>
<td>.643</td>
<td>.431</td>
<td>.959*</td>
</tr>
<tr>
<td>Constipation (ESAS-r)</td>
<td>-.380</td>
<td>.152</td>
<td>.684</td>
<td>.508</td>
<td>.921*</td>
</tr>
</tbody>
</table>

*Note. *p < 0.05, ** p < 0.005, *** p < 0.001.
Abbreviations: ESAS-r, Edmonton System Assessment Scale-revised*
Summary

12.6% (n = 33) of the sample missed more than two RT appointments during their treatment. Significant differences between groups based on adherence included sex, inpatient admission, outpatient IV administration, and mean ESAS-r scores of pain, tiredness, drowsiness, lack of appetite, shortness of breath, depression, anxiety, overall well-being, difficulty sleeping and the total score. The final logistic regression model found significant predictors of nonadherence to RT schedules associated with concurrent chemotherapy status, tumor location, and ESAS-r symptom scores of tiredness, depression, spiritual well-being, and constipation.
Chapter Five: Discussion, Implications and Conclusions

This final chapter of the dissertation includes a summary of significant findings, conclusions including limitations, as well as, implications for clinical practice and future research recommendations. The purpose of this study was to explore whether demographic characteristics, clinical characteristics, or physical and psychosocial symptoms were associated with nonadherence to radiation therapy (RT) treatment schedules among head and neck cancer (HNC) patients.

Nonadherence

Treatment nonadherence was broadly defined as an unplanned treatment break. Missed appointments are potentially harmful to the patient’s cancer treatment and outcomes (Bese et al., 2007), as well as burdensome on the system since the missed appointments are rescheduled at the end of the treatment regimen. This uses resources, such as the treatment machines and therapists, that are often operating at full capacity.

The results of this study demonstrated that nonadherence is a clinical problem. Slightly over 33% (n = 87; 33.2%) of participants missed at least one appointment, consistent with studies that have reported nonadherence between 20 – 57% in the HNC population in the US (Naghavi et al., 2016; Ohri et al., 2015). Naghavi et al. (2016) defined nonadherence as 45 days between the initiation and end of treatment, while Ohri et al. (2015) defined nonadherence as patients that missed two or more appointments. In this study, of patients that missed any appointments (n=87), 23 participants missed one appointment, 31 participants missed two appointments, and 33 participants missed three or more appointments. For the purpose of this
study, nonadherence was defined as patients who missed more than two appointments (n = 33) to focus on those who experienced the most difficulty in adhering to the treatment plan. It is not confirmed why participants missed appointments, but patients who missed one or two appointments may have been more likely to miss for the most common of nonmedical or logistic reasons (Guidry, Aday, Zhang, & Winn, 1997; Thomas et al., 2017), instead of systematic factors such as the ones described in the conceptual framework in Chapter One (World Health Organization, 2003). Future research is needed to explore the reasons patients report for missing appointments.

**Demographic Characteristics**

The only statistically significant difference in demographic characteristics between the nonadherent and adherent groups was biological sex. Females were more likely to be in the nonadherent group. To date, biological sex has not been associated with treatment nonadherence in other literature (Ohri et al., 2015). However, females with HNC have been reported to be more likely to be under-treated, have worse outcomes, and decline treatment plans overall (Dronkers et al., 2015; Park et al., 2018).

None of the demographic characteristics collected were independent predictors of nonadherence in this population, as this study explored in aim one. Other studies did not identify connections between RT nonadherence and age (Ohri et al., 2015), biological sex (Ohri et al., 2015), race (Naghavi et al., 2016; Ohri et al., 2015), or marital status (Naghavi et al., 2016). Previous studies have reported an association between distance traveled to the treatment site and nonadherence to RT in HNC patients (Cosway et al., 2017; Schwam et al., 2015). The present study did not identify a significant relationship between distance traveled to treatment and nonadherence.
Evidence found in the literature suggests that HNC patients who were estimated to have a high school education or greater were more likely to adhere to the timeline of treatments (Graboyes et al., 2017). This study did not find a statistically significant association between education level and nonadherence, but there were more patients with a college education in the adherent group (42.4% versus 27.3% of nonadherent patients). This finding may be explained by what is reported in the literature regarding patients with a college education and their likelihood of choosing an NCI-designated cancer center like the study site selected for the present study (Huang, Ma, Ngo, & Rhoads, 2014). Finally, the nonadherent group had a higher percentage of unmarried patients than the adherent group, which could suggest that the adherent group was more likely to have a consistent support system, but the patient’s level of support is not known from the data collected in this study.

Further research is needed to assess if these demographic characteristics, and factors such as education and level of support influence nonadherence in the HNC population. In addition, the assessment of other factors related to the social and economic dimensions of nonadherence (Chapter One), such as living conditions, transportation barriers, and how the patient defines support could be explored (World Health Organization, 2003).

**Clinical Characteristics**

Aim two explored if clinical characteristics were associated with nonadherence to RT schedules among HNC patients. Clinical characteristics are condition and therapy-related factors from the Five Dimensions of Adherence (World Health Organization, 2003).

The nonadherent group was more likely to be admitted to the CC for an inpatient stay and also to receive outpatient intravenous fluid administration during treatment than the adherent group. This is an expected finding, as patients with more treatment-related side effects or
complications often require higher priority medical interventions that may delay their scheduled RT treatments.

This study found that concurrent chemotherapy status and tumor location were significant predictors of nonadherence. Participants who were receiving chemotherapy and radiation therapy concurrently were nearly five times more likely to be nonadherent. Concurrent chemotherapy was received by 78.8% (n = 26) of the nonadherent group, which was a higher percentage than expected, but treatment recommendations may have been updated since previous studies, or the population at this site may require higher levels of care. One study in the US reported 58% of HNC patients received concurrent chemotherapy and radiation, while two studies in India reported 71% and 66% of HNC patients in India on this treatment regimen (Rangarajan & Jayaraman, 2017; Sharma et al., 2016). Only one of these studies also examined nonadherence to RT schedules, and also found a significant association with concurrent chemotherapy (Sharma et al., 2016). Rosenthal et al. (2014) suggested HNC patients who received concurrent chemoradiation experienced more symptom burden, however, in this study, findings were not similar. Information related to symptoms experienced by patients was restricted to what the patients reported in the ESAS-r form, excluding other symptoms such as mucositis that have been associated with nonadherence (Ferreira et al., 2016).

Tumor location was also found to be a predictor of nonadherence. Patients with tongue tumors, the most common treatment site in this study (30.9%, n = 81), were .197 less likely to be nonadherent. Future research may inform if this subgroup is experiencing fewer symptoms, has a different treatment plan, or perceives treatment importance differently than other groups. These factors may influence their motivation or ability to attend appointments better than patients with cancer at other treatment sites.
Physical and Psychological Symptoms

Aim three explored if physical or psychological symptoms were associated with nonadherence to RT schedules in the HNC population. Symptoms can be condition or therapy-related (World Health Organization, 2003.) The ESAS-r instrument used in this study to measure symptoms that the patient was experiencing (Johnstone et al., 2017; Chang et al., 2000), indicated that tiredness, depression, spiritual well-being, and constipation were significant predictors of nonadherence.

When comparing scores between groups, the nonadherent group had statistically significant higher scores for every one of the 12 ESAS-r symptoms except for nausea, spiritual well-being, and constipation. This indicates that the nonadherent group consistently reported a higher burden of symptoms; including pain, tiredness, drowsiness, difficulty sleeping, shortness of breath, depression, anxiety, lack of appetite, and overall well-being. The total ESAS scores were significantly different between groups as well; the nonadherent group’s mean total score was nearly 12 points higher (38.65 vs. 26.97). The total ESAS-r score used independently may not be of much clinical usefulness because targeted interventions for specific symptoms would be indicated. Clinicians may look at the total ESAS-r score to assess the cumulative effect of treatment in each patient to best manage the most bothersome symptoms.

Symptoms that predicted nonadherence in the regression model were tiredness and depression. Though some studies reported that fatigue was a significant problem in this population (Badr et al., 2014; Poirier, 2011; Sawada et al., 2012), this is the first known study to examine if fatigue-related factors were associated with RT treatment nonadherence. The mean tiredness score was the highest of the symptoms at 3.85 out of 10 (where 0 was no symptom and 10 was the worst possible). The mean score for depression was 1.57. Each one-point positive
difference in these scores (tiredness OR 1.343, 95% CI 1.053, 1.721; depression OR 1.563, 95% CI 1.165, 2.096) increased the chances that patients did not attend their appointments. These findings are consistent with studies that had reported increased depression scores were related to worse completion rates of therapy in HNC patients (Barber et al., 2015; Chen et al., 2018).

The results also suggest that spiritual well-being is protective against nonadherence. Spiritual well-being is a patient-related factor that nurses can help patients explore and improve through nursing intervention and referrals to other disciplines such as social work and chaplains (World Health Organization, 2003). No other studies are known to have examined the relationship between spiritual well-being and nonadherence in this population, but some studies have indicated that patients who report relying on faith or religiosity during treatment helps them cope with their emotions and may lessen the presence of other symptoms such as fatigue (Jagannathan & Juvva, 2016; Lewis, Salins, Rao, & Kadam, 2014).

Constipation also had a significant negative relationship with nonadherence. There is not a known reason at this time for why constipation and nonadherence would have this relationship, although constipation is a side effect of certain medications such as pain medications, so perhaps patients with constipation had other symptoms like their pain controlled better and therefore were more likely to attend. Further research is indicated to explore these findings more.

While there are no criteria for a cut-off value on the ESAS-r, a systematic review of distress assessment instruments in cancer patients found that most tools used a cut-off score of 4 or 5 to indicate distress and further intervention by the healthcare team (Vodermaier, Linden, & Siu, 2009). The CC where this study took place uses a threshold of a score of 7 or higher on a single symptom to intervene, because of the limited availability of some resources such as referrals to supportive care and behavioral medicine providers. Nearly all of the mean scores of
symptoms in this study were less than 4, for both adherent and nonadherent groups. This suggests that some symptoms may affect treatment adherence even at lower numbers and may need to be intervened upon earlier. Providers may consider reviewing screenings with patients individually to determine what symptoms are or may become a barrier and interrupt treatment. Clinicians also may need to look for trends in total scores as well since depression and tiredness became stronger predictors of nonadherence as each score increased.

**Strengths**

The strengths of this study include the data collection method, specifically that each patient’s treatment schedule was reviewed, leading to a more accurate classification of adherence. Other retrospective studies have based adherence status by looking at the length of treatment in calendar days only (Naghavi et al., 2016). This does not account for patients missing appointments for reasons not related to the Five Dimensions of Adherence (e.g. machine malfunctions, clinic closures, or doctor prescribed breaks) (World Health Organization, 2003). This study included the review of how each appointment was coded and only classified those as nonadherent when the appointment was canceled by the participant or the participant was a no-show. The sample also encompassed 12 consecutive months of eligible patients, helping to control for differences in seasons or treatment protocols.

**Limitations**

The design was retrospective, therefore limiting the investigator to the information already present in the electronic medical record (EMR). As a result, there was no opportunity for confirmation of what happened that led to the participant not attending. In addition, other information that could be of value but was not available include the participant’s support system, reasons for inpatient admissions and IV fluid administration, baseline psychosocial co-
morbidities (e.g., depression and anxiety), and past experiences with RT or cancer treatment. The instrument was based on self-reporting on an electronic device. Limitations with self-reporting include the validity and accuracy of the data (Polit & Beck, 2017). Many symptoms are solely subjective reports, but in the future objective measures of some symptoms such as physician documentation on mucositis, could be incorporated as well.

Data associated with this study was collected from a large, academic, National Cancer Institute-designated Cancer Center in the southeast region of the United States. These findings may not be generalized to patients with different cancers, in different geographic regions or different types of cancer care settings.

The instrument used in this study, the ESAS-r, was limited to reporting predefined symptoms, restricting the ability to obtain information about other symptoms directly related to HNC with the potential to impact adherence (mucositis, xerostomia, and dysphagia). The ESAS-r has been validated in outpatient cancer populations (Chang et al., 2000), however, there are other instruments specific to HNC such as the Functional Assessment of Cancer Therapy Head and Neck (FACT-H&N) that may be more effective in assessing the symptom burden of this population (Webster, Cella, & Yost, 2003).

**Implications for Practice**

The American College of Surgeons Commission on Cancer (2020) recommends that the assessment of symptoms experienced by cancer patients undergoing treatment should be regularly included in practice. This study supports the recommendation by illustrating that symptoms may be predictors of nonadherence to their cancer treatment and therefore can affect patient outcomes. Nurses can use the information that they are already collecting in practice to screen for patients at risk for nonadherence and provide early intervention and education.
difference in the ESAS-r scores between the two groups suggested that patients who miss treatments report higher symptom burden. Considering that the total score of the ESAS-r was much higher in the nonadherent group, nurses may need to consider that several symptoms present at one time, even at a level below a typical screening threshold, may be cumulative and become a barrier for the patient to attend treatment. Results of this study suggested that tiredness and depression predict patients were more likely to miss more than two of their RT appointments, and as the scores increase, so does the chance of becoming nonadherent.

Nurses could use findings of this study to recognize other risk factors for nonadherence, including concurrent chemotherapy and radiation regimens and tumor location. Providing education about the side effects of chemotherapy and radiation treatments and intervening early on symptoms may be beneficial. Spiritual well-being was a protective factor, so interested patients may benefit from early referrals to social work or chaplain services to assist the patient with connecting to their preferred spiritual practices.

Implications for Future Research

The findings of this study support the need for future research. Prospective studies are indicated to further investigate if symptom burden is a factor in patients’ ability or desire to attend treatments. A prospective design will provide the opportunity for the investigator to make contact with participants and gain valuable insight on their barriers to attending treatment appointments and expand the patient population to different types of cancer treatment sites and geographic locations. Prospective design will also provide the opportunity to explore variables more closely related to the symptom burden in this specific cancer population, including pain at the tumor location, mucositis, xerostomia, dysphagia, and communication difficulties, using an instrument designed specifically for the HNC population (FACIT, 2010). The relationships
among nonadherence and depression, tiredness, spiritual well-being, and constipation could be investigated further by using additional validated instruments for these concepts.

Mixed methods would be useful to follow the patients through treatment and interview patients to gather information on what motivates them or is a barrier for them to attend their appointments as scheduled. While quantitative measures could be used to assess patient characteristics and symptoms, qualitative semi-structured interviews could be used to get more accurate and diverse views on reasons HNC patients are unable to attend treatment appointments. The contents of the interviews could be used to assist with the interpretation and clarification of quantitative results, presenting a stronger, enriched study (Doorenbos, 2014).

Future research could also discern if there are any systematic patterns of nonadherence among this population, such as missing particular times of day or days of the week. Significant findings may indicate the future development of a screening tool and interventions to improve adherence in this population.

**Conclusion**

The purpose of this retrospective study was to examine whether demographic characteristics, clinical characteristics, or physical and psychological symptoms were related to treatment nonadherence among HNC patients. Nonadherent patients were more likely to be female, experience inpatient admissions, and receive outpatient IV fluids during treatment. Nonadherent patients reported higher mean symptom scores on 9 out of 12 symptoms measured during treatment, illustrating that this group had a higher symptom burden. The regression model showed that independent predictor of treatment nonadherence were concurrent chemotherapy and radiation treatment regimens, tumor location, and symptom scores of tiredness, depression, spiritual well-being, and constipation. The results build on existing literature and add an
important dimension of modifiable factors that may affect the patients’ abilities to attend their treatment appointments. The results support routine distress screening to identify patients at risk and providing early education and interventions to improve symptom burden, treatment adherence, and patient outcomes in the HNC population.
References


Retrieved from ncss.com/software/pass


https://www.who.int/chp/knowledge/publications/adherence_full_report.pdf
Appendix 1:

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11. **Entire Agreement, Amendment.** This Agreement is the entire agreement between you and WHO with respect to its subject matter. WHO is not bound by any additional terms that may appear in any communication from you. This Agreement may only be amended by mutual written agreement of you and WHO.

12. **Headings.** Paragraph headings in this Agreement are for reference only.

13. **Dispute resolution.** Any dispute relating to the interpretation or application of this Agreement shall, unless amicably settled, be subject to conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the parties or, in the absence of agreement, with the rules of arbitration of the International Chamber of Commerce. The parties shall accept the arbitral award as final.

14. **Privileges and immunities.** Nothing in or relating to this Agreement shall be deemed a waiver of any of the privileges and immunities enjoyed by WHO under national or international law and/or as submitting WHO to any national court jurisdiction.
Appendix 2:

IRB Approval

10/30/2019

Jennifer Miller
College of Nursing
Tampa, FL 34612

RE: Exempt Certification
IRB#: Pro00041176
Title: Symptoms and Characteristics Associated with Non-Adherence to Radiation Treatment Schedules among Head and Neck Cancer Patients

Dear Ms. Miller:

On 10/29/2019, the Institutional Review Board (IRB) determined that your research meets criteria for exemption from the federal regulations as outlined by 45 CFR 46.104(d):

(4) Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:
(i) The identifiable private information or identifiable biospecimens are publicly available, (ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects; (iii) The research involves only information collection and analysis involving the investigator’s use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of “health care operations” or “research” as those terms are defined at 45 CFR 164.501 or for “public health activities and purposes” as described under 45 CFR 164.512(b); or (iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.
Your study qualifies for a waiver of the requirement for signed authorization as outlined in the HIPAA Privacy Rule regulations at 45 CFR 164.512(i), which states that an IRB may approve a waiver or alteration of the authorization requirement provided that the following criteria are met: (1) the PHI use or disclosure involves no more than a minimal risk to the privacy of individuals; (2) the research could not practicably be conducted without the requested waiver or alteration; and (3) the research could not practicably be conducted without access to and use of the PHI. A waiver of HIPAA Authorization is granted for this retrospective chart review of adult patients diagnosed with HNC who received curative external beam radiation therapy (EBRT) as their first course of treatment at Moffitt Cancer Center within the date range in the protocol. This waiver allows the study team and/or its honest broker to obtain PHI of patients in this cohort from the Moffitt medical record systems (Cerner/PowerChart and Mosaïq).

The date range in your protocol may be extended and the number of records reviewed may be increased without submitting a new IRB application, so long as your protocol is revised accordingly and complies with the minimum necessary requirement set forth in the Privacy Rule. Other minor changes, such as addition of a data variable, can also be made without resubmission. As per USF HRPP Policy, changes to study design (e.g. changes in inclusion/exclusion criteria, change from retrospective to prospective data collection, changes in study sites, etc.) require a new IRB application. Please keep all protocol versions used throughout the life of the study.

As the principal investigator for this study, it is your responsibility to ensure that this research is conducted as outlined in your application and consistent with the ethical principles outlined in the Belmont Report and with USF HRPP policies and procedures.

Please note, as per USF HRPP Policy, once the exempt determination is made, the application is closed in ARC. This does not limit your ability to conduct the research. Any proposed or anticipated change to the study design that was previously declared exempt from IRB oversight must be submitted to the IRB as a new study prior to initiation of the change. However, administrative changes, including changes in research personnel, do not warrant an Amendment or new application.

We appreciate your dedication to the ethical conduct of human subjects research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,

V. Jorgensen, MD

E. Verena Jorgensen, M.D., Chairperson
USF Institutional Review Board
Appendix 3:

Study Site Approval

November 21, 2019

Sue Hartranft, PhD
Moffitt Cancer Center
12902 Magnolia Drive
Tampa, FL 33612

RE: MCC 20276: “Symptoms and Characteristics Associated with Non-Adherence to Radiation Treatment Schedules among Head and Neck Cancer Patients”

Dear Dr. Hartranft,

The Scientific Review Committee (SRC) has reviewed your research protocol amendment version 3 dated 10/16/2019 and determined it to be exempt from SRC review per Institutional policy. However, the research is subject to the review and approval of an Institutional Review Board (IRB) and must satisfy institutional operational and financial review requirements.

It is your responsibility to ensure that all Moffitt staff (Nursing, Pharmacy, Data Management, etc.) are informed and aware of the project. The SRC encourages the use of an in-service for those projects which are complex or require special attention. All changes made to protocols must be submitted to the PRMS office PRMS@moffitt.org. Changes made to the protocol document require SRC review and approval. Minor changes (i.e., changes to personnel, non-scientific changes, changes that do not affect patient participation) will be expedited through the SRC review process.

It is the responsibility of the Principal Investigator to follow through with all requirements for submission to the IRB. All IRB approvals are required to be documented in Oncore, and all associated regulatory documentation (IRB approval letters, consent forms, etc.) are to be saved in the appropriate study folder in the Florence e-BINDERS application.

Oncore is the Cancer Center’s mechanism for submission and review of materials requiring SRC and Protocol Monitoring (PMC) review. If you need access to Oncore, please submit an iStar request.

Sincerely,

[Signature]

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