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Changes and predictors of radiation-induced oral mucositis in patients with oral cavity cancer during active treatment

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A B S T R A C T

Purpose: Radiation-induced oral mucositis (OM) is the most debilitating side effect of radiation treatment in oral cavity cancer. The purpose of the study was to investigate change of prevalence of severe OM, OM-related symptoms, and predictors in oral cavity cancer patients during active treatment.
Methods and sample: Longitudinal study design with repeated measures was used. Patients with oral cavity cancer were recruited from a head and neck outpatient radiation department at a major medical center in Taiwan. Patients' OM-related symptoms were measured at three time points. Patients' oral mucosa was assessed at nine time points. Generalized estimating equations (GEE) were used to analyze the predictive factors of prevalence of severe OM and OM-related symptoms.
Results: Patients reported highest prevalence of severe OM at T5 (5 weeks after beginning RT) and T6 (6 weeks after beginning radiation therapy, RT), with the combined chemotherapy and RT (CCRT) patients reporting a higher prevalence than those receiving RT alone. The peak of OM-related symptoms was at T8 (8 week after beginning RT), with primary symptoms of mouth pain, mouth dryness, eating difficulties, swallowing difficulties, and taste change. Patients with CCRT, a higher cumulative radiation dose, smoking, and lower body mass index (BMI) were at high risk to develop severe OM. OM-related symptoms were predicted by type of treatment, cumulative radiation dose, and smoking.
Conclusions: Patients with oral cavity cancer suffer from OM and OM-related symptoms during aggressive RT or CCRT. Patient-specific oral care and emotional support are needed to relieve distressful OM-related symptoms during active treatment.

Introduction

In 2012, the incidence rate of oral cavity cancer was 300 per 1000 worldwide (Ferlay et al., 2013). Oral cavity cancer is associated with a high prevalence of cancer risk factors (betel nut chewing, smoking, and drinking) (International Agency for Research on Cancer, 2004; Ko et al., 1995). Approximately 6300 cases of oral cavity cancer were diagnosed in Taiwan during 2010, with many patients diagnosed with Stage III or IV disease (Taiwan cancer registry, 2010). The evidence suggests that radical excision and radiation therapy (RT) and surgery with concurrent chemo-radiation therapy (CCRT) are the most important modalities for successful advanced oral cavity cancer treatment (Shah and Gil, 2009). Radiation-induced oral mucositis (OM) is the most debilitating side effect of radiation treatment in oral cavity cancer.

Radiation-induced oral mucositis (OM) is one of the most severe morbidities in patients with oral cavity cancer receiving RT or CCRT and may adversely affect vital oral functions (Chen et al., 2010). OM refers to inflammation of the oral mucosa due to radiation in head and neck cancer patients, and is characterized by atrophy of squamous epithelial tissue, vascular damage, and evidence of concentrated inflammatory infiltrate (Peterson et al., 2011). Radiation-

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induced oral mucositis begins at cumulative doses of 15 Gy (after around 10 days) and severity at 30 Gy, lasts for weeks or even months (Raber-Durlacher et al., 2010). More than 60% of cancer patients continue to experience severe OM during aggressive RT or CCRT to the head and neck region (Airoldi et al., 2004; Bernier et al., 2004; Cooper et al., 2004). The presence of OM has a significant impact on vital oral function, including the processes of eating, drinking, and speaking resulting in malnutrition, dehydration, treatment interruptions, which may create an inability to cope with the disease (Scully et al., 2003; Putwatana et al., 2009).

Mucositis is a five-phase process: (1) initiation, (2) upregulation and message generation, (3) signaling and amplification, (4) ulceration, and (5) healing (Sonis, 2004). OM may develop at any time from 2 days to 3 weeks after initiation of RT and improves within 2–4 weeks after completion of RT (Cooper, 1994). Epstein et al. (2007) found that head and neck cancer patients reported mouth and throat soreness across radiation therapy, peaking at week 6 after treatment initiation, with a corresponding decline in oral function (eating, swallowing, drinking, and talking). In a study of 52 patients in Ireland receiving a chemoradiation regimen for head and neck squamous cell carcinoma, Grades 3 and 4 oral mucositis were reported by 22 (43.3%) and 6 patients (12%), respectively (Osman et al., 2013). Mitsudo et al. (2014) surveyed 112 advanced oral cancer patients treated with retrograde superselective intra-arterial chemotherapy and daily concurrent radiotherapy and found Grade 3 or 4 toxicities in patients that included mucositis in 92.0%, neutropenia in 30.4%, dermatitis in 28.6%, anemia in 26.8%, and thrombocytopenia in 7.1% correlating with dysphagia, nausea, vomiting, and fever related symptoms.

Numerous studies have reported increased levels of OM-related symptoms in head and neck cancer patients during active treatment associated with oral vital dysfunction (e.g., pain, difficulty swallowing, difficulty drinking, difficulty talking, change in taste, xerostomia, thick secretions, and mucosal sensitivity) (Ganzer et al., 2013; Murphy et al., 2009) and generalized problems (e.g., fatigue, poor oral intake, and weight loss) (Chen et al., 2010; Ganzer et al., 2013) with greater oral mucositis symptoms more often associated with higher depression (Chen et al., 2010; Haddad, 2006).

Studies showed that treatment-related factors during radiation therapy, including higher cumulative dose of RT and concurrent use of chemotherapy, can increase the risk of developing oral mucositis (Machtay et al., 2012; Vera-Llonch et al., 2006; Kazemian et al., 2009). Most studies indicate that smoking status (Wuketich et al., 2012), low BMI (Meyerhardt et al., 2004; Rose-Ped et al., 2002), and high levels of depression or emotional distress (Chen et al., 2010; Rose-Ped et al., 2002) may coexist with OM.

Longitudinal studies are needed to demonstrate the trajectory of the prevalence of OM-related symptoms during active treatment. Understanding the relationships between radiation-induced OM and disease/treatment-related variables can assist healthcare providers in developing strategies to palliate symptoms. Purposes of the study were to investigate the longitudinal changes in the prevalence of severe OM and OM-related symptoms and to identify factors that contribute to predicting the development of OM in oral cavity cancer patients during active treatment.

Methods

Design

The study was a longitudinal survey of radiation-induced OM using repeated measures.

Participants and setting

A convenience sampling method was used to recruit 77 oral cavity cancer patients between August 2011 between March 2013 who were being treated in the head and neck outpatient radiation department of a medical center in northern Taiwan. Inclusion criteria were as follows: (1) 20 years or older; (2) definitive histopathological diagnosis of oral cavity squamous cell carcinoma (OSCC); and (3) receiving active post-operative therapy with radiation therapy or concurrent chemoradiotherapy. Participants received active post-operative therapy within 6–8 weeks CCRT, a dose of 180–200 cGy RT per fraction per day, administered 5 days per week for a total dose of approximately 5400–8000 cGy. Patients underwent concomitant chemotherapy with cisplatin-based regimens (National Comprehensive Cancer Network, 2012). Patients visited the outpatient clinic weekly during active treatment and saw their own physician at that time.

Ethical considerations

Ethics approval for the study was obtained from Chang Gung Memorial Hospital Human Research Ethics Committees and all participants signed consent forms after full explanation of research purposes.

Data collection

After receiving consent to participate, a well-trained research nurse would ask each subject to enter the waiting room where the research nurse would collect data. Each research nurse was a full-time research nurse with clinical cancer experience and 16 h of research training (including training in ethical concerns, methods of approaching eligible subjects, interviewing techniques, and radiation-induced OM issues [mechanisms of mucositis, relevant techniques, procedures for administration and scoring of mucositis measurements and study questionnaires, and patient education]). The principal investigator of this study trained each research nurse.

Subjects were interviewed using structured questionnaires (subjective measures) for OM-related symptoms followed by physical examination of the oral mucosa (objective measures). This sequence of assessment may reduce potential interference of oral mucosa assessment with patients' answers to the questions. Patients were interviewed using questionnaires at three time points: baseline (before RT) and then 4 and 8 weeks after beginning RT (T0, T4, and T8, respectively). Patients' oral mucosa were assessed at nine time points: baseline (before RT) and at 1, 2, 3, 4, 5, 6, 7, and 8 weeks after beginning RT (T0, T1, T2, T3, T4, T5, T6, T7, and T8, respectively). All subjects were interviewed before they visited the physician or received treatment.

A total of 102 eligible subjects were invited to participate in the study with 77 participants completing all follow-up. Of the 25 patients not completing the study, 6 patients were transferred to other hospitals for future treatment after baseline assessment. The loss rate was 5.88%. At T4 (4 weeks after beginning RT), 3 patients refused to continue treatment, 1 patient lacked interest, 2 patients died, and 1 patient was readmitted to the hospital. The loss rate was 6.86%. At T6 (6 weeks after beginning RT), 3 patients refused to continue treatment, 2 patients lacked interest, 3 patients died, and 1 patient was readmitted to the hospital. The loss rate was 8.82%. At T7 (7 weeks after beginning RT), 1 patient lacked interest, 1 patient died, and 1 patient was readmitted to the hospital. The loss rate was 2.94%.

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