ORIGINAL ARTICLE

Oral Health Status and Function of Cancer Patients Undergoing Chemotherapy and/or Radiotherapy: Findings From Two Tertiary Hospitals in Malaysia

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ABSTRACT

Introduction: Cancer treatments are commonly associated with painful oral complications that may influence patients' prognosis. This study aimed to determine the oral health status and function of cancer patients undergoing chemotherapy (CTx) and/or head and neck radiotherapy (H&N RT) and factors associated with presence of oral mucositis (OM). **Materials and method:** This cross-sectional study included hospitalized cancer patient undergoing CTx and/or H&N RT at two tertiary hospitals in Malaysia, excluding those in isolation. Structured proforma and the Oral Assessment Guide (OAG) were used to determine patients' oral health status and function. Factors associated with OM were determined using logistic regression analysis. **Results**: Out of 177 patients, 25.4% reported experiencing oral complications, with xerostomia being the most common (66.7%), followed by mouth ulcers (35.6%), dysgeusia (15.6%), and lip numbness (15.6%). The most affected component of the OAG was the teeth or dentures, with 71.8% of patients showing issues with localized (39.0%) and generalized (32.8%) plaque accumulation. Based on the OAG score, about half of patients (58.8%) had OM. Pediatric cancer patients were 5.60 times more likely to have OM than adult patients ($p < 0.001$).**Conclusion**: OM affected approximately half of the cancer patients undergoing CTx and/or H&N RT, with pediatric patients being significantly more susceptible. Additionally, around 25% of patients reported experiencing at least one oral complication during the course of their treatment, with xerostomia being the most common. These findings highlight the importance of implementing oral care regimens throughout cancer therapy to help prevent or reduce the frequency and severity of oral complications.
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INTRODUCTION

According to the World Health Organization (WHO), there is a rising trend in cancer diagnoses, making cancer the second leading cause of death worldwide in 2020 (1). In Malaysia, the total number of cancer cases has risen drastically from 24,110 cases in 2016 to 43,837 in 2018. This figure is anticipated to treble by 2040 (2). Cancer can now be treated or even cured entirely without surgery owing to advancements in radiotherapy (RT) and chemotherapy (CTx) technology (3). RT modality is based upon the use of high-energy particles or waves such x-rays, gamma rays, electron beams, or protons, given via internal or external beam radiation (4). Meanwhile, CTx involves administration of standardized chemotherapeutic drugs given either intravenously or orally (5,6). Both treatments are very effective in damaging rapidly dividing cancer cells (5,7) and are also used as palliative treatments to relieve cancer symptoms (5).

Chemotherapeutic drugs are specifically designed to have an action on rapidly dividing malignant cells thus, the other normal tissues in patients' body that have a high turn-over rate such as bone marrow, intestinal

mucosa, oral mucosa, hair follicles, and gonads also received the effect of CTx (5). Oral mucositis (OM), intraoral infections, dry mouth (xerostomia), intraoral bleeding and altered taste (dysgeusia) are well reported adverse effects of CTx. In addition, patients with hematologic malignancy receiving intensive or high-dose CTx may be at higher risk of infections secondary to myelosuppression and immunosuppressive condition (3,5,7,8).

Direct radiation to head and neck region (H&N) can damage the glandular cells of salivary glands resulting in changes in the quantity and quality of salivary, making the irradiated patients more susceptible to xerostomia, a subjective feeling of dry mouth due to hyposalivation (9). Xerostomia can impair oral functions like tasting, chewing, swallowing and speaking, and increase the risk of periodontal disease, dental caries and oral infections (4). RT to the H&N region can also damage the mucosal layer of the oral cavity by decreasing cell renewal in the epithelium, resulting in mucosal atrophy, ulceration and OM, with oral symptoms like pain and burning sensation (7,8). Moreover, ionizing radiation is capable of causing irreversible damages to the facial bone and the microvascular system leading to formation of osteonecrosis of the jaw bone, trismus due to temporomandibular joint dysfunction and muscle fibrosis, facial growth disturbance, and tooth anomaly (9–11).

Oral complications related to cancer therapies can cause pain and discomfort, impair oral functions like eating, swallowing and speaking, negatively affect patients' quality of life, alter daily dietary pattern and nutritional intake, disturb the planned cancer treatment, give rise to life-threatening conditions, and increase the overall healthcare and treatment expenses (12–14). Several recent studies reporting the prevalence of CTx- and/or H&N RT-induced oral complications in the pediatric and adult population have been published (8,11,15), however, there is still a scarcity of literature documenting the oral health status and functions of hospitalized cancer patients undergoing cancer treatment in Malaysia. Thus, this present study aimed to assess the oral health status and functions of hospitalized children and adult cancer patients undergoing CTx and/or H&N RT, and factors associated with presence of OM among the patients.

MATERIALS AND METHOD

This cross-sectional study was undertaken at two tertiary hospitals in Kelantan, a state located in the north-eastern corner of the Peninsula Malaysia. The hospitals, Hospital Pakar Universiti Sains Malaysia (HPUSM) and Hospital Raja Perempuan Zainab II (HRPZ II), are in the district of Kota Bharu, with HPUSM being a teaching hospital. Both hospitals serve as the primary referral centers for cancer patients in the state of Kelantan, offering comprehensive medical care. Additionally, HPUSM frequently received referrals from Peninsular Malaysia's east coast state, especially for cancer patients undergoing radiation therapy.

Cancer patients, regardless of the type of malignancy, admitted to HPUSM and HRPZ II for CTx and/or H&N RT were eligible to participate in this study if they fulfil the following inclusion criteria: 1) admitted for curative or neoadjuvant/adjuvant CTx and/ or H&N RT, 2) admitted for management of side effects of CTx and/ or H&N RT received, and 3) able to give full cooperation for oral examination especially for pediatric patients. Those who were critically ill such as having severe lethargy and/or severe pain and requiring isolation during time of study were excluded.

The sample size was calculated using the single proportion formula. The proportion was estimated at 35.5% which was the prevalence of chemotherapy-induced xerostomia among pediatric cancer patients in India (16). At a precision of 0.08 a sample size of 137 was yielded with probability (power) 0.8. Anticipating a 30% non-response rate, a final sample size of 178 was decided. This study was approved by the Universiti Sains Malaysia Human Research Ethics Committee (USM/JEPeM/20040241) and the Ministry of Health Medical Research Ethics Committee (NMRR-20-898-53960 (IIR)).

The Oral Assessment Guide (OAG) is a standardized clinical tool developed by Eilers et al. (1988) was used to assess the oral health status and function of the patients. The OAG was originally developed in English and proven to be valid, feasible, and sensitive to changes in oral cavity (17). Eight components were examined: voice, swallowing ability, lips, tongue, saliva, mucous membrane, gingiva, and teeth or denture hygiene. Each component was graded as 1 (normal), 2 (mild to moderate change), or 3 (moderate to severe change). An OAG score of 8 to 9 indicates normal oral status, score 10 and above indicates OM with functional disturbance (18). Additionally, a structured proforma was used to collect information on sex, age, ethnic group, cancer type, current therapy received, reason for admission, dental referral prior to cancer therapy as well as self-reported experience of oral complications related to previous or current CTx and/or H&N RT.

Data collection was conducted from end of February to May 2021. After eligibility was established, a convenience sample strategy was used in this study, which was based on the patients' accessibility and availability in the designated cancer wards for both hospitals. The eligible patients were informed of the importance, objectives, and procedures involved in this study. Written informed consent was obtained from all adult patients and parents or legal guardian of pediatric patients who agreed to participate.

All oral examinations were conducted by the first author,

who is a qualified, registered dentist with over ten years of clinical experience, including assessing and treating referred cancer patients for dental clearance prior to commencement for planned cancer treatment by the oncology team. The clinical oral examinations were done using a disposable mouth mirror during daytime under bright light with patients lying supine on his or her back or sitting on the hospital bed. The oral cavity of patients was examined carefully in a sequential pattern from the outside (to evaluate oral health function, namely swallowing and talking) to the inside (to evaluate oral health status, namely lips, tongue, saliva, mucous membrane, gingiva, and teeth or denture hygiene).

Data were entered, cleaned, and analyzed using IBM SPSS software version 27.0. Descriptive statistics in the form of mean and standard deviation (SD) were used for continuous numerical variables and frequency and percentage (%) for categorical variables. Factors associated with OM with functional disturbances were determined at univariable level and multivariable level using simple and multiple logistic regression analyses, respectively. For this analysis, a patient with cumulative OAG score of 10 and above was considered as having OM with functional disturbances (18). The following independent variables were tested: age, sex, cancer type, current therapy, and dental referral prior to cancer therapy. In multiple logistic regression analysis, variables for inclusion in the model were selected using forward and stepwise methods. The significance level was set at 0.05.

RESULTS

A total of 177 cancer patients participated in this study, 112 from HPUSM and 65 from HRPZ II. The sociodemographic characteristics of patients are shown in Table I. More than half of patients (60.5%) were female and most (94.9%) were Malay. The other ethnic groups include Siamese and Orang Asli. Most of participating patients were adults (84.2%). The mean age of pediatric and adult cancer patients was 6.4 years (SD 4.61) and 48.6 years (SD 15.63), respectively. More than half (69.5%) were diagnosed with solid tumor (e.g., colorectal, breast, lung, ovarian, endometrial, sarcoma, nasopharyngeal) and others were with hematological tumor (e.g., acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), lymphoma, multiple myeloma). For most patients, CTx alone (94.3%) was their current cancer therapy received, and at the time of study, most patients were admitted for CTx alone (85.9%). Others were admitted for RT alone (4.5%), for management of treatment complications such as fever, lethargy, pulmonary embolism, and neutropenia (6.2%), for specific procedures such as chemo port insertion, bone marrow aspiration, computerized tomography (CT) scan and magnetic resonance imaging (MRI) (2.8%), and for concurrent chemo-radiation therapy (0.6%).

Table I: Characteristics of Participants (n=177)

Variable	Frequency (%)
Sex	
Male	70 (39.5)
Female	107 (60.5)
Age group	
<18 years old	28 (15.8)
≥18 years old	149 (84.2)
Ethnic group	
Malay	168 (94.9)
Chinese	4 (2.3)
Indian	0 (0.0)
Others (Siamese, Orang Asli)	5 (2.8)
Cancer type	
Solid tumour	123 (69.5)
Haematological tumour	54 (30.5)
Current therapy	
CTx	167 (94.3)
H&N RT	9 (5.1)
Both	1 (0.6)
Reason for current admission	
CTx	152 (85.9)
H&N RT	8 (4.5)
CTx and H&N RT	1(0.6)
Specific procedure	5 (2.8)
Complications management	11 (6.2)
Dental referral prior to cancer therapy	
Yes	19 (10.7)
No	158 (89.3)

CTx, chemotherapy; H&N RT, head and neck radiotherapy.

About a quarter of patients (25.4%) experienced oral complications during their current or past cancer therapy session (Table II). The most common self-reported oral complication was xerostomia (66.7%), followed by mouth ulcer (35.6%), dysgeusia (15.6%), and lip numbness (15.6%). The oral health status and functions of participants are shown in Table III. All (100.0%) patients had normal voice. The most affected OAG component was teeth or denture (71.8%), with 39.0% presented with plaque accumulation at localized

area and 32.8% had generalized plaque accumulation on tooth or denture surfaces. Gingiva (51.4%) and lips (30.5%) were ranked the second and third most afflicted component, respectively. In particular, the examined patients presented with swollen gum with or without bleeding, and dry, cracked, ulcerated or bleeding lips. About half of patients (58.8%) had OM with functional disturbances. The OAG score ranged from eight to fifteen. The mean OAG score was 10.10 (SD 1.79).

Table II: Experience of oral complications related to chemotherapy and/or radiotherapy (n=177)

Variable	Frequency (%)
Experience of oral complications	
Yes	45 (25.4)
No	132 (74.6)
Type of oral complication (n=45)[a)]	
Dry mouth	30 (66.7)
Mouth ulcer	16 (35.6)
Loss of taste	7 (15.6)
Lip numbness	7 (15.6)
Oral infection	1 (2.2)
Gum bleeding	2 (4.4)
Difficulty in swallowing	1 (2.2)
Difficulty in speaking	1 (2.2)

[a)]patients may experience more than one oral complications

Table III: Oral health status and functions of cancer patients undergoing chemotherapy and/or radiotherapy (n=177)

Category	Frequency (%)		
	Score 1 (normal)	Score 2 (mild to moderate change)	Score 3 (moderate to severe change)
Voice	177 (100.0)	0 (0.0)	0 (0.0)
Swallow	176 (99.4)	1 (0.6)	0 (0.0)
Lips	123 (69.5)	52 (29.4)	2 (1.1)
Tongue	168 (94.9)	6 (3.4)	3 (1.7)
Saliva	174 (98.3)	0 (0.0)	3 (1.7)
Mucous membrane	159 (89.8)	16 (9.0)	2 (1.1)
Gingiva	86 (48.6)	91 (51.4)	0 (0.0)
Teeth or denture	50 (28.2)	69 (39.0)	58 (32.8)

Table IV shows results of simple logistic regression analysis and multiple logistic regression analysis of factors associated with experience of OM with functional disturbances among the patients. At univariable level, pediatric cancer patients were 5.60 times more likely to have OM with functional disturbances than adult patients (p<0.001), and patients with solid tumors were 52.0% less likely to experience OM with functional disturbances than patients with hematological tumor (p=0.027). The influence of sex, current therapy received and having dental referral before commencement of cancer therapy on the experience of having OM with functional disturbances was not significant. At multivariable level, only variables that are significant in univariable analyses being included to reduce the risk of over fitting model. The result showed that, only age of patients remained significantly associated with the experience of having OM with functional disturbances, particularly with adjusted odds ratio of 4.85 (p=0.001).

Table IV: Factors associated with the experience of OM with functional disturbance among cancer patients (n=177)

Characteristics	SLR		MLR	
	Crude odds ratio (95%CI)	*p*- value	Adjusted odds ratio (95%CI)	*p*- value
Age				
<18 years old	5.60 (2.23,14.03)	<0.001	4.85 (1.75, 12.71)	0.001
≥18 years old	1.00		1.00	
Sex				
Male	1.01 (0.55, 1.87)	0.968	-	-
Female	1.00			
Dental referral				
Yes	1.32 (0.51,3.44)	0.567	-	-
No	1.00			
Cancer type				
Solid tumour	0.48 (0.25,0.92)	0.027	0.71 (0.35,1.45)	0.347
Haematological tumour	1.00		1.00	
Current therapy				
CTx alone	2.96 (0.61,14.36)	0.178		
H&N RT alone/ combine	1.00			

CTx, chemotherapy; H&N RT, head and neck radiotherapy; SLR, simple logistic regression analysis; MLR, multiple logistic regression analysis

DISCUSSION

In CTx and H&N RT, malignant cells that swiftly proliferate in the human body are specifically targeted for destruction. Besides killing the rapidly dividing cancer cells, the oral mucosa which has a high turnover rate, can also be affected. As a result, cancer patients undergoing CTx and H&N RT commonly experience varying degrees of oral complications (5,7). In the

present study, about a quarter of patients reported having at least one oral complication, and the most common complication was xerostomia. Other than the toxicities of chemotherapeutic drugs and the ionizing radiation on salivary glands, xerostomia in cancer patient can also be due to anxiety, stress and/or use of other commonly prescribed drugs related to the therapy such as antiemetic agents, antihistamines, tricyclic antidepressants, benzodiazepines and opioids (19). Our findings were in agreement with those of earlier studies conducted in Malaysia and other settings including Italy and Spain, where xerostomia, that manifested as dry lips, dry mouth, and thick or ropey saliva, was the most common oral complication among adult cancer patients undergoing CTx and surgery-RT of the H&N (15,16,20–23).

In this study, about one-third of patients reported of having mouth ulcers during therapy, the second most common complaint. Our finding was much higher compared to prevalence of mouth ulcer (5.4%) reported by Cakmak et al.(24). Mouth ulcer is defined as a full-thickness breach in the epithelium lining the soft tissues of the mouth. In a healthy individual, mouth ulcer occasionally happens due to an iron or vitamin B deficiency, or trauma to the lining of the mucosa (25). In cancer patients, on the other hand, mouth ulcers (also known as oral mucositis) are thought to occur because of the damage that CTx and H&N RT cause to DNA strands, which in turn traumatize the basal epithelium, submucosa, and endothelial cells found in the mouth mucosa. Moreover, these therapies cause salivary gland atrophy, resulting in low salivary secretion in cancer patients. This condition may exacerbate OM (26).

Other oral complication reported by patients in this study was gum bleeding. CTx can cause myelosuppression, leading to lethargy due to anemia or low red blood cell count, oral infection due to neutropenia or low white blood cell count, and oral mucosal bleeding due to thrombocytopenia or low platelet count. Gingival bleeding is also a cardinal sign of gingival inflammation or gingivitis related to poor oral hygiene. Presence of inflamed gingival tissues may further aggravate spontaneous gum bleeding due to thrombocytopenia in cancer patients receiving CTx (13,27).

Assessment of the oral health status and function of our patients using the OAG revealed that most had poor oral hygiene with either localized or generalized plaque accumulation. In accordance with these findings, about half of our patients had edematous gingiva, another cardinal sign of gingivitis which is often a result of plaque build-up from inadequate oral hygiene. Moreover, the cumulative OAG score indicated that about half of cancer patients undergoing CTx and/or H&N RT in this study suffered from OM with functional disturbances. OM is a common complication of CTx and/or H&N RT, and patients with poor oral hygiene are more likely to develop oral inflammation and infection that can aggravate the existing OM. The onset of OM is as early as three to eight days following administration of CTx and three to 14 days after cumulative doses of H&N RT of 10 to 30 Gy (13,28,29). Clinically, OM manifests as localized to widespread erythema, oral ulcers, and even bleeding (27,28). In India, Ecuador and Mexico, the incidence of OM was reported to range from 30.0% to 75.0% (16,30). A lower OM incidence of 22.3% was reported in a study by Mercadante et al. (20) in Italy.

Several potential risk factors have been associated with an increased risk of OM. These factors were categorized into demographic factors (gender and age) (24,31), health-related factors (such as BMI, oral pH, existing comorbidity, cancer stage, hemoglobin level, creatinine level, lower level of neutrophil count, pre-existing periodontal disease, xerostomia, and oral hygiene) (31–33), lifestyle-related factors (such as smoking and drinking) and therapy-related factors (prior history of CTx, concurrent therapy, type of chemotherapeutic drugs taken, cumulative dose of RT) (20,33–36). However, the evidence for each of these factors was inconclusive. In our study, the age of the patients had a significant association with OM with functional disturbances. In particular, pediatric cancer patients had 5.60 times greater odds of getting OM with functional disturbances. It is possible that the higher prevalence of mucositis in children than in adults is due to the faster cell cycle in the younger age group (37,38). On the contrary, a study by Cakmak et al. (24) reported a higher incidence of OM with increased age. The earlier studies reported that age was significant factors for OM (24) and some were not (31,33,39).

The results of this study, which looked at the risk factors of sex, cancer type, therapy type, and having a dental referral before current cancer therapy, were not statistically significant. According to a recent studies on the factors related with severe OM, males were more likely than females to acquire severe OM (31,36,40). On the other hand, Martin et al. reported otherwise (41). Still, there were no conclusive link between sex and the development of OM in the body of literature (32,39).

Pertaining to cancer therapy, the number of cycles of CTx was significantly associated with increased incidence of OM. Evidence showed that patients with more than six cycles of CTx to treat solid tumor having an increased risk by 9.14 times greater for OM. Additionally, individuals receiving adjuvant, particularly those receiving combine CTx with three or more medications and H&N RT had greater risk of OM (41). In accordance to that, Soutome et al. reported that patients who received concurrent cisplatin or cetuximab treatment were at significantly higher risk severe radiation-induced OM (36). Moreover, a meta-analysis study showed that concurrent chemo-radiation therapy and the use of antibiotics at early treatment stage were treatment-related risk factors for

radiotherapy-induced OM (42). With regard to cancer type, both solid (head and neck, breast, sarcoma, and liver) (41) and hematological tumor (43) were directly associated with OM. The possible reason was strongly associated with the treatment protocols involving the use of methotrexate, cyclophosphamide, docetaxel, doxorubicin, carboplatin, cisplatin, and docetaxel (41,43).

Oral care should be an integral component of inter-professional collaborative management of cancer patients. Implementation of comprehensive oral care before, during, and after cancer therapy can help reduce the incidence and severity of oral complications. It is suggested that prior to commencement of immunosuppressive therapy, all cancer patients should undergo an oral examination and be given the needful dental treatment. The aims of pre-therapy oral examination are to locate and eliminate potential sources of infection such as dental caries and periodontal disease, and to educate patients and parents about the possible acute and long-term oral side effects of therapy, and the importance of optimal oral care to prevent oral side effects and minimize pain or discomfort from the oral complications. Ideally, all needful or urgent dental treatment should be completed before initiation of immunosuppressive therapy (44,45).

In this study, only about one-tenth of the patients were referred to dentists prior to commencement of the respective planned therapy. Our findings were comparable with a previous retrospective study conducted in a similar setting wherein a somewhat higher proportion (22.1%) of patients diagnosed with head and neck cancer had dental referrals prior to receiving cancer treatment (46). The lack of knowledge about the impact of oral complications following cancer therapy and the absence of a protocol on oral care of cancer patients undergoing CTx and/or H&N RT might contribute to the low percentage of dental referral in our study. In addition, the attitude of healthcare personnel was observed to be "neglectful" and "not a health priority," along with a lack of knowledge and awareness, unaware of the importance of consultation with oral medicine specialists, long distance in accessing dental facilities, and uncertainty of the referral procedure posed a barrier to the dental care of palliative patients (47,48).

Oral complications have substantial impact, not only on individual patients and their family members, but also on the health care system due to prolonged hospitalization and disturbance of planned cancer therapy (12–14). Besides pre-therapy dental referrals, the important roles of the medical counterpart in preventive oral care to cancer patients during and after therapy cannot be emphasized enough. In hospitals, nurses usually spend more time with patients than doctors do, hence nurses are in an excellent position to help maintain patients' oral hygiene as part of routine patient care and to detect early signs and symptoms of oral complications by performing regular oral screening and alerting the attending physician about the need to make immediate referrals to dentists if needed.

There are a few limitations in this study that may limit the generalizability of our findings to other contexts. First, our study only involved hospitalized cancer patients receiving CTx and/or H&N RT. We did not include cancer patients who received similar therapies at the day care setting. Second, convenience sampling was used in patient recruitment due to low number of cancer patients admitted during the data collection period, subjecting this study to disadvantages inherent in non-probability sampling. Moreover, this study was conducted during the COVID-19 pandemic. At the beginning of data collection, which took place between the end of February to May 2021, the state of Kelantan was under the Conditional Movement Control Order (CMCO) before reinstatement of Movement Control Order (MCO) from 16 April 2021 in response to a surge of cases. The pandemic has led to a reduction in cancer patients' visits due to reallocation of healthcare services and resources, particularly at tertiary care facilities, to cater for the high number of COVID-19 related hospital admission, as well as the need to balance the delivery of cancer care while reducing the risk of exposing patient to the virus (49).

CONCLUSION

In conclusion, about half of cancer patients undergoing CTx and/or H&N RT in this study were affected by OM with functional disturbances. This condition is more prevalent among pediatric cancer patients. About a quarter of patients self-reported at least one oral complication during their current or past cancer therapy, with xerostomia being the most common complaint. Unmet oral health care needs among the cancer patients in our study is substantial as only a small number was referred to dentists for oral care prior to therapy.

This study highlighted the important roles of the medical care providers, especially nurses who spend more time in the ward with patients and their caregivers, to make sure that dental care is a crucial component of nursing care for cancer patients. In addition, with some do's and don'ts in patient care, nurses can help in preventing or reducing the risk of oral complications, as well as minimizing the pain and discomfort of having oral complications. Development of an oral care protocol for cancer patients with emphasis on the roles of nurses are indicated to empower the nurses with necessary knowledge and skills to provide comprehensive care for cancer patients.

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