Correlation analysis between risk factors and mucositis oral in head and neck cancer patients undergoing radiotherapy

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ABSTRACT

Introduction: Radiotherapy is a cancer therapy that uses ionizing radiation to damage cancer cells. Ionizing radiation in the head and neck area can disrupt the function and integrity of the oral mucosa and cause oral mucositis. In Bandung, the prevalence and risk factors of oral mucositis in head and neck cancer (HNC) patients undergoing radiotherapy have not been studied. Some textbooks claim that the prevalence of radiotherapy-induced oral mucositis in HNC patients occurs at almost 100%. Various risk factors associated with oral mucositis have been studied, giving significantly different results. This research analyzes the correlation between risk factors and mucositis oral in head and neck cancer patients undergoing radiotherapy. **Methods**: This research is a cross-sectional retrospective study with secondary data from medical records of HNC patients at RSHS from January 2015 until December 2019. A consecutive sampling method was used to collect the data that match the Inclusion criteria, including diagnosis of HNC(ICD-10), receiving radiotherapy from the first cycle until the last cycle; having a complete medical record following variables (location of HNC coding by ICD-10, gender, age, education level, smoking habit, the cycle of radiotherapy, oral treatment, body mass index, and comorbid disease). All data were then analyzed using Spearman correlation. **Result**: 171 medical records showed 59 patients had oral mucositis after radiotherapy. 26.9% male and 7.6% female, with susceptible age 40-60 years. Analysis of the Spearman correlation, there is a significant relationship between body mass index (BMI) (ρ = 0,001), smoking habits (ρ = 0,001), and radiotherapy cycles (ρ = 0.001). **Conclusion**: There is a correlation between risk factors of oral mucositis in HNC patients undergoing radiotherapy in RSHS, including body mass index (BMI), smoking habits, and radiotherapy cycles.

Keywords: head and neck cancer; oral mucositis; risk factor; retrospective study

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INTRODUCTION

Head and neck cancer (HNC) is a malignancy that affects the oral cavity, oropharynx, nasopharynx, nose, paranasal sinuses, hypopharynx, larynx, ears, and can also affect salivary glands. Malignancy in the oral cavity can affect the buccal mucosa, gums, floor of the mouth, hard palate, and anterior two-thirds of the tongue. Cancers of the oropharynx are the base of the tongue, tonsils, soft palate, uvula, and posterolateral walls of the pharynx.[1,2,3,4] HNC cases globally increase from year to year. Data from the Global Cancer Observatory (GLOBOCAN) in 2018 stated that HNC is in the fifth position of all malignancies. Data from the Indonesian National Cancer Registration Agency states that HNC in Indonesia was the fourth rank of the top ten cancer in Indonesia and commonly in men.[5,6] History of smoking, alcohol consumption, exposure to carcinogens, diet, infectious diseases (Human Papilloma Virus (HPV) and Epstein Barr Virus (EBV)), and genetics are risk factors for HNC.[6,7,8,9]

Cancer management includes surgery, radiotherapy, chemotherapy, hormone therapy, biotherapy, or a combination of these methods. Toxicity effects of cancer therapy can cause mucositis oral.[1,2,3,4] Oral mucositis occurs due to impaired function and integrity of the oral mucosa due to the toxic effects of cancer therapy which causes direct damage to the DNA of basal epithelial cells.[1,10] Radiation exposure causes physical, chemical, and biological effects on cells, where excitation and ionization are followed by direct damage to DNA or indirectly by ionizing the cytoplasm of cells to form free radicals that cause DNA damage. DNA damage then initiates cells for repair, redistribution, re-oxygenase, repopulation, and radiosensitivity, known as 5R.[11,12] In addition, some risk factors like age, gender, weight, oral hygiene, hyposalivation, systemic diseases, and harmful habits such as smoking can aggravate the condition of mucositis.[3,4]

Patients with severe oral mucositis can reduce food intake through the oral cavity, weakening the patient's body due to lack of nutrition. Weak conditions interfere with the radiation schedule of patients, influence the intensity of anti-cancer therapy, increase the risk of infection, and increase the cost of treatment. Delaying anti-cancer therapy will result in the continued proliferation of cancer cells and potentially endanger the patient's life.[1,3,13] Knowing risk factors that can prevent oral mucositis from becoming more severe is essential for clinicians. This study aims to determine the risk factors of oral mucositis in patients with HNC undergoing radiotherapy.

METHODS

The study design was a cross-sectional retrospective study using secondary data. The population of this study was HNC inpatient and outpatient undergoing radiotherapy between January 2015 to December 2019. Data were collected from the medical record by consecutive sampling from January-march 2021 at the central medical record and radiation-oncology medical records at Dr Hasan Sadikin Hospital (RSHS), with inclusion and exclusion criteria.

Inclusion criteria include diagnosis (ICD-10) are patients with HNC; receiving radiotherapy from the first cycle until the last cycle; have a complete medical record following variables (location of HNC coding by ICD-10, gender, age, education level, smoking habit, the cycle of radiotherapy, oral treatment, body mass index, and comorbid disease). Exclusion criteria include an HNC patient who did not receive radiotherapy.

Statistical analysis, the total number of medical records examined was 349 files, tabulated, coded, and cleaned using Microsoft excel 2019. After cleaning, we found that only 171 medical records followed the researcher's inclusion criteria and were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) 24.0. Spearman correlation used to compare eight risk factors for oral mucositis. The test criteria rejected the null hypothesis (H0) if the significance value $\rho<0.05$ means a relationship between risk factors and the occurrence of mucositis. This research has obtained permission from the Research Ethics Commission of Universitas Padjadjaran, Bandung, with ethics number 74/UN6.KEP/EC/2021.

RESULTS

This study found that 34.5% of HNC patients who received radiotherapy at RSHS from January

Variable	Mucositis		Total	
	n	%	n	%
Head and Neck Cancer Patients	5	34.50%	171	100%
Gender	9			
Male	46	26.90%	123	71.93%
Female	13	7.60%	48	28.07%
Age (Years)				
10-14	0	0%	2	1.17%
15-19	3	1.75%	5	2.92%
20-24	1	0.58%	9	5.26%
25-29	3	1.75%	4	2.34%
30-34	5	2.92%	10	5.85%
35-39	10	5.85%	18	10.53%
40-44	7	4.09%	19	11.11%
45-49	8	4.68%	28	16.37%
50-54	6	3.51%	23	13.45%
55-59	9	5.26%	27	15.79%
60-64	3	1.75%	14	8.19%
65-69	1	0.58%	6	3.51%
70-74	2	1.17%	5	2.92%
75+	1	0.58%	1	0.58%
Education				
Primary Education	34	19.88%	106	61.99%
Secondary education	18	10.53%	48	28.07%
High education (college)	7	4.09%	17	9.94%
Smoking habit				
Yes	44	25.73%	83	48.54%
No	15	8.77%	88	51.46%
Radiotherapy (Cycle)				
0-5	2	1.17%	3	1.75%
6-10	7	4.09%	9	5.26%
11-15	12	7.02%	15	8.77%
16-20	4	2.34%	7	4.09%
21-25	7	4.09%	12	7.02%
26-30	3	1.75%	34	19.88%
31-35	24	14.04%	91	53.22%
Oral Treatment				
Yes	1	0.58%	2	1.17%
No	58	33.92%	169	98.83%
Body Mass Index				
Underweight	23	13.45%	40	23.39%
Normal	34	19.88%	114	66.67%
Pre obesity	2	1.17%	15	8.77%
Obesity	0	0%	2	1.17%
Comorbid				
Yes	13	7.60%	26	15.20%
No	46	26.90%	145	84.80%

Tabel 1. Characteristic of the subject

Abbreviation: n= sample, %= persentation.

2015-December 2019 had mucositis oral. The patient's characteristics in this study are present in Table 1. One hundred seventy-one medical records were collected, and 59 medical records of HNC patients experienced oral mucositis. The patient age range from 10 to >75 years old, dominated by male patients (71.93%). 61.99% of patient with HNC has a primary education level (elementary to junior high school). 51.46% did not smoke. All the patients receive radiotherapy from the first cycle until achieving the 35th cycle (70 Gy). 98.83% of patients did not receive oral treatment, 66.67% had an average body mass index, and 84.8% did not have comorbidity.

Oral mucositis appeared in all age groups, mainly in the age range of 35-39 years (5.85%), dominant in men (26.9%) than women (7.6%). Based on education level, mucositis oral was found more in the primary education level (19.88%) than in the other. Patients with a smoking history have a higher risk of developing oral mucositis (25.73%) than patients who did not smoke (8.77%). Oral mucositis appeared in all cycles of the radiotherapy, starting from the fifth cycle and most occurring in the 33rd cycle.

As much as 98.83% of HNC patients did not undertake oral treatment before and during radiotherapy, and 33.93% experienced oral mucositis. Patients with normal BMI (19.88%) had the most oral mucositis, while obese patients did not experience oral mucositis. Patients without comorbidity (84.8%) experience oral mucositis (26.9%) more than patients with comorbid (7.6%).

The International classification for disease, ten editions (ICD-10), is used in RSHS to classify all diseases. According to ICD-10, HNC is encoded with codes C.00 to C.14 and C.30 to C.32.

The ICD-10 diagnosis coding for HNC patients in RSHS is based on the location of cancer, as shown in Table 2.

Table 2. ICD-10 coding diagnosis for HNC patients included in this research

	Mucositis (n=59)		Not mucositis (n= 112)		n (n=171)	
C.01(Malignant neoplasm of base of tongue)	1	0.58	-	-	1	0.58
C.03 (Malignant neoplasm of upper gum)	1	0.58	-	-	1	0.58
C.04 (Malignant neoplasm of floor of mouth)	-	-	1	1	1	0.58
C.07 (Malignant neoplasm of parotid gland)	-	-	2	1	2	1.17
C.08 (Malignant neoplasm of other and unspecified major salivary glands)	-	-	1	1	1	0.58
C.09 (Malignant neoplasm of tonsil)	1	0.58	-	-	1	0.58
C.11 (Malignant neoplasm of the nasopharynx)	50	29.24	82	48	132	77.19
C.30 (Malignant neoplasm of nasal cavity and middle ear)	3	1.75	9	5	12	7.02
C.31 (Malignant neoplasm of accessory sinuses)	1	0.58	6	4	7	4.09
C.32 (malignant neoplasm of the larynx)	2	1.17	11	6	13	7.6

Abbreviation: n= Sample; %= Persentation

We found that C.11 (nasopharyngeal carcinoma) is the most malignancy of HNC in RSHS. C.30, C.32, C.31, C.01, C.03, and C.09 are more common after C.11. The least of all HNC types are C.00 (Malignant neoplasm of the lip), C.02 (Malignant neoplasm of other and unspecified parts of the tongue), C.05 (Malignant neoplasm of the palate), C.06 (Malignant neoplasm of cheek mucosa), C.10 (Malignant neoplasm of oropharynx), C.12 (Malignant neoplasm of the pyriform sinus), C.13 (Malignant neoplasm of hypopharynx), C.14 (Malignant neoplasm of other and ill-defined sites in the lip, oral cavity, and pharynx).

Bivariate analysis using Spearman correlation in Table 3 determined the significance

Table 3. The correlation analysis result between risk factors and mucositis oral

Variable	r	sig.
Age	0.114	0.138
Gender	0.098	0.205
Education	-0.067	0.383
BMI	0.289	0.001*
Comorbid	0.138	0.072
Smoking habit	0.378	0.001*
Oral treatment	0.035	0.645
Radiotherapy cycle	0.304	0.001*

Abbreviation: *= significant; Sig. Significancy; r= Spearmant coefisient correlation

between risk factors and oral mucositis in HNC patients undergoing radiotherapy. Spearman

correlation analysis found that age (ρ=0.138), gender (ρ=0.05), an education level (ρ=0,376), comorbid diseases (ρ=0.072), oral treatment (ρ=0.645) were not significant (ρ> 0.05) associated with the development of oral mucositis. The risk factors for body mass index (BMI) (r=0.289; ρ=0.001), smoking habit (r= 0.378; ρ=0.001), and radiotherapy cycle (r= 0.304; ρ=0.001) were significantly (ρ<0.05) fairly strong associated with the develop of oral mucositis.

DISCUSSION

Various studies on risk factors for oral mucositis have been carried out, and many risk factors for oral mucositis have been studied and have given significantly different results. The risk factors associated with oral mucositis in radiotherapy patients were divided into host factors and patient-acquired radiotherapy-related factors. Host factors include age, gender[14], medical conditions (comorbid), genetics, and oral cavity conditions.[3,4,13,15] Radiotherapy-related factors include the dose and location of radiotherapy. Knowing risk factors that can prevent oral mucositis from becoming more severe is essential for clinicians to avoid the development of oral mucositis becoming more severe.[16,17]

Some textbooks claim that the prevalence of oral mucositis occurs almost 100% in patients with radiotherapy, but in reality, not all patients experience oral mucositis.[1,4,16,17] The severity grade of oral mucositis in each patient also varies. The results of previous studies concluded that the crucial risk factors that could lead to oral mucositis in patients receiving radiotherapy were the total radiotherapy fractions, smoking habits and Body Mass Index (BMI).[15,17]

The risk factors examined in this study included age, gender, education level, BMI, comorbidity, smoking habit, oral treatment, and radiotherapy cycle. The study's results found the same as some research before that the risk factors associated with oral mucositis in HNC patients undergoing radiotherapy in RSHS are (BMI), smoking habits, and radiotherapy cycles.HNC is more usual in men than women.[5,6,9]

There is no association between gender and the occurrence of mucositis oral in patients with HNC undergoing radiotherapy. Unlike previous studies by Saedi HS et al[13], in their research on the frequency of chemotherapy, they found a significant relationship between gender and oral mucositis (ρ= 0.012). Man and women equally have the same risk of developing oral mucositis.

However, due to anatomical differences, the development of certain types of cancer depends on the anatomy of the cancer site, for example, in the thyroid, breast, or cervical cancer, so women will be more at risk of experiencing oral mucositis than men because women will dominate the number of sufferers than men.[18] The high risk of HNC in male patients is associated with lifestyle habits (smoking), while in women, associated with genetic factors.[5,6,9,17]

Our study found no significant association between age and oral mucositis (sig. 0.138). This study focuses on patients with HNC so that more patients are aged 35-39 years, and very rarely in children.[5,6,13,17] age is not associated with oral mucositis because age is a factor that can aggravate the condition of mucositis oral. Some researchers assume that very young children and the elderly are more vulnerable to developing severe mucositis. Very young children (toddlers) have a high turnover rate, in contrast to the elderly, where there is a decrease in the ability of tissues to repair and replace themselves and maintain standard structure and function (slow healing rate).[17,19]

The result showed that the level of education did not associate with mucositis. These results are the same of Cakmak S. et al. 2018, which found that the level of education was not significantly related to the development of oral mucositis (ρ= 0.383 > 0.05).[20] The occurrence of mucositis oral is highest in patients with low education levels. National Socio-Economic Survey 2019 data shows that only one in four students in age 15 years have graduated from high school/equivalent, and only about 9% have completed their education to the university level.[21]

Data above explains that most Indonesian people only achieve a primary education level compared with secondary education and college; therefore, they are more patients with primary education than the other education level. Education was not a risk factor for mucositis oral, but the educational level influences individual health behavior.

There is a significant association between smoking and oral mucositis. Smoking habit was an essential and crucial risk factor for oral mucositis.[15,17,20,22] The Ingredients in cigarettes, especially nicotine, lower the epidermal growth factor (EGF) level in saliva. EGF is a mitogenic polypeptide secreted mainly by the submandibular gland and functions as a cytoprotective/protection throughout the digestive tract. The oral cavity is a segment of the digestive system and the first exposed to various physical, chemical, and microbial disturbances.[23,24] Epidermal growth factor receptor (EGFR) mutations are also found in 80-100% of HNC patients and are associated with increased EGFR expression in line with the prognosis of cancer severity. The overexpression of EGFR in HNC has led to pharmacotherapy aimed at these cell surface receptors as cancer treatment targets. Decreased EGF secretion due to smoking and EGFR as a cancer treatment target enhances the risk of oral mucositis becoming more severe in patients with a smoking history.

There is a significant relationship between radiotherapy cycles and the incidence of oral mucositis. Oral mucositis onset starts at 10 Gy and continues with increasing radiation dose. Large radiation doses cause epithelial damage, desquamation, necrotic, and ulceration of the oral mucosa. During radiotherapy, changes in the salivary glands, especially head and neck radiation, induce xerostomia and exacerbate oral mucositis.[16,22] The results showed that in the five cycles (10 Gy), two from three patients were experiencing mucositis oral, and the most mucositis oral appeared in the 33 cycles (66 Gy). Nagarajan K[25], states that oral mucositis appeared in fifth cycles (9,99 Gy) to 21 cycles (42 Gy), and oral mucositis appeared for the first time in one week and would become more severe in the fourth week.[25]

There is no significant association between the History of oral treatment and the occurrence of oral mucositis because the data were homogeneous. Indicates the homogeneity is by the sample variance value approaching 0 (Sample Variance (SV): 0.0176). The data characteristic found just only two patients (1%) had oral treatment, and 33.98% of patients had oral mucositis. According to the National Comprehensive Cancer Network (NCCN), oral health care is essential in preventing and managing short-term and long-term oral complications of cancer treatment. Oral hygiene is essential in oral mucositis in HNC patients receiving radiotherapy.[13,23,25] Oral treatment before, during, and after cancer therapy prevents complications/side effects of cancer therapy.[16,26,27,28]

There is a significant relationship between BMI and oral mucositis in HNC patients who received radiotherapy. Shu Z et al, in their prospective study regarding the nutritional status and its relation with oral mucositis due to radiotherapy in nasopharyngeal cancer patients, found that an underweight condition is associated with a slow healing process and increased tissue damage.[29,30] Dysphagia causes a decrease in nutritional intake, resulting, in anemia, decreasing the amount of protein, mainly albumin, reducing the immune system, making the oral mucosa more susceptible to oral mucositis, and delaying the healing process.[29,30,31] HNC patients receiving radiotherapy tend to be underweight.[31] In contrast with our research, almost every patient who reported experiencing oral mucositis was a patient with a normal BMI. This condition happened because the weight and height data on the nutritional care form was taken at the first visit and not updated. Recording nutritional status before and after radiotherapy is essential to reduce complications.[20]

Twenty-six patients (15%) have a history of comorbidities, including adenomyosis, endometrial cysts, anemia, hypertension, dehydration, malnutrition, diabetes mellitus, heart disease, and pulmonary tuberculosis. Cakmak S. et al[20], stated that comorbidities increase the development of oral mucositis and oral complications. Systemic diseases and routine medications may decrease saliva, resulting in the patient's xerostomia. Xerostomia conditions cause a decrease in salivary flow, where the function of saliva is as a lubricant, reducing mechanical effects that can damage the mucosal barrier of the oral cavity.[32,33] The results showed no significant relationship between comorbidities and the incidence of oral mucositis in HNC patients receiving radiotherapy. Comorbidity is not associated with the appearance of oral mucositis. However, it can be an aggravating factor in developing oral mucositis. Limitations of this research are many medical records were not recorded entirely, thus

affecting the information obtained and the final results of the research and some of the mucositis assessment was inappropriate and could not determine the severity grade of oral mucositis. It needed a prospective study in the future.

CONCLUSION

There is has correlation between risk factors of oral mucositis in HNC patients undergoing radiotherapy in RSHS include body mass index (BMI), smoking habits, and radiotherapy cycles.

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