

# Oral Health Status in Patients Undergoing Chemotherapy for Lung Cancer

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**Abstract** *Purpose:* The main purpose of this study was to assess the oral health status of patients receiving two different chemotherapy regimens (cisplatin/etoposide vs cisplatin/vinorelbine) for non small cell lung cancer. We analyzed local and general factors which may influence the prevalence and intensity of oral mucositis in the course of chemotherapy. *Methods:* Patients were examined before, and after, one cycle of chemotherapy. The oral examination was carried out with the use of a dental mirror, dental probe and a head light. For evaluation of the dental status common epidemiological indices were used. To analyze the status of the oral mucosa we used the National Cancer Institute Common Toxicity Criteria Adverse Events v 3.0 scale. We compared the presence and intensity of oral mucosa's changes induced by two different chemotherapy regimens. *Results:* The frequency of oral mucositis was at comparable levels in both the patients receiving cisplatin/etoposide and those treated with cisplatin/vinorelbine. Statistically significant differences were found in the mean simplified oral hygiene index ( $p=0.0038$ ), the impact of removable dentures on the presence of oral mucositis ( $p=0.0038$ ) and the pain intensity in patients with symptoms of oral mucositis ( $p=0.0018$ ). The other factors studied did not show any significant differences between the two groups studied. *Conclusions:* Patients with good oral hygiene had a lower incidence of oral mucositis during chemotherapy. The use of both cisplatin/etoposide and of cisplatin/vinorelbine had a similar, deleterious effect on the condition of the oral mucosa of patients with lung cancer.

**Keywords** Lung Cancer, Oral Hygiene, Oral Mucositis, Chemotherapy

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## 1. Introduction

Lung cancer is the most common cause of death among patients suffering from all types of malignancies. Therefore treatment options form a significant challenge for contemporary medicine [1]. The results of all forms of

current treatment are still unsatisfactory and the 5 year survival rate for all patients is only 9%. The most effective option is surgical resection, but only 20% of diagnosed patients are eligible for this treatment. In the remaining 80% of patients, chemotherapy and radiotherapy, either separately or together are the only choices for life extension [2]. Both types of treatment produce many side effects for the patients. One of these is oral mucositis (OM). The manifestations of OM vary widely starting with erythema and oedema and progressing to extensive painful ulcers affecting the non keratinized mucosa of the mouth. This complication may severely compromise the patients' wellbeing and affect the therapy outcome of the main disease [3].

With advanced stages of OM patients suffer from intense pain and have difficulties in eating and swallowing which may lead to additional loss of weight.

The mechanism underlying oral mucositis is complex and involves molecular, cellular and tissue-based changes. There is increasing evidence of a genetic component of this condition, involving up-regulation of inflammatory cytokines and of nuclear factor kappa – beta [4].

There are many possible risk factors contributing to the occurrence and severity of OM. We can divide them into factors associated with the type of therapy used and those associated with the patient's current general health status [5]. The highest risk of OM occurs in patients receiving long lasting chemotherapy and in those who are treated with 5 fluorouracil or irinotecan [6].

Of the general and local factors potentially influencing the incidence and intensity of oral mucositis, the patient's oral hygiene and periodontal/dental status are of great importance.

The main purpose of this study was to assess the oral health status of patients receiving two different chemotherapy regimens (cisplatin/etoposide vs cisplatin/vinorelbine) for non small cell lung cancer (NSCLC). We analyzed local and general factors which may influence the prevalence and intensity of oral mucositis in the course of chemotherapy.

## 2. Materials and Methods

## 2.1. Setting and Participants

Eighty two patients with NSCLC treated in the Department of Pulmonary Oncology at the Wielkopolska Center of Pulmonology and Thoracosurgery in Poznan were enrolled in this study.

There were 25 female and 57 male patients with a mean age of 58 years .In the majority (80%) of them, the diagnosis was of squamous cell carcinoma (SCC) was diagnosed. The diagnosis in the other 20% was that of adenocarcinoma.

The patients were divided into two groups according to their chemotherapy regimen. One group of patients was given cisplatin/etoposide (PE) in doses of: cisplatin 75-100 mg/ m<sup>2</sup> on day one or 15-30 mg/ m<sup>2</sup> on days 1, 2 and 3 and etoposide 100-120 mg/ m<sup>2</sup> on days 1, 2 and 3 respectively.

Patients in the second group were treated with cisplatin/vinorelbine (PN) in doses of: cisplatin 75-100 mg/ m<sup>2</sup> on day one or 15-30 mg/ m<sup>2</sup> and vinorelbine 25-30 mg/ m<sup>2</sup> on day one and 8 respectively.

Approval for this study was obtained from the Medical Ethics Committees of Poznan University of Medical Sciences.

All the study participants gave their written, informed consent.

## 2.2. Measures

### 2.2.1. Patient and Tumor Characteristics

The clinical and pathological data, including age, sex, BMI, staging of lung cancer and type of chemotherapy regimen were obtained from the patients' records are shown in Table 1 and 2.

**Table 1.** Clinical and pathological data obtained from patients' records

	Female	Male
Sex, % No,	30% (25)	70% (57)
Age in years (mean)	58.5	58
BMI	25	23
Type of neoplasm	squamous cell carcinoma 80%	Adenocarcinoma 20%
Chemotherapy regimen (% of patients)	cisplatin/vinorelbine 56%	cisplatin/etoposide 44%

**Table 2.** Stage of lung cancer in analyzed patients

Stage of lung cancer (AJCC)	% of patients affected
IIa	7%
IIb	11%
IIIa	6%
IIIb	22%
IV	54%

### 2.2.2. Dental Status

Nineteen of the examined patients (23.4%) were edentulous, 21 patients (26%) had a functional dentition

(minimum of 20 teeth present), and 63% of the patients were denture users.

### 2.2.3. Oral Cavity Examination Using Epidemiological Indices

The patients were examined before, and 5-7 days after, one cycle of chemotherapy.

The examination was carried out with the use of a dental mirror, dental probe and a head light.

The results were recorded on a standard dental chart .The patients' dental status was evaluated using the decayed, missed and filled teeth index (DMFT).

The sum of these three figures forms the DMFT-value and describes the prevalence of caries in an individual.

Oral hygiene was evaluated using the simplified oral hygiene index (OHI-S).

This index has two components- the Debris Index and the Calculus Index. These indices, which are based on numerical determinations, represent the amount of debris or calculus found on the preselected tooth surfaces.

The interpretation of the results is based on the Greene and Vermilion standard with 0 standing for very good hygiene, 0.1-1.2 good oral hygiene, 1.3-3.0 satisfactory hygiene and 3.1-6.0 unsatisfactory hygiene.

We also checked for the presence of removable dentures as a potentially important local factor contributing to oral mucositis. The patients using complete or partial, removable dentures were later compared with the group of patients not using any removable dental prosthesis.

The status of the oral mucosa was evaluated using the National Cancer Institute Common Toxicity Criteria Adverse Events v.3 scale (NCI-CTCAE) .The evaluation was made by a dentist and an oncologist.

From the clinical examination OM was graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 3.0) as follows:

Grade 1 = Erythema of the mucosa

Grade 2 = Patchy ulcerations or pseudo membranes

Grade 3 = Confluent ulcerations or pseudo membranes; bleeding with minor trauma

Grade 4 = Tissue necrosis; significant spontaneous bleeding; life-threatening consequences

Grade 5 = Death

The functional/symptomatic effects of OM were then graded as follows:

Grade 1 = Minimal symptoms, normal diet

Grade 2 = Symptomatic but can eat and swallow modified diet

Grade 3 = Symptomatic and unable to adequately aliment or hydrate orally

Grade 4 = Symptoms associated with life-threatening consequences

Grade 5 = Death

In addition, the patients were asked to use a numeric rating scale (NRS – from 0 to 10) to assess the pain intensity in their

mouths.

### 2.3. Statistical Analysis

We performed a statistical analysis of our results using Statistica 8.0 and to evaluate differences between the groups analyzed we used the nonparametric Mann-Whitney test, Fisher's exact test and the Yates' chi-squared test. The level of statistical significance was established at  $p \leq 0.05$ .

## 3. Results

### 3.1. Epidemiological Indexes

#### 3.1.1. OHI-S

In patients with oral mucositis (group A) the OHI-S value was significantly higher than in patients without OM symptoms (group B) / $p=0.038$ / (Table.3)

**Table 3.** Mann Whitney test results for mean OHI-S values in groups A and B.

	Group A		Group B		p value
	mean SD	median	mean SD	median	
mean OHI-S	3.15 SD:1.3	3.0	1.71 SD:0.96	1.8	0.038

There were no significant differences between the groups in their mean DMFT values / $p=0.564$ /.

### 3.2. Impact of Removable Dentures on OM

We found that, in patients using either complete or partial removable dentures, the rate of oral mucositis was significantly higher than in patients without dentures / $p=0.038$ / (Table.4)

**Table 4.** Fisher test results of correlation between denture using and incidence of oral mucositis.

	Group A	Group B	Total	p value
Denture users	10	42	52	0.038
No dentures	1	29	30	
Totals	11	71	82	

### 3.3. NCICTC Scale

Oral mucositis was manifested in 13.5 % of the patients examined with different degrees of severity and intensity ( Table 5). 73% of the OM that occurred in patients was classified as Grade I, according to the NCICTC scale.

**Table 5.** Degrees of OM severity in different chemotherapy regimens.

	Grade I	Grade II	Grade III	Grade IV, V
cisplatin/vinorelbine	11%	4.4%	0	0
Cisplatin/etoposide	8.3%	2.7%	2.7%	0

There were no statistically significant differences in the prevalence of oral mucositis in patients undergoing either chemotherapy regimens /group PN vs PE,  $p=0.8298$ / .

We were unable to find any links between the lung cancer stage, sex, mean BMI and OM incidence.

In patients reporting a high intensity of pain, as might be expected, the occurrence of OM was markedly higher / $p=0.0019$ / (Tab.6).

**Table 6.** The Mann -Whitney analysis of pain intensity in relation to OM presence.

	Group A		Group B		p value
	mean SD	median	mean SD	median	
Mean pain intensity (NRS)	4.9 SD:1.8	5	0.2 SD:0.69	0	0.001898

## 4. Discussion

### 4.1. Oral Hygiene

The mean OHI S index in all the patients was 1.89 which, according to the Greene Vermillion scale, stands for a satisfactory level of oral hygiene [7]. There is limited data available comparing the OHI index level in healthy adults with patients suffering from different diseases. Chroma et al. in their study of patients treated for multiple sclerosis reported OHI S scores of 2.1, similar to the results in our study.

The study of Rooban et al. concerning the oral hygiene level of smokers found a comparable OHI S level of 1.84. [9].

In the study of patients diagnosed with different malignancies Campos de Carvalho et al [10] analyzed their oral cavity status. The mean OHI-S was estimated at 1.54, with up to 30% of patients having poor oral hygiene .In our study, 22% of all the patients had an unsatisfactory level of oral hygiene.

Most authors analyzing the influence of chemotherapy on oral health status confirm the finding that poor oral hygiene increases the risk of OM. Sonis and Kunz [11],in summarizing their 8 years of research ,concluded that constant oral hygiene monitoring reduced the number of OM incidents and their severity in patients treated with anticancer therapies . Our study revealed statistically significant differences in the oral hygiene level of patients with OM symptoms (OHI-S = 3.15) in relation to patients without OM symptoms (OHI-s index at 1.71). This observation is confirmed in most recent publications .In addition to oral hygiene status some authors emphasize the role of other factors influencing the incidence of OM. Óhrn et al [12] found a correlation between an increase in the severity of symptoms of OM with a reduction in the physical status of patients undergoing chemotherapy and radiotherapy. This decline in the patients' physical, and especially manual,

ability had a negative impact on the effectiveness of their oral hygiene routine. Then therefore suggested introducing professional dental hygienists as a part of hospital supervision to enhance and improve oral hygiene levels and overall patient health and wellbeing.

#### 4.2. Patients DMFT Scores

Our study included a high mean percentage of edentulous patients (23.4%) and this number reached 43% in patients above 65 years of age. These data reflect the overall dental status of the Polish population, with 41.6% edentulous [13]. The mean value of DMFT for all patients in our study was 18.6. This level of DMFT is mostly associated with a high number of extracted teeth. Comparing these results with epidemiological data from Germany [14] there is a significant convergence in the mean DMFT in population between 50-60 years of age (mean DMFT 18.7).

The D value in the DMFT index in our study was 0.8 and the mean number of filled teeth was 1.0.

These numbers show that, in our group of patients, the most prevalent treatment method was tooth extraction.

Due to extended chemotherapy treatment and poor health status of patients we were not able to perform radiological evaluation of dental status- it would require patients to additionally visit our dental radiology department. We based all our results on clinical evaluation.

Many of the patients in our study (23.4%) were denture users. Our results revealed a significant correlation between the presence of reported OM symptoms and the presence of a removable denture. Most denture users continued to use their dentures despite experiencing xerostomia and early pain symptoms associated with the inflammation oral mucosa. We suspect that improperly adjusted prostheses with rough edges additionally irritated dry oral mucosae, aggravating any existing inflammation. Moreover, failing to maintain proper denture cleanliness could lead to secondary infection.

It could be expected that many, if not most, patients receiving chemotherapy for advanced lung cancer would also suffer from depression and anxiety. Hopwood et al [15] found this affected almost 33% of their patients but from data obtained in our study only 6% of our patients were diagnosed with depression. This number could be an underestimate due to insufficient psychological care in the department. Unfortunately we were not able to include more detailed information concerning depression diagnosis. Patients' charts did not include severity of depression and time of diagnosis. It is commonly accepted that psychological support plays a major role in cancer patients' recovery. Without proper motivation we cannot expect an improvement in the patients' wellbeing and in their approach to oral hygiene.

#### 4.3. NCICTC

In our study 13.5 % of all patients developed OM symptoms within 5-7 days following the first chemotherapy

application. It is well known that up to 60% of patients treated for different malignancies may develop OM symptoms, most of them in stage I, according to the NCICTCAE. The highest risk occurs in mucotoxic chemotherapy regimens involving 5 fluorouracil, cyclophosphamide, methotrexate or cisplatin. In our study of lung cancer sufferers the frequency of oral mucosa changes was lower than in studies conducted in patients with head and neck cancers and hematological malignancies. The reason for this was the use of less mucotoxic chemotherapy regimens and the lack of radiotherapy.

According to the 2009 European Society for Medical Oncology (ESMO) report [16] about 0.25 % of patients treated for lung cancer with vinorelbine/cisplatin develop grade III and IV oral mucositis. There are no reports on how many of these patients have symptoms of grade I and II according to NCICTCAE.

Danson et al.[17] in their study analyzed patients receiving cisplatin/vinorelbine/mitomycin and reported that almost 38 % of their patients developed OM symptoms with only 2% of them of grade III. Our study showed that grade I oral mucositis symptoms occurred in 11% of the patients receiving cisplatin/vinorelbine and grade II in 2.7% of them.

In terms of oral cavity side effects the cisplatin/etoposide regimen has limited documentation. Oblon et al. [18] noted that etoposide had the most significant effect on the oral mucosa, due to its high concentration in the saliva.

Our study shows that, in patients receiving etoposide/cisplatin, 8.3 % of the oral mucosa' changes were grade I and 2.7% of grade II/III according to the NCICTC.

There were no statistically significant differences between the two chemotherapy regimens in the frequency of OM symptoms. However, it has to be emphasized that grade III changes were only observed in the group of patients receiving etoposide as a part of treatment.

We did not find any patients with grades IV or V oral mucositis. Our further study will additionally analyze apoptosis and inflammatory genes expression in oral mucosa of patients undergoing chemotherapy.

#### 4.4. BMI

We additionally evaluated the patients' BMI index and its possible influence on the occurrence of OM. Cheng et al. [19] reported that, in patients with a low BMI (<20), oral mucositis symptoms were more prevalent and more intense. A low body mass index can be a result of cancer and this may impair the immune system. With the progress of the disease a more intense chemotherapy regimen is required, increasing the risk of side effects. However, Robien and Schubert [20] are of the opposite opinion. In their study OM symptoms were more frequent in patients with BMI above 25. They explain that this phenomenon may result from the necessity for higher dosages of chemotherapeutics in obese patients and disturbed drug pharmacokinetics.

In our study, the BMI had no impact on OM symptoms. Likewise, we did not discover any statistically significant

differences in the prevalence of OM in relation to the patient's gender. However, Grade III OM was diagnosed exclusively in female patients. Tsalic et al. [21] in also noted that oral mucosa changes were twice as often diagnosed in women. Sloan et al. reported increased toxicity of 5 fluorouracil in female patients with more severe side effects. Initially, it was suggested that this phenomenon was associated with fewer women participating in the study but currently, the explanation is based on possible differences in the pharmacodynamics of men and women [22].

## 5. Conclusion

Summarizing our results, and comparing them with those of other authors, we conclude that the etiology of OM is multifactorial. Oral hygiene status and the use of a denture played important roles in the occurrence and severity of OM.

None of the other factors analyzed revealed any statistically significant differences.

The chemotherapy regimens employed had an impact on the oral mucosa condition, exhibiting medium levels of mucotoxicity but there were no significant differences between the two chemotherapy regimens, in terms of OM prevalence.

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