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Smoking during radiotherapy for head and neck cancer and acute mucosal reaction

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ABSTRACT

Aim: We compared the incidence of RTOG/EORTC grade III and higher acute mucositis in patients with head and neck cancer who continued to smoke during radiotherapy with those who quit smoking.

Background: There are conflicting data on the relationship between smoking during radiotherapy and the severity of acute mucosal reaction. More studies dealing with this issue are needed.

Materials and methods: Among 136 patients receiving curative radio(chemo)therapy, 37 (27%) declared that they had not quit smoking during radiotherapy. The intensity of mucositis was scored daily by a nurse and weekly by a physician using the RTOG/EORTC scale. The main end-point of the study was the highest observed RTOG/EORTC grade of mucositis.

Results: Patients who smoked during radiotherapy (smokers) were younger than their counterparts who quit smoking (non-smokers), $p = 0.06$. There were no other differences in the baseline characteristics between smokers and non-smokers. Grade III/IV acute mucositis was observed in 43.5% of all patients. The percentage of patients with grade III/IV acute mucositis was similar in smokers and non-smokers (46% vs. 42%, $p = 0.71$). Nine patients (smokers [13.5%]; non-smokers [4%], $p = 0.05$) required prolonged hospitalization to heal mucositis.

Conclusions: In the whole group, smoking during radiotherapy was not related to acute mucosal toxicity evaluated as the rate of the highest observed grade of mucositis.

1. Background

Head and neck cancers are a very heterogeneous group of tumours, but most are squamous cell cancer associated with smoking history. In Poland, head and neck cancer accounts for about 6% of all cancer cases.[1] Given the ageing of the population, the incidence of this malignancy is expected to grow.[2] Treatment options for patients with head and neck cancer comprise surgery, radiotherapy, chemotherapy or some

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combination of those depending on the cancer location, stage of the disease and patient's condition. Head and neck cancer treatment can cause many complications, and acute mucositis is the most common side effect of radiation therapy. The severity of acute mucositis depends mainly on the technique and dose of radiation, but patient-related factors also influence the severity of mucosal reactions.[3,4]

Because most head and neck cancer patients are former or current smokers, they are asked whether they smoke before receiving radiation therapy, and current smokers receive smoking cessation counselling. Despite this counselling, a proportion of patients continue their habit during radiotherapy. Some studies have reported an inferior outcome of radiotherapy for such patients compared with patients who quit smoking before treatment.[5–10] There are scarce data on the relationships between smoking during treatment and the incidence and severity of radiotherapy-related complications, but some studies have reported a negative impact of continuous smoking on treatment tolerance.[11–14]

2. Aim

The aim of this study was to evaluate the relationship between cigarette smoking during radiotherapy or radiochemotherapy and the severity of acute mucosal reactions in head and neck cancer patients. We hypothesized that patients who did not smoke during treatment would experience less severe acute mucositis than their counterparts who continued smoking during treatment, independently of the intensity of the radiation therapy schedule.

3. Materials and methods

One hundred and thirty-six consecutive head and neck cancer patients treated with radiation on an in-patient basis between 2011 and 2012 in our institution were included in the analysis. They all had a history of smoking; i.e., were either current or former smokers. Details of the duration of their smoking and the amount smoked were not available. A list of the included patients was generated from the institutional database, and their case histories were available for the purpose of the study.

It is a departmental policy to ask all patients about their smoking habits during the baseline interviews with the doctor and nurse before treatment and to counsel them to quit smoking. During treatment, patients were also asked about their smoking by doctors and nurses, and their replies, as well as the nurses' observations, were recorded in the medical charts. According to the departmental policy, all patients were evaluated for the severity of acute mucosal reaction according to the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) criteria[15] daily during radio(chemo)therapy by a nurse and once a week by a physician. Nurses evaluated acute mucositis at the level of the oral cavity only. Evaluations performed by doctors were more complex, included evaluation of oral cavity, pharynx and larynx using the mirror indirect laryngoscopy. All our staff had a special training in the scoring of mucosal reaction in the RTOG/EORTC scale. Less experienced nurses were supervised by a senior nurse and all complex cases were collectively discussed. The highest RTOG/EORTC grade of the acute mucosal reaction during treatment was scored for each patient as the end-point of the study. Grade III and higher acute mucosal toxicity was considered severe. Any breaks in radiotherapy equal or longer than three days and prolongation of treatment time were also recorded.

Departmental policy of management of acute mucositis including pain control, nutritional support, oral decontamination, palliation of dry mouth, prevention of bleeding followed international guidelines.[16] The following variables were analyzed with regard to the incidence of grade III and higher acute mucosal toxicity during radiotherapy: smoking status during treatment (smoker vs. non-smoker), sex (woman vs. man), age ($\leq$65 vs. >65 years), schedule of radiotherapy (accelerated fractionation comprising 63.6–69.96 Gy with 2.12 Gy per fraction vs. conventional fractionation comprising 60–70 Gy with 2 Gy per fraction), technique used to deliver radiotherapy (intensity-modulated radiation therapy [IMRT] vs. three-dimensional conformal radiotherapy [3D-CRT]), the use of combined treatment methods (radiotherapy with surgery vs. without surgery, radiotherapy with chemotherapy vs. without chemotherapy), overall duration of radiotherapy ($\leq$43 days vs. >43 days) and cancer location (oral cavity vs. all other locations, oropharynx vs. all other locations, larynx vs. all other locations).

Ninety-nine patients (73%) who reported that they did not smoke during radiation therapy were classified as non-smokers. Thirty-seven patients (27%), who declared that they had not quit smoking completely during radiotherapy were classified as smokers. The characteristics of the patients and the treatment given are presented in Table 1. All patients were treated with external-beam radiation using a 6 MV photon beam from linear accelerators. All patients who were treated with the accelerated radiotherapy (2.12 Gy per fraction) schedule had IMRT. Seventy patients (52%) received definitive radiotherapy alone or radiochemotherapy, and 68 patients (48%) were treated with adjuvant radiotherapy or radiochemotherapy following curative surgery. Mean radiation doses were 65 Gy (range: 46–70 Gy) and 62 Gy (range: 50–66 Gy) for patients treated with definitive and postoperative radiotherapy, respectively. In patients given combined treatment, chemotherapy comprised cisplatin given concurrently with radiation (100 mg/m^2 every 3 weeks or 40 mg/m^2 weekly).

Statistical analysis was performed using STATISTICA software (version 10; 2012). The chi-square test was used to compare the percentage of smokers in relation to treatment- and other patient-related factors, and to compare the frequency of severe acute mucositis in relation to the variables analyzed. Possible interactions between smoking status and other variables in relation to the occurrence of grade III and higher acute mucositis were also tested with the correlation Pearson coefficient. To adjust for possible interactions, a multiple regression analysis was carried out to adjust the smoking status to other patient and treatment related parameters. A p-value $\leq$0.05 was considered significant.

4. Results

Sex distribution, cancer location, schedule and radiotherapy technique did not differ significantly between smokers and

Table 1 – Patient and treatment characteristics.

Variable	Number (%) unless otherwise stated
Sex	
Men	115 (85)
Women	21 (15)
Age (years)	Range: 35–83 Median: 60
Cancer localization	
Lip	4 (3)
Oral cavity	20 (15)
Salivary gland	7 (5)
Oropharynx	27 (20)
Maxillary sinus and nasal cavity	5 (3.5)
Nasopharynx	4 (3)
Hypopharynx	5 (3.5)
Larynx	58 (43)
Others	6 (4)
Type of treatment	
Radiotherapy alone	27 (20)
Radiochemotherapy	43 (32)
Postoperative radiotherapy	49 (36)
Postoperative radiochemotherapy	17 (12)
Fractionation schedule	
63.60–69.96 Gy in 30–33 fractions	57 (42)
60–66 Gy in 30–33 fractions	59 (43.5)
68–70 Gy in 34–35 fractions	11 (8)
46–50 Gy in 23–25 fractions	5 (3.5)
51 Gy in 17 fractions	4 (3)
Technique of radiotherapy	
IMRT	119 (88)
3D-CRT	17 (12)
Overall duration of radiotherapy (days)	Range: 21–54 Median: 43
Smoking status during radiotherapy	
Smokers	37 (27)
Non-smokers	99 (73)

non-smokers. The frequency of non-smokers was nonsignificantly higher in patients aged >65 years and in those who received radiotherapy alone (without chemotherapy) (Table 2). In eight instances, there was a disagreement between physician's and nurse's score (despite that they were aware of each other's result). In such a scenario, a higher reported degree of acute mucositis was scored for a purpose of this study.

None of the 136 patients exhibited a grade V acute mucosal reaction. Fifty-nine (43.5%) patients exhibited grade III or IV acute mucositis during radiation therapy. Similar percentages of patients exhibited a grade III or IV acute mucosal reaction in smokers and non-smokers (46% vs. 42%, $p = 0.71$) (Table 3). Smoking had no effect on the severity of acute mucositis in any subgroup of patients, except the division of patients into those with laryngeal cancer location and all others. Among patients with laryngeal cancer non-smokers had a significantly higher rate of grade III and higher acute mucositis than did patients who smoked during radiotherapy. On the other hand, in the subgroup with exclusion of laryngeal cancer, the incidence of grade III or IV acute mucositis was higher in smokers than in non-smokers (Table 4). The significant correlation was found for the occurrence of grade III and higher mucositis and location in division into the larynx ($R = -0.33$; $p = 0.01$) and other than the larynx ($R = 0.27$; $p = 0.02$).

Table 2 – Distribution of smokers and non-smokers in relation to the variables that may affect the severity of acute mucositis.

	Non-smokers No. (%)	Smokers No. (%)	p
Women	17 (17)	4 (11)	0.36
Men	82 (83)	33 (89)	
≤65 years	67 (68)	31 (84)	0.06
>65 years	32 (32)	6 (16)	
63.6–69.96 Gy	40 (40)	17 (46)	0.61
60–70 Gy	52 (52.5)	18 (49)	
IMRT	86 (87)	33 (89)	0.72
3D-CRT	13 (13)	4 (11)	
Chemotherapy	39 (39)	21 (57)	0.07
No chemotherapy	60 (61)	16 (43)	
Surgery	51 (52)	15 (41)	0.25
No surgery	48 (48)	22 (59)	
Oral cavity	14 (14.1)	6 (16)	0.76
Oropharynx	17 (17.2)	10 (27)	0.20
Larynx	42 (42.4)	16 (43)	0.93
Others	26 (26.3)	5 (14)	

Among patient-related factors, sex was not significantly related to the severity of the acute mucosal reaction ($p = 0.67$) and patients older than 65 years had fewer grade III or IV acute mucosal reactions than their younger counterparts ($p = 0.08$). However, the older patients received less intense radiotherapy (data not shown). Cancer location was significantly related to the severity of the acute mucosal reaction. A grade III or IV acute mucosal reaction was more frequent in patients with oropharynx cancer ($p = 0.006$) and less frequent in patients with laryngeal cancer ($p < 0.001$) compared with other locations (Table 3). Patients with laryngeal cancer had less intense radiotherapy (without chemotherapy and acceleration) compared with oropharyngeal cancer patients (data not shown). Additionally, the mucosa of the buccal cavity that contributes largely to the incidence of acute mucositis is excluded from radiation volume in large proportion of laryngeal cancer patients.

A significant relationship between treatment-related factors and the incidence of grade III or IV acute mucositis was found for patients treated with radiotherapy alone and those treated with the combination of radiotherapy and chemotherapy. The incidence of severe mucositis was higher in patients who received accelerated fractionation compared with those who received conventional fractionation ($p < 0.001$). A similar pattern was found for the addition of chemotherapy to radiotherapy compared with radiotherapy alone ($p = 0.002$). Half of the patients treated with IMRT had a grade III or IV acute mucosal reaction, but none of the patients treated with 3D-CRT developed this grade of mucosal toxicity ($p < 0.001$). However, all patients treated with 3D-CRT received conventionally fractionated radiotherapy. More patients who received radiotherapy without surgery had a grade III or IV acute mucosal reaction compared with those treated with radiotherapy and surgery ($p < 0.001$). However, 82% of patients treated in the postoperative setting had conventional fractionation

Table 3 – Distribution of the highest reported RTOG/EORTC grades of acute mucosal reaction during radiotherapy in relation to patient- and treatment-related factors.

Variables	Grade of acute mucosal reaction		
	I/II° No. (%)	III/IV° No. (%)	*p*
Smoking status			
Non-smokers	57 (58)	42 (42)	0.71
Smokers	20 (54)	17 (46)	
Sex			
Women	11 (52)	10 (48)	0.67
Men	66 (57)	49 (43)	
Age			
≤65	51 (52)	47 (48)	0.08
>65	26 (68)	12 (32)	
Schedule of radiotherapy			
63.6–69.96 Gy (df = 2.12 Gy)	18 (32)	39 (68)	0.00001
60–70 Gy (df = 2 Gy)	50 (71)	20 (29)	
Radiotherapy technique			
IMRT	60 (50)	59 (50)	0.0001
3D-CRT	17 (100)	0 (0)	
Combination of radiotherapy and chemotherapy			
With chemotherapy	25 (42)	35 (58)	0.0018
Without chemotherapy	52 (68)	24 (32)	
Combination of radiotherapy and surgery			
With surgery	47 (71)	19 (29)	0.00085
Without surgery	30 (43)	40 (57)	
Cancer localization: oral cavity			
Oral cavity	9 (45)	11 (55)	0.26
Others	68 (59)	48 (41)	
Cancer localization: oropharynx			
Oropharynx	9 (33)	18 (67)	0.006
Others	68 (62)	41 (38)	
Cancer localization: larynx			
Larynx	45 (78)	13 (22)	0.00002
Others	32 (41)	46 (59)	

compared with 34% of patients who received definitive radiotherapy.

In a multivariate regression model, smoking status during treatment also did not have an impact on the occurrence of severe mucosal reaction; only location other than larynx ($p = 0.004$), treatment acceleration ($p < 0.00001$), and lack of surgery ($p < 0.00001$) were related to the occurrence of grade III and higher mucosal reaction. When patients with laryngeal cancer were excluded, the multivariate regression model also did not demonstrate significant impact of smoking on the occurrence of severe mucositis.

The overall duration of radiotherapy ranged from 21 to 54 days (median: 43 days). Eighteen patients (13%) required extended hospitalization beyond the duration of radiotherapy to heal the mucosal and/or skin reaction and/or because of other treatment complications. Seven smokers (19%) and 11 non-smokers (11%) had an extended hospital stay because of complications ($p = 0.36$). Nine patients (five [13.5%] smokers and four [4%] non-smokers) required an additional 3–34 days of hospitalization to heal the mucosal reaction ($p = 0.05$).

Table 4 – Distribution of RTOG/EORTC grades of acute mucositis during radiotherapy among smokers and non-smokers in relation to other patient- and treatment-related factors.

Variable	Grade of acute mucosal reaction		
	I°/II° No. (%)	III°/IV° No. (%)	*p*
Women			
Non-smokers	9 (53)	8 (47)	0.65
Smokers	2 (50)	2 (50)	
Men			
Non-smokers	48 (59)	34 (41)	0.70
Smokers	18 (55)	15 (45)	
Age ≤ 65 years			
Non-smokers	35 (52)	32 (48)	0.95
Smokers	16 (52)	15 (48)	
Age > 65 years			
Non-smokers	22 (69)	10 (31)	0.71
Smokers	4 (67)	2 (33)	
63.6–69.96 Gy (df = 2.12 Gy)			
Non-smokers	13 (32.5)	27 (67.5)	0.82
Smokers	5 (29)	12 (71)	
60–70 Gy (df = 2 Gy)			
Non-smokers	37 (71)	15 (29)	0.93
Smokers	13 (72)	5 (28)	
IMRT			
Non-smokers	44 (51)	42 (49)	0.79
Smokers	16 (48)	17 (52)	
3D-CRT			
Non-smokers	13 (100)	0	–
Smokers	4 (100)	0	
Chemotherapy			
Non-smokers	15 (38)	24 (62)	0.49
Smokers	10 (48)	11 (52)	
No chemotherapy			
Non-smokers	42 (70)	18 (30)	0.79
Smokers	10 (62.5)	6 (37.5)	
Surgery			
Non-smokers	36 (71)	15 (29)	0.84
Smokers	11 (73)	4 (27)	
No surgery			
Non-smokers	21 (44)	27 (56)	0.82
Smokers	9 (41)	13 (59)	
Oral cavity			
Non-smokers	8 (57)	6 (43)	0.24
Smokers	1 (17)	5 (83)	
Other than oral cavity			
Non-smokers	49 (58)	36 (42)	0.72
Smokers	19 (61)	12 (39)	
Oropharynx			
Non-smokers	6 (35)	11 (65)	0.89
Smokers	3 (30)	7 (70)	
Other than oropharynx			
Non-smokers	51 (62)	31 (38)	0.94
Smokers	17 (63)	10 (37)	
Larynx			
Non-smokers	29 (69)	13 (31)	0.01
Smokers	16 (100)	0	
Other than larynx			
Non-smokers	28 (49)	29 (51)	0.02
Smokers	4 (19)	17 (81)	

5. Discussion

We found no relationship between smoking during radiotherapy and the incidence of severe acute mucositis in patients

with head and neck cancer. As expected, the severity of the acute mucosal reaction depended mainly on the intensity of the radiotherapy schedule, treatment acceleration and the use of concomitant radiochemotherapy. Despite these findings, however, we still believe that tobacco use should be discouraged in patients who smoke at the time of their cancer diagnosis. The adverse effects of smoking on survival, health status and the risk of developing other tobacco-use related malignancies are well recognized.[8] Providing smoking cessation support for oncological patients is recommended by the American Society for Clinical Oncology.[17,18]

Our study has some limitations. The group studied was heterogeneous with regard to cancer location, radiotherapy technique and treatment intensity. However, we found no significant relationships between smoking status during treatment and co-variables that might affect the severity of the acute mucosal reaction. Smokers tended to be younger than non-smokers, which is consistent with another study that reported that patients who smoked during cancer radiotherapy tended to be younger than non-smokers.[19] We were unable to control for the potential confounding effects of other patient-related factors, such as alcohol use and buccal and dental hygiene status because this information was not collected. However, other studies have suggested that smokers have less-favourable baseline characteristics, such as socio-demographic characteristics (lower educational level, less familial support, poorer self-rated baseline health status), which increase their risk of developing treatment-related complications.[18] Thus, we would expect a higher rate of side-effects in the current smokers because of the possible interactions with these uncontrolled risk factors. However, this was not observed, suggesting that the effect of smoking during radiotherapy on the early treatment tolerance is not as detrimental as is commonly believed.

Smoking during radiotherapy was not associated with more severe acute mucositis in any subgroup of patients except for patients with laryngeal cancer, for whom smoking during radiotherapy had a surprisingly protective effect on the incidence of this side-effect. This finding can be discounted because, in this particular location, the buccal cavity was excluded from the radiation field and obviously affected the reporting of acute signs of mucositis. When excluding the laryngeal location, smoking during treatment was positively correlated with the frequency of occurrence of severe acute mucositis. This finding may additionally support our hypothesis about a possible adverse effect of smoking on the incidence of severe mucositis. This may have been revealed for radiotherapy cases with larger volume of irradiated mucosa. However, the multiple regression model did not retain smoking as detrimental factor for the occurrence of severe mucositis in our study. Probably, multiple analyses and a relatively small subgroup size prevented us from controlling for this confounding factor of volume-effect.

The system to assess smoking status during radiotherapy was based on self-report and medical staff observations, which may not have been completely reliable or accurate. In a study that evaluated objective measures of smoking status in 20 patients with head and neck cancer during the course of radiotherapy by measuring carbon monoxide content in expired air and the serum concentration of cotinine, the sensitivity, specificity and positive predictive values of self-reporting were 79%, 80% and 92%, respectively.[20] Another weakness of our study is the lack of detailed information about smoking behaviour, such as the amount smoked and years of smoking before radiotherapy for both the smokers and non-smokers. In one study, smoking during radiotherapy did not influence the outcome, but baseline smoking status was a predictor of overall survival and local control.[21] It is probable that quitting smoking at the time of diagnosis or just before treatment does not improve treatment tolerance because the vascular damage caused by long-time smoking is irreparable and adversely affects tissue regeneration during and after radiotherapy.

Our estimation of the relationship between smoking during radiotherapy and the rate of severe mucositis was based on the highest RTOG/EORTC grade of the acute mucosal reaction. Other reports based this evaluation on the duration of the mucosal reaction or the need for enteral nutrition.[11,13] Changes of body mass index during radiotherapy would be another useful indication of the treatment tolerance. The choice of our end-point was related to the retrospective nature of our study because only such data were complete in the database, whereas the exact duration of severe mucositis would have been lacking in some patients. This is an obvious limitation of our study, because a longer duration of the severe acute mucosal reaction may negatively influence local control by the prolongation of the overall radiotherapy time. Rugg et al.[11] found a significant correlation between smoking during treatment and the duration of acute mucositis. In our study, the hospitalization time required to heal the mucosal complications was borderline significantly ($p = 0.05$) longer in smokers than in non-smokers. This may indicate that smoking has some influence on the occurrence of early mucosal side-effects. However, the relatively small group size, likely presence of confounding factors and choice of the end-point did not allow us to reveal the magnitude of this relationship.

Another limitation of our study was a schedule of evaluations of acute mucosal reactions by physicians. Examination of mucosa performed once a week during radiotherapy might have missed some events. It was proven that the pattern of mucositis development and healing may be more appropriately estimated when performed on daily basis.[22] On the other hand, we believe that daily nurses' examinations and a policy to react earlier and more frequently if clinically indicated compensated this lack of daily doctors' examinations.

Although the possible adverse effects of smoking on the risk of either acute or late toxicity are commonly accepted in clinical practice, the observations to support this assertion are scarce or conflicting. Our study is not the only one that did not find any impact of smoking on the early mucosal tolerance to radiotherapy in head and neck cancer patients. Other reports have also demonstrated no effect of smoking during radiotherapy on early treatment tolerance in these patients.[5,21,23] Acute mucositis in head and neck cancer patients has a complex pattern and aetiology, and many treatment and patient-related factors that were not evaluated in our study may interact with the intensity and duration of acute mucositis. Thus, it remains uncertain whether smoking during radiotherapy affects the early treatment tolerance. Because smoking is associated with an increased risk of

other tobacco use-related cancer and increased mortality from cardiovascular diseases, smoking cessation should be encouraged at the time of the cancer diagnosis. It is postulated that cancer diagnosis may be a "teachable moment" for heavily tobacco-addicted patients, and a nurse-led smoking cessation programme may be especially effective if started at the time of the diagnosis in such patients.[24]

6. Conclusions

We conclude that in this study, smoking during radiotherapy for head and neck cancer was not related to the early acute mucosal toxicity evaluated as the rate of the highest observed grade of mucositis. However, drawing firm conclusions on no effect of smoking on the occurrence of severe acute mucositis is limited by the heterogeneity of treatment techniques, radiation treatment volume and cancer locations. Demonstration of effect of smoking on the higher incidence of grade III or IV acute mucositis in locations other than the larynx and the trend to the prolonged hospital stay for healing mucosal reactions in those who continued smoking during treatment suggest a possible effect of smoking on the normal tissues tolerance. The recognized adverse effects of smoking on the survival and health status are an important reason to encourage patients to cease smoking totally before radiotherapy. Nevertheless, we did not confirm our hypothesis about the effect of smoking during radiotherapy for head and neck cancer on the occurrence of severe acute mucosal reaction.

Conflict of interest

None declared.

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