ACUTE MUCOSAL REACTIONS IN PATIENTS WITH ADVANCED HEAD AND NECK CANCER TREATED WITH CONCURRENT CHEMORADIOTHERAPY

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Abstract **–We conducted a clinical study to analyze the acute reactions in the oral cavity and the oropharyngeal (OCOPH) mucosa in patients with advanced head and neck cancer (HNC) undergoing a definitive treatment consisted of 3-D conformal radiotherapy combined with concomitant chemotherapy.**
Twenty nine patients with HNC who were treated between February 2008 and October 2009 were included in the study. The median age was 55 years (range 29-70). The site distribution was as follows: oropharynx, 20.7%; hypopharynx, 41.4%; larynx, 37.9%. The radiation technique used for 3-D conformal radiotherapy was named "oblique photon fields" technique. The OCOPH mucosa as a critical normal tissue was delineated in every patient. Extraction of planning target volume (PTV50) from the volume of OCOPH mucosa led to formation of an OCOPH mucosa with extracted PTV50 (OCOPHEx mucosa). Acute mucosal reactions were recorded using Radiation Therapy Oncology Group (RTOG) grading system. The duration of a maximum grade of reaction was also recorded. A time intensity parameter, so-called Severity-Time Units (STU), quantifying the area under the acute reaction curve, was used to express the intensity of mucositis over time in every patient.
Grade 3 acute mucosal reaction was manifested in 19 patients (65.5%). The median duration of confluent mucositis was 21 days (range 14-35). The STU less than 1000 mm^2 and the STU more than 1500 mm^2 was calculated in equal number of patients (9 patients, or 31.0%). Statistically significant difference in the distribution of the grade 3 reaction was found among patients with different site of the primary tumor ($p = 0.003$). Statistically significant difference was found between the grade of the acute mucositis and the volume of OCOPHEx mucosa, the dose in 50% of the volume of OCOPHEx (D50%, OCOPHEx) mucosa, and the mean dose to OCOPHEx mucosa ($p = 0.02$, $p = 0.0002$, $p = 0.00001$, respectively). The tested relation between STU and delineated volumes (PTV50 and OCOPHEx mucosa) showed the presence of statistically significant difference ($p = 0.044$ and $p = 0.02$, respectively). Statistically significant difference was also found between STU and the mean dose to OCOPHEx mucosa ($p = 0.0003$). Linear regression showed negative correlation between STU and the volume of OCOPHEx mucosa ($r = - 0.7$; $p < 0.05$).
The incidence and the duration of confluent mucositis were significantly greater in patients with oropharyngeal primary lesions. The intensity in time of acute mucosal reactions was significantly higher in patients with the greatest PTV50 and in those with the smallest volumes of OCOPHEx mucosa.

Keywords **– acute mucositis, head and neck cancer, radiotherapy, chemotherapy**

1. INTRODUCTION

Head and neck cancers (HNCs) are frequent tumors with an estimated annual global incidence of more than 550,000 cases diagnosed worldwide [1, 2]. About two-thirds of the patients are diagnosed with locoregionally advanced disease. Although radiotherapy and surgery remain the two main treatment options, the systemic therapy has become an integral part of multimodality treatment with radiotherapy and concurrent platinum-based chemo-radiotherapy being an evidence-based recommended standard of care in patients with locally advanced HNC [3-5]. The intensification of radiotherapy treatment for advanced HNC using concurrent chemotherapy, has resulted in significantly improved locoregional control and survival [4-6] but these improvements are obtained at the price of increased acute toxicity due to the interaction between chemo-therapy and radiotherapy [7, 8]. The increased patient morbidity, notably an increase in severe mucositis

that cause a substantial pain and interfere with the patient's ability to chew and swallow, inevitably worsens the patient's quality of life [9].

Mucositis is understood as a complex interaction of mucosal injury, inflammatory response, ulceration, and healing. Acute mucositis is the result of hypoplasia of the sqamous epithelium due to sterilization of mucosal stem cells and inhibition of proliferation of transit cells. In agreement with the normal cell turnover rate, the lack of supply of new cells caused by radiation, leads to a gradual, linear decrease in epithelial cell numbers [10]. If the cellularity of the mucosa drops bellow a certain critical level (about 70%), the cell production rate from surviving cells increases dramatically [11]. As fractionated radiotherapy continues, the cell production can not keep up with the cell killing and partial or complete denudation develops presenting as spotted or confluent mucositis. Once a peak of a confluent mucositis is reached, further increase in dose and cell killing will not produce any increase in the intensity of acute reaction, but directly influences the duration of the confluent mucositis and its healing [10, 11].

The severity and the duration of the mucositis are variable, depending on field size and shape, total dose, dose per fraction, and duration of radiotherapy. According to Van der Schueren [12], the irradiated mucosal surface, the sites treated and the general condition of the patient represent important factors influencing the mucosal reaction pattern. Also, the incidence of confluent mucositis doubles with the usage of concurrent chemoradiotherapy compared with radiotherapy alone [13].

The introduction of the conformal radiotherapy with 3-D treatment planning on computed tomography (CT) scans as the standard of practice in clinics around the world with tight target definitions of the primary tumor and neck nodal levels enables improvement of tumor coverage while sparing the surrounding critical tissues [14-16].

The aim of our study was to analyze the frequency and the intensity of the acute mucosal reactions in patients with advanced HNC treated with external-beam radiotherapy performed using a 3D conformal technique and a chemotherapy consisting of cisplatin given on a weekly basis administered concurrently with the radiotherapy course.

2. MATERIALS AND METHODS

Patient population and charateristics

A total of 29 patients with previously untreated stage III-IV HNC who received concurrent chemo-radiotherapy as their primary treatment between February 2008 and October 2009 at the University Clinic of Radiotherapy and Oncology in Skopje were included in this study. Detailed patients' characteristics are given in Table 1. The site distribution was as follows: oropharynx, 6 patients (20.7%); hypopharynx, 12 patients (41.4%); and larynx, 11 patients (37.9%). Patients were staged according to the 2002 criteria of the American Joint Committee on Cancer [17]. All patients had at least 6 months follow-up.

Table 1. Patients characteristics (n = 29)

Characteristics	Number of patients (%)
Gender	
Male	25 (86.2)
Female	4 (13.8)
Age, years	
Median	55
Range	29-70
Performance status (ECOG)	
0	19 (65.5)
1	10 (34.5)
Tracheostomy	
Yes	10 (34.5)
No	19 (65.5)
Site of primary tumor	
Oropharynx	6 (20.7)
Hypopharynx	12 (41.4)
Larynx	11 (37.9)
T stage	
T3	11 (37.9)
T4	18 (62.1)
N stage	
N0	13 (44.8)
N1	1 (3.4)
N2	11 (37.9)
N3	4 (13.8)
N– vs. N+	
N–	13 (44.8)
N+	16 (55.2)
Stage	
III	4 (13.8)
IV	25 (86.2)

ECOG, Eastern Cooperative Oncology Group.
*Because of rounding not all percentage total 100.

Treatment

Patients were immobilized in supine position with a thermoplastic head and neck mask. They were treated by photons with beam qualities of 6 MV and 15 MV and electrons with energies 9-16 MeV. For the treatment planning, we used the Eclipse Version 7.3.10, a commercial 3-D treatment planning system manufactured by Varian Medical Systems. The CT scanning was made for each patient in the treatment position with slice thickness of 0.5 cm.

The gross tumor volume of the primary tumor (GTVt70) and the metastatic lymph nodes (GTVn70) were defined as any visible tumor and the gross nodal disease revealed on imaging studies and/or physical examination. The neck lymph nodes were considered metastatic when their smallest axis diameter was greater then 1.0 cm. The clinical target volume (CTVt50) encompassed the GTVt70 plus a margin of

1.0-2.0 cm for the potential microscopic extension of the disease. In patients with negative neck lymph nodes the CTVn50 included the nodal regions in the neck at levels II–IV. In patients with clinically involved neck lymph nodes, CTVn50 included GTVn70 with a margin of 0.5-1.0 cm and also encompassed retropharyngeal lymph nodes and nodal regions at levels I-V. Level VI was included in CTVn50 only in cases when primary tumor invaded subgllotis or esophagus. A CTV50 was created by integration of CTVt50 and CTVn50. The planning target volumes were PTV50 and PTV70. The PTV50 provided a margin of 0.5 cm around CTV50. If there were no positive lymph nodes in the neck, the PTV70 encompassed the GTVt70 plus a 0.5 cm margin. In patients with a nodal disease, the GTV70 was union of GTVt70 and GTVn70, and by adding a margin of 0.5 cm around it, we obtained PTV70. The oral cavity and the oropharyngeal (OCOPH) mucosa as a critical normal tissue was also delineated in every patient. Then, the PTV50 was extracted from the volume of the OCOPH mucosa. This procedure led to formation of the OCOPH mucosa with extracted PTV50 (OCOPHEx mucosa).

Details of the radiation technique used have been already published [18]. All treated patients received the full planned dose of radiotherapy (70 Gy). In 24 patients (82.8%), the overall treatment time (OTT) for radiotherapy completion was ≤ 7 weeks. In the other 5 patients (17.2%) the radiotherapy was completed in a period of time longer than 7 weeks.

Chemotherapy consisted of cisplatin 30 mg/m^2 in 0.5 L of normal saline over 1 hour given to the patients concomitantly with radiation on a weekly basis, starting on the first day of radiotherapy. The complete blood picture and the biochemistry were checked weekly before chemotherapy. Fourteen patients (48.3%) completed all seven cycles of concurrent chemo-therapy. Six cycles of cisplatin was given in 11 patients (37.9%), while 4 patients (13.8%) had less than six cycles of cisplatin with patients' refusal being the only cause for concurrent chemotherapy cessation. The median total dose of cisplatin given was 180 mg/m^2 (range 120-210).

Characteristics of delineated volumes

The median value of the GTV was 91 cm^3 (range 29-354). The GTV ≤ 65 cm^3 and the GTV between 66 cm^3 and 130 cm^3 were present in equal number of patients (10, or 34.5%). The GTV more than 130 cm^3 was present in 9 patients (31.0%). The median value of the PTV50 was 642 cm^3 (range 340-936). The PTV50 between 501 cm^3 and 660 cm^3 was measured in 12 patients (41.4%). The PTV50 more than 660 cm^3 was present in 11 patients (37.9%) while the PTV ≤ 500 cm^3 was seen in 6 patients (20.7%). The PTV70 median value was 161 cm^3 (range 70-527). The PTV70 ≤ 130 cm^3 was present in 8 patients (27.6%). In 12 patients (41.4%) the measured PTV70 was between 131 cm^3 and 200 cm^3 and 9 patients (31.0%) had the PTV70 more than 200 cm^3. The median volume of OCOPH mucosa was 166 cm^3 (range 104-226). The median volume of the OCOPHEx mucosa was 106 cm^3 (range 18-172). Volume of the OCOPHEx mucosa ≤ 100 cm^3 was measured in almost half of the patients (12, or 41.4%). Eight patients (27.6%) had a volume of the OCOPHEx mucosa between 101 cm^3 and 103 cm^3, and 9 patients (31.0%) was with volume of the OCOPHEx mucosa more than 130 cm^3. Values of the volumes of the OCOPHEx mucosa according to the site of the primary tumor are summarized in Table 2. The lowest median value was seen in patients with oropharyngeal carcinoma, while the highest median value was present in patients with carcinoma of the larynx (47 cm^3 and 135 cm^3, respectively).

Table 2. Volumes of oral cavity and oropharyngeal mucosa with extracted PTV50 according to the site of the primary tumor

Tumor characteristics	No of pts	Volume of OCOPH mucosa with extracted PTV50 (cm^3)	
		Median	Range
Site of the primary tumor			
Oropharynx	6	47	18-74
Hypoharynx	12	106.5	64-151
Larynx	11	135	78-172

Doses to oral cavity and oropharyngeal mucosa with extracted PTV50

The median values of the calculated doses were as follows: maximum dose, 71 Gy (range 54-74); mean dose, 42 Gy (range 26-64); and D50%, OCOPHEx mucosa, 47 Gy (range 22-69). Mean dose ≤ 40 Gy was delivered in 13 patients (44.8%). In the rest 16 patients (55.2%) the mean dose to the OCOPHEx mucosa was more than 40 Gy.

Assessment of acute mucositis

Weekly assessments of acute mucositis during chemoradiotherapy were performed by the radiation oncologist according to the Acute Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group (RTOG) (quantal descriptive scoring system from 0 to 4) [19]. Patients were also evaluated for acute mucositis during early post-irradiation follow-up visits. The severity (grade) of acute mucositis, the time to development of acute reaction (spotted or confluent mucositis i. e. days to Grade > 1), and the duration of the maximum grade of reaction were recorded. The intensity of mucositis over time was used as an additional endpoint of the normal tissue acute reaction. This time intensity parameter, so-called Severity-Time Units (STU), quantifyed the area under the acute reaction curve expressing grade of acute mucositis vs. time, starting at the first day of treatment up to 12 weeks following radiotherapy commencement. STU was considered to be a more appropriate indicator of the radiosensitivity

of a normal mucosa incorporating the severity of acute mucosal reaction and its kinetics i.e. the time to maximum grade of acute mucositis, its duration, and the time of healing. For each patient, grades of mucositis were plotted as a function of time at day 1 through day 84. Adjacent data points were than connected using straight line segments, and the STU as an area under the curve was calculated. So, mathematically, the STU was the sum of consecutive severity-scores multiplied by their duration in days.

Statistical analysis

In the analysis of the significant differences between the grade of acute mucosal reaction and tumor characteristics, delineated target volumes, volume of OCOPHEx mucosa, and doses delivered to OCOPHEx mucosa, Chi-square test or Fisher exact test were used. Significant differences between the duration of confluent mucositis and tumor characteristics and delineated target volumes were tested with Mann-Whitney U test or Fisher exact test. Significant differences between the STU and characteristics of delineated target volumes, volume of OCOPHEx mucosa, and the doses delivered to OCOPHEx mucosa were tested with Kruskal-Wallis ANOVA or Chi-square test. Correlation between STU and the volume of OCOPHEx mucosa and between STU and the mean dose delivered to the volume of OCOPHEx mucosa was tested by linear regression.

3. RESULTS

Characteristics of acute reactions in OCOPH mucosa are summarized in Table 3. Confluent mucositis (grade 3 reaction) as a maximum grade of reaction was manifested in 19 patients (65.5%). The median time to development of confluent mucositis was 21 days (range 14-21). The median duration of confluent mucositis was 21 days (range 14-35). In almost two thirds of patients (12, or 63.2%) the duration of the grade 3 reaction was ≤ 21 days. The STU less than 1000 mm^2 and the STU more than 1500 mm^2 were calculated in equal number of patients (9, or 31.0%).

There was a stastistically significant difference found in the distribution of the acute mucosal reactions among patients with different sites of the primary tumor (Chi-square test; p = 0.003) (Table 4). The confluent mucositis was significantly more expressed in patients with oropharyngeal and hypopharyngeal primary lesions. The grade of the acute mucosal reactions significantly differed among the three classes of the volume of OCOPHEx mucosa (Chi-square test; p = 0.02) (Table 4). The incidence of confluent mucositis was signficantly higher in patients with volume of OCOPHEx mucosa ≤ 100 cm^3. A significant difference existed between the grade of the acute mucositis and the D50%, OCOPHEx mucosa, and between the grade of the mucositis and the mean dose to the volume of OCOPHEx mucosa (Fisher exact test; p = 0.0002 and p = 0.00001, respectively) (Table 4). The confluent mucositis was significantly more expressed in patients with D50%, OCOPHEx mucosa > 45 Gy and in those with a mean dose in OCOPHEx mucosa being > 40 Gy.

Table 3. Characteristics of acute reactions in oral cavity and oropharyngeal mucosa

Characteristics	Number of patients (%)
Maximum grade of reaction (n =29)	
Grade 2	10 (34.5)
Grade 3	19 (65.5)
Time to grade 2 reaction, days	
Median	21
Range	14-28
Duration of grade 2 reaction, days	
Median	14
Range	14-28
Time to grade 3 reaction, days	
Median	21
Range	14-21
Time to grade 3 reaction (n =19)	
≤ 14 days	5 (26.3)
> 14 days	14 (73.7)
Duration of grade 3 reaction, days	
Median	21
Range	14-35
Duration of grade 3 reaction (n =19)	
≤ 21 days	12 (63.2)
> 21 days	7 (36.8)
Severity-Time Units (STU) (n =29)	
< 1000 mm^3	9 (31.0)
1000-1500 mm^3	11 (38.0)
> 1500 mm^3	9 (31.0)

A stastistically significant difference was found between the duration of the grade 3 acute mucositis and the site of the primary tumor and between the duration of the grade 3 acute mucositis and the PTV70 (Mann-Whitney U test; p = 0.013 and p = 0.047, respectively). (Table 5). The duration of grade 3 mucositis > 21 days was apparently more represented in patients with oropharyngeal cancer and in those with PTV70 > 200 cm^3.

When testing the differences between STU and delineated volumes we found the existence of a statistically significant difference between STU and PTV50 and between STU and the volume of OCOPHEx mucosa (Kruskal-Wallis ANOVA; p = 0.044 and p = 0.02, respectively), showing that intensity in time of acute mucosal reactions was significantly higher in patients with the greatest PTV50 and in those cases with the smallest volumes of OCOPHEx mucosa (Table 6).

Table 4. Grades of maximal acute mucosal reaction according to tumor and treatment characteristics

Characteristics	No of pts	Grade of mucosal reaction		p
		Grade 2	Grade 3	
		No of pts (%)		
Site of the primary tumor				
Oropharynx	6	0 (0.0)	6 (100.0)	
Hypoharynx	12	2 (16.7)	10 (83.3)	0.003
Larynx	11	8 (72.7)	3 (27.3)	
T stage				
T3	11	4 (36.4)	7 (63.6)	0.590
T4	18	6 (33.3)	12 (66.7)	
N- vs N+				
N-	13	7 (53.8)	6 (46.2)	0.064
N+	16	3 (18.8)	13 (81.2)	
Stage				
III	4	3 (75.0)	1 (25.0)	0.100
IV	25	7 (28.0)	18 (72.0)	
PTV50 (cm^3)				
≤ 500	6	4 (66.7)	2 (33.3)	
501-660	12	4 (33.3)	8 (66.7)	0.131
> 660	11	2 (18.2)	9 (81.8)	
PTV70 (cm^3)				
≤ 130	8	4 (50.0)	4 (50.0)	
131-200	12	5 (41.7)	7 (58.3)	0.192
> 200	9	1 (11.1)	8 (88.9)	
Volume of OCOPH mucosa with extracted PTV% (cm^3)				
≤ 100	12	1 (8.3)	11 (91.7)	
101-130	8	3 (37.5)	5 (62.5)	0.020
> 130	9	6 (66.7)	3 (33.3)	
Dose in 50% volume of OCOPHEx mucosa (Gy)				
≤ 45	12	9 (75.0)	3 (25.0)	0.0002
> 45	17	1 (5.9)	16 (94.1)	
Mean dose to OCOPHEx mucosa (Gy)				
≤ 40	13	10 (76.9)	3 (23.1)	0.00001
> 40	16	0 (0.0)	16 (100.0)	

PTV, planning target volume; OCOPHEx mucosa, oral cavity and oropharyngeal mucosawith extracted PTV50.

Fig. 1 - Linear regression between STU and the volume of OCOPHEx mucosa

The presence of a negative correlation between STU and the volume of OCOPHEx mucosa was confirmed with linear regression (r = - 0.7; p < 0.05) (Fig 1).

Table 5. Duration of grade 3 reaction according to tumor and treatment characteristics (n = 19)

Characteristics	No of pts	Duration of grade 3 mucositis (days)		p
		≤ 21	> 21	
		No of pts (%)		
Site of the primary tumor				
Oropharynx	6	1 (16.7)	5 (83.3)	
Hypoharynx	10	8 (80.0)	2 (20.0)	0.013
Larynx	3	3 (100.0)	0 (0.0)	
T stage				
T3	7	4 (57.1)	3 (42.9)	0.110
T4	12	8 (66.7)	4 (33.3)	
N- vs. N+				
N-	6	5 (83.3)	1 (16.7)	0.332
N+	13	7 (53.8)	6 (46.2)	
Stage				
III	1	1 (100.0)	0 (0.0)	0.631
IV	18	11 (61.1)	7 (38.9)	
PTV50 (cm^3)				
≤ 500	2	2 (100.0)	0 (0.0)	
501-660	8	6 (75.0)	2 (25.0)	0.128
> 660	9	4 (44.4)	5 (55.6)	
PTV70 (cm^3)				
≤ 130	4	4 (100.0)	0 (0.0)	
131-200	7	5 (71.4)	2 (28.6)	0.047
> 200	8	3 (37.5)	5 (62.5)	

PTV, planning target volume.

There was also a statistically significant difference found between STU and the D50%, OCOPHEx mucosa and between STU and the mean dose to the volume of OCOPHEx mucosa (Chi-square test; p = 0.0001 and p = 0.0003, respectively) (Table 6). Correlation between STU and the mean dose delivered to the volume of OCOPHEx mucosa was confirmed with linear regression (r = 0.9; p < 0.05) (Fig. 2).

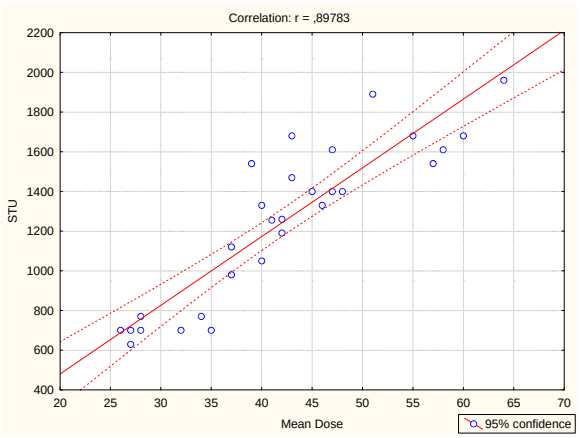

Fig. 2 - Linear regression between STU and mean dose to OCOPHEx mucosa

Table 6. Severity-Time Units according to treatment characteristics

Characteristics	Total number of patients	STU (mm^2)			p-value
		< 1000 (n = 9)	1000-1500 (n =11)	> 1500 (n =9)	
		Number of patients (%)			
PTV50					
≤ 500	6	4 (66.7)	2 (33.3)	0 (0.0)	
501-660	12	3 (25.0)	6 (50.0)	3 (25.0)	0.044
> 660	11	2 (18.2)	3 (27.3)	6 (54.5)	
PTV70					
≤ 130	8	3 (37.5)	4 (50.0)	1 (12.5)	
131-200	12	5 (41.7)	4 (33.3)	3 (25.0)	0.150
> 200	9	1 (11.1)	3 (33.3)	5 (55.6)	
Volume of OCOPHEx mucosa (cm^3)					
≤ 100	12	1 (8.3)	4 (33.3)	7 (58.3)	
101-130	8	3 (37.5)	4 (50.0)	1 (12.5)	0.020
> 130	9	5 (55.6)	3 (33.3)	1 (11.1)	
Dose in 50% volume of OCOPHEx mucosa (Gy)					
≤ 45	12	9 (75.0)	2 (16.7)	1 (8.3)	0.0001
> 45	17	0 (0.0)	9 (52.9)	8 (47.1)	
Mean dose to OCOPHEx mucosa (Gy)					
≤ 40	13	9 (69.2)	3 (23.1)	1 (7.7)	0.0003
> 40	16	0 (0.0)	8 (50.0)	8 (50.0)	

PTV, planning target volume; STU, Severity-Time Units; OCOPHEx mucosa, oral and oropharyngeal mucosa with extracted PTV50.
*Because of rounding not all percentage total 100.

4. CONCLUSION

Considering the results of our study we take the liberty to recommend delineation of OCOPH mucosa to be established as a routine procedure in contouring normal tissue volumes. This procedure, in conditions of implemented Intensity Modulated Radiation Therapy (IMRT), is expected to enable delivering doses equal or less that 40 Gy at OCOPHEx mucosa in order to prevent a high incidence of confluent mucositis. Regarding the results that showed the incidence of the confluent mucositis and it's intensity in time being significantly higher in patients with smallest volumes of OCOPHEx mucosa and taking into account that the incidence and the duration of the confluent mucositis were significantly greater in patients with oropharyngeal primary lesions, we can conclude that this procedure would be expected to be most valuable in this patients' category that is characterized with the lowest median value of OCOPHEx mucosa.

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