Primary, secondary and tertiary prevention of oral malignant tumors

Prof. Dr. Katalin Nagy PhD DSc
Faculty of Dentistry, University of Szeged
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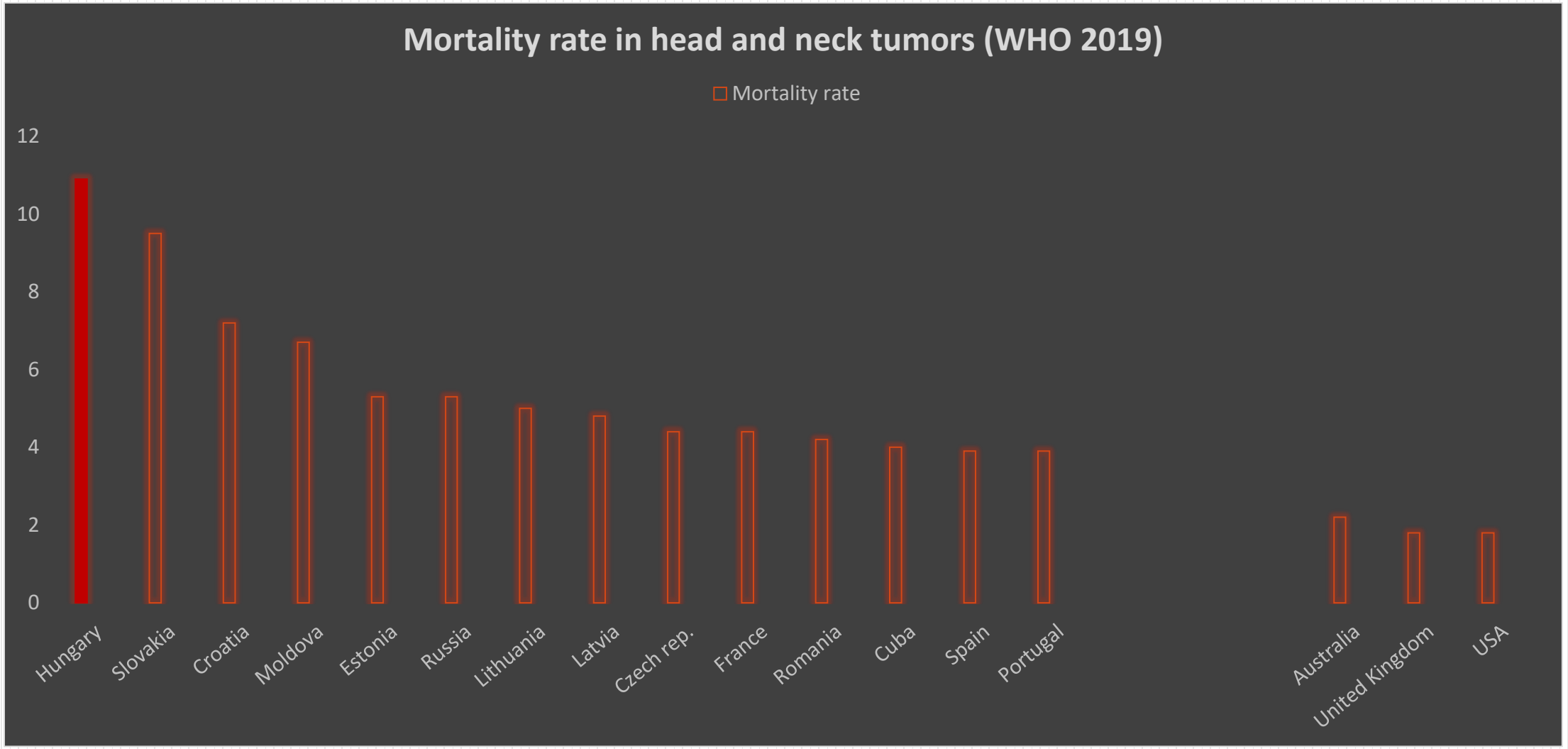
Background data



Overview

- **Primary prevention**
  - aims to prevent disease or injury before it ever occurs.
- **Secondary prevention**
  - is early disease detection, making it possible
    - to prevent the worsening of the disease
    - to minimize complications and limit disabilities before the disease becomes severe
    - early detection of disease in asymptomatic patients with screening or diagnostic testing
    - preventing the spread of diseases
- **Tertiary prevention**
  - to reduce the negative impact of an already-established disease by restoring function and reducing disease-related complications, also aims to improve the quality of life for people with disease

Primary prevention (education, prevention campaigns)

- The Faculty of Dentistry of the University of Szeged was the first to introduce a new subject into the graduate dental curriculum that focuses on educating new generation of dentists aiming to reduce smoking as a major etiological factor in oral cancer.

/International Tobacco and Health Research and Capacity Building Program (RFA-TW-06-006) *Wake Forest University/*

Antal M, Forster A, Zalai Z, Barabas K, Spangler J, Braunitzer G, **Nagy K**.: A video feedback-based tobacco cessation counselling course for undergraduates-preliminary results. *European Journal of Dental Education*. 2013;17(1):e166-72**.**

Secondary prevention

- It is necessary for dentists to consciously, regularly perform and organize **screening,** specifically for conditions predisposing to lip and oral cancer (this is also the obligation of the Ministry of National Economy Decree 51/1997 XII.18. that within the scope or framework of compulsory health insurance, that health care services are available for the prevention and early detection of diseases.

- Vulnerable (at risk) population! (insufficient oral hygiene, diet)

Tertiary prevention

- Throughout my research and clinical work, my colleagues and I have been working to find solutions that can be put into practice and directly improve patients' health and quality of life.

- we focused mainly on the **tertiary prevention**.

The main objectives:

I. In the field of **microbiology**
   A. description of oral microflora
   B. *antimicrobial* treatments to prevent complications and subsequent morbidity
   C. Investigation of proliferating *fungi colonizing* the tumor surface

II. In the field of **prosthetic rehabilitation** of head and neck cancer patients
   A. Improving their *quality of life*
   B. Measurable demonstration of *restoring function and esthetics* as much as possible or to the largest possible extent

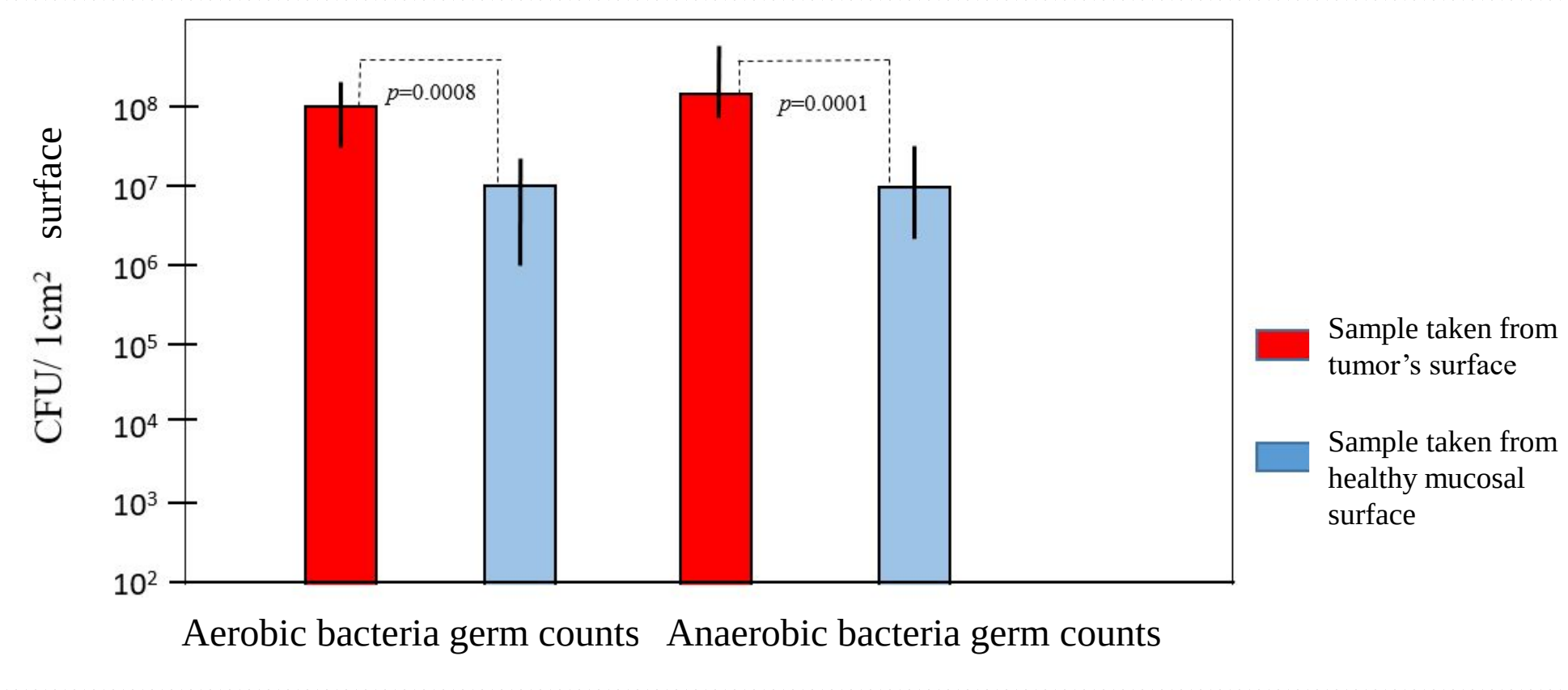
I/A Examination of microflora associated with human oral carcinoma surfaces

Based on our observations, we decided to compare a sample taken from a patient's tumor surface with samples taken from a healthy mucosal surface of the same individual (aerobic and anaerobic bacterial count and composition of isolated species)

Nagy, K., Sonkodi, I., Szőke, I., Nagy, E., & Newman, H. N. (1998) The microflora associated with human oral carcinomas. *Oral Oncol,* 34: 304-308

I/A Examination of microflora associated with oral carcinoma surfaces (quantitative)

Figure 1. Mean number of aerobic and anaerobic germ count with standard deviation, from culturing samples from 21 patients with squamous cell carcinoma of the oral cavity



I/A Examination of oral tumor surface microflora (qualitative)

Aerobic bacterial strains isolated from tumor surface and contiguous healthy mucosal surfaces in 21 patients. The numbers indicate the number of cases (number of patients) in which these strains were detected. In addition, it should be noted that *Candida albicans* was found at 8 of the 21 tumor sites, but since it is not a bacterial species, it was not included in the table.

Species	Tumor	Control
Gram-positive		
Streptococcus α-haemolyticus	21	21
Streptococcus β-haemolyticus	3	0
Staphylococcus spp. (coagulase neg.)	15	15
Stphylococcus aureus	2	1
Enterococcus faecalis	12	9
Corynebacterium spp.	5	7
Gram-negative		
Haemophilus influenzae	14	11
Haemophilus parainfluenzae	3	4
Haemophilus haemolyticus	1	1
Serratia liquefaciens	3	1
Klebsiella pneumoniae	2	0
Escherichia coli	1	1
Citrobacter freundii	1	0
Pseudomonas spp.	1	1
Neissera spp.	13	20
Branhamella spp.	2	3

I/A Examination of microflora associated with oral carcinoma surfaces

Anaerobic bacterial strains isolated from tumor and healthy mucosal surfaces in 21 patients. The numbers indicate the number of cases (number of patients) in which these strains were detected.

Species	Tumor	Control
Gram-positive		
Peptostreptococcus spp.	21	20
Lactobacillus spp.	12	8
Actinomyces spp.	11	1
Propionibacterium spp.	9	1
Clostridium spp.	5	1
Gram-negative		
Veillonella spp.	18	9
Fusobacterium spp.	14	1
Prevotella spp.	11	2
Porphyromonas spp.	9	0
Bacteroides ureolyticus/gracilis	8	2
Capnocytophaga spp.	1	0

I/A Examination of microflora associated with oral carcinoma surfaces

The previously mentioned research results have shown that the presence of squamous cell carcinoma in the oral cavity:

Significantly changes the local microflora (especially the proliferation of *Candida* species and various anaerobic bacterial species)

- Consequently:
  - Causing local complications and various effects on the quality of life (e.g. halitosis)
  - It can also have systemic consequences [Newman, 1996], focal infections.

? Topical treatment of the microflora have a beneficial effect on quality of life ?

I/B Antimicrobial treatment of oral tumor surface

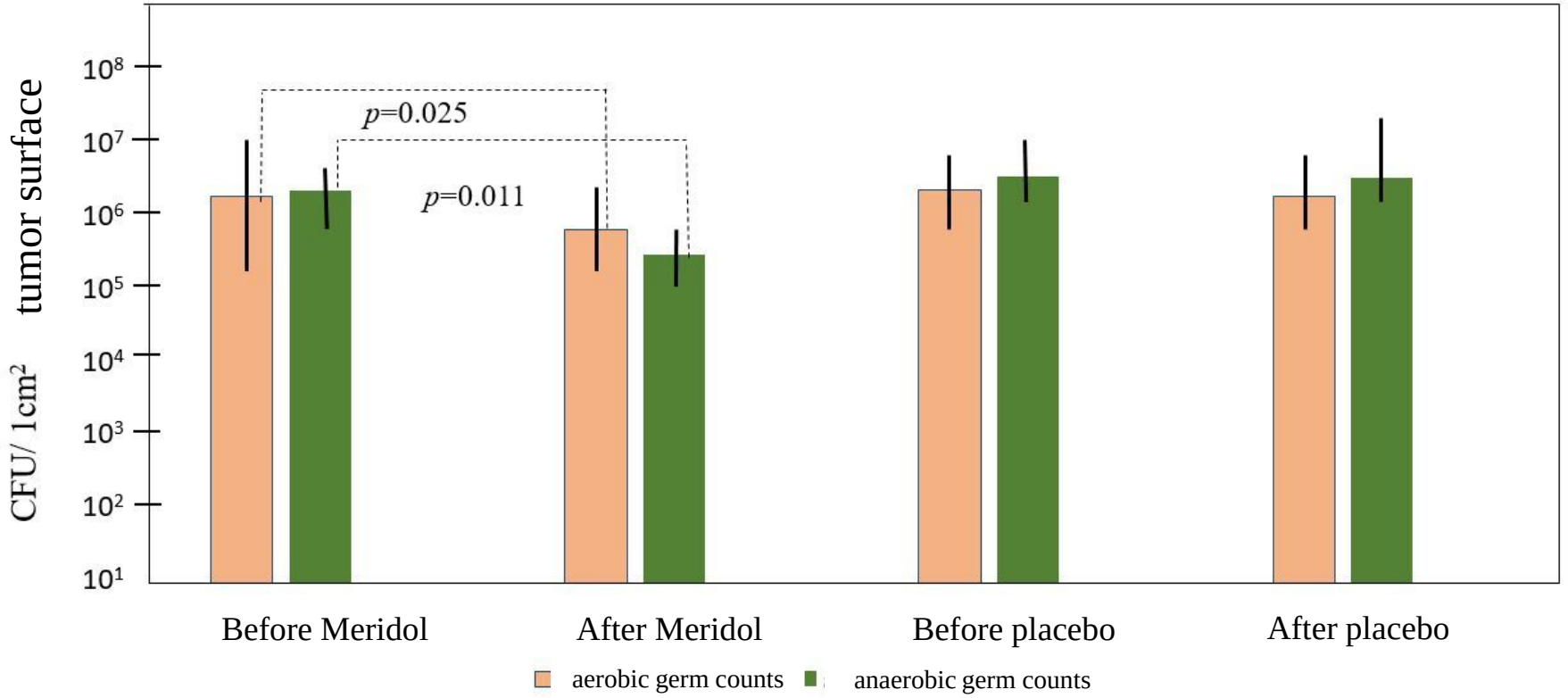
Effect of non-alcoholic aminofluoride-containing mouthwash was used

To assess the efficacy, we performed microbiological studies, monitored the clinical condition of our patients, and also considered subjective symptoms.

Nagy, K., Szoke, I., Sonkodi, I., Nagy, E., Mari, A., Szolnoky, G., & Newman, H. N. (2000) Inhibition of microflora associated with oral malignancy. *Oral Oncol,* 36: 32-36.

I/B Antimicrobial treatment of oral tumor surface

Figure 2. Changes in the aerobic and anaerobic germ count on a 1cm^2 squamous cell carcinoma tumor surface sample of 5-5 patients after rinsing with Meridol and placebo



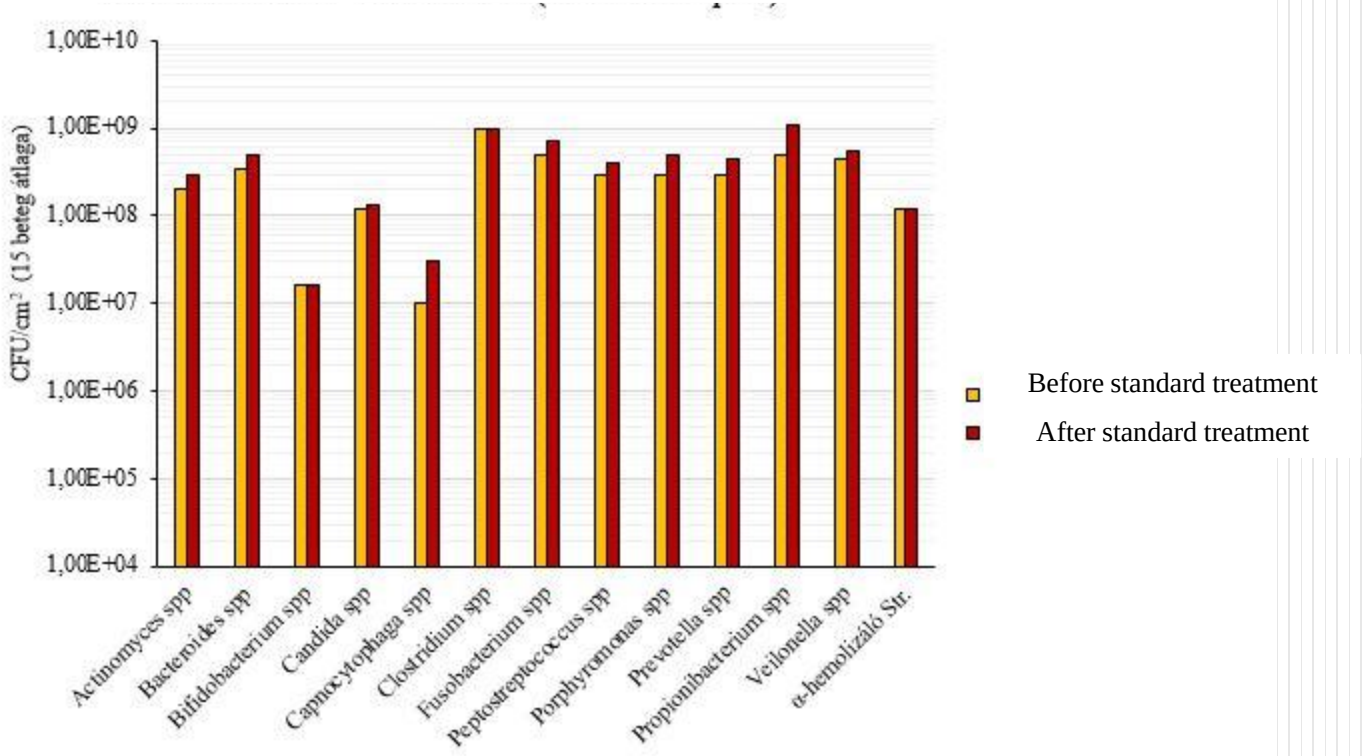
I/B Treatment of xerostomia and mucositis with lactoperoxidase (Biotène) after radiotherapy

Bacteriological examination of a sample of 1 cm^2 of irradiated and ulcerated mucosal surfaces of 30 patients using the same aforementioned methods.

Nagy, K., Urbán, E., Fazekas, O., Thurzó, L., & Nagy, E. (2007) Controlled study of lactoperoxidase gel on oral flora and saliva in irradiated patients with oral cancer. *J Craniofac Surg,* 18: 1157-1164.

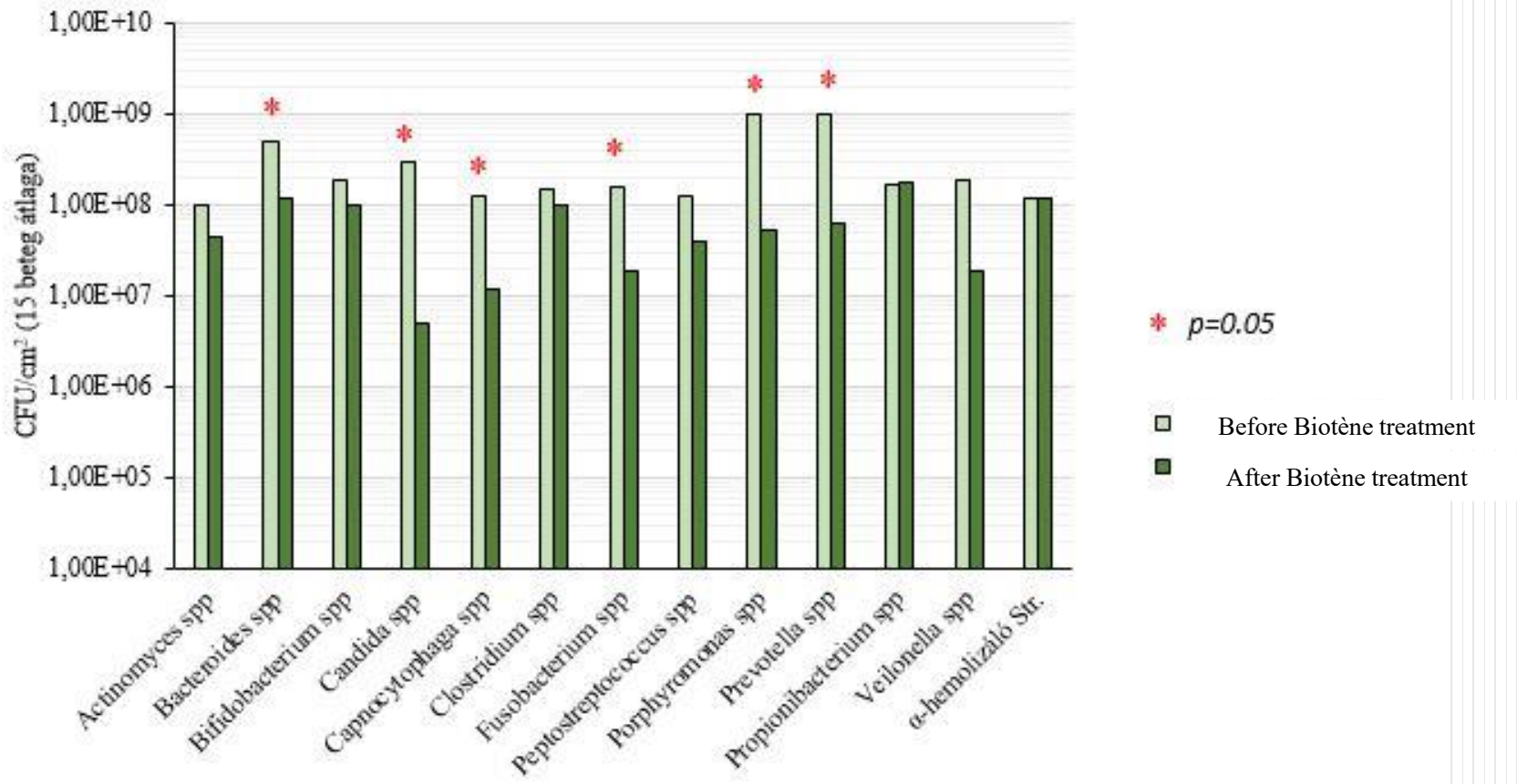
I/B Treatment of xerostomia and mucositis with lactoperoxidase (Biotène) after radiotherapy

Figure 3. Mean germ count of different bacterial / fungal species before and after standard treatment (control group)



I/B Treatment of xerostomia and mucositis with lactoperoxidase (Biotène) after radiotherapy

Figure 4. Mean germ count of different bacterial / fungal species before and after Biotène treatment (test group)



I/C Examination of proliferating fungi colonizing the tumor surface

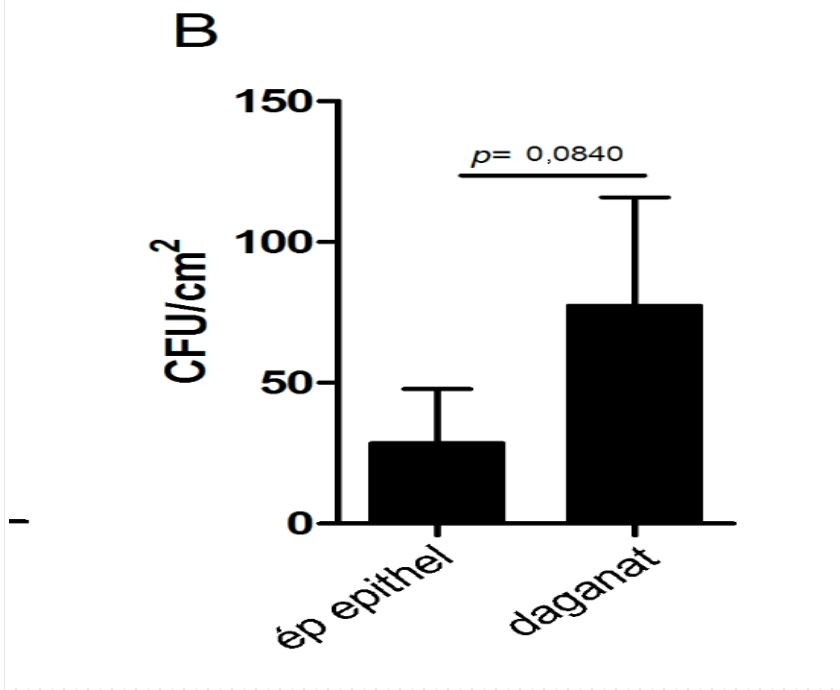
Berkovits, C., Tóth, A., Szenzenstein, J., Deák, T., Urbán, E., Gácser, A., & **Nagy, K**. (2016) Analysis of oral yeast microflora in patients with oral squamous cell carcinoma. *Springerplus,* 5: 1257.

I/C Examination of proliferating fungi colonizing on tumor surface

Group		Positive, n (%)	Negative, n (%)
Control (n=40)	Original sample	3 (7,5)	37 (92,5)
	Subculture	12 (30)	28 (70)
Patient (n=20)	Original sample	10 (50)	10 (50)
	Subculture	18 (90)	2 (10)

Genus	**Number of isolates (%)**	
	Control (n=12)	patient (n=22)
Candida	10 (83,3)	15 (68,2)
Rhodotorula	-	2 (9,1)
Saccharomyces	-	2 (9,1)
Kloeckera	-	1 (4,5)
other (not exactly identified)	2 (16,7)	2 (9,1)

I/C Detection of proliferating *Candida spp* colonizing on the tumor surface compared to a healthy control



We also compared the tumorous and healthy epithelium of the same patients. On the tumorous surface, an average of 77.38 ± 38.53 CFU / cm2 colony forming units was counted, compared to only 28.58 ± 19.18 CFU / cm2 on the healthy surface. The difference here, despite the seemingly large difference, did not prove to be significant (p = 0.084).

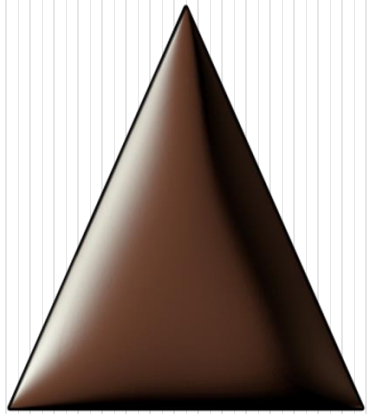
I/C Examination of lipase and protease activity in Candida species

Extracellular enzymatic activity (MALDI-TOF) of isolate samples from healthy and pathological/diseases mucosa

		lip+	lip-	prot+	prot-	lip+/prot+	lip+/prot-	lip-/prot+	lip-/prot-
Control (*N*=40)	*N*	13	27	15	25	6	7	9	18
	%	32,5	67,5	37,5	62,5	15	17,5	22,5	45
Patient (*N*=140)	*N*	53	87	66	74	37	16	29	58
	%	37,86	62,14	47,14	52,86	26,43	11,43	20,71	41,43

Tertiary prevention by prosthetic means

Increase in survival time and number of survivors



Quality of Life (QOL)

QOL (WHO definition)

- „A state of complete physical, mental, and social well-being not only the absence of disease,” (1947)

- „individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns’’(current definition)

Facial defects

- Esthetics
  - Visibility
- Functional
  - Speech
  - Swallowing
  - Eating
  - Drooling
- Psychological (as a result of the abovementioned)

QOL

The informed consent to use patient's photographs

NYILATKOZAT

Kijelentem, hogy fertőző betegségben (AIDS, Hepatitis, TBC) nem szenvedek.

.....

(beteg/törvényes képviselő)

Hozzájárulását kérjük ahhoz, hogy Önről Önt fel nem ismerhető módon ábrázoló fénykép és/vagy videofelvétel készüljön, s az különösen oktatási, kutatási, tudományos célból felhasználásra, nyilvánosságra hozatalra kerüljön. Tájékoztatjuk, hogy hozzájárulásának megadása önkéntes.

A felvétel elkészítésének célja a Szegedi Tudományegyetem, illetve annak közalkalmazottai oktatási, kutatási, tudományos tevékenységének támogatása. A fénykép-, videofelvétel készítésére, felhasználására, azzal kapcsolatos műveletek végzésére a Szegedi Tudományegyetemen, valamint az adatfeldolgozó érdekkörébe tartozó személyek jogosultak. Ön az SZTE Fogorvostudományi Karhoz intézett írásbeli nyilatkozatával kérhet tájékoztatást képmásának felhasználásáról, valamint tiltakozhat képmásának kezelésével szemben.

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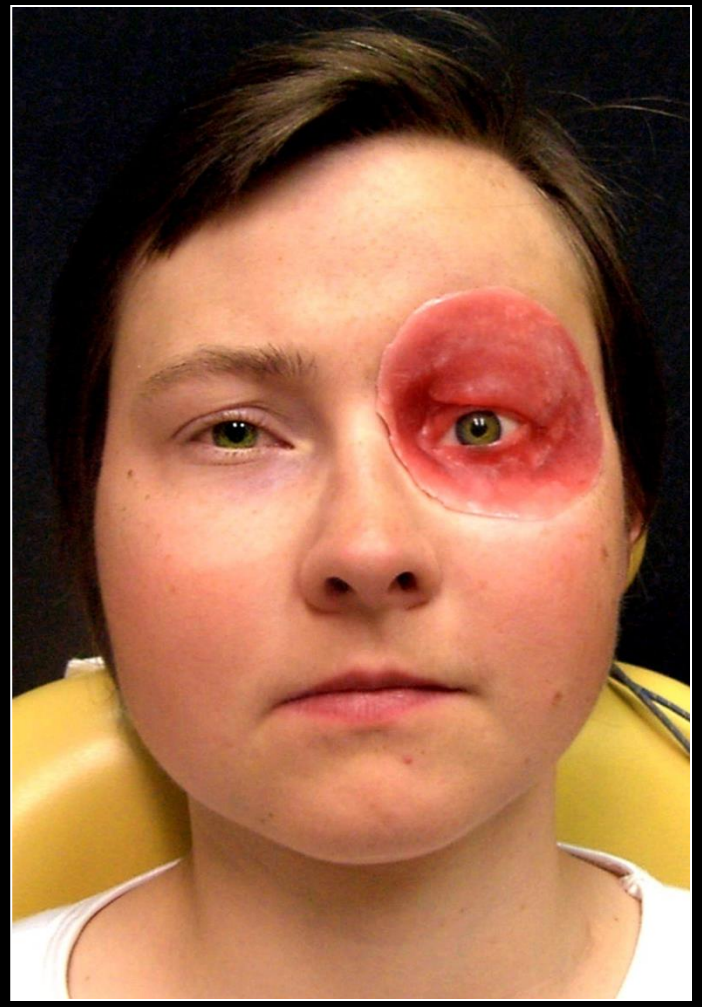
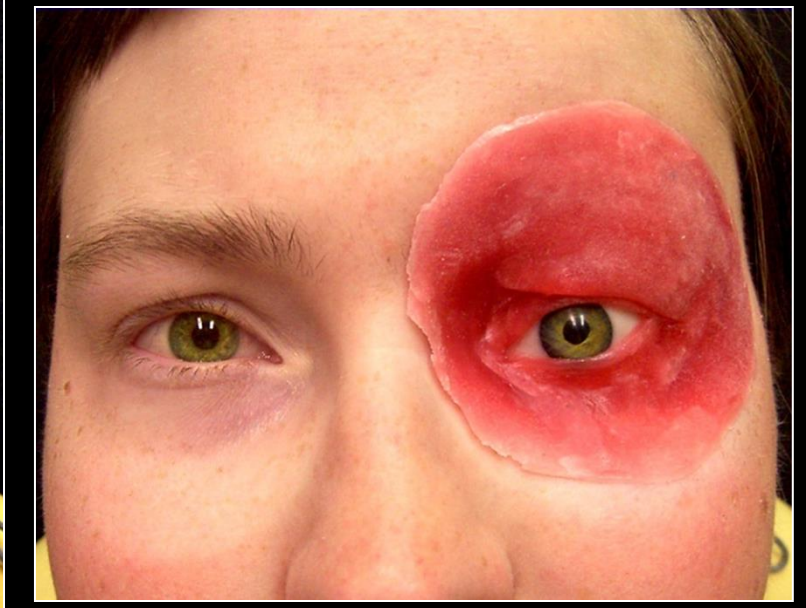
(beteg/törvényes képviselő)

Facial defect rehabilitation in the early 80s in Hungary





Nagy, K, Kiss, E., Erdei, C., Oberna, F., Fejérdy, P., Márton, K., Vajó, Z. (2008) Complex care by multiple medical and dental specialists of a patient with aggressive Gorlin-Goltz syndrome. *Postgrad Med J,* 84: 330-332.

NASAL DEFECTS

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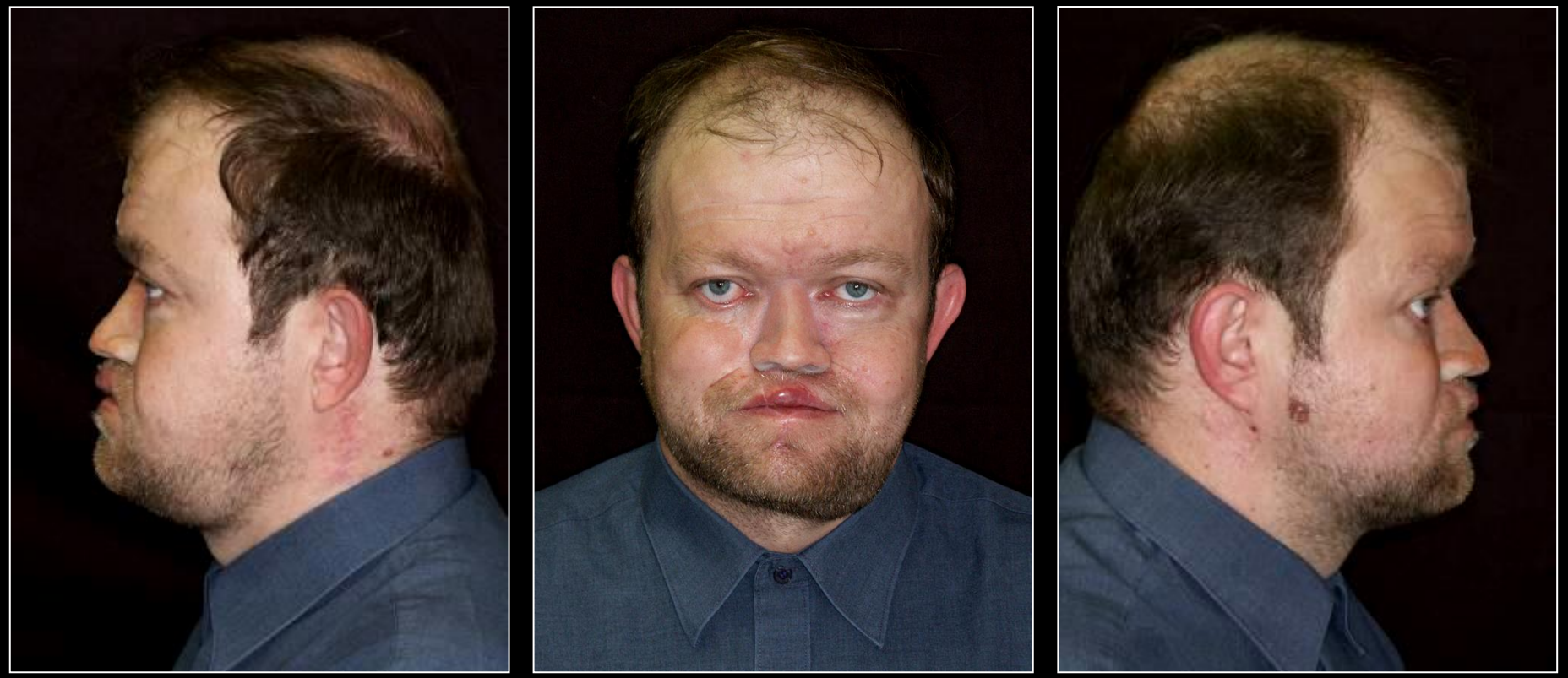
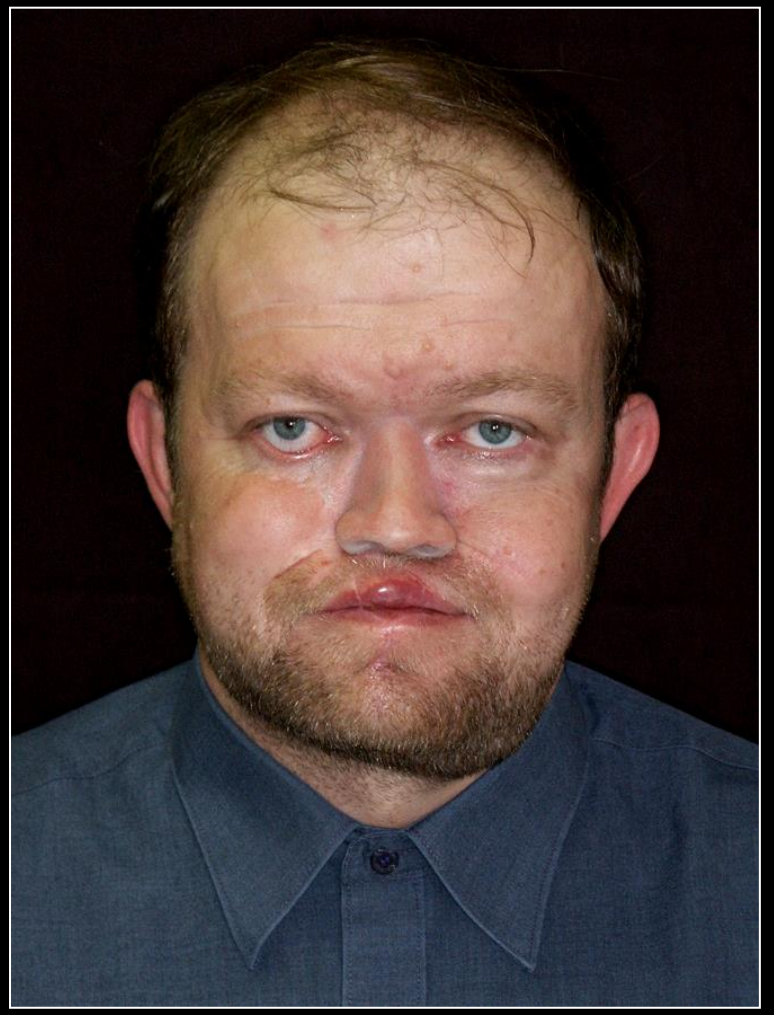


NASAL DEFECTS



The impact of prosthetic rehabilitation on quality of life of head and neck cancer patients

Nagy, J., Braunitzer, G., Antal, M., Berkovits, C., Novak, P., & **Nagy, K**. (2014) Quality of life in head and neck cancer patients after tumor therapy and subsequent rehabilitation: an exploratory study. *Quality of Life Research,* 23: 135-143.

The impact of prosthetic rehabilitation on quality of life of head and neck cancer patients

- Between 1994 and 2010, **92** of the patients who received prosthetic rehabilitation following surgical tumor therapy at the Faculty of Dentistry, University of Szeged were available
- Among those, **12** patients did not wish to participate in the study
- **80** patients were enrolled in this study

Basic epidemiological characteristics of the study population

		n(%)
Nem	férfi	53 (66,25%)
	nő	27 (33,75%)
Kor a kezelés idején (években)	<40	9 (11,25%)
	40-49.9	18 (22,5%)
	50-59.9	26 (32,5%)
	60-69.9	19 (23,75%)
	>70	8 (10%)
Dohányzás	igen	60 (75%)
	nem	20 (25%)
Alkoholfogyasztás	igen	45 (56,25%)
	nem	35 (43,75%)

Oncological characteristics of the study population

Category		n (%)
Tumor localization	Maxillary and mandibular gingiva	36 (61,02)
	Tongue	6 (10,17)
	Floor of the mouth	12 (20,34)
	Face (eyes, ear, nose)	3-1-1 (5,08-1,7-1,7)
Type of treatment	Surgery	15 (25,4)
	Radiotherapy	2 (3,39)
	Surgery with radiotherapy	35 (59,32)
	Surgery with chemotherapy	2 (3,39)
	Surgery, radio- and chemotherapy	5 (8,47)

The used prosthetic methods for rehabiliation

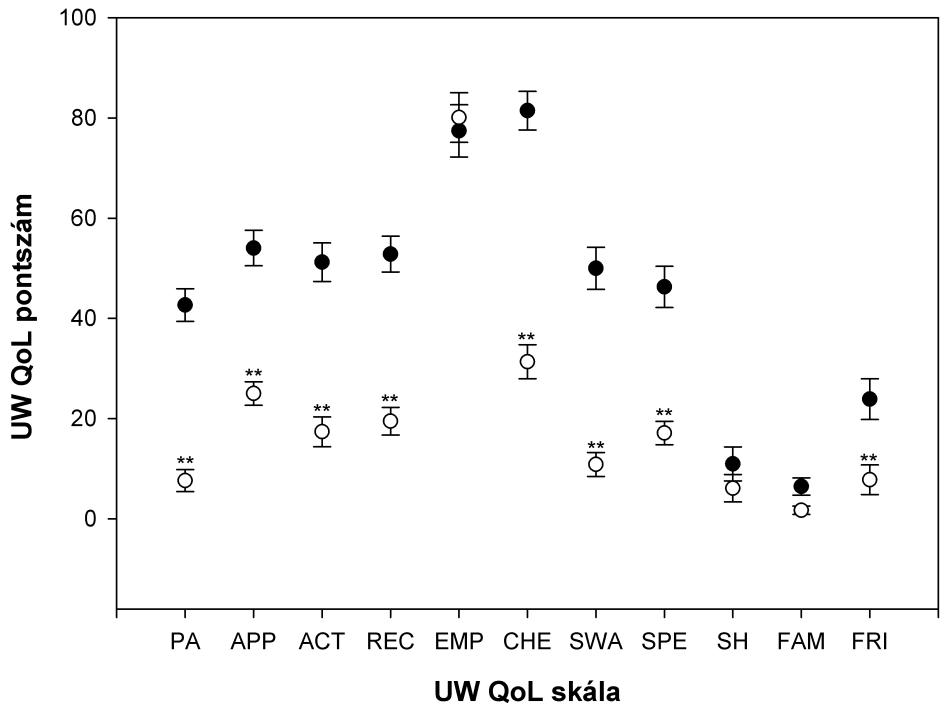
Type	**n (%)**
Obturator type of prosthesis	14 (12,5%)
Complete denture (lower and/or upper)	32 (28,57%)
Implant-supported removable denture	23 (20,54%)
Combined prosthesis	28 (25%)
Bridge (Fixed partial denture)	3 (2,7%)
Eye epithesis	7 (6,25%)
Nose epithesis	2 (1,8%)
Ear epithesis	3 (2,7%)
Total number	112 (100%)

Measuring quality of life (QOL)

- UW QOL
- EORTC H&N35
- The evaluation questionnaire was filled twice
  - After tumor therapy, before rehabilitation
  - 6 months after rehabilitation

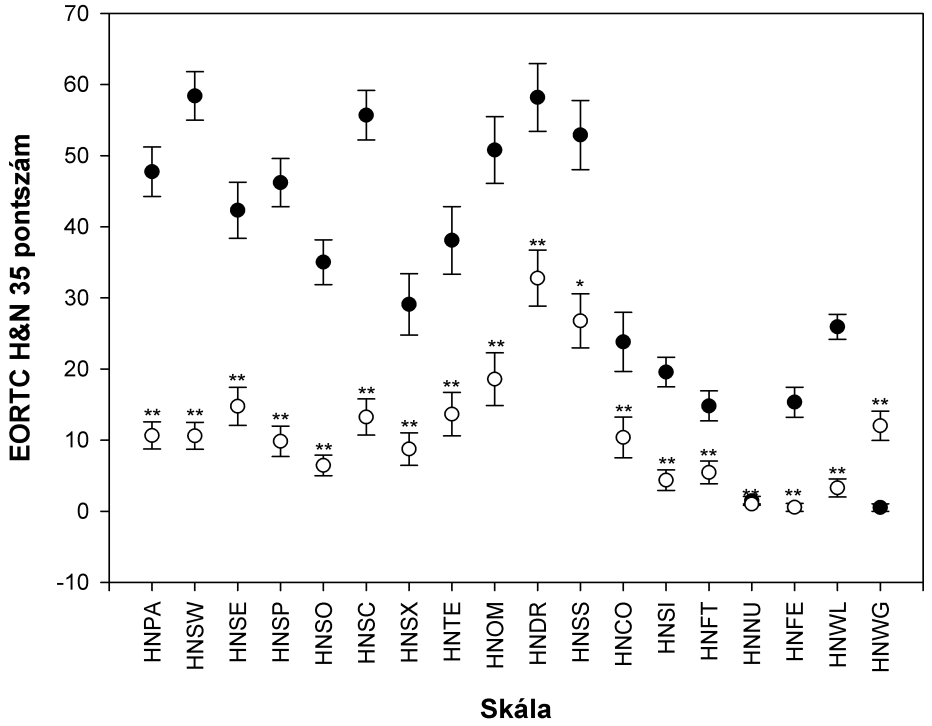
Results

UW QoL



Chewing, swallowing, speaking, social contacts, activity level increase (P<0.001)

EORTC H&N 35 QoL



Swallowing, dry mouth, social relationships, mouth opening, pain (p<0.001)

Maxillofacial prosthetic rehabilitation based on our results

- This is the first study in Hungary focusing on multiple effect of maxillofacial prosthetic rehabilitation
- **after** receiving intra- **and** extraoral rehabilitation quality of life improved
- **rehabilitation-treatment** for patient with head and neck cancer not only restores lost physical skills, but it also results in profound, positive changes on the overall quality of life of patients (with all its personal and health-economic aspects).

Summary of results (I.)

1. We were the first to perform a comprehensive ***microbiological study*** to characterize the surface of oral squamous cell carcinoma, as a focal infection

2. We found that the ***diversity of aerobic and anaerobic bacterial species*** and the ***number of colony-forming units*** of each species were significantly higher in the biofilm covering the tumor area than that on the surface of the healthy mucosa.

3. We have shown that the members of different type of *Veilonella, Fusobacterium, Prevotella, Porphyromonas, Actinomyces and Clostridium* (anaerobic) *and Haemophilus, Enterobacteriaceae and Streptococcus* (aerobic) form the defining elements of the bacterial flora **on the squamous cell carcinoma surface**.

4. We have shown that Candida albicans did not occur in any of the healthy control areas, whereas it was ***present in about 40% of the examined tumor surfaces***.

Our study summarizing the above has now become a defining reference in literature.

Summary of results (II.)

5. We have shown that ***direct antimicrobial treatment*** of the tumor surface is ***essential to reduce or suppress the complications*** of oral squamous cell carcinoma. We have shown that regular rinsing with ***amino-fluoride*** can ***alter the microflora*** of the oral cavity, especially in the case of ***Gram-negative anaerobic species and Candida albicans***. The therapy significantly alleviated patients' subjective and objective symptoms.

6. Supported by microbiological analysis, we have shown that the regular topical use of ***lactoperoxidase***-containing oral hygiene products ***significantly reduces the number of potential pathogens after radiotherapy***, especially Candida species (mainly C. albicans). The applied protocol also brought a ***significant improvement*** in ***dry mouth***, which is a very significant problem after irradiation. We found that with the presented antimicrobial protocol it is possible to significantly reduce the harmful side effects of radiation therapy.

7. In our relevant study, we demonstrated that ***Candida*** colonizing the ***oral epithelium of cancer patients*** not only significantly ***exceeded the values*** observed in healthy controls (this confirmed our previous knowledge), but also in their ***variability***. We examined and, within the limits of our studies, refuted the hypothesis that the lipase and protease production of Candida would be decisive in determining whether the epithelium colonized by them would become malignant or shift into the direction of cancerous degeneration.

Summary of results (III.)

8. We proved that patients' overall quality of life (who underwent adequate prosthetic rehabilitation after tumor surgery surgery) significantly improves