Treatment Modalities in the Complex Therapy of Head and Neck Tumours

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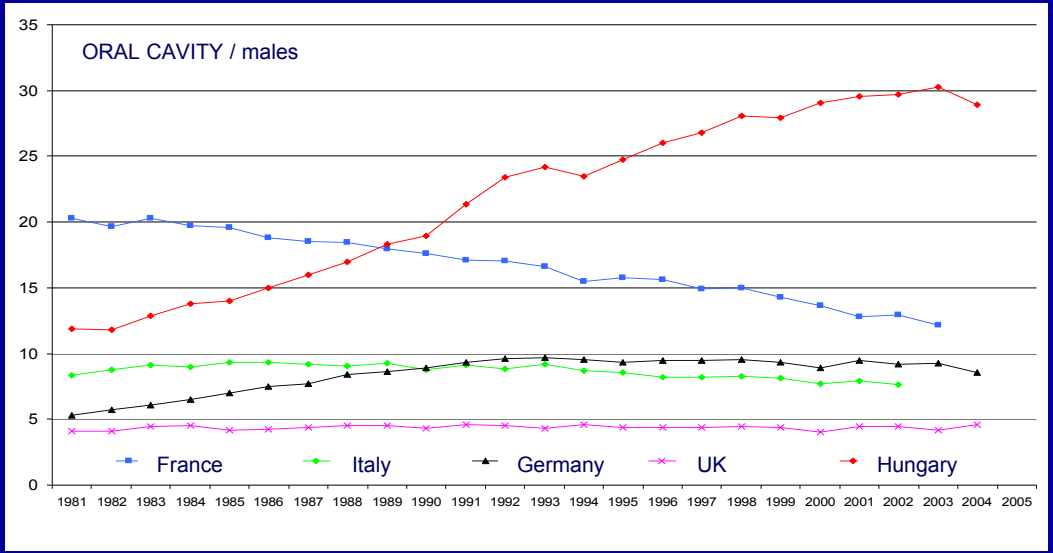
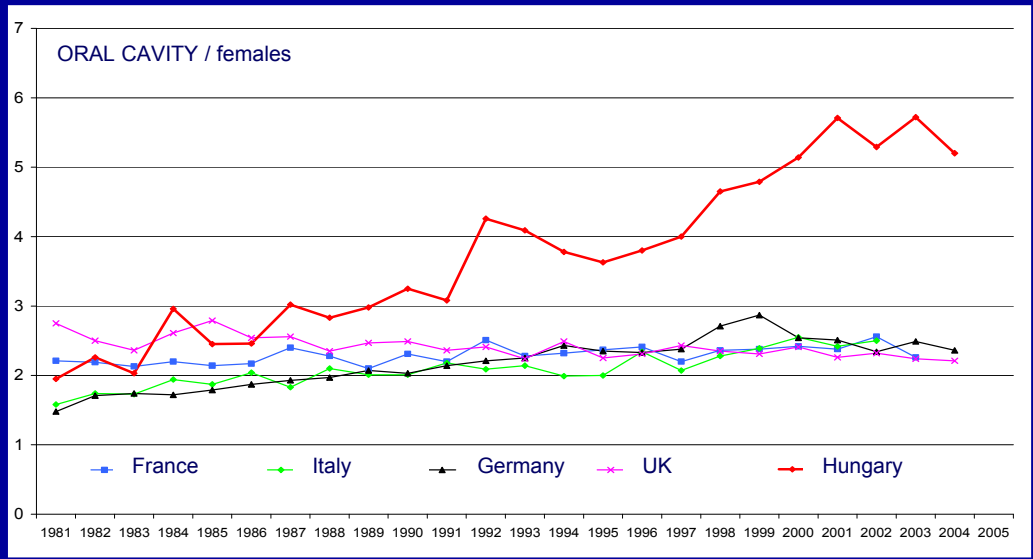
GROSS MORTALITY RATES OF CANCER OF THE LIP, ORAL CAVITY AND PHARYNX IN FIVE EUROPEAN COUNTRIES (1981-2006)





1. In case of cancer of the lip and oral cavity, international comparisons show that the Hungarian male and female mortality rates are the worse
2. The situation is similar in other head and neck subregions, too

Kásler M., Ottó Sz.: Orv. Hetil. 134. 473-480. 1993.
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Growth dynamics of the mortality of six leading cancers (1975-2010)

Tumour	Case number		Increase (%)	Case Number	Change (%)
	1975	1999		2010	
Lip and oral cavity (C00-C14)	462	1618	250	2022	+25
Tracheal-bronchi, lung	4169	7883	89	8648	+9
Colon and rectum (C18-C21)	3025	4912	62	4965	+2
Pancreas	1076	1562	45	1848	+15
Breast	1650	2381	44	2011	-15
Prostate	1196	1387	16	1209	-13

Gaudi I., Kásler M.: Magy. Onkol. 46. 291-295. 2002.
Kásler M., Ottó Sz.: Magy. Onkol. 52. 21-33. 2008.

OBJECTIVES

1. Evaluation of the epidemiological and etiological status of head and neck cancer in Hungary
2. The development and introduction of laser surgical techniques for the management of head and neck cancer in Hungary
3. The introduction of new reconstructive surgical techniques in Hungary
4. The introduction of radiotherapy and salvage surgery for head and neck cancer treatment in Hungary
5. Use of immunotherapy for head and neck cancer
6. Genomic analysis of head and neck cancer progression

RISK FACTORS IN HEAD AND NECK CANCER

1. Smoking:
- third place out of 111 countries
- constantly increasing
- shift towards young adults and women (men smoke twice as much as women)

▪ Resulting **carcinogenic metabolites**

2. Alcohol:
- among the first ones in quantity (men consume four times more)
- among the last ones in quality

▪ Alcoholism: **liver damage** (changes in hormone levels)

▪ **increasing the efficacy of metabolites deriving from smoking**

3. Smoking and alcohol:
- relative risk is 40-fold
- total abstinence: mortality rate decreases by 60-80%

4. Genetic susceptibility:
- **mutagenic disposition**
- **DNA repair genes**
- **carcinogen metabolizing genes**

} polymorphism

5. Oral hygiene: - infection: HPV, EBV, Herpes simplex

Csuka O., …, Kásler M.: Magyar Onkológia 45 (2) 161-167, 2001.
Székely G., …, Kásler M., Gundy S.: Magy. Onkol. 45. 152-157. 2001.
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Szentirmay Z., ..., Kásler M.: Cancer Metast. Rev. 24. 19-34. 2005. IF:8.017
Székely G., …, Kásler M. et al: Mutagenesis, 20, 381-385, 2005. IF:2,094

HORMONES SYNTHETIZED IN THE LIVER, PROGNOSTIC SIGNIFICANCE OF CLINICAL STAGE AND HISTOLOGICAL GRADE IN THE SURVIVAL OF HEAD AND NECK CANCER PATIENTS

1. **Patients: 130 male patients** (mean age: 52,1 years)
2. **Method:**

- Complete hormone determination from the serum
  - steroid hormones (estradiol – E_2, progesterone – Prog, testosterone – TE)
  - adenohypophyseal hormones (follicular stimulation – FSH, luteinization – LH, prolactin – Prol)
    - stage, TNM, survival analysis

3. **Results:**

3.1 **Prognostic significance** (survival rate decreased significantly)

- **alcoholic liver disease:** over 90 IU/l gamma GT (p=0,039), 29,2% of the patients
- **testosterone below the lower normal limit** (<10nmol/l, [p=0,046]), 28,5% of the patients
- **FSH level beyond the upper normal limit** (>10nmol/l, [p=0,0153]), 27,7% of the patients
- stage IV. (p=0,001)
- lymph node metastasis (p=0,0078)

3.2 No prognostic significance (no significant difference)

- gamma GT increased to a value one and a half time as great as the normal value (< 90 IU/l)
- estradiol and progesterone level
- prolactin and luteinizing hormone level
- stage I-III
- grade I-III

3.3 **Cummulatively unfavourable prognosis**

- **low testosterone and high FSH level**

(16 out of 17 patients died within two years. Patient 17 had vocal cord cancer T1)

Remenár É., …, Kásler M., Gundy S.: Magy. Onkol. 46. 329-332. 2002.
Remenár É., ..., Kásler M., Gundy S.: Magy. Onkol. 43. 155-159. 2003.

Incidence of HPV according to age, gender and localization in head and neck tumours

1. **Patient group:** **177 patients** (oral cavity, pharynx, larynx)
   - 136 cancer patients
   - 41 papiloma patients

2. **Method:** from tissue sample (fixed or embedded in paraffin)
   – DNA isolation PCR examination
   (virus typing with 34 PCR primers)

3. **Results:**

3.1 Incidence of HPV according to age

Age	HPV negative %	HPV positive %
<54	44	56
>54	56	44

Correlation between the age of cancer patients and the HPV origin of squamous cell carcinoma. [P=0, 07]

3.2 Incidence of HPV according to gender

	HPV negative %	HPV positive %
Male	62	38
Female	45	55

Gender distribution of HPV negative and positive head and neck squamous cell carcinoma [P=0,0346]

3.3 Incidence of HPV according to localization

oral cavity	**48,5%**
pharynx	**48,5%**
larynx	**35,7%**

Szentirmay Z. …, Kásler M: Orv. Hetil. 142. 1429-1436. 2001.
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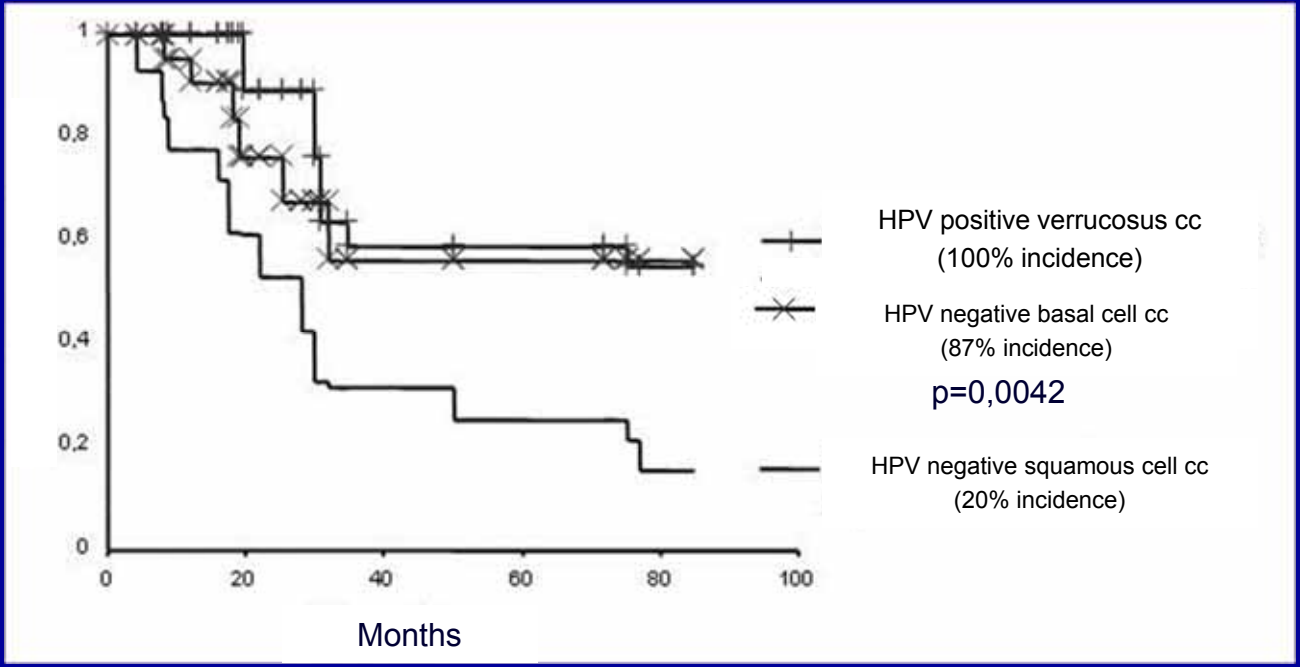
The correlation between the presence of HPV and survival

3.4 Correlation between the histological structure and the types of HPV strains

(HPV positive and negative cancers, p<0,0001)

Papiloma: high risk strains (incidence: 50%)
Verrucose carcinoma: low risk HPV strains (incidence: 100%)
Typical squamous cell carcinoma: high risk strains (incidence: 20%)



Kaplan-Meier survival curve of 114 oral cavity-, pharyngeal-, and laryngeal cancers

3.5 There was no significant correlation between the positivity of the HPV and the stage and the grade of the tumour.

3.6 **The incidence of HPV refers to a better prognosis** (significant correlation)

Szentirmay Z., …, Kásler M.: Magy. Onkol. 46. 35-41. 2002.
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Szentirmay Z., ..., Kásler M.: Cancer Metast. Rev. 24. 19-34. 2005. *IF:8.017*

Mutagen sensitivity study

1. **Patient group:** **451** subjects
   156 cancer patients (heavy smokers and alcohol consumers)
   146 healthy subjects (non-smokers)
   149 healthy subjects (smokers)

2. **Method:**
   - spontaneous chromosomal fragility – conventional chromosomal analysis
   - mutagen sensitivity due to environmental factors – Bleomycin test

   (Lymphocyte culturing for 72 hours. In the 67th hour 30µg/ml Bleomycin. Colcemid blocking, lysis, staining.)

3. **Results:**
   - **Considering spontaneous and induced chromosomal fragility, the genetic susceptibility level is twice as high in Hungary than in the American and European populations studied so far.**

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Székely G., Remenár É., Kásler M., Gundy S.: Mutagenesis, 18, 59-63, 2003. *IF:1,821*
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Polymorphism of genes repairing DNA errors in case of head and neck cancer

1. **Patient group:** **531 examined pts**
   293 cancer pts(264 m/ 29 f)
   238 healthy controls
   - 91% smokers
   - physiological accumulation: 45-65 yrs 77,5%
   - localization: lip, oral cavity, pharynx, larynx, tonsil

2. **Method:** genotyping (DNA repair gene polimorphism)

3. **Results:**

3.1 **Smoking and non-smoking cancer patients; smoking and non-smoking healthy subjects; and the different regions show different genotypes.**

XRCC1cd280 AA: **Did not occur in the control group and amongst non-smoker patients.**

allele A: non-smoking patients/smoking patients = 0%/5,2%
healthy non-smoking subjects/healthy smoking subjects = 2,8%/6,4%
in the absence of smoking genetic factors are probable: p53cd72 allele C 49,2%, XRCC3cd241 allele T 40,1%

XRCC1cd399 AA: non-smoking/smoking patients = 6,7%/13,5% **(twice as frequent amongst smoking patients)**

MTHFRcd1298 CC:
non-smoking patients/smoking patients = 6,7%/10,4%
healthy non-smoking subjects/healthy smoking subjects = 3,4%/12,1% **(three times as frequent amongst smoking patients)**

Juhász A., ..., Kásler M. et al: Magyar Epidemiológia, 1.2. 51-55, 2005.

3. Results:

3.2 genotypes vary in head and neck cancers of different localizations and in healthy subjects

No XRCC1cd194 **mutation in cancer patients** – **its lack is a predisposing factor**

- **The frequency of the codon differs by subregions**
- The frequency of the codon is significantly different in healthy subjects and in patients (p=0,0357)
- The proportion of heterozygote genotype is less by 5 % in cancer patients (patients/healthy subjects = 11,6%/16,9%)
- homozygote: the proportion of CC (wild) genotype is 7 % higher in cancer patients (patients/healthy subjects = 88,4%/81,9%)
- allele C (more frequent): predisposing
- TT genotype: protective (occurs only in healthy subjects)
- allele T (less frequent): protective (cancer of the lip 10%, tonsil, salivary glands 0%) its lack is a risk factor
- mutation (AA): does not occur in head and neck cancer (its presence is protective)

No XRCC1cd280 **mutation in healthy subjects** – its presence is a predisposing factory

- **The frequency of the codon differs by subregions**
- The frequency of the codon is significantly different in healthy subjects and in patients (p=0,0206)
- the proportion of heterozygote genotype is 6 % higher in cancer patients (patients/healthy subjects = 17,1%/11,3%)
- homozygote: the proportion of GG (more frequent) genotype is 7 % less in cancer patients (patients/healthy subjects= 81,2%/88,7%) significant (p=0,0206) presence of protective factor
- AA (less frequent) genotype: does not occur in healthy subjects (its presence is a predisposing factor), shows varying proportion in cancers of different localizations (cancer of the lip 20%, oral cavity 1,2%, pharyngeal 2%, tonsillar-, salivary gland-, and laryngeal cancer 0%)

XRCC1cd399 **G>A substitution frequent in pharyngeal cancer:**

- allele A 49%, AA mutation 23,5% (patients/healthy subjects = 12,3%/12,6%, p=0,1322 not significant)

XRCC3cd241: **frequent in tonsillary-, salivary gland cancer**

- TT genotype: patients/healthy subjects = 13,3%/12,6%
- **CC genotype: patients/healthy subjects** = 46,1%/45,8%, p=1,00 not significant, **differs by subregions**

Juhász A., ..., Kásler M. et al: Magyar Epidemiológia, 1.2. 51-55, 2005.

Analysis of optimal application of surgical lasers and their impact on tissues

1. **Animal model:**

- Surgical incision on the tongue and bucca of 10-30 albino rats in narcosis
- excision of specimen, fixation in 10% formalin, embedding in paraffin
- 7 µm sections, staining, examination by light microscope under different magnifications
- measurements with ocular micrometers

2. **We examined:**

-The optimal conditions for laser application

- The features of laser destruction and wound healing under different parameters

- different duration (0,1-0,2-0,5 sec. continuous, focused) given capacity (5-10-15-20-25 W), given angle of incidence (30º, 45º, 60º és 90º)
- different capacity (5-10-15-20-25 W), given duration (0,1; 0,2; 0,5 sec.; continuous), given angle of incidence (30º, 45º, 60º és 90º)
- different angle of incidence (30º, 45º, 60º és 90º), given duration (0,1; 0,2; 0,5 sec.; continuous), given capacity (5-10-15-20-25 W)

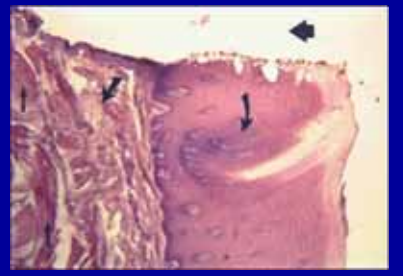
-The effect of the combined application of CO_2 and Nd-YAG laser on tissues and on wound healing

- different CO_2 laser parameters (5-25 W, 1 sec.) given Nd-YAG laser parameters (10-60 W)
- different Nd-YAG laser parameters (10-60 W), given CO_2 laser parameters (5-25 W, 1 sec.)

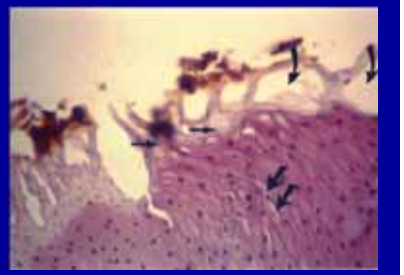
- The effect of surgical incisions with CO_2 laserbeam, electrocautery and scalpel on tissues and on wound healing

- CO_2 laser with different capacity (5-15-25 W)
- electrocautery with different capacity (25-250-500 W)
- surgical scalpel

A) Typical picture of a laser crater penetrating to the mascular layer, 50x



B) The rim of crater in the epithelial and connective tissue layers. In deeper layers cross-striated muscles, most of them sectioned longitudinally, 100x



C) Carbonized layer dotted with vacuoles. Deeper, a few necrotic zones can be detected. Squamous epithelium shows sporadic intracellular oedema, 250x

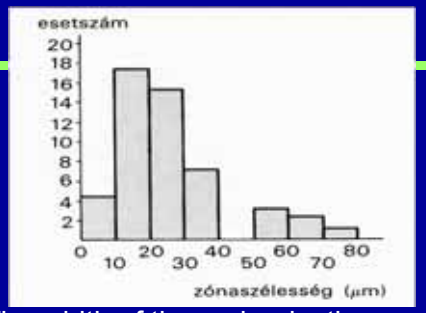
Kásler M. et al: Orv. Hetil. 128. 1945-1946. 1987.
Gáspár L., Kásler M.: Fogorv. Szemle, 84. 243-246. 1991.
Gáspár L., Kásler M.: J. Clin. Laser Med. Surg. 9. 381-383. 1991.
Gáspár L., Kásler M.: Szén-dioxid-laser a klinikai gyakorlatban. Budapest, Tungsram Kiadó, 1990.

Results

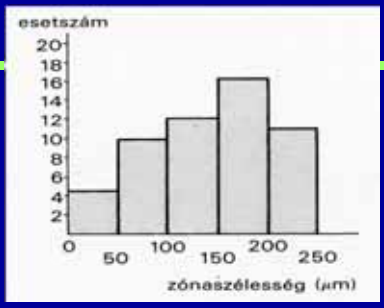
Analysis of the effects of surgical lasers on tissues

- Heat-affected zones are produced on the surface of the surgical incisions (irrespective of duration, capacity and angle of incidence)

- **CO_2 laser**
  - **irreversibly damaged zone**
    - carbonization zone: 20-40 µm
    - necrosis zone: 100-200 µm
  - **reversibly damaged zone**
    - transitory zone: 300-800 µm
    - hyperthermia and oedema zone: varying



A) The width of the carbonisation zone based on 50 measurements.



B) The width of the necrosis zone based on 50 measurements.

- In case of ND-YAG laser the width of the heat-affected zones is 3-5 mm (mainly coagulation)
- In case of electrocutery the width of the heat-affected zones is 5-8 mm (mainly the irreversible zones)

The width of the heat-affected zones and their relation to each other depends on:

- the capacity
- the duration of the application
- the angle of incidence
- the quality of the tissue

1. Capacity

The greater the capacity is , the deeper is the laser cutting, and the narrower is the widths of the irreversibly damaged zones.

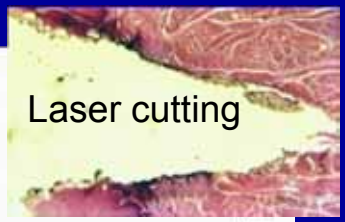
three kinds of destruction may develop:

- Coagulation (≤5W capacity, ≤0,1 sec. or continuous mode)
  - 0,1 mm heat-affected zone (50% irreversible) – ND-YAG laser
- Vaporization (10-15 W capacity, application time ≥0,1 sec.)
  - 0,2 mm heat-affected zone (40% irreversible)
- laser cutting (≥20 W capacity, application time ≥0,1 sec.)
  - 0,3 mm heat-affected zone (30% irreversible)- CO_2 laser

2. Duration

The longer the application time is, the deeper is the laser cutting, without any change in the histological picture of the wound surface.

Types of laser destruction



Laser penetration depth in tissues using varying output but identical duration and angle of incidence

Gáspár L., Kásler M., Orosz M.: J. Clin. Laser Med. Surg. 9. 209-213. 1991.
Gáspár L., Kásler M.: Szén-dioxid-laser a klinikai gyakorlatban. Budapest, Tungsram Kiadó, 1990.

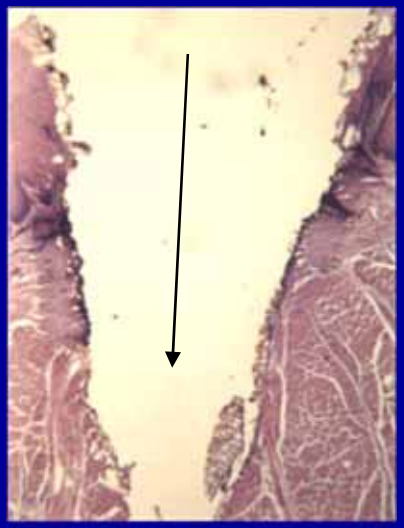
Results

Angle of incidence of the laser beam

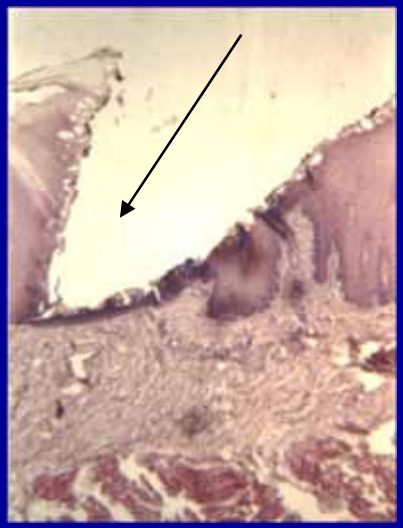
(has not been analysed before us)

– **deviation from 90% angle of incidence is associated with ever decreasing depth of surgical incision**

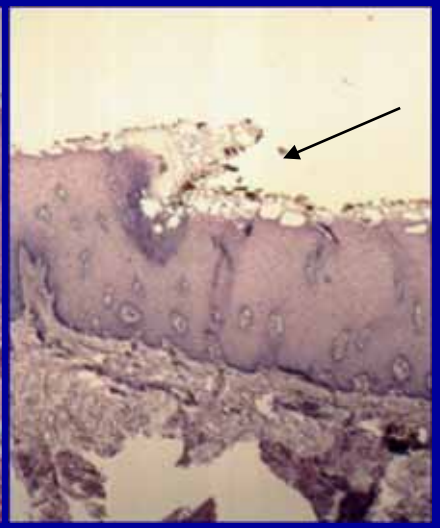
angle of incidence	difference in depth
60º	-15 %
45º	-30 %
30º	-50 %



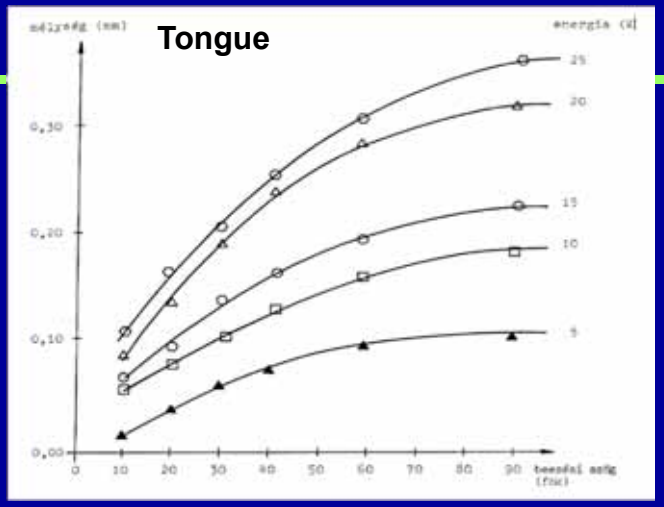
A) Laser beam from angle of incidence under 90° penetrates into the muscular layer, symmetric crater

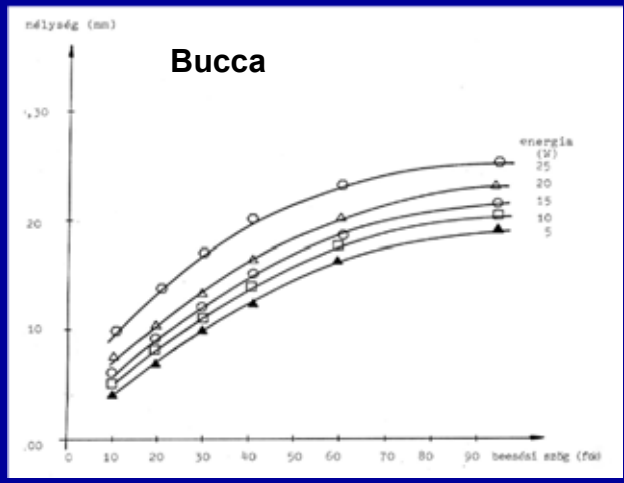


B) Laser beam from less than 60° angle of incidence results in an asymmetric crater extending to the basal membrane



C) Laser beam arriving from angle of incidence under 20° leads to intraepithelial crater





Bánhidy F., Kásler M. et al: Magy. Onkol. 38. 187-190, 1984.
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Gáspár L., Kásler M.: J. Clin. Laser Med. Surg. 9. 381-383. 1991.
Gáspár L., Kásler M.: Laserek az orvosi gyakorlatban. Budapest, Berlin, Heidelberg, New York, London, Paris, Tokyo, Hong Kong, Barcelona, Springer-Verlag, 1993.

Results

3. Tissue type

In case of identical angle of incidence, duration and capacity, a laser cutting of the same quality is produced in both tissues

4. Combined (CO_2 and ND-YAG) application:

- **the ND-YAG laser coagulates and the CO_2 laser vaporizes**
- **their simultaneous use combines their individual advantages**

5. When laser is used, the healing of surgical incisions is more favourable compared to those by standard surgical tools.

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The introduction of surgical lasers in Hungary (from 1980)

1.1 **Patient group:** between 1980 and 2007 **7977 patients** had been operated

Histological type	
• benign	3640
• precancerous	298
• malignant	4108
	7977

Localization	
• skin	6137
• oral cavity	474
• larynx	848
• pharynx	518

1.2 **Method:**

– Anaesthesia
  • Local anaesthesia (1%-os Lidocain):
    - skin alterations
    - benign and precancerous lesions in the oral cavity and mesopharynx
  • Narcosis: malignant lesions of the oral cavity, pharynx and larynx

– **Laser mode:**
  • coagulation: superficial layers of the epithelium
  • vaporization: lesions infiltrating the epithelium
  • excision: extended infiltrating lesions

– Laser protection:
  • the patient and the operating staff (protective clothes)
  • operating theatre (isolation with physiological saline)

– histological control
– Control: 1-3-6 months, 1 year

Krémer I., ..., Kásler M.: Anaesthesiológia és Intensiv Therapia, 13. 61-69. 1983.
Bánhidy F., Kásler M.: Gegenüberstellung der Ergebnisse von laserchirurgischer und mikrolaryngoskopischer Behandlung von Larynxpraekanzerosen. In: Aktuelles in der Otorhinolaryngologie, 1983. Georg Thieme. Stuttgart, New York, (szerk.: Mayer E., H. Zrunek M.) 1983.
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Gáspár L., ..., Kásler M. et al: Bőrgyógy. Venerol. Szle. 67. 207-212. 1991.
Kásler M. et al: Magy. Onkol. 52, 301-312, 2008.

The introduction of surgical lasers in Hungary (from 1980)

Results:

- „no touch" technique: ablative, sterile, atraumatic
- No bleeding, wound surface covered by coagulum: ablative, protected from superinfection
- Absolute targeting accuracy
- Short surgical intervention time
- Only pathological tissue is removed
- Oedema-free surgical margin
- Painless wound
- Quick and undisturbed wound healing
- Minimal (the less deep and the smaller surface it has) or no cicatrization (surgeries not involving the basal membrane)
- Preserves structure, function and aesthetic quality
- Can be repeated in case of a relapse

Bánhidy F., Kásler M.: Gegenüberstellung der Ergebnisse von laserchirurgischer und mikrolaryngoskopischer Behandlung von Larynxpraekanzerosen. In: Aktuelles in der Otorhinolaryngologie, 1983. Georg Thieme. Stuttgart, New York, (szerk.: Mayer E., H. Zrunek M.) 1983.
Krémer I., ..., Kásler M.: Anaesthesiológia és Intensiv Therapia, 13. 61-69. 1983.
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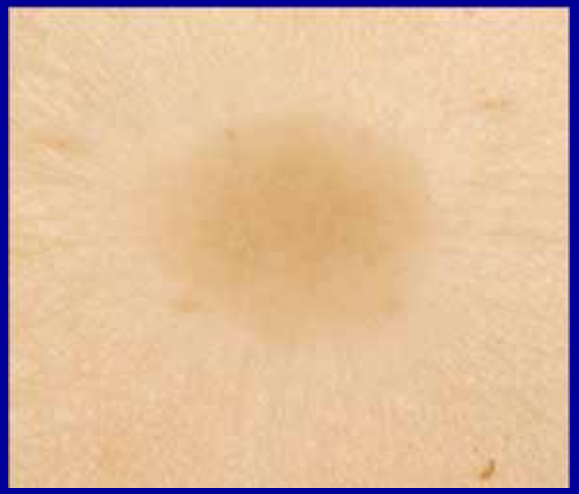
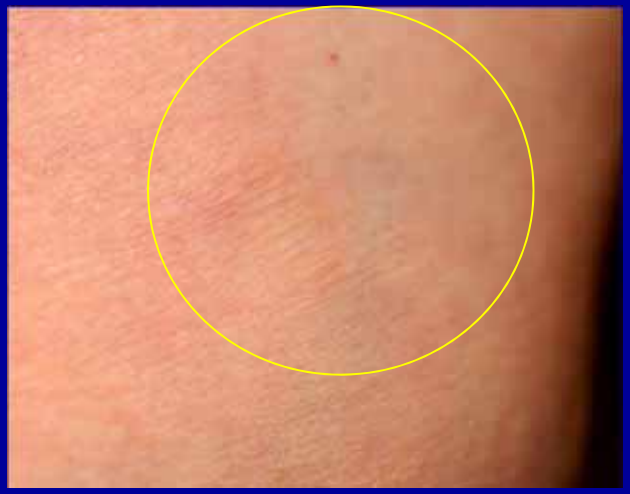
Kásler M. et al: Magy. Onkol. 52, 301-312, 2008.

Laser surgeries preserving aesthetic qualities

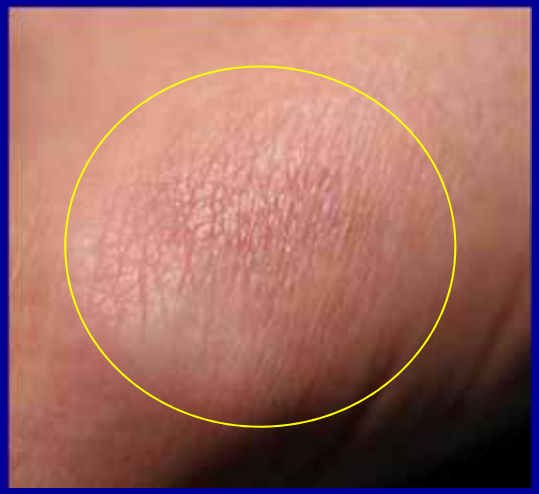
(6137 skin lesions of the head and neck - first in Hungary)



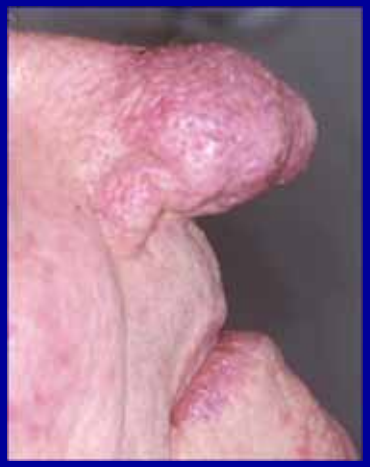
A) Coagulation.



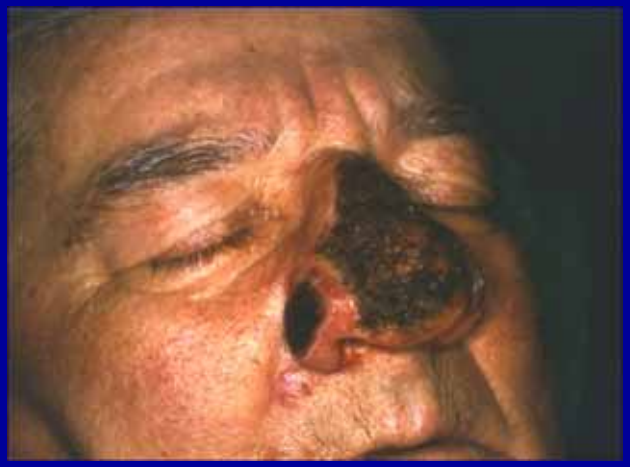
B) Healed laser wound over the elbow joint



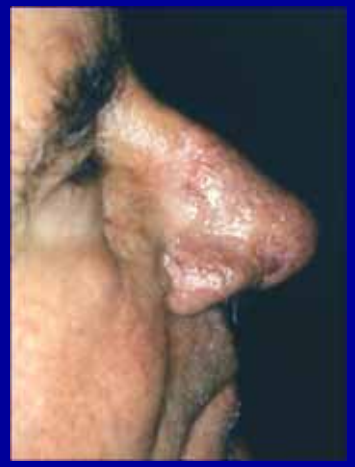
C) Healed laser wound over the I. MCP joint



A) Before surgery (rhinophyma)



B) Surgical site after CO2 laser vaporization And excision



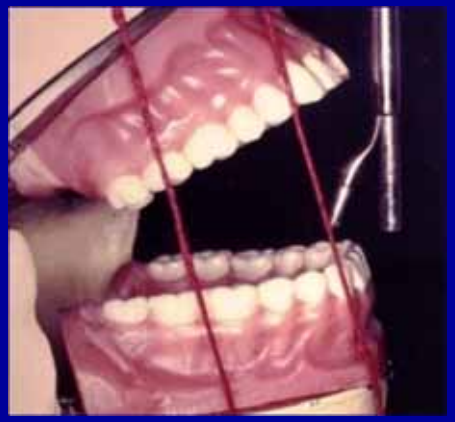
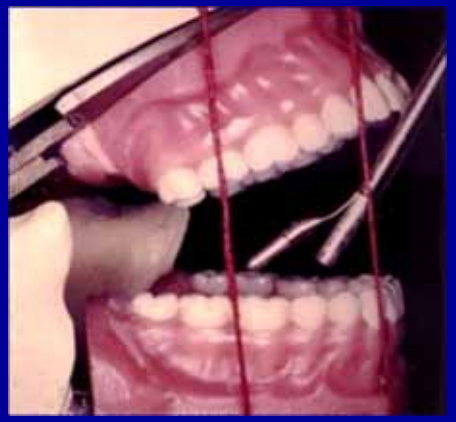
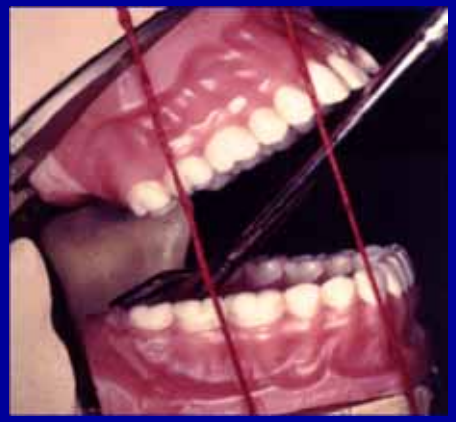
C) postoperative healed condition

Results

Ever extending surface involvement (shift toward coagulation)

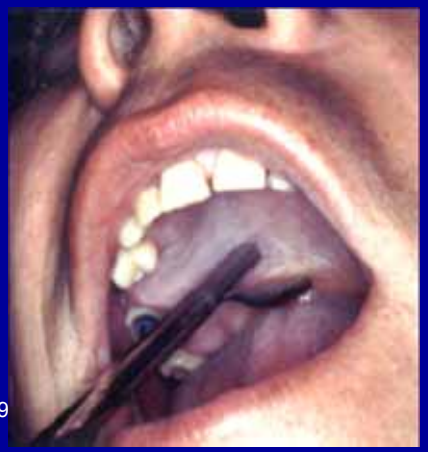
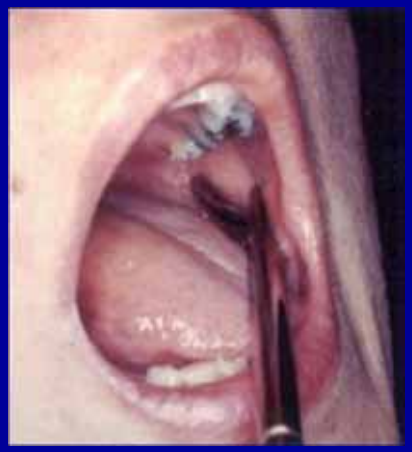
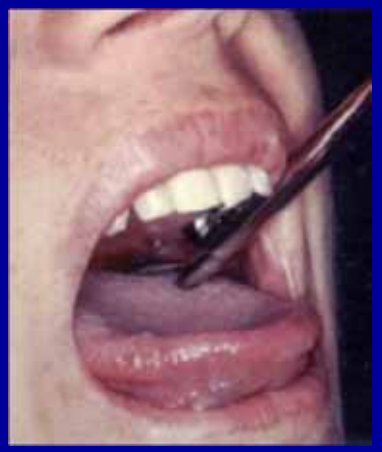
angle of incidence	deviations in surface area
60º	+15 %
45º	+40 %
30º	+100 %

– by means of the oral endoscope constructed by us the angle of incidence can be optimized


Method:

- Model examination (to approach surface lesions of different localization in the oral cavity)
- measurements on oral cavity surface lesions with 30 patients

Bánhidy F., Kásler M. et al: Magy. Onkol. 38. 187-190, 1984.
Gáspár L., Kásler M.: Szén-dioxid-laser a klinikai gyakorlatban. Budapest, Tungsram Kiadó, 199
Gáspár L., Kásler M.: Fogorv. Szemle, 84. 243-246. 1991.
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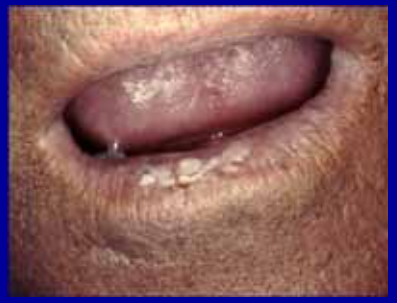
Gáspár L., Kásler M.: Laserek az orvosi gyakorlatban. Budapest, Berlin, Heidelberg, New York, London, Paris, Tokyo, Hong Kong, Barcelona, Springer-Verlag, 1993.

Structure- and function preserving laser surgeries

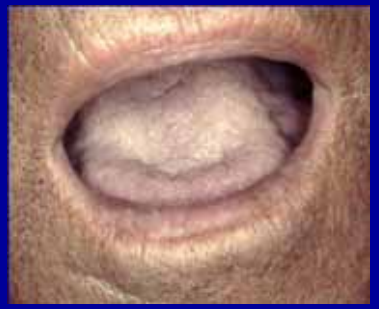
(423 oral cavity, 518 pharynx, 848 larynx - first in Hungary)

Lower lip leucoplachia



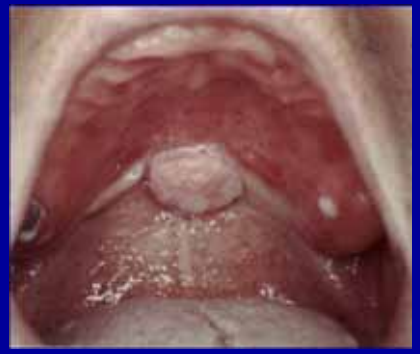
A) Before surgery

B) After vaporization and coagulation

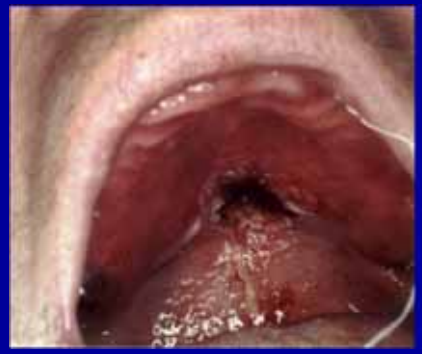


C) Healed surgical site

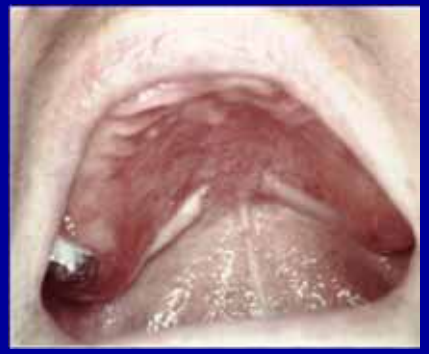
T_2 oropharyngeal



A) Before surgery

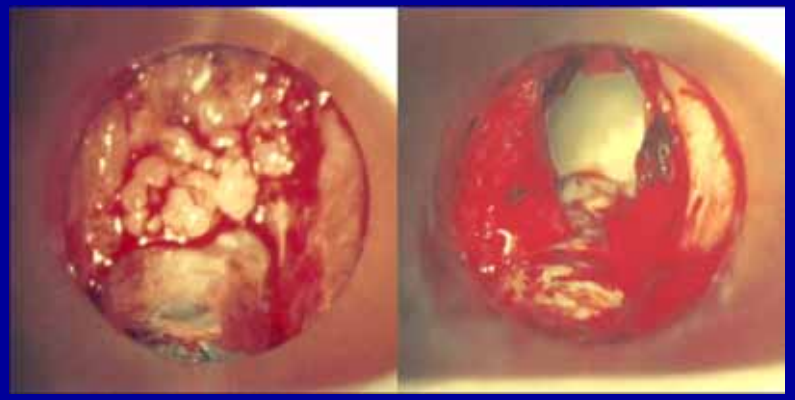


B) After surgery



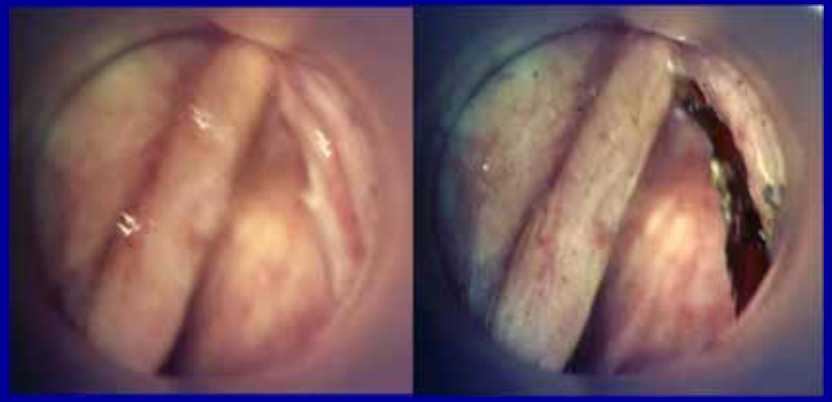
C) Healed surgical site

Papilomatosis



Before surgery

After surgery



Before CO_2 surgery

After surgery

Residual laryngeal tumour

Laryngeal – tracheal stenoses

Laser surgeries: **129** pts

Recurrence:

- Circural stenoses wider than 1cm
- Lesion of the cartilage

Non-malignant laryngeal lesions

Laser surgeries: **459** pts

Recurrence:

50-66% of that of laryngo microsurgery

Laryngeal cancers

Laser surgeries: **260** pts

T1: 76%

T2: 20%

T3-T4: 4%

Recurrence:

T1-2: 13%

- Laser surgery for relapses: 40%
- Irradiation for relapses: 44%

Combination of different treatment techniques and treatment modalities

(definitive treatment of advanced cancer ot the root of the tongue with radiotherapy and „salvage" surgery)

1. **Patient group:** between 1992 and 2005 **94 patients**

- Localization: root of the tongue
- Stage: $T_{1-4}N_{0-3}M_0$; AJCC: I-II: 6, III-IV: 88; (CT, MR)
- Operated patients: N_{0-1} ↑ (72%, p=0,0523)
- Non-operated patients: T_4N_2 ↑, N_{0-1} ↓ (41%)

2. **Method:**

- Type of irradiation:
  - **External beam irradiation**: 50 patients (átl. dózis 63 Gy, 60-72 Gy)
  - **External beam irradiation and BT**: 44 patients (average dose 61 Gy, 50-66 Gy)

(and BT average dose 17 Gy, in 1-8 fractions)

- Narcosis (for introducing a catheter)

- Control (annu
  - In the first two years: once in two months
  - From the third year on: once in 3-6 months

Details	No loco-regional failure (n= 37)	Locoregional failure (n= 57)		P
		Salvage surgery done (n=18)	No salvage surgery (n=39)	
Mean age (yrs)	55.6 (38-73)	57.1 (44-72)	57.4 (36-77)	NS
Gender				
Male	27	17	34	NS
Female	10	1	5	-
Primary tumours				
T1	4	0	0	-
T2	6	0	2	-
T3	12	8	9	NS
T4	15	10	28	0.0763
Initial N status				
N0	16	6	5	NS
N1	15	7	11	NS
N2	6	4	19	0.0435
N3	0	1	4	NS
AJCC stage				
I-II	6	0	0	-
III-IV	31	18	39	NS
Hystologic grade				
1	11	5	11	NS
2	19	9	15	NS
3	7	4	13	NS
Clinical picture				
Exophytic	3	0	2	-
Infiltrating	19	4	15	NS
Ulcerating	15	14	22	NS

Definitive treatment of advanced cancer of the root of the tongue by irradiation and „salvage" surgery

3. **Results:**

- **Initial evaluation** 2 months after radiotherapy:
  - **complete regression** **64%** (60 patients)
    5-year tumour specific survival **62%**
  - **partial regression** **36%** (34 patients)
    5-year tumour specific survival **0%**
  - the initial regression's effect on survival: significant (p<0,0001)

- **Evaluation at a later time**:
  - estimated 5-year overall and DS survival, resp. : **39**% (37/94 patients), **45**% (43/94)
  - **remained locoregionally tumour-free** (95 months): **39%** (37 patients)
    - 65% live (24 patients)
    - 35% died (13 patients: distant metastases, 6: secondary tumours., 6: medical diseases)
  - Locoregional failure (95 months): **61%** (57 patients)
    - Locoregional recurrence (CR): 21% (23 patients)
    - Locoregional residuum (PR): 36% (34 patients)
    - Localization:
      - primary tumour 20 patients (5-year survival: 30%)
      - Regional metastases 7 patients
      - locoregional 30 patients (2-year survival: 12%)
    - Operability: 32% (18 patients)
    - Inoperability: 68% (39 patients)

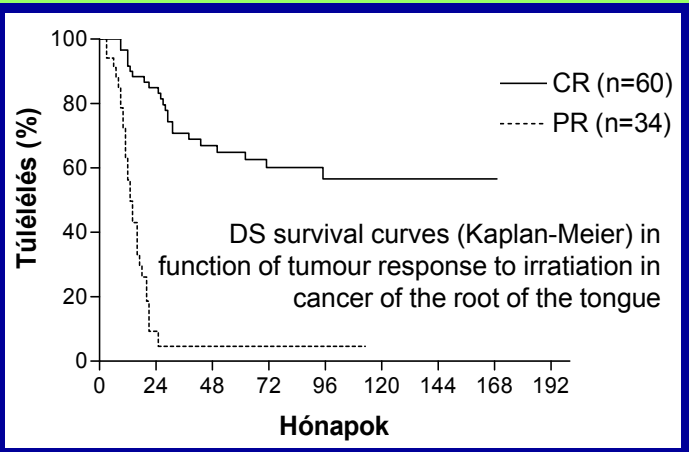
Kásler M. et al:. In Vivo 2008, vol: 22, ***IF: 1,273***

Effects of prognostic factors on DS survival in cancer of the root of the tongue after definitive radiotherapy and „salvage" surgery (multivariate analysis)

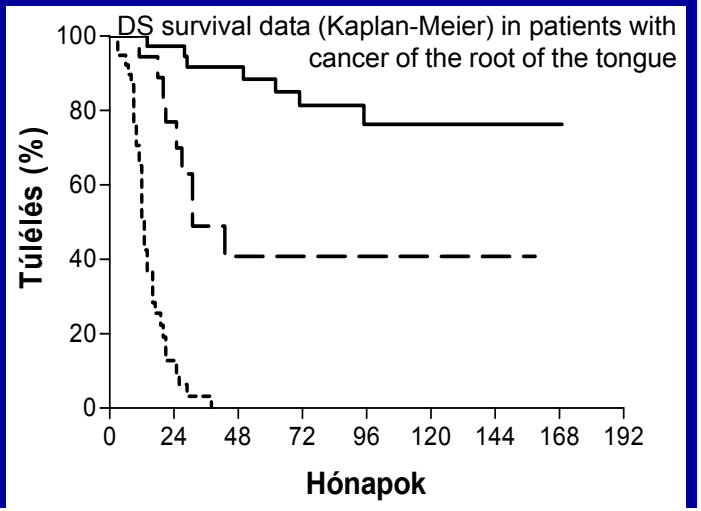
- Significant factors:
  - Lymph node status: N_{0-1} vs. N_{2-3}
    (RR=2,33; 95% CI 1,34-4,09; p=0,0050)
  - Histological grade: Grade 1-2 vs. 3
    (RR=2,05; 95% CI 1,16-3,63; p=0,0144)
  - **Response to irradiation**
    (RR=6,82; 95% CI 3,43-13,54; p<0,0001)
  - **Lack of residuum or recurrence: 88% survival rate**
  - **residuum after irradiation: ↓ 7x lower survival rate**
  - In case of residuum or recurrence (within 5 years):
    - **Surgery** **41% (8/18 patients) survival**
    - **No surgery** **0% (39 patients) survival**

    (RR=6,99; 95% CI 3,07-15,93; p<0,0001)

Locoregionally tumour-free patients (n = 37). Patients treated by „salvage" surgery because of locoregional lesions (n = 18). No surgery after locoregional residuum or recurrence (n = 39). The 5-year tumour-specific survival rate was 88%, 41% and 0%, in identical order (all p values < 0,02).



With patients with cancer of the root of the tongue the 5-yr survival with CR (complete regression) or PR (partial regression) was 63% and 5% resp., in identical order (p<0,0001). The locoregional residual tumour after radiotherapy caused more than 7-fold rise in mortality risk (RR, 7,77; 95% CI, 4,07-14,83).

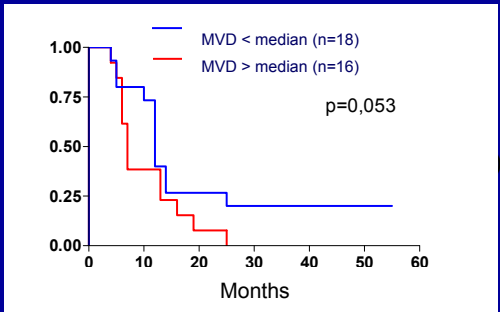


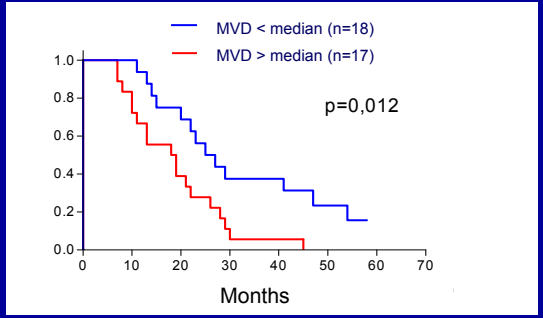
Considerable vascular density changes upon radiotherapy; correlation of radiotherapy efficacy and survival

1. **Patient group: 35 patients** (localization: oropharynx; mean age: 51 years (37-73 years); male:female= 34:1)
   stage: III.: (60% - 21 patients) IV.: (40% - 14 patients)

2. **Method:**
   - Percutaneous treatment with 6 MV linear accelerator photon beam from two lateral and adjusted a-p fields to the upper and lower neck region. To the dorsal lymph node chain ± boost, maximal burden of the spinal cord 46 Gy (dose: 66 Gy (60-70 Gy) to the midline. Length of the radiotherapy: 56 days (46-71 days)
   - biopsy (before irradiation and after 20 Gy)
   - Embedding in paraffin + HE staining
   - Determination of the grade and mitotic count
   - Determination of microvascular density (MVD) in 5 hot spots

The Kaplan-Meier curves of progression-free (A) and complete survival (B) based on the value of MVD after irradiation with 20 Gy





Significant difference (p=0,012)

- **MDV Initial values:** varying
  - before irradiation - median values: 1,09x10^4 mm^2 (S.E.M.: 0,13x10^4 mm^2)
  - after irradiation: decreased 0,825x10^4/mm^2 (S.E.M 0,1x10^4 mm, p=0,052) significant
- **MDV Predictive values**
  - **initial values:** non-significant for radiation response
    to survival: (Progression-free and complete) **non- significant**
  - **Vascular density decrease after irradiation (20Gy) :**
    decreased MVD: **significant for therapeutic response** (p=0,04)
    For survival: significant
    the effect of unchanged MVD on therapeutic response: non-significant
  - The correlations of clinicopathologic factors and MVD: non-significant

Lövey J., …, Kásler M. et al: Magy. Onkol.,. 49: 307-13. 2005
Lövey J., ..., Kásler. M. et al: Strahlenther. Onkol., 182. 149-156. 2006. *IF: 3.682*

Immune therapy of head and neck cancer

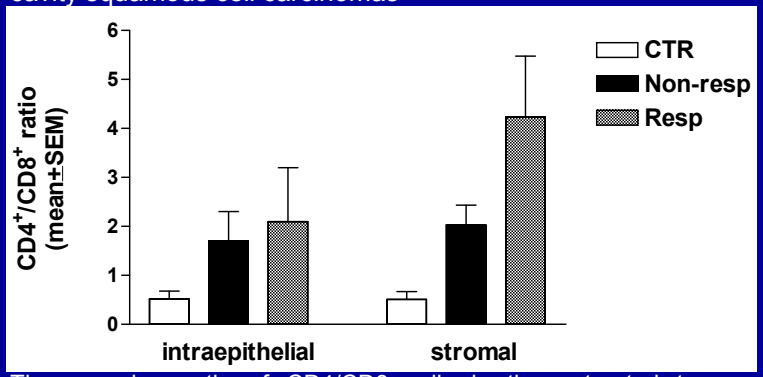
1. **Patient group: 21 untreated patients**, 21 controls (selected retrospectively, mean age: 59,4 yrs (40-87 years)
   - localization: oral cavity, histology: squamous cell carcinoma; **20 control patients**, mean age: 57,5 yrs (40-77 years)
2. **Method:**
   - Day 1: Cyclophosphamide infusion, Indomethacin tablets. (75 mg/day)
   - Day 3: Multikine 400 IU/day (peritumorally) Multikine 400 IU/day (perinodularly) total dose 12000 IU (3 weeks)
   - Day 6: Zink sulphate (50 mg/day), multivitamin preparation
   - MR examination: before and after immunotherapy
   - Pathological processing: 22 days in average (14-54 days) after: radical surgery
3. **Results:**

–- Tumour response
- Complete remission: 2 patients (histology: negative) - 10,5%
- Partial remission: 6 patients [2 patients (50% volume decrease) - 10,5%; 4 patients (30% volume decrease)]
- Stable condition: 10 patients (no change in volume)
- Progression: 1 patient (40% volume increase)
- **Summary: total change: 42%; objective change: 21%**
- A multicentric phase II trial started (with the permission of FDA)
- In the tumour and its adjacent tissues in the **responder group**

–- Cellular studies:
- » no change in the features of infiltrating cells
- » rise in intra-peritumoural leukocyte count
- » **$CD4^+$ T cells ↑**
- » **$CD8^+$ T cells ↓**
- » **$CD4^+$ T/ $CD8^+$ T ratio rose from the initial value 1 to 2-4 fold of the physiological value**

- **Group of non-responders**
  - » the features of the infiltrating cells did not change
  - » $CD4^+$ / $CD8^+$ cell proportion increased (in the stroma and intraepitelium)
  - » Connective tissue accumulation

Effect of high dose Multikine treatment on the T cell subpopulation density and ratio of CD4/CD8 cells, resp in oral cavity squamous cell carcinomas



The very low ratio of CD4/CD8 cells in the untreated tumour population significantly increased ($p<0.05$) in the intraepithelium and stroma in tumours treated with Multikine. From this point of view patients responding and not responding to therapy did not differ from one and other.

Tímár J., …, Kásler M. et al.: Laryngoscope 113:2206-2217, 2003. ***IF:1,449***
Tímár J., ..., Kásler M. et al: J. Clin. Oncol. 23 3421-3432. 2005. ***IF: 11.81***

Introduction of new reconstruction techniques into home clinical practice

Pectoralis maior myocutaneous flap modified by us – first in this country

1. **Patient group:** 1981-2007: **150 surgeries**
   1981-1985: 50 surgeries (subject of PHD dissertation)

Localizations:
- floor of the mouth, mandible, tongue, root of the tongue
- Tonsillolingual area, lateral pharyngeal defects
- dorsal pharyngeal wall, circular pharyngeal defects
  (laryngectomy) Intratracheal narcosis

2. **Results:** based on 150 operations performed from 1981 to 2007

- To the height of the os zygomaticum:

• a defect of any size (4-6x8-11x1-6 cm)

• suitable for closing a defect of any localization

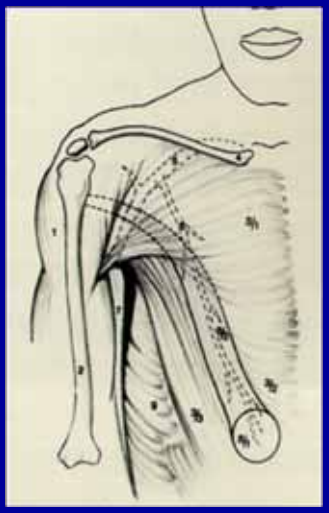
- Excellent viability:
  total necrosis: 0% (1/150 cases)
  Partial: 5% (7/150 cases)

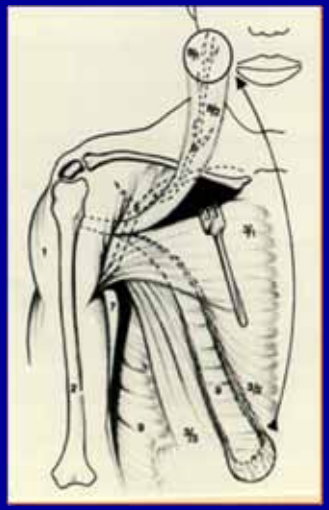
- healing disorder of the donor site: 9% (13/150 cases)

- **disadvantages:**
  - Excess tissue volume and excess contour in case of a defect not deeper than 1.5 cm
  - Functional deficiency after the reconstruction of the mandible

Sketch of the Ariyan's PM myocutaneous flap

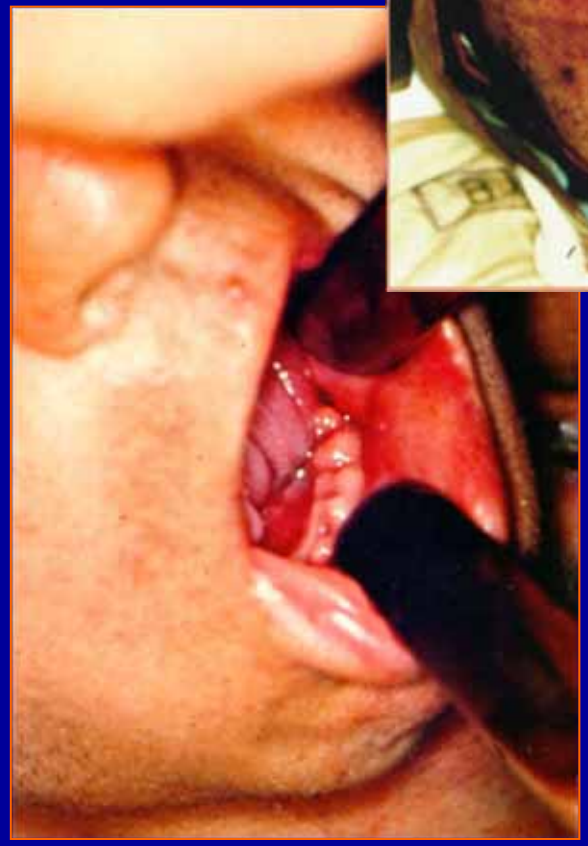
Sketch of a PM flap modified by us

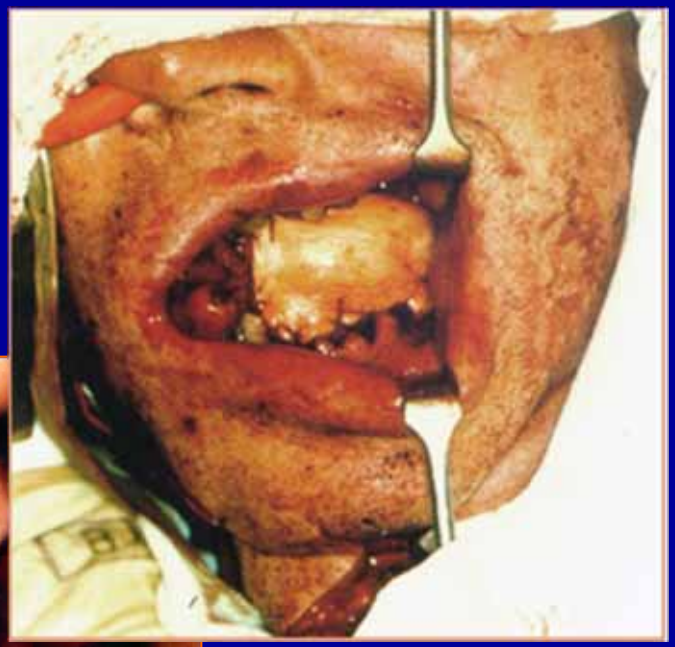


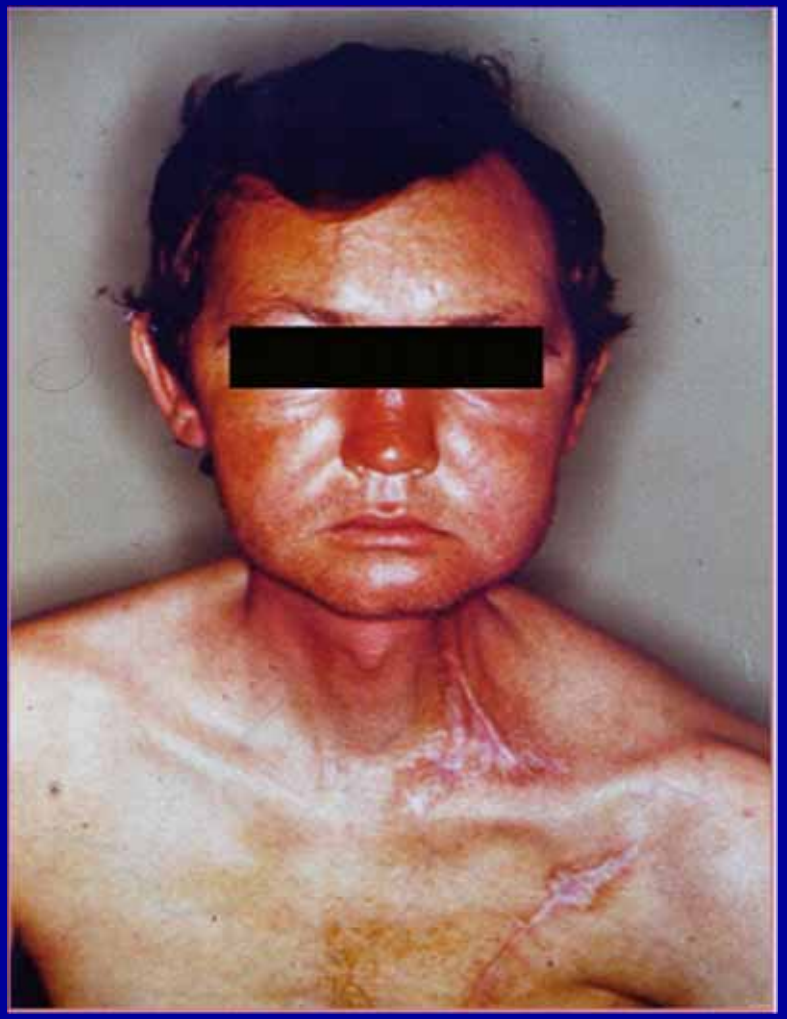


Kásler M.: Fül-orr-gégegyógy. 34, 157-163, 1988.
Kásler M., Bánhidy F., Trizna Z.: Arch. Otolaryngol Head Neck Surg. 118. 931-932. 1992. ***IF:0.940***
Kásler M., Bánhidy F.: Eur. J. Surg. Oncol. 19. 587-591. 1993. ***IF:0.415***
Fülöp M., ..., Kásler M.: Magy. Onkol. 52: 261-267, 2008.

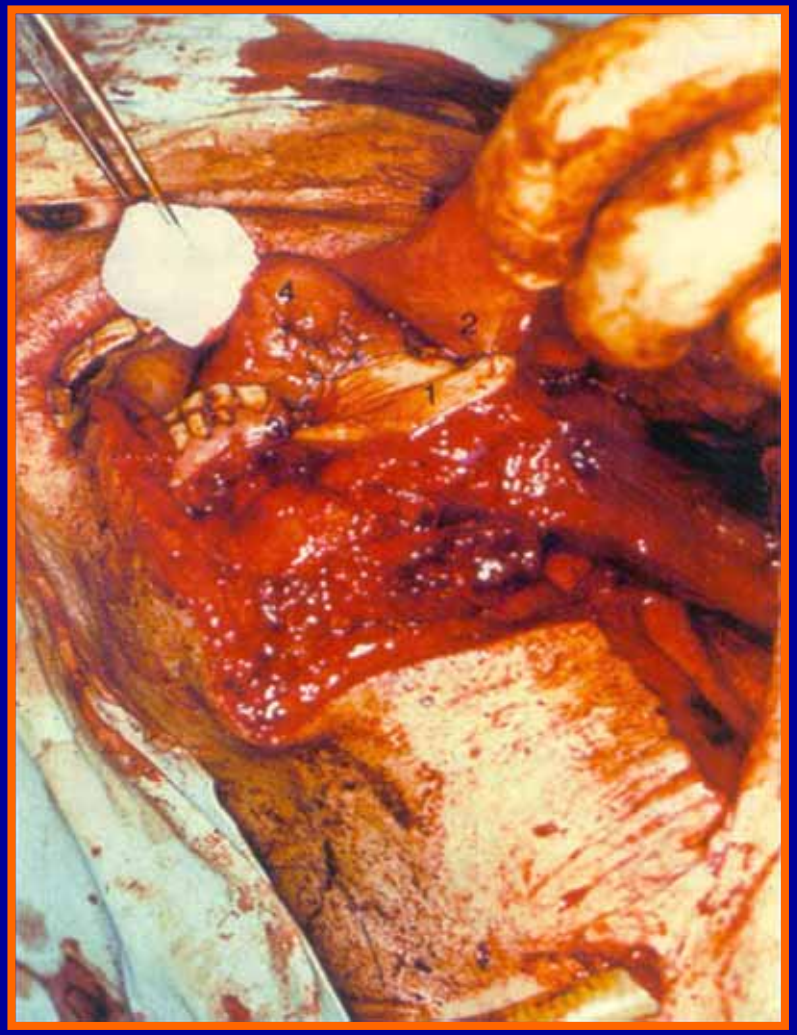
Resection of the tongue

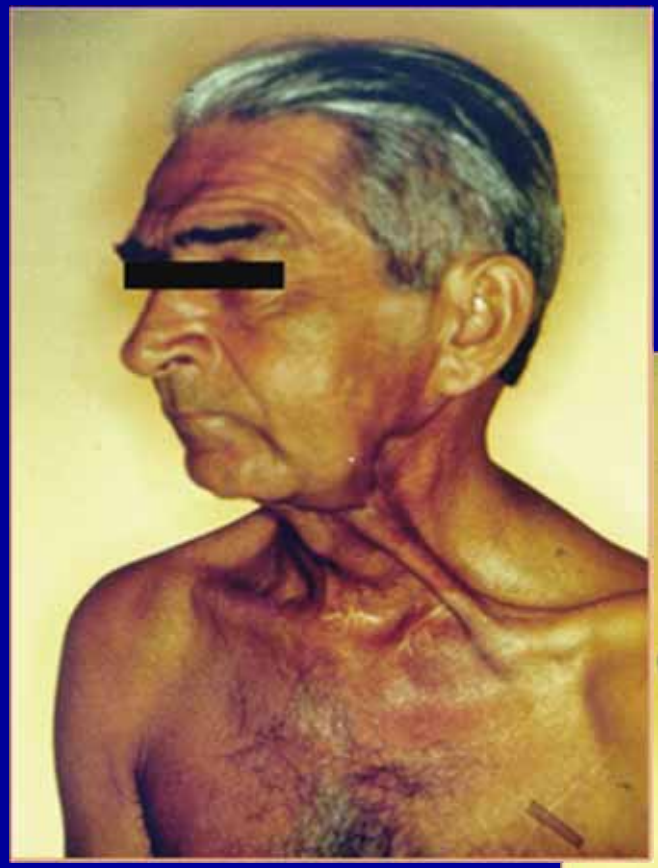


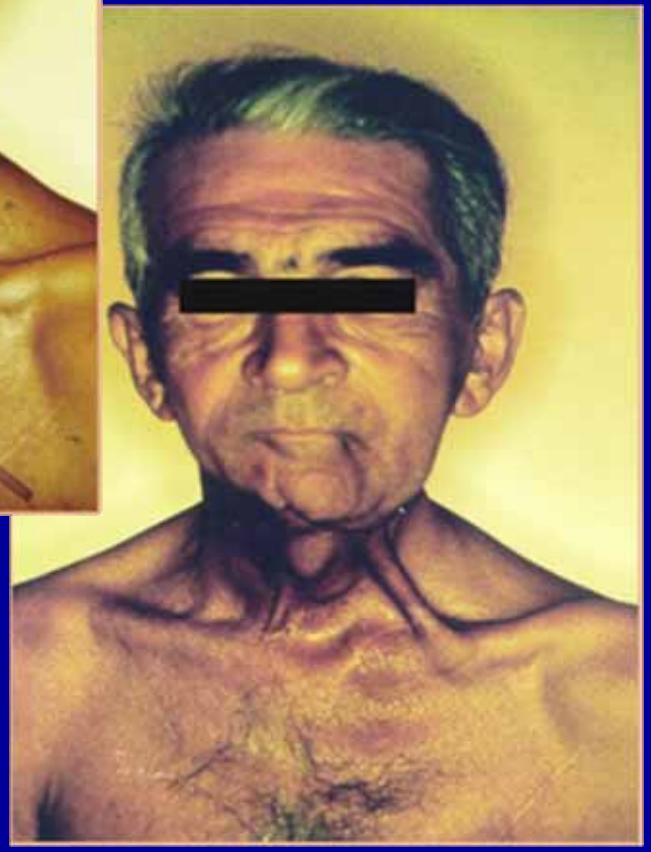




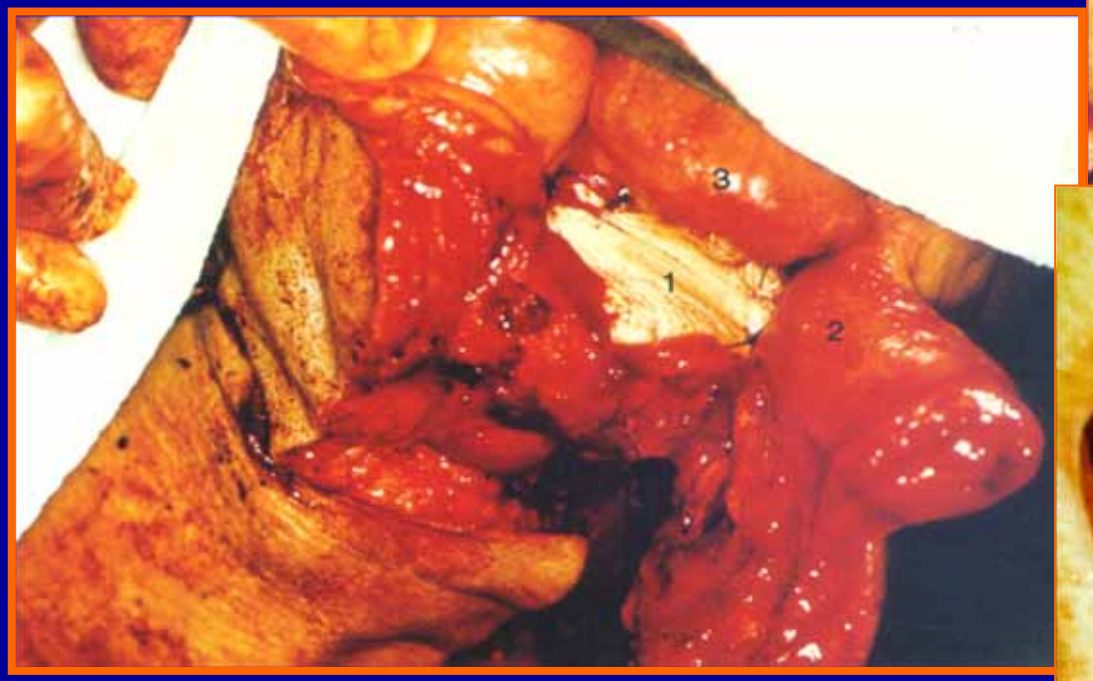
Resection of mandible, floor of the mouth and tongue

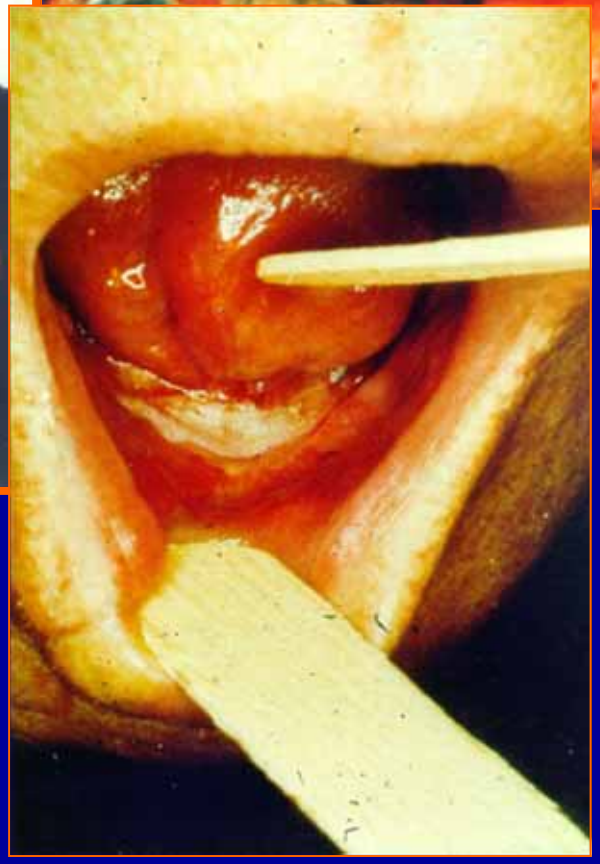




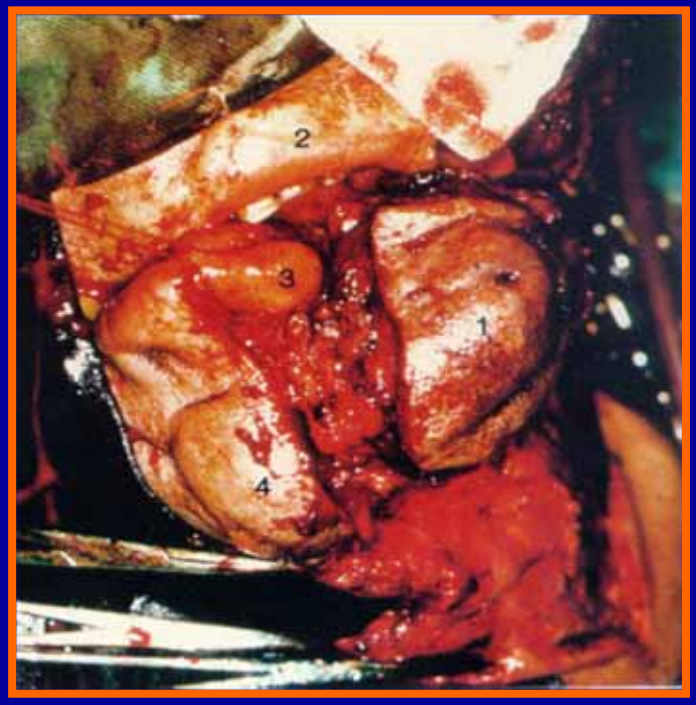


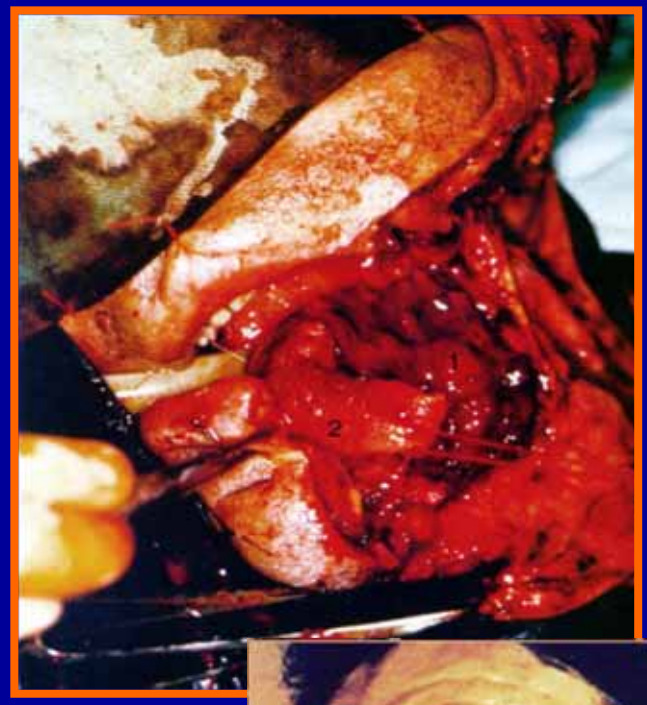
Resection of the corp of mandible and floor of the mouth

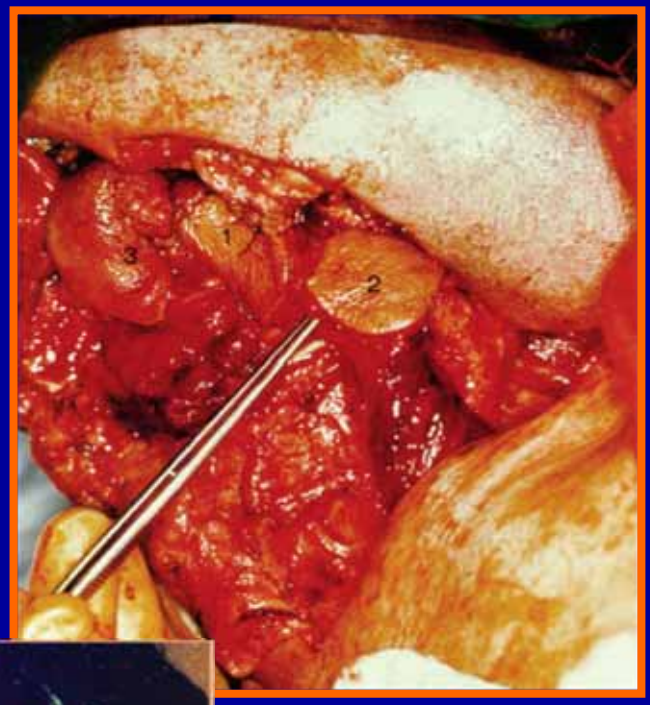


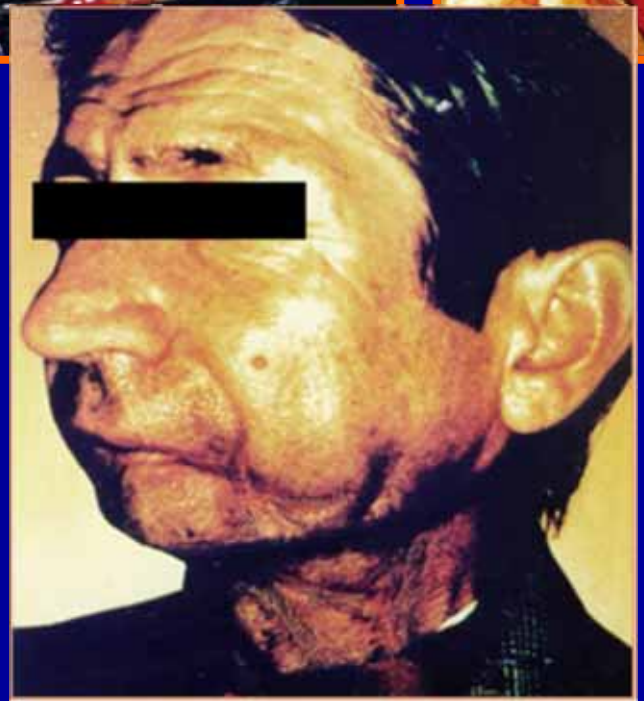


Resection of floor of the mouth, tongue, mandible, mentum

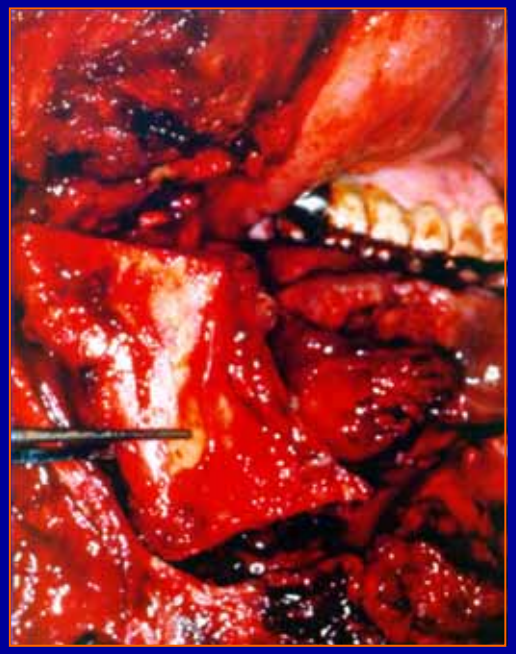


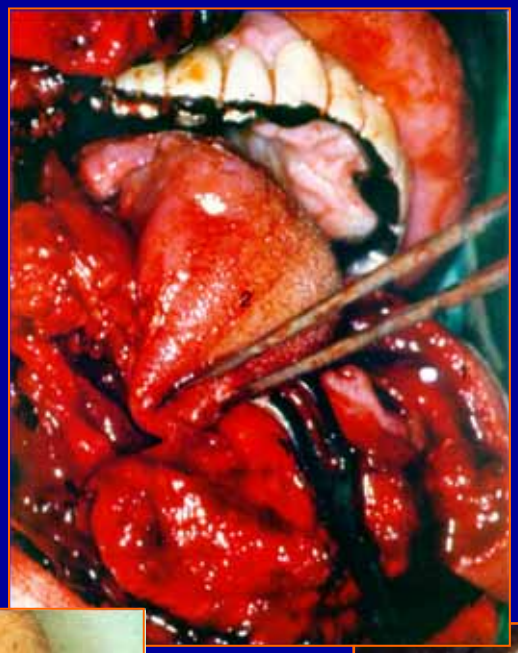


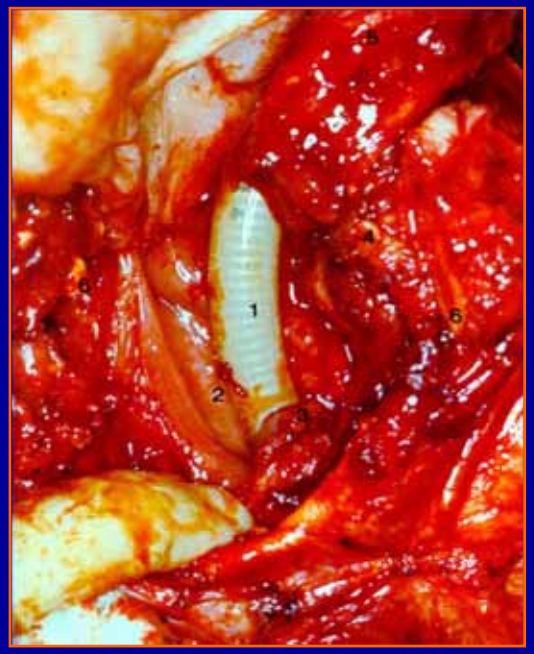


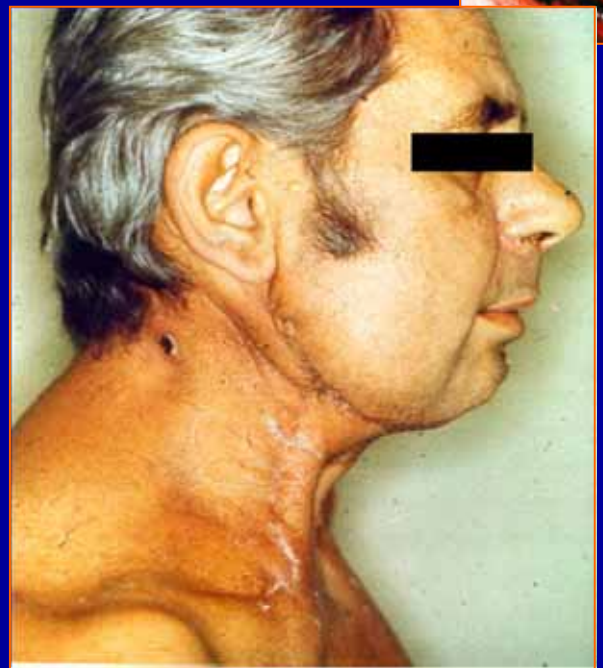


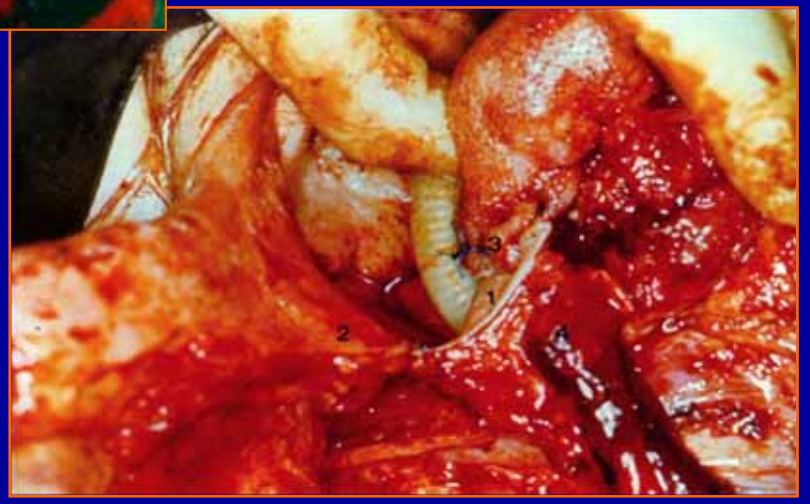
Resection of mandible, floor of the mouth, tongue, tonsils, root of the tongue



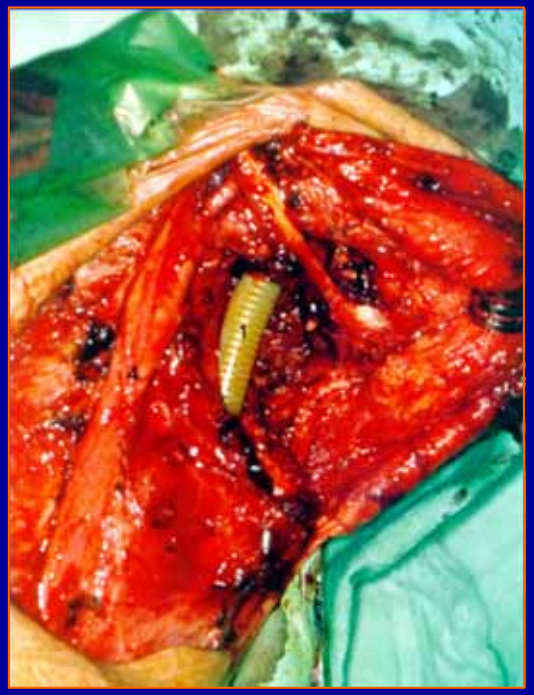


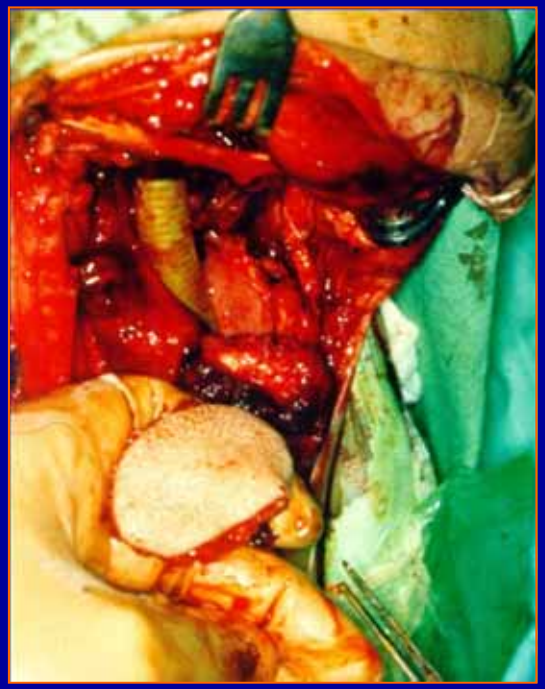


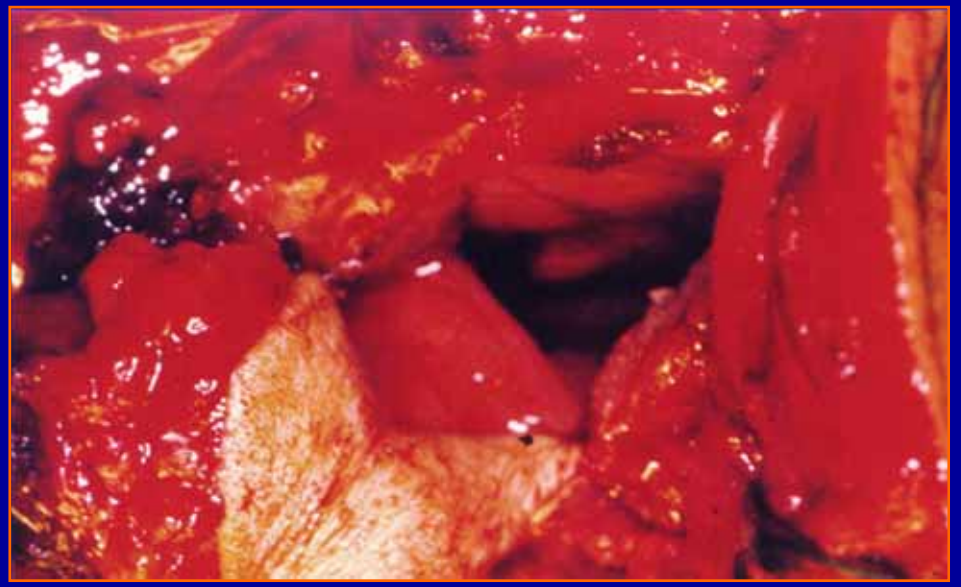


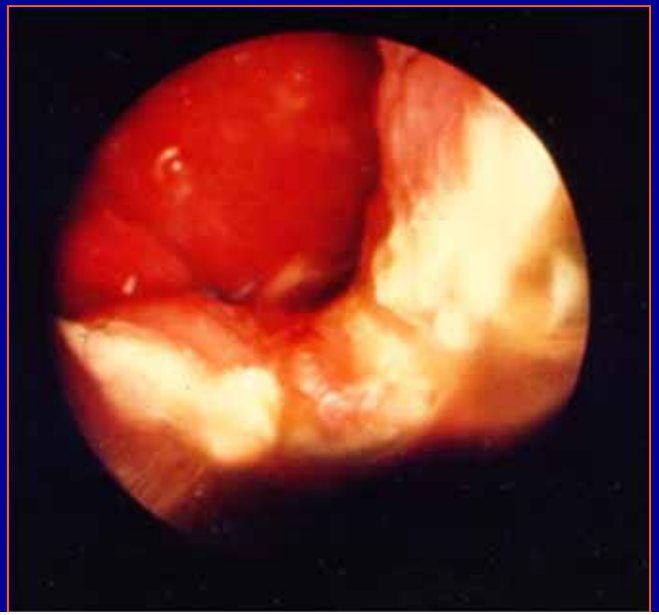


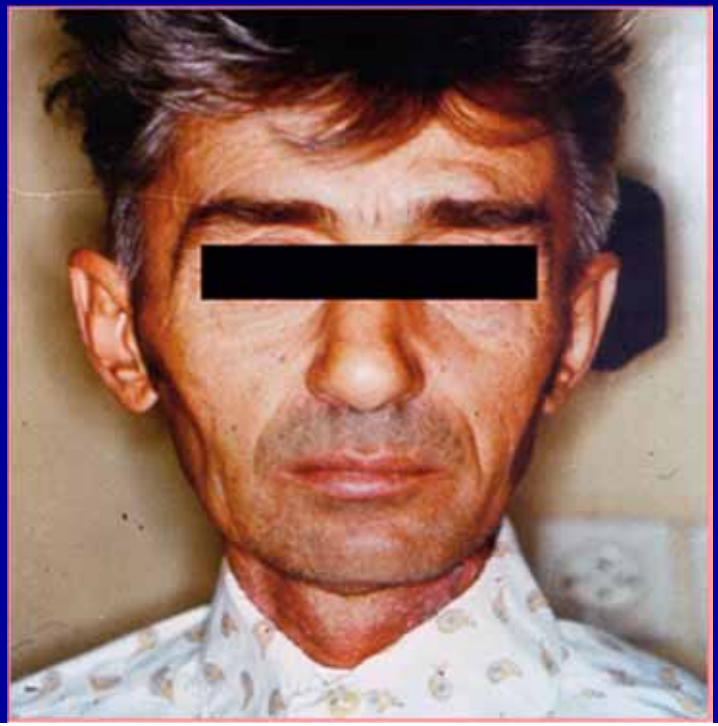
Resection of root of the tongue, horizontal laryngeal resection



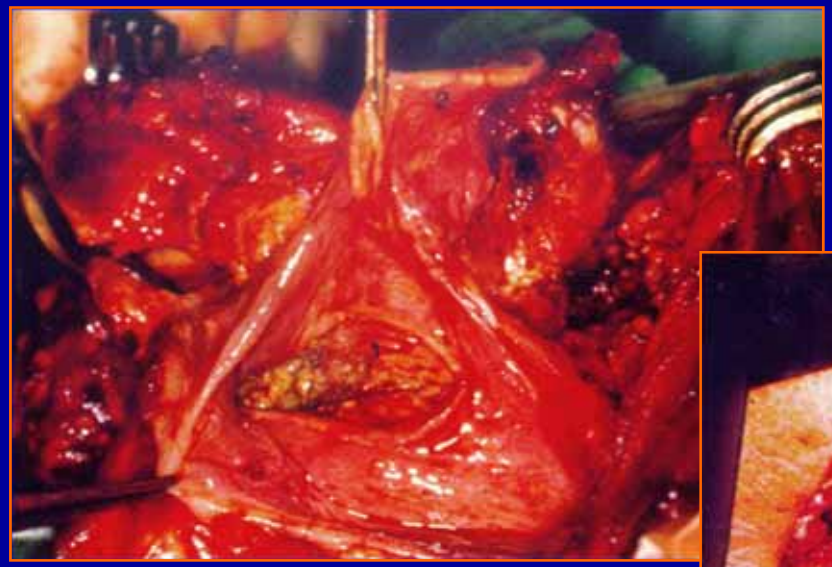


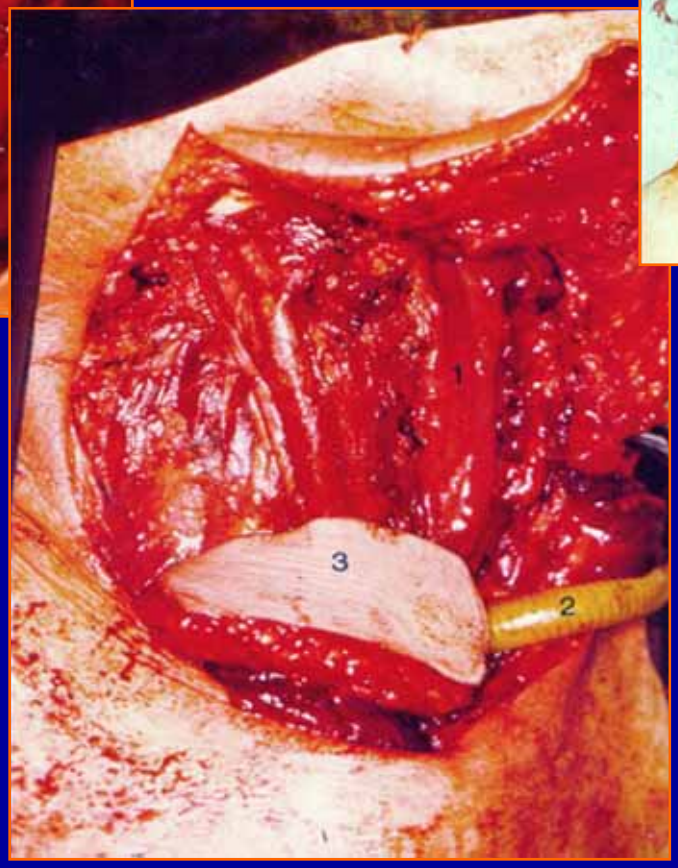


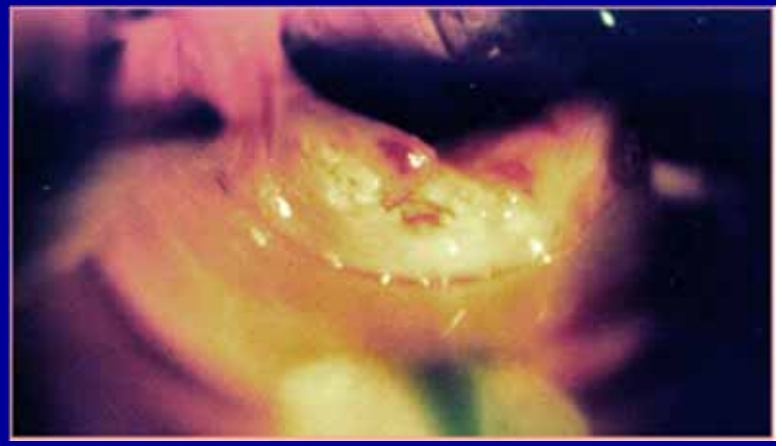




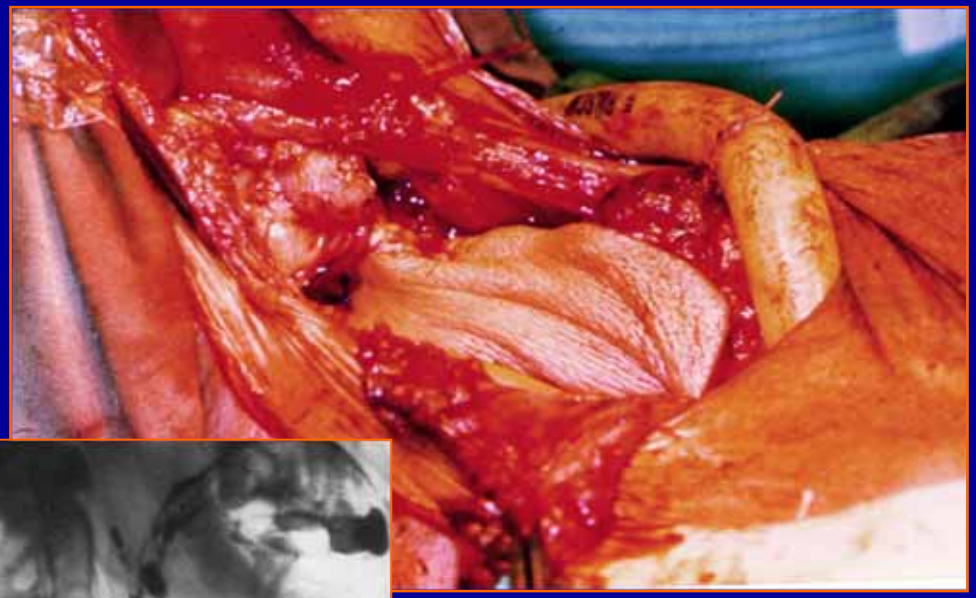
Laryngectomy, subtotal pharyngectomy

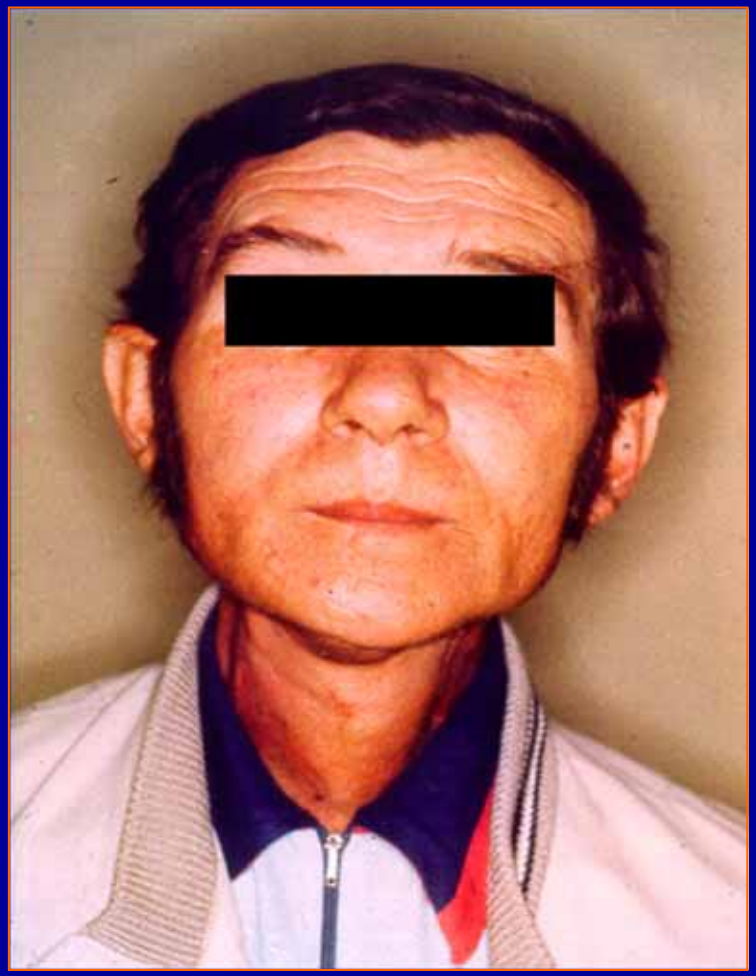




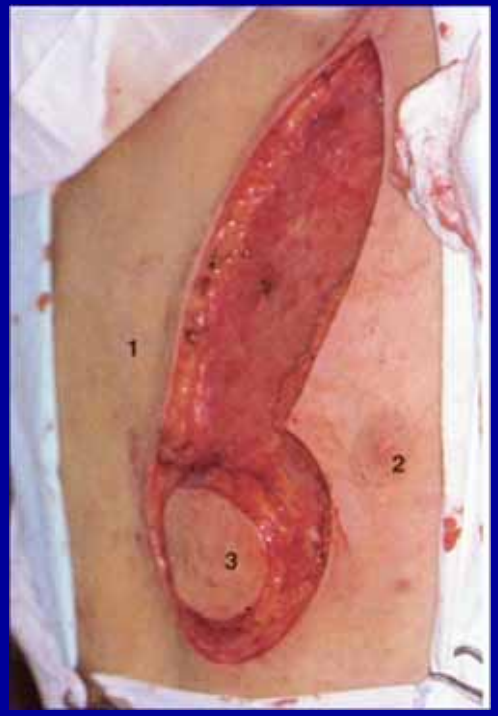


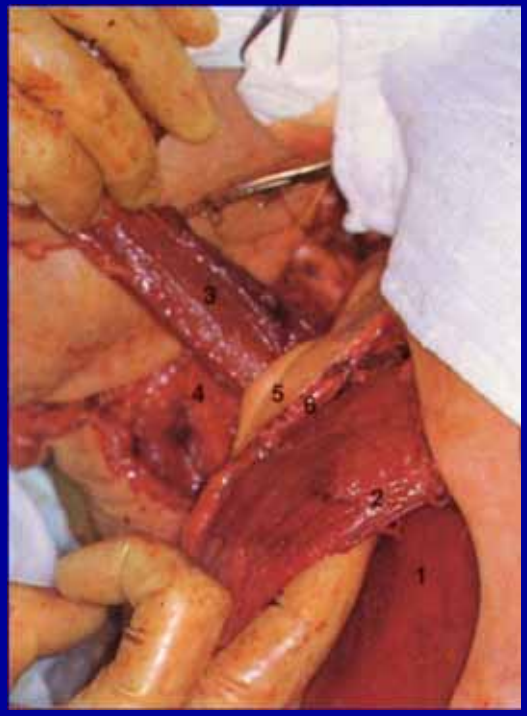
Laryngo-pharyngectomy

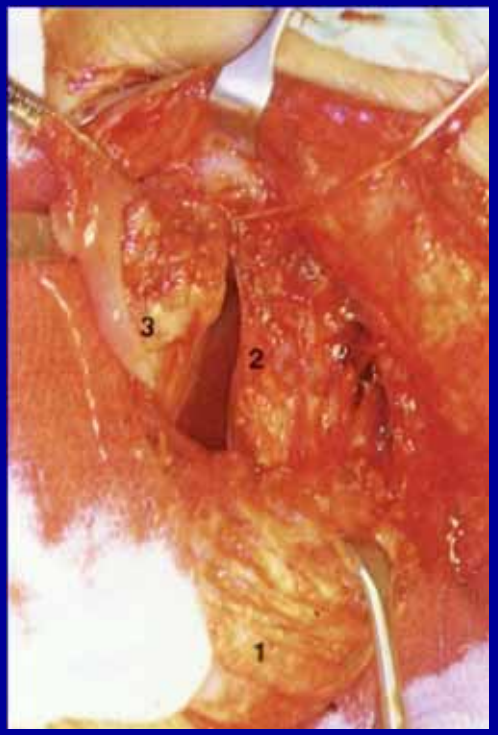


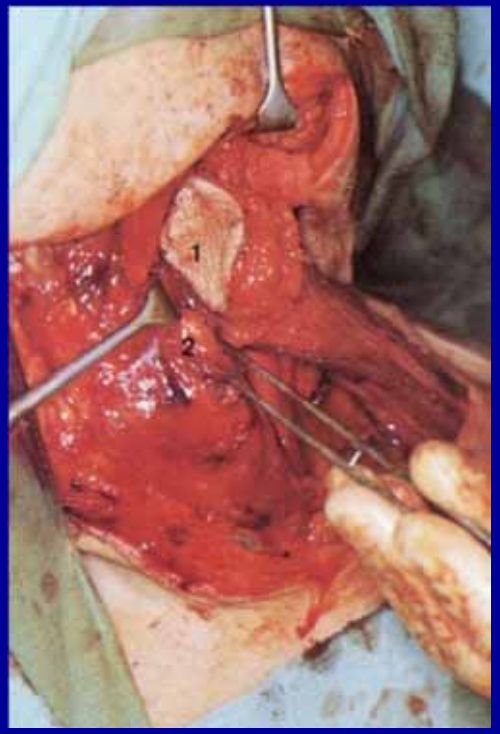


Resection and reconstruction of dorsal wall defects of the pharynx – first in Hungary









Introduction of new reconstruction techniques into home clinical practice

For closing extended defects non invading deeper layers

1. Localization and histological **type** of the defect :

- oral cavity-mesopharyngeal soft tissue: anterior- mid third (NL, B)
  lateral wall, palate (B, NL)
- mandible –oral cavity- mesopharyngeal soft tissue: corpus + anterior oral cavity, angulus+lateral oral cavity and oropharynx (F)
- meso-hypopharynx: dorsal wall, dorsal-lateral wall (PM, A)
- hypopharynx – larynx: circular defect (A)

2. Size of the **defect**:

- surface greater that 2x4 cm (min. 1 cm)
- depth less than 2-3 cm (min. 1 cm)

3. **Surgical techniques** used for reconstruction:

- nasolabial transposition flap (NL)
- buccal transposition flap (B)
- forearm free flap – transposed with microvascular anastomosis (A)
- fibular free flap – transposed with microvascular anastomosis

4. Wound healing

nasolabial transposition flap (NL)	26 patients	100%
buccal transposition flap (B)	11 patients	100%
forearm free flap – transposed with microvascular anastomosis (A)	146 patients	87%
fibular free flap – transposed with microvascular anastomosis	27 patients	82%

210 patients

Oberna F., …, Kásler M.: Magy. Onkol. 45. 169-172. 2001.
Fülöp M., …, Kásler M.: Magy. Onkol. 45. 177-180. 2001.
Oberna F., …, Kásler M.: Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 99. 550-55. 2005. *IF: 1.193*
Fülöp M., ..., Kásler M.: Magy. Onkol. 52: 261-267, 2008.
Kásler M. et al: Magy.Onkol. 52: 279-281, 2008.

Introduction of new reconstruction methods into the home clinical practice

Application of nasolabial transposition flap – first in Hungary

1. Patient group: 26 patients

Mean age: 58,2 years (40-73)
- Localization: tongue(3), lateral and anterior part of the floor of the mouth (23)
- Stage: $T_2N_0M_0$ -$T_4N_0M_0$, respectively $T_2N_2M_0$
- Size of tissue defect: 3-5x2-3 cm

2. Results:

- flap necrosis complete: 0% (0/26 patients), partial: 4% (1/26 patients)
- **Anatomical-functional-aesthetic restitution ad integrum**
- Avoidance of disadvantages concomitant to other techniques

A) Superficial tissue loss on the floor of the mouth

B) Donor site

C) Suturing of nasolabial flap mobilized from two sides to the tissue defect

D) Oral cavity after complete wound healing

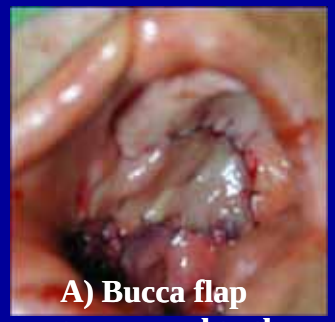
Application of bucca transposition flap – first in Hungary

1. Patient group: 1996-2001, 6 patients

- Localization: oral cavity, lateral-dorsal wall of the oropharynx, soft palate
- Stage: T_2-$T_4N_0M_0$, resp. $T_2N_2M_0$ (1 recurrence, 1 residuum)
- Size of tissue defect: 4x2-7x3,5x <1 cm
- Postop. irradiation: 50-66 Gy

2. Results:

- Flap necrosis 0% (0/6 patients)
- Anatomical-functional-aesthetical restitution ad integrum
- Avoidance of disadvantages concomitant to other techniques



A) Bucca flap transposed to the palate.

B) The transposed buccal flap on day 21.

C) The transposed buccal flap after 3 months

Oberna F., ..., Kásler M.: Magy. Onkol. 45. 169-172. 2001.
Oberna F., …, Kásler M.: Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 99. 550-55. 2005. *IF: 1.193*
Fülöp M., ..., Kásler M.: Magy. Onkol. 52: 261-267, 2008.

Introduction of new reconstructive techniques in Hungary

Application of forearm free flaps with microvascular anastomosis transposition for oral cavity and pharyngeal defects - first in the country

1. **Patient group: 146 patients, 1993-2007**
– average age: 51 years (26-77), male/female: 10:1
– localization: any site in the head-neck: bucca (13), floor of the mouth (42), tongue (43), tonsillolingual area (31), root of the tongue (9), lateral pharyngeal wall (6), dorsal pharyngeal wall (2)
– Size of the tissue defect: 4-8x6-10x <1 cm

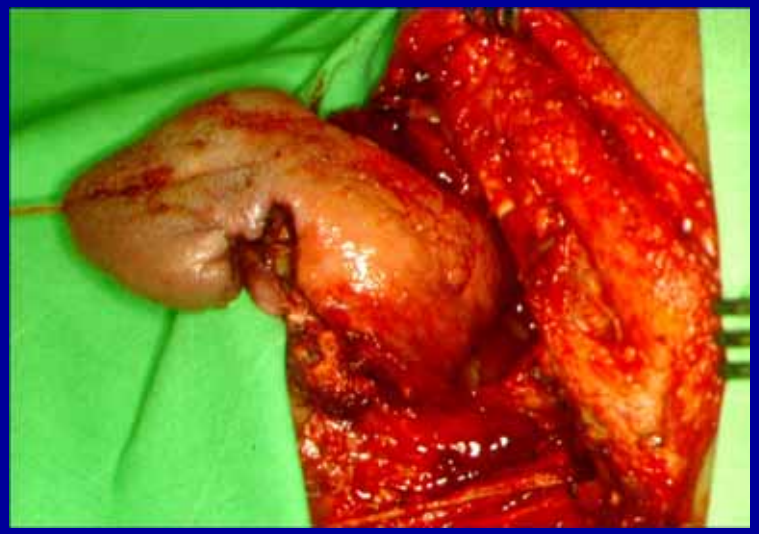
2. **Results:**

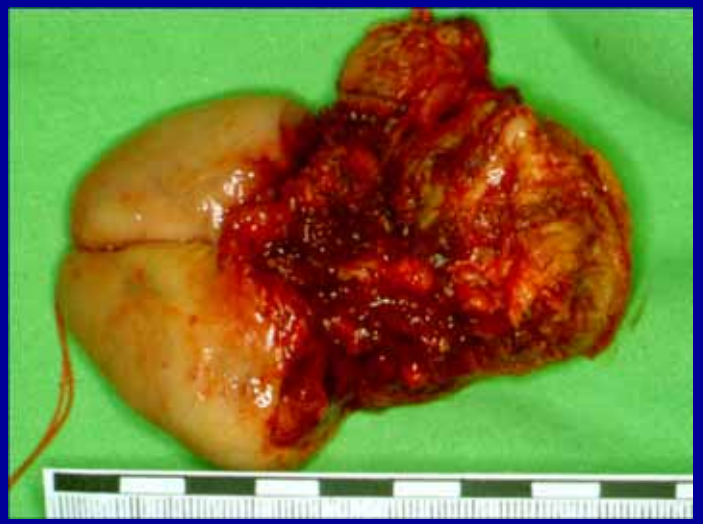
- **Primary wound healing: 87 %**
- Flap necrosis (initially venous circulatory disturbance): complete 13% (25/146 pts)
  partial 2% (3/146 pts)
- **Acceptable anatomical and functional reconstruction:100 %**
  - acceptable: 87% (121/146 beteg)
  - restitutio ad integrum: 7% (11/146 beteg)
- Complications:
  - Dysphagia 2% (4 pts),
  - Aspiration 2% (4 pts)
  - Wound healing disorder at donor site: 4,5% (7 pts)
  - Secondary wound healing (6 pts)
  - Digital motility disorder (1 pt)

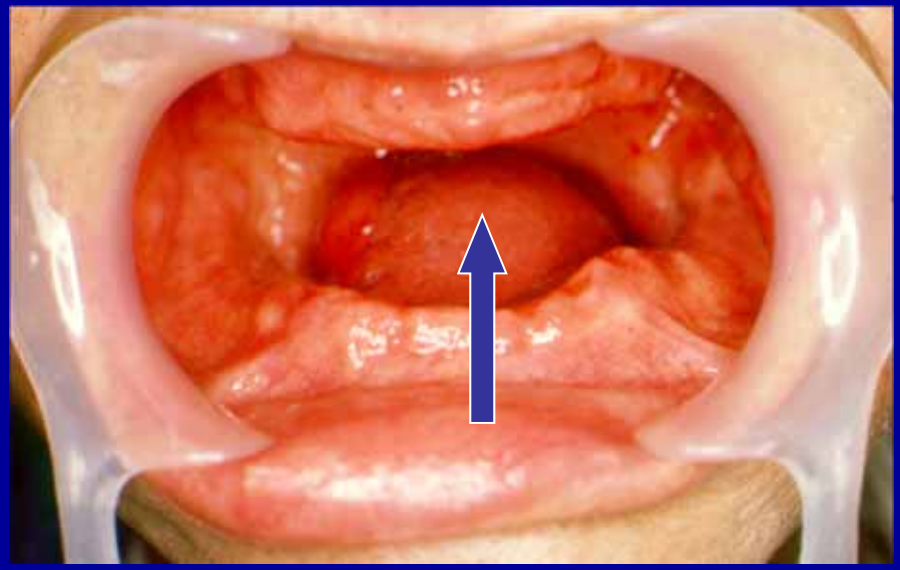
Forearm flap preparation

Fülöp M., …, Kásler M.: Magy. Onkol. 45. 177-180. 2001.
Fülöp M., ..., Kásler M.: Magy. Onkol. 52: 261-267, 2008.

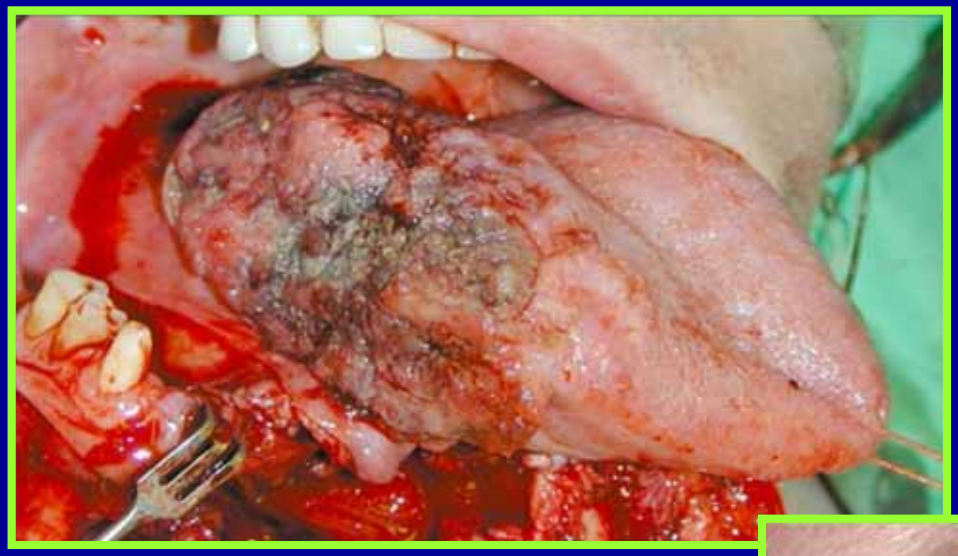
Resection of the tongue
Reconstruction: free forearm flap

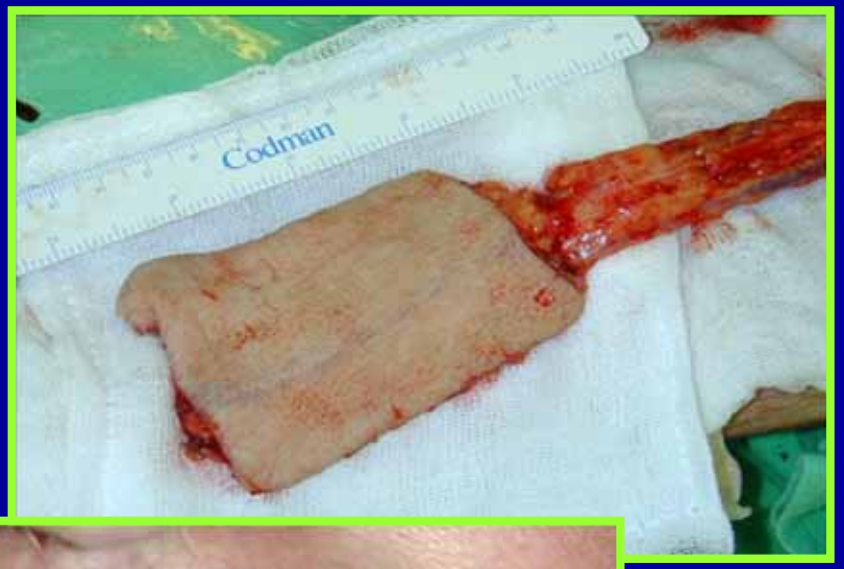




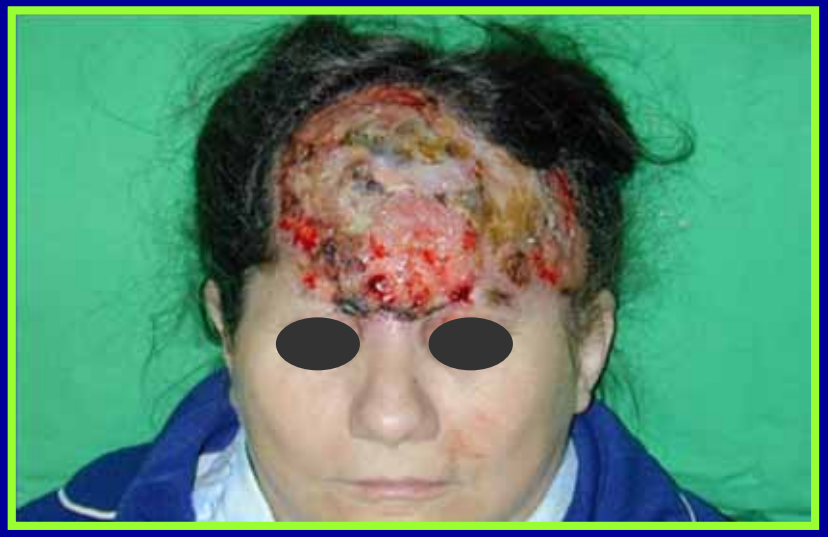


Resection of the tongue
Reconstruction: free forearm flap





Resection and reconstruction of forehead: free forearm flap



Introduction of new reconstructive techniques in Hungary

Application of fibula free flaps with microvascular anastomosis transposition for mandible and soft tissue defects – first in Hungary

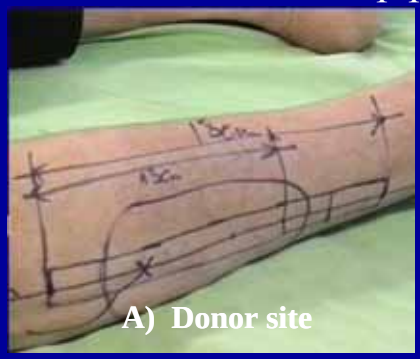
1. Patient group: 1995-2007, 27 patients

- Mean age: 50,6 years (38-66) male/female: 23:4
- Localization: different areas of the mandible and surrounding soft tissue
- Stage: $T_{3(3)-4(22)}N_{0(4)-1(23)}M_0$
- Histology: squamous cell carcinoma (23), ameloblastic cc. (1), mammary

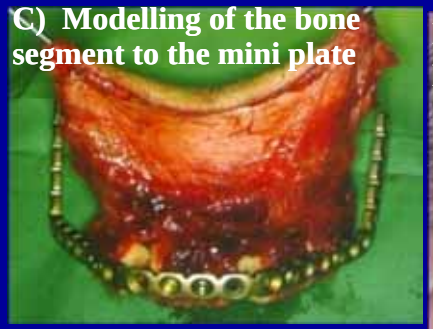
2. Results:

- Flap necrosis (complete): 18% (5/27 venous circulation disorder)
- Complication of donor area 0%
  - knee and ancle stability is perfect
- Full recovery: 82%
- Avoiding laryngo-pharyngectomy
- **Anatomical restitution ad integrum**
- **Functional** (occlusion, chewing, speech) **satisfactory restitution** (dental prosthesis is possible)
- Aesthetical restitution is good

Fibula flap preparation


A) Donor site


B) A flap prepared


C) Modelling of the bone segment to the mini plate


D) Fixation of dental prosthetis


E) Implanted dental prosthetis


F) Aesthetical result

Fülöp M., …, Kásler M.: Magy. Onkol. 45. 177-180. 2001.
Fülöp M., ..., Kásler M.: Magy. Onkol. 52: 261-267, 2008
Kásler M. et al: Magy.Onkol. 52: 279-281, 2008.

Analysis of head and neck cancer progression

Genetical marker analysis for the detection of gene-inactivation and tumour-trasformation

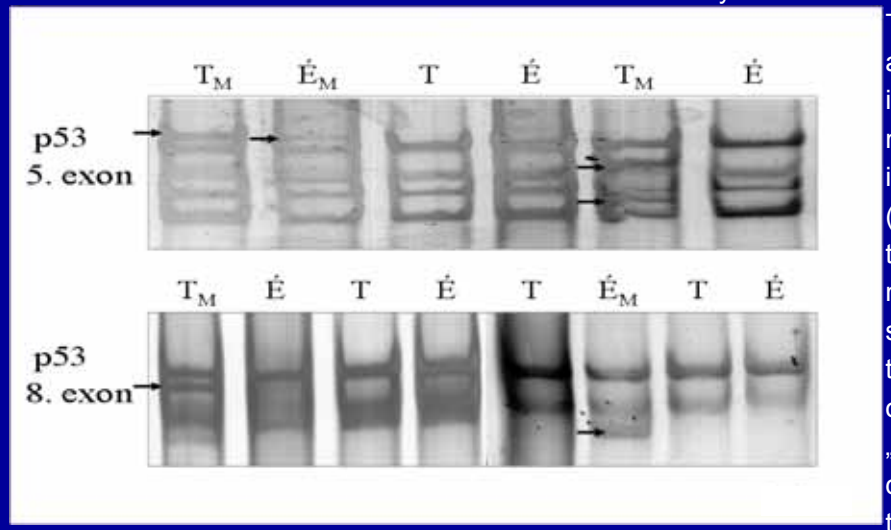
1. **Patient group:**
   - **152 untreated patients**
   - Stage: $T_1N_0 – T_3N_2$
   - sample: intact tissue, tumour

2. **Results:**

Genes that influence the genetic stability of tumours

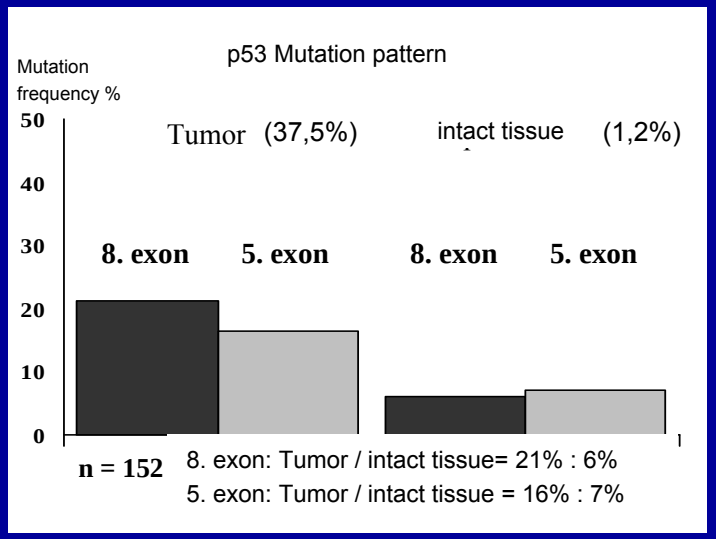
- identifying p53 mutation is good for:
  - **indicating tumour transformation**
  - **detecting secondary tumours**

Identification of P53 mutation with PCR-SSCP analysis



The arrow points to the abnormal mobility band, indicating mutation. The p53 mutations can be detected even in „intact" mucous membranes (É). It is interesting that one of the p53 mutations in „intact" mucous membranes is of the same type as the primary tumour (exon 5. ÉM). All the other p53 mutations in the „intact" mucous membranes are different from the primary tumour (exon 8. ÉM).

P53 mutation influencing genetic stability in head and neck cancers and in „intact" peritumoral mucous membranes.



Csuka O., ..., Kásler M.: Magyar Onkológia 45 (2) 161-167, 2001.

Tímár J., ..., Kásler M.: Cancer Metast Rev 24: 105-125, 2005. *IF:8,017*

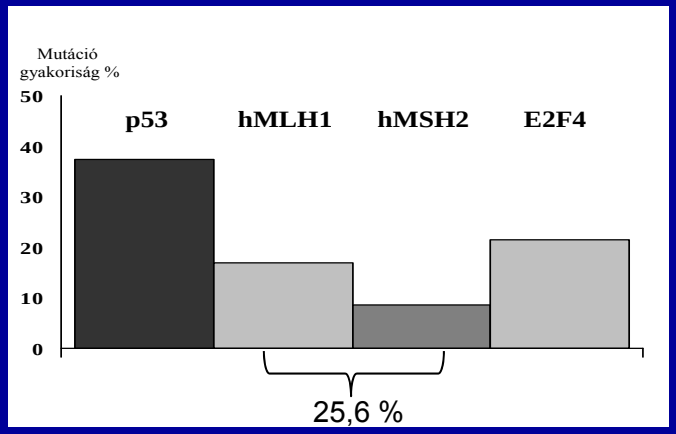
Analysis of head and neck cancer progression

Genetical marker analysis for detecting MMR gene-activation

The inactivation and mechanism of mismatch repair (MMR) (hMLH1, hMSH2 gene mutation frequency) based on **128 patients** examinations

Mutation frequency:

- hMLH1 mutation 17,0%-ban
- hMSH2 mutation 8,6%-ban

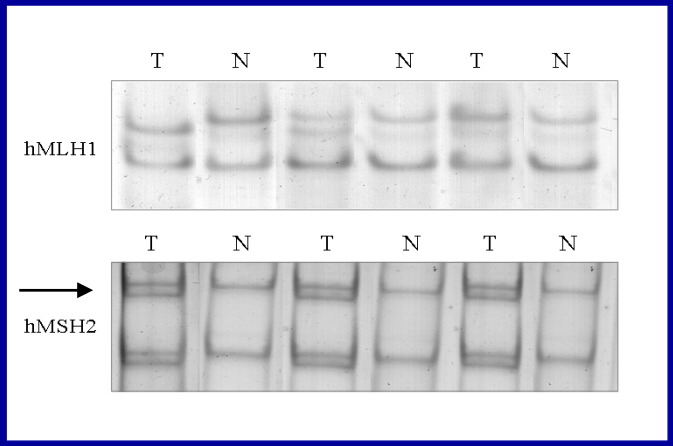


Mutation frequency of DNA mismatch repair (MMR, gene stability influencing) genes in head and neck squamous cell carcinomas evaluated with PCR-SSCP analysis,

PCR-SSCP analysis of hMLH1 and hMSH genes

Hypermethylation frequency in the promoter region:

- p16 gene 37,0%
- hMLH gene 14,0%



The arrow points to the mutational band

Identifying hMLH1 and hMSH2 gene mutations with PCR-SSCP analysis. The figure shows some representative cases.

Juhász A., …, Kásler M. et al: Magyar Epidemiológia, 1.2. 51-55, 2005.

Tímár J., ..., Kásler M.: Cancer Metast Rev 24: 105-125, 2005. *IF:8,017*

Expression of sex-hormone-receptors and their prognostic significance in head and neck cancers

1. Patient group: **67 head and neck squamous cell carcinoma patients**

- Genders: male/female = 56:11
- Localization: pharyngeal and laryngeal /oral cavity = 2/3 : 1/3 (43:24 pts)
- Stage: $T_{1-4}N_0M_0$
- Grade: 2

2. Method: detection of estrogen and progresterone receptors

- With immunohistochemical method in frozen samples
- Molecular procedures
- Estrogen receptors with α, β and progesterone primers, with nested-PCR method from mRNA after RNA isolation
- Identifying the resulting PCR products with sequenation

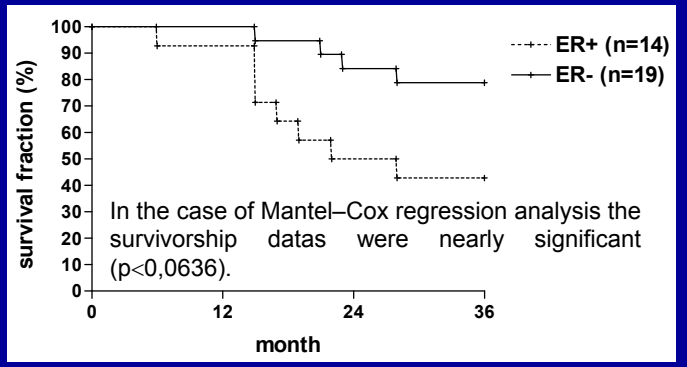
3. Results

Survival and receptor-state:

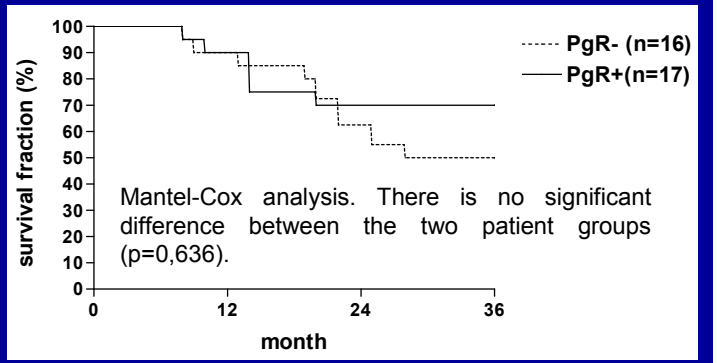
-**The entire patient group:** the 3 year (55-70%) survival **was not affected** significantly by the expression of the estrogen-progesterone receptor, or by the joint expression of the two receptors (the small oral cavity group showed marked scattering).

- **The 3-year survival of glottic cancer patients**
  - **was significantly impaired by the α_1- or β estrogen expression (prognostic factor)**
  - was not affected by the progresterone expression

3-year survival of laryngeal cancer patients according to their estrogen-receptor state. The estrogen expression is a prognostic factor.



3-year survival of laryngeal cancer patients according to the progresterone-receptor state. The progresterone-receptor is not a prognostic factor.



Lukits J., ..., Kásler M. et al: Int. J. Oncol. 30, 155-160, 2007. ***IF: 2.556***

Progressive gene patterns of pharyngeal and hypopharyngeal cancers (96 examined genes)

1. Expression patterns of the common genes in progressing tumour in these two localizations

		Common	(n=10)	(n=10) fatal
E-cadherin	NM-004360	*Cadherin 1, epithelialsuppressor*		
CD31	NM-000442	*Platelet/endothelial adhesion molecule*		
MT1-MMP	NM-004995	*Maix metalloproteinase 14 (membrane-ins)*		
Cystatin C	NM-000099	*Cystatin C*		
MUC-18	NM-000247	*MHC-I polypeptide related sequence-A*		
c-Fos	NM-05252	*V-fos FBJ m. osteosarcoma viral oncogene h.*		
DCC	NM-005215	*Deleted in colorectal cancer*		

2. Hypopharyngeal cancers

- **Progressive gene set: 11 gene** → **4 characteristics (7 common with laryngeal cancers)**
- Characteristic: Losing the Caspase 8 (apoptosis effector) and the PAI-1 protease inhibitor

		Hypopharynx-specific	(n=5)	(n=5)
PAI-1	NM-000602	*Plasminogen activator inhibitor type 1*		
NME4	NM-005009	*Non-metastatic cell-4, protein*		
c-Fes	NM-002005	*Feline sarcoma oncogene*		
FLICE	NM-001228	***Caspase 8, cystein protease***		

Signs: absent= white, present =black, down-regulated=green, over-expressed=red, deviation >2fold

In italics: in this localization unpublished in literature

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Progressive gene patterns of pharyngeal and hypopharyngeal cancers

3. **Pharyngeal cancers**

- **Progressive gene set: 28 genes (7 are common with those of sublaryngeal cancer).** Out of the 21 typical genes 17 metastasis genes are expressed in the aggressive group.

➢ Increased expression of metastasis associated genes:

- c-Myc-oncogene (known)
- MMP1 collagenase (known)
- cathepsin B (known)
- **API5 apoptosis inhibitor (unknown in the pharynx)**
- **caveolin1 (unknown)**
- TSP1 (known)
- **MMP11 (unknown)**

➢ Decreased expression of metastasis suppressor genes:

- NME1 (known)
- **RAF1 (unknown in the pharynx)**
- a5 integrin (known)
- **TSP2 (unknown in the pharynx)**

4. Conclusion: head and neck cancers can be divided into heterogenous groups, that have different

- gene expression patterns
- progression
- therapeutic sensitivity

		Larynx specific	(n=5)	n=5 fatal
S100A4	NM-002961	**S100 calcium binding protein A4**		
Osteopontin	NM-000582	*Secreted phosphoprotein-1 (osteopontin)*		
Integrin α6	NM-000210	*Integrin, alpha 6*		
Collagenase 1	NM-002421	*Maix metalloproteinase 1 (interstitial)*		
TMPRSS4	NM-019894	*Transmembrane protease, serine 4*		
NGF	NM-002506	***Nerve growth factor beta polypeptide***		
PDGFα	NM-002607	*Platelet-derived growth factor alpha*		
c-Fes	NM-002005	*Feline sarcoma oncogene*		
c-Myc	NM-002467	*V-myc myelocytomatosis viral oncogene hom.*		
AAC-11	NM-006595	***Apoptosis inhibitor 5***		
Caveolin-1	NM-001753	***Caveolin-1, 22 kD***		
OC	NM-002539	***Ornithine decarboxylase 1***		
KISS1	NM-002256	***KiSS-1 metastasis suppressor***		
COL4A2	NM-001846	***Collagen type IV, alpha2***		
TSP1	NM-003246	***Thrombospondin-1***		
CathepsinB	NM-001908	***Cathepsin B***		
ST3	NM-005940	*Maix metalloproteinase 11 (somelysin3)*		
RAF1	NM-002880	*V-raf-. leukemia viral oncogene homolog1*		
NME1	NM-000269	*Non-metastatic cells-1 protein (NM23A)*		
Integrin α5	NM-002205	*Integrin, alpha 5 (fibronectin receptor alpha)*		
TSP2	NM-003247	**Thrombospondin-2**		

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