Ph.D. Thesis

Quality of life of head and neck cancer patients after tumor treatment and subsequent maxillofacial rehabilitation

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Szeged, Hungary

2011

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Ph.D. Thesis

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Szeged, Hungary

2011

List of scientific publications related to the subject of the thesis

Articles:

I. **Nagy, J.**, Feher, L., Sonkodi, I., Lesznyak, J., Ivanyi, B., Puskas, L.: A second field metachronous Merkel-cell carcinoma of the lip and the palatine tonsil confirmed by microarray-based CGH.
Virchows Arch 446: (3) 278-286, 2005.
IF: 2.224

II. **Nagy J.,** Iványi B., Sonkodi I.: Merkel-sejtes carcinoma.
Fogorvosi Szle, 99; (4) 135-139, 2006.

III. **Nagy J.,** Seres L., Novák P., Nagy K.: Implantáció a szájüregi rák miatt sugárkezelésben részesült betegeken.
Fogorvosi Szle 102; (1): 7-11, 2009.

Published abstracts:

I. **Nagy J**, Piffkó J, Nagy K: Quality of life of H&N cancer patients after prosthetic rehabilitation. ID: 0294 CED- IADR Budapest, August 31- September 4, 2011. J Dent Res 90, Spec. Is B (IF abstrakt: 3, 773)

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I. ABBREVIATIONS

AR:	after rehabilitation
BR:	before rehabilitation
CARES:	Cancer Rehabilitation Evaluation System
EORTC:	European Organization for Research and Treatment of Cancer
EORTC C30:	QLQ of EORTC for cancer patients as concerns the general staging
EORTC H&N 35:	QLQ of EORTC for head and neck cancer patients
HRQOL:	health- related quality of life
IARC	International Agency for Research on Cancer
KPS:	Karnofsky Performance Scale
PSS-H&N:	Performance Status Scale - Head and Neck
UW QOL:	University of Washington Quality of Life Questionnaire
QOL:	quality of life
QLQ:	quality of life questionnaire

II. HYPOTHESIS

Head and neck cancer and its associated treatment regimens can decrease the quality of life (QOL) of patients in consequence of the loss of structural and functional integrity in this region. Important functions such as eating, speech and aesthetics can be damaged by surgical treatment, irradiation or chemotherapy, with resultant adverse effects on the patient's physical, psychological and social functioning.

We hypothesize that methods of maxillofacial rehabilitation can improve the QOL of head and neck cancer patients through reconstruction of the damaged anatomical parts in this region.

III. INTRODUCTION

Head and neck cancer is a very common tumor worldwide. The statistical analysis by the International Agency for Research on Cancer (IARC) indicated that the lip and oral cavity is the tenth most common tumor site in the human organism. Annually, more than 640 000 patients worldwide are diagnosed with primary cancer in this area, and approximately 350 000 die of this disease (Parkin *et al.*, Rinkel *et al.*, 2009). It can be treated surgically, with irradiation, with chemotherapy, or with a combination of these. Progress achieved in the treatment of oral cancer has made it possible to reduce the post-treatment mortality, and the survival rate has increased (Hassanein *et al.,* 2005). Hovewer, the length of survival alone is an unsatisfactory measure of success (Kazi *et al.,* 2010). Despite major advances in cancer biology and therapeutics, cancer and its treatment continue to cause devastating suffering, not only for patients who die from their illness, but also for those who are successfully treated (Morton *et al.*, 2003, Kazi *et al.,* 2010). This is especially true as regards the treatment of head and neck cancer: important anatomical parts of the face or oral cavity can be removed surgically because of the tumor, and this may be accompanied by severe problems relating to eating, swallowing and speech. Facial disfigurement can cause huge aesthetic problems for the patient. Moreover radiotherapy has side-effects, such as destruction of the salivary glands, causing xerostomia extending to the whole of the survival time. Xerostomia can be associated with oral infections, dental caries, pain and discomfort (Murphy *et al.,* 2009). Defects after surgical treatment and the side-effects of irradiation decrease the QOL, and if this post-treatment status is left without medical and prosthetic rehabilitation, the physical, psychic and social state of head and neck cancer patients can suffer a major deterioration.

III.1. Maxillofacial rehabilitation

Maxillofacial rehabilitation is the final step in the treatment of head and neck cancer. It is a complex process of restoration of a previous state following a major change. It is very important after tumor treatment to strive to attain a return to the pre-illness function. As a result of treatment such as surgery and/or radiation therapy, chemotherapy, cryosurgery or laser surgery, many patients are left with various defects in this area. Oral tumor resection

often results in serious disabilities, and aesthetic and functional disorders, as concerns mastication, phonation, swallowing, breathing, etc. The degree of disability varies with the location and extent of the defect (Watson *et al.*,1984, Hurst, 1985, Kudo *et al.*1978). Anatomical damage and functional integrity of the oral cavity or face can be restored either with microvascular reconstruction flaps or with prosthethic methods when surgery is not feasible. Maxillofacial prosthetics is used as an adjunct to or a replacement for reconstructive surgery (Converse, 1977).

By definition, „Maxillofacial prosthetics is the art and science of anatomic, functional and cosmetic reconstruction, by the use of non-living substitutes, of those regions in the maxilla and mandible and face that are missing or defective." (Bulbulian, 1965) The field of plastic and maxillofacial reconstructive surgery has now developed to the stage where gross deformities can be corrected or improved by surgical means. When this is possible, it offers the best solution and is always preferable when a satisfactory result can be obtained. Use of the patient's own tissues is far more desirable than employing synthetic materials. However, reconstructive surgery alone produces satisfactory results in only a very limited number of cases.

Maxillofacial rehabilitation, and hence prosthodontics, occupies a special position in the achievement of a complex somatic, psychic and social improvement. The deterioration in the QOL can lead to socio-economic failure, depression and suicide (Shontz, 1975, Finesinger *et al.*, 1952, Baile *et al*,.1992). The maximal rehabilitative effort is essential in order to correct the physiological deficit whenever possible and to provide the necessary emotional and occupational support in returning these patients to society. A team approach is required to attain successful rehabilitation. A key role should be played throughout this process by the maxillofacial prosthodontist, who can establish early contact with the patient prior to surgery and be actively involved in the planning of the surgical treatment. During the healing period, the prosthodontist makes the first daily contact with the patient, when several temporary prostheses are required. In the long- term management, the prosthodontist can aid in restoring the physiological function and the facial aesthetics to enable the patient to return to normal life as fully as possible.

There are two main aspects of maxillofacial rehabilitation: intraoral and extraoral reconstruction, depending on the site of the defect.

III.1.1. Intraoral rehabilitation

Surgical treatment of malignancies in the oral cavity and subsequent radiotherapy can result in a challenging environment for prosthodontic rehabilitation (Rogers *et al.,* 1999, Paze-Balzan *et al.,* 2004, 2006). Maxillary and mandibular tumor patients after surgical treatment may exhibit intraoral defect differences as regards the method of rehabilitation, the postsurgical QOL and the psychosocial function (Sprangers *et al.,*1993). Patients who have undergone some form of surgical treatment can have various problems involving important functions such as eating, swallowing and speech. Which function suffers the greatest deterioration, depends on the location of the defect.

III.1.1.1. Prosthetic rehabilitation of patients with oral malignancy-acquired maxillary defects

Postsurgical maxillary defects can cause food and fluid leakage into the nasal cavity, an impaired masticatory function, inadequate swallowing, hypernasal speech and various degrees of cosmetic deformity (Beumer *et al.*, 1990, Huryn *et al.*, 1989, Kornblith *et al.,* 1996). The size of the defect influences the method of reconstruction. Small defects can be closed surgically with local flaps, but if it is necessary to check on the cavity directly during the follow-up, an obturator must be made to keep the defect open. Larger defects are more suitable for prosthetic rehabilitation with an obturator (Rahn *et al.,* 1979). The intraoral disabilities are minimized or eliminated almost immediately on obturation, and maxillary resection prostheses also reduce the cosmetic deformity by supplying the missing teeth and supporting the lip and cheek. Facial changes can arise from the treatment: the surgical procedure may result in some loss of facial form due to the removal of the zygoma from the cheeks, and in drooping of the eyelid and clasps becoming visible due to the incision causing contracture of the upper lip (Kornblith *et al.,* 1996). Prosthetic rehabilitation of maxillary surgical defects is so effective that neither reconstructive surgery nor osseointegrated implant use is usually indicated in most cases (Steadman, 1957). In other cases, such as those involving edentulous patients, implants can be used as retaining elements of obturators to

improve their stability. The most suitable sites for implant placement are the remaining premaxillary segment and the maxillary tuberosity (Davis *et al.*, 1995). In cases after bilateral maxillectomy, zygoma implants can be used, or more rarely pterygoid implants to bear the obturator without any hard and soft tissue retention and support (Bidra *et al.,* 2011).

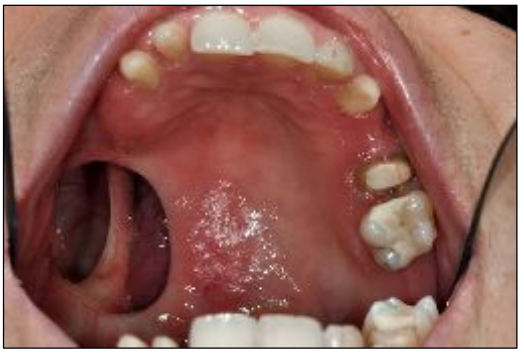
Prosthodontic therapy for patients with maxillary defects can be divided into three phases:

(a) immediate surgical obturation, at after surgery or shortly, fabricated on the cast made before surgery (Fig. 1d);

(b) interim obturation: 2-6 weeks postoperatively;

(c) definitive prostheses: 3 to 6 months after surgery and/or irradiation.

Figure 1 illustrates a maxillary defect after partial maxillectomy because of an epithelial cell carcinoma and its restoration with an obturator.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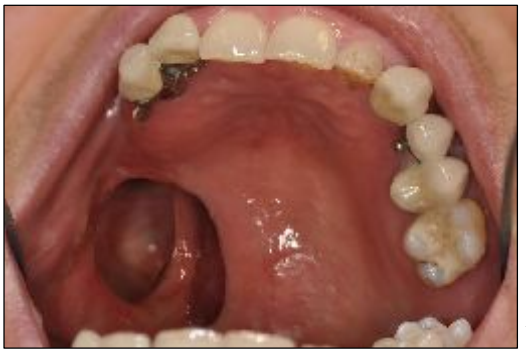
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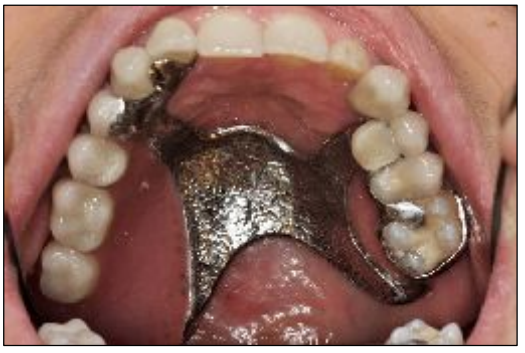
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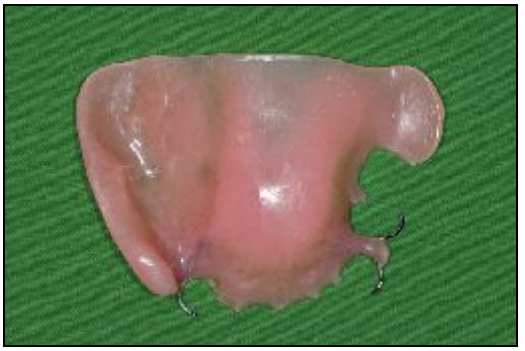

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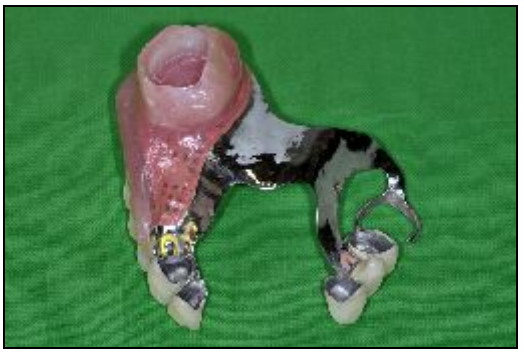

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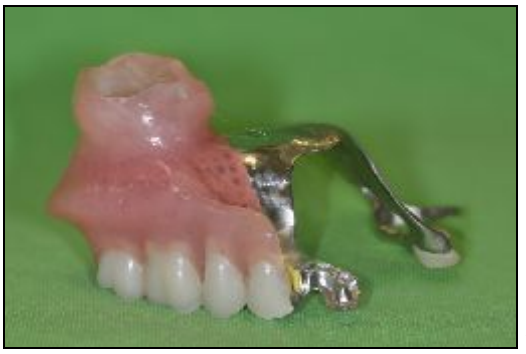

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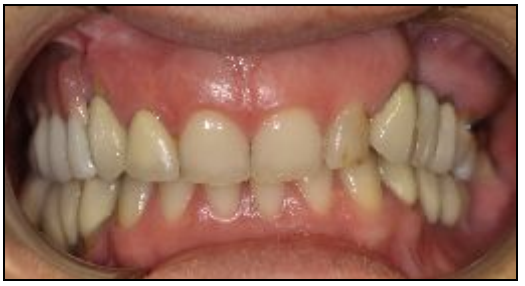

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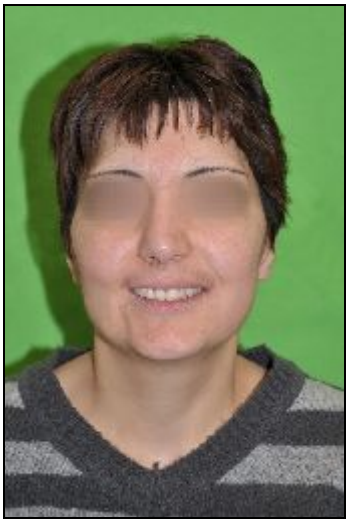

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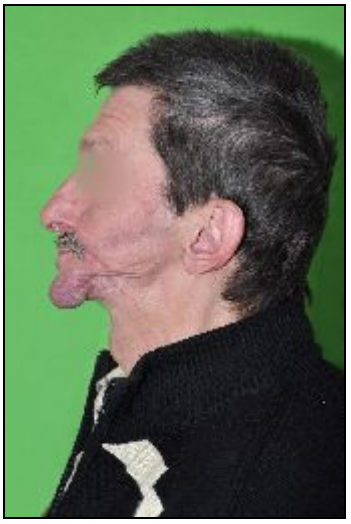
Figure 1. a) Maxillary defect. b) Intraoral status with bridges and preci-vertix. c) Intraoral status with obturator. d) Immediate surgical obturation. e) f) Definitive prosthesis. g) Occlusion with obturator. h) Full-face frontal view after rehabilitation.

III.1.1.2. Prosthetic rehabilitation of patients with oral malignancy-acquired mandibular defects

An other intraoral functional problem arises after the surgical treatment of a tumor of the tongue or floor of the mouth. Both locations predispose the mandible to tumor invasion, often necessitating its resection in conjunction with large portions of the tongue and surrounding sublingual tissues and regional lymphatics (Harold, 1971). Because of the problem of tongue movement the speech can be ununderstandable and the lack of the vestibulum causes difficulties in the fixation of prostheses. In cases affecting the mandible, the involved segment must be resected. The major causes of mandibular discontinuity are tumor resection, trauma and, to a lesser degree, osteoradionecrosis and osteomyelitis. Loss of a mandibular segment results in serious disabilities, including impairments of chewing, swallowing and speech, drooling and a cosmetic disfigurement. The oral rehabilitation of these patients with mandibular discontinuity defects is the most challenging problem facing both the surgeon and the prosthodontist. The remaining mandibular segment is often displaced medially, causing an inappropriate occlusal position (Figure 2).

The conventional denture fitted on the remaining mandibular segment is frequently unstable and the unsatisfactory result can be frustrating to both patient and restorative dentist. It is recommended to replace the missing bone and to reconstruct the functional and aesthetic demands of the patients. The best method for this comprises free vascularized bone grafting, such as an iliac or a fibula graft as vital bone graft (Keller *et al.*, 1998, Urken *et al.*,1991). Often, however, reconstruction of the bony defect alone does not guarantee an adequate foundation for successful conventional prosthetic rehabilitation. Osseointegrated implants placed into the microvascularized grafted bone offer an opportunity for an improved function and patient satisfaction.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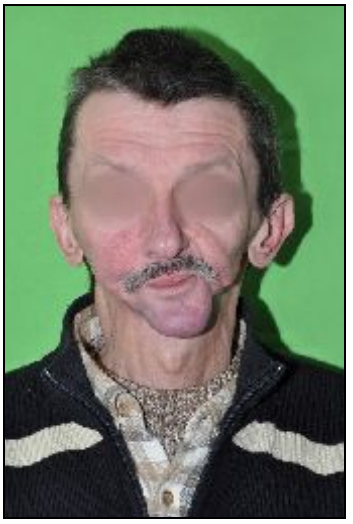
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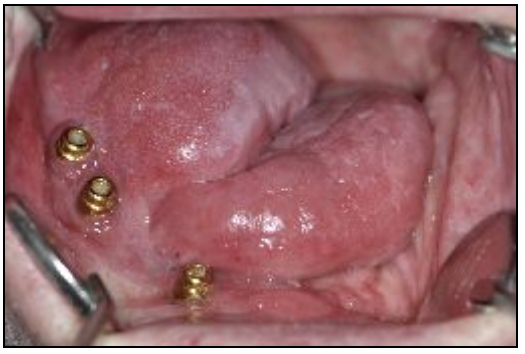
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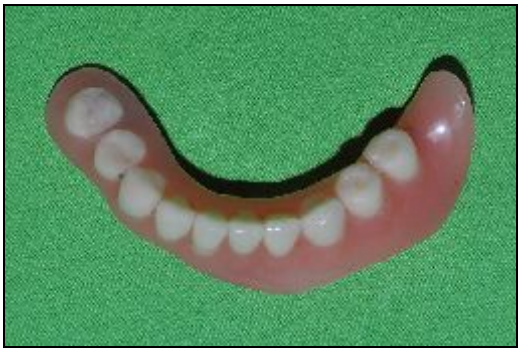
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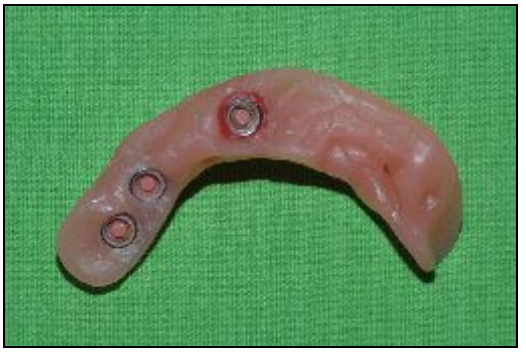
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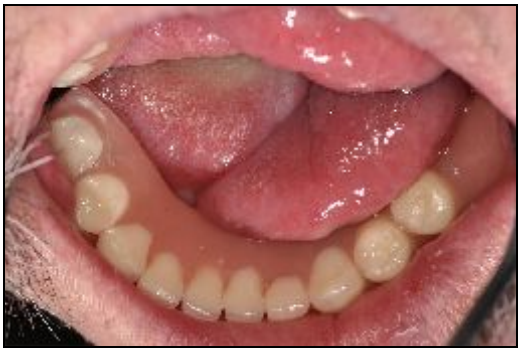
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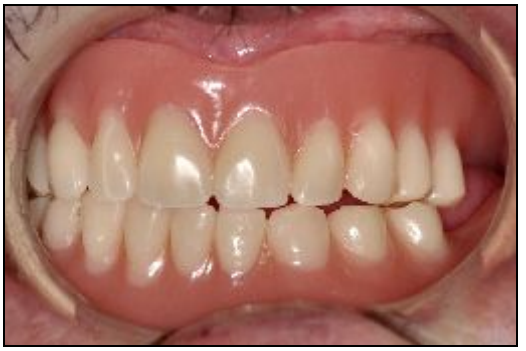

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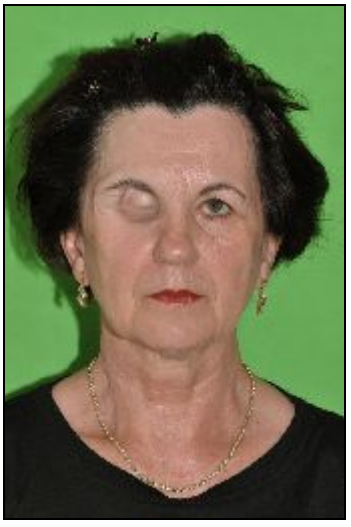
Figure 2. a) Full-face lateral view after operation and osteoradionecrosis. b) Full-face frontal view after operation and osteoradionecrosis. c) Intraoral situation after operation and osteoradionecrosis (with implants). d) e) Implant-retained defect prosthesis. f) Implant-retained prosthesis *in situ*. g) Occlusion after rehabilitation. h) Full-face frontal view after rehabilitation.

III.1.2. Extraoral rehabilitation

The restoration in cases of persons who have lost a portion of their faces through surgical removal of a malignant tumor or through a congenital absence or trauma poses one of the greatest challenges for the maxillofacial prosthodontist (McKinstry, 1995). A defect of the face, as the most conspicuous body part, means a huge handicap for patients. It leads to a decreased QOL, depression and barriers in resocialization. Restoration of these defects is very important from functional and aesthetic aspects (Kadar, Nagy, 2009).

The success of the prosthetic restoration of any part of the body, including the head, depends on the availability of a method of attaching the artificial substitute securely in the appropriate place without causing discomfort or irritation to the tissues with which it comes in contact (Bulbulian, 1973). Methods of retention used for facial prostheses fall into four categories: (a) adhesive, when adhesive materials are used to retain the prosthesis, (b) mechanical, (c) anatomical, when the retentive contours existing at the site of the deformity are used to retain the prosthesis, and (d) extraoral implant, when implant fixtures anchored into the bone are used to fix the facial prosthesis (McKinstry, 1995) Which method of retention is chosen depends on the anatomical situation of the facial defect, the treatment method and the general staging of the patient.

Figure 3 depicts the case of a facial defect after exenteration because of malignant melanoma and the maxillofacial rehabilitation with an adhesive-retained epithesis.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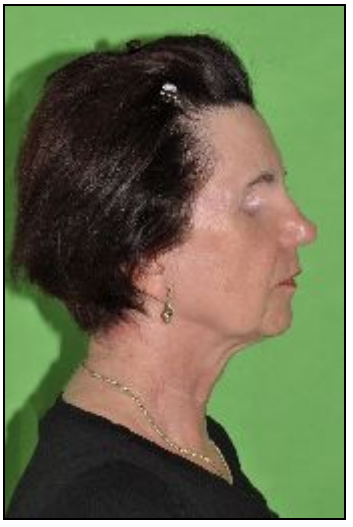
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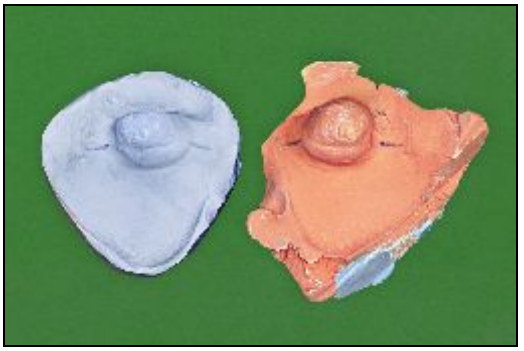
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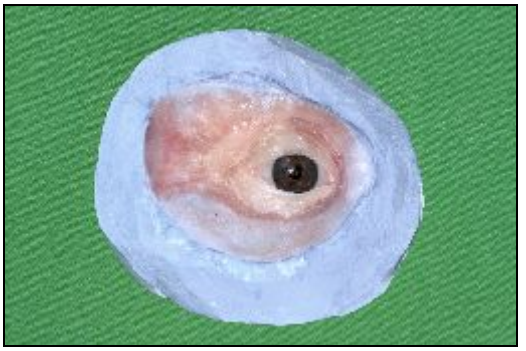
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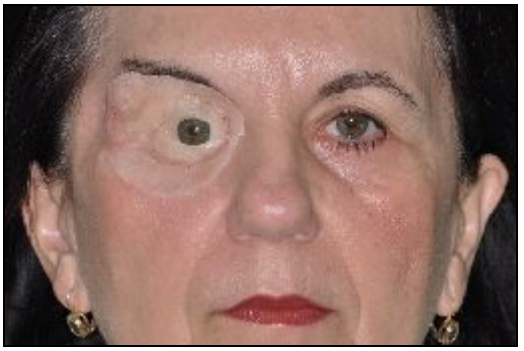
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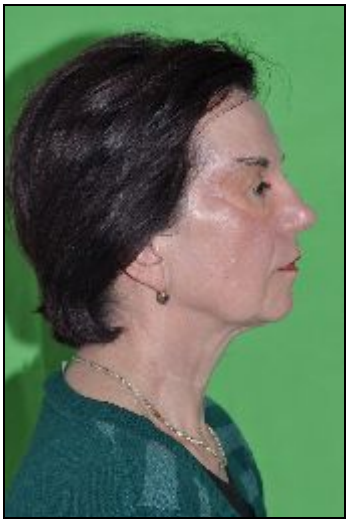
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Figure 3. a) b) Situation after exenteration because of malignant melanoma. c) Impression and stone cast from the defect with signs. d) Wax model in position on the patient. e) f) Epithesis after extrinsic coloring. g) h) Full-face frontal view after maxillofacial rehabilitation. h) Full-face lateral view after maxillofacial rehabilitation. i) Protection and camouflage with spectacles

III.2. Quality of life

The QOL in patients treated for head and neck cancer is an important outcome parameter in the post-treatment follow-up. QOL has been defined in many ways by numerous of groups. The WHO originally defined QOL in 1947 as a „complete physical, mental and social welfare state and not only the absence of the disease" (Torres Carranza *et al*., 2008). Nowdays, it is defined by the WHO as „an individual's perception of their own position in life, in the context of the culture and value systems in their life and in relation to their goals, expectations, standards and concerns" (Kazi *et al.,* 2008, Sayed *et al.,* 2009).

QOL can be defined as a concept that reflects several aspects of life, and an individual's perception of overall well-being with regard to disease and treatment-related symptoms is specifically called the „health-related HRQOL". (Boscolo-Rizzo *et al.*, 2009, Kim *et al.*, 2010).

Revicki *et al* define QOL as a „broad range of human experiences related to one's overall well-being that minimally includes the broadly-defined assessments of the physical, psychological and social domains of functioning". (Revicki *et al.*, 1997, Sayed *et al.*, 2009).

QOL has also been defined as a multidimensional construct that includes, at a minimum, physical, functional, psychological and social well-being. Other dimensions include spirituality, sexuality, occupational functioning, treatment satisfaction and the overall rating of the QOL. (Montazeri, 2009) Cella defined it as an individual's perceived physical, mental and social health status.

Cancer and its treatment regimens can result in the disruption of one or more dimensions of the QOL. That is why the QOL is a parameter increasingly used in daily clinical practice to assess the effectiveness of a treatment and has possibly become a parameter that helps patients and physicians make therapeutic decisions (Lopez *et al.*, 2009).

III.3. Measurement of quality of life

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Study Group has developed a measurement strategy for the assessment of QOL in clinical trials (Bjordal *et al.,* 1999).

The ideal measurement procedure for routine clinical practice should be short, easy for patients to understand, address pertinent QOL issues, and be reliable and responsive to change (Rogers *et al.,* 1998) Patients are themselves unable to complete exhaustive questionnaires and a short, simple measurement which takes less than 10 minutes to complete is ideal for routine review (Sadura *et al.,* 1992).

There are specific instruments with which to measure the QOL of head and neck cancer patients, e.g. questionnaires- the University of Washington Quality of Life Questionnaire (UW QLQ), the QLQ of EORTC for head and neck cancer patients (EORTC H&N 35), the QLQ of the Cancer Rehabilitation Evaluation System (CARES) and the Performance Status Scale- Head and Neck (PSS-H&N), indices such as the Karnofsky Performance Scale (KPS), the Obturator Functioning Scale and the quantity of saliva measure. The QLQ measures the individuals' perceptions of their own physical, mental and social health status, or some aspects of their health status resulting from cancer and its treatment. Sayed *et al.* have given a list of 10 attributes necessary in the selection of QLQs as a final study tool: *valid*: appropriateness, meaningfulness and usefulness of a measure for a specific purpose; *reliable*: stability and reproducibility of a measure over time; *interpretable*: clinically relevant; *sensitive*: responsive to change; *short*: minimal time-burden; *easy to score*; *have an overall global score and domain scores; multidimensional:* covers a broad range of items in multiple domains; *self-administered*; *no floor or ceiling effect*: ability to detect changes at two extremes of QOL.

The questionnaires are self-administered but, depending on the patient input, with minimal assistance from a health-worker if absolutely necessary.

III.3.1. UW- QOL questionnaire

The UW QOL questionnaire is a well-validated QOL instrument. It is potentially suitable as an instrument for busy clinical practice as it is quick and simple for patients to complete and is easy to process (Rogers *et al.*, 1999).

The UW QOL questionnaire is a simple, brief, well-validated and widely-used head and neck cancer-specific, self-administered scale (Hassan *et al*., 1993, Kazi, 2008). Version 1 comprises 9 domains that cover a range of disease-specific functional items including pain, disfigurement, activity, recreation/entertainment, employment, speech, chewing, swallowing and shoulder disability. It was revised in 2002-2003 to its current version 4 by Rogers SN *et al*. in an attempt to eliminate inconsistencies and improve on important missing elements in the spectrum of disease-specific responses to treatment (Rogers SN, 2002, Hassan *et al*., 1993, Kazi *et al*. 2010). Version 4 contains 12 domains: pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder function, taste, saliva, mood and anxiety.

III.3.2. EORTC H&N 35 questionnaire

The EORTC H&N 35 (version 1.0) questionnaire, which includes 35 items, has been translated into many languages, including Hungarian, following the EORTC QOL Study Group guidelines (Bjordal *et al*., 1999, Cull *et al.*, 1998). The original questionnaire was validated by Bjordal and co-workers (Bjordal *et al*., 1992, Bjordal *et al*., 1994).

The EORTC H&N 35 QLQ is sometimes used together with the EORTC C30 QLQ, which comprises physical, role, emotional, cognitive and social functioning scales and other items such us fatigue, nausea, vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea and financial difficulties.

The EORTC H&N 35 QLQ comprises 35 tumor- specific questions assessing symptoms and side-effects of treatment. Most items are scored on a four-point response scale: 1 (not at all) to 4 (very much). 25 questions are organized into 7 multi-item subscales: pain (HNPA:

items 1-4 regarding pain in the mouth, pain in the jaw, soreness in the mouth and painful throat), swallowing (HNSW: items 5-8 and 17 items that assess different degrees of swallowing problems: problems in swallowing liquid, pureed food or solid food, and choking when swallowing), senses (HNSE: items 13-14 regarding smell and taste), speech (HNSP: items 16 and 23-24 assess hoarseness and problems with talking to other people or on the phone), social eating (HNSO: items 19-22 regarding trouble in eating, individually or in front of family or others), social contact (HNSC: items 18 and 25-28 regarding trouble with body image and having physical and social contact with family and others) and sexuality (HNSX: items 29-30 assess interest in sex and sexual enjoyment). The remaining 10 single items address problems with teeth, dry mouth, sticky saliva, cough, mouth opening, weight loss, weight gain, use of nutritional supplements, feeding tubes and pain medication (Rinkel *et al*., 2009).

IV. AIMS OF THE STUDY AND QUESTIONS TO BE ANSWERED

The aims of my study were to examine the patients treated and rehabilitated at our Maxillofacial Rehabilitation Department, to establish how the QOL of head and neck cancer patients deteriorates after treatment (operation, radiotherapy and chemotherapy) and to determine how it can be improved through maxillofacial rehabilitation.

Questions to be answered

I set out to collect epidemiological data on head and neck cancer patients in order to learn their distribution and information concerning their smoking and alcohol drinking habits and oncological characteristics. I wished to establish which treatment and rehabilitation methods are most frequent.

I wished to know which of the important functions such as speech, eating, swallowing and aesthetics are mainly impaired after treatment.

A further question to be answered related to whether the QOL of head and neck cancer patients can be improved through maxillofacial rehabilitation and, if so, which of the impaired functions is most improved by rehabilitation.

I additionally wished to learn whether the QLQ can be used as a routine examination in the post- treatment follow- up of head and neck cancer patients, and which questionnaire is best or gives more information about the QOL.

V. MATERIALS AND METHODS

The study protocol and the informed consent form were approved by the Ethics Committee of the Faculty of Medicine, at the University of Szeged.

V. 1. Clinical study

V. 1. 1. Patient selection

In the period between 1994 and 2010, 92 head and neck cancer patients were rehabilitated following tumor treatment at the Maxillofacial Rehabilitation Unit, Departement of Oral Surgery, Faculty of Dentistry, University of Szeged. In the above period, 21 of the patients subsequently died and 12 patients failed to respond to the invitation letter. The remaining 59 patients completed two QLQs. The eligibility criteria included tumor treatment administration due to head and neck cancer, followed by maxillofacial rehabilitation, and the patient's ability to understand written and spoken Hungarian.

V.1.2. Data collection

The following data were obtained from patients who had undergone rehabilitation and from them who later died: (a) socio-demographic characteristics such as age at treatment, and gender; (b) behavior: smoking and drinking habits and (c) clinical status: site of primary tumor, type of treatment and nature of rehabilitation. The information on these patients was recorded retrospectively from the clinical documentation.

Additional investigations were performed to review the changes in QOL after maxillofacial rehabilitation in comparison with the QOL status after tumor treatment without rehabilitation. Two questionnaires were used for this study.

V.1.3. Patient self-report questionnaires

Two QLQs were completed: one of them was the UW QOL, version 1.0 questionnaire and the other was the EORTC QOL H&N 35 questionnaire. Both of them were the official translated Hungarian version. We did not wish to utilize the EORTC C30 together with EORTC QLQ H&N 35 because we wished to use these other two special questionniares for head and neck

cancer patients and we concidered that three questionnaires would be too much for the patients. The questionnaires were completed on two occasions: first, following treatment but before rehabilitation, and then following maxillofacial rehabilitation. On both occasions, the patients were recalled to complete the QLQs as part of an interview and follow-up. All the patients completed the questionnaires themselves, but received helpful instructions if this was necessary. A doctor who rehabilitates head and neck cancer patients and had been specifically trained in connection with the questionnaires was therefore present at the interview. The completed forms were carefully checked.

V.2. Statistical analysis

Statistical analysis based on the program Stata was carried out by the Statistics Team of the Faculty of Medicine at the University of Szeged.

The collated data were entered into an Excel worksheet.

The sociodemographic data such as the age at treatment, the gender and mortality were collected in Tables. The site of the primary tumor, the treatment mode and the rehabilitation methods were recorded in other Tables. The program Stata was used. Descriptive statistics were utilized to describe the mean, the standard deviation (SD), and the distributions of the treatment and rehabilitation methods.

The Wilcoxon signed-rank test was used to compare the situations after tumor treatment with and without maxillofacial rehabilitation. A p value less than/equal to 0.05 was considered significant.

VI. RESULTS

VI.1. Demographic results / Patient characteristics

In the period in question, 92 patients underwent tumor treatment and maxillofacial rehabilitation at the Faculty of Medicine and the Faculty of Dentistry, at the University of Szeged. 21 of the 80 processed patients had died before the start of the present study. The related mortality was therefore 26.25%. However since these patients had received treatment for their tumor and also undergone maxillofacial rehabilitation, their epidemiological data were nevertheless included in the study. The surviving patients were recalled several times during the follow-up period for control purposes and to complete the UW QLQ and the EORTC H&N 35 QLQ. 12 patients failed to reply to the invitation letter. The epidemiological data on 80 patients were therefore processed. The recorded information included the age at treatment, the gender, the tumor localization, the treatment method and the type of rehabilitation. 53 (66.25%) of the patients were men and 27 (33.75%) women. The male: female ratio was therefore 2:1. The average age was 53.86 years (ranging from 9 to 74 years), with more than half of the patients (55 (56.25%)) aged between 50 and 69.9 years.

The epidemiological data are listed in Table 1. The age distribution is presented in Figure 4.

The incidence of smoking and alcohol consumption was rather high. 60 (75%) of the patients were smokers, and 45 patients (56.25%) drank alcohol regularly.

Categories		n(%)
Gender	**Male**	**53 (66.25%)**
	Female	27 (33.75%)
Age	<40	9 (11.25%)
at tumor treatment	40-49.9	18 (22.5%)
	50-59.9	**26 (32.5%)**
	60-69.9	19 (23.75%)
	>70	8 (10%)
Tobacco use	Yes	60 (75%)
	No	20 (25%)
Alcohol consumption	Yes	45 (56.25%)
	No	35 (43.75%)
Mortality		21 (26.25%)

Table 1. Epidemiological characteristics of study population

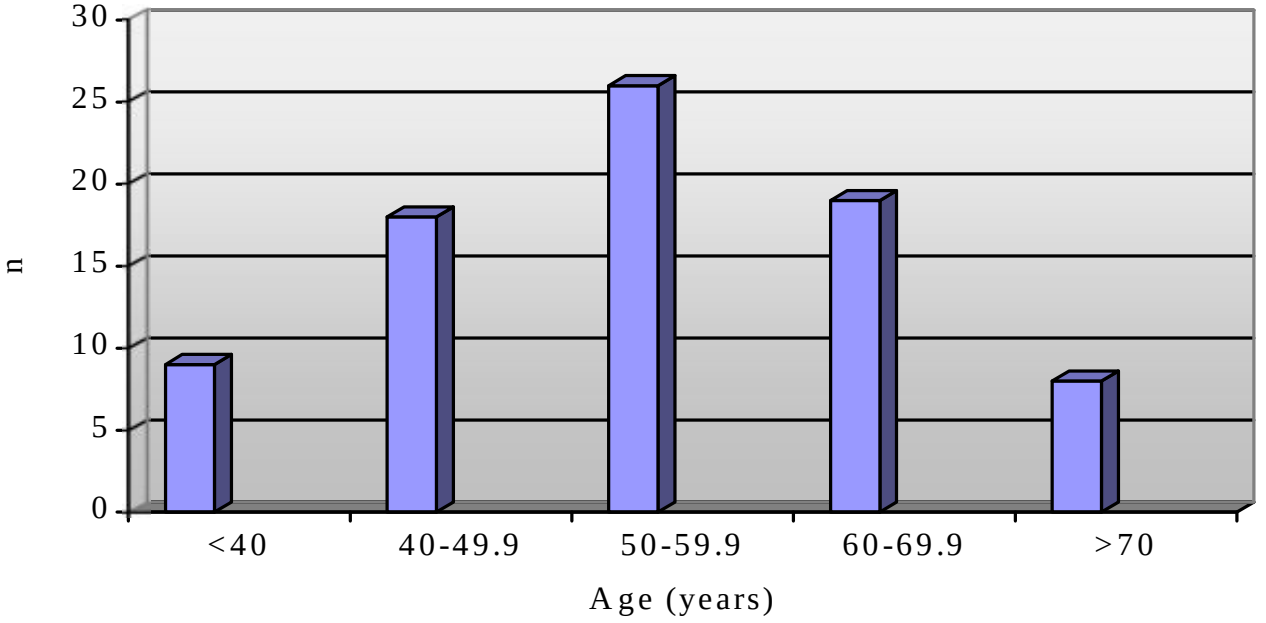

Figure 4. Age distribution among rehabilitated head and neck cancer patients.

The oncological data are to be found in Table 2. The distribution of the tumor localization and the types of treatment methods are shown in Figures 5 and 6. As far as the locations were concerned, the cancer developed most frequently in the floor of the mouth area, in 21 patients (26.25%), followed by the mandibular or maxillar gingiva in 17 cases (21.25%), the maxilla in 12 cases (15%) and the tongue in 9 cases (11.25%).

41 patients (51.25%) received combined surgery and radiotherapy. 26 patients (32.5%) were treated surgically alone, and 2 patients (2.5%) with radiotherapy alone. 11 patients (13.75%) participated in other forms of combined therapy.

Categories		n (%)
Tumor localization	maxilla	12 (15%)
	tongue	9 (11.25%)
	floor of the mouth	**21 (26.25%)**
	facial defect (eye-ear-nose)	3-2-1 (3.75%- 2.5%-1.25%)
	others	32 (40%)
Type of treatment	surgery alone	26 (32.5%)
	radiotherapy alone	2 (2.5%)
	surgery and radiotherapy	**41 (51.25%)**
	surgery and chemotherapy	2 (2.5%)
	surgery, radiation and chemotherapy	9 (11.25%)

Table 2. Oncological characteristics of study population

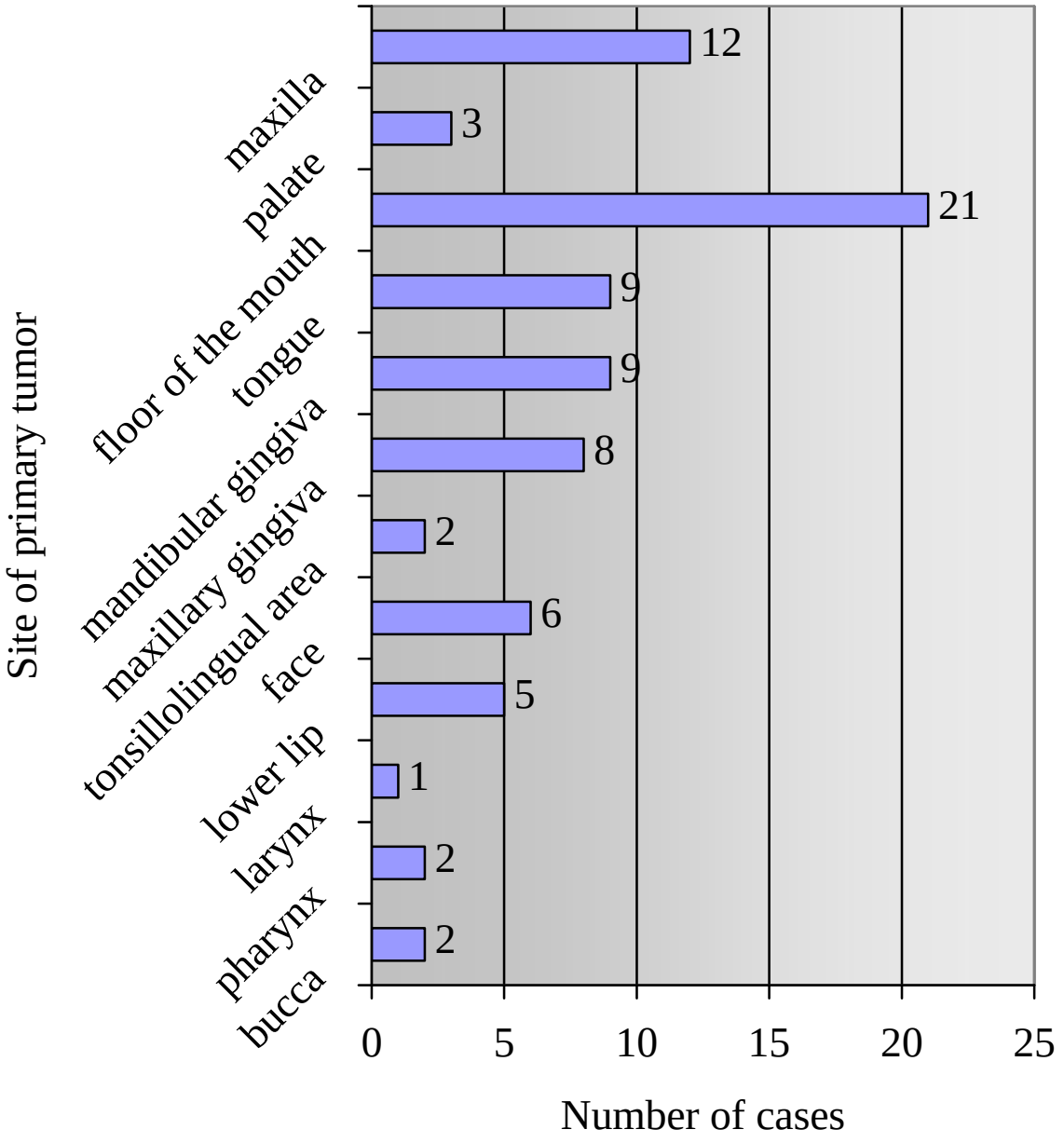

Figure 5. Distribution of sites of primary tumor

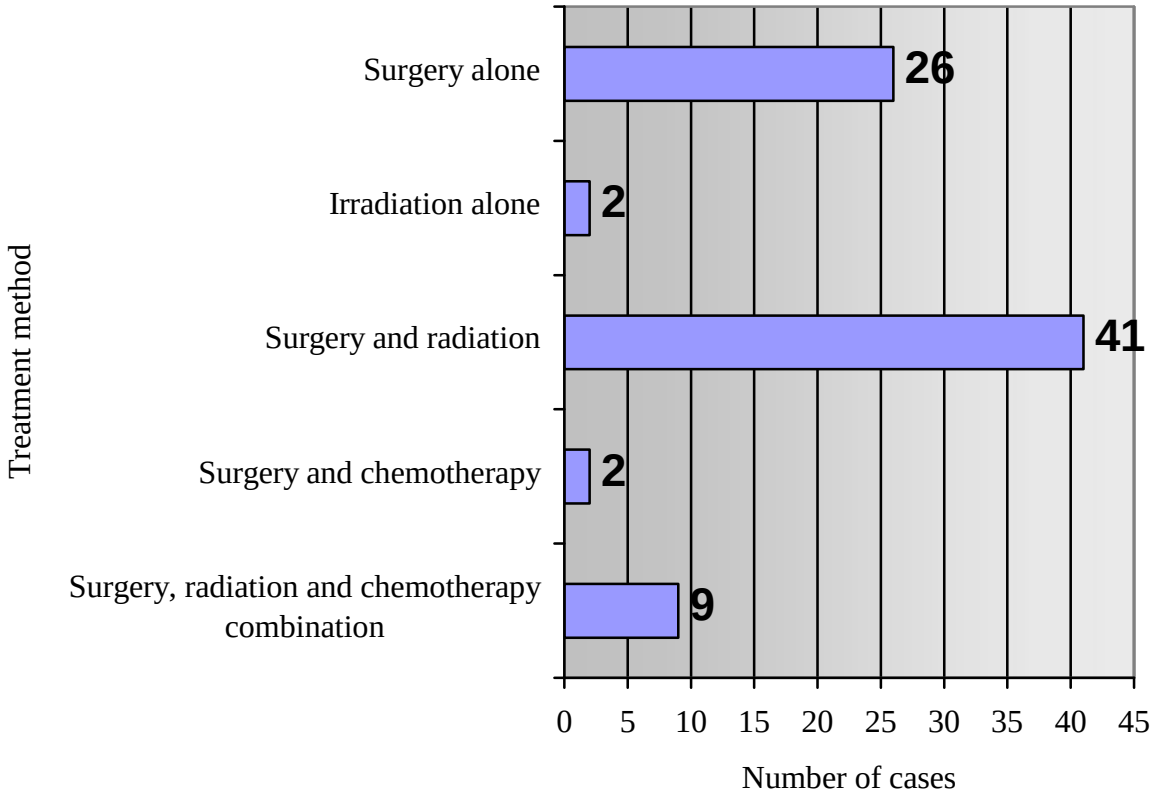

Figure 6. Distribution of treatment methods.

The types of prostheses are presented in Table 3, and their distribution in Figure 7. In the course of rehabilitation, a special defect prosthesis was prepared for about half of the patients (43.75%): an obturator was fitted in 14 patients (12.5%), an implant-retained removable denture was applied in 23 patients (20.54%), and reconstruction with an epithesis was applied in 12 patients (10.71%). Most of the epitheses were for an orbital defect, in 7 cases (6.25%). Other parts of the face were also rehabilitated, with an ear epithesis in 3 cases (2.7%) and a nasal epithesis in 2 cases (1.8%).

Type of prosthesis	n (%)
Obturator prosthesis	14 (12.5%)
Removable denture (lower and/or upper)	32 (28.57%)
Implant-retained removable denture	23 (20.54%)
Combined prosthesis	28 (25%)
Bridge (fixed, cemented prosthesis)	3 (2.7%)
Orbital epithesis	7 (6.25%)
Nasal epithesis	2 (1.8%)
Aural epithesis	3 (2.7%)
Total number of prostheses	112

Table 3. Type of rehabilitation

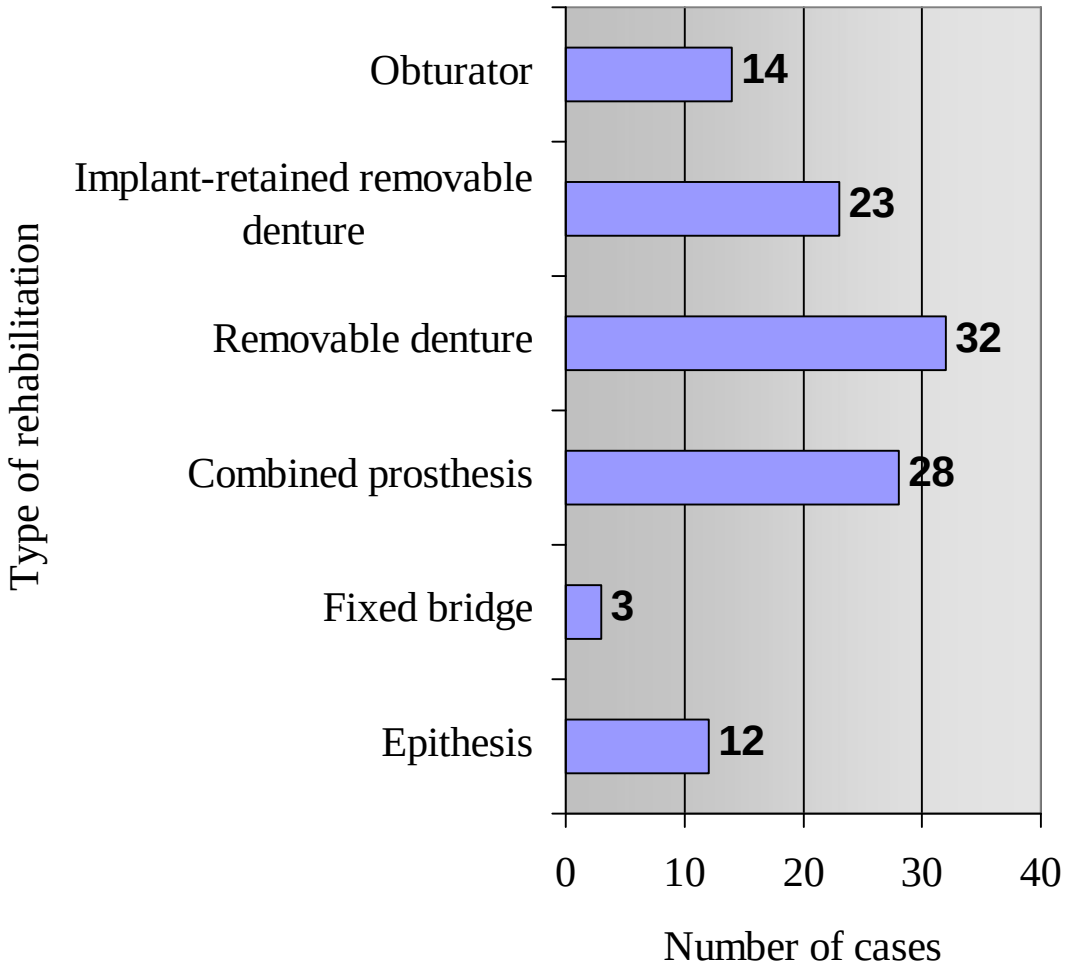

Figure 7. Distribution of rehabilitation methods

VI.2. Statistical results of QOL questionnaires

The UW QOL and EORTC H&N 35 questionnaires were well accepted by the patients, who appeared cooperative; none of the eligible participants refused to complete the questionnaire.

VI.2.1. Results of UW QOL questionnaire

The UW QOL questionnaire, which was well accepted by the patients, included 9 questions, each answer is scaled from 0 (best) to 100 (worst). A composite score was calculated by adding together the scores for 9 answers for the various domains and then dividing by 9 to give a result on the scale from 0 to 100. The composite score, which before rehabilitation was

reasonably high, at 66.62, improved to 36.2 following rehabilitation. The change was significant (p=0.000)

The scores before (BR) and after rehabilitation (AR) are reported in Table 4, and the improvement in the QOL is shown in Figure 8.

The greatest problems after treatment but before rehabilitation were associated with chewing (BR: 88.58), activity (BR: 68.8) and recreation (BR: 68.2). All of these improved considerably after rehabilitation. Nevertheless, especially the subscale of pain was increased after rehabilitation.

Employment displayed a high score both before and after rehabilitation (87.8 and 92), and tended to deteriorate in the course of time after rehabilitation. As concerns the question of family relations, the scores were good in both situations (BR: 25.4 and AR: 21.4), as was the shoulder function (BR: 26 and AR: 23.6).

HRQOL domain	BR score	AR score	Variation
Pain	67.4	25.6	p=0.000
Appearance	64.6	39.2	p=0.000
Activity	68.8	31.6	p=0.000
Recreation	68.2	32.8	p=0.000
Employment	87.8	92	p=0.732
Chewing	88.58	53.94	p=0.000
Swallowing	65.25	33.25	p=0.000
Speech	62.25	39.5	p=0.000
Shoulder function	26	23.6	p=0.452
Family relations	25.4	21.4	p=0.062
Resocialization with friends	36.2	24.8	p=0.000
Overall (Composite score)	66.62	36.2	p=0.000

Table 4. Results of UW QLQ before and after rehabilitation, with the level significance

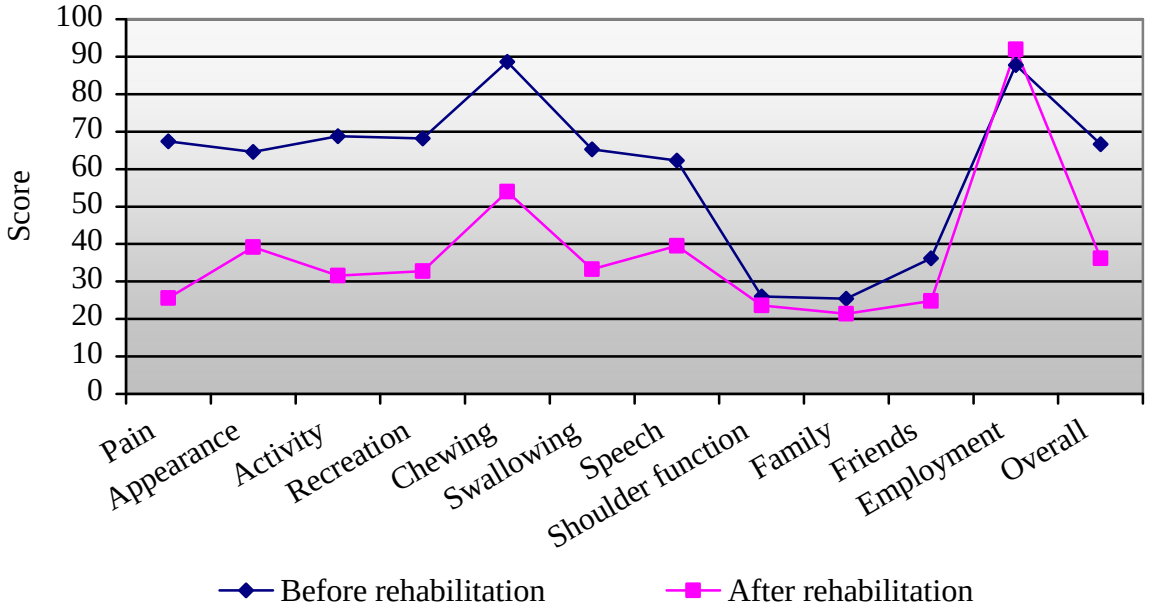

Figure 8. Changes in results of UW QLQ after rehabilitation

Significant improvements after rehabilitation were observed as regards pain, appearance, activity, recreation, chewing, swallowing, speech, resocialization with friends and the overall score. There was no significance from the aspects of employment (p=0.732), shoulder function (p=0.452) and family relations (p=0.062).

VI.2.2. Results of EORTC H&N 35 QOL questionnaire

The mean EORTC H&N 35 scores, standard deviations and ranges after treatment but before rehabilitation are presented in Table 5, the corresponding statistical results after rehabilitation in Table 6, and the improvement in QOL in Figures 9 and 10.

EORTC H&N 35 QLQ	Mean	Standard deviation	Range
Pain (HNPA)	69.95763	18.63425	26-104
Swallowing (HNSW)	77.22881	20.83935	26-104
Senses (HNSE)	56.99153	24.1528	25-100
Speech (HNSP)	61.52542	17.28649	24.75-99
Social eating (HNSO)	75.24576	17.91127	32.5-104
Social contacts (HNSC)	53.81356	17.64934	25-90
Sexuality (HNSX)	47.0339	26.09034	25-100
Teeth (HNTE)	2.271186	1.095925	1-4
Mouth opening (HNOM)	2.728814	.9970734	1-4
Dry mouth (HNDR)	3.033898	.889907	1-4
Sticky saliva (HNSS)	2.79661	.9961938	1-4
Coughing (HNCO)	1.79661	.9961938	1-4
Feeling ill (HNFI)	3.508475	.6531853	1-4
Pain killers (HNPK)	1.847458	.3626321	1-2
Nutritional supplements (HNNU)	1.576271	.4983902	1-2
Feeding tube (HNFE)	1.627119	.4877218	1-2
Weight loss (HNWL)	1.79661	.4059752	1-2
Weight gain (HNWG)	1.067797	.2535545	1-2

Table 5. Means, standard deviations and ranges after treatment, but before rehabilitation

EORTC H&N 35 QLQ	Mean	Standard deviation	Range
Pain (HNPA)	32.62264	7.908677	26-58.5
Swallowing (HNSW)	30.66038	6.421698	26-58.5
Senses (HNSE)	34.66981	15.43471	25-100
Speech (HNSP)	30.50943	8.650389	24.75-57.75
Social eating (HNSO)	32.37736	8.5978	26-65
Social contacts (HNSC)	28.67925	5.895806	25-55
Sexuality (HNSX)	32.54717	14.1548	25-75
Teeth (HNTE)	1.396226	.7162837	1-4
Mouth opening (HNOM)	1.509434	.7751586	1-3
Dry mouth (HNDR)	1.962264	.8311777	1-4
Sticky saliva (HNSS)	1.830189	.8023008	1-4
Coughing (HNCO)	1.301887	.6380531	1-4
Feeling ill (HNFI)	1.264151	.4863895	1-3
Pain killers (HNPK)	1.075472	.2666788	1-2
Nutritional supplements (HNNU)	1.150943	.3614196	1-2
Feeding tube (HNFE)	1	0	1-1
Weight loss (HNWL)	1.056604	.2332953	1-2
Weight gain (HNWG)	1.415094	.4974536	1-2

Table 6. Statistical results relating to the changes in the QOL after rehabilitation

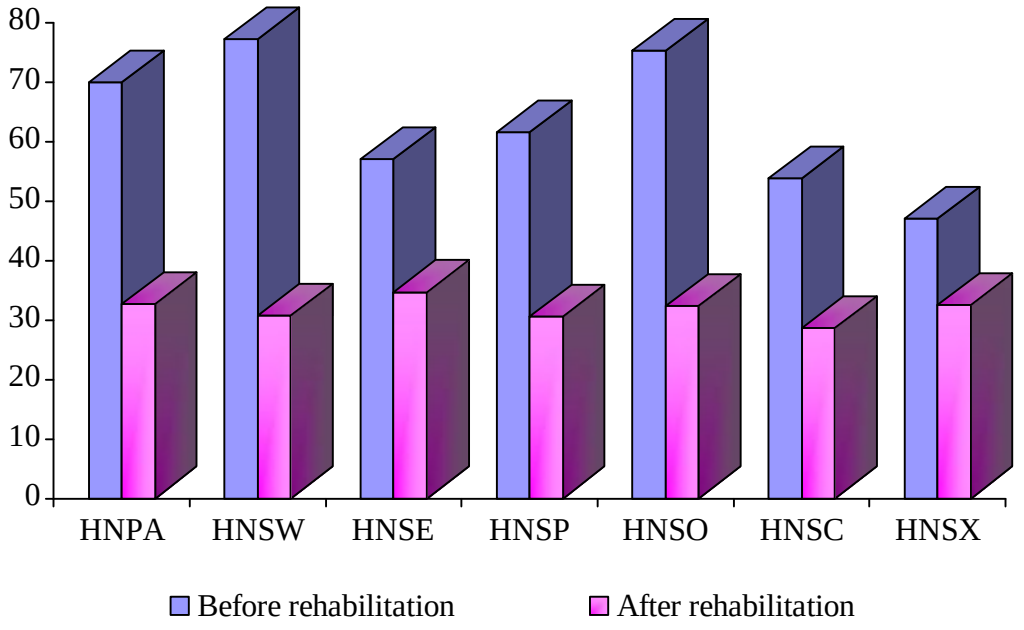

Figure 9. Means of results of 7 scales in EORTC H&N 35 QLQ before and after rehabilitation (HNPA: pain, HNSW: swallowing, HNSE: senses, HNSP: speech, HNSO: social eating, HNSC: social contacts, HNSX: sexuality)

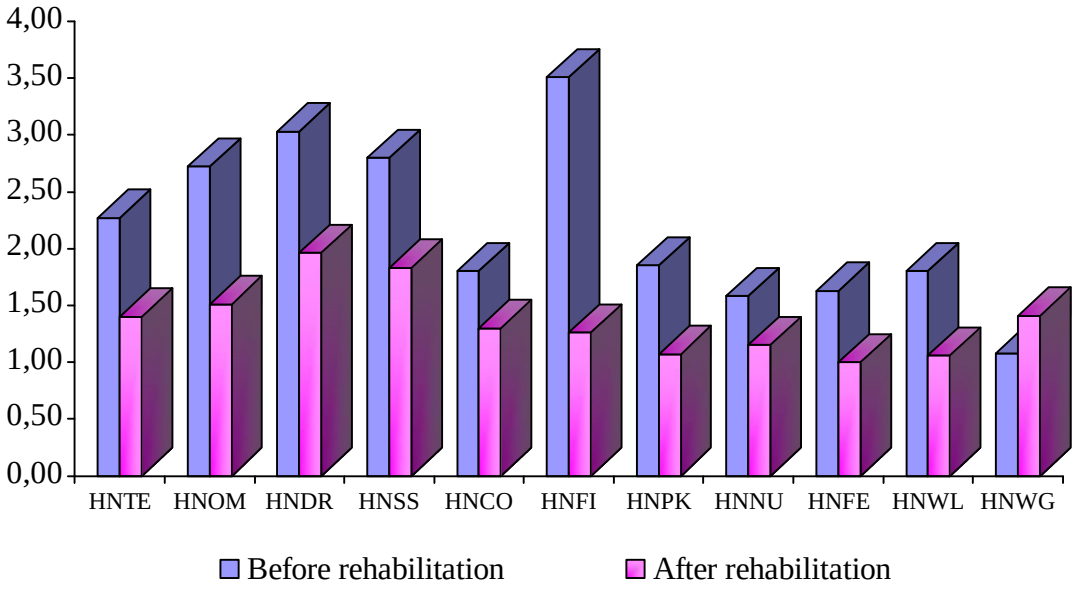

Figure 10. Means of results of single items in EORTC H&N 35 QLQ before and after rehabilitation

(HNTE: teeth, HNOM: mouth opening, HNDR: dry mouth, HNSS: sticky saliva, HNCO: coughing, HNFI: feeling ill, HNPK: pain killers, HNNU: nutritional supplements, HNFE: feeding tube, HNWL: weight loss, HNWG: weight gain)

After tumor treatment, the worst score in the subgroups was that for HNSW (swallowing), followed by HNSO (social eating) and HNSP (pain). From the single items, the worst problem was an illness feeling and dry mouth with sticky saliva as side-effects of irradiation. The rehabilitation led to considerable effects on swallowing, social eating and speech. The highest improvement for the single items after rehabilitation was in the illness feeling. Only the weight gain gave an inverse result.

All of the items showed a significant increase ($p<0.05$) after rehabilitation in comparison with the results before rehabilitation.

VII. DISCUSSION

In my study, I set out to collect data on rehabilitated head and neck cancer patients in the descriptive part of the search. I was looking for the most affected age, the primary tumor site, and the treatment and rehabilitation methods, and was seeking answers concerning which primary tumor site and its treatment need special maxillofacial rehabilitation most frequently. A further aim of my study was to examine the changes in the QOL of head and neck cancer patients through comparisons before and after maxillofacial rehabilitation and to investigate whether our prosthetic methods can improve the QOL of head and neck cancer patients significantly.

Head and neck cancer and its treatment can have a profound effect on the patient's physical, functional and emotional well-being, especially decreasing the QOL. (Evans *et al.*, 2003, Jones *et al.*, 1992, Rogers *et al.*, 1999, Kazi *et al.*, 2010). QOL evaluation has increasingly become an important supplement in the interpretation of the outcome information in head and neck cancer treatment (Hassan *et al.*, 1993, Murphy, 2009, Vartanian *et al.*, 2004, Nazar e*t al.*, 2010) It can be measured by the administration of specific questionnaires to the affected patients. In Hungary, there have been no such examinations of the QOL. A survey of the international literature revealed numerous papers related to the comparison and validation of different QLQs, the comparative analysis of the QOL before and after treatment, and the comparison of the outcome following several treatment methods, but I have found no studies involving a review of the QOL of head and neck cancer patients before and after maxillofacial rehabilitation. This was the background in my selection of the goals in my study.

VII.1. Sociodemographic and epidemiologic analysis

I found that the male:female ratio in this patient group was 2:1. This correlates with the results of Gritz *et al.*, Hassan *et al.*, Hassanein *et al.*, Kornblith *et al.*, Lam Tang *et al.* and Yang *et al.*, but differs from the findings of Head *et al.* (6.88:1), Silveira *et al.* (5:1), de Graeff *et al.* (4:1), Alicikus *et al.* (4:1), Lopez *et al.* (4:1), Kim *et al.* (3.6:1), Arstaad *et al.* (3:1),

Nazar *et al.* (3:1), Scharloo *et al.* (3:1), Thomas *et al.* (3:1), Hammerlid *et al.* (3:1), Schoen *et al.* (1.2:1) and Kruse *et al.* (1.15:1). Hammerlid *et al.* examined patients with oral, pharyngeal and laryngeal cancer and found that the oral cavity was more common as tumor location among females (52%) than among males.

The mean age of the patients was 53.8 years (SD: 12.8 years). This correlates with the results of Hassan *et al.* (55 years), Hassanein *et al.* (58 years), Lam Tang *et al.* (55.5 years), Gritz *et al.* (58.4 years), Kim *et al.* (60.6 years), Scharloo *et al.*, (59.5 years), Silveira *et al.* (59.4 years), Alicikus *et al.* (53 years), Lopez *et al.* (55.78 years), Stevens *et al.* (56.1 years), Verdonck-de Leeuw *et al.* (59 years) and Kornblith *et al.* (59.5 years). In several studies, the mean age was over 60 years: Bjordal *et al.* (61 years), Rinkel *et al.* (62 years), Head *et al.* (60.2 years), Nalbadian *et al.* (62.57 years), Rogers *et al.* (62 years), Rinkel *et al.* (62 years), Nazar *et al.* (64.4 years), Hammerlid *et al*. (63 years) and Schoen (63.5 years). Only one study reported a mean age under 50 years: Kazi *et al.* found it to be 49.6 years.

Among the present head and neck cancer patients, 60 (75%) were smokers and 20 (25%) were non-smokers, and 45 patients (56.25%) consumed alcohol regularly. These habits have been considered in only a small proportion of the analogous investigations, although they are very important factors in the development of tumors in the head and neck region, and later play a considerable role in the changes in the QOL after treatment, as confirmed by the xerostomia. In the study by Hammerlid *et al.*, 29% of the patients had never smoked. Our result correlates with this finding. Meyer *et al.* found a 64% incidence of tobacco use among their studied patient group. Vartanian *et al.* (2006) started that 80% of their patients reported previous tobacco use and 75.7% alcohol consumption. Gritz *et al.* observed a significant reduction in smoking status after a 1-year follow-up, and a significant decline in alcohol use following treatment, with a significant increase in alcohol use between 1 month and 1 year.

The most commonly affected primary site was the floor of the mouth, in 21 patients (26.25%), followed by the gingiva in 17 patients (21.25%), the maxilla in 12 patients (15%) and the tongue in 9 patients (11.25%). Our results are similar to those of Hassanein *et al.*: the floor of the mouth (29%), the tongue (21%) and the mandibular alveolus (18%). Lopez *et al.* found that the tongue was the most affected (38%), followed by the floor of the mouth, with 10%. In the study by Lam Tang *et al.*, the mandible was the most affected area (44%). Hassan *et al.* examined patients with pharyngeal and laryngeal tumors, too and found the oral cavity to be most affected (36%). Thomas *et al.* examined 77 patients, in 34 (44%) of whom the tumor

was in the tonsillar fossa, and in 20 patients (26%) in the tongue. Kruse *et al.* studied 99 elderly patients with head and neck cancer and found that the maxillary and mandibular alveolar ridges (24% each) were the most affected, followed by the tongue (18.9%). In the 47 patients in the study by Biazevic *et al.*, the tumor was in the oral cavity (the floor of the mouth, the gingiva, the retromolar area or the palate) in 19 cases (40%) and, in the oropharynx in 12 cases (25.5%), with 11 in the tongue (23.4%). Kim *et al.* conducted a study on 133 patients, and found the tonsillar area to be affected in 89 cases (66.9%), the base of the tongue in 23 (17.29%) and the soft palate in 15 patients (11.28%).

The most frequently applied treatment method was surgery together with radiotherapy (51.25%). This confirms with the results of Rinkel *et al.* (50%), Nazar *et al.* (47.2%) and Kim *et al.* (71.2%). Scharloo *et al.* found that the use of irradiation alone was the most frequent treatment method (40.7%). In the investigation by Thomas *et al.*, 88.3% of the patients received primary or adjuvant radiotherapy. Vartanian *et al.* (2004) examined 301 patients, 158 of whom (52.5%) underwent only surgery, 34 (11.3%) were irradiated, and 98 (32.6%) recieved a combination of surgery and radiotherapy. Nalbadian *et al.* found surgery alone to be the most commonly applied treatment method (54.1%). In the study by Verdonck-de Leeuw *et al.*, radiotherapy was the most frequently applied treatment (32%), followed by a combination of surgery and radiotherapy (27%). Hassanein *et al.* reported surgery as the most common (70%) treatment method, with surgery combined with radiotherapy (18%) in second place.

The tumor localization and the treatment method, together with the general disease stage, play essential roles not only in the treatment of head and neck cancer, but also in the incidence and intensity of the side-effects and the QOL (Alicikus *et al.*, 2009, Zackrisson *et al.*, 2003).

During the period examined, 106 prosthetic rehabilitations were performed on 92 patients. Some of patients received both upper and lower prostheses, or several prostheses during this period. Most of these prostheses were special prostheses for defect situations (43.75%): 23 implant-retained removable dentures were prepared for mandibular or maxillary defects, 14 obturators (12.5%) were made for maxillary defects after maxillectomy, and in 12 (10.71%) cases epitheses were made for facial defects: 7 orbital (6.25%), 3 aural (2.7%) and 2 nasal (1.8%) epitheses. The other rehabilitations involved 63 conventional prostheses (56.25%): 32 total removable dentures (28.7%), 28 combined prosthesis (25%) and 3 fixed

cemented bridges (2.7%). I do not have exact information about whether some of the 28 combined prostheses were made for an intraoral defect situation.

Schoen *et al.* studied a group of 67 patients with an edentulous mandible after the treatment of squamous cell carcinoma in the lower region of the oral cavity (the tongue, floor of the mouth, mandibular gingiva, buccal mucosa or oropharynx). Half of the patients (n=33) never wore their mandibular conventional prosthesis, or at most for only a few hours per day for cosmetic reasons. Insufficient retention of the mandibular prosthesis was noted in 55% of the patients, and diminished stability in 23% of the patients. Interforaminal located implants in the mandible for improvement of the stability of a fully removable lower denture are increasingly used by healthy patients. This is more to be expected in cases of mandibular defects because of the decayed mucosal supplement and diminished vestibulum. Most of our head and neck cancer patients with this intraoral situation are rehabilitated with an implant-retained removable denture on 2 or 4 interforaminal implants.

VII.2. Comparative analysis of measurements of QOL questionnaires

In my study, I analyzed which function is especially damaged by tumor treatment and measured the changes in the QOL through a comparison before and after rehabilitation.

Most of the available studies made comparisons between some special QLQs (e.g. comparative studies with KPS, CARES or UW QOL questionnaires) or with only one or two domains (e.g. the speech domain), or between healthy and tumor patient groups, or between the pretreatment and the posttreatment situation, or on the longitudinal effects of cancer treatment. Merely a few studies extended to the changes in the QOL after maxillofacial rehabilitation. This study can give a new comparison profile and data for the Hungarian and international literature.

VII.2.1. Results with the UW QOL questionnaire

The mean composite score in my study was reasonably high, at 66.62. This is lower than the result determined in 2008 by Kazi *et al.* (73.6), who studied a subgroup of patients after partial glossectomy.

The worst results in the UW QOL questionnaire before rehabilitation in my study related to employment (BR: 87.8) and chewing domain (BR: 88.58). In the employment domain, a common answer was ’’I am retired-due to the cancer treatment or not related to it”. It was connected with the basic tumor disease, with habitual problems of smoking and drinking alcohol, and the age and general health status of the patients. It means that most of the patients were retired and the majority of the treatment did not seem to alter the employment status. This scale was the only one for which the result after rehabilitation was decreased. Rehabilitation had much less influence at this stage of life.

I observed a worse result in the scale of chewing, which correlated with the result of Kazi *et al* (2010). Other wise, Biazevic *et al.* found chewing (48%) and speech (44%) to be the most prevalent complaints at the time of treatment, and chewing (60%) and swallowing (24%) at the 1-year follow-up. In their study, chewing was the QOL domain which exhibited the largest reduction in rating, from 74.0 at baseline to 34.0 1 year after surgery. It is interesting that Rogers *et al.* (1999) found no trouble with chewing in 45% of the patients in their study group.

There was no significant change in shoulder function before and after rehabilitation and in this scale the score was already low after treatment (BR: 26). This means that most of the surgical procedures do not affect the accessorial nerve which is responsible for the abductor movement of the shoulder.

The family relations did not show any significant change and the BR and AR answers were equally positive. This is good from the aspect of the QOL because it means that the family stands up for the patients in their enormous problems and help them in the healing period.

The best improvements following rehabilitation were in activity and recreation. This is related with the overall feeling ill, mood and global health status. A great improvement in pain emerges with the passage of time.

VII.2.2. Results of EORTC H&N 35 QOL questionnaire

The international literature relating to the QOL most frequently involves studies with the EORTC H&N 35 QLQ. It is usually used together with EORTC C30, but I decided to apply

two questionnaires specific for head and neck tumors, and did not wish to overburden the patients with too many questionnaires demanding a long completion time.

The questionnaire has 35 items concerning tumor and treatment-related physical symptoms. The worst subscale scores after treatment were observed for swallowing (BR: 77.22), social eating (BR: 75.24), pain (BR: 69.95) and speech (BR: 61.52), while the worst score for a single item was that for dry mouth (BR: 3.03). The maxillofacial rehabilitation resulted in the best effects on swallowing (AR: 30.66, change: 46.56), social eating (AR: 32.37, change: 42.87) and speech (AR: 30.50, change: 31.02). Other wise all of the examined subscales and single items displayed significant changes in comparison with the situation before rehabilitation.

Hammerlid *et al.* studied the QOL domains in connection with tumor localization, stage, sex and age. They found that different primary tumor sites were associated with different scores: Patients with nasopharyngeal carcinoma exhibited the worst social and role functioning and highest pain score and they felt ill more often than patients with other tumor locations. Patients with laryngeal carcinoma had the highest scores after treatment as regards speech and coughing problems, while patients with tongue carcinoma scored highest on the pain scale and for nutritional supplements. Their study revealed statistically significant differences in connection with gender (all in favor of men), pain, social eating, social contacts and painkiller use. Older patients tended to score more poorly than younger ones. De Graeff *et al.* conducted a longitudinal study and found significantly increased problems involving pain, swallowing, social eating, speech and taste/smell at 12 months after treatment. They observed a correlation between the results on age and gender: women and older patients furnished worse scores. Alicikus *et al.* carried out a study with EORTC H&N35 on factors influencing the QOL. They found that the treatment modality had a major impact on speech ability and dry mouth: postoperative irradiation led to a worse score for speech, and chemoradiotherapy did so for sticky saliva and social eating. They further determined that the primary tumor site influenced the results of EORTC H&N 35: Patients with nasopharyngeal tumor had the worst scores for mouth opening, dry mouth, sticky saliva, swallowing and social eating, whereas patients with laryngeal tumor indicated that speech was the worst problem. Murphy found through the use of the EORTC H&N 35 QLQ that a number of symptoms remained problematic 12 and 24 months post-treatment: swallowing, taste/smell, speech, social eating, sexuality, trismus, xerostomia and sticky saliva. They did not study patients with or without rehabilitation, and examined only the treatment's longitudinal effects. Nalbadian *et al.* studied Greek patients

with pharyngeal or laryngeal carcinoma after treatment and found the most common problems with the EORTC H&N 35 QLQ in the areas of speech, sexuality, dry mouth, sticky saliva and coughing. Speech and dry mouth were in the worst problem group after treatment in my study. Kim *et al.* compared the outcome of surgery-based and radiation-based therapy. They found no significant differences in the results of the EORTC H&N 35 QLQ between the two groups, although members of the irradiated group had more problems with dry mouth, and more difficulties in weight gain and were more dependent on pain killers.

VII.2.3. Comparison of results of UW QOL and EORTC H&N 35 questionnaires

For my study, I chose these two questionnaires because they complement each other well, and both of them are very extensively applied in their own field. The UW QLQ contains more questions about the psychological and social well-being of the patients. The EORTC H&N 35 questionnaire deals much more with the physical tumor- and treatment-related symptoms of head and neck cancer patients. This causes difficulties in comparisons of the answers of the two questionnaires: In the former, swallowing, activity, recreation and pain gave the worst results before rehabilitation, while activity and recreation displayed the best increases after maxillofacial rehabilitation. In the other questionnaire, swallowing, social eating, pain and dry mouth were the worst problems for the patients, and the rehabilitation led to the greatest changes in swallowing, social eating and speech. Swallowing and pain proved to be the most serious problems before rehabilitation in both QLQs.

The study by Kanatas *et al.* demonstrated that the UW QOL was the most frequently used questionnaire (72%) among members of the British Association of Head and Neck Oncologists, followed by the EORTC C30 and the EORTC H&N 35 (52%).

VIII. SUMMARY AND CONCLUSIONS

Progress in the treatment of oral cancer has made it possible to reduce the post-treatment mortality, and the survival rate has increased. However, the length of survival alone is an unsatisfactory measure of the success. The tumor treatment of head and neck cancer patients causes the QOL of the patients to deteriorate considerably after treatment, owing to the impairment of such important functions as eating, swallowing and speech on the one hand, and aesthetic aspects related to socialization on the other. This is why maxillofacial rehabilitation has such an important place as the last step in the tumor treatment procedure.

In our study, the gender difference, with a male:female patient ratio of 2:1, appeared to be significantly less marked than reported in earlier studies, which is explained by increasingly higher rates of women smoking and drinking alcohol.

The majority of our patients consumed alcohol and smoked on a regular basis, which further worsen the QOL through increase of the risk (and the related stress) of a local recurrence, and affect the patients' family and social relations.

A majority of the patients (51.25%) had received a combination of surgery and radiation as therapy, which is in line with the oncotherapy protocol applied nowadays.

In the course of the rehabilitation, about half (43.75%) of the cases involved the preparation of a special prosthesis as a solution: the application of obturators after maxillectomy (14 cases/12.5%), implant-retained dentures (23 cases/20.54%) in cases of an acquired mandibular defect or after surgery on a tumor of the tongue or the floor of the mouth, or epitheses (12 cases/10.75%) in cases of facial defects.

As a means of assessing changes in the QOL with the aim of a subsequent improvement, QOL questionnaires appear to provide an easily applicable, routine procedure in the care of head and neck cancer patients. We conclude that the UW QLQ and the EORTC H&N 35 questionnaires are useful tools for the evaluation of the HRQOL in patients with cancer in this region.

Statistical analysis of the results of the questionnaires suggests that post-treatment patients awaiting rehabilitation experienced the greatest difficulties in the areas of eating and speech.

The results of the UW QLQ demonstrated that the worst problems after treatment related to chewing, employment, activity and recreation, and the best increase after rehabilitation was experienced as concerns pain, with additional significant improvements in activity and recreation. There was no change in the level of family relations. This means that tumor as a disease does not affect personal contacts in the family in a negative way and it does not need improvement. There was no positive change in employment, because most of the head and neck cancer patients had already retired before the tumor treatment, because of the general staging or some other illness. There was no significant difference between the results before and after rehabilitation as concerns the shoulder function.

The EORTC H&N 35 questionnaire was somewhat easier to complete. It indicated that the worst subscale problems after tumor treatment were the swallowing and social eating, followed by pain. Among the single items, the worst problems were dry mouth and sticky saliva as side-effects of irradiation. The rehabilitation resulted in the greatest changes in swallowing, social eating and speech and feeling ill.

Overall, maxillofacial rehabilitation leads to significant improvements in all impaired functions and to positive changes affecting the QOL. The results of my investigations allow me to state that prosthetic rehabilitation can play a key role in the life of head and neck cancer patients through the resulting improvement in their QOL.

IX. ACKNOWLEDGMENTS

First and foremost, I would like to express my sincere thanks to Professor Katalin Nagy, Head of the Faculty of Dentistry, for providing me with the opportunity to work on this special field of dentistry and for her enormous help, encouraging support and constant enthusiasm and professionalism in the supervision on my professional work in general and this study in particular.

I am very grateful to Professor István Sonkodi, Head of the Department of Oral Medicine, for his endless knowledge, support and tolerance throughout my whole clinical and scientific life.

I express my very special thanks to Professor József Piffkó, Head of the Department of Maxillofacial Surgery, for his creation of an unique oasis in Hungarian medicine, and for his efforts and support relating to my work. Many thanks too to the other members of the staff of the Department of Maxillofacial Surgery for their co-operation.

I wish to express my appreciation to Professor Béla Iványi, Head of the Department of Pathology, and to Dr. László Puskás, molecular researcher at the Biological Research Center in Szeged, for adding their professional knowledge to my articles.

Many thanks are also due to Tibor Nyári at the Statistics Team of the Faculty of Medicine at the University of Szeged for his work by statistical analysis.

I would like to express my thanks to my assistants and primarily Éva Körmendi and Györgyi Vágó, without whom I could not have worked during the weekdays in this clinical professional field.

I am grateful to Katalin Márton Pappné for her library help, and to Zsuzsa Kiss-Dózsai for the photos and her technical help in my practical work and completion of this study.

I owe many thanks to my head and neck cancer patients, who have taught me love and respect for health and human life.

Last, but not least, I am most grateful to my parents for their encouragement and especially my daughter, Anna for her endless love and childlike adoration for my profession.

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Virchows Arch (2005) 446: 278–286
DOI 10.1007/s00428-004-1176-0

ORIGINAL ARTICLE

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A second field metachronous Merkel cell carcinoma of the lip and the palatine tonsil confirmed by microarray-based comparative genomic hybridisation

Received: 9 September 2004 / Accepted: 8 November 2004 / Published online: 25 February 2005

Abstract Merkel cell carcinoma was diagnosed in a 79-year-old Caucasian woman. The tumour was localised to the upper lip and was in stage T2. After successful cryosurgery and a 7-year tumour-free period, a new tumour developed in her palatine tonsil. Histologically and immunohistochemically, this resembled the tumour in the lip. The regional lymph nodes were devoid of metastasis. The paraffin-embedded material of the two tumours and the unaffected lymphatic tissue were analysed with DNA microarrays for comparative genomic hybridisation to assess the genetic relationship of the tumours. In both tumours, regions on 2p and 10p were commonly over-represented, while 41 regions on chromosomes 1–4, 6, 8–9, 11 and 14–22 were commonly under-represented. Chromosomes 1, 3, 4, 16–18 and X were most frequently involved in the DNA losses. In gene copy numbers in the two tumours, 31 chromosome locations were found to be differently affected. The partly similar and partly different molecular patterns indicated a genetic relationship between the tumours and excluded the possibility that the tonsillar tumour was a metastasis. The findings suggest that a genetically altered field was the reason for the development of the tonsillar cancer; thus, it can be regarded pathogenetically as a second field tumour.

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Keywords Merkel cell carcinoma · Second field tumour · Comparative genomic hybridisation · DNA microarray · Chromosome imbalances

Introduction

Merkel cells are found in the skin and in those parts of the mucosa derived from the ectoderm [11]. These cells are the origin of a rare, malignant neuroendocrine tumour that occurs predominantly in the sun-exposed areas of the skin called Merkel cell carcinoma (MCC) [1, 2, 4, 19, 20, 22, 28]. Local recurrence and regional or distant metastases generally develop within a short period of time. Oropharyngeal metastasis is very rare, and metastasis to the palatine tonsil has been described in only one case [27]. A perioral or intraoral localisation of the MCC is very infrequent: [13, 20] to date, 10 cases of MCC of the lip [35] and 14 cases of intraoral MCCs have been described [3, 16, 20]. During the past decade, we treated and followed up an elderly woman with MCC of the upper lip. After a long tumour-free period, an anaplastic carcinoma with neuroendocrine features developed in her palatine tonsil, raising the possibility of a late haematogenous metastasis, a second field tumour or a second primary tumour.

The term "secondary field tumour" was introduced in 1953 by Slaughter et al., who examined slides from patients with head and neck cancer [29]. It was observed that all of the epithelium beyond the margins of the tumours displayed histological alterations, and 11% of the patients were found to have more than one independent area of malignancy. The authors concluded that the mucosa of the head and neck had undergone a change, perhaps due to carcinogen exposure, and was, therefore, more susceptible to the development of foci of malignant transformation. Organs in which field cancerisation has been described since then are the oral cavity, oropharynx, larynx, lung, oesophagus, colon, skin, vulva, cervix, breast, renal pelvis, ureter and bladder [5–7, 10].

The determination of molecular patterns of first and second tumours has become a valuable tool to explore the

relationship between them: similar aberrations indicate a metastasis, partly different aberrations indicate a second field tumour and different aberrations denote a second primary tumour [5, 6, 10]. In the present study, we identified the molecular patterns with comparative genomic hybridisation (CGH) with microarray technology. Array-based CGH consists of a series of mapped artificial bacterial chromosomes or sequenced cDNA clones on glass slides, to which DNA from test and control samples is hybridised [8, 19–21, 30]. This approach allows the determination of copy number changes of chromosome regions without a need for tissue cultures and the preparation of metaphase spreads, as DNA extracted from a tumour specimen is used. Another major advantage of CGH is that archived specimens can be also studied. We applied human cDNA microarrays as a tool, DNA from paraffin-embedded tumour materials (from both the primary and secondary tumours) as test probes and DNA from normal lymph nodes as control probes.

Previous CGH studies of MCCs have identified divergent regions that are affected, with a small number of similarities between the samples analysed. Recurrent chromosomal imbalances detected using CGH analysis were loss of 3p, 4p, 5-pter, 10q, 13q and 17p and gains of 1q, 3q, 5p, 6, 8q, 18 and 20 [12, 24, 33, 34]. In the present study, we detected some of the previously found regions and also numerous novel regions with chromosomal imbalances. Copy number changes of nine chromosome regions detected by CGH were analyzed using real-time quantitative polymerase chain reaction (QPCR). Potential oncogenes, tumour suppressor and apoptotic genes mapped to regions detected as changed were also recorded. The results suggest that a genetically altered field was the reason for the development of the tonsillar cancer; thus, it can be regarded pathogenetically as a second field tumour.

Materials and methods

Case report

Between 1970 and 2003, 4418 patients with malignant orofacial tumours were treated in our clinic. One of these patients suffered from MCC. A 79-year-old Caucasian woman presented with a tumour in her upper lip. She was an outdoor worker and never smoked. She was disturbed only about the aesthetics. The physical examination revealed a 2–3-cm firm, compact mass in the skin of the upper lip on the left side. It was sharply separated from its surroundings and had a telangiectatic surface (Fig. 1). The tumour was classified as stage T2. No regional lymph-node metastasis was detected. Surgical resection of the tumour and removal of the regional lymph nodes were suggested, but she refused it. As an alternate therapy, a biopsy was taken, and cryotherapy was applied according to the standard protocol. Light microscopy revealed that the tumour was confined to the dermis and was sharply separated from the epidermis (Fig. 2a). The tumour cells were arranged in nests and cords. Cytologically, the tumour cells were

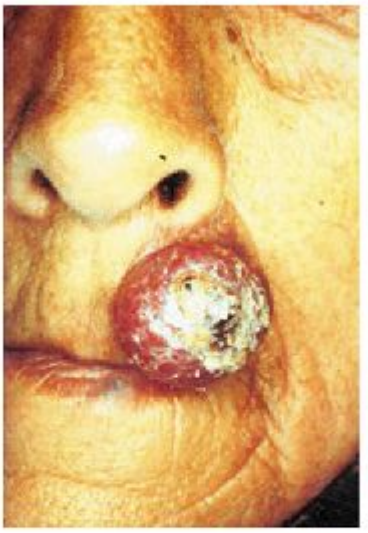

Fig. 1 Tumourous mass sharply separated from the surroundings in the skin of the upper lip

monomorphic, the nuclei were round and the chromatin pattern was finely granular and "dusty". The nucleoli were small; often two or even three were detected. The cytoplasm was scanty. The mitotic rate was high (six to ten figures/high-power field). The Grimelius staining was negative. The results of immunostainings are shown in Table 1 and Fig. 2. The histological and immunohistochemical features pointed to MCC of the lip. Following the histological diagnosis, distant metastases in the lungs and bones were searched for, with negative results.

In the 7-year follow-up, the patient was in a tumour-free condition. After 7 years, she was admitted to the County Hospital with a left palatine tonsillar tumour. This tumour was resected in part, and the regional lymph nodes were removed. Histologically, the tumour displayed features of anaplastic carcinoma (Fig. 3). The results of immunostainings are summarised in Table 1. The histological and immunohistochemical features pointed to MCC of the lip. Following the histological diagnosis, distant metastases in the lungs and bones were searched for, with negative results.

The morphological appearance of the tumour resembled that of the MCC of the lip. A further excision was performed 3 months later. The morphological and immunohistochemical features of the tonsillar tumour were essentially the same as observed 3 months earlier. The patient died at home on the 20th postoperative day. Autopsy was not performed.

Sample preparation, labelling

Paraffin-embedded tissues (200–500 mg) were deparaffinised in hexane and washed with ethanol. DNA was purified

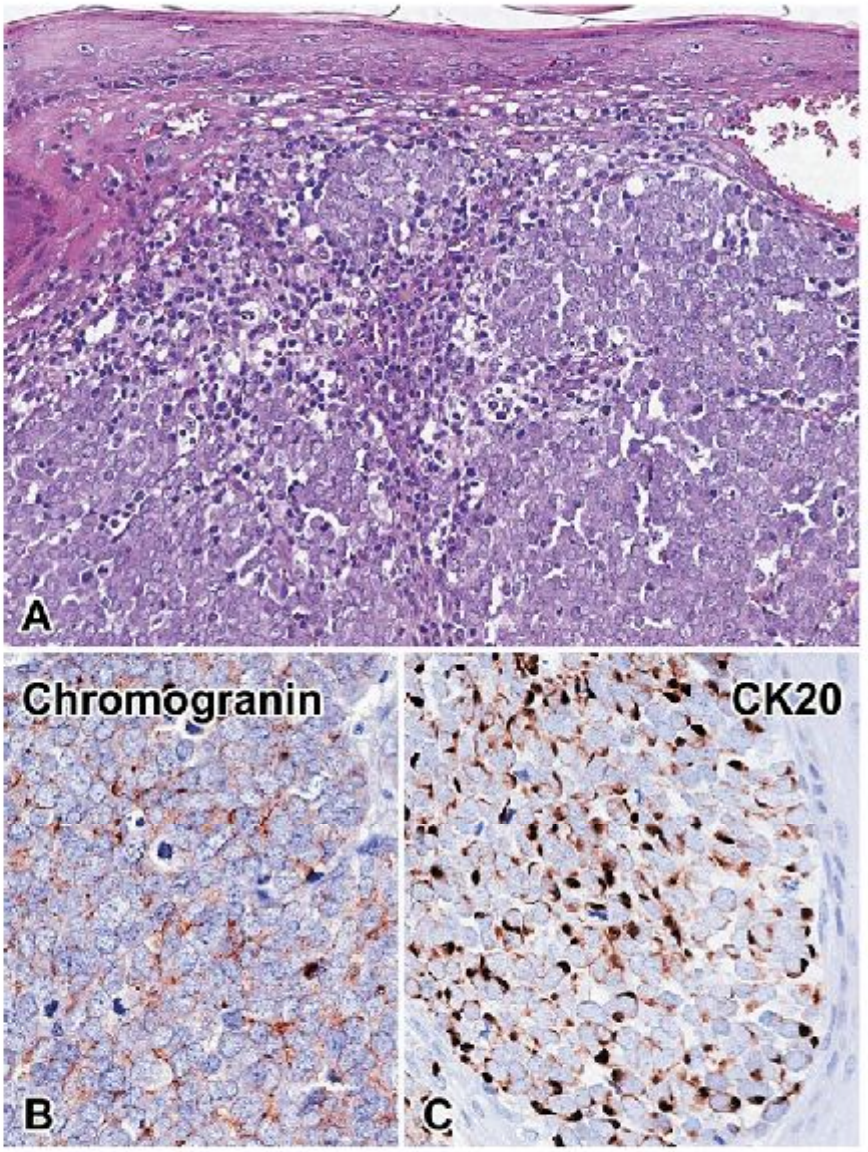

Fig. 2 Merkel cell carcinoma of the lip. A Small, monomorphic tumour cells fill the dermis arranged in nests and cords. The nuclei exhibit moulding. Haematoxylin-eosin ×200. **B** Chromogranin positivity of tumour cells ×400. **C** Paranuclear dots by cytokeratin-20 staining ×400

Table 1 Immunohistochemical findings

Immunohistochemical markers	Lip tumour	Tonsillar tumour
AE1/AE3	+–+	+++
Cytokeratin	20	20
Paranuclear dots	+–+	++
Chromogranin	+–	+
Synaptophysin		
TTF	–	–
EMB-45	–	–
CEA	–	–
Lymphoid markers	–	–

by using the DNA purification kit from Macherey-Nagel (Düren, Germany) according to the manufacturer's instructions. First, 100 ng genomic DNA from each sample was amplified with a modified version of the DOP (degenerate oligonucleotide primed) PCR protocol using a real-time PCR instrument to follow the amplification [9, 15]. Reactions were performed in a total volume of 100 µl. The cycling parameters were as follows: heat start at 95°C for 4 min, 8 cycles of 94°C denaturation for 50 s, 45°C annealing for 2 min to 72°C with 0.2°C/s and extension at 72°C for 90 s. After the 8 cycles, the reaction mix was separated into two 50-µl portions, and SybrGreen was added to the mix (1× final concentration, Molecular

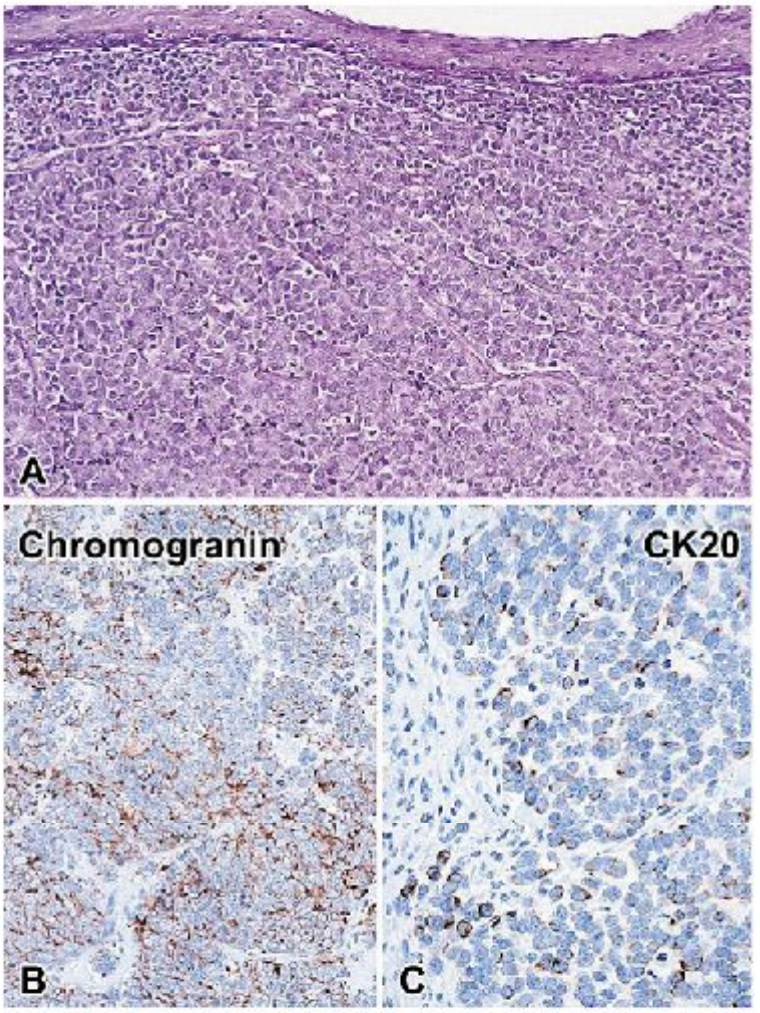

Fig. 3 A Anaplastic carcinoma of the tonsil. Hematoxylin-eosin ×200. B Chromogranin positivity in the tumour cells ×400. C Some tumour cells display paranuclear dots by cytokeratin-20 staining ×400

Probes, Eugene, USA). The following cycling protocol was performed in a real-time PCR instrument, RotorGene 2000 (RotorGene, Sydney, Australia): denaturation at 95°C for 40 s, annealing at 58°C for 1 min and extension at 72°C for 80 s. The cycling was performed just before the reaction reached the plateau to avoid over-amplification of the products (usually in 18–22 cycles). The PCR products were purified on PCR-purification columns (Bioneer, Daejeon, Korea). Next, 100 ng purified DNA was labelled with another round of PCR in the presence of Cy3-dUCTP (0.05 mM) in a total volume of 50 µl with the same parameters for 20 cycles as in the second PCR. In all these reactions, UN primer (5′-CCGACTCGAGNNNNNNATGTGG-3′) was used in a 1-µM concentration [31]. The reactions were performed with ExTaq DNA polymerase in 1× buffer (Takara, Tokyo, Japan). The labelled PCR products were purified with the PCR purification kit (Bioneer). The eluted DNA was dried in a Speed-Vacuum.

Hybridisation, scanning, data processing

The labelled DNA was reconstituted in ChipHyb hybridisation buffer (Ventana Discovery, Tucson, USA) containing 20 µg human Cot DNA and 5 µg salmon sperm DNA (Invitrogen). Hybridisation was performed on human cDNA microarrays having 3200 gene-specific samples in duplicate in 200 µl using the Ventana hybridisation station (Ventana) at 42°C for 8 h [25, 26]. After hybridisation, the slides were washed twice in 0.2×sodium saline citrate at room temperature for 10 min and then dried. Scanning and data analysis were performed as described previously [21]. Briefly, data presented in this study were calculated from the results of four data points obtained from two separate labelling and hybridisation protocols. The background-corrected intensity data was filtered for flagged spots and weak signal. Technical replicates on the same array were averaged. Data were excluded in cases where technical replicates were significantly different. Normalisation was

performed using the print-tip LOWESS method [36]. Next, we used the one-sample *t*-test to determine the genes to be regarded as changed in copy number. Logarithm was taken from each ratio to fulfil the *t*-test's requirement for a normal distribution. Genes for which the mean of log-ratios across the biological replicates was equal to zero at a significance level α=0.05 were considered to have an unchanged copy number. However, genes with a *P* value smaller than α and where the average-fold change (over- or under-representation) of the four data points were at least twofold were considered as changes in DNA copy number.

Real-time QPCR

The confirmatory real-time QPCR was performed on a RotorGene 2000 instrument with gene-specific primers and the SybrGreen protocol on non-amplified genomic DNA. Reactions were performed in a total volume of 20 µl (50 ng genomic DNA from each sample, 5 pmol/each forward and reverse primer, 1× BioRad SYBRGreen buffer, BioRad, Hungary) with the following protocol: denaturation for 10 min at 95°C, and 45 cycles of 25 s denaturation at 95°C, 25 s annealing at 59°C and 25 s extension at 72°C. Fluorescent signals were collected after each extension step at 72°C. Curves were analysed with the RotorGene software, using dynamic tube and slope correction methods, ignoring data from cycles close to baseline. Primers were designed by using the ArrayExpress software (Applied Biosystems). Relative ratios were normalised to the Ct values obtained with the dihydrofolate reductase gene probe and calculated with the Pfaffl method [23]. The PCR primers used in this study are listed in Table 2. All the PCRs were performed four times in separate runs.

Results

CGH analysis

We analysed the primary MCC and the tumour of the tonsil, applying CGH with DNA from paraffin-embedded tumour material as the probes. Relative DNA losses and gains were determined for each tumour sample by normalising the intensities to the values obtained after hybridisation with labelled probes from normal lymphoid tissue.

Using microarray-based CGH, numerous changes in chromosome copy numbers were observed in both tumours investigated. Both tumours showed complex DNA copy number changes, with an abundance of DNA losses and a few DNA gains. Of the regions, 41 were detected with a DNA loss and 4 regions with a DNA gain (Table 3). CGH revealed regions on 2p and 10p to be commonly over-represented and regions on 1p, 1q, 2p, 2c, 3p, 3q, 4q, 5q, 6p, 6q, 7q, 8p, 9p, 9q, 11p, 11q, 12c, 14q, 15q, 16p, 16q, 17p, 17q, 18q, 19p, 20p, 21q, 22q and X to be commonly under-represented. Chromosomes 1, 2, 3, 17 and 18 were most frequently involved in the DNA losses. According to the intensity ratios, monosomy of the X chromosome is postulated. Besides the commonly affected regions, 31 additional chromosome locations were found to be differently affected in gene copy numbers in the two tumours. Common, primary MCC-specific and secondary tumour-specific changes are listed in Table 3. While 22 regions could be observed with the secondary tonsil cancer-specific DNA loss, only 6 regions were specifically under-represented in the case of the primary MCC. All other DNA losses were common in both tumours. Only 2 regions, 2p23 and 10p15, exhibited common gains, and 3 regions, 2p25, 12q12 and 15q14, showed over-representation in the case of MCC.

Potential oncogenes and tumour suppressor and apoptotic genes mapped to regions detected as changed were

Table 2 Sequences of the oligonucleotides (5'-3') used in this study

Gene	Chromosome location	Forward primer	Reverse primer	Product size (bp)
Steroid 5-alpha-reductase 2	2p23	CAGAAGCCCCAAGCAACTTT	CCTTCTTGAACAGGTCCTGAGAA	69
Hepatocyte nuclear factor-3 alpha	14q12-q13	CTCAAGAGTTGCTTGACCGAAA	GGGCCATCTGTGGGTAGAGA	67
Zinc finger protein	19q13.43	GAAATTCCCCTGCCAGACCTT	CATGAAGCCCCACTCTGAGAGT	73
Androgen receptor (dihydro-testosterone receptor)	Xq12	CGGAAATGATGGCAGAGATCA	TGGGCTTGACTTTCCCAGAA	66
C8FW phosphoprotein	8q24.13	GGACGATACCCCTTCCATGA	GTCCACGCCGAATTTTGG	61
Cardiac myosin binding protein C	11p11.2	GCCTAAATCCGAGCATCTGTTT	TGCACTCTCAGGGAATTTGAGA	70
EST	15q14	CCTGATTCCAGAAAAGCAAGTGT	CACTGAGATTACCGGGCATGA	76
Cytochrome P_{450} subfamily XIA	15q22	CTGGTGCAAGTGGCCATCTA	AATTTTCCGGGTCGAAGAAGA	64
EST similar to phosphatidylcholin transfer protein	17q23	CACAAGGCTATGCACAAAGCA	GGAAACTGAGGCGTCAAGATG	68
Dihydrofolate reductase	5q14	CTGTCATGGTTGGTTCGCTAAA	TGCCGATGCCCATGTTC	60

Table 3 Common and individual gains and losses of Merkel cell carcinoma and the tonsillar tumour detected using comparative genomic hybridization

	Deletion	Amplification
Both tumours	1p36, 1p31, 1p13, 1q21–23, 1q32, 1q42.13, 2p13, 2p11.2, 2q35, 3p21, 3q13.2, 3q14.3, 3q26–28, 4p16, 4q21, 5q35, 6p21, 6q24, 7q21, 8p21, 8q24, 9p12, 9q34, 11p11.2, 11q13, 11q23.3, 12q24.1, 14q11.2, 15q23–24, 16p13–12, 16q24, 17p13, 17q12, 17q23, 18q12, 18q21, 19p13, 20p13, 21q22, 22q13.1, X monosomy	2p23, 10p15
Merkel cell carcinoma	11p11.2, 11q12.3, 12q13, 16p13.1, 17q21.1, 17q25	2p25, 12q12, 15q14
Mesopharynx	1p34.1–32.2, 1p21–22, 1q42, 2q37, 4p16.3, 4q28.3, 5q11.1, 5q22, 5q31–32, 7p14, 8p22–24.13, 10q21.1, 11pter-p15.5, 12q14.3, 14q11.2, 14q31–32, 15q11–13, 16q23–24, 17q21.2-q23, 20q13.1, 21q22.13, 22q11	

Table 4 Apoptotic genes and tumour suppressors mapped to regions with common chromosomal aberrations. Apoptotic and tumour suppressor genes in bold character. Apoptotic and tumour suppressor-related genes in italics in brackets

Chromosome location in both tumours	Apoptotic genes	Tumour suppressors
1p36	**DFFB, TP73, CASP9** *(CDC42, MFN2)*	**UBR4B, TUSC3, PRDM 2, C1orf1, ALPL** *(E2F2, TP73)*
1p31	–	**CLCA2**
1p13	–	**ST7L**
1q21–23	**MCL1, DAP3, TNFSF6** *(JAUC1, APCS, CRP, SELL)*	
2p13		**MAD**
3p21.3	*(CCR3)*	**RASSF1, BAP1** *(SEMA3B)*
3q26–28	*(ETV5, OPA1)*	**TSBF1**
4p16		*(GAK)*
4q21	*(SNCA)*	
5q35		*(PDLIM7)*
6p21	**BAK1, TNF** *(HSPA)*	*(CDKN1A)*
6q24		**SASH1** *(PLAGL1)*
8p21	**BNIP3** *(CLU)*	***PDGFRL*** *(CNOT7, PDLIM2)*
8q24		*(RNF139)*
9q34	**TRAF2** *(ABL1)*	
11p11.2	*(MADD)*	
11q13	**DPF2, BAD, FADD** *(RELA, CCND1, RAD9A)*	**DOC-1R, MEN1** *(ST5, CCND1, SHANK2)*
11q23.3		**THY1**
12q24.1	*(SCA2)*	
16p13–12	**ASC**	**TSC2**
16q24		**WTDC1, GAS8, MGC15419, CBFA2T3**
17p13		***TP53, HIC1, OVCA2, DPH2L1***
17q12	*(CCR7)*	*(MPP3)*
18q21	*(BCL2)*	**DCC, SERPINB5 (R2F5)**
19p13		**DIRAS1** *(TJP3, SMARCA4, GIFC3)*
21q22	*(MX1)*	
22q13.1	*(HMOX1)*	**ST13**
Xp22.1	*(SH3KBP1)*	
Xq12		**ING2**
Xq28		**RPL10**

also analysed. The genes mapped to regions that were changed in both tumour samples are listed in Table 4, while changes characteristic of only one tumour are presented in Table 5.

Confirmation of CGH data

The copy number changes of several chromosome regions detected using CGH were submitted for QPCR analysis. Specific primers were designed (Table 2) and used to amplify affected DNA regions of the genome using non-amplified genomic DNA as template. Relative ratios were normalised to the copy numbers of the dihydrofolate reductase gene, because this did not show any alteration in copy number in either tumour and gave reproducible results in all cases. Nine regions exhibiting DNA losses or gains in both tumours were selected for QPCR. In seven cases, the common alterations were confirmed, while in two cases, only MCC-specific changes could be detected (Table 6).

Discussion

MCCs are highly divergent when analysed for chromosome aberrations [12, 24, 34]. Reported recurrent chromosomal imbalances detected using CGH analysis were loss of 3p, 10q, 13q and 17p and gains of 1q, 3q, 5p and 8q [34]. In the present study, we could also detect the loss of 3p and 17p, but none of the above-mentioned amplified regions could be confirmed (Table 3, Fig. 4). In another study, only 3 of the 10 MCCs exhibited common gains and losses, and they shared a gain of 8q21-q22 and a loss of 4p15-pter [24]. In the present study, the 4p16 region was also found to be deleted in both the primary and secondary tumours. Unfortunately, to date, no known tumour suppressor gene has been mapped to this region (Table 4). Speleman's group detected losses involving the entire chromosome 10 or

Table 5 Apoptotic genes and tumour suppressors mapped to regions with chromosomal aberrations specific to Merkel cell carcinoma or tonsillar tumour. Apoptotic and tumour suppressor genes in bold character. Apoptotic and tumour suppressor related genes in italics in brackets

Chromosome location	Apoptotic genes	Tumour suppressors
In Merkel cell carcinoma		
11p11.2	*(MADD)*	
12q13	*(CDK2, KRT18, NR4A3, WNT1)*	
17q25	**BIRC5**	
In mesopharynx		
1p34.1–32.2		**FABP3**
3p22–21		**ADPRTL3**
5q11.1	*(LOC145908)*	
5q22		**MCC**
5q31–32		**C5orf7**
10q21.1	*(CDC2)*	
11pter-p15.5	*(CTSD HRAS)*	**MRV11**
14q31–32	**SIVA**	
16q23–24	*(LOC145908)*	**CBFA2T3**
21q22.13		**RUNX1**
22q11	**BID**	**MYO18B**

partial loss of the chromosome 10 long arm in one-third of the MCC cases they analysed with a possible loss of heterozygosity of 10q23, including the PTEN tumour-suppressor gene [33]. In our case, deletion of this region was not observed in either tumour sample.

In previous observations, series of MCCs showed no evidence of high-level amplification [34]. Recurrent gains of chromosomes 1, 6, 18q and 20 were detected in 2 cases [12]. In our case, only two regions, 2p and 10p were commonly over-represented. In a very recent study, 19 primary MCCs were analysed by CGH, and, in 13 samples, extensive gains and losses were detected [17]. It was shown that a majority of the alterations were gains, while only a few common losses were detected, mainly in regions 4q, 13q and 16q. Neither of our gains was found in any of the 19 cases they analysed. Most of the losses were detected in at least 1 case reported in the above-mentioned study, but the 13 MCCs exhibited a very heterogeneous pattern, with diverse regions with losses.

Our CGH results revealed several new and a few other previously known chromosomal regions that have been presumed to be involved in the pathogenesis of MCC. We found 2 common gains and 41 common losses in the two samples. However, in 31 chromosome locations, we observed differences in gene copy numbers between the two tumours. From the results obtained by CGH analysis, we believe that the mesopharynx cancer and the MCC of the lip derived from the same, genetically altered field; thus, the mesopharynx cancer can be regarded as a second field tumour. From the results obtained using CGH analysis, we hypothesise that Merkel cells in two adjacent anatomical sites, i.e. in the lip and mesopharynx, underwent same precancerous genetic alteration, and both tumours arose from a common cell clone. If our hypothesis is correct, the mesopharynx cancer can be regarded as a second field tumour.

Several oncogenes and tumour-suppressor and apoptotic genes were assumed to be changed in their copy number, as many of them were mapped to the regions having changes in their copy number in one or both of the tumours (Table 4 and Table 5). The limitation of this list is that, in these cases, the deletions of the genes themselves were not proved in this study; only those regions were determined that were located to certain regions or proximity to regions where DNA segments on the microarrays originated.

The microarray-based CGH techniques used in this study could result in distorted data, especially when paraffin-embedded tissue is the target. Another limitation of this study is that the deleted regions were determined using hybridisations based on complementary cDNA – genomic DNA annealing events, which could generate more biases. In consequence of the above problems, we determined the reliability of the results obtained by the CGH microarray using real-time QPCR. Ten genes were selected to follow

Table 6 Confirmation of comparative genomic hybridisation data using quantitative real-time polymerase chain reaction (QPCR). Only two common losses could not be confirmed. Gains are indicated as grey background

Microarray data confirmed using QPCR	Clone name	Accession no.	Chromosome location	Distance
Both tumours	Steroid 5-alpha-reductase 2 (SRD5A2)	M74047	2p23	31724
	Hepatocyte nuclear factor-3 alpha	U39840	14q12-q13	36052
	Zinc finger protein	AF020591	19q13.43	63450
	Androgen receptor (dihydrotestosterone receptor)	M23263	Xq12	63075
	CREW phosphoprotein	AJ000480	8q24.13	126404
	ESTs, Highly similar to Phosphatidylcholine transfer protein	AA933627	17q23	54340
	Cytochrome P_{450}, subfamily XIA	M14565	15q23–24	70670
Merkel cell carcinoma	EST	N22765	15q14	no data
	Cardiac myosin binding protein-C	U91629	11p11.2	49310

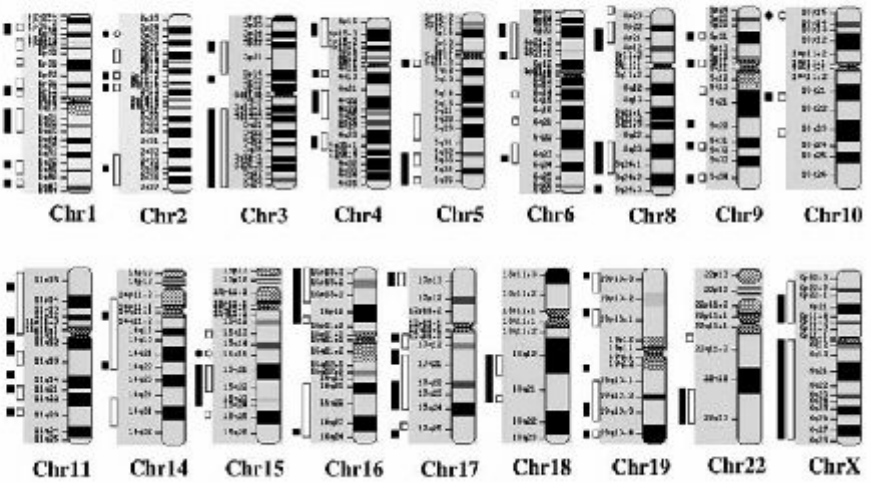

Fig. 4 Copy number aberrations found using microarray comparative genomic hybridisation analysis and real-time polymerase chain reaction of primary Merkel cell carcinoma (MCC) and the tonsillar cancer. *Boxes* on the left side of each chromosome ideogram show regions of reduced copy number (losses of DNA in the tumour genome). *Circles* on the left side of each chromosome ideogram show regions of increased copy number (gains of DNA in the tumour genome). *Filled boxes* denote MCC and *empty boxes* tonsillar tumour

the copy number changes by QPCR. Of the ten genes, one exhibited no changes in the copy number found using CGH microarray analysis in all cases: the dihydrofolate reductase gene. Therefore, it was used as an internal control. The copy numbers of all the other nine genes (sequences and chromosome locations are listed in Table 2, accession numbers are listed in Table 6) were related to this inner control. We used DNA purified from normal lymphoid tissue as control and determined copy number changes of the other two tumours (Table 3, Fig. 4). We confirmed the deletions in seven cases for both tumours, and two were confirmed for only MCC. Although the number of the confirmatory real-time QPCRs was limited and, therefore, does not allow determine the reliability of the CGH methods, the main purpose of the study was to determine the relation of the two tumours, not a precise determination of the deleted regions.

In summary, the partly different molecular patterns obtained using CGH, the similar histological features and the close proximity to the primary tumour indicate that the tonsillar cancer was a second field tumour. The common origin was further confirmed, because of three early markers (9p, 3p and 17p) two of them (9p and 17p) were common in both cancer samples, one (17p) bearing the tp53 tumour suppressor marker gene. The common copy number changes do not support the possibility that the tonsillar cancer was a second primary tumour. The tonsils are very rare and unusual sites of metastatic disease in MCC. There are three reports in the literature describing oropharyngeal metastasis of a MCC [18, 27, 31]. In all these reports, the metastasis occurred within 24 months after resection of the primary tumour. In our case, it was clinically very unlikely that the tonsillar tumour was a metastasis of the MCC of the lip, because no local recurrence, regional lymph-node metastasis or distant haematogenous metastases were observed in the 7-year follow-up. In harmony with the clinical situation, the molecular patterns of the two tumours were not similar, therefore, the possibility of a metastasis could be rejected. Although the concept of second primary tumours and field cancerisation has been formulated for oral and oropharyngeal squamous cell carcinomas [5], our results indicate that Merkel cells in adjacent anatomic sites may also be the targets of field cancerisation.

Acknowledgements This work was supported by a grant from the Hungarian Ministry of Health (ETT 400/2003). LGP is supported by the Janos Bolyai fellowship of the Hungarian Academy of Sciences.

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II.

FOGORVOSI SZEMLE ■ 99. évf. 4. sz. 2006. 135–139.

Szegedi Tudományegyetem, Általános Orvostudományi Kar, Fogászati és Szájsebészeti Klinika* Szegedi Tudományegyetem, Általános Orvostudományi Kar, Pathologiai Intézet**

Merkel-sejtes carcinoma

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A szerzők az eseti smertetés kapcsán egy ritka előfordulású, neuroendokrin eredetű, rosszindulatú daganat, a Merkel-sejtes carcinoma bemutatását tűzték ki célul.
A Szegedi Tudományegyetem Fogászati és Szájsebészeti Klinika új betegforgalma 1970 és 2004 között 158 056 volt, ebből az Orális Medicina Részlegre 23 807 beteget utaltak be. Ebből egy esetben volt Merkel-sejtes carcinoma a szövettani diagnózis. A tumort ritka előfordulása mellett agresszív viselkedése jellemzi, korán jelentkezik lokális recidíva, regionális vagy távoli áttét.
A 79 éves nőbeteg felső ajakon megjelent Merkel-sejtes carcinomáját cryosebészi módszerrel kezelték a szerzők. A háromléves követési időszakban a betegnél helyi recidívát, regionális és távoli áttétet nem észleltek. Hét évvel később egy második, tonsillaris eredetű Merkel-sejtes carcinoma jelent meg a betegnél a mesopharynx területén. Ez a körülmény tovább növelte az eset ritkaságát.
A klinikai, szövettani, immunhisztokémiai és genetikai vizsgálatok eredményei alapján a később megjelent daganatot a genetikailag módosult mező második daganatának, ún. „second field tumour"-nak tartják a szerzők.

Kulcsszavak: Merkel-sejtes carcinoma, cryosebészet, immunhisztokémia, differenciáldiagnózis

Bevezetés

A Merkel-sejtes carcinoma (Merkel cell carcinoma – Mcc) ritka, rosszindulatú, neuroendokrin eredetű daganat. Leggyakrabban napnak kitett bőrön jelentkezik, így a fej-nyak régióban és a végtagokon [2, 9, 12, 14]. Előfordulása a szájüregben és az ajakon igen ritka [14, 26]. A hazai stomatológiai irodalomban Mcc-át eddig nem közöltek.

A Mcc agresszív viselkedésű daganat, gyakran és korán alakul ki lokális recidiva, regionális vagy távoli metastasis [11, 13, 18].

Jelen közleményünkben egy a felső ajak bőrében megjelent Mcc-ról számolunk be. A daganat cryosebészi kezelése után hét évvel helyi recidíva nélkül újabb Mcc-t diagnosztizáltak a mesopharynx területén. Ez a Mcc ritka előfordulása mellett további kérdéseket vet fel a daganatok klinikai-onkológiai viselkedésével kapcsolatban.

Esetismertetés

79 éves nőbeteg azzal a panasszal kereste fel a Szegedi Tudományegyetem Általános Orvostudományi Kar Fogászati és Szájsebészeti Klinikájának Orális Medicina osztályát, hogy a felső ajak bőrén panaszt, fájdalmat nem okozó, esztétikailag zavaró elváltozást észlelt *(1a. ábra)*.

Klinikai vizsgálattal a felső ajak feletti bőr bal oldalán egy 2-3 cm átmérőjű, tömött tapintatú, körülhatárolt, a környezetből kiemelkedő, erythémás, teleangiectásiás felszínű daganat volt megfigyelhető, melyet $T_2N_0M_0$ stádiumba soroltunk be [23, 24]. Regionális nyirokcsomóduzzanatot nem tapintottunk.

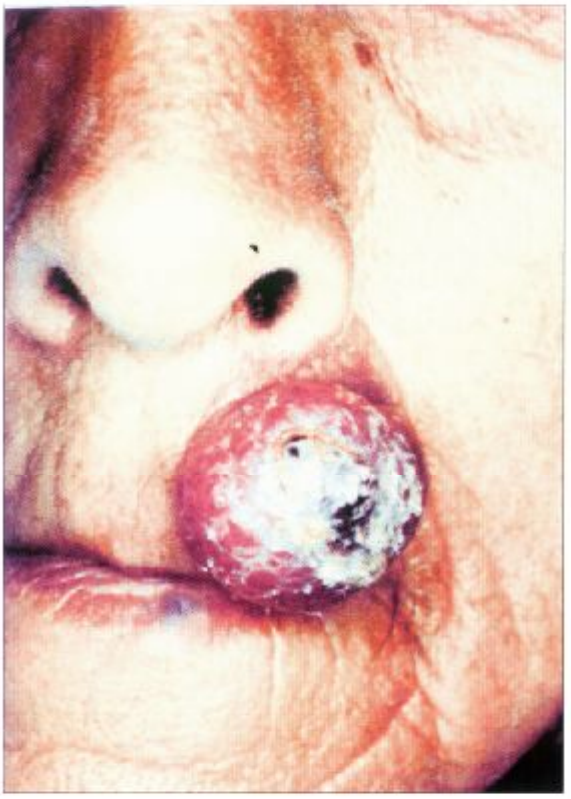
A beteg a javasolt sebészi eltávolításba és sugárterápiába nem egyezett bele. Ezért a daganat kezelését cryosebészeti (Erbokryo OP) módszerrel végeztük. A daganatsejt-szóródás elkerülésére a próbakimetszés cryofixált állapotban történt. Ezután a kezelést cryoszondás és cryospray-módszerrel folytattuk [23].

A fénymikroszkópos és az immunhisztokémiai eredmények alapján az ajak daganata Mcc volt.

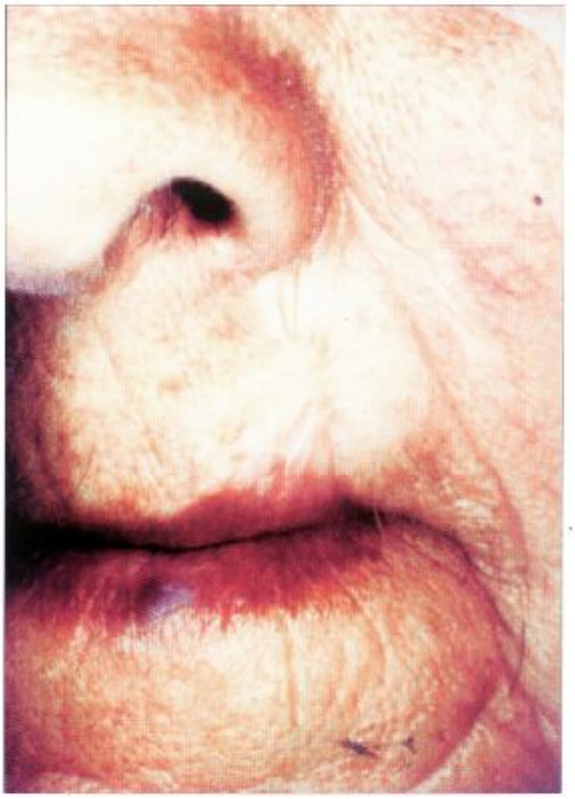
A daganat regionális és távoli áttétképzési hajlama miatt további vizsgálatokat végeztünk, de a röntgenlelet alapján a csontmetastasis kialakulását kizárhattuk, és távoli metastasis jelenléte sem volt igazolható.

Ezt követően a beteget kéthavonta ellenőriztük másfél évig, majd félévenként újabb másfél évig. A három év alatt a beteg rendszeres ellenőrzése során daganat- és tünetmentességet állapítottunk meg *(1b. ábra)*. Ezt követően a beteg a legközelebbi kiírt ellenőrzésen nem jelent meg. Utólagos keresés alapján megtudtuk,

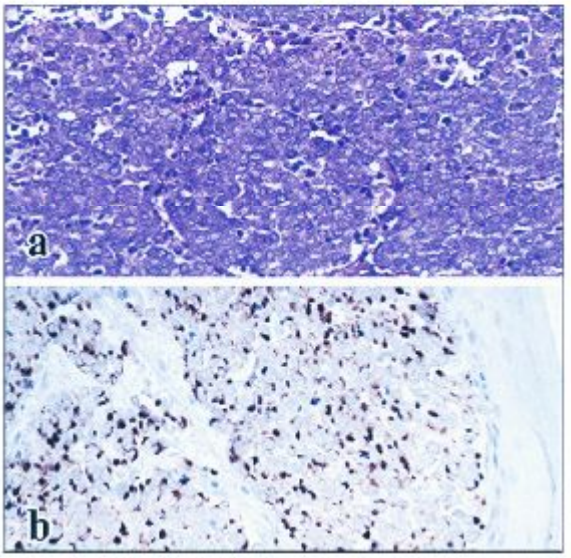
Érkezett: 2005. október 7.
Elfogadva: 2006. január 17.



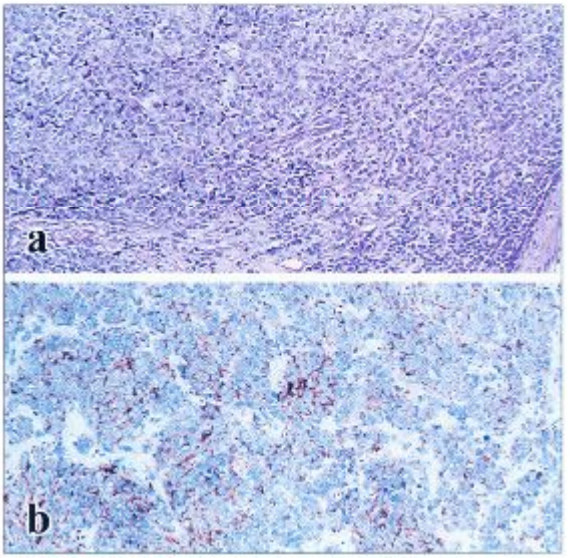
1a. ábra. A felső ajak felett a bőrben kialakult Merkel-sejtes carcinoma



1b. ábra. Gyógyult állapot a Merkel-sejtes carcinoma cryosebészi terápiája után (1 év)



2. ábra. Ajak: Merkel-sejtes carcinoma
a) A dermist anaplasiás, kereksejtes tumor szúri be. Hematoxilin-eozin; 40x.
b) A daganatsejtek cytoplasmájában citokeratin 20-ellenes savóval diffúz pettyezett festődés; 40x.



3. ábra. Tonsilla: rosszul differenciált carcinoma
a) Anaplasiás, kereksejtes tumor a hám alatt. A cytologiai sajátosságok az ajak Merkel-sejtes daganatára emlékeztetnek. Hematoxilin-eozin; 20x.
b) A daganatsejtek cytoplasmájában citokeratin 20-ellenes savóval gócos, néhol pettyezett jellegű festődés; 20x.

hogy a beteget hét évvel az általunk alkalmazott cryoterápia után, 86 éves korában a Kecskeméti Kórház Fül-orr- gégészeti osztályán operálták a mesopharynx tonsillaris eredetű daganata miatt. A kiindulási helyen (felső ajak) recidívát nem írtak le. A műtétet a rossz általános állapot és az idős kor ellenére a nagy térfoglaló tumor és a következményes fulladásos panaszok abszolút indikálták. Ennek megfelelően a sebészi beavatkozás palliatív célból történt.

A tonsillaris tumor fénymikroszkópos vizsgálata neuroendokrin tulajdonsággal rendelkező anaplasticus carcinomát mutatott *(3. ábra)*. A később elvégzett immunhisztokémiai vizsgálatok alapján a tonsillából származó daganatszövet morfológiailag hasonlított a korábban az ajakon észlelt Mcc-hoz. Arra a kérdésre, hogy a később megjelent tonsillaris tumor a felső ajak daganatának metastasisa, vagy új primer daganat, genetikai vizsgáló módszerek segítségével kaptuk meg a választ.

A klinikai és a genetikai vizsgálatok a metastasis lehetőségét kizárták. A genetikai vizsgálat eredménye alapján a tonsillában megjelenő tumort a genetikailag módosult mező második tumoraként (ún. „second field tumour") határoztuk meg [21].

A beteg a műtétet követő 20. napon, otthonában halt meg. A halotti bizonylatban a mesopharyngealis tumor mellett halálokként heveny keringési és légzési elégtelenséget tüntetett fel a családorvos.

Megbeszélés

A Merkel-sejtet 1875-ben írta le Friedrich Sigmund Merkel. A sejtek ectodermalis eredetűek, így a bőrben, a körömben és az oralis mucosában is megtalálhatók [7, 26]. A Merkel-sejt felelős egy ritka, rosszindulatú daganat – a Merkel-sejtes carcinoma – kialakulásáért, melyet *Toker* [25] írt le először 1972-ben.

A Mcc klinikai képe változó. A bőrben kialakuló Mcc gyakran körülírt, a felszínből kiemelkedő, domború, jól körülhatárolt, de fájdalmatlan tumorként jelentkezik először. Mély rózsaszín, vörös vagy kék színű, felszíne gyakran erythémás, teleangiectásiás [10, 12, 26]. Egyes szerzők [15, 19] a daganat lassú növekedését írják le. Ez a növekedés a későbbiekben felgyorsulhat. Ennek megfelelően más szerzők gyors növekedésű daganatként jellemzik [2, 10, 27] a Mcc-t.

A Mcc ritka előfordulású daganat. Klinikánkon 1970–2004 között 158 056 új beteg jelentkezett, közülük 23 807 beteget az Orális Medicina Részlegre irányítottak. Ebből 4621 esetben rosszindulatú daganatot diagnosztizáltunk. A 34 év alatt egy betegnél volt a diagnózis Mcc.

A daganat lokalizációját tekintve leggyakrabban bőrben: a fej-nyak tájékon és a végtagokon alakul ki [2, 12, 14]. *Hitchcock és mtsai* [9] 400 Mcc esetét vizsgálva a következő előfordulási sorrendet figyelték meg: fej-nyak régió (48,9%), alsó végtag (30,2%), felső végtag (15,6%), törzs (3,8%). Ennek a vizsgálatnak az eredményei alapján az esetek közel felében a Mcc a fej-nyak régióban jelenik meg. *Pitale és mtsai* [14] vizsgálata alapján a fejnyaki Mcc-k 9%-a fordul elő az ajakon vagy perioralisan. *Vigneswaren és mtsai* [26] tíz olyan Mcc-ről számoltak be, mely ajakon fordult elő, ebből csupán két esetben jelent meg a daganat a felső ajakon.

Az általunk kezelt Mcc a leggyakoribb lokalizációs csoportnak megfelelően a fej-nyak régióban, a felső ajak körében alakult ki.

Több szerző [5, 6, 8, 26] fontos etiológiai tényezőnek tartja a daganat kialakulásában a napsugárzást, az UV-sugárzást. Ezt a megfigyelést az is alátámasztja, miszerint a Mcc gyakran más, bőrön kialakuló praecarcinomás elváltozással, malignus daganattal együtt jelentkezik, így keratosis actinica, laphámrák, melanoma malignum és basalioma szinkron vagy metakron előfordulását is leírták [3, 6, 8].

A napsugárzás etiológiai szerepét a betegünk anamnézise is igazolta, mert elmondása szerint hosszú éveken keresztül mezőgazdasági munkát végzett.

A Mcc nagyon agresszív viselkedésű daganat. Nagy százalékban fordul elő lokális recidíva, regionális nyirokcsomó-áttét vagy távoli metastasis. Ezek előfordulását a legtöbb szerző a primer daganat diagnosztizálását követő két éven belüli időpontban írja le. *Meland és Jackson* [11] 91 Mcc-t vizsgálva az esetek 35%-ában figyelt meg lokális recidívát, 41%-ában regionális nyirokcsomómetastasist, 18%-ában távoli áttétet. *Murphy és mtsai* [13] ennél is gyakoribb lokális recidívát (40%), regionális nyirokcsomó-metastasist (55%), valamint távoli áttétet (36, 3%) írtak le. *Shaw és Rumbell* [18] pedig 67%-ban figyeltek meg lokális recidivát, amit rossz prognosztikai jelnek tartanak. A távoli szervekbe adott áttét leggyakrabban a májban, a csontban, az agyban, a tüdőben és a bőrben jelenik meg [16].

Az általunk diagnosztizált és kezelt primer daganat cryoterápiáját követően a rendszeres kontrollt három éven keresztül végeztük. Ez idő alatt sem lokális recidívát, sem regionális- nyirokcsomó-áttétet nem tapasztaltunk, a beteg tünetmentes volt. Az irodalomban leírt agresszív viselkedésnek ellentmond az általunk diagnosztizált és kezelt Mcc.

A pontos diagnózis felállításában első lépés a fénymikroszkópos vizsgálat, melynek eredménye a felső ajak tumoránál a következő: a daganatszövet a dermisben helyezkedik el, az epidermistől élesen elhatárolódik *(2a. ábra)*. A tumorsejtek kötegeket képeznek, monomorphak, anaplásiásak, a sejtmag kerek, a chromatinállomány finoman pettyezett. A sejtmagvacska kicsi; egy sejtmagban gyakran két-három sejtmagvacska látható. A citoplazma gyér. A mitózisszám magas (6-10 osztódás/nagy nagyítás).

A kórszövettani vizsgálat során csak hematoxilin-eozinos festéssel gyakran nehezen különböztethető meg a Mcc a malignus lymphomától, az amelanotikus melanomától, a kis sejtes tüdőcarcinoma metastasisától [12, 26]. Éppen ezért ma már elengedhetetlennek tartják a fénymikroszkópos diagnózis mellett az immunhisztokémiai

vizsgálatot. A neuroendokrin daganatok közül a Mcc immunhisztokémiai képére a paranuclearisan pettyezett citokeratin 20-pozitivitás jellemző [17, 26]. A mi esetünkben az immunhisztokémiai vizsgálat citokeratin 20 savóval paranuclearis pettyezett pozitivitást mutatott *(2/b. ábra)*, a daganatsejtek chromogranin savóval is reagáltak. A synaptophysin, a TTF-1 (tüdőrák marker), a HMB-45 (melanoma marker), valamint a lymphoma-markerek negatívak voltak.

Esetünkben a fénymikroszkópos és a később elvégzett immunhisztokémiai vizsgálat azt igazolta, hogy mind a felső ajak, mind a tonsilla palatina daganata *(3a, b. ábra)* a ritka előfordulású Mcc. A primeren a felső ajakon észlelt bőrdaganat szokatlan klinikai-biológiai viselkedése miatt a fénymikroszkópos és az immunhisztokémiai eredményeken túl genetikai módszerrel is kiegészítettük a klinikai és a szövettani eredményeket.

A hét évvel később kialakult tonsillaris tumor késői megjelenését feltehetően a cryosebészeti kezeléssel kiváltott immunológiai válasz magyarázhatja [1, 22, 23].

A daganatok klinikopathológiájának megfelelően mind a két tumor elhelyezkedése (ajak-tonsilla), mind a két daganat megjelenése között eltelt idő megkérdőjelezi a metastasis lehetőségét. A genetikai vizsgálat eredménye alátámasztotta a klinikai álláspontot, mely szerint a tonsillaris tumor nem metastasis. A két daganatos szövet genetikai állományának nagy százalékú egyezése miatt azonban az új primer tumor lehetőségét is kizártuk. Így a klinikai, az immunhisztokémiai és a genetikai vizsgálat alapján az időben később megjelenő daganatot a genetikailag módosult mező második daganatának, ún. „second field tumour"-nak tartjuk [21].

Differenciáldiagnosztikailag a fej-nyak régióban, perioralisan kialakult Mcc esetében basalioma, melanoma malignum, laphámrák jön szóba [20], míg intraoralis elhelyezkedésű daganat esetén gondolni kell pyogen granulomára, óriássejtes epulisra és fibromára is [4, 17].

A felső ajak Mcc-jának diagnosztizálásakor több kórkép szóba került differenciáldiagnosztikai szempontból. A klinikai diagnózis felállításakor kezdetben az elváltozást laphámráknak ítéltük, de a keratoacanthoma és a granuloma pyogenicum diagnózisának a lehetőségét sem zártuk ki. Mcc-ra az extrém ritka előfordulása miatt nem gondoltunk.

A praecancerosisok közül a keratoacanthoma klinikai képe hasonlít leginkább az általunk vizsgált és kezelt tumor klinikai képéhez. A keratoacanthomára utaló centralis szaruképlet azonban hiányzott.

A szóba jöhető granuloma pyogenicum esetében a gyakori spontán vérzés miatt panaszkodnak a betegek. A daganat ilyen jellegű panaszt nem okozott. Így első lépésben klinikai diagnózisként a laphámrákot határoztuk meg, mivel előfordulása jóval gyakoribb a szájüregi daganatok esetében, mint a Mcc előfordulása.

A Mcc terápiájában valamennyi szerző [5, 9, 11, 17, 18, 19, 20, 26] az első választandó eljárásként a primer daganat széles sebészi excisióját javasolja. A primer daganat eltávolítása mellett egyes szerzők [18, 20] a radikális nyaki dissectiót feltétlenül ajánlják, mások [5] csak abban az esetben, ha a regionális nyirokcsomók érintettségének a gyanúja áll fenn.

A daganat sugárérzékenysége miatt a sugárterápia bizonyos esetekben indokolt lehet mind kiegészítő, mind palliatív terápiaként is. Több szerző [4, 9, 10, 18, 20] javasolja a sebészi eltávolítás utáni kiegészítő sugárkezelést adjuváns kezelésként.

A daganat kemoszenzitív tulajdonsága ugyan igazolt, de a kemoterápia alkalmazását a Mcc kezelésében csak kevés szerző [16] ajánlja. Egyrészt csak palliatív terápiaként, amikor a daganat lokális sebészi eltávolítására nincs lehetőség, másrészt idős, legyengült betegeknél, vagy távoli metastasis kialakulása [4] esetén. A primer daganat kemoterápiás ellátását több szerző [10, 18] nem tartja megfelelően hatásosnak.

A betegünk esetében első választandó terápiaként a sebészi eltávolítás mellett döntöttünk, azonban a beteg ezt visszautasította, és a sugárterápiát mint alternatív kezelést sem fogadta el. Ezért a primer daganat eltávolítását cryosebészi módszerrel végeztük.

Ez ideig Mcc cryosebészi kezeléséről sem a hazai, sem a külföldi irodalomban közlemény nem jelent meg. Az idős, cardiorespiratoricus betegségben szenvedő beteg (rizikóbeteg) esetében azért is volt előnyös a döntés, mert ez a módszer terheli meg legkevésbé a beteget és a szervezetet, valamint nem jár daganatsejt-szóródással, maradéktumor vagy recidiva esetén pedig akkor is megismételhető, amikor már egyéb kezelési módok (sebészi, sugár-, kemoterápia) okozta szövődmények nem teszik lehetővé az újabb beavatkozást [23]. Esetünkben az is a cryosebészi kezelés mellett szólt, hogy így a felső ajak funkcionális stabilitása is megmarad, és a kozmetikai eredmény is jobb, mint a nagyobb szöveti feláldozással járó sebészi kezelésé.

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Merkel Cell Carcinoma

Merkel cell carcinoma (Mcc) is a very rare, malignant, neuroendocrine tumour. Mcc has an aggressive behavior, local reccurence, and regional or distant metastasis generally develop within a short period of time.
At the Oral Medicine Departement 158,056 patients were treated between 1970 and 2004. A single case of Mcc was diagnosed, in a 79-year-old woman. The tumour was localized to the upper lip. After successful cryosurgery and a 7-year tumour-free period, a new tumour developed in her palatine tonsil. It was an anaplastic carcinoma with neuroendocrine features, raising the possibility of a late haematogenous metastasis, a second field tumour, or a second primary tumour. The clinical, histological, immunhistochemical and genetic findings suggested that the tumour of the palatine tonsil is a second field tumour.

Key words: Merkel cell carcinoma, cryotherapy, second field tumour, immunhistochemical study, differential diagnosis

III.

FOGORVOSI SZEMLE ■ 102. évf. 1. sz. 2009. 7–11.

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Implantáció a szájüregi rák miatt sugárkezelésben részesült betegeken

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A szájüregi rák műtéti és sugárkezelése utáni rehabilitáció célja a rágó- és beszédfunkció, valamint az arc esztétikumának helyreállítása. A protézis elkészítését nehezíti a műtét után megváltozott anatómia és az irradiáció következtében kialakult szájszárazság, szájzár, a lágyrészek és az állcsontok szövettani elváltozásai. A fogászati implantátumok nagymértékben javítják a fogpótlások és obturátorok elhorgonyzási és megtámasztási lehetőségeit. Az állcsontokat érintő sugárterápiát korábban az implantáció kontraindikációjának tekintették. A tanulmány célja az implantáció eredményességének vizsgálata szájüregi rák miatt sebészi beavatkozáson és sugárterápián átesett betegek esetében. Szerzők kilenc beteg állcsontjába összesen 23 implantátumot helyeztek. Huszonegy műgyökér (91,3%) osszeointegrálódott és funkcionál gyulladás vagy diszkomfort érzés nélkül. Tanulmányuk azt mutatja, hogy a dentális implantátumok bővítik a szájüregi rák miatt sugárterápiában részesült betegek protetikai rehabilitációjának eszköztárát.

Kulcsszavak: szájüregi rák, sugárterápia, implantáció, osszeointegráció, protetikai rehabilitáció

Bevezetés

A szájüregi daganatok terápiájában a sebészi ellátás mellett jelentős szerepet kap a sugárterápia. A tumor méretétől, elhelyezkedésétől, szövettani differenciáltságától, illetve nyaki nyirokcsomó vagy távoli áttét jelenlététől függően szükségessé válhat kombinált terápia is. A sebészi beavatkozás során a daganat elhelyezkedésének megfelelően olyan anatómiai képletek részleges vagy teljes eltávolítása is elkerülhetetlenné válik, mint az ajak, a nyelv, a maxilla, a mandibula, a fogak. Különböző élettani funkciók, mint a beszéd, a rágás, a nyelés jelentős mértékben károsodnak. Az állcsont- és lágyrész-defektusok esztétikai problémához is vezetnek [9]. A szájüregi daganatműtéten átesett betegeknél kiemelt jelentőségű a protetikai rehabilitáció a beszéd- és rágófunkció, valamint az esztétikum helyreállítása céljából. A megváltozott anatómiai viszonyok következtében sokszor csökken a megtámasztás és elhorgonyzás lehetősége. A sugárterápia számos mellékhatása közül a szájszárazság, az esetlegesen fellépő szájzár és az állcsontokban végbemenő szövettani változások hatnak leginkább kedvezőtlenül a protetikai rehabilitációra és annak sikerességére [13].

A dentális implantátumok térhódításával azonban új lehetőségek kínálkoznak mind az elvesztett fogak pótlására, mind a hagyományos és speciális fogpótlások elhorgonyzására. Az implantáció eredményességét különböző rizikófaktorok csökkentik, melyek közül a rossz szájhigiéné, a dohányzás és a rendszeres alkoholfogyasztás a szájüregi rák kialakulásának fontos etiológiai tényezői. A sugárterápia következtében az állcsontokban csökken az oszteoblaszt és oszteoklaszt aktivitás, valamint a véráramlás, és emiatt a műtéti terület megelőző irradiációja esetén a fogászati implantátumok alkalmazását korábban nem javasolták [10].

Tanulmányunk célja, hogy szájüregi rák miatt operált és sugárkezelésben részesült betegeknél implantátumokat alkalmazva vizsgáljuk azok osszeointegrációját és az implantáció eredményességét.

Anyag és módszer

Kilenc olyan beteget választottunk ki, akiket rosszindulatú szájüregi daganat miatt operáltunk klinikánk szájsebészeti osztályán 2001–2003 között, pre- vagy posztoperatív sugárterápiában részesültek, és a protetikai rehabilitáció részeként implantátumok kerültek behelyezésre. Páciensek között 6 férfi és 3 nő volt. Az életkor 26 és 59 év között változott, az átlagéletkor 45,8 év volt. Nyolc beteg rendszeresen dohányzott. A tumor lokalizációját tekintve 3 a szájfenéken, 3 a tonsillolinguális régióban, 2 a mandibuláris gingiván, és 1 a buccában helyezkedett el. A szövettani vizsgálat valamennyi esetben carcinoma epidermoidest igazolt. Négyen a műtétet megelőzően, öten ezt követően részesültek

Érkezett: 2008. március 10.
Elfogadva: 2008. december 4.

sugárterápiában, átlagosan 60 Gy dózisú besugárzást kaptak *(I. táblázat)*.

Az implantációt átlagosan két évvel a sugárterápia befejezése után végeztük el. Fontos kritérium volt, hogy az implantátumok behelyezését legalább egyéves, klinikailag tumormentes időszak előzze meg. A betegek minden esetben osztályos felvételre kerültek, a beavatprimér stabilitás hiánya miatt), egy másikat pedig 23 hónappal a terhelés megkezdése után (valószínűleg elégtelen szájhigiénés viszonyok miatt). A többi implantátum jelenleg is, 5 évet meghaladóan, sikeresen funkcionál.

A vizsgálat időszakában 3 rögzített, és 6 kivehető fogmű készült el, melyeket azóta megelégedéssel hasz

I. táblázat

	1.	2.	3.	4.	5.	6.	7.	8.	9.
Neméletkor (év)	♀/58	♂/42	♂/49	♂/59	♂/36	♀/26	♂/55	♂/49	♂/44
Daganat típusa	carcinoma epidermoides								
Lokalizáció	oldalsó szájfenék	elülső szájfenék	bucca	mandibula gingiva	tonsillo-lingualis	mandibula gingiva	elülső szájfenék	tonsilláris és mandibula moláris régió	tonsillo-lingualis
Resectio	alagútműtét marginális mandibula resectio tumor excisio	composite-műtét	maxilla és bucca resectio	szegmentális mandibula resectio	composite-műtét	hemimandibulectomia	composite-műtét	composite-műtét	composite-műtét
Rekonstrukció	nyelvlebeny	osteocutan csípőcsont	latissimus dorsi	osteocutan csípőcsont	osteofascio-cutan alkar	osteofasciocutan fibula	osteofascio-cutan fibula	osteofasciocutan fibula	osteocutan csípőcsont
Besugárzás/ dózis	posztop. 70 Gy	posztop. 50 Gy	preop. 66 Gy	posztop. 60 Gy	posztop. 70 Gy	posztop. 60 Gy	preop. 54 Gy	preop. 70 Gy	preop. 40 Gy
Implantátumok száma (db)	2	4	2	2	2	4	2	2	3

kozás napján intravénás, ezt követően négy napig orális antibiotikum kezelésben részesültek. Minden esetben az implantológiában járatos szakorvos végezte a beavatkozást. Pácienseinket részletes szájhigiénés tanácsokkal láttuk el. Naponta háromszor Corsodyl® szájöblítőt használtak. Összesen 23 Camlog® dentális implantátumot helyeztünk be, 21-et a mandibulába, kettőt a maxillába. Az implantátumok megterhelésére fél év után került sor.

Az osszeointegrációt klinikailag és radiológiailag vizsgáltuk. Az implantációt sikeresnek tartottuk, amennyiben a protézis elkészülte után egy évvel az implantátum nem volt mozgatható, perimplantitiszt vagy más gyulladásra utaló lágyrész-elváltozást nem tapasztaltunk, a beteg panaszmentes volt, valamint a röntgenfelvételen az implantátum körül a fiziológiásnál nagyobb csontpusztulás nem volt látható.

Eredmények

A 23 behelyezett implantátumból 21 (91,3%) sikeresen osszeointegrálódott, kettőt (8,7%) veszítettünk el: egyet néhány nappal a beültetést követően (valószínűleg a

ná nak pácienseink *(1/a–d. ábra)*. A radikális csonkoló műtétet követően az említett fogpótlások kielégítő rágófunkciót, érthető beszédet és megfelelő esztétikumot biztosítanak betegeink számára.

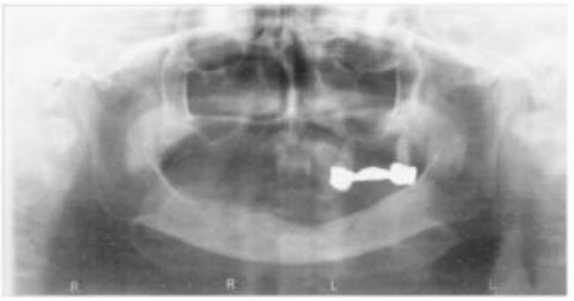
Megbeszélés

A szájüregi daganatok diagnosztikájának és terápiájának fejlődésével az idejében felfedezett és kezelt betegek életkilátásai lényegesen javulnak [5]. A műtétek során a szájüreg anatómiája nagymértékben megváltozhat, s ezáltal jelentősen romolhat a páciensek beszéde, táplálkozása, és nem utolsósorban az esztétikum [9]. A gyógyulás utáni években, évtizedekben a betegek társadalmi beilleszkedése komoly nehézségeket okozhat. A protetikai rehabilitáció jelentős fejlődésével, speciális pótlások, obturátorok segítségével javulhat a páciens beszéde, táplálkozása, a külső megjelenés. A pótlások rögzítéséhez azonban gyakran nem elegendőek a megmaradt anatómiai képletek. Az implantátumok segítségével fokozható a megváltozott környezetben a pótlások retenciója, stabilitása [6]. A szájüregi daganatos betegeknek viszont jelentős ré-

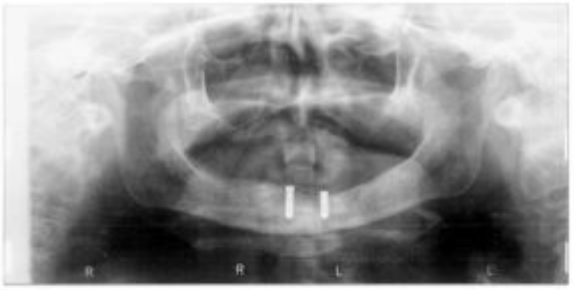
sze sugárkezelést kap a terápia részeként. A sugárkezelt állcsontba történő implantációt a nemzetközi irodalom vitatja.

1988-ban az egyesült államokbeli National Institutes of Health a sugárkezelést a műgyökér-beültetés kontraindikációjának deklarálta [10]. Azóta több szerző is végzett vizsgálatokat ebben a témában.

Granström [5] 107 sugárkezelt betegben 631 implantátum osszeointegrációját vizsgálta. Kimutatta, hogy a terápia módja befolyásolja azt: kemo- és sugárterápia kombinálva, valamint pre- és posztoperatív irradiáció együttesen, vagy nagy dózisú sugárterápia szignifikánsan csökkenti az osszeointegráció eredményességét.



1a. ábra.

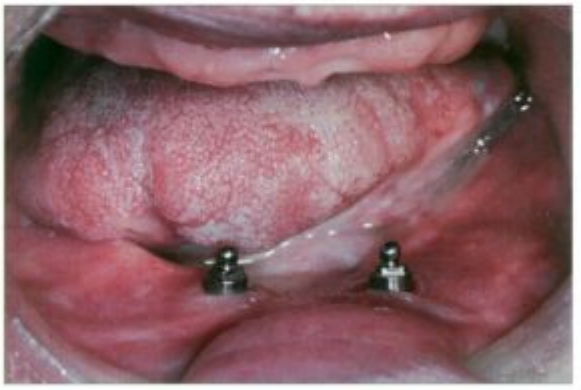


1b. ábra

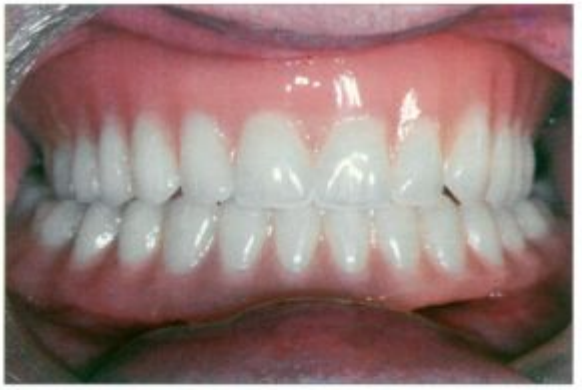
Taylor és mtsai [12] hasonló tanulmányokat végeztek, melyekben magasabb, mint 98%-os sikerességről számoltak be, azonban az alacsony betegszám miatt nem vonható le ebből a vizsgálatból általános következtetés.

Wagner és mtsai [15] 97,9%-ban, *Keller és mtsai* [7] 10 éves vizsgálati időszakban 99%-ban értékelték az osszeointegrációt sikeresnek beteganyagukban. Ezzel szemben *Marunick és Roumanas* [9], *Werkmeister és mtsai* [16] szignifikáns különbséget találtak az implantátum körüli lágyrész-gyógyulásban és az implantátumok túlélésében az irradiált és a nem irradiált csontok esetén.

Eckert és mtsai [2] külön vizsgálták az implantátumok osszeointegrációját: A mandibulába 89, a maxillába 22 és extraoralisan 13 műgyökér került beültetésre. Tapasztalataik alapján a sikeresség a mandibulában 99%, a maxillában 64% és extraoralisan 46% volt.



1c. ábra



1d. ábra

1. ábra: Oldalsó szájfenék tumor miatt részleges nyelv-, szájfenék- és marginális mandibula reszekciót végeztünk (1/a. ábra). Félvastag bőrrel történt nyelvfelszabadítás után a megváltozott anatómiai környezet hagyományos teljes kivehető protézis készítését nem tette lehetővé, ezért az alsó fogpótlás retencióját két implantátum beültetésével növeltük a radiológiai (1/b. ábra) és a klinikai képen (1/c. ábra) látható módon. Erre gömbretencióval elhorgonyzott kivehető fogpótlás készült (1/d. ábra).

Goodacre és mtsai [4] átfogó irodalmi áttekintést készítettek az implantátumok és az implantációs pótlások klinikai komplikációiról 217 közlemény eredményeinek összegzése alapján. Ezek közül 16 dolgozat foglalkozott a sugárterápia és az implantációs beavatkozás sikeressége közötti összefüggéssel. Különböző munkacsoportok összesen 217 implantátumot ültet-

tek be a felső és 1296-ot az alsó állcsontba előzőleg sugárkezelésben részesült betegeknek. Ezek közül a maxillában 56 (25%), a mandibulában 79 (6%) nem osszeointegrálódott.

Fontos kérdés a sugárkezelt csontok esetében az implantációs műtét időzítése az irradiáció után. *Marunick és Roumanas* [9] véleménye, hogy 2–5 évvel a sugárterápia után érhetjük el a legjobb eredményt, *Oelgiesser és mtsai* [11] 13–24 hónap várakozási időt ajánlanak.

Az implantátumok túlélési icejét szignifikánsan befolyásolja a sugárzás cózisa, valamint, hogy melyik állcsontba történt a beültetés [14]. *Yerit és mtsai* [17] 71 sugárkezelt betegnél 316 centális implantátum sikerességét vizsgálva megállapították, hogy az 5 éves túlélési idő esélye 91%, a 8 éves túlélési idő esélye 75%. *Franzen és mtsai* [3] 3–6 éves vizsgálati időszakban 95%-os, míg *Kovacs* [8] 6 éves túlélés figyelve 83,5%-os sikerességről számoltak be. *Visch és mtsai* [14] 130 sugárkezelt betegnél elemezte 446 implantátum túlélését a szignifikánsan befolyásoló tényezők (sugárdózis, lokalizáció) figyelembevételével. A 10 éves túlélést a mandibula esetében 85%-osnak, a maxillánál 60%-osnak találták. A sugárzás dózisát is vizsgálva szignifikánsan jobb eredményt kaptak 50 Gray alatti irradiáció mellett (84%), mint az ennél nagyobb dózissal besugárzott csont esetében (71%).

Egyes szerzők [1. 6] vizsgálatai kifejezetten arra irányulnak, hogy a kiegészítő hiperbárikus oxigénterápia hogyan hat az osszeointegrációra. Vizsgálatunk idején Magyarországon ez a kezelési mód nem volt elérhető, így tanulmányunk a hiperbárikus oxigénterápia esetleges előnyeivel nem foglalkozik.

Klinikánkon saját beteganyagunkon vizsgáltuk az irradiált csontba történő implantációt. Eredményeink alapján megállapíthatjuk, hogy a megelőzően sugárkezelt csontokban megfelelő műtéti technika, gondos szájhigiéné és antibiotikum védelem esetén az implantáció eredményessége igen magas, s bár kissé elmarad az egészséges csontba ültetett implantátumok osszeointegrációjának sikerességétől, a protetikai rehabilitáció tervezésekor a műgyökér beültetés lehetőségét mindenképpen érdemes szem előtt tartani.

Köszönetnyilvánítás
A szerzők köszönetet mondanak Molnárné Kiss-Dózsai Zsuzsának a felvételek elkészítéséért.

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