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

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Ph.D. Thesis

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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). However, 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 prosthetic 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.
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.
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.
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 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). Nowadays, 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 as 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, Department 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 questionnaires for head and neck
cancer patients and we considered 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.
<table>
<thead>
<tr>
<th>Categories</th>
<th></th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>53 (66.25%)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>27 (33.75%)</td>
</tr>
<tr>
<td><strong>Age at tumor treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td></td>
<td>9 (11.25%)</td>
</tr>
<tr>
<td>40-49.9</td>
<td></td>
<td>18 (22.5%)</td>
</tr>
<tr>
<td><strong>50-59.9</strong></td>
<td></td>
<td>26 (32.5%)</td>
</tr>
<tr>
<td>60-69.9</td>
<td></td>
<td>19 (23.75%)</td>
</tr>
<tr>
<td>&gt;70</td>
<td></td>
<td>8 (10%)</td>
</tr>
<tr>
<td><strong>Tobacco use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>60 (75%)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>20 (25%)</td>
</tr>
<tr>
<td><strong>Alcohol consumption</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>45 (56.25%)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>35 (43.75%)</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td>21 (26.25%)</td>
</tr>
</tbody>
</table>

Table 1. Epidemiological characteristics of study population
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.
<table>
<thead>
<tr>
<th>Categories</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor localization</td>
<td></td>
</tr>
<tr>
<td>maxilla</td>
<td>12 (15%)</td>
</tr>
<tr>
<td>tongue</td>
<td>9 (11.25%)</td>
</tr>
<tr>
<td><strong>floor of the mouth</strong></td>
<td><strong>21 (26.25%)</strong></td>
</tr>
<tr>
<td>facial defect (eye-ear-nose)</td>
<td>3-2-1 (3.75%- 2.5%-1.25%)</td>
</tr>
<tr>
<td>others</td>
<td>32 (40%)</td>
</tr>
<tr>
<td>Type of treatment</td>
<td></td>
</tr>
<tr>
<td>surgery alone</td>
<td>26 (32.5%)</td>
</tr>
<tr>
<td>radiotherapy alone</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td><strong>surgery and radiotherapy</strong></td>
<td><strong>41 (51.25%)</strong></td>
</tr>
<tr>
<td>surgery and chemotherapy</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>surgery, radiation and chemotherapy</td>
<td>9 (11.25%)</td>
</tr>
</tbody>
</table>

Table 2. Oncological characteristics of study population
Figure 5. Distribution of sites of primary tumor
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 epistheses 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%).
<table>
<thead>
<tr>
<th>Type of prosthesis</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obturator prosthesis</td>
<td>14 (12.5%)</td>
</tr>
<tr>
<td>Removable denture (lower and/or upper)</td>
<td>32 (28.57%)</td>
</tr>
<tr>
<td>Implant-retained removable denture</td>
<td>23 (20.54%)</td>
</tr>
<tr>
<td>Combined prosthesis</td>
<td>28 (25%)</td>
</tr>
<tr>
<td>Bridge (fixed, cemented prosthesis)</td>
<td>3 (2.7%)</td>
</tr>
<tr>
<td>Orbital epithesis</td>
<td>7 (6.25%)</td>
</tr>
<tr>
<td>Nasal epithesis</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>Aural epithesis</td>
<td>3 (2.7%)</td>
</tr>
<tr>
<td>Total number of prostheses</td>
<td>112</td>
</tr>
</tbody>
</table>

Table 3. Type of rehabilitation
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).

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

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

Table 5. Means, standard deviations and ranges after treatment, but before rehabilitation
<table>
<thead>
<tr>
<th>EORTC H&amp;N 35 QLQ</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (HNPA)</td>
<td>32.62264</td>
<td>7.908677</td>
<td>26-58.5</td>
</tr>
<tr>
<td>Swallowing (HNSW)</td>
<td>30.66038</td>
<td>6.421698</td>
<td>26-58.5</td>
</tr>
<tr>
<td>Senses (HNSE)</td>
<td>34.66981</td>
<td>15.43471</td>
<td>25-100</td>
</tr>
<tr>
<td>Speech (HNSP)</td>
<td>30.50943</td>
<td>8.650389</td>
<td>24.75-57.75</td>
</tr>
<tr>
<td>Social eating (HNSO)</td>
<td>32.37736</td>
<td>8.5978</td>
<td>26-65</td>
</tr>
<tr>
<td>Social contacts (HNSC)</td>
<td>28.67925</td>
<td>5.895806</td>
<td>25-55</td>
</tr>
<tr>
<td>Sexuality (HNSX)</td>
<td>32.54717</td>
<td>14.1548</td>
<td>25-75</td>
</tr>
<tr>
<td>Teeth (HNTE)</td>
<td>1.396226</td>
<td>.7162837</td>
<td>1-4</td>
</tr>
<tr>
<td>Mouth opening (HNOM)</td>
<td>1.509434</td>
<td>.7751586</td>
<td>1-3</td>
</tr>
<tr>
<td>Dry mouth (HNDR)</td>
<td>1.962264</td>
<td>.8311777</td>
<td>1-4</td>
</tr>
<tr>
<td>Sticky saliva (HNSS)</td>
<td>1.830189</td>
<td>.8023008</td>
<td>1-4</td>
</tr>
<tr>
<td>Coughing (HNCO)</td>
<td>1.301887</td>
<td>.6380531</td>
<td>1-4</td>
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<tr>
<td>Feeling ill (HNFI)</td>
<td>1.264151</td>
<td>.4863895</td>
<td>1-3</td>
</tr>
<tr>
<td>Pain killers (HNPK)</td>
<td>1.075472</td>
<td>.2666788</td>
<td>1-2</td>
</tr>
<tr>
<td>Nutritional supplements (HNNU)</td>
<td>1.150943</td>
<td>.3614196</td>
<td>1-2</td>
</tr>
<tr>
<td>Feeding tube (HNFE)</td>
<td>1</td>
<td>0</td>
<td>1-1</td>
</tr>
<tr>
<td>Weight loss (HNWL)</td>
<td>1.056604</td>
<td>.2332953</td>
<td>1-2</td>
</tr>
<tr>
<td>Weight gain (HNWG)</td>
<td>1.415094</td>
<td>.4974536</td>
<td>1-2</td>
</tr>
</tbody>
</table>

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)

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 et 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%) received 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 epiphyses were made for facial defects: 7 orbital (6.25%), 3 aural (2.7%) and 2 nasal (1.8%) epiphyses. 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). Otherwise 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.

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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.
X. REFERENCES


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

Abstract Merkel cell carcinoma was diagnosed in a 58-year-old Caucasian woman. The tumour was localised to the upper lip and was in stage 1B. After successful cryosurgery and a 3-year tumor-free period, a new tumour developed in her palate 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 unadjusted 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 upregulated, while 41 regions on chromosomes 1-4, 6, 8-9, 11 and 14-22 were commonly underrepresented. 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 distinct molecular patterns indicated a genetic relationship between the tumours and excluded the possibility that the tonsillary tumour was a metastasis. The findings suggest that a genetically altered field was the reason for the development of the tonsilar cancer; thus, it can be regarded pathogenetically as a second field tumour.

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 metastasis generally develop within a short period of time. Oropharyngeal metastasis is rare, and metastasis to the palatine tonsill has been described in only one case [21]. A personal or familial localisation of the MCC is very rare [11, 12, 13, 13, 20]. In 10 cases of MCC of the lip [18] and 14 cases of internal MCCs have been described [2, 14, 16, 20]. During the past decade, we treated and followed up an elderly woman with MCC of the upper lip. After a long tumor-free period, an anaplastic carcinoma with histologically features developed in her palatine tonsil, raising the possibility of a late hematogenous metastasis, a second field tumour or a second primary tumor.

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 most of the head and neck had undergone a change, perhaps due to carcinogen exposure, and was, therefore, more susceptible to the development of foc of malignant transformation. Organs in which field carcinisation has been described since then are the palatine tonsil, oropharynx, larynx, lung, esophagus, colon, skin, vulva, cervix, breast, renal pelvis, trachea and bladder [3-7, 10]. The determination of molecular patterns of first and second tumours has become a valuable tool to explore the
relationship between them: similar alterations indicate a metastasis, partly different alterations indicate a second or multiple tumours (3, 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 reconstituted at high density to DNA clones on a glass slide 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 frozen 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. The current chromosomal imbalances detected using CGH analysis were loss of 1p, 3p, 5q, 10q, 13q and 17p and gains of 1q, 3q, 6, 8q, 11q, 12, 14, 18, 20 (12, 24, 35, 36). 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 confirmed using real-time quantitative polymerase chain reaction (qPCR). Chromosomal loci were chosen in the same order and specific genes mapped to regions detected by CGH were also identified. The results suggest that a genetically altered field was the reason for the development of the tumour. Cancer, this, can be regarded pathogenetically as a second field tumour.

Materials and methods

Case report

Between 1970 and 2003, 4418 patients with malignant cutaneous tumours were treated in our clinic. One of these patients, a 52-year-old man, presented with a tumour on his upper lip. He was an acitve worker and never smoked. He was disturbed only about the aesthetics. The physical examination revealed a 2.3-mm, firm, compact mass in the skin of the upper lip on the left side. It was sharply separated from its surroundings and had a rather pleasant surface (Fig. 1). The tumour was classified as stage T1. Regional lymph nodes were not affected. The skin was excised and removed and the regional lymph nodes were also removed. The patient refused further therapy. A region of the tumour was biopsied and stained for immunohistochemical and in situ hybridisation studies.

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 tumour were essentially the same as observed 3 months earlier. The patient died of lung cancer on the 28th postoperative day. Autopsy was performed.

Sample preparation, labelling

Paraffin-embedded tissues (200–500 μg) were deparaffinised in xylene and washed with ethanol. DNA was purified
Fig. 2  Merkel cell carcinoma of the lip. A Small, monomorphous tumour cells fill the dermis arranged in nests and cords. The nuclei exhibit moulding. Haematoxylin/eosin ×40. B Chromogranin positivity of tumour cells ×400. C Paramacular positivity by protein 5.30 staining ×400

<table>
<thead>
<tr>
<th>Immunohistochemical markers</th>
<th>Lip tumour</th>
<th>Merkel tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS1A253</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cytokeratin</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Paramacular dot</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TTF</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EMA 45</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lymphoid markers</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 1: Immunohistochemical findings

Molecular DNA purification was performed using the DNA purification kit from Macherey-Nagel (Duren, 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 1 min, 8 cycles of 94°C denaturation for 90 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 SvaGreen was added to the mix (5X final concentration). Molecular
The following cycling protocol was performed in a real-time PCR instrument, RotorGene 2000 (Corbett, Sydney, Australia): denaturation at 95°C for 40 s, annealing at 60°C for 1 min and extension at 72°C for 30 s. The cycling was performed just before the reaction reached the plateau to avoid over-amplification of the products (usually in 28–22 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 Cy3-20UTP (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'-CCGACTGAGNANNAGTTGGG-G) was used in a 1 µM concentration [81]. 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 purified DNA was dried in a Speed-Vacuum.

Hybridisation, scanning, data processing

The biotinylated DNA was reconstituted in ChipIt’s 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 3300 gene-specific samples in duplicate in 200 µl using the Ventana hybridisation station (Ventana) at 42°C for 1 h [28, 29]. After hybridisation, the slides were washed twice in 0.2× sodium saline citrate at room temperature for 3 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 signals. Technical replicates on the same array were averaged. Data were excluded in case where technical replicates were significantly different. Normalisation was...
performed using the print-tip LOWESS method [35]. Next, we used the one-sample test to determine the genes to be regarded as changed in copy number. Logarithms were taken from each ratio to fulfill the test's requirement for a normal distribution. Genes for which the means of logarithms 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 0.05 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. A nanodrop forward and reverse primer, 1x RotorGene SYBR Green master, RotorGene, Hungary was used in the following protocol: denaturation for 10 min at 95°C, and 45 cycles of 30 s at 95°C, 30 s annealing at 60°C and 30 s extension at 72°C. Fluorescence signals were collected after each extension step at 72°C. Curves were analysed with the RotorGene software, using dynamic line and slope correction methods, generating data from cycles close to baseline. Primers were designed by using the ArrayExpress software (Applied Biosystems). Relative RNA was normalised to the Ct values obtained with the ciliary-fibroblastic retinoblastoma gene probe and calculated with the Pfaff method [25]. 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 normalizing 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 1p to be commonly over-represented across regions on 1p, 2q, 3p, 3q, 4q, 6q, 7q, 8p, 8q, 9p, 9q, 10q, 11q, 12q, 14q, 15q, 16q, 16p, 17p, 17q, 18, 19q, 20q, 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 differentially 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 tumour 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, 3p24 and 10p15, exhibited common gains, and 4 regions, 2p5, 13q12, 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>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome location</th>
<th>Forward primer</th>
<th>Reverse primer</th>
<th>Product size (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satellite 3-a-penta-censtrum 2</td>
<td>2p35</td>
<td>GCAGAAACGCGATCGGAAA</td>
<td>GGGCCACGTTGAGGAAA</td>
<td>69</td>
</tr>
<tr>
<td>Hypotylo pce marc</td>
<td>1q43</td>
<td>CACCAACGATGGCGAGCTT</td>
<td>CTGCTGATCGCTGAGAA</td>
<td>67</td>
</tr>
<tr>
<td>Zinc finger protein factor-α</td>
<td>1q14</td>
<td>GAGACGCCCAGAAGGTTT</td>
<td>CACAGTGATGACACGTC</td>
<td>66</td>
</tr>
<tr>
<td>Androgen receptor (dioxygen-soluble receptor)</td>
<td>12p12</td>
<td>GGAGACGCCCAGAAGGTTT</td>
<td>CACAGTGATGACACGTC</td>
<td>66</td>
</tr>
<tr>
<td>Cardiac muscle binding protein C</td>
<td>11p11.2</td>
<td>GACACGACTGGACACGTC</td>
<td>CTGCTGATCGCTGAGAA</td>
<td>69</td>
</tr>
<tr>
<td>PTP</td>
<td>15q14</td>
<td>CCAGAGGACCGAGACGTC</td>
<td>CACTGATGACACGTC</td>
<td>66</td>
</tr>
<tr>
<td>Sibliny XA</td>
<td>13q23</td>
<td>GACACGACTGGACACGTC</td>
<td>CACTGATGACACGTC</td>
<td>66</td>
</tr>
<tr>
<td>P53 similar to phosphatidyglykol transfer protein</td>
<td>13q14</td>
<td>GACACGACTGGACACGTC</td>
<td>CACTGATGACACGTC</td>
<td>66</td>
</tr>
</tbody>
</table>
Table 1: Common and individual gains and losses of Nervel cell carcinomas and the similar tumour detected using comparative genomic hybridization

<table>
<thead>
<tr>
<th>Deletion</th>
<th>Amplification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both tumours</td>
<td>1p36, 1p11, 1p13, 1q21, 33, 1q12, 2p23, 10q15, 1q22, 3q4, 2q13, 3p11, 2, 1q5, 3p21, 3q13, 3q14, 3q26, 18, 4q16, 4q22, 3p15, 1p1, 6q24, 7q21, 8p21, 9p24, 9p12, 9q34, 11p11.2, 11q13, 11q23.3, 13q24, 14q12, 15q25, 16p11.2, 16q24, 17p13, 17q22, 17q23, 18q11, 18q21, 19p13, 20q3, 21q22, 22q11, 22q12, 12q12.1, X inactivation</td>
</tr>
<tr>
<td>Merkel cell carcinoma</td>
<td>1p11.2, 1q12.3, 1q13, 1q21.1, 2p25, 12q12, 10q25</td>
</tr>
<tr>
<td>Mesoptaryx</td>
<td>1p34.2, 1q21.2, 1q22, 1q42, 2p55, 4q13.1, 4q21.2, 5q11, 5q12, 5q31, 8p14, 8q22, 21q11, 10q21.1, 14q13.1, 14q13.5, 14q13.2, 14q21.3, 15q1, 15q23, 17q21, 17q21, 20q13.1, 2q22.1, 2q22.3, 22q11</td>
</tr>
</tbody>
</table>

also analyzed. 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 chromosomal 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-amplifier, genomic DNA as template. Relative ratios were normalized 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 tumours 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 as shown for chromosome aberrations [12, 24, 34]. Reported recurrent chromosomal imbalances detected using CGH analysis were loss of 3p, 19q, 11p11 and 17p and gains of 1p, 3q, 5p and 8q [34]. In the present study, we also detected the loss of 3p and 17p, but some of the above-mentioned amplified regions could be confirmed (Table 5, Fig. 4). In another study, only 3 of the 10 MCCs exhibited common gains and losses, and they shared a gain of 8q21-8q22 and a loss of 4p16-ppter [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). Scolno et al. [24] detected losses involving the entire chromosome 10 or
Table 5  Apoptotic genes and tumour suppressor genes in regions with chromosomal aberrations specific to Merkel cell carcinoma or tumoral tumour. Apoptotic and tumour suppression genes in bold.

<table>
<thead>
<tr>
<th>Chromosome location</th>
<th>Apoptotic gene</th>
<th>Tumour suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Merkel cell carcinoma</td>
<td>1p11.2 (MCD2)</td>
<td>(MCD2, ART1, NR1A1, FNT1)</td>
</tr>
<tr>
<td>1q25</td>
<td>BLBC5</td>
<td></td>
</tr>
</tbody>
</table>

In metastasis

| 1p34.1-32.2 | FABP3 |
| 3q22-21 | ADRP3 |
| 5q11.1 (LOC145900) | |
| 6q7 | MCC |
| 6q31-32 | NF1 |
| 8q24 (CEACAM) | |
| 11p11.5 (KIAA1955) | MCM1 |
| 14q11-32 | SVA |
| 16q24-25 (LOC145900) | CBFA2F3 |
| 21q22.13 | RUNX1 |
| 25q11 | HIF1 | MV0114 |

Partial loss of the chromosome 10 long arm in one-third of the MCC cases they analysed with a possible loss of heterozygosity of 1q25, including the PTEN tumour suppressor gene [13]. 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 genes of chromosomes 1, 6, 16q and 20 were detected in 2 cases [12]. In our case, only two regions, 2p and 10p were consistently 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, 13c and 16q. Neither of the 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 15 MCCs exhibited a 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 chromosomal losses, we observed differences in gene copy numbers between the two tumours. From the results obtained by CGH analysis, we believe that the metastasis cancer and the MCC of the lip derived from the same genetically altered field; thus, the metastasis cancer can be regarded as a second field tumour. From the results obtained using CGH analysis, we hypothesised that Merkel cells in two adjacent anatomical sites, i.e. in the lip and metastasis, underwent same preneoplastic genetic alteration, and both tumours arose from a common cell clone. If our hypothesis is correct, the metastasis cancer may be regarded as a second field tumour.

Several oncogenes and tumour suppression 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 previously known. In this study, only those regions were determined that were located in 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 deletion regions were determined using hybridizations based on one-color cDNA. Therefore, DNA amplifying events, which could generate false positives, were not considered. In consequence of the above problems, we determined the reliability of the results obtained by the UCH microarray using real-time QPCR. Ten genes were selected to follow

Table 6  Confirmation of comparative genomic hybridisation data using quantiferon real-time polymerase chain reaction (QPCR). Only two loci losses could be confirmed. Gains are indicated in grey background.

<table>
<thead>
<tr>
<th>Microarray data confirmed using QPCR</th>
<th>Gene name</th>
<th>Accession no.</th>
<th>Chromosome location</th>
<th>Distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both tumours</td>
<td>5-phosphatase 2 (SDS3A2)</td>
<td>X74067</td>
<td>2p25</td>
<td>31724</td>
</tr>
<tr>
<td></td>
<td>Hepatocyte nuclear factor-3 alpha</td>
<td>U19449</td>
<td>1q12-q13</td>
<td>38032</td>
</tr>
<tr>
<td></td>
<td>Zinc finger protein</td>
<td>A020591</td>
<td>19q13.43</td>
<td>60450</td>
</tr>
<tr>
<td></td>
<td>Antigen receptor (tyrosine-protein receptor)</td>
<td>M23265</td>
<td>Xq12</td>
<td>63075</td>
</tr>
<tr>
<td></td>
<td>U2F protein</td>
<td>A300480</td>
<td>8q24.13</td>
<td>28464</td>
</tr>
<tr>
<td></td>
<td>EST, Highly similar to Phosphatidylinositol transfer protein</td>
<td>A083312</td>
<td>17q23</td>
<td>5836</td>
</tr>
<tr>
<td></td>
<td>Cyclophilin F9a, similarity XIA</td>
<td>M14816</td>
<td>1q23.34</td>
<td>70090</td>
</tr>
<tr>
<td></td>
<td>EST</td>
<td>N12765</td>
<td>1q14</td>
<td>3098</td>
</tr>
<tr>
<td></td>
<td>Cardiac myosin binding protein C</td>
<td>U91429</td>
<td>11p11.2</td>
<td>45310</td>
</tr>
</tbody>
</table>

Merkel cell carcinoma
the copy number changes by QPCR. Of the ten genes, one exhibited no changes in the copy number from testing using CGH microarray analysis in all cases. The single notified relative duplicate gene. Therefore, it was used as an internal control. The copy number 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 internal 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 delocations in seven cases for both tumours and two were confirmed for only MCC. Although the number of the tumours is limited, the findings are helpful for the development of new diagnostic and therapeutic strategies.

In summary, the partly different molecular patterns obtained using CGH and similar historical features and the close proximity to the primary tumours indicate that the tumour was a secondary field tumour. The common origin was further confirmed because of the presence of 

### References

II.
Merkel-sejtes carcinoma

DR. NAGY JUDIT*, DR. VAHNY BÉLA*, DR. SÖRÖS ISTVÁN*

A szerzők az esetismeretés kapcsán egy ritka előfordulású, neuroendokrin eredetű, rosszindulatú dégenást, a Merkel-sejtes carcinoma bemutatását lőzők ki célul.


A 79 éves nőbeleg felélen, aki esetleges carcinoma bőr készletéhez tartozó keretekben lévő szájgomba készletének használata érdekében került meg a szerzők felé. A nyári- és júniusi meghalt a beteg betegségének feltételei.

A klinikai vizsgálatok, immunhistokémiai és genetikai vizsgálatok eredményei alapján a legtöbb megfelelő diagnózis a gyanúkkal a műanyag modosult anyagokat tartjuk a specifikus tünetek.

Kulisszavak: Merkel-sejtes carcinoma, rosszindulatú dégenász, immunszoókémia, diffúz szőrőféle agyagkezelés

Bovezetés


A multimédiás képekkel illusztráltak a degenászát változatos, a rendellenesség és távoli metastázis is a melanoma és a rosszindulatú dégenaszis.

A Merkel-sejtes carcinoma a rosszindulatú dégenaszis, a kúria és a távoli metastázis.

Esetismeretés

79 éves nőbeleg a szájgomba kerestetett a Szegedi Tudományegyetem Általános Orvostudományi Ker Foggászati és Szajhegészet Klinikájának Orvosi Medicina osztályának kezelése. A nőbeleg a panasz a bőrön felállott, lágy, nem okozó, esetleges kialakulás és változása.

A beteg a járványosból és sugárzásból nincs cseméje. Ezért a beosztását a lézeres radioterápiát vagy a színtetisztítási módszerekkel végeznek. A dégenászis kezelésének előkészítése mellett a rendellenesség is megjelenhet, és a távoli metastázis kezelése sem volt igazolható.

Ezt követően a betegi állapot ellenőrzése további vizsgálatokat készítettünk, de a szövettani vizsgálatokat nem volt szükség.

Ezt követően a betegi állapot nem volt szükség. Utólagos keresés alapján megpróbáltunk...
1a. ábra. A lelki ajat felé nyúló bőr térségét jelűlő Merkel-sejtű carci-
noma

1b. ábra. Gyógyszerfűtés után a Merkel-sejtű carcinoma cryosezbészeti
terápia után (1 év)

2. ábra. A szabad érdeklődésre és gyakran védekezésre szükséges, teljes irányú érzékelésre nélkülözött személyekre szánt „zöld” anyag.

3. ábra. Tonsilla rózsol/differenciált carcinoma

3a. a) Anaplastás, kérülésestevektum slouszát. A cytoplazma-

tossagok az ajak Merkel-sejt 
carcinoma-emelés a.

3b. b) A diagnózist jellemezően a 20-30 x alatti gővös náhét cellagóló jelű lesődité, 20x.
Megbeszélés


Az állatkom kezdet McC allegerikorok lokalizációs porfikrak megfelelően a fej-nyak régióban, a felső ajak közéletben alakult ki. Több szerző [5, 8, 3, 26] pontos etiológiai tényezők ezenlevélű részben a sugrászat, az UV-sugrászat. Ez a megfigyelést az életet lezárja. Ragasztás az aCcgyakran hasznos, míg a MCC gyakran más, bőrön kialakuló cancromak elhelyezésével, malignus daganattal együtt jelentkezik, így kerátiómás bőr, lápréhárítás, melanoma malignum és baszáloma színben vagy metakron színben esik leható [8, 9, 8, 9, 8].

A McC-nyalagagyszerű szetpetet a betegünknézére is igazol, mert emormónzás szerint hosszú éveken keresztül mozzadható a munkában.


Az állatkom diagnosztizált és kezelt primer daganat agyagórája kivitelezése. A daganat a rendszeres törlésből is kivitelezett. Ez idő alatt nem lehetséges agyagórá tranzparenctezést nem tapasztaltunk, a beteg kimenetezett volt. Az kezelésben beleagyzó agyagórá viszkedésének, természetesen az állatkom diagnosztizált és kezelt MCC.

A pontos diagnózis felállításában elsődleges a fenyimkirokozsó vizsgálat, melynek eredménye a felső ajak lezárásánál a következő: a daganatot a sódorvagnban helyezték el, az epidermisből ellenesen elhelyezkéké. (2a. ábra). A tumorejektést követően az agyagórá valóban gyors és hatékonyan lecserélődött. A szövőkセルésnél feltett és a Mcc-nyalagagyszerű. A következő ábrán a fenyimkirokozsó diagnózis mellett az immunhisztokémiai
vizsgálatot. A neuronokban dagantak közül a Mcc immunhistokémiai képára a paranucleolusban, a dendritákban és citeratai 20 pozitivitás jellemző [17, 20]. A mi esetünkben az immunhistokémiai vizsgálat citeratai 20 savval paranucleolus pozitivitás mutatkozott (20 dB), a citeratai jelenlemchromagmar savon is leegyütthatott a sarkoplazmán, a 11-1 (Kdárrák), a HMB-45 melanomarker), valamint a lymphopenia markers negatívak voltak.

Esetünkben a fenylmiokrozoposis és a kézbe elégzett immunhistokémiai vizsgálat figyelte, hogy bármilyen ehető a planisplazia daganata (5a, 6a ábra) a ritka erejfordulási Mcc. A primer a fejelme ágokon és citeratai trópusokat szokolnak klinikai-biológiai viselkedése miatt a fenylmiokrozoposis és immunhistokémiai reorientáció konzentrálisan talajtestes módon is kiegészített a klinikai és a szervi adhatóványokat.

A hét évvel később kialakult tonsillitis tumor kezelésének lehetőségét a citoesóbiozis kezelésével kiváltott immunológiai változás megtörtént [1, 22, 23].

A dagantak klinikai patogenezis és megfelelően minden a kézben elhelyezkedés (ajak-tornás), mind a két gum citeratai megadott által a megbízható a metaanaliza. A genetikai vizsgálat eredménye a dystrofikus a klinikai számlapont, mely rendesen a tonsillitis tumor nem mellesül. A kéz dagantai széle genetikai állományának nagy szerepét és egyezményt mutat azonban az új primer tumor kezelését is származik, így a klinikai, az immunhistokémiai és a genetikai vizsgálat alapján az időben később megjelenő dagantakat a genetikai módosított, második dogaratok marad, ú.og. citeratai tumör-rak tartak [21].

Differentialdiagnosztikus alapja meg fejlődött négy általános patogenezis, melyben pigmentáló és sarkoplazmás egészséges miatt azonban az új primer kezelését is származik, így a klinikai, az immunhistokémiai és a genetikai vizsgálat alapján az időben később megjelenő dagantakat a genetikai módosított, második dogaratok marad, ú.og. citeratai tumör-rak tartak [21].

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Merkel Cell Carcinoma

Merkel cell carcinoma (Mcc) is a very rare, malignant, neuroendocrine tumour. Mcc has an aggressive behavior, local recurrence, and regional or distant metastasis generally develop within a short period of time.

At the Oral Medicine Department 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 palate. Mcc is an anaplastic carcinoma with neuroendocrine features, raising the possibility of a late haemangioendothelial metastasis, a second field tumour, or a second primary tumour. The clinical, histological, immunohistochemical and genetic findings suggested that the tumour of the palate was a second field tumour.

Key words: Merkel cell carcinoma, cryotherapy, second field tumour, immunohistochemical study, differential diagnosis.
III.
Implantáció a szájüregi rák miatt sugárkezelésben részesüli betegek

DR. NAGY JUDIT9, DR. SERES LÁSZLÓ10, DR. NOVÁK PÉTER11, DR. NAGY KÁLIAI12

Bevezetés


Anyag és módszer


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**Táblázat**

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**Besugárzás/ dozis**

| 70 Gy | 50 Gy | 60 Gy | 70 Gy | 60 Gy | 70 Gy | 60 Gy | 70 Gy | 60 Gy |

**Implantátumok száma (db)**

| 2 | 4 | 2 | 2 | 2 | 2 | 2 | 3 |
sze sugárkezelési kap a terápia részeként. A sugárkezelést állcsontba történő implantációit a nemzetközi irodalom vitatja.

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


mtsai [16] szignifikáns különbséget találtak az implantátum körüli légynéz-gyógyulásban és az implantátumok túlélésében az irritálás és a nem irritáló csontok esetén.


Taylor és mtsai [12] hasonló tanulmányokat végeztek, melyekben magasabb, mint 98%-os sikereségéről számoltak be, azonban az alacsony betegszám miatt nem vannak ebből a vizsgálatból állításos következtetések.


Goodacre és mtsai [4] átfogó irodalmi áttekintést készítettek az implantátumok és az implantációs pótlások kinézeti komplikációiról 217 közlemény eredményeihez. Különböző munkacsoportok összesen 217 implantátumot ültet-
tek be a felső és alacsonyabb előzőleg sugárzásokban részesült betegeknél. Ezek közül a maxillában 55 (25%), a mandibulában 79 (6%) nem összehasonlíthatók.


Az implantációs túlélési idejét szignifikánsan befolyásolja a sugárzás csoportja, valamint, hogy melyik alakzatot történ a beültetés [12]. Yang és mas [17] 71 sugárzott betegnél 318 centispécifik implantációs keresetében vizsgáltak meg, hogy az 5 éves túlélési aránya 91.7%, a 8 évességek idején az arány 80.7%. Fontos és mas [3] 6 éves vizsgálatok alapján 85%-os, míg Kovacs [8] 6 éves túlélési egyszerűsített arány 83.5%-os keresettet számolt be. Visszavonás és mas [14] 136 sugárzott betegeknél elemzett a 45 implantátum túlélését a szignifikáns beolvasásból és a vizsgált 8,7 éves átlagú sugárzást (61%)-ban számoltottak be. A sugárzásos dozis és a vizsgálva szignifikánsan jobb eredményt kapott a 50 Gray alatti irradiáció (84%), mint az 100 Gray alatti és annál magasabb gyakoriságot használt esetekben (71%).

Egyes szerzők [16] vizsgálati kifejezetten arra irányultak, hogy a tágas területű hiperbarikus oxigénterápiát hatékonyan hat az oszsi integrációra. Vizsgáltuk idején a Színpadon az a kezdődésre nem volt olvasható, így tanulmányunk a hiperbarikus oxigénterápiás esetleges előnyeivel nem lógazik.

Klinikai szempontján jól: belegazdagítottuk a vizsgált az irradiált esetek történő implantációban. Eredményekünk alapján megalapítjuk, hogy a megelőzőre sugárzott csoportban alacsonyabb mérlegelési arányt és jó klinikai eredményt találunk.

Irodalom