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Patients with head and neck cancer treated by radiotherapy: The impact of fixed dentures on wellbeing and oral health related quality of life.

Introduction

Head and neck neoplasms are defined as tumours in the upper aerodigestive tract. The tumours origin from different tissues such as the carcinomas arising from the epithelium, and sarcomas from bone, cartilage, fat, muscle, vascular, or hematopoietic tissues. Lymphomas are tumours in the lymphoid system, and melanomas arise from melanocytes, melanin-producing cells in the skin. The sites affected by the tumour are the lips, oral cavity, pharynx, larynx, and cervical oesophagus, the nose and paranasal sinuses, salivary glands, thyroid gland and parathyroid glands, and melanoma and non-melanoma skin cancers of the head and neck (1). Head and neck cancer is the fifth most common cancer worldwide with an estimated global incidence of more than 500 000 cases per year (2). Tobacco use and alcohol consumption are the most important risk factors for these cancers, while a subgroup is caused by viral infections. Patients with early-stage disease are treated by surgery or radiotherapy, whereas patients in advanced stages receive a combination of these modalities or concurrent chemotherapy and localized radiation. The five-year survival rate after treatment is around 40-50 % (3).

Patients with head and neck cancer treated by radiotherapy suffer from acute and long-term oral side effects. Oral mucositis, pain, dysphagia, and superficial opportunistic infections are common acute side effects that in most cases cease within one month after radiotherapy has been completed. However, long-term side effects like hyposalivation, impaired taste, and trismus may be life long conditions. Moreover, altered microbiological flora of the mouth, attenuated tooth enamel, and hyposalivation are risk factors for dental caries (4-6). Other hard tissue damages caused by radiotherapy are periodontitis, and more severely osteoradionecrosis of the jaws (7). The latter condition

is caused by poor vasculated bone. Teeth with poor prognosis should be extracted before radiotherapy begins, leading to impaired occlusion including dysfunctional aesthetics and mastication. The Swedish National Board of Health and Welfare regulations compensate extracted teeth with removable dental prostheses/dentures (8). However, using removable dentures in patients with hyposalivation after radiotherapy is complicated. Removable dentures retain poorly, or chafe the oral mucosa leading to pain in function. Also, there may be problems maintaining good dental and denture hygiene leading to dental caries and periodontitis.

To date, the impact of dental occlusion on these patients' quality of life is sparsely investigated. In one study, implant-retained mandibular overdentures in patients treated for oral cancers were followed over five years (9). Overall, the survivors' oral function and patient satisfaction were high and did not change. Impaired global health and quality of life were associated with concurrent comorbidity. Malnutrition, associated with increased morbidity and mortality, in patients treated for oral/oropharyngeal cancers was shown to impair physical functioning and hence quality of life (10). In this study dental status was poorly described, although dry mouth, pain in the mouth, and problems with social contact correlated well to malnutrition and fatigue. Speech after surgery was more impaired in patients with oral cancers than with oropharyngeal cancers because of loss of anatomically important articulatory structures leading to decreased quality of life. However, there are no prospective studies supporting better speech outcome after radiotherapy alone compared with surgery (11).

Therefore, the aim of this project was to evaluate the effect and cost effectiveness of prosthodontic rehabilitation on oral health related quality of life, general wellbeing, and nutrition in patients treated by radiotherapy, with or without combination of

chemotherapy or surgery against head and neck cancer.

Methods

Design and setting

In this project, an interventional case-control study will be undertaken in four middle sized counties in the south of Sweden. Based on the case control sample also a methodological study will be realized in order to test the measurements' validity and reliability, but also a descriptive qualitative content analysis study will be accomplished. All these measurements – called triangulation – are done in order to strengthen the case-control study as a power calculation is not relevant to do due to the restricted eligible/consecutive sample as well as the restricted time schedule. Finally, based on all available data, a cost-effectiveness analysis will be undertaken with the use of a decision analytic model.

Intervention

Standard treatment

In order to replace extracted teeth after radiotherapy, the standard treatment is temporary removable dental prostheses/dentures (partial or complete). Depending on the teeth remaining, those may be completely tooth or tissue supported, or tissue and tooth supported. Temporary partial dentures are completely out of acrylic. Efforts are made to design a self-cleansing partial denture that preserves the remaining teeth and oral structures. The chewing forces are distributed evenly over the entire remaining teeth and soft tissues. Oral health related quality of life in healthy patients wearing removable dentures has previously been shown (12).

Fixed dentures

The special treatment is to within a year after completed radiotherapy replace removable dentures with tooth- or implant-supported dentures. The special treatment will begin six months after completed radiotherapy, or later depending on the severity of the side effects. Tooth- and implant-supported dentures are accepted modalities in patients with total or partial edentulous (13, 14). Patients with head and neck cancers usually follow the dental implant protocol valid for healthy individuals (15, 16). However, the fixture installation will be within a year after finished radiotherapy, when the jaws are still well supplied.

Participants

The study will take place in four middle sized counties in the south of Sweden. The intervention will include 30 patients with head and neck cancer recruited from a Department of Maxillofacial and Oral Surgery (the City of Jönköping, Jönköping County Council), and from the Department of Orofacial Medicine (the City of Stockholm, Stockholm County Council). Another 30 patients with the same disease will be matched controls recruited from another Department of Maxillofacial and Oral Surgery (the City of Linköping, County Council of Östergötland) and from five Departments of Orofacial Medicine (the Cities of Kalmar, Oskarshamn, and Västervik, Kalmar County Council; the Cities of Ljungby, and Växjö, Kronoberg County Council). If possible but not necessary, those controls may be prosthodontically rehabilitated with temporary removable dentures. The retest described in data collection study one will include ten patients diagnosed with head and neck tumor. All patients in the retest will be residents in the County of Jönköping.

The inclusion criteria are patients with head and neck tumours considered to receive radiotherapy, with or without combination of chemotherapy or surgery, good oncological prognosis at baseline (≤T2). After referral from an ENT-specialist, those patients being diagnosed with dental infections and therapy planned for dental extraction(s) will be included.

The following general exclusion criteria will be applied: any communication problems; any comorbidity with poor prognosis; poor oncological prognosis (TNM-classification >T2) at baseline; imminent risk of recurrence; any technical, biological, or any other reasonable obstacle of treating patients with fixed dentures; and finally patients in the matched control group financing fixed oral prosthesis themselves.

Background data like sex, age, diagnosis, TNM-classification, hyposalivation, vertical jaw mobility, dysphagia, number and sites of extracted teeth, and weight will be investigated.

Study one – quantitative approach

Instruments

SF-36v2

SF-36v2 is a well established psychometric instrument with 36 items measuring eight domains of health-related quality of life: Physical function, physical role function, bodily pain, general health, vitality, social function, emotional role function, mental health. The two comprehensive indices – physical health and mental health - can be estimated for. The instrument is translated and validated into Swedish (17-19).

EQ-5D

EQ-5D is an instrument containing five items measuring mobility, self-care, pain, role function, and anxiety/depression. There is also one item considering change of health condition and a VAS scale for general health. This instrument is also translated and validated into Swedish (20-22).

Oral health impact profile (OHIP)

OHIP-14 is an instrument consisting of 14 items (23). It was designed to provide a comprehensive measure of the dysfunction, discomfort and disability attributed to oral conditions. Validated Swedish versions of the OHIP-14 are available (24, 25).

General oral health assessment index (GOHAI)

GOHAI is a 12-item instrument originally developed for use with older adult populations, although more recently it has been used with populations of younger adults. It measures oral functional problems and also assesses the psychosocial impacts associated with oral disease (26). A Swedish version has been validated (27).

The Jaw Functional Limitation Scale (JFLS-8)

The JFLS-8 was developed for assessing limitations in mastication, jaw mobility, and verbal and emotional expression. It is recommended for clinical and research use in patient groups with varying functional limitations of the jaw. The instrument has been tested for reliability and validity (28, 29).

The Orofacial Aesthetic Scale (OAS)

The OAS consists of seven separate aesthetic aspects of the face, teeth, lips, and mouth — devoid of psychosocial aspects. These seven items create the OAS summary score. There is also an eight item, global assessment of overall impact. A Swedish version has

been validated (28, 30, 31).

Data collection

The written consent among with the instruments will be distributed to the patients at the clinic at baseline (before any treatment), appendix 4. The completed documents will be returned to a research coordinator/dental assistant at the Department of Maxillofacial and Oral Surgery (the City of Jönköping, Jönköping County Council). Measurements and administration of the instruments after baseline follow the study protocol, appendix 13. The study protocol after completed radiotherapy states measurements at approximately 6 and 12 months respectively, or in severe cases after the prostheses have been used for one month. Those patients who receive the instruments by mail, will be requested to immediately respond to the instruments and return them to the research coordinator in attached envelopes (prepaid postage). A reminder is sent to the patient after one and two weeks if not responding. If necessary after another week, the patient will be contacted by telephone by the research coordinator. The patients weight will be recorded at the clinic, or self-reported by mail.

Data analysis

Parametric as well as non-parametric methods will be used in the statistical inference testing. Thus, for comparison between two groups the Student t-test and the Mann-Whitney U-test and between three groups or more Two-Way Analysis of Variance the Kruskal–Wallis One-Way Anova will be applied. For comparison of proportions between groups the Chi-square-test including standardized residual are to be used. For analysing changes over time the paired t-test or the Wilcoxon Signed Rank Test (for continuous variables) or the McNemar Test (for dichotomised variables) will be applied. For estimating relation between two continuous variables the Pearson test or Spearman

Rank Order Correlation will be used. For prediction, multiple and logistic regression are to be used and in order to adjust for confounding variables such as age logistic regressions also are to be used. The pre-chosen level of significance will be $p<0.05$ in all analyses.

Study two – qualitative approach

Interviews

A dental assistant experienced in methodological or subject experiences will interview the patients during approximately one hour twice. The dialogue will start with questions on general wellbeing, and then approaching oral health related quality of life. All the interviews will start with the question "How do you feel with regard to your health?", followed by "Can you tell me more?". Eventually the dental assistant asks, "How do you feel with regard to your mouth?" The interview will result in a detailed and exhaustive story from different point of views. All interviews will be recorded on minidiscs.

Data collection

The first interview will take place approximately six months after completed radiotherapy, and the second one after approximately 12 months.

Data analysis

Qualitative content analysis described by Hsieh and Shannon (32) will be used in analysing the interviews. Each interview will be listened to in order to gain a general understanding of the content. Any content relevant to the aim will be analyzed. The text will be condensed and labelled using codes, being careful not to change the core of the meaning units based on the aims. The codes will be matched and grouped into

categories in accordance with similarities and dissimilarities. The categories will be scrutinised for underlying meanings, which will generate a number of sub-themes that reflect the content. The sub-themes will eventually be grouped under a few comprehensive themes.

Study three – validity and reliability test

Data collection

Eight patients with head and neck cancer from the Department of Maxillofacial and Oral Surgery (City of Jönköping), and eight healthy controls from the Public Dental Service Clinic (City of Jönköping) from study one will be recruited consecutively. The instruments described in study one will be completed at baseline. After 1-2 weeks, those patients (n=16) will complete the same instruments to evaluate test-retest reliability and validity.

Data analysis

Reliability

Homogenity: Cronbach's alpha assesses internal consistency. According to Bland & Altman, Cronbach alphas of 0.70 to 0.80 are satisfactory for comparisons between groups, while an alpha of 0.90 is needed for clinical use.

Stability: Intraclass correlation coefficients (ICCs) with 95% confidence intervals are calculated per Shrout & Fleiss's ICC method based on a one-way analysis of variance (ANOVA). The concordance correlation coefficient (CCC) assesses reproducibility (temporal stability).

Validity

Content validity: Patients are asked, “Do you think the questions on aesthetics reflect the concerns you have with your mouth, your teeth and your tooth replacements (prostheses, crowns, bridges, and implants)?” They respond on a 0–10 VAS-scale with the anchors “very dissatisfied” and “very satisfied”.

Discriminative validity: Comparisons are made of OHIP-14 and GOHAI summary scores of each patient group with control groups and between patient groups. Relevant and statistically significant differences using t-tests and ANOVA are expected.

Convergent validity: Spearman rank order correlations (rho), assess convergent validity between (i) OHIP summary scores and self-reported health and (ii) OHIP subscale scores and subscale scores of the SF-36 and EQ-5D.

Study four – Cost-effectiveness analysis

Background

In order for a method in health- and dental care to be considered cost-effective, it has to be a decent relation between its extra costs and effects (no exact threshold value exist in Sweden). A cost-effectiveness analysis estimates the incremental cost-effectiveness ratio (ICER) of a method in comparison with the best option (33). The outcome measure can be of any (relevant) kind, but usually it is recommended to use quality-adjusted life-years (QALYs) which also is preferred by the Swedish Dental and Pharmaceutical Benefits Agency (34). QALY combines preferences for health states (QALY-weight) with the number of years of that health state.

In order to capture the full consequences of a treatment, it is often necessary to model future costs and effects into a longer time horizon. Even though these models cannot be seen as evidence, they can provide the most accurate estimate on the long-term cost-

effectiveness and they can furthermore handle uncertainty in order to provide a decision-maker with relevant information (35).

Data collection

Costs and effects of different prosthodontic rehabilitations, fixed and removable dentures, will be compared with costs and effects of radiotherapy of patients with head and neck cancer. Data on resource use will be gathered in the intervention and translated into costs, representing their best alternative use. Productivity loss of patients unable to work will be estimated using the human capital approach. The main outcome measure in the analysis will be QALY. QALY-weights are derived indirectly from the instruments EQ-5D and SF-6D, and directly from the EQ-VAS, all of which are analysed in Study one in this project. Other outcome measures that are more directly derived from oral health related quality of life will be used too in order to examine their relevance.

Data analysis

A decision analytic model will be created that simulates the costs and effects of a long time horizon. In order to take into account the uncertainty in the parameter estimates derived from the intervention study, the model is run probabilistic. This means that the analysis is repeated 1,000 times, and each time the parameters are selected randomly from the distribution of the uncertainty surrounding the parameters. In this way, the total statistical uncertainty is illustrated. The results will be presented with and without including productivity losses.

Ethics

Ethical approval for the study was obtained from the Regional Ethical Committee (EPN) at Linköping University (2012/200-31; 2013/66-32).

Relevance of the project

The relevance of the project will be increased knowledge about the impact of replacement of extracted teeth with fixed dentures on oral health-related quality of life and general wellbeing, in patients with head and neck cancer after radiotherapy. Patients' recovery after disease in terms of wellbeing and oral health related quality of life may improve by fixed teeth. Professionals will benefit since this is an evaluation of the treatment outcomes. The society will also find the results important in order to evaluate the rehabilitation of patients that has received extensive oncological care. This may lead to overall reduced costs for medical and dental care.

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