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Follow-up of nutrition requirements of patients with head and neck cancer

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Abstract
Background: Head and neck cancer constitutes approximately 5.1% of all cancers worldwide. In these patients, nutritional problems present an immense and complex range of challenges. If the patient cannot swallow and the gastrointestinal tract is functioning normally, nutritional support is mainly given with enteral nutrition. The most common way to administer enteral feeding is via a polyurethane nasogastric feeding tube (NGT) or via a percutaneous endoscopic gastrostomy (PEG) tube.
Objectives: Different cohorts of patients with Head & Neck cancer have been studied with the aim to identify patients requiring nutritional support and to improve the nutritional surveillance.
Methods: In study I, the predictive value of systematic inflammatory and metabolic markers was prospectively studied in 21 patients undergoing RT. In Study II, a retrospective study of 151 patients with a PEG tube is presented. Study III Consecutive patients (n=147) with HEAD AND NECK cancer who were seen for nutritional control were evaluated for factors contributing to body weight loss. Study IV Using a prospective design, interviews about what in life is influenced by disease and feeding (oral feeding, NGT or PEG) were conducted.
Results: In Study I, all patients lost body weight with the greatest loss at the end of RT. Highly sensitive C-reactive protein (hsCRP) increased during RT. In study II, complications were seen in 40% of the patients. In study III, lowest body weight was observed at 6 months after RT. In total, 82 patients with no evidence of residual tumour after treatment received enteral nutrition. Body weight loss was not found to be associated with post-operative infections or mortality. In Study IV, more than 45% of the patients manifested eating-related problems.
Conclusion: Body weight and CRP are valuable variables to follow-up. NGT should be regarded as the first choice of enteral nutrition in patients with an expected limited time of tube feeding, whereas in patients in which prolonged treatment is needed PEG can be the choice. The extended body weight loss after treatment indicates that a pre-treatment nutritional surveillance programme is important..

Keywords: Body weight loss, nutrition, enteral nutrition, head and neck cancer, percutaneous endoscopic gastrostomy (PEG), nasogastric feeding tube (NGT)

Introduction
Head and neck cancer comprises malignant tumours located in the lip, oral cavity, nose, sinuses, nasopharynx, oropharynx, hypopharynx, larynx, salivary glands and ear. Worldwide, 633,000 new cases per year are recorded [1] Nutritional problems affect many patients with head and neck cancer, problems that can lead to body weight loss and under nutrition that are caused by several dysfunctions (e.g., xerostomia, chewing and swallowing disturbances) [2, 3]. There is increased eating time and altered pleasure of eating [4]. Patients with dysphagia often avoid eating with others and many feel embarrassed at meal times [5]. Problems with eating may not only lead to the loss of eating food but also to the loss of eating with others, i.e. the social aspect of eating [6]. The positive meaning of food intake is changed for patients with Head and neck cancer treated with RT because they often experience physical problems with eating (e.g., chewing, opening of the mouth, loss of taste and experiencing pain) [7].
We designed 4 cohorts of patients with Head & Neck cancer with the aim to identify patients requiring nutritional support and to improve the nutritional surveillance.
Study I to explore the predictive value of systematic inflammatory and metabolic markers in patients with Head and neck cancer undergoing RT.
Study II to describe the incidence of fatal, severe and minor complications in patients with Head and neck cancer receiving PEG at a Government Medical College and hospital, Baramati,

Maharashtra; from March 2019 to December 2019. This study was conducted to describe the duration of PEG use and the long-term survival rate after PEG tube placement in patients with Head and neck cancer and to evaluate whether the complication rate is related to the method of PEG tube placement.

Study III to evaluate if therapeutic approach, tumour site, tumour stage, BMI, sex, age and civil status predict body weight loss in Head and neck cancer patients. Also, to examine the association between body weight loss on postoperative infections and mortality in a cohort of patients with Head and neck cancer during RT and up to 2 years after the termination of RT.

Study IV to describe patients with Head and neck cancer from the time of diagnosis up to 3 months after the termination of RT and to assess the patient's views on

1. Overall quality of life (QoL).
2. Aspects of life affected by the disease.
3. Aspects of life affected by having enteral nutrition or oral feeding.
4. Aspects of life affected by the feeding tube (NGT or a PEG tube).

Materials and methods

All patients were recruited from the Department of Otolaryngology and Head and neck Surgery, Government Medical College and hospital, Baramati, Maharashtra; from March 2019 to December 2019. The different anatomical sites of the head and neck cancer tumours were the lip, oral cavity, oropharynx, hypopharynx, nasopharynx, larynx and salivary glands.

Methodology

In study I: 45 patients were asked to participate. 29 agreed. 8 did not fulfil the study, leaving a final sample of 21 patients. They were enrolled shortly after receiving a Head and neck cancer diagnosis and were planned for RT. Exclusion criteria were a 5% pre-therapy body weight loss at diagnosis, diabetes mellitus, severe alcoholism, evident secondary malignant disease, having dementia or a psychiatric disorder.

In Study II, a total of 151 consecutive patients with Head and neck cancer who were candidates for PEG between the periods of nine months from March 2019 to December 2019; were included in this retrospective study on complications of PEG insertion. Indications for PEG were swallowing disorders and 5% body weight loss or more or advanced tumour stage with expected nutritional problems.

In study III: Totally, 200 patients with Head and neck cancer were offered nutritional follow-up at the hospital before start of RT. 147 agreed to participate.

In study IV: 69 patients were allocated at a weekly multidisciplinary team conference. 62 were eligible according to the inclusion criteria (i.e. patients planned to receive RT with a curative intention either as a single modality treatment or in combination with other treatment modalities). Of these 62 patients, 39 agreed to participate and 31 completed the whole study. Exclusion criteria were severe alcoholism, dementia or a psychiatric disorder.

Data Collection

Study I involved a follow-up between the time of diagnosis and 4 weeks after the termination of RT. During this period, serial (non-fasting) blood tests were collected and measurement of body weight and assessment of oral mucositis were performed according to the WHO scale for acute and subacute toxicity [8].

The schedule for assessments was pre-RT, at week 3 of RT, at the end of RT and within 2-4 weeks after the termination of RT. The following inflammatory and metabolic parameters were analysed in serum: highly sensitive C-reactive protein (hsCRP), an acute-phase protein used to determine small changes in concentrations of inflammation, with a reference range of <2 mg/L, albumin, a protein marker for inflammation and malnutrition, with a reference range of 35-48g/L and insulin-like growth factor 1 (IGF-1) (µg/L), a liver-synthesised mediator of growth hormone with a number of important metabolic effects and may be associated with malnutrition and systematic inflammation. IGF-1 is an age-dependent marker that decreases with increasing age. Plasma concentrations of the multifunctional peptide hormone ghrelin were also determined. Ghrelin is produced by endocrine cells in the stomach and has been reported to influence appetite, food intake and body weight [9, 10].

In study II: Data were collected from medical records during the above said period. The patients were retrospectively followed from diagnosis to June 2001 or until death. A data matrix was developed to collect diagnosis, TNM classification, stage, RT, surgery, date of insertion of the PEG, PEG related to RT and surgery, type of PEG method, indications for PEG, duration of PEG, deceased, PEG at time of death, survival after PEG tube placement and complications.

In study III: Nutritional data (BMI and body weight) were collected from the first clinical visit and up to 2 years after the termination of RT. Body weight was measured at initial diagnostic endoscopy, at start of RT, after 2 weeks of RT, after 4 weeks of RT, at the end of RT, 1 month after RT completion, at the time of surgery, 6 months after the termination of RT and 1-2 years after RT. In addition, information about nutritional support was collected: enteral nutrition or no enteral nutrition and when nutritional support was given to the patient in relation to the treatment.

In Study IV: SEIQoL-DW118, 119 was used, including a generic (SEIQoL-G) and a disease-related (SEIQoL-DR) part124, 125. For the purpose of this study, a third part was developed to capture patient perceptions and problems related to enteral nutrition (SEIQoL-EN). This version has not been used previously. However, it is used in the same way as the other two evaluated versions (SEIQoL-G and SEIQoL-DR).

The patients were interviewed at three time points: at start of RT (T1), 2 weeks after the termination of RT (T2) and 3 months after the termination of RT (T3). The patients were asked the following questions: In the SEIQoL-G the respondents were asked, "If you think about your life as a whole, what are the most important things, both good and bad, in your life at present, and which are crucial for your QoL?" The respondents could identify as many areas as they wanted. SEIQoL-DR and SEIQoL-EN were used in the same way but with different questions. For SEIQoL-DR, the question was, "If you think about the fact that you will/are being/have been treated for cancer, what things in your life are influenced, both positively and negatively, by the disease?" For SEIQoL-EN, the question was, "If you think about the feeding tube (NGT or PEG), what things in your life are influenced, both positively and negatively, by this experience?" Demographic and clinical data were collected and before each interview, the patient's body weight

was measured.

An overview of the design, samples, follow-up and data collection included in the studies are shown as follows.

Table 1: The age of the patients ranged from 28-83 years.

	Design	Samples	Follow-up	Data collection
Study I	Prospective Explorative	n=21	At diagnosis to 4 weeks after RT	Blood test
				Body weight
				Oral Mucositis
Study II	Retrospective Case Control	n=151	From PEG insertion up to 9.5 years or death	Matrix from medical records
Study III	Retrospective Non randomised	n=147	First clinical visit to 2 years after RT	Matrix from medical records
Study IV	Prospective Descriptive	n=39	At start of RT	Semi-structured interviews (SEIQoL)
			2 weeks after RT	
			3 months after RT	

Analyses

In study I, all patients could initially eat orally. The patients were divided into three clinical groups based on maximum body weight loss in relation to their initial body weight at diagnosis: <5%, 5-10% and >10%. Kruskal-Wallis test or the rank sum test was used for comparison between groups and linear regression was applied to determine the association between two variables.

In study II, treatment, duration of PEG use (in weeks), PEG complications and the PEG method are described. Chi-square analysis was used to compare the complication rate and the relation to the PEG technique used. PEG complications were categorised into three groups: fatal, severe and minor. Patients with fatal complications all died directly related to the PEG procedure or indirectly because of the PEG tube placement that was caused by a non-surgical origin. Severe complications signified major discomfort for the patient, such as subileus, septicaemia, indurations that were caused by the PEG, subcutaneous emphysema around the PEG incision, bleeding, peritonitis, major leakage, wound infections with a positive culture.

In study III, the data were stratified and analysed according to the therapeutic approach and outcome: either RT as single modality treatment with complete response (the RT group) or combined modality treatment with preoperative RT and surgery with radical surgery or no evidence of microscopic tumour (the RT & surgery group).

The lowest registered body weight loss during the entire study period was compared with the first pre-treatment body weight and defined as the maximum body weight loss expressed in per cent. Analyses of group differences were done with the unpaired t test or one-way ANOVA. Comparison of proportions between groups was done with Fisher's exact test.

To predict maximum body weight loss linear regression was used to analyse the relationship between selected variables (independent variables) and maximum body weight loss in percent (dependent variable). The independent variables used in the linear regression analysis were tumour stage (1=I, 2=II, 3=III, 4=IIII), tumour site (1=larynx, 2=oropharynx or oral cavity), surgery (1=no, 2=yes), sex (1=men, 2=women) and age (numerical).

In study IV, 115 semi-structured interviews were performed. Most interviews (n=93, 81%) were conducted at the Government Medical College and hospital, Baramati, but some interviews at T2 and T3 were performed by telephone (n=22, 19%). Fisher's exact test was performed to determine proportional differences between groups. Mann- Whitney's U test was used to test any difference between the groups regarding percentage of body weight loss.

Results

Study I

All participants (n=21) lost body weight, with the lowest body weight observed at the end of RT. 2 patients lost <5%, 12 patients from 5-10% and 7 patients >10%. Nineteen patients needed enteral nutrition. At the end of RT, all patients had mucositis. For the four assessments occasions (pre-RT, 3 weeks of RT, at end of RT and within 2-4 weeks after the termination of RT) only small changes were observed in IGF-1, IGFBP-1 and ghrelin. A decrease of 18.2% was seen in the albumin concentration. HsCRP significantly increased during RT and decreased during the recovery period, although it did not return to pre-therapy levels. For all patients, maximum hsCRP was 35.8±8.5 mg/l, which can be compared with 5.2±1.0 mg/l at diagnosis ($p<0.01$).

HsCRP of more than 40 mg/l was noted in seven patients. No significant correlation was detected between hsCRP and body weight loss or grade of mucositis. Albumin or mucositis was not related to body weight loss. The regression analysis showed that the metabolic markers were not predictive of body weight loss; nor were the values of the age-transformed IGFSD.

Study II

Totally, 160 attempts to place a PEG tube were made and 151 (91%) were placed successfully. 120 (77%) had tumour stage III or IV. RT was given to 144 (92%) of the 151 patients. Methods used were the "introducer" technique (n=89), the "pull" method (n=59) and the "push" technique (n=1). No significant difference in complication rate (including fatal, severe and minor complications) was seen between the two most commonly used methods, i.e. the "introducer" technique and "pull" method (chi-square analysis). Complications occurred in 61. 5 patients had fatal complications, 29 had severe complications and 21 had minor complications. Fatal complications were either procedure-related (two with postoperative lethal peritonitis and one with pneumoperitoneum with renal failure) or PEG-related (one with necrotising fasciitis around the PEG site, two with gastrointestinal bleeding and one with paralytic ileus). All 5 patients died directly or indirectly (within 12 weeks) because of PEG tube placement.

Table 2: The most frequently occurring severe and minor PEG complications in 151 patients

Types of complications	
Severe	
Wound infections	26
Major leakage	5
Peritonitis	4
Minor	
Abdominal pain around the PEG site	22
Minor leakage1	12
Granulation tissue	11
Problems with PEG material	10

Study III

This cohort (n=147) was stratified according to the therapeutic approach. 40 of the patients received single modality RT and 107 received combined modality treatment. Of the 40 patients given RT, 3 showed clinical complete response and thereby constituted the RT group. Of the 107 patients receiving combined modality treatment, 101 had radical surgery or no evidence of microscopic tumours after RT and thus constituted the RT and surgery group.

Both groups showed an increase of body weight between start of RT up to 2 weeks of RT; thereafter, a decrease was seen for both groups, with the lowest point coming 6 months after RT. Maximum body weight loss was significantly greater in the RT and surgery group than in the RT group. The linear regression analysis showed that only tumour stage was significantly predictive of maximum body weight loss. In total, the model explained 19.7% of the variance.

Study IV

This study involved two groups of patients, namely those who could maintain oral feeding during the study period (OF group, n=18) and those who received enteral nutrition (EN group, n=23). In the EN group 14 patients received PEG and 9 NGT. At the 3-month follow-up, no significant difference was found in body weight loss between the OF group (median 9.4%) and the EN group (median 6.8%). Median body weight loss in the NGT group was 9.6% and in the PEG group 5.9% (this difference was not statistically significant). SEIQoL-G. Thirteen categories describe areas that the participants nominated as most important in their life. There were significant differences over time in two of the categories: Interest/leisure activities ($p<0.001$) and Housing/living conditions ($p<0.01$). The two categories were more often mentioned as being important before RT than after treatment. The three most frequently reported categories were Family/relation to family, Personal health and Interest/leisure activities.

Discussion

In the four studies of this thesis all patients received nutritional counselling and were informed that a high-caloric intake is important in order to avoid body weight loss during RT. In addition, most patients were followed-up at the hospital. Many patients gained body weight before the start of RT. Despite this support with nutritional counselling, almost all patients in study I, III and IV suffered to some extent to body weight reduction during and after treatment. Seventy-percent lost >5% in body weight in study I, 73% in study III and 65% in study IV. In all, as much as 70% (study I), 59% (study III) and 56% (study IV) needed enteral nutrition. In study III lowest of mean body weight loss was seen 6 months after the termination of RT and patients receiving combined modality treatment (RT followed by surgery) had significantly greater body weight loss than patients only given RT.

In study I an attempt was made to predict body weight loss using systematic inflammatory and metabolic markers. The results from the blood tests showed that hsCRP increased during RT, most probably as a response to irradiation-induced inflammation. It was found that hsCRP >40 mg/ml indicated a poor prognosis (results not shown). It can be speculated that the hsCRP measurement could have highlighted a biomarker of great clinical importance if a larger cohort had been studied. A few studies on Head and neck cancer patients have shown a similar pattern of CRP changes during RT [11, 12]

In study I, the age-transformed value IGFSD1 [13] was generally low, indicating a catabolic state. However, the hypothesis that the systematic inflammatory and metabolic markers (hsCRP, albumin, IGF-1, IGFBP-1 and ghrelin) could predict body weight loss was not established. When using univariate analysis to look at different factors to predict body weight loss in study III, tumour site, tumour stage and treatment modality were correlated to maximum body weight loss. However, when applying multivariate analysis the only predictive variable of maximum body weight loss was tumour stage.

Even though, in study III, the patients with laryngeal cancer lost less body weight (compared with patients with oropharyngeal and oral cavity cancer), these patients also require nutritional follow-up. In study IV the patients mentioned a variety of different issues or problems that indicate the importance of asking the patients individually what their expected specific needs are and to follow-up their problems.

When discussing which method to employ (i.e. NGT or PEG), risks and benefits and the estimated time of enteral nutrition use should be considered together with each patient's individual preferences and needs. Shared decision making between patient and health care givers is often a goal, even though it is not always easy to apply in clinical practice. One limitation in study I is the small sample size. A major concern for the patients was the number of blood samples collected. Another limitation of study I was that the serial of blood samples collected was of non-fasting origin. The blood samples were taken after the patients had been irradiated which mostly occurred at midday. Furthermore, it would be unethical to have them fast as this is a very vulnerable group.

Conclusion

The strongest prognostic predictor for maximum body weight loss was tumour stage (body weight loss was greater in patients with more advanced stage tumours). Mean body weight was lowest at about 6 months after termination of RT. Patients who underwent combined modality treatment (RT and surgery) lost significantly more body weight and more often required enteral nutrition than patients who underwent RT only. Regular measurements of body weight, as well as assessment of oral mucositis and CRP were important to carry out in the nutritional follow-up of patients with Head and neck cancer before, during and after treatment. More than 50% of the patients manifested eating-related problems that affected their daily life. The patient's level of disease-related QoL was not negatively affected by having enteral nutrition. Suitable candidates for PEG should be identified with respect to the risk for fatal complications. Regardless of type of feeding tube (NGT or PEG), the patients seem to present similar problems. Although inter-individual variations were observed, patients with NGT or PEG expressed positive and negative attitudes towards enteral nutrition. The major differences between NGT and PEG patients

were that patients with NGT expressed negative views regarding social limitations and patients with PEG felt confined by the tube. The patient's perspective should be incorporated into the decision-making process in how best to treat and provide nutrition to the target groups.

In conclusion, it is suggested that with appropriate pre-assessment and high standards of aftercare and follow-up, the risks for feeding tube-related complications might be significantly reduced. NGT should be the first method to consider for enteral nutrition because it is easy to use, relatively safe, cost-effective and acceptable to most patients. Moreover, NGT has a relatively low rate of complications and the length of use seems to be shorter than PEG. On the other hand, PEG is preferred to NGT when prolonged treatment is anticipated or for patients who cannot eat orally because of advanced cancer.

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