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ORIGINAL ARTICLE

Baseline depression predicts malnutrition in head and neck cancer patients undergoing radiotherapy

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Abstract
Purpose Poor nutritional status is common and associated with mortality and morbidity in patients with head and neck cancer (HNC). While there are several established clinical risk factors for poor nutritional status during HNC radiotherapy, the complete aetiology is not known. The association of malnutrition with psychological factors has been recognised in other chronic illnesses but has not been studied in HNC patients who have higher levels of malnutrition and psychological disorder than many other patient populations.
Method Patients with HNC were assessed at three time points: week 1 of radiotherapy treatment (T1, $n=72$), end of radiotherapy treatment (T2, $n=64$) and 4 weeks post-radiotherapy treatment (T3, $n=58$). Nutritional outcome was measured using the Patient-Generated Subjective Global Assessment, and psychological factors measured were depression, anxiety and adjustment style.
Results Linear mixed models indicated that a model containing the variables time, tumour site and baseline depression best explained malnutrition at T2 and T3 (−2 restricted log likelihood=695.42). The clinical risk factors: cancer stage, number of radiotherapy fractionations, a PEG feeding tube, availability of a care giver and dietitian's informal clinical assessment did not predict later nutritional status.
Conclusions Depression is a modifiable risk factor for malnutrition among HNC patients undergoing radiation therapy, offering the potential to ameliorate malnutrition in this group. While the nature of any causal relationship between depression and malnutrition in HNC is yet to be understood, the utility of a short depression screen in predicting malnutrition has been demonstrated and could be adopted in clinical practice.

Keywords Cancer · Malnutrition · Depression · Head and neck · Radiation

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Background

Malignancies of the upper aerodigestive tract and its connected structures, known collectively as head and neck cancer (HNC), are the eighth most commonly diagnosed cancers worldwide [1]. HNC has a relatively high mortality rate, approaching 50% [2]. Due to the location of the tumour and the common treatments of surgery and radiotherapy, a particular challenge for HNC patients is malnutrition [3].

The consequences of inadequate nutritional status in cancer patients include impaired immune function, reduced vitality and reduced resistance to the disease, which lead to increased morbidity and an increase in complications due to side effects of the treatment [3]. Poor nutritional status during treatment is a strong predictor of mortality in HNC [4].

There are several established clinical risk factors for poor nutritional status during HNC radiotherapy including age [5], being male and living alone [6, 7], tumour site and tumour stage [3]; however, the complete aetiology is not yet known. Psychological factors have been associated with nutrition in other disease populations that endure significant nutritional risk including bowel disease [8]; kidney disease [9]; coronary heart disease [10]; obesity [11] and diabetes [12]. Changes in appetite are a common feature of depression and anxiety, leading directly to alterations in nutrition [DSM]. Depression and adjustment style can also affect patients' nutritional self-care behaviours [13–15].

The relationship between malnutrition and psychological factors has not been well-studied in the nutritionally high-risk HNC population. Since it is well established that the HNC population has significant levels of psychological disorder, particularly depression and anxiety [16, 17], any association between malnutrition and psychological factors could have important implications for risk of malnutrition and subsequent management.

The aim of this study was to investigate the relationship between nutritional status and psychological factors in HNC patients undergoing radiation therapy, specifically:

1. To determine the relationship between nutritional outcome and the baseline psychological factors of depression, anxiety and adjustment style, whilst controlling for clinical risk factors of tumour site, stage, number of radiotherapy fractionations, age, gender and availability of a care giver.
2. To develop the explanatory model above into a clinically practical model that predicts malnutrition using binary baseline characteristics, thus identifying potential targets for intervention.

Method

Study design

The study used a longitudinal cohort design, with three time points for assessment: week 1 of radiotherapy treatment (T1), end of radiotherapy treatment (T2) and 4 weeks post-radiotherapy treatment (T3). Predictor variables and nutritional outcome variables were collected at all three time points.

Participants and setting

This study was carried out in the Radiation Oncology Outpatients clinic of the Calvary Mater Newcastle (CMN), which is a tertiary referral centre for oncology in New South Wales, Australia. Ethics approval was granted by the Hunter New England Human Research Ethics Committee NSW.

Patients over 18 years, with primary HNC, referred to the Radiation Oncology Outpatient clinic were eligible to participate in the study. Patients who could not communicate in English and those being treated with palliative intention, defined as less than 20 fractions of radiotherapy [18] were excluded.

Predictor variables

Clinical risk factors

Data were collected through a combination of self-report and extraction from medical records including the continuous variables of age and number of radiotherapy fractions and the categorical variables of gender, tumour site, tumour stage, presence of a care giver, presence of a PEG feeding tube, and the 'usual care' clinical assessment of malnutrition conducted by a dietitian.

Psychological factors

Depression The Patient Health Questionnaire-9 (PHQ-9) is the nine-item depression component of the larger PHQ [19]. It asks the participant to rate the frequency of criteria for a major depressive episode over the last 2 weeks from 0 to 3, and the scores are summed to provide a continuous measure of depression symptom severity which was used in the explanatory model. A binary outcome was created for the clinical model by defining patients with scores ≥15 as depressed (moderately severe and severe) and patients with scores <15, as not depressed (none, mild and moderate). The PHQ-9 has sensitivity of 0.88 and specificity of 0.88 for major depression compared to clinical interview by a mental health professional [19].

Anxiety The anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A) was used as a continuous variable to assess anxiety. In addition, a description of anxiety caseness used author-supplied cut-offs of a score greater than 7 as a possible case and greater than 11 probable [20]. The HADS-A is commonly used in the oncology literature, and a review of 747 studies found both the sensitivity and specificity of the HADS-A to be approximately 0.8 [21].

Adjustment style Adjustment styles were measured using the Mini-Mental Adjustment to Cancer Scale (Mini-MAC). The 29-item scale scores respondents on five dimensions of mental adjustment to cancer: Helplessness–Hopelessness; Anxious Preoccupation; Fighting Spirit; Cognitive Avoidance; and Fatalism [22]. Adjustment subscales were analysed as continuous covariates.

Nutritional outcome over the duration of radiotherapy treatment

The outcome variable was malnutrition, assessed using the Patient-Generated Subjective Global Assessment (PG-SGA). Developed at the Fox Chase Cancer Centre, the PG-SGA is considered the 'gold standard' of nutritional assessments in oncology [23]. The assessment examines known prognostic indicators of nutrition such as weight change, dietary intake, gastrointestinal symptoms, changes in functional capacity, nutritional intake, metabolic stress, subcutaneous fat, muscle wasting, disease and treatment [23]. Although analysed as a continuous measure, in clinical use, a score of 9 or more on the PG-SGA, suggests a critical need for dietetic intervention (17).

Analyses

SPSS [24] was utilised to analyse the data. Differences between participants and non-participants were tested using Chi-square tests and Fisher's exact tests where appropriate for categorical variables. Descriptive statistics were used to examine sample characteristics and to quantify patients' nutrition and psychological status over the course of their treatment and recovery. The Wilcoxon signed-rank test was used to test differences in nutritional status over the three time points.

Linear mixed models were used to take advantage of the repeated measures nature of the study, using an individual's PG-SGA score at both end of treatment (T2) and 4 weeks post-treatment (T3) as the nutritional outcome. Two models were developed, one using predictor variables as continuous measures (an explanatory model) and a second model, based on the first, with predictor variables as categorical measures (the clinical model). The clinical model was developed because clinical implementation requires binary outcomes on which to base actions (for example, to order a referral or not). To do this, the significant continuous variables in the explanatory model were made categorical using the author-supplied cut-offs.

Model development procedure

First, the ability of each baseline variable to predict outcome nutrition was tested by entering each variable into the model with the variable time, which accounted for the repeated measures nature of the study. Second, the significant variables that were considered commonly accepted risk factors for malnutrition were entered into a model, and backward elimination was used to find the most efficient biomedical risk factors sub-model. Third, the significant psychological factors were added to the clinical risk factors sub-model. Backwards elimination was again used to determine which baseline factors best predicted malnutrition at T2 and T3. In the fourth step, the model was tested for any possible interactions between each of the significant variables at the univariate level. Only the significant main effects and interaction variables were kept. To check that no discarded variables had since become significant, each was added to the model individually to verify that they did not contribute significantly to the prediction of malnutrition. Finally, the residuals of the model were checked for normality, constant variance and independence.

Results

Characteristics of participants

Of the 92 eligible patients that attended CMN Radiation Oncology Outpatients in a 10-month period, 70 (76%) agreed to participate in the study and completed the baseline assessment (T1). Sixty-four participants completed the end of treatment assessment (T2), two died and four were lost to follow-up. By post-treatment (T3), a further two participants had died and another four were lost to follow-up, leaving 58 participants who completed the study. Tests for sampling bias demonstrated no significant differences between participants and non-participants in gender, number of fractions of radiation therapy or tumour site (Table 1).

The mean age of the sample was 63.6 years (SD=13.7), 44 (63%) participants reported having a live-in care giver and 11 (16%) had a PEG feeding tube in situ at baseline.

Nutritional outcome over the duration of radiotherapy treatment

PG-SGA scores were not normally distributed and therefore the medians and interquartile ranges (IQR) are reported. The median PG-SGA at T1 was 4 (IQR 6), at T2, the median was 11 (IQR 10) and at T3, the median was 6 (IQR 8). The non-parametric Wilcoxon signed-rank test for paired samples found significant differences in PG-SGA scores and were observed between T1 and T2 ($z=-5.39$, $p<0.01$) and between T2 and T3 ($z=-4.73$, $p<0.01$). However, the difference between T1 and T3 was not significant ($z=-1.77$, $p=0.08$).

Table 1 Comparison of participants and non-participants

	Participants $n=70$		Non-participants $n=22$		Statistics		
	n	Percentage	*n*	Percentage	χ^2	*df*	*p*
Female	10	14	2	9	0.40	1	0.53
Male	60	86	20	91			
Number of fractionations					2.36	3	0.75
35	20	29	5	23			
30	29	41	9	41			
25	10	14	6	27			
20	11	16	2	9			
Tumour site					1.23	4	0.88
Oral cavity	21	30	6	27			
Pharynx	12	17	3	14			
Larynx	5	7	1	5			
Salivary glands	12	17	6	27			
Cutaneous cancers	20	29	6	27			

Psychological variables over the duration of radiotherapy treatment

There were no significant differences in any of the psychological variables over the course of the study. The frequency of moderately severe to severe depression cases remained approximately 10–15%, while the frequency of possible and probable anxiety cases stayed between 10% and 20% (Table 2). Scores describing adjustment also remained steady (Table 3).

Explanatory model for predicting malnutrition using baseline characteristics

Of the accepted clinical risk factors, a model containing the variables time and tumour site best explained malnutrition at T2 and T3. Upon adding significant psychological factors to the model, backward elimination yielded baseline PHQ-9 as the only additional significant factor that contributed predictive value (Table 4) (−2 restricted log likelihood of 695.42). The model did not breach any assumptions of normality, constant variance or independence.

Table 2 Psychological caseness during treatment and recovery

Tools		T1		T2		T3	
		n	Percentage	*n*	Percentage	*n*	Percentage
PHQ-9	None	43	61	34	57	38	66
	Mild	13	19	11	18	7	12
	Moderate	6	9	7	12	7	12
	Moderately severe	5	7	5	8	5	9
	Severe	2	3	3	5	1	2
HADS-A	None	55	79	51	86	47	81
	Possible	9	13	4	7	7	12
	Probable	6	9	4	7	4	7

Table 3 Mean scores for adjustment style subscales of Mini-MAC

	T1		T2		T3	
	Median	IQR	Median	IQR	Median	IQR
Helpless adjustment	10	7	11.5	7	10	7
Anxious preoccupied adjustment	18	9	17	10	16	10
Fighting spirit adjustment	12	4	12	4	12	3
Anxious avoidant adjustment	10	4	10	4	10	5.25
Fatalistic adjustment	13.5	6	14	6.5	14	5.75

Clinical model for predicting malnutrition using binary baseline characteristics

The clinical model, based on the explanatory model but using categorical variables, also identified time, tumour site and depression as significant independent predictors of malnutrition at T2 and T3 (−2 restricted log likelihood= 691.84) (Table 4).

Discussion

This study found an independent association between baseline depression and the nutritional status of HNC patients over the course of radiation therapy. The results support the assertion that psychological factors play a role in the development of malnutrition in HNC patients undergoing radiotherapy; and that a short depression screen at baseline is a more efficient way to predict those patients who will decline nutritionally than commonly accepted risk factors such as stage, number of radiotherapy fractionations, PEG, age, gender or availability of a care giver.

Nutritional outcome over the duration of radiotherapy treatment

Most of the samples were malnourished at the beginning of the study, became worse through treatment and then recovered to somewhere near baseline by the 4-week recovery assessment. This is in keeping with the literature that suggests that HNC malignancies cause malnutrition [3, 25] and that treatment of HNC, particularly through

Table 4 Baseline predictors of malnutrition (PG-SGA scores) over time (T2 and T3) using linear mixed models

Clinical risk factors controlled for time	*df*	*F*	*p*	Explanatory model			Clinical model[a]		
				df	*F*	*p*	*df*	F	*p*
Time				1, 53	27.5	<0.01	1, 53	28.51	<0.01
Sex	1, 56	0.03	0.88						
Age	1, 58	0.09	0.76						
Live-in care giver	1, 57	1.37	0.25						
Tumour site[b]	4, 55	4.83	<0.01	4, 51	3.90	<0.01	4, 52	5.25	<0.01
Tumour stage[c]	3,55	2.72	0.05						
No. of RT fractionations	1, 56	2.63	0.11						
PEG tube inserted	1, 56	0.58	0.45						
Subjective global assessment (SGA)b	1, 58	3.83	0.06						
Dietitian attending	3, 55	0.27	0.85						
Baseline psychological factors									
PHQ-9 a	1, 55	13.89	<0.01	1, 52	9.94	<0.01	1, 54	7.05	0.01
HADS-A	1, 57	2.13	0.15						
Helpless adjustment	1, 57	2.30	0.14						
Anxious adjustment[b]	1, 56	10.78	<0.01						
Fighting spirit adjustment[b]	1, 58	4.28	0.04						
Anxious avoidant adjustment[c]	1, 58	3.97	0.05						
Fatalistic adjustment	1, 56	1.92	0.17						

[a] Uses PHQ-9 cut point score of ≥15

[b] Significant at $p<0.05$

[c] Also included in initial models due to proximity of p to 0.05

radiotherapy and the damage it does to mucosa, exacerbates the nutritional decline [26]. It is worth noting that although no significant differences were found between T1 and T3, the recovery period did not signify a return to a healthy level of nutrition. All but the cutaneous and the salivary gland tumour groups scored over 9 on average on the PG-SGA at T3, suggesting that they were still in 'critical need of nutritional intervention'.

Depression, anxiety and adjustment style over the duration of radiotherapy treatment

The point prevalence of cases of depression was similar to findings of other studies in HNC [27–29]. The baseline levels of anxiety caseness corresponded with previous findings of pre-radiotherapy anxiety levels among HNC patients of approximately 7% [30]. No particular pattern was apparent in the adjustment styles measured by the Mini-MAC. However, it was noted that there was a larger variation in the scores of the anxious preoccupied adjustment subscale than any of the other categories. This could be a result of early treatment anxieties leading to anxious preoccupied adjustment, which eventually resolved over the course of several weeks of radiotherapy.

Relationship between nutritional outcome and baseline psychological factors

Clinical risk factors

Two of the three variables predicting nutritional status following radiation therapy have been previously established, tumour site and time (Fig. 1). Because tumour site is not a variable that changes over the course of treatment, this finding is analogous to the various cross-sectional studies that have found an association between

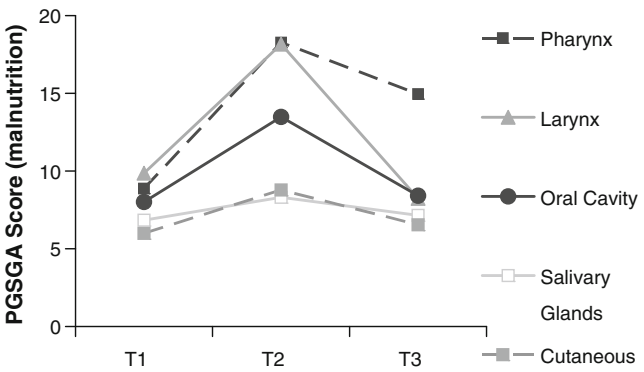

Fig. 1 Malnutrition over time by tumour site

the location of the tumour and malnutrition in HNC [31, 32].

Time can be viewed as the effect of treatment; at T1, patients had had very little treatment, by T2, they had received almost all of their treatment and at T3, they had not received treatment for 4 weeks. The significance of time in the model means that there were significant differences in nutrition over the time points. However, as a predictive tool, the inclusion of time imparts very little information to the clinician aside from the fact that patients will become more malnourished with more treatment. It does not allow for a baseline prediction of which patients will deteriorate because all of the patients are about to receive treatment and time (treatment) is not a potentially modifiable risk factor.

It was surprising to note that the other clinical risk factors [3, 5, 6]: cancer stage, number of radiotherapy fractionations, a PEG feeding tube, availability of a care giver and even the dietitian's own baseline clinical assessment did not predict later nutritional status.

Psychological risk factors

No other studies have reported on the relationship between depression and malnutrition in HNC. The finding that depression was related to malnutrition is in accordance with the findings of studies in other illnesses [7–12]. The consistent finding of an association, despite large differences between populations in factors such as age, gender and disease effects, suggests that depression warrants consideration in studies of malnutrition in physical illness (Fig. 2).

It is not possible to discern any specific causal relationship between depression and malnutrition from this study. It is reasonable to infer from the already high levels of malnutrition at baseline that pre-treatment malnutrition might lead to depression. Alternatively, it is equally valid to suggest that the mechanisms of reduced appetite and reduced self-care behaviours caused by depression were actually the origin of the pre-treatment malnutrition. A third and potentially more appropriate suggestion may be that a bidirectional relationship exists between depression and malnutrition.

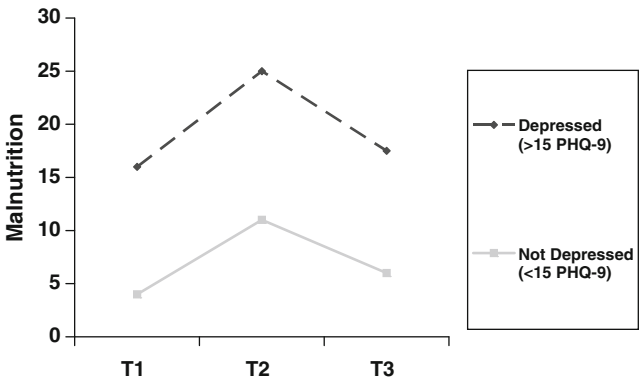

Fig. 2 Malnutrition over time by dichotomised depression caseness

No association was observed between anxiety and adjustment style in multivariate analyses. This is in some contrast to expectation, since fighting spirit and active coping have been associated with better self-care behaviours in other illnesses [33]. It may be that different factors apply in HNC than other illnesses. Alternatively, since several adjustment styles (anxious adjustment, fighting spirit, anxious avoidant) were significant at the univariate level, it may be that the relationships did not have sufficient large effect sizes to be detected in our sample. These may be worth pursing in future research.

Clinical implications

The finding of this study, if replicated, has potential clinical utility in predicting which patients are at higher risk of malnutrition. This finding could be integrated into medical decision making since the association with malnutrition remained significant when depression was treated as a binary variable (depressed/not depressed).

Should future research find that depression scores are simply a marker of malnutrition, the PHQ-9 could still be an important clinical tool. Just as cytometric markers are used for the diagnosis of infections in medicine, so too could the PHQ-9 be used as ‘shorthand’ for predicting malnutrition in HNC patients. Alternatively, if further research demonstrates a causal link between depression and malnutrition, dietitians would be provided with a course of action (referral to psychological services for treatment of depression) for the subset of patients with medically unexplained decline who do not seem to respond to best-possible dietetic care. We are currently evaluating an intervention model that combines psychological and nutritional strategies in a phase II clinical trial [34].

Strengths and limitations of the study

There were several strengths to this study. The study design was prospective and available data on non-participants demonstrated no significant differences between participants and non- participants. The time points chosen represented clinically important points in the trajectory of HNC patients' nutritional status [35]. The week 1 baseline assessment was psychologically well conceived, allowing for assessment of depression and malnutrition prior to the development of radiation therapy morbidities, while avoiding the anxiety associated with the first day of radiotherapy treatment. The study utilised well-validated, standardised self-report psychological questionnaires and a dietitian-

completed gold standard in nutritional assessment. Furthermore, the commonly used biomedical prognostic factors were recorded and were appropriately controlled for in the analyses.

Another strength was that the dietitians who administered the nutritional assessments were blinded to the psychological scores of the patients. The setting in which they provided this assessment was the actual time and place of treatment. Therefore, the observations obtained were likely to be representative of a HNC patient undergoing radiotherapy, enhancing the external validity of the study.

Limitations of the study include the relatively small sample size, which meant that only large effect sizes could be detected. It should also be noted that the demonstrated association was with a depression screen score, not with a clinical diagnosis of depression. A further limitation was the inability to make absolute causal attributions between depression and malnutrition, given the longitudinal cohort design.

Conclusion

In this sample of HNC radiotherapy patients, malnutrition was best predicted by tumour site, the effects of radiotherapy treatment (time) and baseline depression as measured by the PHQ-9. Commonly used clinical risk factors like stage, age, sex, PEG insertion and the availability of a care giver did not predict later malnutrition. Unlike the other components of the model, depression is a potentially modifiable risk factor for malnutrition. While the true relationship between depression and malnutrition in HNC is yet to be understood, the utility of a short depression screen in predicting malnutrition has been demonstrated. With replication, this has potential for adoption in clinical practice.

Disclosures None.

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