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Randomised controlled trial of early prophylactic feeding vs standard care in patients with head and neck cancer

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Background: Weight loss remains significant in patients with head and neck cancer, despite prophylactic gastrostomy and intensive dietary counseling. The aim of this study was to improve outcomes utilising an early nutrition intervention.

Methods: Patients with head and neck cancer at a tertiary hospital in Australia referred for prophylactic gastrostomy prior to curative intent treatment were eligible for this single centre randomised controlled trial. Exclusions included severe malnutrition or dysphagia. Patients were assigned following computer-generated randomisation sequence with allocation concealment to either intervention or standard care. The intervention group commenced supplementary tube feeding immediately following tube placement. Primary outcome measure was percentage weight loss at three months post treatment.

Results: Recruitment completed June 2015 with 70 patients randomised to standard care (66 complete cases) and 61 to intervention (56 complete cases). Following intention-to-treat analysis, linear regression found no effect of the intervention on weight loss ($10.9 \pm 6.6\%$ standard care vs $10.8 \pm 5.6\%$ intervention, $P=0.930$) and this remained non-significant on multivariable analysis ($P=0.624$). No other differences were found for quality of life or clinical outcomes. No serious adverse events were reported.

Conclusions: The early intervention did not improve outcomes, but poor adherence to nutrition recommendations impacted on potential outcomes.

Treatments for head and neck cancer (HNSCC), including surgery, radiotherapy and chemotherapy have a number of side effects, which can impact on nutritional intake (Talwar and Findlay, 2012), with multi-modality therapy having higher toxicity (Moroney *et al*, 2017). As a consequence, many patients experience significant weight loss and develop malnutrition during the course of treatment (Hebuterne *et al*, 2014). This is associated with a number of detrimental outcomes, including reduced physical functioning, quality of life and immune function, and increased

treatment interruptions, toxicities, hospital admissions, and mortality (Gorenc *et al*, 2015). Critical weight loss of 5% or more during treatment has been associated with worse survival outcomes (Langius *et al*, 2013a), demonstrating the importance of optimal nutrition to minimise weight loss. Improvements in nutritional status have also been linked to improved aspects of quality of life (Isenring *et al*, 2004; Ravasco *et al*, 2004).

A number of systematic reviews have recommended the importance of dietary counselling to improve nutritional and

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patient outcomes (Garg *et al*, 2010; Langius *et al*, 2013b); however, the role of tube feeding remains unclear due to a lack of well-designed clinical trials to inform optimal tube type and timing of placement (Orphanidou *et al*, 2011; Nugent *et al*, 2013; Wang *et al*, 2014). A recent meta-analysis comparing outcomes with nasogastric tubes and either prophylactic or reactive gastrostomy tubes, found the prophylactic tubes resulted in a reduction in treatment interruptions and nutrition related hospital admissions, but had no superiority in managing nutritional status (Zhang *et al*, 2016). Either way, clinically significant weight loss of > 10% occurs with either the prophylactic or reactive approach (Chang *et al*, 2009; Clavel *et al*, 2011; Rutter *et al*, 2011; Silander *et al*, 2012; Olson *et al*, 2013).

Of those studies that report specific details on the actual timing of the commencement of nutrition support through the prophylactic gastrostomy, the majority are after the commencement of treatment when it becomes clinically indicated in response to deterioration in swallowing or nutritional status (Scolapio *et al*, 2001; Rayker *et al*, 2009; Nugent *et al*, 2010). Hence, it is not surprising that there are similar nutrition outcomes with reactive tube use; as although the prophylactic tube is *in situ* and ready for access, the initiation and indication for nutrition support is reactive in both groups. Some studies have reported the commencement of enteral feeds prior to treatment (Marcy *et al*, 2000; Beer *et al*, 2005; Nguyen *et al*, 2006; Wiggenraad *et al*, 2007) but these patients had poor nutritional status or dysphagia at baseline, and therefore nutrition support was clinically indicated immediately.

This is the first study to our knowledge to trial an early prophylactic tube feeding intervention prior to treatment in a target population who are primarily well-nourished with minimal dysphagia. This group may be considered to have low motivation to use their tube as there is no current obvious problem with eating, but despite good baseline nutritional and swallowing status, these patients have still been shown to have high rates of tube feeding and weight loss during treatment (Brown *et al*, 2015). The validation of the protocol used at our institute to identify patients for prophylactic gastrostomy also supports this finding (Brown *et al*, 2016). The criteria used in this protocol are primarily based on tumour site and treatment, and so the majority of patients selected are those receiving chemoradiotherapy for unresectable tumours or as organ-preserving treatment. By increasing nutritional intake through prophylactic supplementary tube feeding, it was assumed this would assist in reducing weight loss. The additional rationale for this interventional approach was based on the psychological impact of gastrostomy tube placement, including anxiety and fear associated with tube use (Salas *et al*, 2009; Merrick and Farrell, 2012). Therefore, this period of early tube feeding could assist patients to adapt to the tube more easily.

The aim of this study is to compare nutritional, clinical and patient outcomes following an early tube feeding approach via the prophylactic gastrostomy vs standard care of commencing tube feeding via the prophylactic gastrostomy when clinically indicated. The null hypothesis being no difference in the outcomes between the two groups. It is anticipated that the intervention group will have improved nutritional outcomes, according to an established nutrition framework, which in turn is expected to improve patient outcomes, such as quality of life, and other clinical outcomes (Splett, 1996).

MATERIALS AND METHODS

This was a single-centre randomised controlled trial conducted in Queensland, Australia. The full protocol is published (Brown *et al*, 2014). The study design was a parallel group study using equal

randomisation (1:1). No changes occurred to the study design or outcome measures following commencement.

Participants and study setting. Patients with HNSCC were eligible for the study if referred for a prophylactic gastrostomy prior to treatment. A local protocol was used by the multi-disciplinary clinic to identify high nutrition risk patients suitable for prophylactic gastrostomy (Brown *et al*, 2016); however, the final decision of tube placement was made by the treating team. Excluded patients included: age < 18, pregnant, cognitively impaired or with an intellectual disability or mental illness, planned for non-curative intent treatment, or if diagnosed as severely or moderately malnourished with significant dysphagia requiring a liquid or puree texture modified diet.

The study was approved by the Royal Brisbane and Women's Hospital Human Research Ethics Committee on 19 July 2012 (HREC/12/QRBW/162) and The University of Queensland Medical Research Ethics Committee on 8 August 2012 (2012000890). All patients provided written informed consent to participate. This trial has been registered in the Australian New Zealand Clinical Trials registry as ACTRN12612000579897. Available at <http://www.anzctr.org.au>.

Patients were recruited from the Royal Brisbane and Women's Hospital from September 2012 to June 2015. This is a major tertiary/quaternary hospital providing specialist cancer care services to patients throughout Queensland, Australia. All patients see the dietitian and speech pathologist as part of routine care, with access to other allied health services as required. Dependent on the patient's home address and local health service district location, follow-up care post treatment may continue at the tertiary centre or be transferred to a regional cancer centre. Level of allied health services and thus access to follow-up care at each regional centre may vary, particularly for patients from rural or remote areas.

Interventions. All patients received education on the care of their feeding tube during their overnight elective admission for gastrostomy placement. Prior to discharge patients were randomly allocated to either the standard care or intervention arm and booked into the joint dietitian and speech pathology clinic for weekly review during treatment.

In the standard care arm, patients were commenced on enteral nutrition via their prophylactic gastrostomy by the dietitian when indicated. Indicators included: oral intake < 60% of estimated energy requirements (based on 125–145 kJ kg⁻¹) for a period of, or anticipated to be, > 10 days; the patient was unable to maintain weight; the patient required significant texture modification of diet; or the patient had increased or uncontrolled nutrition impact symptoms. The regimen was determined by the clinical dietitian to suit the patients' individual requirements and adapted as required during treatment.

For patients in the intervention group, this meant initiation of enteral nutrition via their prophylactic gastrostomy immediately following tube placement prior to commencement of treatment. The prophylactic enteral nutrition was in addition to their current oral intake and consisted of 2 × 200 ml bolus feeds (1.5 kcal ml⁻¹ polymeric formula with fibre) per day. Patients were provided with weekly supplies and were given guidance and suggestions on how to incorporate the enteral feeding into their daily routine (e.g., behavioural strategies and reminders; appropriate timings for administration, such as between meals). This enteral nutrition recommendation was continued until completion of treatment, and was increased as necessary during treatment if the patient had any of the clinical indicators for starting enteral nutrition as described in standard care. If patients required an increase in enteral nutrition, they were converted to a home enteral nutrition prescription and were required to pay a co-payment for the product as per standard care. If patients described enteral feed intolerance, an alternative non-fibre formula was trialled.

To monitor adherence, patients in both arms were asked to maintain a self-reporting diary of their daily prescribed enteral nutrition intake, and any barriers to this prescription. These were verified by the clinical dietitian on weekly review. Overall adherence was defined as achieving $\geq 75\%$ of prescribed enteral nutrition intake (Hubbard *et al*, 2012). All patients were encouraged to maintain oral intake as much as possible during treatment and as long as it remained safe to do so as per the speech pathologist. On completion of treatment, all patients were referred to their local dietitian service for ongoing care as required.

Outcomes. The primary endpoint was percentage weight change with additional nutrition outcomes, including body composition (fat mass and fat-free mass) and nutritional status. Weight and body fat percentage were measured on digital bioelectrical impedance analysis (BIA) scales (Tanita body composition monitor BC-582 (Tanita Corporation, Japan)) at recruitment (baseline) and three months post treatment. Patients were asked to remove shoes, socks and outer clothing, and to empty their pockets. Nutritional status was assessed by the Patient-Generated Subjective Global Assessment tool (PGSGA) (Bauer *et al*, 2002), a validated tool recommended to assess nutritional status in patients with cancer (Isenring *et al*, 2013).

The secondary endpoint was quality of life, which was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) tools (Aaronson *et al*, 1993). The questionnaires included the quality of life of cancer patients (EORTC QLQ-C30) and the module for head and neck (EORTC QLQ-H&N35). The raw data was transformed into scores ranging from 0–100, following established procedures (Fayers *et al*, 2001). A higher score for global quality of life and functioning scales was indicative of higher quality of life and function. A higher score for symptom scales was indicative of a higher level of symptom burden. Guidelines for interpretation of longitudinal changes in quality of life scores for EORTC QLQ-C30 were used to determine clinical impact (Cocks *et al*, 2012) and these were graded as either an improvement or deterioration, with trivial, small, medium or large clinical effect.

Tertiary endpoints included tolerance to chemotherapy and radiotherapy, rate of unplanned hospital admissions and gastrostomy complications. Dose of chemotherapy and radiotherapy received were recorded. Delays to radiotherapy were recorded as days beyond expected finish date and a prolonged treatment time was defined as those >7 days. Completion of planned chemotherapy was defined as either completion of three cycles of high-dose cisplatin, seven cycles of weekly cisplatin or eight cycles of cetuximab. Completion of target dose was defined as $\geq 200 \text{ mg m}^{-2}$ cisplatin or \geq six cycles of cetuximab. Reasons for changes to chemotherapy were coded as toxicities (gastrointestinal, haematological, renal, or other). Unplanned hospital admissions and length of stay were prospectively recorded during treatment and classified as either a medical admission, or management of gastrostomy complications or management of nutrition impact symptoms. Gastrostomy complications were recorded during the first three months post insertion. Major complications were defined as those requiring hospital admission. Minor complications were defined as site infections or other stoma issues such as hypergranulation, excoriation, erythema, pressure injury or leakage.

Monthly follow-up was completed via the telephone to assess gastrostomy use and date of removal for up to 6 months post treatment. If the tube was still *in situ* at 6 months, then follow-up was repeated at 12 months. The day of gastrostomy removal was recorded in relation to the day of treatment completion.

Treatment response was assessed via the 3-month post treatment PET/CT scan and defined as either complete metabolic response, or persistent disease requiring salvage surgery or

persistent disease requiring palliative care. Survival outcomes were assessed at 12 months post treatment and time (in months) to disease relapse and/or death were recorded.

To enhance the quality of the measurements and to reduce any inter-rater variability in assessment, the data was collected by the designated research dietitian. If patients failed to attend their follow-up appointment, quality of life data were obtained by telephone interview and/or completion of postal surveys, and weight and the PGSGA data were obtained following face-to-face assessment by the local dietitian.

Sample size. The primary outcome for the study was a continuous response variable of percentage weight loss. The aim was to reduce the absolute amount of percentage weight loss by 5% in the intervention group compared to the percentage weight loss seen in the standard care group. A sample size of 123 patients was required to detect a 5% difference in percentage weight loss between the intervention and control groups, with a two-sided 5% significance level, power of 80% and an attrition factor of 10%. Recruitment continued until sample size was attained.

Randomisation. Patients were stratified according to baseline nutritional status (well nourished (PGSGA A) vs moderate/suspected malnutrition (PGSGA B)), and then randomly assigned to one of the two groups (with an allocation ratio 1:1) following simple randomisation procedures. The randomisation sequence was computer-generated using MS Excel. This allocation sequence was concealed to the researcher enrolling participants, but the participants, healthcare team or outcome assessor were not able to be blinded to the allocation.

Statistical methods. Baseline participant characteristics were summarised using mean and s.d. for continuous variables and frequency, and percentage for categorical variables. Differences between groups were assessed using χ^2 tests for categorical variables (or Fishers exact test if assumptions could not be met due to small expected cell counts) and two sample *t*-tests for continuous variables (or two-sample Wilcoxon tests, if assumptions could not be met for normally distributed data and homogeneity of variance). Normal distribution was formally assessed using Shapiro–Wilk test and variance assessed using Levene's test.

Analysis was performed on an intention-to-treat basis. To determine the effect of the nutrition intervention group vs the control group (the independent categorical variable) on the primary outcome of % weight loss (the dependent continuous variable), analysis of variance (ANOVA) was used. For the secondary outcomes (% fat-free mass, % fat mass, PGSGA score and quality of life scores), the mean change over time from baseline to 3 months was also analysed between groups using ANOVA. Bivariate analysis determined the association of any other independent variables on the outcome measures. Any variables with statistically significant associations ($P < 0.1$) were entered into a linear regression model (or logistic regression for any binary outcome variables). Any variables with baseline differences between groups were also added into the model as covariates to adjust for any confounding effects. Final variable selection for each multivariable model used Akaike's Information Criteria (AIC) with a backward stepwise algorithm. The final models reported were those with the smallest objective AIC. Time to event outcomes (gastrostomy removal, disease relapse, death) were analysed using the Kaplan–Meier method with the log rank test.

Statistical significance was set at $P < 0.05$. The data were analysed using R Commander Version 2.1–7 and R version 3.1.3 (2015–03–09) (R Foundation for Statistical Computing, Vienna, Austria). For any results that were not statistically significant, any relevant clinically significant results were reported.

RESULTS

Patient characteristics. Eligible patients ($n = 174$) were invited to participate in the study between September 2012 to June 2015 with 131 patients recruited and randomised (Figure 1). The final 12 month outcomes were completed in August 2016 and all patients were analysed on an intention-to-treat basis. Patient, clinical and treatment characteristics and their baseline nutrition measures are summarised in Table 1 and baseline quality of life measures are available in Supplementary Table 1. In the standard care group, two patients received surgery alone and one patient had radiotherapy alone. There were five patients in the intervention group who had post-operative radiotherapy. All other patients in the study received definitive or adjuvant chemoradiotherapy (94%), of which five also had neoadjuvant chemotherapy. Radiotherapy was delivered by helical intensity modulated radiotherapy for 98% of patients, with definitive doses at >66 Gy ($n = 111$) and adjuvant doses at 60–66 Gy ($n = 12$). Most patients had their gastrostomy placed via endoscopy (93%) vs radiologically (7%), a median of 5 days prior to treatment in each group ($P = 0.277$).

Nutrition outcomes. There were no significant differences for weight loss, body composition or nutritional status once adjusted for any differences at baseline or any other confounding variables

in multivariable models (Table 2). The only predictors of weight loss in the multivariate model were baseline BMI and P16 status; with every 10 unit increase in BMI, there was $\sim 4\%$ more weight loss, and patients with p16 negative disease had $\sim 4\%$ less weight loss than those with p16 positive disease. No variables were identified to predict loss of fat-free mass. Predictors of other nutritional outcomes (fat mass and PGSGA) from multivariable models are summarised (Supplementary Table 2).

Quality of life outcomes. There were no statistical differences in any of the domains of quality of life or functional scales after adjusting for any baseline differences (Supplementary Table 3). Multivariable models were created for global quality of life, functioning scales and selected symptoms scales for which the intervention may have impacted on (e.g., fatigue, appetite, gastrointestinal symptoms, dysphagia and social eating); however, no significant effects of the intervention were found following adjustment for other confounding variables (Supplementary Table 4). On review of the clinical impact of quality of life (EORTC QLQ-C30), the majority of domains showed some degree of deterioration over time (particularly loss of appetite, role functioning and fatigue) but comparisons between groups was limited due to baseline differences. The only exception was social functioning, which was similar at baseline, but clinical differences

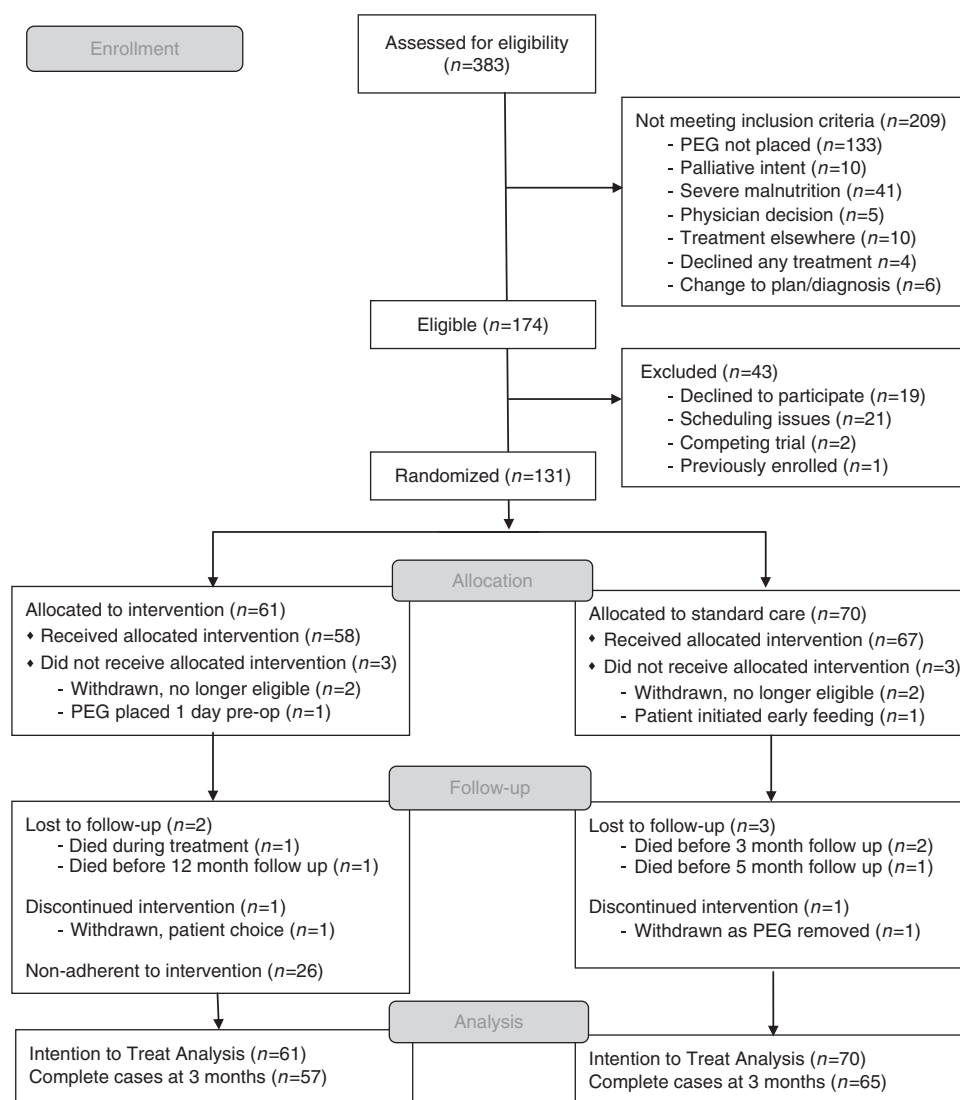


Figure 1. CONSORT flow diagram. Abbreviation: PEG = gastrostomy.

Table 1. Summary of patients enrolled in the trial and comparison of baseline characteristics between standard care and intervention groups

Variable	Total (n = 131)	Standard care (n = 70)	Intervention (n = 61)	P-value
Age				
Years (mean ± s.d.)	60.5 ± 10.1	60.0 ± 10.9	61.1 ± 9.1	0.558
Sex				
Male	115 (88)	59 (84)	56 (92)	0.19
Female	16 (12)	11 (16)	5 (8)	
Smoking history				
Non smoker	26 (20)	14 (20)	12 (20)	0.147
Former	81 (62)	39 (56)	42 (69)	
Current	24 (18)	17 (24)	7 (11)	
Tumour site				
Oral cavity	14 (11)	7 (10)	7 (11)	0.885
Oropharynx	101 (77)	56 (80)	45 (74)	
Nasopharynx	4 (3)	2 (3)	2 (3)	
Hypopharynx	8 (6)	3 (4)	5 (8)	
Larynx	2 (1)	1 (1)	1 (2)	
UKP	1 (1)	0 (0)	1 (2)	
Other	1 (1)	1 (1)	0 (0)	
T stage				
T0	1 (1)	0 (0)	1 (2)	0.111
T1	8 (6)	4 (5)	4 (7)	
T2	44 (34)	20 (29)	24 (39)	
T3	37 (28)	26 (37)	11 (18)	
T4	41 (31)	20 (29)	21 (34)	
N stage				
N0	12 (9)	7 (10)	5 (8)	0.629
N1	13 (10)	8 (11)	5 (8)	
N2a	4 (3)	1 (1)	3 (5)	
N2b	55 (42)	30 (43)	25 (41)	
N2c	42 (32)	20 (29)	22 (36)	
N3	5 (4)	4 (6)	1 (2)	
P16 status				
Positive	85 (69)	43 (65)	42 (72)	0.385
Negative	39 (31)	23 (35)	16 (28)	
Treatment				
ChemoRT	123 (94)	67 (96)	56 (92)	0.472
Other	8 (6)	3 (4)	5 (8)	
Chemotherapy				
HD cisplatin	68 (58)	36 (56)	32 (60)	0.382
Weekly cisplatin	25 (21)	12 (19)	13 (25)	
Cetuximab	24 (21)	16 (25)	8 (15)	
Weight loss 6 months				
Nil	51 (39)	22 (31)	29 (48)	0.266
<5%	43 (33)	27 (39)	16 (26)	
5–10%	22 (17)	12 (17)	10 (16)	
≥10%	15 (11)	9 (13)	6 (10)	
Nutritional status				
PGSGA A	99 (76)	50 (71)	49 (80)	0.237
PGSGA B	32 (24)	20 (29)	12 (20)	
PGSGA C	0 (0)	0 (0)	0 (0)	
Diet				
Full	87 (66)	47 (67)	40 (66)	0.579
Soft	35 (27)	20 (29)	15 (25)	
Minced	8 (6)	3 (4)	5 (8)	
Puree	1 (1)	0 (0)	1 (1)	
Anthropometry				
Weight (kg)	82.6 ± 18.7	79.7 ± 18.7	85.8 ± 18.4	0.063
Fat-free mass (kg)	59.2 ± 10.4	57.6 ± 10.5	60.9 ± 10.1	0.073
BMI (kg m ⁻²)	27.2 ± 5.5	26.4 ± 5.7	28.1 ± 5.2	0.078
Nutrition risk				
PGSGA score (median, range)	6 (1–21)	6 (1–21)	5 (1–20)	0.052

Abbreviations: BMI = body mass index; ChemoRT = chemoradiotherapy; HD = high dose; PGSGA = Patient-Generated Subjective Global Assessment; UKP = unknown primary.

Table 2. Summary of unadjusted and adjusted linear regression analysis for the effect of the early nutrition intervention on nutrition outcomes in patients with head and neck cancer

		Comparison of outcomes between groups				Summary of regression analysis for the effect of early nutrition intervention on outcomes (ref: standard care)					
Outcome variable	Standard care		Intervention		Unadjusted		Adjusted for baseline differences		Adjusted in full multivariable model		
	Mean	± s.d.	β	P-value	β	P-value	β	s.e.	95% CI	P-value	
Weight (% change)	-10.9 ± 6.6	-10.8 ± 5.6	0.1	0.93	1.01	0.326	0.48	0.98	-1.46	2.43	0.624
Fat-free mass (% change)	-4.2 ± 4.9	-6.3 ± 5.4	-2.06	0.036*	-1.51	0.104	-1.22	0.92	-3.03	0.6	0.187
Fat mass (% change)	-28.5 ± 16.7	-22.7 ± 15.2	5.85	0.056	NA	NA	1.72	2.64	-3.52	6.96	0.515
PGSGA risk score (change)	3.2 ± 6.0	3.7 ± 5.3	0.45	0.665	-0.52	0.534	-0.28	0.86	-1.98	1.42	0.743
SGA nutritional status (% decline)	31%	26%	OR 0.79	0.551	NA	NA	OR 0.78	1.55	0.33	1.83	0.569

Abbreviations: PGSGA = Patient-Generated Subjective Global Assessment; SGA = Subjective Global Assessment. *P < 0.05.

were seen with a medium deterioration in the intervention group and no change in the standard group (Supplementary Table 5).

Radiotherapy tolerance. The proportion of patients completing planned radiotherapy treatment was 100% in standard care ($n = 65$ of 65) and 95% in the intervention group ($n = 55$ of 58) ($P = 0.102$). Two patients in the intervention failed to attend scheduled treatment (one patient completed 62 of 70 Gy and one patient completed 66 of 70 Gy), and one further patient died during treatment from liver failure due to complications of chemotherapy. There was no difference in rates of treatment re-planning (22% standard care vs 19% intervention, $P = 0.723$) or delays to radiotherapy treatment ($n = 9$ standard care vs $n = 7$ intervention, $P = 0.381$). Three patients in the intervention and one patient in standard care had a prolonged treatment time, which were due to: admission for myocardial infarction; admission to a regional hospital for neutropenia and infection; admission to manage severe mucositis and secretions; and identification of a new node requiring re-scanning and planning.

Chemotherapy tolerance. Although only approximately half of patients completed their planned chemotherapy prescription (59% standard care vs 51% intervention, $P = 0.361$), almost all completed the target dose of chemotherapy (95% standard care vs 98% intervention, $P = 0.407$). Overall, there was no statistical difference in the changes to the planned chemotherapy (45% standard care vs 53% intervention, $P = 0.418$). The toxicity reasons for deviations from the prescribed chemotherapy plan were similar in each group: haematological (42%), renal (27%), gastrointestinal (5%) and other (22%).

Unplanned admissions. Unplanned admissions affected approximately half of all patients in each group (47% standard care vs 57% intervention, $P = 0.270$) with no statistical differences for reasons for admissions or associated length of stay (Table 3). Nutrition-related admissions accounted for 47% of all admission events in the standard care group ($n = 20$ out of 43) and 53% in the intervention group ($n = 20$ out of 38).

Gastrostomy outcomes. There was no gastrostomy placement-associated mortality. Major tube complications were similar in each group (12% standard care vs 10% intervention, $P = 0.775$). Pain management accounted for 45% of all major complications ($n = 9$ out of 20). Minor tube complications affected 40% of patients in both groups ($P = 0.995$), and events included: site infections requiring oral antibiotics ($n = 27$), other site/stoma complications ($n = 29$). Fifty percent of all patients had commenced clinically indicated tube feeding by week three. Tube use was high at the end of treatment with no differences between groups (88% standard care and 86% intervention, $P = 0.776$). The mean day of tube removal from completion of treatment was 104.7 ± 54.0 days in the standard care group vs 115.5 ± 62.5 days in the intervention group ($P = 0.333$).

Survival and disease outcomes. The outcomes on PET at 3 months post treatment were no different between groups ($P = 0.661$). A complete response was seen in 78% of patients in standard care ($n = 49$) and 81% in the intervention ($n = 42$). Salvage surgery for persistent disease was carried out for six patients in each group, and palliative care was required for eight patients in standard care and four patients in the intervention. At 12 months, there were no differences in disease-free survival or overall survival, with 19 cases of disease relapse in the standard care group and 10 cases in the intervention group ($P = 0.135$) (Figure 2A) and six and five deaths in the standard care and intervention group, respectively ($P = 0.946$) (Figure 2B).

Additional analysis. Adherence to the intervention was defined as consuming $\geq 75\%$ of the prescribed enteral feeding and unfortunately this was only achieved by 51% of patients. Due to this poor

Table 3. Summary of the effect of the early nutrition intervention on unplanned admissions and LOS in patients with head and neck cancer

	Standard care	Intervention	P-value
Total number of patients with an unplanned admission	31	33	0.27
Reason for unplanned admission	n (%)		
Clinical	15 (48)	12 (36)	0.33
Nutrition	20 (65)	20 (61)	0.747
G tube	8 (26)	6 (18)	0.461
LOS per unplanned admission	Median (range)		
Clinical	3 (1–23)	6 (1–36)	0.182
Nutrition	4 (1–24)	5 (2–25)	0.981
G tube	3 (1–22)	1 (1–2)	0.154

Abbreviations: G tube = Gastrostomy tube; LOS = length of stay.

adherence, a per-protocol analysis was also performed to compare those patients who adhered to the intervention ($n=29$) to standard care ($n=57$), but no significant differences were found for any outcomes.

When adherence to the therapeutic phase of feeding was compared (i.e., when tube feeding became clinically indicated in each group) the intervention group had a higher adherence (58 vs 38%, $P=0.037$). Adherent patients ($n=49$) had less weight loss than non-adherent patients ($n=55$) (-10.3 vs -12.6% , $P=0.038$).

Weight outcomes at the end of treatment were reviewed using routine clinical data. Weight change was $-6.7 \pm 5.3\%$ in standard care vs $-6.1 \pm 4.5\%$ in the intervention group on an intention-to-treat basis ($P=0.466$) and $-5.6 \pm 4.6\%$ in the adherent intervention group on a per-protocol basis ($P=0.299$).

DISCUSSION

This randomised controlled trial investigating an early tube feeding intervention was primarily conducted in a well-nourished group of patients with HNSCC who had a prophylactic gastrostomy placed prior to treatment without any significant dysphagia. The results from the intention-to-treat analysis found no impact on weight loss outcomes at three months post treatment, with both groups losing ~10% of their body weight. Consequently, there were no statistical differences in any of the other secondary outcomes in regards to nutritional status, body composition, quality of life or other clinical outcomes.

The overall body composition results are very similar to a recent report (although they measured outcomes at one month post treatment), with an absolute percentage fat mass loss of 3.9% and a FFM loss of 2.4kg, vs our measures of 4.3% and 3.3kg (De Carvalho *et al*, 2015). One study has reported lean mass accounts for 62% of weight loss mass (Jager-Wittenaar *et al*, 2011); however, this present study found the reverse with fat mass accounting for 67% of weight loss. The preservation of fat-free mass with nutrition intervention has been reported in other studies (Isenring *et al*, 2003). Further research is required on changes in body composition during and post treatment to understand any long term implications. Meanwhile, routine monitoring of body composition is suggested as this provides more information than body weight alone.

This is the first study to report on outcomes following an early prophylactic tube feeding intervention. There has been one other study, which has described an early nutrition intervention of dietary counseling pre-chemoradiotherapy compared to a historical control group, which found statistically significantly less weight loss, fewer breaks in radiotherapy and less unplanned admissions (Paccagnella *et al*, 2010). However, their early nutrition intervention was essentially equivalent to our control group. A similar style of study has recently been undertaken in patients

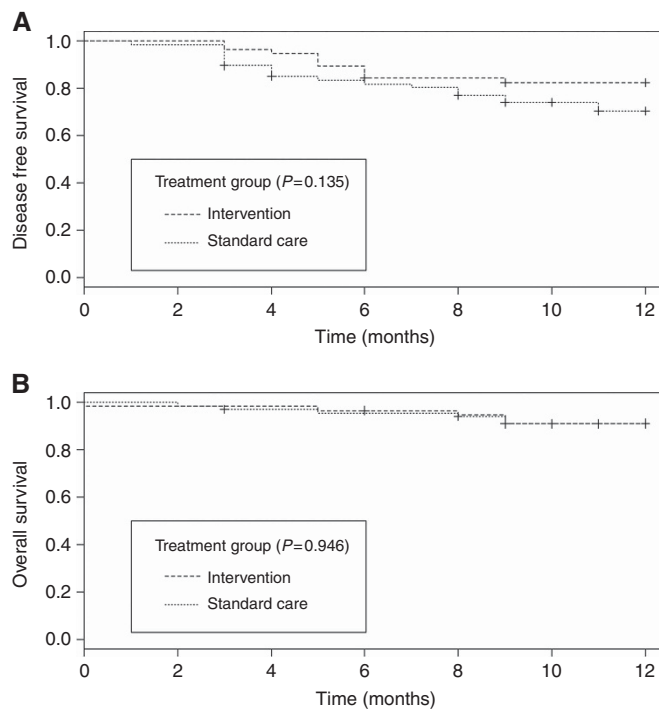


Figure 2. The effect of the early nutrition intervention on survival outcomes in patients with head and neck cancer. Kaplan–Meier curves to compare disease-free survival (A) and overall survival (B) at twelve months post-treatment between standard care and intervention groups.

with lung cancer (Kiss *et al*, 2016). Our current study design initiates supplementary prophylactic tube feeding prior to commencement of treatment and so could be described as an even more intensive early intervention.

The only other study to our knowledge, which has looked at early nutrition interventions in patients with HNSCC, is a secondary analysis in patients undergoing definitive radiotherapy as part of a larger prospective RCT ($n=1073$) (Rabinovitch *et al*, 2006). Their results showed that although patients who received nutrition support prior to treatment had benefits in terms of less weight loss and less grade three or four mucositis, they ultimately had poorer overall survival (Rabinovitch *et al*, 2006). Their patients who received pre-treatment nutrition support had more advanced stage tumours, lower performance status, more weight loss in last 6 months and more grade three and four dysphagia at baseline, and the detrimental impact of malnutrition at diagnosis on overall survival is well known (Datema *et al*, 2011). The methodological limitations of these exploratory findings are acknowledged by the authors and they recommend that RCT's are required to explore how nutrition

support in the malnourished patient may negatively impact upon treatment outcomes (Rabinovitch *et al*, 2007); however, there have been no further studies in this field. Other factors also need to be taken into consideration in interpretation of these findings such as evolving treatment and disease, with patients now primarily receiving chemoradiotherapy (compared to radiotherapy alone) and a higher incidence of human papilloma virus (HPV) associated tumours (Hocking *et al*, 2011). The profile of patients selected for our study was also quite different as the eligibility criteria focused on well-nourished patients with minimal dysphagia. Given critical weight loss during treatment is also an independent prognostic indicator of worse disease-specific and overall survival rates (Langius *et al*, 2013a) and even subtle weight loss of 2.4% is related to decreased survival (Martin *et al*, 2015), these studies highlight the importance of including mortality as an outcome for any nutrition intervention studies. Our 1-year survival outcomes to date have not demonstrated any differences with respect to the timing of nutrition intervention, although this was not the primary outcome and sample size may be a limiting factor to draw any firm conclusions. Further survival analysis is planned at 5 years post treatment.

One of the potential reasons for the negative findings from this trial was the poor adherence to the prescribed nutrition intervention (51%), which was much lower than expected. A study in hospitalised patients found 87% of prescribed tube feedings were met, however this was in a group of patients that were entirely dependent on enteral nutrition (Van den Broek *et al*, 2009). A systematic review on adherence to prescribed oral nutrition supplements, which is perhaps more akin to the supplementary bolus feeds used in this study, found a mean adherence of 79% (Hubbard *et al*, 2012). The prescribed daily tube feeds for the intervention were provided to the patients at no extra cost to facilitate adherence, as it has been shown that provision of complimentary nutritional supplements can improve outcomes (Lee *et al*, 2008), but this did not appear to help in this case. Key barriers patients encountered to tube feeding recommendations were nausea and early satiety, as well as a perception that the extra tube feeding was not required as patients felt they were eating normally. Further qualitative research is recommended to investigate these barriers in depth, as they are potentially modifiable and can be addressed. Improving adherence to dietary recommendations has been shown to result in improved outcomes both within this study and others (Capuano *et al*, 2008; Hopanci Bicakli *et al*, 2017). The characteristics of this patient population also suggest that adherence may be particularly challenging given the high rate of mental health problems, substance use and social issues which increases psychological distress and depression (DiMatteo *et al*, 2000; Kugaya *et al*, 2000). Adherence to other aspects of clinical management, such as adherence to radiotherapy protocols by the clinician, has also been shown to influence patient outcomes (Peters *et al*, 2010).

The main limitation of this study is that, despite a motivated patient cohort, poor adherence to the intervention impacted on the power of the study which may also explain why no significant differences were found on the post *hoc* per-protocol analysis. Steps were taken through the study by the research dietician to improve adherence such as; increased communication to the multidisciplinary team and more regular contact with the intervention patients. The clinician staff did change over the course of the study period, which may have led to variations in clinical practice, however this is reflective of the pragmatic nature of nutrition care delivery in healthcare settings, and was minimised as much as possible, particularly for the intervention care arm. Whilst attrition from the study was generally very low, geographical location of patients did inhibit some follow-up care for the study, particularly for physical measurement of BIA. Our study identified P16 status as a strong confounding variable associated with a number of outcomes which was adjusted for in the multivariate models, however, given the impact of HPV status on survival outcomes

(Ang *et al*, 2010) it is increasingly being suggested that clinical trials should stratify for smoking, staging and HPV (P16) status. Differences in quality of life related to tube feeding may also not have been addressed with the tools used; however, they are the most widely accepted tools used in this population (Ojo *et al*, 2012). Future studies could consider additional tools specifically related to tube feeding, such as the QOL-EF (Stevens *et al*, 2011). Finally, swallowing outcomes were not measured using a validated assessment tool in this study, but there was no impact of long term gastrostomy dependency as a surrogate measure of dysphagia.

This interventional approach is not only restricted to hospitals that utilise prophylactic gastrostomy placement. Although designed as a tube feeding intervention, it could still be used by sites who prefer the reactive approach to nutrition management during treatment, as the supplements could be prescribed orally, and this is actually what some of our patients preferred to do. They were still included in the study as their nutritional intake was still being supplemented whether it was by the oral or enteral route. Only 11% of eligible patients (19 out of 174) declined to participate, which demonstrated a high acceptability of the trial, although this did not translate into adherence.

The use of prophylactic gastrostomy tubes remained high in this cohort of pre-defined high nutritional risk patients, with 87% of all study patients using their tube at the end of treatment, which confirms appropriate decision-making regarding tube placement. Although the early nutrition intervention did not minimise weight loss or improve other associated outcomes, this study has highlighted the significant barriers that patients encounter. Given the finding that patients who followed the early nutrition intervention had higher levels of adherence to nutrition recommendations later on in treatment, which did reduce weight loss, it is planned to introduce this approach into practice.

In conclusion, this research demonstrates the high complexity of managing patients with head and neck cancer, as desired outcomes have not been attained even with intensive intervention and support. While this novel early nutrition intervention can be considered to assist adherence, it is but one of many potential strategies. A multi-component intervention by the multidisciplinary team is recommended to adequately address and overcome patient barriers to healthcare recommendations before further improvements in nutrition outcomes are realised.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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