ISSN (electrónico): 1699-5198 - ISSN (papel): 0212-1611 - CODEN NUHOEQ S.V.R. 318

Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

Early nutrition support therapy in patients with head-neck cancer

Soporte nutricional precoz en pacientes con cáncer de cabeza y cuello

María Rosa Alhambra Expósito[1], Aura D. Herrera-Martínez[1], Gregorio Manzano García[1], María Espinosa Calvo[2], Carmen María Bueno Serrano[2] and María Ángeles Gálvez Moreno[1]

[1]Endocrinology and Nutrition Service. Hospital Universitario Reina Sofía. Córdoba, Spain. [2]Radiotherapy Oncology Service. Hospital Universitario Reina Sofía. Córdoba, Spain

Abstract

Background: weight loss is commonly observed in head-neck cancer patients, affecting 75-80% of them during their treatment period; weight loss is severe in 30-50% of cases. According to ESPEN publications, nutritional assessment in cancer patients should be frequently performed and nutrition support therapy must be started when any deficiency is observed.

Objective: to evaluate the effect of early nutrition support (ENS) in nutritional markers and treatment response in patients with head-neck cancer receiving radiotherapy (RT).

Patients and methods: one hundred and two patients with head-neck cancer and more than two points in the malnutrition screening tool (MUST) before receiving RT were included. ENS was provided to all patients consisting in nutrition counselling, oral supplements and/or enteral nutrition.

Results: one hundred and two patients were included; 76% had a stage IV of disease. At the end of RT, after ENS, a slightly decreased body mass index (BMI) with an increased fat-free body mass was observed ($p < 0.001$); biochemical nutrition parameters remained stable despite decreased oral intake. Less than 40% of patients had severe epithelitis or mucositis; 92% of patients received the total amount and doses of originally planned RT sessions, while 22.8% required RT-sessions interruption. Patients with caloric malnutrition had a lower fulfillment of RT than those without caloric malnutrition ($p < 0.001$). Mortality was related to lower Karnosfsky, higher weight loss before RT and higher grade of mucositis/epitelitis ($p < 0.05$).

Conclusions: patients who receive ENS keep their nutritional condition instead of associated effects due to RT. ENS represents an efficient treatment and could prevent malnutrition associated comorbidities in oncologic patients.

Key words:

Head-neck cancer. Nutrition. Radiotherapy.

Resumen

Antecedentes: la pérdida de peso es un síntoma frecuente en el cáncer de cabeza y cuello (CCC), afecta a un 75-80% de los pacientes y es severa en un 30-50% de los casos. Según las publicaciones de la ESPEN, la valoración nutricional puede realizarse periódicamente y se debe comenzar el soporte nutricional cuando se observe algún déficit nutricional.

Objetivo: evaluar el efecto del soporte nutricional precoz (SNP) en marcadores nutricionales y la respuesta terapéutica en pacientes con CCC que reciben radioterapia (RT).

Pacientes y métodos: se incluyeron 102 pacientes con CCC que tuviesen al menos dos puntos en la escala de *screening* nutricional (MUST) antes de recibir RT. Todos los pacientes recibieron SNP, que consistió en asesoramiento nutricional y suplementos orales o nutrición enteral.

Resultados: se incluyeron 102 pacientes, el 76% de ellos en estadio IV de la enfermedad. Al final de la RT, después de recibir SNP, se observó una disminución discreta en el índice de masa corporal (IMC) acompañada de aumento de la masa libre de grasa ($p < 0,001$); los parámetros bioquímicos nutricionales permanecieron estables a pesar de la disminución en la ingesta. La incidencia de mucositis o epitelitis severa fue menor al 40%; el 92% de los pacientes recibieron la totalidad de las sesiones de RT planeadas, mientras que solo el 22,8% interrumpió parcial o totalmente la RT. Aquellos pacientes con desnutrición calórica previa tuvieron un menor cumplimiento terapéutico ($p < 0,001$). La mortalidad se relacionó con el índice de Karnosfsky, con una mayor pérdida de peso previa a la RT y mayor grado de mucositis o epitelitis ($p < 0,05$).

Conclusiones: aquellos pacientes que reciben SNP mantienen su estado nutricional a pesar de los efectos asociados con RT. El SNP representa una estrategia terapéutica eficiente para prevenir complicaciones relacionadas con la nutrición en pacientes oncológicos.

Palabras clave:

Cáncer de cabeza y cuello. Nutrición. Radioterapia.

Received: 14/09/2017 • Accepted: 16/11/2017

Alhambra Expósito MR y Herrera-Martínez A equally contributed to the work and should be considered co-first authors.

Alhambra Expósito MR, Herrera-Martínez AD, Manzano García G, Espinosa Calvo M, Bueno Serrano CM, Gálvez Moreno MA. Early nutrition support therapy in patients with head-neck cancer. Nutr Hosp 2018;35:505-510

DOI: http://dx.doi.org/10.20960/nh.1560

Correspondence:

Aura Dulcinea Herrera-Martínez. Endocrinology and Nutrition Service. Hospital Universitario Reina Sofía. Av. Menéndez Pidal, s/n. 14004 Córdoba, Spain
e-mail: aurita.dhm@gmail.com

INTRODUCTION

Head and neck cancer includes oral cavity, pharynx, larynx, hypopharynx and paranasal sinus (1). The majority are squamous cell carcinomas, affecting specially men, with a male to female ratio ranging from 2:1 to 4:1 (2). Some risk factors have been described, including alcohol abuse, smokeless tobacco and papilloma virus (VPH) infection (3). Its incidence is approximately 550,000 cases and 300,000 deaths per year (1). In Europe, during 2012, 250,000 new cases and 63,500 deaths were reported (4).

Treatment goals include local disease control and increase of the survival with minimal adjacent tissue damage; more than 60% of patients with head-neck cancer can be cured with surgery and/or radiotherapy (RT). Treatment options are determined by the disease localization, extension and histology. Patients with stage I and II are treated with surgery or radiotherapy (curative rate 77-91%), while stages III and IV require the combination of extensive surgery, radiotherapy or chemoradiation (curative rate ranges 25-61% depending on tumor localization) (2).

Malnutrition affects 30-50% of patients with head-neck tumors, especially those localized in the oropharynx or the hypopharynx; around 30% have severe malnutrition during the six months prior to diagnosis. Chemotherapy worsens the nutritional condition due to tract digestive system related symptoms including taste loss, mucositis, xerostomia, nauseas and vomits (5). Malnutrition in head-neck cancer patients has been related to a higher rate of postsurgical complications, worse treatment response and higher tumor recurrence. Malnutrition increases the risk of infections, treatment related toxicity and decreases quality/expectative of life (6). Several studies have suggested more treatment interruptions and worse treatment effectiveness related to mucositis (7); fat-free body mass loss has been proposed as the responsible for the increase in mortality and worse prognosis related to malnutrition in cancer patients (8).

Early nutrition support (ENS) seems to improve the outcome in patients with gastrointestinal tract and head-neck tumors who receive RT (5), suggesting that maintaining body weight stable avoids deterioration in nutritional status (5). International guidelines suggest early dietary counselling and oral supplements for avoiding treatment related weight loss and not-planned interruptions in RT (9); even the improvement in nutritional status could be related to decreased RT toxicity (5).

Based on this, our aim was to evaluate the effect of early nutritional support using dietary counselling, oral supplements or enteral nutrition on anthropometric, biochemical markers and RT tolerance in patients with head-neck cancer.

PATIENTS AND METHODS

PATIENTS

The Ethics Committee of the Hospital Universitario Reina Sofía (Cordoba, Spain) approved the study, which was conducted in accordance with the Declaration of Helsinki and according to national and international guidelines. Every individual or family member accepted the informed consent before inclusion into the study. We included both sex patients, older that 18-years old, with minimal two points in the malnutrition screening tool (MUST) (10). All patients had a head-neck cancer requiring RT and they were evaluated minimal in two different occasions in our outpatient clinic before the inclusion into the study. All the evaluated patients that fulfilled the inclusion criteria were included. Patients were treated according to the current guidelines for head-neck cancer (11,12). Radiotherapy consisted in external radiation using high-energy photon beams (4-6 MV) generated by a linear accelerator. The total doses was 46-70 Gy divided in 1.8-2 Gy per day, five days per week (doses per week: 10 Gy). RT tolerance was measured using the oncology toxicity grading (RTOG) as follows (9):

- Grade 0: none.
- Grade 1: asymptomatic, mild symptoms.
- Grade 2: local symptoms; intervention is required.
- Grade 3: severe without life threatening effect.
- Grade 4: life threatening, urgent intervention is required.
- Grade 5: death related to adverse effect.

For our analysis, the five levels of the RTOG were combined in three different groups as follows: good tolerance, grades 0-1; regular tolerance, grades 2-3; and bad tolerance, grades 4-5.

CLINICAL EVALUATION

Anthropometric evaluation included body mass index (BMI) calculated as weight (kg)/height (m^2). The percentage of weight loss (%EWL) was calculated using the following formula: (initial weight –follow-up weight)/(initial weight– ideal body weight) x 100; the ideal body weight was calculated for a BMI of 21 kg/m^2 in women and 23 kg/m^2 for men (13,14). The mean Karnofsky index (KI) (15) was calculated for each patient.

Mucositis evaluation was performed according to the World Health Organization (WHO) classification (16):

- Grade 0: none.
- Grade I (mild): oral soreness erythema.
- Grade II (moderate): oral erythema, ulcers, solid diet tolerated.
- Grade III (severe): oral erythema, ulcers, liquid diet only.
- Grade IV (life-threatening): oral erythema, ulcers, oral alimentation impossible.

Epithelitis evaluation was performed following the scale:

- Grade 0: no change from baseline, asymptomatic.
- Grade 1: follicular faint or dull erythema epilation, dry desquamation, decreased sweating.
- Grade 2: bright erythema, confluent moist desquamation, pitting edema.
- Grade 3: ulceration, hemorrhage, necrosis.

This scale was adapted from the toxicity criteria of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (17).

Anemia was also divided in four different groups according to the hemoglobin (Hb) level:

- Grade 0: Hb > 11 GM%.
- Grade 1: Hb 11-9.5 GM%.
- Grade 2: Hb 9.5-7.5 GM%.
- Grade 3: Hb < 7.5 GM%.

NUTRITIONAL INTERVENTION

All patients received nutritional counselling based on the Mediterranean diet (18), oral supplements/enteral nutrition and a close follow-up by a nutritionist in our hospital. The volume of enteral nutrition per day was adjusted according to the basal situation of the patient, and was modified according to the food intake and the presence of RT related complications.

STATISTICAL ANALYSIS

Normality distribution of the data was determined using the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation. Categorical variables were reported in percentage values. Univariate analysis in continuous variables was performed using the Wilcoxon test. Chi-squared compared categorical data. Cox regression curves were performed for the evaluation of mortality associated variables. Statistical analyses were performed using SPSS statistical software v15. Data in graphs are expressed as mean ± SEM. p-values < 0.05 were considered as statistically significant.

RESULTS

A total of 102 patients with head-neck cancer were included in the study. The clinical features of patients are summarized in table I. In our group, 47.9% of patients were active smokers and 42.1% had active alcohol abuse. Otalgia and oral ulcer were the most prevalent symptoms (23.5% and 20.6% respectively), related to the most common primary tumor localization (oropharynx, 34.3%; larynx, 21.4%). A stage IV of disease was observed in 76% of patients when included; stage IVa was the most prevalent (63%). The mean Karnofsky index (KI) was 89.2%.

Early nutritional support was systematically performed in all patients before RT. More than 55% had decreased or different oral intake before RT but almost 90% of the included patients had abnormal oral intake after RT. At that moment, enteral nutrition was the only support in 26.6% of patients (Table II) while more than 20% required a feeding tube. A non-clinically significant decreased BMI was observed after RT ($p < 0.001$), with an increase in fat-free body mass ($p < 0.001$). Interestingly, biochemical markers including albumin, prealbumin and transferrin remained stable after the treatment period (Table II).

In our group, more than 55% of patients tolerated well the RT, 92% of cases attended to all the originally planned RT sessions and only 27.7% of patients interrupted the RT schedule, while 29.7% required hospitalization. More than 60% of patients had grade 0-1 mucositis and epithelitis and more than a half tolerated the RT treatment adequately (Table III).

In our study, eight patients died. These patients characteristically had lower KI (81.25% *vs* 90.18%; $p < 0.01$), higher weight loss before RT (19.9 *vs* 4.6%; $p < 0.001$), higher grade of mucositis ($p < 0.05$) and higher epithelitis ($p < 0.05$). There were no significant differences between age or initial biochemical nutrition parameters.

Table I. General characteristics of the studied population

Characteristic	Total 100% (n = 102)
Sex: male	79.4% (81)
Age (years old)	64.06 ± 10.81
Smoke habit	
Active	47.9% (48)
Ex-smoker	30.9% (32)
Alcohol abuse at diagnosis	
Active	42.1% (40)
Previous	22.1% (21)
Symptoms	100% (102)
Otalgia	23.5% (24)
Oral ulcer	20.6% (21)
Dysphonia	19.6% (20)
Odynophagia	16.7% (17)
Others: (epistaxis, polyp, hemoptysis)	8.7% (9)
Dyspnea	5.8% (6)
Cervical nodule	3.9% (4)
Histologically confirmed localization	
Oropharynx	34.3% (35)
Larynx	21.4% (32)
Salivary glandules	11.8% (12)
Oral cavity	7.8% (8)
Hypopharynx	7.8% (8)
Nasopharynx	4.9% (5)
Metastasis of unknown primary tumor	1.9% (2)
Stage of disease	
Stage I	4.3% (4)
Stage II	3.3% (3)
Stage III	16.3% (15)
Stage Iva	63% (58)
Stage IVb	13% (12)
*Previous treatment**	
Surgery	52.9% (54)
Concomitant or induction chemotherapy	63.7% (65)

**Radiotherapy was a therapeutic option in all included patients.*

Table II. Nutritional support before and during RT in head-neck cancer patients

Characteristic	Before RT (102)	End of RT (94)	p
BMI (kg/m^2)	25.99 ± 5.10	25.43 ± 7.37	< 0.001
Fat-free body mass (%)	73.42 ± 9.38	74.34 ± 14.42	< 0.001
Albumin (g/dl)	3.91 ± 0.59	3.77 ± 0.44	0.339
Prealbumin (mg/dl)	23.88 ± 5.60	23.03 ± 5.89	0.797
Transferrin(mg/dl)	231.12 ± 52.51	203.16 ± 61.55	0.319
Lymphocytes (mm^3)	1,738.38 ± 762.81	1,140.45 ± 1,030.65	< 0.001
Oral intake			0.200
Normal	42.6% (43)	10.1% (10)	
Less than usual	26.7% (27)	32.6% (31)	
Crushed only	21.8% (22)	24.1% (23)	
Liquids only	3% (3)	6.3% (6)	
Oral supplements only	5.9% (6)	26.6% (24)	
Feeding system			0.007
Oral	90.1% (92)	78.3% (74)	
Feeding tube	9.9% (10)	21.7% (20)	
PEG	0% (0)	0% (0)	
Enteral nutrition*	63% (74)	97.6% (92)	0.041
Number or oral supplements per day			0.032
Less than two		4.8%(5)	
Two	32% (33)	15.5% (15)	
Three	51.5% (53)	48.8% (46)	
Four	7.2% (7)	17.9% (17)	
More than five	2.1% (2)	13.1% (12)	
Enteral nutrition formula			0.125
Normocaloric-normoproteic	6.5% (7)	7.2% (7)	
Normocaloric-hyperproteic	4.9% (5)	19.3% (18)	
Hypercaloric-hyperproteic	81.5% (83)	73.5% (69)	

*PEG: percutaneous enteral gastrostomy. *Enteral nutrition refers to oral supplements or total enteral nutrition.*

Interestingly, patients with previous caloric malnutrition (defined as minimal body weight loss in the last three months of 5%), had a higher non-completion rate of RT compared to those patients without caloric malnutrition (66.5 *vs* 97.8%, respectively; $p < 0.001$). Those patients requiring induction or concomitant chemotherapy had more non-desired RT interruptions ($p < 0.05$) and higher number of hospitalizations ($p < 0.05$) (data non-shown).

DISCUSSION

The majority of patients with head-neck cancer have locally advanced disease at diagnosis. For this reason, treatment is usually aggressive, with a therapeutic goal of achieving a cure while minimizing toxicity (6). Patients are frequently malnourished prior to the beginning of treatment. Malnutrition in head-neck cancer affects 30-50% of patients (6,7,19); since malnutrition has been related to higher post-operative complication rates, worse treatment response and higher tumor recurrence, early nutritional intervention is required (6). Enteral nutrition is based on the use of oral supplements or gastro-enteric tube feeding; its goal is to guarantee and, if possible, increase the nutrients intake when oral intake is not adequate or safe (9).

Our studied population presented the most common risk factors and staging at diagnosis that are currently described in head-neck cancer patients (2,20). It represents, then, an appropriate group of patients for analyzing results and driving conclusions.

It is well known that some nutritional parameters should be controlled in cancer patients in order to initiate early interventions and to prevent excessive deficits (21). Nutritional evaluation should be performed frequently and ENS should be initiated when deficits are detected (level of evidence C); according to

Table III. Treatment evolution under early nutrition support in head-neck cancer patients

Characteristic	n = 102
Treatment tolerance-ROTG	
Good	53.0% (52)
Regular	16.3% (16)
Bad	26.5% (26)
Dead	8.2% (8)
Complete RT schema	92% (94)
Non-organized RT interruption	22.8% (23)
Duration of non-organized RT interruption (mean in days)	5.37 ± 4.22
Hospitalization need	29.7% (28)
Mucositis	
Grade 0	3.2% (3)
Grade 1	18.1% (17)
Grade 2	43.6% (41)
Grade 3	31.9% (30)
Grade 4	3.2% (3)
Epithelitis	
Grade 0	25.5% (24)
Grade 1	40.4% (38)
Grade 2	27.7% (26)
Grade 3	6.4% ()
Anemia	
Grade 0	90.1% (64)
Grade 1	2.8% (2)
Grade 2	7% (5)
Grade 3	0% (0)

the current guidelines, enteral nutrition with standard formulas should be initiated if malnutrition is detected or if oral intake has decreased during the last 7-10 days (9). Intensive early nutrition support with regular follow-up helped attenuate the natural weight loss history of treatment in our study group, as it has been previously reported (5). ESPEN guidelines suggest nutritional counseling and oral supplements use in patients under chemo-radiotherapy for avoiding weight loss (9,21); oral, enteral or parenteral route may be used depending on the clinical situation of each patient and specially, the level of function of the gastrointestinal tract (21).

Energy requirements in cancer patients should be similar to those of healthy subjects; protein intake should be above 1 g/kg/day, or even above 1.5 g/kg/day (21). Clinical features and treatment options in head-neck tumors may make reaching these goals difficult, suggesting the importance and necessity of nutritional supplements in these group of patients.

A slightly decrease in weight loss and BMI (< 0.6 kg/m^2) was observed in our patients, whereas serum proteins and nutritional markers remained stable. Only lymphocytes were decreased, which could be probably related to chemotherapy effects or to the tumor itself (22). Despite body weight loss, an increase in fat-free body mass was observed. Similar results have been reported in randomized studies evaluating early and intensive nutrition intervention in patients with gastrointestinal and head-neck tumors (5) and advanced stage IV solid tumors (23).

It is well known that RT is associated with acute side effects (whose incidence increases when concomitant or induction chemotherapy is administered), especially oral mucositis (24,25). In our group, the incidence of severe mucositis was lower than 10%, contrasting with other studies reporting mucositis rates of 89-97% in head-neck cancer patients receiving RT (26). The incidence of severe mucositis (grades 3-4) has been reported in 34-53% of patients depending on the RT method (26). Interruption rates of 86% have been also described, especially due to mucositis (27). Interestingly, a four-fold decrease in non-organized interruptions has been observed in our study group.

Oral mucositis has been related to unscheduled breaks or delays in RT administration (24,25). Unscheduled RT interruptions were observed only in 22% of the evaluated patients; this rate tends to be higher in other reports (28). Even RT interruption rates of 36% exclusively due to mucositis have been previously described (27). Remarkably, it has been suggested that when inadvertent or deliberated gaps in RT occur, reduced tumor control may result because of accelerated tumor clonogen repopulation (28). Based on this, nutritional counseling and oral supplements use are recognized as important tools to reduce weight loss and avoid treatment interruptions in patients receiving chemo-radiotherapy (9).

Compared to clinical guidelines which suggest the use of standard supplements (9,21), we mostly used specific enteral formulas depending on the patient's nutritional status, daily oral intake and regular use of the nutrition supplements. In our group, previous caloric malnutrition and combined chemo-radiotherapy was related to worse treatment adherence and fulfillment; probably in these cases, enteral nutrition and/oral supplements should be started earlier, since the diagnosis is performed.

A limitation of this study was the number of participants, the absence of a control group and the absence of other anthropometric and nutritional markers (for example, dynamometry or tomography guided fat-free mass measuring). Despite this, the ENS in our group showed relevant clinical benefits.

In conclusion, treatment in head-neck cancer patients requires a multidisciplinary approach including ENS. Enteral nutrition should be started previous to the systemic treatment and kept during and after it, in order to decrease weight loss. This strategy would allow to decrease treatment interruptions and systemic related complications and improve quality of life. Nutritional advice and oral supplements should be started earlier in previous malnourished patients and in those receiving combined chemo-radiotherapy or induction chemotherapy. Randomized, large studies are required to confirm and increase these results.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61(2):69-90.
2. Licitra L, Locati LD, Bossi P. Head and neck cancer. Ann Oncol 2004;15(Suppl 4):iv267-73.
3. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev 2009;18(2):541-50.
4. Gatta G, Botta L, Sánchez MJ, Anderson LA, Pierannunzio D, Licitra L. Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: the EUROCARE-5 population-based study. Eur J Cancer 2015;51(15):2130-43
5. Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. Br J Cancer 2004;91(3):447-52.
6. Bossola M. Nutritional interventions in head and neck cancer patients undergoing chemoradiotherapy: a narrative review. Nutrients 2015;7(1):265-76.
7. De Luis DA, Izaola O, Aller R. Nutritional status in head and neck cancer patients. Eur Rev Med Pharmacol Sci 2007;11(4):239-43.
8. Tchekmedyian NS, Zahyna D, Halpert C, Heber D. Assessment and maintenance of nutrition in older cancer patients. Oncology (Williston Park) 1992;6(2 Suppl):105-11.
9. Arends J, Bodoky G, Bozzetti F, Fearon K, Muscaritoli M, Selga G, et al. ESPEN guidelines on enteral nutrition: non-surgical oncology. Clin Nutr 2006;25(2):245-59.
10. Stechmiller JK. Early nutritional screening of older adults: review of nutritional support. J Infus Nurs 2003;26(3):170-7.
11. Chan AT, Gregoire V, Lefebvre JL, Licitra L, Hui EP, Leung SF, et al. Nasopharyngeal cancer: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(Suppl 7):vii83-5.
12. Gregoire V, Lefebvre JL, Licitra L, Felip E, Group E-E-EGW. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21(Suppl 5):v184-6.
13. Isabel RRJMCMCRP. Valoración del estado nutricional. Sociedad Andaluza de Nutrición Clínica y Dietética; 2010. Available from: http://sancydes/comedores/discapacitados/recomendacionesnutricionalphp
14. Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. Ann Pharmacother 2000;34(9):1066-9.
15. List MA, D'Antonio LL, Cella DF, Siston A, Mumby P, Haraf D, et al. The performance status scale for head and neck cancer patients and the functional assessment of cancer therapy-head and neck scale. A study of utility and validity. Cancer 1996;77(11):2294-301.
16. World Health Organization. Handbook for reporting results of cancer treatment. Geneva: World Health Organization; 1979. pp. 15-22.
17. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31(5):1341-6.
18. Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies. Cancer Med 2015;4(12):1933-47.
19. Van Bokhorst-de van der S, Van Leeuwen PA, Kuik DJ, Klop WM, Sauerwein HP, Snow GB, et al. The impact of nutritional status on the prognoses of patients with advanced head and neck cancer. Cancer 1999;86(3):519-27.
20. Shaw R, Beasley N. Aetiology and risk factors for head and neck cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol 2016;130(S2):S9-S12.
21. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2017;36(1):11-48.
22. Kuss I, Hathaway B, Ferris RL, Gooding W, Whiteside TL. Decreased absolute counts of T lymphocyte subsets and their relation to disease in squamous cell carcinoma of the head and neck. Clin Cancer Res 2004;10(11):3755-62.
23. May PE, Barber A, D'Olimpio JT, Hourihane A, Abumrad NN. Reversal of cancer-related wasting using oral supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine. Am J Surg 2002;183(4):471-9.
24. Bieri S, Bentzen SM, Huguenin P, Allal AS, Cozzi L, Landmann C, et al. Early morbidity after radiotherapy with or without chemotherapy in advanced head and neck cancer. Experience from four nonrandomized studies. Strahlenther Onkol 2003;179(6):390-5.
25. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350(19):1945-52.
26. Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiother Oncol 2003;66(3):253-62.
27. Santos RC, Dias RS, Giordani AJ, Segreto RA, Segreto HR. Mucositis in head and neck cancer patients undergoing radiochemotherapy. [Mucosite em pacientes portadores de cancer de cabeca e pescoco submetidos a radioquimioterapia]. Rev Esc Enferm USP 2011;45(6):1338-44.
28. James ND, Williams MV, Summers ET, Jones K, Cottier B, Royal College of Radiologists Clinical Audit S. The management of interruptions to radiotherapy in head and neck cancer: an audit of the effectiveness of national guidelines. Clin Oncol (R Coll Radiol) 2008;20(8):599-605.