

Original Paper

Importance of Nutritional Status in Treatment Response of Patients with Nasopharyngeal Carcinoma

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REZUMAT

Introducere: In mod obișnuit, pacienții cu cancer nazofaringian prezintă o scădere în greutate de cauză tumorală și ca urmare a radio- și chimioterapiei. Scăderea în greutate crește incidența complicațiilor în timpul tratamentului, influențează statusul de performanță și prognosticul bolii. Scopul acestui studiu este de a investiga influența IMC, vârstei, tipului histopatologic de tumoră, precum și a stadializării afecțiunii, asupra prognosticului pacienților cu cancer nazofaringian.

Metode: Am analizat 27 pacienți cu cancer rinofaringian internați în Clinica de Oncologie Medicală a Spitalului Universitar de Urgență Elias în perioada 2012-2015. Toți pacienții au efectuat radio- și chimioterapie concomitentă, chimioterapie adjuvantă și terapie genică țintită. Înainte de inițierea tratamentului s-a calculat IMC.

Rezultate: S-a remarcat că pacienții cu greutate normală și cei supraponderali au avut cele mai bune rezultate la 3 ani de la terminarea tratamentului. 78% din pacienții cu răspuns complet după radio-chimioterapie au avut remisie completă la 3 ani de la terminarea tratamentului. Pacienții subponderali au avut rezultate mai slabe și un prognostic prost din cauza persistenței tumorale și recidivelor loco-regionale.

Concluzii: Statusul nutrițional are un impact important asupra ratei de răspuns terapeutic și asupra toleranței tratamentului, asupra statusului de performanță și a calității vieții. Fiind asociată cu un prognostic prost, casexia neoplazică trebuie tratată adecvat cu scopul de a îmbunătăți statusul fizic și funcțional, calitatea vieții și supraviețuirea.

Cuvinte-cheie: cancer nazofaringian, scădere în greutate, indice de masă corporală, casexie, anorexie

ABSTRACT

Introduction: Usually patients with nasopharyngeal carcinoma have weight loss due to the tumor itself and to the radio-chemotherapy. Weight loss increases the incidence of complications during the treatment, influences the performance status and the prognostic of the disease. The aim of this retrospective study is to investigate the influence of BMI, age, histological type of NPC and stage of disease on the prognostic of patients with nasopharyngeal carcinoma.

Methods: We analyzed 27 patients with nasopharyngeal cancer, admitted in Medical Oncology Clinic of Elias University Emergency Hospital between 2010-2015. All patients undergo radiotherapy with concurrent chemotherapy, adjuvant chemotherapy and gene targeted therapy. We calculated BMI before the beginning of the treatment.

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Results: We remarked that normal and overweight patients had the best results at 3 years after the treatment. 78% of patients with complete response post radio-chemotherapy had complete remission at 3 years after finishing treatment. Underweight patients had the worse results and poor prognostic due to higher rates of tumor remnants or local-regional recurrence

Conclusions: Nutritional status has an important impact over the response rate and tolerance of the treatment, performance status and quality of life. Being associated with a poor prognostic, cachexia must be treated properly, in order to improve patient's physical and functional status, quality of life and overall survival.

Key words: nasopharyngeal carcinoma, weight loss, body mass index, cachexia, anorexia

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is the most frequent type of malignant tumor of nasopharynx. It represents 2% of all upper aero-digestive tract cancers (1). There is no uniform geographic spread of NPC with the highest rate in Southern China (Guangdong Region) 20-50/100.000 inhabitants, then South-Eastern Asia, Eskimos population, Northern Africa and Middle East.

The incidence is higher in male gender than in women with a ratio of 2-3:1 (2). It has been observed in both high and low incidence areas.

Nasopharyngeal cancer may occur quite often among adolescents and young people, but the peak of the incidence is between 40-60 years (3).

Nasopharyngeal carcinoma has a multifactorial etiology. It was proved familial aggregation and hereditary susceptibility in both high and low-incidence areas (2), which may explain the high risk maintained at people immigrating from endemic areas to low-incidence areas.

The presence of Epstein-Barr (EBV) antibodies in patients serum was associated with the risk of NPC appearance. Although most people get infected with EBV during their lives, only a small part of them develop nasopharyngeal cancer, showing the influence of environmental factors in activating of EBV.

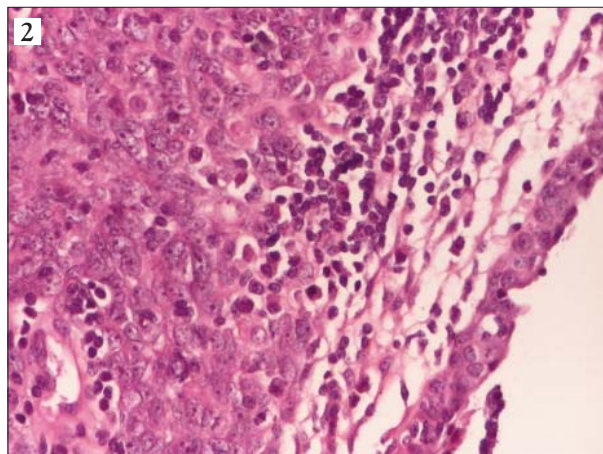
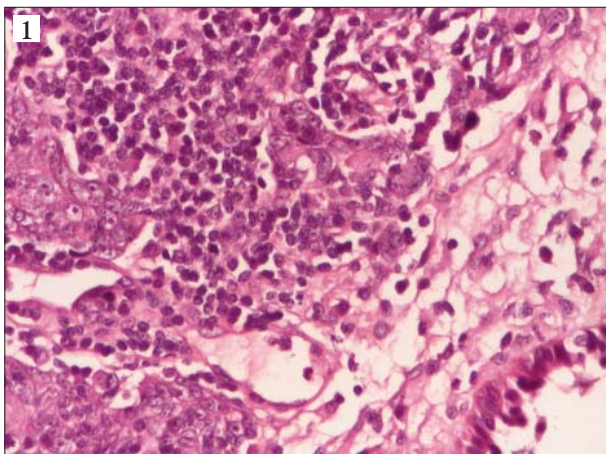
Lifestyle may influence the development of NPC. The

heavily consumption of salty fish or conserved food in endemic areas (Cantonese people) represents an important risk factor in appearance of NPC because of their content of N-nitrosamine. The relative risk for development of NPC to people who frequently eat conserved and salty food from the early childhood was estimates to be 1.1-37.7 (4).

As in other cases of malignant tumors, smoking and professional exposure (formaldehyde, wood dust) are also risk factors for NPC. Different studies revealed that the risk of NPC in smokers is 2-6 times higher than in non-smokers (2).

In the last years, economic development led to important lifestyle changes. In high- and low-incidence areas (including Romania), eating and living habits and also increasing number of smokers have determined a higher risk of NPC appearance.

Nasopharyngeal carcinoma is a malignant epithelial tumor which usually develops in Rosenmuller fossa of the lateral wall of the nasopharynx. It represents about 70% of all malignant tumors of nasopharynx (1). According to World Health Organization (WHO) classification, there are three histological types of NPC: "keratinizing squamous cell carcinoma", "non-keratinizing carcinoma" (divided in two subtypes: "differentiated" and "undifferentiated"), and "basaloid squamous cell carcinoma". (Fig. 1, 2)



Figures 1, 2. Histological aspects of non-keratinizing nasopharyngeal carcinoma

Undifferentiated carcinoma is the most frequent type of NPC, reaching in endemic areas up to 92% and the differentiated non-keratinizing was found in 7-49 % of cases (5). It was proved that the difference between these two histological subtypes has no clinical significance which leads to similar prognosis (6). Keratinizing squamous cell carcinoma is common in western countries and it has been reported in up to 67% (5). Some studies suggest that this subtype has a lower response to radiotherapy and worse prognosis.

Its position in a "silent area" and wide spectrum of symptoms make difficult early diagnosis of nasopharyngeal carcinoma. Therefore, most patients present to the first clinical exam with advanced loco-regional disease or distant metastasis. Advanced stage of disease is often accompanied with malnutrition and cachexia. There were issued several definitions of cachexia, one of the recent definition describing cachexia as "a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass" (7). Evans et al. established diagnostic criteria of cachexia (Table 1).

The etio-pathogenic mechanisms of cachexia are not well understood. Two mechanisms are involved in development of neoplastic cachexia:

1. The neoplasm itself produces anorexia, nausea, taste disorders. The extension of tumor at oro- or hypopharynx may produce dysphagia which affects food intake and consecutively determine weight loss.

The treatment of nasopharyngeal cancer is complex and aggressive, especially in advanced stages. Radiotherapy is standard treatment of NPC and it is associated

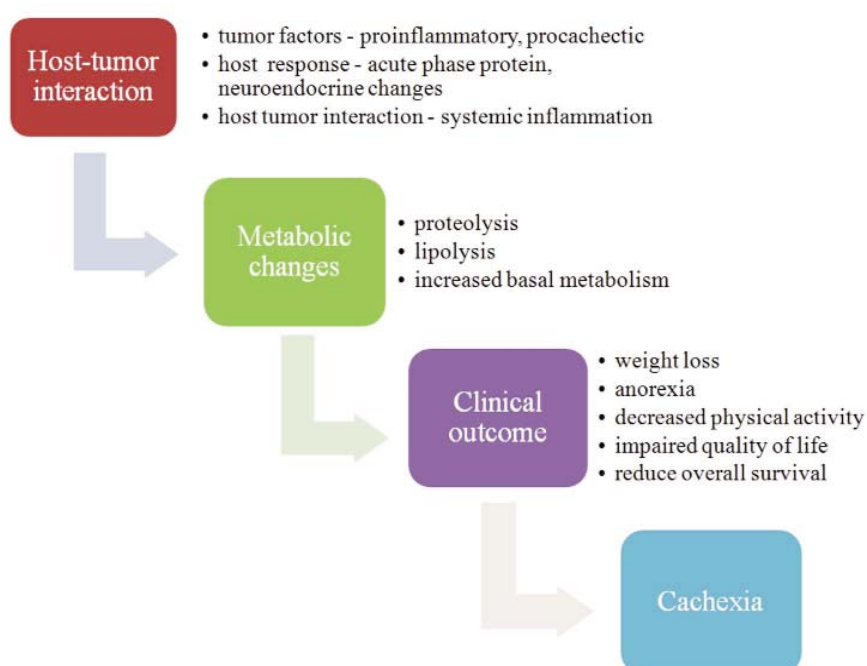
Table 1. Diagnostic criteria of cachexia

Major criteria	Minor criteria (3 of 5)
Weight loss of at least 5% in 12 months or less BMI <20 kg/m ²	Increased muscle strength Fatigue Anorexia Low fat-free mass index Abnormal biochemistry: - Increased inflammatory markers (CRP, IL-6) - Anaemia (Hb < 12 g/dL) - Low serum albumin (<3.2 g/dL)

with induction, concurrent or adjuvant chemotherapy in advanced stages. It is well-known that radiotherapy induces odynophagia, dysphagia, xerostomia, oral mucositis, taste and smell disorders. Also, chemotherapy produces nausea, vomiting, abdominal pains, paralytic ileus. All these acute or late side-effects of the antineoplastic treatment impair nutritional status and may determine interruption of the treatment with consecutive poor loco-regional control and poor survival (8).

2. The second mechanism of producing cachexia is due to metabolic changes and tumor and host inflammatory response. It's not the result of nutritional deprivation, in fact is the result of increasing energy consumption, raised levels of acute phase proteins, changes of protein and lipid metabolisms (9) (Graphic 1).

Knowing the mechanisms of producing cachexia and evaluating the nutritional risk of every patient with cancer, we are able to identify the early signs of malnutrition, in



Graphic 1. Mechanisms of producing cachexia

order to reduce the morbidity and mortality and improve quality of life (10).

Body mass index (BMI) is a screening tool for measure nutritional status and it may influence the prognosis of patient with nasopharyngeal cancer (**Table 2**).

Multiple studies showed the importance of BMI in the treatment of head and neck cancer. In his literature review, Hollander et al. remarked that pretreatment high BMI is associated with better prognosis (11).

The curative-intent radio-chemotherapy of NPC determine a weight loss greater than 5% at more than 60% of patient, according to some studies (12, 13). This condition led to poorer treatment response, interruption of the treatment and worse prognosis.

In this retrospective study, we investigated the influence of BMI, age, histological type of NPC and stage of disease on the prognosis of patients with nasopharyngeal carcinoma.

PATIENTS AND METHODS

Patients

We analyzed 27 patients diagnosed with nasopharyngeal cancer, admitted in Medical Oncology Clinic of Elias University Emergency Hospital between 2010-2015. Table 3 details patients characteristics. Of these, 19 were men and 8 women, with age between 32-72 years (mean age=52.2 ± 10.3 years old). All patients were staged according to American Joint Committee on Cancer (AJCC) as follows: 4 patients stage II, 8 patients stage III and 15 patients stage IV.

In conformity with WHO classification of histological type of nasopharyngeal carcinoma, we found 3 patients with type 1, 10 patients with type 2 and 13 patients with type 3.

All patients have undergone radiotherapy with concurrent chemotherapy, followed by adjuvant chemotherapy and gene targeted therapy. Before the beginning of the treatment, we calculated BMI at 20 patients with mean BMI=23.6 ± 4.6kg/m².

Regarding the treatment response, we followed two criteria: the immediate disease response and the disease response at 3 years after finishing radio-chemotherapy. (**Table 4**)

RESULTS

Table 5 shows that after finishing radio-chemotherapy, 65% of male patients and 50% of female patient had complete response. Almost 90% of patients had type 2 and type 3 NPC and more than 60% of them had complete response after finishing combined therapy, without significant differences between these two types. We remarked that all patients with stage II of disease had complete response after CRT (chemo-radiotherapy),

Table 2. The international classification of an adult weight

Classification	BMI
Underweight	<18.50
Severe thinness	<16.00
Moderate thinness	16.00 - 16.99
Mild thinness	17.00 - 18.49
Normal range	18.50 - 24.99
Overweight	≥ 25.00
Pre-obese	25.00 - 29.99
Obese	≥ 30.00
Obese class I	30.00 - 34.99
Obese class II	35.00 - 39.99
Obese class III	≥ 40.00

Table 3. Patient characteristics

		Cases number	%
Gender	Males	19	70.4
	Females	8	29.6
	Total	27	100.0
Body mass index	Obese class I	2	10.0
	Overweight	6	30.0
	Normal weight	8	40.0
	Underweight	4	20.0
	Total	20	100.0
Histopatological type	Type 2	10	38.5
	Type 3	13	50.0
	Type 1	3	11.5
	Total	26	100.0
Stage of disease	I	0	0.0
	II	4	14.8
	III	8	29.6
	IV	15	55.6
	Total	27	100.0

Table 4. Treatment response

		Cases number	%
Post treatment response	Complete response	14	60.9
	Partial response	9	39.1
	Total	23	100.0
Disease response at 3 years after CRT	Complete response	9	60.0
	Partial response	6	40.0
	Total	15	100.0

while almost 50% of stage IV patients responded the same. There are no differences between complete and partial responses related to mean age and mean BMI.

In **Table 6** we observed that it was a slight increase of mean BMI and small reduction of the mean age towards complete response at 3 years after finishing CRT. From all patients with partial response post-CRT, only 33% had

Table 5. Post treatment response by patient characteristics

	Post treatment response - %		
	Complete response	Partial response	Total
Mean age	51.1	51.3	
Mean BMI	22.5	24.0	
Males	65.0	35.0	100
Females	50.0	50.0	100
Obese class I	100	0.0	100
Overweight	67.0	33.0	100
Normal weight	63.0	37.0	100
Underweight	50.0	50.0	100
HP - Type 2	60.0	40.0	100
HP - Type 3	64.0	36.0	100
HP - Type 1	50.0	50.0	100
Stage II	100.0	0.0	100
Stage III	67.0	33.0	100
Stage IV	46.0	54.0	100

obtained complete remission at 3 years after CRT. At 3 years after treatment, the percentage of women (from the total number of female patients) with complete response is higher than the percentage of male patients (from the total number of male patients).

Table 7 reveals that almost 80% of patients with complete remission after radio-chemotherapy were men and only 20% were women. Also, a high percentage of patients with partial response were men. It was observed that patients with normal weight had a better percentage in both complete and partial response. No significant difference of mean BMI between patients with complete and partial response. 93% of patients with WHO type 2 and type 3 had complete response and also, 88% of patients had partial response. Post- chemo-radiotherapy patients with stage IV represented 80% of all patients with partial response.

Regarding the 3 years post-CRT response, we determined that the patients with normal weight had a better complete response comparing with the others. Patients with stage III of disease had the highest rate of complete remission. 78% of patients with complete response after CRT had complete remission at 3 years post-therapeutic.

DISCUSSION

BMI is the most common tool for evaluation of nutritional status. Multiple studies have demonstrated the predictive effect of weight loss and BMI. In a study of 400 patients with loco-regionally advanced nasopharyngeal carcinoma, the authors showed a strong impact of BMI on failure-free survival and overall survival (14).

On the other hand, there were studies that couldn't find significant correlation between BMI or weight loss and survival. Van Bokhorst - de van der Schueren et al.

Table 6. Response at 3 years after CRT by patient characteristics

	Response at 3 years after CRT - %		
	Complete response	Partial response	Total
Mean age	48.0	53.0	
Mean BMI	24.0	20.1	
Males	56.0	44.0	100
Females	67.0	33.0	100
Obese class I	100.0	0.0	100
Overweight	50.0	0.0	50
Normal weight	50.0	13.0	63
Underweight	25.0	25.0	50
HP - Type 2	57.0	43.0	100
HP - Type 3	57.0	43.0	100
HP - Type 1	100.0	0.0	100
Stage II	100.0	0.0	100
Stage III	67.0	33.0	100
Stage IV	33.0	67.0	100
Post-CRT immediate complete response	88.0	12.0	100
Post-CRT immediate partial response	33.0	67.0	100

Table 7. Post - CRT immediate response by different categories of patient characteristics

	Post-CRT immediate response - %	
	Complete response	Partial response
Mean age	51.1	51.3
Mean BMI	22.5	24.0
Males	79.0	67.0
Females	21.0	33.0
Total	100.0	100.0
Obese class I	15.0	0.0
Overweight	31.0	20.0
Normal weight	39.0	40.0
Underweight	15.0	40.0
Total	100.0	100.0
HP - Type 2	43.0	44.0
HP - Type 3	50.0	44.0
HP - Type 1	7.0	11.0
Total	100.0	100.0
Stage II	29.0	0.0
Stage III	29.0	22.0
Stage IV	43.0	78.0
Total	100.0	100.0

(15) reported the prognostic value of preoperative weight loss in male patients and the lack of influence on survival of all nutritional parameters used.

Evaluating the impact of nutritional status on treatment outcome in patients with locally-advanced head and neck squamous cell carcinoma, Rabinovitch et al. (16)

Table 8. 3 years post-CRT response by different categories of patient characteristics

	3 years post-CRT response - %	
	Comple response	Partial response
Mean age	48.0	53.0
Mean BMI	24.0	20.1
Males	56.0	67.0
Females	44.0	33.0
Total	100.0	100.0
Obese class I	0.0	0.0
Overweight	38.0	0.0
Normal weight	50.0	50.0
Underweight	12.0	50.0
Total	100.0	100.0
HP – Type 2	44.0	50.0
HP – Type 3	44.0	50.0
HP – Type 1	12.0	0.0
Total	100.0	100.0
Stage II	33.0	0.0
Stage III	44.0	33.0
Stage IV	23.0	67.0
Total	100.0	100.0
Post-CRT immediate complet response	78.0	20.0
Post-CRT immediate partial response	22.0	80.0
Total	100.0	100.0

remarked that patients who received nutrition support before treatment had an increased loco-regional failure and a poor overall survival.

In our study we tried to demonstrate the influence of nutritional status in treatment response. We remarked that patients with normal weight and overweight had the best results at 3 years after the treatment. 78% of patients with complete response post radio-chemotherapy had complete remission at 3 years after finishing treatment. After statistical evaluation, we selected the patient characteristics with the best treatment response, as follows: male patient with mean age 48 years, mean BMI 24 kg/m², stage II or III of disease, with histological type 3 (non-keratinizing undifferentiated carcinoma).

Underweight patients had the worst results and poor prognosis due to higher rates of tumor remnants or local-regional recurrence.

This study has some limitations. First of all, it is a retrospective study with a small number of patients and statistical significance of obtained data should be interpreted with caution.

We evaluated the nutritional status only using BMI before treatment. It might be necessary to continue with a prospective study which will evaluate nutritional status using a bigger sample size and more nutrition related factors in order to be more precise in diagnosis of malnutrition.

CONCLUSIONS

Lifestyle and eating habits influence both development and evolution of nasopharyngeal carcinoma.

The impact of nutritional disorders is significant, because nutritional status influences the response and the tolerance of the treatment, hospitalization period and overall survival.

Improving patient's nutritional status with adequate methods of treatment will increase the favorable response rate of oncologic treatment, enhancing patient's quality of life and survival.

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