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ORIGINAL ARTICLE

Screening for malnutrition in lung cancer patients undergoing radiotherapy

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Abstract
Purpose The assessment of nutritional problems is vital to support patients undergoing radiotherapy. Poor nutritional status may occur as a result of preexisting problems, older age, the cancer itself, or treatment side effects. Malnutrition impairs the outcome of the disease and affects patients. This prospective study aimed at developing two simple tools to screen malnutrition before radiotherapy and to assess, prior to treatment, the risk of malnutrition after radiotherapy.
Methods Forty-seven lung cancer patients treated with curative intent were evaluated before radiotherapy and after completion of the treatment. To assess patient's malnutrition, two well-known screening tools (PG-SGA and NRS-2002) were used, complemented by patient-specific characteristics, yielding a 59-item questionnaire. Malnutrition status was defined using Thoresen's criteria. The two screening tools derived by multivariate analyses were validated by comparing anthropometric, biological, and nutritional variables between patients at risk of malnutrition and those who are not.
Results Malnutrition detection prior to radiotherapy was based on the equation "$\text{MDS}=5.88-0.20\times\text{BMI}+0.05\times$(percent weight loss over past 6 months)," while malnutrition prediction after radiotherapy was given by "$\text{MPS}=3.67+0.98\times(\text{age}\geq70)-0.12\times\text{BMI}+1.20\times\text{edema}$." Agreement between observed and estimated outcomes was quite high for the two scores (kappa coefficient 0.80 and 0.85, respectively).
Conclusions The two assessment tools were found parsimonious and easy to use. Further studies are needed to validate them in larger lung cancer groups and in other cancer populations.

Keywords Screening tools · Malnutrition · Lung cancer · Radiotherapy

Introduction

The prevalence of malnutrition in cancer patients ranges from 30 to 80 %. Poor nutritional status may result from preexisting problems, such as older age, the cancer itself, or treatment side effects. Weight loss, anorexia, and cachexia affect many patients with cancer, particularly those with an advanced stage of the disease and those with cancer of the lung, of the head, and neck region or of the gastrointestinal tract [1]. Since nutritional problems are usually multifactorial, it is important that physical, psychological, social, and functional aspects are also taken into consideration.

The assessment and management of nutritional problems are essential in supportive care of patients undergoing radiotherapy. Altered nutritional status affects patients and their

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families physically, psychologically, and socially. Malnutrition also alters disease outcome with increased morbidity, mortality, length of hospital stay, and healthcare costs [2, 3]. Unfortunately, malnutrition is often unrecognized [4]. This may have deleterious consequences, in particular for cancer patients treated by radiotherapy, where the treatment itself is known to enhance weight loss. Thus, there is an imperative need for adequate nutritional assessment tools that provide early detection of malnutrition in patients scheduled to undergo radiotherapy. Several nutritional screening tools have been proposed in the literature but none of them gives entire satisfaction [5, 6].

The aim of the present study was to develop two simple nutritional tools for lung cancer patients scheduled for ambulatory radiotherapy. The first one aimed to detect malnutrition before initiation of the radiation therapy and the second one to predict the risk of malnutrition at the end of radiotherapy. Both tools were designed to be used by caregivers with no or limited experience in dietetics and nutrition in their daily practice.

Material and methods

The study protocol was approved by the local ethics committee and patients had to provide informed consent. To be included in the study, lung cancer patients had to be aged ≥18 years, be treated with curative intent, and have an expected survival of at least 6 months. The patients were assessed before radiation therapy and after treatment completion.

To assess patient's malnutrition, two well-known screening tools (PG-SGA and NRS-2002) were used, complemented by specific patient characteristics, yielding a 59-item questionnaire. The patient-generated subjective global assessment (PG-SGA) and the nutrition risk screening (NRS-2002) are two recognized tools for assessing nutritional status [7, 8]. The PG-SGA entails seven sections as follows: weight history, food intake, symptoms, functional capacity (completed by the patient), disease, and its relation to nutritional requirements, metabolic stress, and physical examination (completed by the caregiver) [7]. The NRS-2002 consists of four questions regarding percent weight loss, dietary intake, BMI, and metabolic stress [8].

According to PG-SGA and NRS-2002, the new questionnaire consists of two parts. The first part of the questionnaire comprises eight modules to be completed by the caregiver. The first module investigates the "social support" of the patient. The second module entitled "weight loss" includes the body mass index (BMI) and the weight losses during the past month and the past 6 months. BMI was calculated from weight (in kilograms) divided by squared height (in meters). All patients were weighed on the same calibrated scale and their height was measured on the same height gauge. Patients were asked whether they had lost weight unintentionally over the last month and the last 6 months. The third module "diseases and their relation to nutritional needs" looks for a set of conditions that could potentially alter the patient's nutritional status. In the fourth module, the metabolic stress, fever, and use of corticosteroids are assessed. The fifth module "physical examination" includes mid-upper arm circumference (MUAC), triceps skinfold (TSF), mid-arm muscle circumference (MAMC), and the presence of edema. MUAC and TSF were measured midway between the acromion and the olecranon. MAMC was calculated using the formula MAMC (in centimeters)=MUAC (in centimeters) − $\pi \times$TSF (in millimeters) [9]. The sixth "specific pathology" and seventh "specific to radiotherapy" modules capture cancer information and treatment parameters. Finally, the eighth module "functional capacity" records the Karnofsky performance scale (KPS) and the WHO performance status (PS) [10, 11]. KPS and PS are widely used to quantify the functional status of cancer patients. The KPS was designed to measure the level of patient activity and medical care requirements. It runs from 100 to 0 %, where 100 % is "perfect" health status and 0 % is death [10]. The PS describes the status of symptoms and functions with respect to ambulatory status and need for care. It runs from 0 to 5, where 0 means normal activity and 5 is death [11]. The second part of the questionnaire consisted of five questions filled out by the patient: age (<70 or ≥70 years), symptoms, functional capacity, food intake, and addiction.

Because there is no generally accepted clinical definition of malnutrition and no "gold standard" for determining nutrition status [12], Thoresen's score was chosen as the "gold standard" throughout the present clinical study. According to this score, based on objective criteria, patients were classified as "malnourished" if two or more of the following variables were out of range: weight loss >5 % during past month, >10 % during past 6 month, or >15 % of weight before diagnosis of the cancer disease, BMI <20 kg/m^2, TSF ≤5th percentile, MAMC ≤5th percentile, serum albumin ≤30 g/l, serum pre-albumin ≤0.21 g/l [13].

Food intake was assessed by a diet history covering the last month. Subjects were asked about their food taken from sunrise to sunset, during meals and between meals for the week and the weekend. Frequency and quantity were recorded either based on household estimations or on direct weights [14]. The food intake resulted in nutritional values calculated by a computer program integrating the food composition table used in the context of the epidemiological study "SU.VI.MAX" [15]. Consequently, the nutritional status of the patient was also assessed on six variables as follows: the total energy intake relative to energy needs, protein intake, vitamin A, C, and E intakes, and the $\omega6/\omega3$ ratio. All variables were assessed and expressed as proportions of the recommended daily intakes [16–18].

Anthropometric measures and several biomarkers have been proposed to assess nutritional status. Their clinical interest is to help detecting malnutrition. Anthropometric parameters measured in this study were BMI, TSF, MUAC, and MAMC. For the biological parameters, we examined albumin, prealbumin, creatinine, lymphocytes, transferrin, and total cholesterol.

Statistics

Results were expressed as mean and standard deviation for quantitative variables and as counts and percentages for categorical variables. The correlation coefficient was used to measure the association between quantitative variables. Mean values were compared by the classical Student *t* test or the Mann–Whitney *U* test when normality assumptions were not satisfied. Multiple linear regression analysis with stepwise variable selection was used to assess the relationship between a quantitative dependent variable and a set of covariates. ROC curve analysis was used to derive an optimal cutoff for the risk indexes obtained by multiple regression analysis. Specifically, the development of the two nutritional assessment tools proceeded in two steps. First, univariate regressions were used to measure the effect of the baseline potential factors on the "gold standard" malnutrition score. Next, multiple regression analysis with stepwise variable selection was applied to select the most predictive variables for malnutrition and to combine them into a risk index. ROC curve analysis was then used to define an optimal cutoff point combining best sensitivity and specificity. Patients with a score above (below) cutoff were at high (low) risk of malnutrition. Cohen kappa coefficient was calculated to assess agreement between observed and estimated outcomes. The validity of the two indexes was further based on the comparison of anthropometric, biological, and nutritional parameters between normal and malnourished patients before treatment and after radiotherapy. Results were considered to be significant at the 5 % critical level ($P<0.05$). The data analysis was carried out using SAS (version 9.2 for Windows) and S-PLUS (version 8.1) statistical packages.

Results

Patient characteristics

A total of 47 lung cancer patients (39 men and 8 women) were included in the study. Their demographic and clinical characteristics before radiotherapy treatment are summarized in Table 1. The mean age was 61.1±7.0 years (range 46–76 years), the BMI averaged 23.7±4.4 kg/m^2 (range 16 – 35 kg/m^2), and there were 36 % smokers. The WHO performance scale was 0.91±0.35 (range 0–2). Most subjects (70.2 %) were stage III cancer patients, two (4.3 %) patients had metastases, but there was no case of cancer recurrence.

Table 1 Lung cancer patients characteristics before radiotherapy (N=47)

Characteristic	Number (%)	Mean±SD	Range
Age (years)		61.1±7.0	46–76
Gender			
Male	39 (83.0)		
Female	8 (17.0)		
Body mass index (kg/m^2)		23.7±4.4	16–35
WHO performance status		0.91±0.35	0–2
Cancer stage			
I	7 (14.9)		
II	5 (10.6)		
III	33 (70.2)		
IV	2 (4.26)		
Presence of metastasis	2 (4.26)		
Cancer recurrence	0 (0.00)		
Smoker	17 (36.2)		

Screening malnutrition prior to radiotherapy

The undernutrition score established by Thoresen and considered as the "gold standard" was calculated for each subject. The mean score obtained was 1.31±1.49 (range 0–6). Using the critical threshold of 2, it turned out that 14 (29.8 %) patients suffered malnutrition and 30 did not. The score of Thoresen was subsequently correlated to each of the 59 items of the questionnaire. It appeared that only BMI, MAMC, weight loss (%) in the past month and in the past 6 months, difficulty to eat during past 2 weeks, TSF thickness, and pulmonary insufficiency were found significant. No association was found for the other items (see Table 2).

When combined into a stepwise multiple regression analysis (N=44 patients), it turned out that only BMI ($P<0.0001$) and the percentage of weight loss over the past 6 months (P=0.012) remained statistically significant, yielding the MDS (for Malnutrition Detection Score prior to radiotherapy) equation as follows:

$$\mathrm{MDS} = 5.88\text{-}0.20 \times \mathrm{BMI} + 0.05 \times (\text{percent weight loss in past 6 months}).$$

By ROC curve analysis, a cutoff value of 1.8 (close to that of Thoresen) was found to be the best tradeoff between true positives and false positives. Patients with an MDS score ≥1.8 were declared "malnourished," whereas those with an MDS below that level were considered to be "normal." As seen in Table 3, when cross-classifying patients according to the "gold standard" (cutoff 2.0) and the MDS (cutoff 1.8), the

Table 2 Questionnaire items significantly correlated to Thoresen malnutrition score measured before radiotherapy (N=44)

N°	Parameter	Category	Mean±SD	Pearson correlation	P value
1	Body mass index (kg/m^2)			−0.70	<0.0001
2	Mid-arm muscle circumference (cm)			−0.69	<0.0001
3	Percentage weight loss in the past month (%)			0.49	0.0009
4	Percentage weight loss in the past 6 months (%)			0.48	0.0009
5	Triceps skin fold thickness (mm)			−0.43[a]	0.003
6	In the last 2 weeks, I have had other problem that kept me from eating enough	Yes	3.2±2.2		0.0021
		No	1.1±1.2		
7	Pulmonary insufficiency	Yes	2.0±1.7		0.047
		No	1.0±1.3		

[a] Spearman correlation

percentage of correct allocation (sensitivity 92.9 %; specificity 90.0 %) was equal to 90.9 % (40/44). Four patients were misclassified, yielding an error rate of less than 10 %. Cohen kappa coefficient between gold standard and estimated outcomes was equal to 0.80 (95 % CI 0.61–0.99).

The validity of the MDS was further reassessed for every anthropometric parameter. The latter were found to be significantly lower in patients with malnutrition before radiotherapy treatment. Among the biological parameters, only albumin differed significantly between the two groups of patients. No significant difference was observed for the nutritional parameters (data not shown).

Predicting malnutrition after radiotherapy

Thoresen's score was again calculated for each subject after radiotherapy (N=32 patients). The mean score obtained was 0.94±1.08 (range 0–4). Using the critical threshold of 2, it turned out that 8 (25 %) patients suffered malnutrition whereas 24 did not. The score of Thoresen was then correlated to each of the 59 items of the questionnaire recorded before radiotherapy. It appeared that only four parameters were significantly related to the score of Thoresen: BMI, MAMC, age (≥70 years), and presence of edema. No association was found for the other items (see Table 4).

When combined into a stepwise multiple regression analysis (N=32 patients), it turned out that only BMI (P<0.0001), presence of edema (P=0.009), and age (P=0.016) remained statistically significant, yielding the MPS (for Malnutrition Prediction Score after radiotherapy) equation as follows:

$$\mathrm{MPS} = 3.67 + 0.98 \times \mathrm{age}{\geq}70 - 0.12 \times \mathrm{BMI} + 1.20 \times \mathrm{oedema}.$$

Where age ≥70=1 if patient ≥70 years and 0 otherwise, and edema=1 if present and 0 if absent.

By ROC curve analysis, a cutoff value of 1.2 was found to give the best tradeoff between true positives and false positives. Patients with an MPS score ≥1.2 were predicted to be at "high risk of malnutrition," whereas those with an MDS below that level were considered to be at "low risk."

As seen in Table 5, when cross-classifying patients according to the "gold standard" (cutoff 2.0) and the MPS (cutoff 1.2), the percentage of correct allocation (sensitivity 100 %; specificity 91.7 %) was equal to 93.8 % (30/32). Two patients were misclassified, yielding a prediction error rate of about 6 %. Cohen kappa coefficient between gold standard and estimated outcomes was equal to 0.85 (95 % CI 0.50–1.00).

The validity of the MPS was established for every anthropometric parameter. These parameters were found to be significantly lower in patients with malnutrition after radiotherapy treatment. Among the biological parameters, creatinine and prealbumin differed significantly between the two groups of patients. The only significance found for the nutritional parameters was for vitamin C (data not shown).

Table 3 Cross-classification of the lung cancer patients based on MDS and the gold standard method (N=44)

		Gold standard	
		<2	≥2
MDS	<1.8	27	1
	≥1.8	3	13

Discussion

When predicting the outcome of lung cancer patients, host-related factors need to be considered in addition to tumor-related ones. Since almost 25 years, nutrition has emerged as an important component in treatment planning not only for patients who are newly diagnosed, but also for those contending with active treatment and those who survived many years beyond their cancer treatment. If by definition

Table 4 Questionnaire items recorded before radiotherapy correlated to Thoresen malnutrition score measured after radiotherapy (*N*=32)

N°	Parameter	Category	Mean±SD	Pearson correlation	*P* value
1	Body mass index (kg/m^2)			−0.63	<0.0001
2	Mid-arm muscle circumference (cm)			−0.62	0.0002
3	Age	≥70 years	2.3±0.9		0.007
		<70 years	0.8±0.9		
4	Presence of edema	Yes	2.3±2.1		0.016
		No	0.8±0.9		

malnutrition encompasses over- and undernourishment, the present study focused on the latter aspect.

Many cancer patients undergo radiotherapy either as part of the curative management of their disease or for palliative treatment. Some patients receive several radiation treatments [19]. In our department, we plan to screen every new patient at the first visit in order to establish a baseline evaluation of the nutritional status. The goal is to identify patients malnourished prior to radiotherapy and those at risk of being malnourished at the end of treatment. The aim is to select those patients for a more formal and extensive nutrition assessment, in order to prevent and/or treat malnutrition.

Malnutrition is a common problem in cancer patients whom anorexia and weight loss occur frequently [20, 21]. Altered nutritional status may occur as a result of preexisting problems, the cancer itself or the side effects of treatment [22]. In addition, about 25 % of cancer patients addressed to the radiotherapy department are older than 70 years. Malnutrition is a real problem in elderly patients [20]. If the prevalence of malnutrition is relatively low in elderly persons living at home (less than 10 %), it increases considerably in hospitalized or institutionalized settings (30–60 %) [23]. Amongst the 47 lung cancer patients of this study, 6 (13 %) were older than ≥70 years and required sometimes assistance. Nutritional screening is the process of discovering characteristic or risk factors known to be associated with dietary nutritional problems. The nutritional screening tools (MDS and MPS) derived in this work are not used for in-depth nutritional assessment but to quickly categorize patients in two risk groups on the basis of simple and easily available parameters. Identification of patient at risk of malnutrition should lead to consultation with an appropriate professional for further assessment. Numerous screening tools have been developed to identify patients at risk of malnutrition. No one is unanimously adopted. Limitations of these tools include screening parameters based on clinical judgment and intuition, development in specific patient populations, time consuming measurements, and the need of special training of dieticians. Additionally, their sensitivity, specificity, validity, reliability, and cost-effectiveness have not been well established [24, 25].

Table 5 Cross-classification of the lung cancer patients based on MPS and the gold standard method (*N*=32)

		Gold standard	
		<2	≥2
MPS	<1.2	22	0
	≥1.2	2	8

The “gold standard” score used in this study was the score of Thoresen, established from anthropometric and biological objective parameters [13]. Fifty-nine parameters related to nutritional status were included in this nutritional survey. All PG-SGA and the NRS parameters were involved. Specific features to pathology and radiation treatment were added. Among the parameters, only two were related to undernourishment prior to radiotherapy, namely BMI and weight loss over the last 6 months, which allowed diagnosing malnutrition with less than 10 % errors. For predicting malnutrition after radiotherapy, three parameters were sufficient, namely age ≥70 years, presence of edema, and BMI (6 % prediction errors).

The study has indeed a number of shortcomings. The limited number of patients may induce a selection bias. In fact, only lung cancer patients treated with curative intent were included. This homogeneous group limited the power of multiple regression analysis of Thoresen’s score on the many different factors potentially known to influence nutrition. Furthermore, these patients were in sufficiently good condition to be submitted to treatment delivered with curative intent and to have a minimum of 6 months of life expectancy. Among the 41 patients with performance status 1, 7 had a Karnofsky score of 80 %. Only one patient had performance status 2. Furthermore, in our selected group of patients, this parameter was not associated with undernourishment. Finally, the mean age was only 61±7 years old.

To the best of our knowledge, this is the first study establishing malnutrition before radiotherapy and predicting it after radiation based on data collected prior to treatment. These two scores need to be validated in a larger cohort of lung cancer patient. Its application to other cancers also requires further investigation.

Conclusion

In the present study, two malnutrition indexes were created. The first one was designed to detect, before radiation treatment, malnutrition in lung cancer patients receiving radiotherapy with curative intent. The second one was to predict, before treatment, the risk of malnutrition after radiotherapy. The two indexes are based on simple and easily retrievable patient data, even by unskilled caregiver, allowing them to identify before irradiation malnourished patients and patients at risk of malnutrition after radiotherapy. These patients should also be referred to dietitians. The two indexes have to be validated on a larger population of lung cancer patients and on more general cancer patient groups.

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Conflict of interest The authors declare no conflict of interest.

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