Nutritional assessment in overweight and obese patients with metastatic cancer: does it make sense?

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Background: Obesity is causally related with tumor development, and thus, many cancer patients are overweight or obese at diagnosis. Whether these patients need regular nutritional assessment is not known. In the present study, we evaluated the utility of Mini Nutritional Assessment (MNA), a nutritional screening/assessment questionnaire, in overweight or obese patients with metastatic tumors.

Patients and methods: Overweight or obese patients referred for initiation of systemic therapy in three cancer centers were eligible. Basic demographics and clinical data were recorded. MNA was completed at baseline and patients were divided into three groups: A (well nourished), B (at risk), and C (malnourished). Survival data were subsequently collected. The prevalence of malnutrition and prognostic significance were evaluated.

Results: In total, 1469 patients with metastatic primaries were identified. Of them, 594 (41.9%) were overweight or obese and included in the analysis. According to MNA, almost 50% were at risk and around 12% were already malnourished at presentation. A significant difference in overall survival was found between groups [group A 17.8 (15.5–20.1) months, group B 8.2 (7.3–9.3) months, and group C 6.4 (3.2–9.6) months, P < 0.001]. Moreover, MNA was the only independent predictor of survival.

Conclusions: Our findings support that a significant percentage of overweight or obese cancer patients may be at nutritional risk and this is moreover related with adverse prognosis. An MNA score could be used for the identification of this risk.

Key words: assessment, cancer, MNA, nutrition, obesity, overweight

introduction

Increased caloric intake and obesity represent common risk factors for cancer development, and thus, a significant percentage of cancer patients are expected to be overweight or even obese at diagnosis [1]. However, >60% of these patients, particularly those with primaries of the lung and of the upper gastrointestinal (GI) tract, will develop cancer-associated malnutrition in the context of cachexia, a multifactorial syndrome characterized by progressive weight loss, metabolic alterations, and adverse clinical outcomes [2, 3].

In routine oncology practice, overweight or obese cancer patients do not typically receive regular nutritional screening due to the fact that they are generally considered well nourished (i.e. they appear to possess substantial energy reserves). This might be attributed in part to the inability of oncologists to identify factors that place patients at risk from malnutrition [4].

Some physicians may also be aware of ‘the obesity paradox’, where decreased of risk of death is observed in obese cancer patients compared with those with lower body mass index (BMI); this is also seen in nonmalignant disease [5]. However, the presence of sarcopenic obesity, another condition that results from the simultaneous loss of skeletal muscle and concurrent gain of adipose tissue, further complicates the landscape as it is related with exceptionally adverse prognosis [6, 7]. Within this scope, some form of nutritional risk assessment in obese and overweight patients might be significant from both clinical and prognostic perspectives.

Weight loss history, in a predefined time period, is most commonly used in routine oncology practice and research, but it represents an oversimplification or unimodal method of nutritional evaluation. Alternatively, nutritional screening tools, like the Mini Nutritional Assessment (MNA), Patient-Generated Subjective Global Assessment (PG-SGA), Nutritional Risk Screening-2002 (NRS-2002), and Malnutrition Universal Screening Tool (MUST), that cover additional details required for a comprehensive assessment might be used for precise risk identification in cancer patients [8]. Although various studies

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aimed to compare these different screening tools in this setting, there were important methodological limitations and, up to now, there is no gold standard tool [9, 10]. As a result, while some form of baseline and regular nutritional screening is recommended for every cancer patient, no specific tool has been proposed [11].

The MNA (www.mna-elderly.com) is both a screening and assessment tool, recommended by the European Society of Clinical Nutrition and Metabolism (ESPEN), the International Association of Gerontology and Geriatrics (IAGG), and the International Academy Nutrition and Aging (IANA), and it is also an integral part of Comprehensive Geriatric Assessment (CGA) of oncologic patients [12–14]. It provides a multidimensional assessment of general health and incorporates four domains: performance status and independence, anthropometric measurements, dietary intake, and self-view of health and nutrition status [15]. By this means, MNA not only estimates energy stores—found in abundance in overweight/obese patients—but it additionally evaluates important aspects of functionality. Moreover, it accounts for alterations in food consumption and changes in body image. Completion of the protocol by any healthcare provider regularly will take <10'.

We had previously reported that MNA is better than weight loss alone in terms of its predictive and prognostic value in patients with metastatic lung cancer primaries and, moreover, it is related with laboratory parameters indicative of the cachexia syndrome [16, 17]. Recently, Velázquez AlvaMdel et al. [18] demonstrated that MNA is additionally related to the presence of sarcopenia in elderly patients.

In the present study, we evaluated the clinical implication of evaluation with the MNA in overweight or obese patients with metastatic tumors.

**patients and methods**

Our study cohort was accrued in three different cancer centers: Institute of Cancer, Montpellier, France; University Hospital of Herakleion, Crete, Greece; and University Hospital of Larissa, Thessaly, Greece. Accrual periods were between 1 January 2009 and 12 December 2011 for patients in Montpellier, between 6 February 2006 and 12 October 2010 for patients in Herakleion, and between 30 March 2010 and 16 June 2013 for patients in Larissa.

**eligibility**

Consecutive patients referred to the aforementioned centers for initiation of systemic antineoplastic therapy for histologically and/or cytologically proven metastatic cancer primaries were assessed using the MNA. Patients with a history of a second primary cancer, with the exception of non-melanoma skin tumor, were excluded. The rest of the eligibility criteria was slightly different between the two countries: French patients were all older than 70 years of age and were recorded irrespective of primary cancer site. MNA was carried out as part of the recommended clinical evaluation of nutritional status in this population (http://www.hassante.fr/portal/upload/docs/application/pdf/malnutrition_elderly_guidelines.pdf). Greek patients were older than 18 years, with metastatic primaries of the lung and the upper GI tract. In this case, MNA was carried out in the context of a prospective clinical study [17].

The study was approved by the Ethics and Scientific Committees of the participating institutions.

**patient demographics and baseline clinical characteristics**

Basic demographics (gender, age, body weight, and height) as well as patient’s baseline characteristics [Eastern Cooperative Oncology Group Performance Status (PS) and primary location of the tumor] were recorded.

**assessment of nutritional status**

Body mass index \( [\text{BMI} = \frac{\text{weight} (\text{kg})}{\text{height} (\text{m})^2}] \) was calculated and patients were classified as overweight if their BMI was between 25.0 and 28.9 or as obese if it was 30 or above, according to the World Health Organization (WHO) classification [19].

**statistical analysis**

Data were analyzed using standard statistical methods. Patients were monitored during their regular chemotherapy or follow-up visits (continuous monitoring). Overall survival (OS) was defined as the interval from diagnosis to death from any cause. The date of death was recorded from the death certificate or by phone calls to caregivers within 2 months of the last recorded visit. Patients, who were lost to follow-up during the study period or those who were alive after the end of follow-up period, were censored using the date of the last visit or the termination date of study, respectively (point censoring method).

Survival analysis included: the Kaplan–Meier method (comparisons with Mantel–Cox log-risk tests) and the Cox proportional hazards model [estimated hazard ratios and 95% confidence intervals (CI)]. Statistical significance was reported at \( P < 0.05 \) level. Analyses were completed using the IBM SPSS Statistics for Windows (version 22.0, IBM Corp., Armonk, NY).

**study end points**

The primary end point was to identify the incidence of malnutrition and nutritional risk according to the MNA protocol (groups C and B, respectively) in overweight and obese cancer patients with metastatic primaries. The secondary end point was the evaluation of the association between MNA and its components with overall survival.

**results**

**study flow and baseline characteristics**

During the reported accrual period, 1469 metastatic cancer patients were admitted in all three centers. The vast majority of them were outpatients and referred to the participating centers for initiation of systemic antineoplastic therapy. MNA was completed at baseline in 1419 (96.6%) patients and after initial
evaluation, a total of 594 (41.9%) patients were overweight or obese and included in this analysis.

Baseline clinical characteristics of the total cohort and of the overweight and obese patients are depicted in supplementary Table S1, available at Annals of Oncology online. The mean (±SD) BMI of the analyzed patients was 28.6 (±3.3) and the majority (72.6%) of patients in this sample were classified as overweight. There were very few differences between overweight and obese patients. Overweight patients were on average 3 years older, and had more cases of genito-urinary cancer compared with obese patients. In total, 253 (42.6%) patients reported a loss >5% over the previous 3–6 months. There was no difference in reported weight loss between overweight and obese patients.

The mean (±SD) MNA scores of the total cohort, overweight, and obese patients were 22.4 (±8.8), 22.3 (±10.1), and 22.4 (±3.5), respectively. Overall, the prevalence of malnutrition according to the MNA classification in overweight and obese was 12.8%, with almost 50% of patients classified as being at risk for malnutrition.

**Survival Analysis**

In 357 (60.1%) patients, survival data were available. Median OS (CI) was 11.1 (9.7–12.5) months, with a median follow-up of 27.0 (23.3–30.5) months. There was a significant difference in median OS by the MNA group: group A 17.8 (15.5–20.1) months, group B 8.2 (7.3–9.3) months, and group C 6.4 (3.2–9.6) months (P < 0.001). Kaplan–Meier curves for the total cohort and by BMI subgroup according to MNA groups are shown in supplementary Figure S2A–C, available at Annals of Oncology online. The largest difference in survival was seen in obese cancer patients where MNA group A had a median survival of 15.2 months and MNA group C of 4.9 months (supplementary Figure S2B and C, available at Annals of Oncology online).

When patients were divided according to age, median survival of elderly patients was 18.9, 7.7, and 4.8 for groups A, B, and C, and of non-elderly patients 15.7, 8.8, and 8.3 months, respectively. These survival differences were important for elderly patients (P < 0.001), while for non-elderly patients they were of borderline significance (P = 0.053). Kaplan–Meier curves for MNA groups according to age classification are shown in supplementary Figure S2D and E, available at Annals of Oncology online.

The prognostic impact of MNA groups was modeled (supplementary Table S3, available at Annals of Oncology online). Due to the redundancy of performance status with the mobility component of the MNA, the former was not included in the multivariate analysis. MNA classification was the only independently prognostic variable in metastatic overweight and obese cancer patients.

For 91 patients, there were available data regarding each particular component of the MNA questionnaire. Uni- and multivariate analysis examining the prognostic significance of these components is presented in supplementary Table S4, available at Annals of Oncology online. Seven components were predictive of survival, but food intake, weight loss, mode of feeding, and dementia retained their significance in the multivariate level.

**Discussion**

We now know that cancer patients with elevated BMI face several specific challenges related to diagnostic procedures and therapeutic modalities, like exposure to decreased chemotherapy dose, development of more surgical complications, and that they attain poorer outcomes of endocrine and/or radiation treatment [19]. Indeed, in current clinical practice, we lack specific assessment tools that clearly reveal certain risks for overweight and obese cancer patient populations.

In the present study, we evaluated the clinical significance of a widely used nutritional screening/assessment tool, the MNA, in overweight or obese patients with metastatic primaries, at baseline. The inclusion in the analysis of non-elderly patients could not be considered as standard, because MNA has never been validated in this cohort. Given the restricted sample size of the younger subset, the survival difference between MNA groups was of borderline significance.

Overweight and obese patients represented a substantial subgroup (40%) of our original cohort, consistent with many other reports in which BMI data for contemporary cancer patient populations appear. This number was almost identical to that reported by Tan et al. [20], evaluating patients with pancreatic primaries and comparable with that reported by Ramos Chaves et al. [21]. In the latter cross-sectional study, >60% of patients with early stage, endocrine-related tumors, like breast and prostate cancer had a BMI of 25 or above. Moreover, the prevalence of obesity was quite similar to that reported in other studies; one evaluating patients with primaries of the lung (11%) and the upper GI tract (15%) and another those with early colon cancer (18%) [22, 23]. However, for particular tumor types, like endometrial cancer, the incidence of obesity is found to be as high as 50%, underscoring the diversity of its frequency between various cancer primaries [24].

In our study, according to MNA, >60% of overweight or obese patients were either at nutritional risk (49.5%) or were already malnourished (12.8%) at the time of evaluation. Leibowitz et al. [25] evaluated the nutritional status of overweight or obese, and hospitalized patients with nonmalignant diseases using the NRS-2002. In this case, the prevalence of malnutrition was as high as 20% and this condition was additionally related with prolonged hospital stay and increased risk of inhospital mortality. It has been reported that severely obese patients, on the waiting list for bariatric surgery, might present significant deficiencies in particular micronutrients [26].

The identification of malnourishment in these patients implies a need for some form of nutritional consultation and/or intervention [27]. However, there are no specific guidelines or nutrition protocols designed for this group for the time being. Multiple facets of their nutritional status may be taken into account. It is unclear, for example, whether cancer patients experiencing obesity-related morbidity benefit from maintenance of their heavy body weight or whether some [limited] degree of weight loss could be in some way desirable. The target energy intake as well as the target body weight remains to be defined. Separate from energy considerations, it might be reasonable to evaluate protein intake and increase it with the purpose of preventing erosion of the lean body mass. In any case, depletion of essential nutrients should be identified and corrected as
indicated. Finally, considering obese patients, in particular, other commonly present comorbidities like glucose intolerance, restricted mobility, and depression that might affect nutritional support, should be taken into account [28].

This is the first report in which overweight and obese cancer patients have been evaluated with an established, validated nutrition screening/assessment tool. However, there are a few studies now available, evaluating the presence of severe muscle depletion (sarcopenia) in these patients from CT image analysis. In a landmark study, Prado et al. [22] demonstrated that the incidence of sarcopenia in obese cancer patients with primaries of the upper GI tract and lung was 15%, and that this was independently associated with increased mortality. This percentage was similar to that reported by Tan et al. [20] in pancreatic cancer (~16%). It may be coincidental that the CT-based studies find ~15% of obese cancer patients to be affected by sarcopenia, and that the evaluation done here reveals that again ~15% of obese cancer patients fell into ‘group C’ (malnourished) category based on MNA. Whether ‘malnourished’ overweight/obese patients correspond also to ‘sarcopenic’ is not known, there is some evidence that these are overlapping in geriatric as well as in cancer patients [18, 29]. Elements of the MNA that are potentially related to muscle include protein intake, muscle mass, and physical function: i.e. assessment of mobility, and independence, the presence of skin ulcers, selected consumption markers for protein intake, mode of feeding, as well as two somatometric measurements (mid-arm and calf circumference).

We have previously argued that nutrition assessment tools possess double clinical utility in the sense that the information derived from them can usefully inform more than one category of health care professional involved in patient care. The MNA is used by and is endorsed by oncology dietitians, and used to inform nutrition intervention. This same information has an independent prognostic value and therefore can be used to inform cancer care. Overall, MNA groups were independently related with survival for the total cohort, indicating the prognostic significance of such a nutritional screening in these patients. When overweight patients were considered alone, there was a meaningful survival difference between well nourished (group A) and the other two groups, whereas in obese patients this difference was more evident for those belonging to the group C.

BMI is an objective measurement, and is commonly used to identify individual patients as overweight or obese, but we argue that it is too superficial to guide clinical practice. In particular, this form of categorization does not provide an insight as to whether they are adequately nourished. It would be concerning if overweight and obese cancer patients were categorically ignored with respect to nutritional risk. It is also a significant concern that BMI does not provide any information regarding the body composition and because of potentially occult muscle wasting, this might mislead clinicians regarding decisions concerning nutritional support [20, 22, 30, 31]. At the current time, it is not clinically practical in oncology for routine objective measures of body composition such as dual-energy X-ray absorptiometry or computed tomography imaging to be widely deployed. So, while body composition analysis remains an integral part of a comprehensive nutritional evaluation, its use in everyday practice is restricted due to time and cost issues [32].

Nutrition screening tools such as the MNA appear to be broadly applicable and practical tools. While screening and any identified nutritional therapy are associated costs, recent data imply that the cost-effectiveness of nutrition interventions do offer clinical benefit for patients as well as value for money [33, 34].

In conclusion, based on our study, MNA could be a clinically useful nutritional screening and assessment for overweight/obese cancer patients.

disclosure

The authors have declared no conflicts of interest.

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references

Active and passive smoking in relation to lung cancer incidence in the Women’s Health Initiative Observational Study prospective cohort

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Background: Lung cancer is the leading cause of worldwide cancer deaths. While smoking is its leading risk factor, few prospective cohort studies have reported on the association of lung cancer with both active and passive smoking. This study aimed to determine the relationship between lung cancer incidence with both active and passive smoking (childhood, adult at home, and at work).

Patients and methods: The Women’s Health Initiative Observational Study (WHI-OS) was a prospective cohort study conducted at 40 US centers that enrolled postmenopausal women from 1993 to 1999. Among 93 676 multiethnic

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