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Staging of nutrition disorders in non-small-cell lung cancer patients: utility of skeletal muscle mass assessment

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Abstract

Background An international consensus proposed in 2011 a definition and classification system for cachexia (CAX), mainly based on weight loss, sarcopenia [skeletal muscle mass (SMM) loss], inflammation, and anorexia. The aim of this study was to stage CAX in non-small-cell lung cancer (NSCLC) patients by using a classification based on the Fearon criteria and supported by quantifiable parameters.

Methods This was a cross-sectional and non-interventional multicentre study. SMM was assessed by analysing L3 computed tomography-scan images. Patients completed the anorexia/CAX subscale of the Functional Assessment of Anorexia/Cachexia Therapy, EORTC QLQ-C30 quality of life (QoL) and International Physical Activity Questionnaire (IPAQ).

Results Patients were recruited in 56 sites. The analysis population comprised 531 patients, and SMM was assessed in 312 patients. Male patients were 66.5%, with a mean (SD) age of 65.2 (10.0) years, 79.9% were PS 0–1, and the tumour stage was mainly IIIB-IV (87.3%). Overall, 38.7% of patients had CAX, 33.8% pre-CAX, and 0.9% refractory CAX. Molecular tumour profiles were significantly associated with the presence of CAX: 23.9% in EGFR, ALK, ROS1, BRAF, or HER2+ patients, 41.4% in K-RAS+, and 43.2% in patients with no molecular abnormality ($P = 0.003$). The more advanced the CAX stage, the poorer the scores of functional items of the QoL ($P < 0.001$) and International Physical Activity Questionnaire ($P < 0.001$). Sarcopenia was present in 66.7% of CAX and 68.5% of pre-CAX patients. Overall, 43.8% of pre-CAX patients had only sarcopenia with limited weight loss (≤2%) and no anorexia.

Conclusions This is the first study to show the distribution of CAX in a population of NSCLC patients and an association between molecular abnormality in NSCLC and CAX. The original Fearon classification for CAX stages was supported by the associated functional QoL scores and physical activity levels, resulting in a clinically relevant system for detection of early stages of CAX.

Keywords Cachexia; Pre-cachexia; Non-small-cell lung cancer; Sarcopenia; Anorexia; Physical activities; SMM depletion

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Introduction

Non-small-cell lung cancer (NSCLC) is the most common cause of cancer-related deaths in western countries with little improvement in survival over the past 30 years.[1] The high mortality rate associated with lung cancer depends on multiple, heterogeneous, and complex factors, including host resistance to the disease.[2,3] Among resistance capacities, malnutrition and especially cachexia (CAX) have been described as relevant prognostic outcome parameters.[4,5]

Despite the role of CAX on cancer survival and quality of life (QoL), the lack of a universally accepted definition and of classification criteria has impeded the development of therapies to reverse or delay its progression. A significant milestone was reached in 2011, when an international panel of experts reached consensus on the definition and classification of CAX associated with cancer. It was defined as a multifactorial syndrome characterized by a loss of skeletal muscle mass (SMM) that cannot be fully reversed by nutritional support and that leads gradually to functional impairment.[6]

In lung cancer, SMM waisting (sarcopenia) has been linked to shorter survival,[7–9] reduced tolerance to chemotherapy,[10,11] decreased QoL, and diminished functional ability.[12,13] The importance of detecting sarcopenia has been stressed by many, and as obesity continues to increase, high body mass index (BMI) in patients diagnosed with cancer could lead clinicians to underestimate the extent of muscle loss. In a North American study, 47.4% of NSCLC patients were overweight or obese at referral, and among those classified as overweight, 59% met the criteria for muscle depletion.[14]

The experts defined CAX as a continuum of three stages: pre-CAX, CAX, and refractory CAX.[6] While the criteria to diagnose CAX are well defined, recognizing pre-CAX and refractory CAX stages is challenging. In pre-CAX, early clinical and metabolic signs (i.e. anorexia, protein breakdown, and impaired glucose tolerance) can precede substantial involuntary weight loss (WL $\leq$ 5%). The final refractory-CAX stage is characterized by a low performance status (Eastern Cooperative Oncology Group 3–4) and a life expectancy $<$3 months. The use of quantifiable parameters may help in identifying early-stage patients likely to benefit from early intervention, compared to late-stage patients for whom treatment would be of no benefit.

The aim of this study was to stage CAX in NSCLC patients by using a classification based on the Fearon criteria and supported by quantifiable parameters. Secondary objectives were to assess the relationship of CAX stages with tumour stage, histology, molecular abnormalities associated with NSCLC, inflammatory markers, and sarcopenia; to describe QoL and the level of physical activity associated with the different stages of CAX; and to identify the scale that best detects WL and sarcopenia.

Methods

General methodology

This was a cross-sectional, non-interventional, and European (France and Belgium) multicentre study conducted on a population of NSCLC. We used a method close to the two-stage sampling. First, all oncologists, lung specialists, and radiation oncologists treating patients with a malignant lung tumour from France were contacted exhaustively to ensure representativeness in the territory. Then, each physician recruited patients consecutively. The study was carried out according to the professional code of ethics and good practice guidelines developed by Association of French Speaking Epidemiologists and was authorized by the French Committee of Informatics and Liberty and the Ethics Committee of Ghent University Hospital (Belgium). The study was registered in the clinicaltrials.gov database (NCT02968979). Data from the study were analysed and are reported according to the STROBE statement.

Patients and data collection

Included patients were $\geq$18 years, with histologically proven NSCLC and able to complete a self-assessment questionnaire. Patients with a complete resection of an early-stage NSCLC or with a history of head and neck cancer were ineligible. French patients signed an information leaflet and Belgian patients an informed consent form.

Demographic and clinical data, NSCLC characteristics and laboratory values were collected during a single patient visit to the medical oncologist or lung specialist as part of routine care. If the weight 6 months prior to the study was missing in the patient's medical file, the documented weight closest to that date was used. If this information was not available, the weight 6 months prior to the study according to patient's recollection was used.

Patients completed the following self-assessment surveys: the visual analogue scale for food intake [Ingesta VAS (IVAS)],[15] the anorexia/CAX subscale of the Functional Assessment of Anorexia/Cachexia Therapy questionnaire,[16] the EORTC QLQ-C30 questionnaire, and the short form of the International Physical Activity Questionnaire.[17]

Skeletal muscle index assessment

Abdominal computed tomography (CT) scans performed as part of patients' routine management within 8 weeks prior to inclusion were centrally analysed by a trained technician who was blinded to patients' clinical data. The cross-sectional areas (cm^2) of the sum of the muscles in the L3 region were computed using SliceOmatic Software (version 4.3,

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TomoVision, Magog, Canada). Skeletal muscle index (SMI) was calculated as the skeletal muscle area (cm^2)/height (m^2) ratio.[18] In our quality control plan, 2 × 21 randomly selected dossiers were checked by a trained researcher (SA) for assessment and reporting accuracy. If the area difference between the two assessments was >6.05 cm^2, all measurements had to be re-performed. No difference was detected. Sex-specific and BMI-specific threshold values for sarcopenia and skeletal muscle density (SMD) were those defined by Martin *et al.*[18]

Cachexia staging definitions

Patients were classified as CAX, pre-CAX, and refractory CAX using a staging system based on the Fearon criteria and supported by quantifiable parameters (Table 1).[6,19]

Statistical analyses

Quantitative variables were described by the number of values entered, number of missing data, mean, standard deviation (SD), 95% confidence interval (CI) (if applicable), median, 1st and 3rd quartiles (Q1–Q3), minimum, and maximum. Qualitative variables were described by the number of values entered, number of missing data, frequency, percentage of each method, and the CI of each method. Missing data in questionnaires were handled according to the scoring manual.

The primary outcome was the frequency of CAX, defined as the number of patients with CAX to the total population with CAX information not missing. The sarcopenic status could only be determined for patients with available CT scans.

Secondary outcomes were the relationship of CAX stages with tumour stage, histology, molecular abnormalities associated with NSCLC, inflammatory markers, and sarcopenia; the QoL and the level of physical activity associated with the different stages of CAX; and the scale that best detects WL and sarcopenia.

A comparison of the distribution of disease characteristics (histology, TNM stage, number of metastatic sites, molecular abnormalities, and number of chemotherapy lines received), clinical symptoms [loss of appetite, inflammatory markers (neutrophil-to-lymphocyte ratio, N/L, and C-reactive protein, CRP), muscle parameters (sarcopenia and SMD)], QoL scores, and physical activity according to different CAX stages was conducted using a chi-squared (qualitative variables) or a Student's *t*-test (quantitative variables). The best thresholds for inflammatory markers associated to CAX were determined using a receiver-operating characteristic curve, including the sensitivity and specificity.

The responses from the anorexia questionnaires were compared with the chi-squared McNemar test to determine the scale that best detects WL and SMM loss.

Assuming that 40% of patients meet the objective, with a precision of 4.5%, it was estimated that 455 patients would be required. Considering an expected 10% of non-assessable patients, 500 patients had to be included [20].

Analyses were performed using SAS® software, version 9.3.

Table 1. Cachexia stage definitions used for the study and Fearon criteria

CAX stage	Criteria used in the study	Fearon criteria [a]
Normal nutritional status	• WL $<$ 2% or weight gain and no anorexia • No sarcopenia [b]	No definition
Pre-CAX	• 2% $\leq$ WL $\leq$ 5% and BMI $\geq$ 20 and no features of CAX • Anorexia [c] and no CAX • WL $<$ 2% and sarcopenia and no anorexia [c]	• WL $\leq$ 5% • Anorexia [d] • Metabolic change [d]
CAX	• WL $>$ 5% and no features of refractory CAX • 2% $\leq$ WL $\leq$ 5% and BMI $<$ 20 and no refractory CAX • WL $>$ 2% and sarcopenia [b] and no features of refractory CAX	• WL $>$ 5% • BMI $<$ 20 and WL $>$ 2% • Sarcopenia [e] and WL $>$ 2% • Often reduced food [d]
Refractory CAX	• ECOG PS 3–4 and BMI $<$ 20 and WL $\geq$ 6% [f] • ECOG PS 3–4 and 20 $\leq$ BMI $<$ 22 and WL $\geq$ 11% [f] • ECOG PS 3–4 and 22 $\leq$ BMI and WL $\geq$ 15% [f]	• Variable degree of cachexia [d] • Cancer disease both pro catabolic and not responsive to anticancer treatment [d] • Low performance score [d] • $<$3 months expected survival [d]

Abbreviations: CAX, cachexia; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; WL, weight loss.
[a]Fearon definitions[6]
[b]Sarcopenia defined in men as SMM index <43 cm^2/m^2 if BMI $<$ 25 kg/m^2 and SMM index <53 cm^2/m^2 if BMI $\geq$ 25 kg/m^2 and in women as SMM index <41 cm^2/m^2 [18]
[c]Anorexia is defined by the answer to question 13 of the EORTC questionnaire: a little, quite a bit, or very much.
[d]No further precision provided.
[e]Definition of sarcopenia based either on CT scans images, anthropometric, dual energy X-ray absorptiometry, or bioelectrical impedance assessment.[6]
[f]Combination of BMI and WL associated to poorest survival.[19]

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Table 2. Patients' baseline clinical, biological, and nutritional characteristics

	Patients without CT (N = 219)		Patients with evaluable CT (N = 312)		Total (N = 531)	
	N	%	*N*	%	*N*	%
Characteristics [a]						
Gender						
Male	158	72.1	195	62.5	353	66.5
Female	61	27.9	117	37.5	178	33.5
Age (years)						
Mean	65.4		65.1		65.2	
SD	9.9		10.1		10.0	
ECOG PS						
0	45	20.5	79	25.3	124	23.4
1	128	58.4	172	55.1	300	56.5
2	40	18.3	47	15.1	87	16.4
3	6	2.7	13	4.2	19	3.6
4	0	0.0	1	0.3	1	0.2
Smoking status (*n* with available data)	(213)		(307)		(520)	
Non-smoker	21	9.9	43	14.0	64	12.3
Past smoker	151	70.9	208	67.8	359	69.0
Current smoker	41	19.2	56	18.2	97	18.7
Tumour histology						
Squamous cell carcinoma	60	27.4	80	25.6	140	26.4
Adenocarcinoma	139	63.5	209	67.0	348	65.5
Large cell carcinoma	6	2.7	12	3.8	18	3.4
Other	14	6.4	11	3.5	25	4.7
Molecular abnormalities (*n* with available data)	(124)		(205)		(329)	
None	84	67.7	130	63.4	214	65.0
K-RAS	20	16.1	41	20.0	61	18.5
EGFR, ALK, ROS1, BRAF, HER2	20	16.1	34	16.6	54	16.4
Stage (*n* with available data)	(197)		(307)		(504)	
Stages I–II	16	8.1	18	5.9	34	6.7
Stage IIIA	10	5.1	11	3.6	21	4.2
Stage IIIB-IV	168	85.3	272	88.6	440	87.3
Unknown	3	1.5	6	2.0	9	1.8
Current stage of tumour progression						
No treatment administered yet	24	11.0	30	9.6	54	10.2
Current line not evaluated yet	83	37.9	55	17.6	138	26.0
Progression	24	11.0	57	18.3	81	15.3
Stability	49	22.4	92	29.5	141	26.6)
Response (partial or complete)	39	17.8	78	25.0	117	22.0
Weight at inclusion (kg)						
Median	68		66		67	
Q1–Q3 range	58–79		57–78		58–78	
Body mass index (kg/m^2)						
Median	23.9		23.4		23.6	
Q1–Q3 range	21.0–26.6		20.4–27.0		20.6–26.6	
BMI category						
Underweight (<18.5)	15	6.8	39	12.5	54	10.2
Normal status (18.5–24.9)	118	53.9	165	52.9	283	53.3
Overweight (25.0–29.9)	70	32.0	77	24.7	147	27.7
Obese (≥30.0)	16	7.3	31	9.9	47	8.9
WL category (*n* with available data)	(184)		(270)		(454)	
No WL or WL < 2%	93	50.5	139	51.5	232	51.5
2% ≤ WL ≤ 5%	32	17.4	41	15.2	73	16.1
5% < WL < 10%	32	17.4	54	20.0	86	18.9
10% ≤ WL < 15%	12	6.5	20	7.4	32	7.0
WL ≥ 15%	15	8.2	16	5.9	31	6.8
CRP mg/L (*n* with available data)	(50)		(99)		(149)	
Median	19.5		11.0		15.0	
Q1–Q3 range	6.0–52.0		3.9–43.4		4.0–47.0	
CRP (mg/L) category						
<10	16	32.0	45	45.5	61	40.9
≥10	34	68.0	54	54.6	88	59.1
Alb g/L (*n* with available data)	(69)		(114)		(183)	
Median	35.3		37.0		36.3	
Q1–Q3 range	31.0–40.0		33.0–40.6		33.0–40.0	
Alb (g/L) category						

(*Continues*)

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Table 2 (continued)

	Patients without CT (N = 219)		Patients with evaluable CT (N = 312)		Total (N = 531)	
	N	%	*N*	%	*N*	%
Characteristics [a]						
<Normal	30	43.5	41	36.0	71	38.8
Normal	39	56.5	71	62.3	110	60.1
>Normal	0	0.0	2	1.8	2	1.1
TTR mg/L (*n* with available data)	(12)		(41)		(53)	
Median	210.0		240.0		230.0	
Q1–Q3 range	150.0–245.0		190.0–280.0		180.0–270.0	
TTR (mg/L) category						
<Normal	3	25.0	12	29.3	15	28.3
Normal	9	75.0	29	70.7	38	71.7
>Normal	0	0.0	0	0.0	0	0.0
Hb g/L (*n* with available data)	(167)		(233)		(400)	
Median	119.0		120.0		120.0	
Q1–Q3 range	108.0–133.0		109.0–133.0		108.0–133.0	
Hb (g/L) category						
Severe anaemia	2	1.2	0	0.0	2	0.5
Moderate anaemia	43	25.7	64	27.5	107	26.8
Mild anaemia	68	40.7	75	32.2	143	35.8
Normal Hb levels	54	32.2	93	39.9	147	36.8
>Normal Hb levels	0	0.0	1	0.4	1	0.3
Glucose g/L (*n* with available data)	(56)		(81)		(137)	
Median	1.0		1.0		1.0	
Q1–Q3 range	0.9–1.2		0.9–1.2		0.9–1.2	
Glucose (g/L) category						
Normal, glucose < 1	30	53.6	38	46.9	68	49.6
Moderate, $1 \leq$ glucose ≤ 1.26	14	25.0	26	32.1	40	29.2
High, glucose > 1.26	12	21.4	17	21.0	29	21.2

WL = (W at inclusion—previous W)/previous W × 100; previous W = W assessed 6 months prior to inclusion visit or at the nearest date and recorded in patient file (63%) or W 6 months prior to inclusion visit as stated by the patient (37%). Percentages were rounded to one decimal place and do not always add up to 100%. Abbreviations: Alb, albumin; BMI, body mass index; CRP, C-reactive protein; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Hb, haemoglobin; TTR, transthyretin; W, weight; WL, weight loss.

[a]The characteristics are given for the analysis population (n = 531), unless otherwise specified.

Results

Baseline characteristics

Between July 2016 and October 2016, 539 patients were recruited 56 centres, 52 (92.8%) of which were in France. Overall, 52.6% (n = 278) of patients were enrolled during admission to day care, 32.5% (n = 172) during a visit to the medical oncologist, and 14.9% (n = 79) during admission to hospital. Baseline characteristics are presented in Table 2. Male patients were 66.5%, with a mean (SD) age of 65.2 (10.0) years; 79.9% were PS <2, and the tumour stage was mainly IIIB-IV (87.3%). Over a third (36.6%, n = 194) of patients were overweight or obese. WL over the past 6 months was significant (>5%) for 32.8% (n = 149) of patients and severe (≥10%) for 13.8% (n = 63). N/L was recorded for 63.1% (n = 335) of patients and was normal in 51.0% (n = 171); CRP was recorded for 28.1% (n = 149) of patients and was normal in 40.9% (n = 61).

Overall, 312 patients had evaluable CT scans (Figure 1). Median (Q1–Q3) SMI was 47.7 cm^2/m^2 (42.2–53.8 cm^2/m^2) in men and 37.9 cm^2/m^2 (34.9–42.2 cm^2/m^2) in women. Sarcopenia was observed in 53.5% (n = 167) of patients, 28.7% (n = 48) of which were overweight or obese. Median (Q1–Q3) SMD was 36.7 HU (30.3–42.6 HU) and was below the threshold value defined by Martin *et al*. for 57.2% (n = 178) of patients.

Primary endpoint

CAX (Table 1) was observed in 38.7% (n = 173/447), pre-CAX in 33.8% (n = 151/447), and refractory CAX in 0.9% (n = 4/447) of patients. The remaining 26.6% (n = 119) were classified as having normal nutritional status.

Among CAX patients with available CT scans (n = 111), 78.3% (n = 87) presented with WL > 5%. Sarcopenia was observed in 66.7% (n = 74) of patients and was the only indicator of CAX in 12.6% (n = 14) (Figure 2A).

In pre-CAX (n = 89 available CTs) patients, sarcopenia with no clinically significant WL (<2%) was observed in 66.3% (n = 59) of patients and was the only indicator of pre-CAX for 43.8% (n = 39) (Figure 2B). Anorexia was observed in 42.7% (n = 38) of patients and was the only criterion for 14.6% (n = 13).

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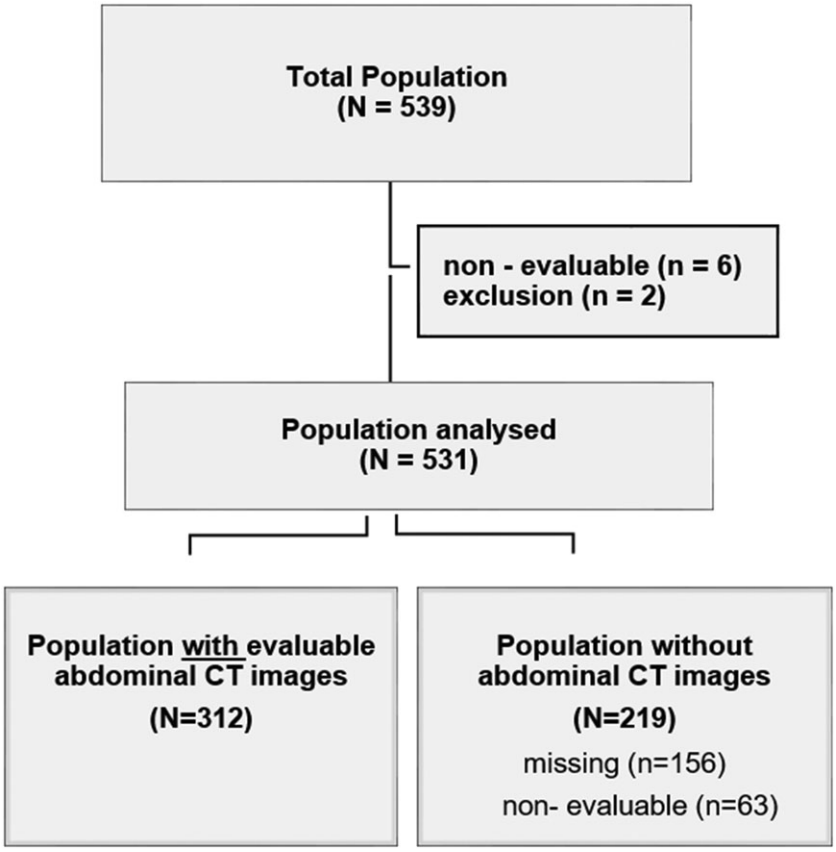
Figure 1 Patient disposition. CT, computed tomography.



No differences were observed in sarcopenia between pre-CAX and CAX stages, with median (Q1–Q3) SMI values of 47.3 (42.4–52.9 cm^2/m^2) and 45.8 cm^2/m^2 (41.1–50.4 cm^2/m^2) in men and 36.9 (34.9–39.7 cm^2/m^2) and 36.7 cm^2/m^2 (33.9–39.7 cm^2/m^2) in women.

Secondary endpoints

The presence of anorexia was associated with more advanced CAX stages (Table 3): IVAS ($P < 0.0001$), AC/C ($P < 0.0001$), and QLQ-C30 ($P < 0.0001$). The concordance between scales was weak, with Kappa coefficients of 0.45 between IVAS and AC/S; 0.54 between QLQ-C30 and AC/C; and 0.51 between QLQ-C30 and IVAS. The positive predictive values (PPV) and negative predictive values of the scales associated to SMM loss were, respectively, 37% and 76% for IVAS ≥ 7, 61% and 60% for AC/S ≥ 37, and 53% and 68% for QLQ-C30 (a little, quite a bit, or very much).

Comparison analyses revealed that histology type ($P = 0.29$), the number of chemotherapy lines received ($P = 0.07$), or the number of metastatic sites ($P = 0.09$) did not differ significantly with CAX stages. Molecular profile ($P = 0.003$ and $P = 0.0008$ among patients without refractory CAX), stage of progression at inclusion ($P < 0.0001$), and Eastern Cooperative Oncology Group Performance Status at inclusion ($P < 0.0001$) were significantly associated (Table 4). N/L ($P = 0.004$) and CRP ($P = 0.02$) levels increased significantly with advanced CAX stages but were weak markers of CAX, with low sensibility and specificity (50.8% and 69.5% for N/L > 3.7 and 42.2% and 83.3% for CRP) (Table 5).

The functional score (except for cognitive) of the QoL questionnaire decreased significantly with advanced CAX stages ($P < 0.001$) and with lower physical activity levels according to International Physical Activity Questionnaire, whether this activity was evaluated as a continuous ($P < 0.001$) or as a categorical variable ($P < 0.001$) (Table 6).

Discussion

This is, to our knowledge, the first study to show the distribution of CAX in a population of NSCLC patients and an association between molecular abnormality in NSCLC and CAX. CAX stages were defined using the original Fearon classification, which was supported by associated functional QoL scores and physical activity levels.

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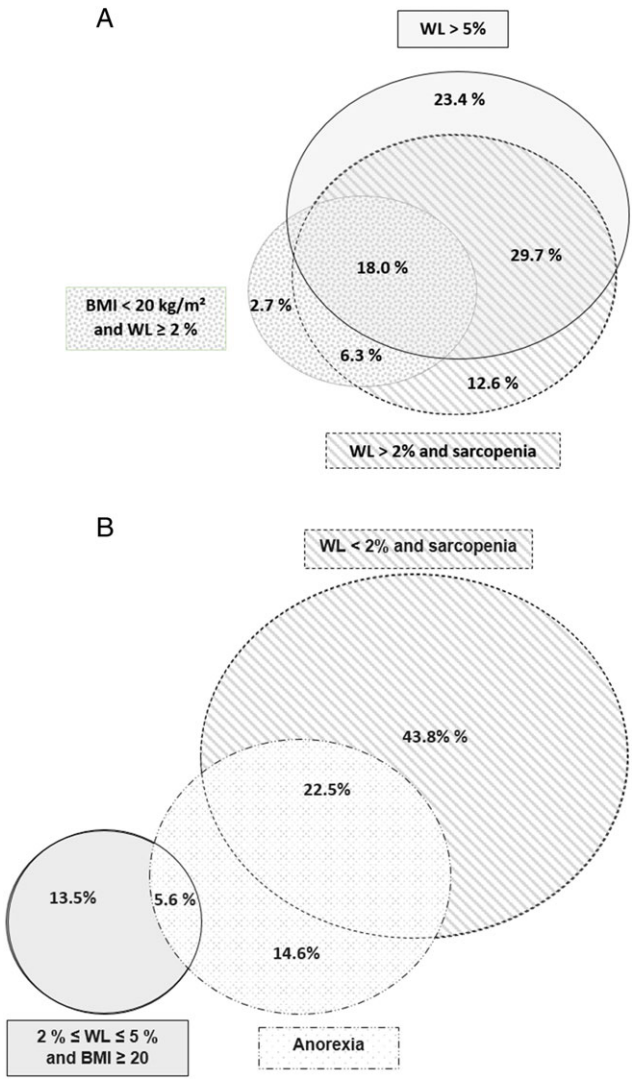
Figure 2 (A) Prevalence of each criterion in CAX patients, for whom all the criteria are evaluable (n = 111). (B) Prevalence of each criterion in pre-CAX patients, for whom all the criteria are evaluable (n = 89). Abbreviations: BMI, body mass index; CAX, cachexia; WL, weight loss.



Conducting studies and initiating nutritional treatment in patients with refractory CAX is of no benefit because tumour burden and active catabolism outweigh nutritional support in advanced stages. As reported by Prado *et al*., the analysis of 783 scans on 342 patients showed that only a minority (15.7%) experienced muscle gain <3 months before death.[21]

Detecting sarcopenia in patients with weight gain or WL <2% could lead to more appropriate treatment and better prognosis. The high percentage of sarcopenia in overweight or obese patients suggests that protein breakdown happens soon before WL and that an early treatment could prevent, decrease, or even reverse SMM loss. This hypothesis has been supported by one experimental and one computational modelling study integrating clinical data, as well as in a series of pre-CAX cancer patients.[22–24] Using radiolabelled amino acids, Deutz *et al*. observed that an anabolic resistance exists early in pre-CAX cancer patients without any sign of malnutrition (with or without small WL, and with a normal or overweight BMI). This resistance could be reversed and muscle protein synthesis increased by giving patients high levels of specific amino acids.[24]

The potential reversible effect of metabolism dysfunctions when treated early is a plea for a precise definition of pre-CAX. Blum *et al*. defined pre-CAX as WL > 1 kg but <5% of the usual body weight in the previous 6 months. This definition was not discriminatory enough, with similar survival rates in pre-CAX patients and those without CAX.[25] The authors suggested including CRP (>10 mg/L) and appetite loss to better define pre-CAX. A study by Blauwhoff-Buskermolen *et al*., however, showed that this definition identified very few pre-CAX patients.[26] Vigano *et al*. suggested to define CAX stages using non-nutritional criteria such as white blood cell count, serum albumin, or haemoglobin.[27] The present study describes early protein metabolism dysfunction and a staging method that is supported by the significant association of CAX stages with QoL and physical activity levels. While these definitions would be more robust if they had been associated to survival, this study was not designed for that purpose. Similarly, we did not assess the correlation between treatment toxicity and CAX and sarcopenia because patients received several different treatments.

We have observed, for the first time, an association between molecular tumour profiles in NSCLC and CAX, with lower CAX percentages among patients with molecular abnormalities. This association could be related to the decrease in catabolism of NSCLC patients with molecular abnormalities. SMM loss has been shown to be driven by tumour evolution, and therapies for molecularly driven lung cancer are associated with better response to treatment and stable disease.[28] The lower rate of CAX could be also attributed to chemotherapy. We reported before that anti-cancer treatment could decrease muscle anabolism by interfering with the mTOR and with the intracellular pathways of muscle anabolism.[29] Cisplatin has been the chemotherapeutic agent most often used for NSCLC before the advent of immunotherapy. Experimental studies in mice have shown that intraperitoneal injection of cisplatin could decrease muscle mass.[30,31] In our study, 78.9% of patients were previously treated with, at least, one line of chemotherapy, 77.1% of which received cisplatin. Forty-eight per cent of NSCLC patients with molecular abnormalities other than K-RAS never received cisplatin.

Besides being associated to important clinical outcomes in many cancers,[18] SMM could be valuable to detect early stages of CAX, but not CAX. In this study, SMM loss was conclusive to diagnose CAX in only 12.6% of patients. These results are consistent with those of Blauwhoff-Buskermolen

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Table 3. Anorexia assessment by the three scales according to cachexia stages

Scale	Normal nutritional status (*N* = 119)	Pre-CAX (*N* = 151)	CAX (*N* = 173)	Refractory CAX (*N* = 4)	*P* [a] *P* [b] *P* [c]
Ingesta VAS (*n* with available data)	(117)	(146)	(168)	(4)	<0.0001
Median	10	8.6	7.1	3.1	<0.0001
Q1–Q3 range	9.6–10.0	6.2–10.0	4.3–9.4	2.2–4.1	0.0003
Ingesta VAS category					<0.0001
<7/≥7[d] (*n*)	4/113	46/100	82/86	4/0	<0.0001
Ingesta VAS <7 (%)	3.4	31.5	48.8	100.0	0.002
A/CS-FAACT score (*n* with available data)	(119)	(148)	(167)	(4)	<0.0001
Median	41	37.0	33.8	23.0	<0.0001
Q1–Q3 range	38.0–43.0	31.0–41.0	27.3–38.0	19.0–32.5	0.001
A/CS-FAACT score category					<0.0001
≤37/>37[e] (*n*)	28/91	80/68	116/51	3/1	<0.0001
A/CS-FAACT score ≤ 37 (%)	23.5	54.1	69.5	75.0	0.005
QLQ C30 questionnaire (*n* with available data)	(119)	(146)	(160)	(4)	
Have you lacked appetite?					
Not at all (*n*, %)	119 100.0	64 43.8	65 40.6	0 0.0	<0.0001
A little (*n*, %)	0 0.0	51 34.9	41 25.6	1 25.0	<0.0001
Quite a bit (*n*, %)	0 0.0	20 13.7	28 17.5	1 25.0	<0.05
Very much (*n*, %)	0 0.0	11 7.5	26 16.3	2 50.0	

Percentages were rounded to one decimal place and do not always add up to 100%. Abbreviations: A/CS-FAACT, anorexia/cachexia subscale of the Functional Assessment of Anorexia/Cachexia Therapy; CAX, cachexia; VAS, visual analogue score.
[a]Total CAX stages.
[b]Without refractory CAX.
[c]Between pre-CAX and CAX.
[d]Threshold defined by Thibault *et al*. in a general population[15]
[e]Threshold defined by Blauwhoff-Buskermolen *et al*. for cancer patients[16]

et al., who showed that WL > 5% appeared to be the determining criterion to diagnose CAX.[26] Our study shows that SMM was the most important component to detect pre-CAX in 66.3% of patients with no clinically important WL (<2%), and the only criterion for detecting pre-CAX in 43.8% of patients without either anorexia or WL. Less than half of the pre-CAX patients presented both a decrease in SMM and a normal appetite. The driver of protein breakdown could be the systemic inflammation as it was observed in rheumatoid CAX, for which SMM loss was observed without anorexia.[32,33] The importance of systemic inflammation in CAX genesis and classification has been recognized by many. The guidelines developed by Arends *et al*. recommend obtaining and documenting inflammatory status (CRP and albumin).[34] The N/L ratio has been linked to different degrees of SMM loss.[35] However, in this study, the serum levels of CRP were available for only 24.5% of the patients for whom the CAX stage was evaluable and could not include it as a staging criteria.

Anorexia is the other criterion of pre-CAX, and it was the only component for 14.6% of the patients. This symptom could be an early signal of nutritional disorder, leading to decreased weight and SMM loss. Surprisingly, we observed a large level of disagreement between the three scales that were used to measure anorexia. The discordance could probably be attributed to the cut-off values, which have been validated but not extensively studied. The survey that detected anorexia most accurately was anorexia/cachexia subscale of the Functional Assessment of Anorexia/Cachexia Therapy (PPV 61%) followed closely by QLQ-C30 (PPV 53%) and then by IVAS (PPV 37%). Pre-CAX patients had lower appetite scores than CAX patients regardless of the survey and the cut-off values. Over 40% of pre-CAX and CAX patients claimed no lack of appetite at all.

The best method to measure food intake would have been to have a trained dietician conduct a 24-h dietary recall or a 3-day food record. In our study, we chose the questionnaire that would be associated to the consequences of anorexia, that is, to either weight or muscle loss. It should also be noted that, while the evaluation of anorexia was carried out at a specific point in time, muscular mass and WL result from a process are happening over time.

Our current study has other limitations. Even though we intended to include a representative NSCLC sample, over half of the population were outpatients, and only 15% of patients were enrolled during admission to hospital. This may explain the low percentage of refractory CAX patients.

We used abnormalities in protein metabolism to define pre-CAX. This arbitrary decision was based on the study by Deutz *et al*. We believe that lipid and glucose metabolic abnormalities should be further investigated and included in the CAX staging system. Also, while we wanted to define the pre-CAX stage using the protein metabolic disorders, we do not know how these abnormalities will respond to

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Table 4. Prevalence of cachexia stages according to disease characteristics

		Normal nutritional status		Pre-CAX		CAX		*P*
	N	*N*	%	*N*	%	*N*	%	
Disease characteristics								
ECOG PS	443							0.0001
0	106	51	48.1	35	33.0	20	18.9	
1	251	59	23.5	97	38.6	95	37.9	
2	74	9	12.1	15	20.3	50	67.6	
≥3	12	0	0.0	4	33.3	8	66.7	
Histology	443							0.4530
Squamous cell carcinoma	116	35	30.2	38	32.8	43	37.1	
Adenocarcinoma	292	79	27.1	98	33.6	115	39.4	
Large cell carcinoma	35	5	14.3	15	42.9	15	42.9	
TNM stage	410							0.98
Stages I–II	30	9	30.0	10	33.3	11	36.7	
Stage IIIA	13	3	23.1	5	38.5	5	38.5	
Stage IIIB-IV	367	95	25.7	124	33.5	148	40.0	
Number of metastatic sites	263							0.09
0	51	16	31.3	18	35.3	17	33.3	
1	108	30	27.7	41	38.0	37	34.3	
>1	104	20	17.2	31	26.7	53	45.7	
Molecular abnormalities	285							0.0008
No mutation	181	48	26.5	54	29.8	79	43.6	
EGFR, ALK, ROS1, BRAF, or HER2	46	8	17.4	27	58.7	11	23.9	
K-RAS	58	21	36.2	13	22.4	24	41.4	
Stage of progression at inclusion	339							0.0001
Response (partial or complete)	95	28	29.5	45	47.4	22	23.1	
Stability	128	48	37.5	40	31.2	40	31.2	
Progression (including patient at first line therapy)	116	16	13.8	36	31.0	64	55.2	
Number of lines received	442							0.08
None	41	6	14.6	11	26.8	24	58.5	
1	81	18	22.2	31	38.2	32	39.5	
2	134	42	31.3	42	31.3	50	37.3	
3	79	26	32.9	22	27.8	31	39.2	
4 or more	107	27	25.2	44	41.1	36	33.6	

The four patients with refractory CAX were excluded from the report in this table. Percentages were rounded to one decimal place and do not always add up to 100%. Abbreviations: CAX, cachexia.

Table 5. Prevalence of cachexia stages according to levels of systemic inflammatory markers

Markers	Normal nutritional status	Pre-CAX	CAX	Refractory CAX	*P* [a] *P* [b]
N/L ratio (n with available data)	(86)	(113)	(132)	(4)	
Median	2.5	2.7	3.7	7.1	0.004
Range	1.9–3.9	1.8–4.4	2.0–6.1	3.5–15.3	0.004
N/L category					
N/L > 3/≤3 (*n*)	34/52	49/64	78/54	3/1	0.01
N/L > 3 (%)	39.5	43.4	59.1	75.0	0.007
N/L > 3.7/≤3.7[c] (*n*)	24/62	35/78	67/65	3/1	0.0006
N/L > 3.7 (%)	27.9	31.0	50.8	75.0	0.0005
CRP mg/L (*n* with available data)	(27)	(37)	(64)	(2)	
Median	18.0	7.0	21.5	16.5	0.05
Range	5.6–30.1	3.0–25.0	7.8–53.0	15.0–18.0	0.02
CRP category					
CRP > 33.7/≤33.7[d] (*n*)	4/23	7/30	27/37	0/2	0.01
CRP > 33.7 (%)	14.8	18.9	42.2	0.0	0.008

Neutrophil to lymphocyte ratio (n = 335 evaluable patients) and C-reactive protein (n = 130 evaluable patients). Continuous parameters are presented as medians (interquartile range Q1–Q3), and categorical parameters are presented as number of patients plus the percentage. Percentages were rounded to one decimal place and do not always add up to 100%. Abbreviations: CAX, cachexia; CRP, C-reactive protein; N/L, neutrophil-to-lymphocytes ratio.
[a]Total CAX stages.
[b]Without refractory CAX.
[c]It is the best value for N/L ratio determined by the ROC curves which gives the best sensibility (50.8%) and the best specificity (69.5%).
[d]It is the best value for CRP in mg/L determined by the ROC curves which gives the best sensibility (42.2%) and the best specificity (83.3%).

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Table 6. Functional quality of life (QLQ-C30) and physical activity level (IPAQ) according to cachexia stages

	Normal nutritional status	Pre-CAX	CAX	Refractory CAX	P^a / P^b
QLQ-C30					
Physical scale (*n* with available data)	(119)	(146)	(162)	(4)	<0.0001
Median	80.0	73.3	66.7	16.7	<0.0001
Q1–Q3 range	66.7–93.3	53.3–80.0	46.7–80.0	6.7–9.4	
Role scale (*n* with available data)	(119)	(146)	(161)	(4)	<0.0001
Median	83.3	66.7	66.7	0.0	<0.0001
Q1–Q3 range	66.7–100.0	33.3–100.0	33.3–100.0	0.0–0.0	
Cognitive scale (*n* with available data)	(118)	(145)	(164)	(4)	0.1
Median	83.3	83.3	83.3	83.3	<0.05
Q1–Q3 range	83.3–100.0	66.7–100.0	66.7–100.0	66.7–100.0	
Emotional scale (*n* with available data)	(118)	(145)	(164)	(4)	<0.0001
Median	86.1	75.0	75.0	45.8	<0.0001
Q1–Q3 range	75–100	58.3–91.7	50.0–91.7	16.7–75.0	
Social scale (*n* with available data)	(118)	(144)	(163)	(4)	<0.0001
Median	100.0	83.3	66.7	16.7	<0.0001
Q1–Q3 range	66.7–100.0	50.0–100.0	50.0–100.0	8.3–16.7	
IPAQ survey (*n* with available data)	(87)	(111)	(126)	(4)	
Activity total, MET-min/week					<0.0001
Median	2712.0	840.0	495.0	0.0	<0.0001
Q1–Q3 range	693.0–6228.0	0.0–3600.0	0.0–2666.0	0.0–0.0	
Activity score category (*n* with available data	(102)	(128)	(144)	(4)	
Slight (*n*, %)	30 29.4	56 43.8	78 54.2	4 100.0	0.0005
Moderate (*n*, %)	34 33.3	42 32.8	39 27.1	0 0.0	0.001
Intense (*n*, %)	38 37.3	30 23.4	27 18.8	0 0.0	
Sedentary score, min/week					0.3
Median	2100.0	2100.0	2100.0	1890.0	0.2
Q1–Q3 range	1260.0–2520.0	1260.0–3360.0	1260.0–3360.0	420.0–4620.0	

Continuous parameters are presented as medians (interquartile range Q1–Q3) and categorical parameters are presented as number of patients plus the percentage. Percentages were rounded to one decimal place and do not always add up to 100%. Abbreviations: CAX, cachexia; IPAQ, International Physical Activity Questionnaire; MET-min, metabolic equivalent minutes.
[a]Total CAX stages.
[b]Without refractory CAX.

treatment, and whether all pre-CAX patients will evolve to CAX. The observational nature of the study did not allow us to obtain enough data on systemic inflammatory markers, and we could not include cut-offs for the classifications of CAX stages. Similarly, CT scans were not available for all patients, but this did not lead to a bias because baseline characteristics of patients with and without CT were similar.

Last, in order to stay as close as possible to Fearon criteria, we did not include the aspect of muscle strength loss in the definition of sarcopenia. This is a factor that is being increasingly considered to stage CAX, especially in the elderly population with sarcopenia.

Conclusions

In summary, we propose the use of appetite loss and sarcopenia with limited (<2%) or no WL to define the pre-CAX stage. SMM loss should be part of NSCLC assessment because it allows detecting early protein metabolism abnormalities. While we have considered appetite loss to be an early sign of nutritional disorder, anorexia as the only symptom to define pre-CAX patients should be further investigated. Additional studies are also warranted on inflammatory markers and on the role of lipid and glucose metabolism abnormalities in the pre-CAX stage.

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Conflict of Interest

S.A., P.-J.S. V.S., and D.D. were related to corporate-sponsored research - Chugai Pharma France; H.M. to corporate-sponsored research - Chugai Pharma France, Roche, Astra, Lilly, MSD, Pfizer, BMS, Amgen; D.P. to corporate-sponsored consultancy - AstraZeneca, Boehringen Ingelheim, BMS, Lilly, MSD, Pfizer, Roche, Novartis, Chugai Pharma France, Celgene. I.K. participated in membership on an advisory board and/or symposium: Chugai Pharma France, Kyowa Kirin, Pfizer, Astellas, Janssen, Takeda, P Fabre. H.G. is an employee of Chugai Pharma France. All remaining authors have declared no conflicts of interest.

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