

# Hypermetabolism is an independent prognostic factor of survival in metastatic non-small cell lung cancer patients

Anne Jouinot, Guillaume Ulmann, Clara Vazeille, Jean-Philippe Durand, Pascaline Boudou-Rouquette, Jennifer Arrondeau, Camille Tlemsani, Ludovic Fournel, Marco Alifano, Marie Wislez, et al.

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## 2 small cell lung cancer patients

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#### 38 Abstract

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Abstract <u>Background and aims</u>: Metastatic non-small cell lung cancer (NSCLC) is the first cause of cancer death worldwide. Increased resting energy expenditure (REE) is frequent among cancer patients and may contribute to cancer cachexia. The aim of this study was to examine the prognostic value of increased REE in metastatic NSCLC patients. <u>Methods</u>: This observational study was conducted between June 2012 and November 2017 in

the outpatient unit of the oncology department of Cochin hospital, Paris. Consecutive patients

45 with newly diagnosed stage IV NSCLC underwent measurement of REE by indirect

46 calorimetry before treatment initiation. Uni- and multivariate analysis of overall survival (OS,

47 Cox models) included age, sex, smoking habit, histological subtype, performance status, body

48 mass index, weight loss, albumin and CRP levels and the ratio of measured REE to the REE

49 predicted by the Harris Benedict formula (mREE/pREE).

50 <u>Results</u>: 144 patients were enrolled: mean age 64 years, 63% male, 90% non-squamous

51 carcinoma, including 17% with ALK/EGFR alteration. In univariate analysis, tobacco

52 consumption (p = 0.007), histo-molecular subtype (p <  $10^{-3}$ ), performance status (p = 0.04),

53 weight loss (p <  $10^{-4}$ ), albumin (p <  $10^{-4}$ ), CRP (p = 0.001) and mREE/pREE ratio (> vs  $\leq$ 

54 120%: HR = 2.16,  $p < 10^{-3}$ ) were significant prognostic factors of OS. Median OS were 6.1

and 17.3 months in patients with mREE/pREE ratio > and  $\leq 120\%$ , respectively. In

56 multivariate analysis, histo-molecular subtype (non-squamous ALK/EGFR mutated vs

57 squamous carcinoma: HR = 0.25, p = 0.006), weight loss (>  $vs \le 5\%$ : HR = 1.98, p = 0.004),

albumin ( $\geq$  vs < 35 g/L: HR = 0.56, p = 0.02) and mREE/pREE ratio (> vs  $\leq$  120%: HR =

59 1.90, p = 0.004) were identified as independent prognostic factors.

60 <u>Conclusions</u>: Elevated resting energy expenditure emerges as an independent prognostic

61 factor in metastatic NSCLC.

- 62 **Keywords**: resting energy expenditure, malnutrition, prognosis, survival, non-small cell lung
- 63 cancer
- 64
- 65 Abbreviations:
- 66 ALK, Anaplastic Lymphoma Kinase
- 67 BMI, Body Mass Index
- 68 CI, Confidence Interval
- 69 CRP, C-Reactive Protein
- 70 *EGFR*, Epidermal Growth Factor Receptor
- 71 HR, Hazard Ratio
- 72 LBM, Lean Body Mass
- 73 mREE, measured REE
- 74 NSCLC, Non-Small Cell Lung Cancer
- 75 OS, Overall Survival
- 76 pREE, predicted REE by the Harris Benedict formula
- 77 REE, Resting Energy Expenditure
- 78 SMA, Skeletal Muscle Area
- 79 VO2, Oxygen consumption

#### 80 Introduction

81 Lung cancer is the first cause of cancer death worldwide. Non-small cell lung cancer

82 (NSCLC) represents 80% of lung cancer diagnoses and only 50% of patients with NSCLC

83 present with a resectable disease at the time of diagnosis(1). Despite recent advances in

84 immunotherapy, the 5-year survival rate of patients with metastatic NSCLC remains less than

30 %(2). Half of NSCLC patients already show weight loss > 5% at diagnosis(3,4). Weight

loss and cachexia are associated with poor prognosis and up to 20 % of patients will die from

cancer cachexia rather than from the tumor burden itself(5-7).

88 Cancer-associated weight loss results from negative energy balance, due to decreased food

89 intake, increased energy expenditure or both(8). Resting energy expenditure (REE) represents

90 the main component of total energy expenditure, well ahead of energy expenditure induced by

91 diet or physical activity. Increased REE, i.e. hypermetabolism, occurs in approximately half

92 of cancer patients(9,10). Hypermetabolism is related to proinflammatory cytokines and

93 neuroendocrine responses(11,12), and is frequent in advanced NSCLC(9,11).

94 Increased REE is considered as an early and major contributor to cancer cachexia(10).

95 However, the prognostic value of REE has been poorly evaluated so far(13). Survival was not

96 the main endpoint in most of REE studies in cancer patients. Moreover, studies evaluating the

97 impact of REE on survival included different tumor types and stages, ranging from adjuvant

98 to advanced palliative setting, leading to discordant results(10,14–17).

99 The aim of this study was to examine the prognostic value of increased REE in a large cohort100 of patients with metastatic NSCLC, and to compare it to standard prognostic factors.

101

**102** Materials and Methods

103

104 <u>Patients</u>

We conducted a prospective, observational study between June 1<sup>st</sup> 2012 and November 30<sup>th</sup> 105 106 2017 in Cochin Hospital. We enrolled consecutive patients who participated in a multidisciplinary risk assessment program in the outpatient unit of the oncology department. 107 108 This program is proposed to every cancer patient before chemotherapy initiation and aims at providing personalized supportive care. 109 Key eligibility criteria were age 18 years or older, stage IV histologically proven NSCLC, 110 111 first line therapy for metastatic disease. Main exclusion criteria were the absence of REE measurement at steady state or active malignancy other than NSCLC. Patients were followed 112 until the date of their death or their last examination. Follow-up period ended on May 31<sup>th</sup>, 113 114 2018. Written informed consent was obtained for all patients. The study was approved by the 115 Cochin Institutional Review Board according to the declaration of Helsinki. 116 117 Multidisciplinary risk assessment 118 Patients underwent a multidisciplinary evaluation including consultation with an oncologist, a 119 120 dietitian, a psychologist, a pharmacist, and, if required, a social worker, a palliative care physician, or any other specialist (e.g., geriatrist or cardiologist). 121 REE was determined prior chemotherapy initiation, under standard resting conditions, i.e. 122 after 12 hours of fasting and 15 minutes of complete bed rest, in a thermo-neutral 123 environment. For each patient, oxygen consumption (VO2) was measured during 15 minutes 124 by indirect calorimetry using a face mask connected to an oxygen analyzer (Fitmate, 125 COSMED, Italy). The calorimeter was calibrated before each measurement. The first 5-126 minutes of measurement were used to ensure that the steady state, i.e. VO2 variation by less 127 than 10%(18), was achieved, and were discarded for the analysis. Measured REE (mREE, 128

- kcal/d) was determined from VO2 using Weir's equation(19), with a fixed respiratoryquotient of 0.85.
- 131 To evaluate the extent of REE alteration compared to healthy individuals, mREE was
- 132 compared to predicted REE (pREE), calculated with revised Harris and Benedict
- equations(20):
- 134 males: pREE (kcal/d) =  $88.362 + 13.397 \times W + 479.9 \times H 5.677 \times A$
- 135 females: pREE (kcal/d) = 447.593 + 9.247 x W + 309.8 x H 4.33 x A
- 136 with W, weight in kilograms; H, height in centimeters; and A, age in years.

137 Although a majority of studies classified hypermetabolic patients based on the standards of

138 Boothby(21) – i.e. mREE/pREE > 110% -, this ratio is often very high in NSCLC

patients (11,22), making that up to 80% of patients are classified as hypermetabolic. Thus,

- 140 several cut-off values of mREE/pREE have been proposed in the literature to define
- 141 hypermetabolism in this specific population(11,23). In face of this ongoing debate, we have

evaluated cut-off values of 110, 115 and 120% to define hypermetabolism.

143 Anthropometric measurements included body weight – measured with a medical balance –

144 and height – measured with a stadiometer. Body mass index (BMI) was calculated as weight

145 (kg)/height (m<sup>2</sup>). Weight loss in the last 6 months and Eastern Cooperative Oncology Group

- 146 performance status was also recorded.
- 147 Since REE depends mainly on lean body mass (LBM), LBM was estimated from CT-scans
- 148 performed for diagnosis procedures within the month of REE measurement. Skeletal muscle
- 149 area (SMA) at the third lumbar vertebra (L3) was measured using ImageJ® software (NIH,
- USA) and LBM was calculated as(24): LBM (kg) = L3 SMA ( $cm^2$ ) x 0.30 + 6.06. For
- 151 comparative analyses, mREE/LBM ratio was dichotomized into 2 groups ("high" and "low")
- 152 according to its median value.

153 Routine biological tests included serum albumin and plasmatic C-reactive protein (CRP)

levels, measured by nephelometry (BN II, Siemens) and liquid turbidimetry (Cobas, RocheDiagnostic) respectively.

156

157 <u>Statistical analyses</u>

Calculations were performed using R statistical software (version 3.5.1, R Stats Package).
Comparisons between groups were performed with Student t-test for quantitative variables
and with chi-square test for qualitative variables.

Overall survival (OS) was defined as the time elapsed between evaluation and death or last 161 162 follow-up visit. Survival curves were obtained with Kaplan-Meier estimates and compared with log-rank test. We calculated that we would need to enroll 57 patients in normo- and 163 hypermetabolic groups to show a 30% difference of overall survival at 12 months (65% vs 164 165 35% respectively) with a two-sided 5% significance level and a 90% statistical power. Cox proportional hazards regression was used to identify clinical and biological variables 166 associated with OS. Variables with p value < 0.1 in univariate analyses were then combined 167 into multivariable models. In a sensitivity analysis, we also investigated the prognostic value 168 of mREE/pREE ratio after adjustment on variables associated with elevated mREE/pREE 169 ratio, of mREE/pREE ratio after exclusion of outliers -defined by values of mREE/pREE ratio 170 exceeding 2 standard deviations above or below the mean (9 patients)-, and of mREE/pREE 171 ratio as continuous variable. To consider the potential confounding effect of body 172 composition, we also evaluated the prognostic value of mREE/LBM. The proportional 173 hazards assumption was checked for each model using graphical methods based on Kaplan-174 Meier curves and the scaled Schoenfeld residuals. 175 All p-values were two-sided, and the level of significance was set at p < 0.05. 176

178 **Results** 

179

180 Patient characteristics

181 From June 2012 to November 2017, 170 patients underwent a multidisciplinary risk and need

assessment for newly diagnosed metastatic NSCLC, among which 144 (85%) met all the

study criteria for analysis (**Figure 1**). The main reason for exclusion (n = 24) was the absence

184 of REE measurement.

185 Baseline population characteristics are presented in **Table 1**. Study population included a vast

186 majority of non-squamous carcinoma (90%), with 17% of *ALK/EGFR* alteration. Most

187 patients showed a fairly preserved physical condition at the time of evaluation, with 56% of

188 patients having a performance status of 0 or 1 (Table 1).

189 mREE in study patients estimated by indirect calorimetry was higher than pREE calculated

190 from revised Harris and Benedict equation (mean 1653 vs 1421 kcal/d,  $p < 10^{-6}$ ). Mean

mREE/pREE ratio was 116%, ranging from 46 to 182%. Using cut-off values of 110, 115,

and 120% in mREE/pREE ratio, a total of 91 (63%), 77 (53%) and 57 (40%) patients were

193 classified as hypermetabolic respectively. In the subgroup of patients with body composition

assessment (n=81), mean mREE/LBM was 38.5 kcal/kg/d and was correlated to mREE/pREE

195 ratio (r=0.77,  $p < 10^{-16}$ ).

196 Median follow-up period was 9.8 months, with 13 patients (9%) lost to follow-up. No

197 significant differences in mREE/pREE ratio were observed between lost to follow-up patients

and the rest of the cohort (mean 112 and 116% respectively, p = 0.36).

199

200 Hypermetabolism is associated with clinical and biological features of cachexia

201 Comparisons of baseline characteristics between hypermetabolic (mREE/pREE ratio > 120%)

and normometabolic (mREE/pREE ratio  $\leq 120\%$ ) patients is presented in Table 1.

203	Hypermetabolism was more frequently observed in men than in women. Hypermetabolism
204	was associated with diffuse metastatic disease (> 2 metastatic sites) and with clinical and
205	biological features of pre-cachexia and cachexia (altered performance status, weight loss, low
206	albumin and trend towards high CRP level, Table 1). Altered performance status and weight
207	loss $\geq$ 5% were observed in 58% and 62% of hypermetabolic patients, and in 29% and 34% of
208	normometabolic patients, respectively ( $p=0.009$ and $<10^{-3}$ ).
209	In the subgroup of patients with LBM measurement (n=81), mREE/LBM was significantly
210	higher in hypermetabolic than in normometabolic patients (43.7 vs 34.8 kcal/kg/d, $p < 10^{-6}$ ).
211	
212	Hypermetabolism is an adverse prognostic factor in metastatic NSCLC
213	During the follow-up period, 98 death events (68% of patients) were observed. Median OS for
214	the study population was 11.9 months (95% confidence interval (CI): 9.6 -17.5). The 1- and
215	2- year OS rates were 49 and 26% respectively.
216	In univariate analysis of OS, tobacco consumption, absence of EGFR or ALK molecular
217	alteration, altered performance status, weight loss, low albumin, high CRP, and increased
218	mREE/pREE ratio were identified as adverse prognostic factors (Table 2). A mREE/pREE
219	ratio over 120% was associated with a worse prognosis (hazard ratio (HR): 2.16, 95% CI:
220	1.45-3.21, p < 10 <sup>-3</sup> ) than mREE/pREE ratio > 110% or 115% (Table 2). Median OS were 6.1
221	(95% CI: 4.4-10.9) and 17.5 months (95% CI: 13.8-24.6, log-rank $p < 10^{-3}$ ) in patients with a
222	mREE/pREE ratio over or below 120% respectively (Figure 2).
223	In multivariable analysis of OS, histo-molecular subtype ( $p = 0.002$ ), weight loss ( $p = 0.004$ ),
224	and mREE/pREE ratio (> 120 vs $\leq$ 120%, HR: 1.84, 95% CI: 1.19-2.85, p = 0.006) were
225	independent prognostic factors (Table 3).
226	In sensitivity analyses, increased mREE/pREE ratio was an independent prognostic factor of
227	OS in multivariable models after adjustment on sex (HR: 1.92, 95% CI: 1.22-3.05, p = 0.005)

228	or on number of metastatic sites (HR: 1.90, 95% CI: 1.22-2.95, $p = 0.004$ ), after exclusion of
229	outliers (HR: 1.73, 95% CI: 1.09-2.73, p = 0.02), using cut-offs of 110% (HR: 1.64, 95% CI:
230	1.05-2.56, p = 0.03) or 115% (HR: 1.58, 95% CI: 1.03-2.41, p = 0.03) to define
231	hypermetabolism or by using mREE/pREE ratio as continuous variable (HR: 1.09 per 10%
232	increase, 95% CI: 1.01-1.19, $p = 0.03$ ). In the subgroup of patients with LBM measurement,
233	high mREE/LBM was also an independent prognostic factor in multivariable analysis (high
234	versus low, HR: 1.97, 95% CI: 1.11-3.50, p = 0.02).
235	

236 Discussion

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242

In this prospective cohort of 144 metastatic NSCLC patients, our data show that

hypermetabolism is associated with decreased survival. To the best of our knowledge, the

current study is the first to describe energy expenditure as an independent prognostic factor inmultivariable models in cancer patients.

•

patients. Most of them suggest that elevated REE is associated with poor outcome(10,14,16).

So far, only few studies have described the relationship between REE and survival in cancer

However, none has evaluated the prognostic value of REE in comparison with standard

prognostic factors. In a previous study, we have compared overall survival of metastatic

246 cancer patients according to REE measured before chemotherapy initiation. Hypermetabolic

247 patients showed a shorter overall survival compared with normometabolic patients(10,14).

However, survival analysis could have been biased by the inclusion of different tumor types,

since tumors most frequently associated with hypermetabolism, such as lung cancer, are also

those associated with worse prognosis.

251 One study has focused specifically on REE and disease-free survival in lung cancer patients.

Jatoi et al. included 17 NSCLC patients with early-stage disease (stages IA–IIIB) before

treatment initiation. Although the statistical power was limited by the small number of 253 254 patients included, hypermetabolic patients surprisingly showed a significantly longer diseasefree survival than hypometabolic patients(15). However, hyper- and hypometabolism were 255 256 defined by the simple existence of a positive or negative difference between patient's REE and that of a matched (sex, age  $\pm 5$  years, and BMI  $\pm 3$  kg/m<sup>2</sup>) healthy control. Overall, REE 257 was not significantly different between cancer patients and their matched controls. Moreover, 258 259 another study including different cancer types among which 134 NSCLC showed that stage I-III tumors exert a smaller effect on REE than stage IV tumors(9). One can hypothesized that 260 at least some patients in the study of Jatoi et al. would have been classified as 261 262 normometabolic according to the standards of Boothby (mREE/pREE ratio between 90 and 110%). 263 Actually, none of these studies included a sufficiently large and homogeneous cohort to 264 265 compare REE to other prognostic factors. On the contrary, our study included only newly diagnosed stage IV NSCLC, which represents a homogeneous population, in whom a high 266 proportion of truly hypermetabolic patients is expected(9). We evaluated the prognostic 267 significance of REE, along with common prognostic factors in metastatic cancer patients, 268 such as performance status, weight loss, CRP and albumin levels, and also with specific 269 270 prognostic factors in NSCLC such as histological subtype and molecular alterations. In our series, the value of 120% in mREE/pREE ratio appears as the most discriminant cut-off 271

for prognosis. Finally, given that REE depends mainly on lean body mass and that altered

body composition is frequent among cancer patients, mREE/pREE ratio may not be an

appropriate surrogate for evaluating energy metabolism in this population. In the current

study, mean mREE/LBM was higher in patients with mREE/pREE ratio > 120% (43.7

kcal/kg/d) than in patients with mREE/pREE ratio  $\leq 120\%$  (34.8 kcal/kg/d). Moreover,

277 mREE/LBM was also identified as an independent prognostic factor. Overall, our results

underline that patient energy expenditure at diagnosis is an important factor for oncologicoutcome.

280

Hypermetabolism, defined by mREE/pREE ratio > 120%, was associated with some clinical 281 and biological features of pre-cachexia and cachexia(25), i.e altered performance status, 282 weight loss, low albumin and trend towards elevated CRP. These results are in agreement 283 with previous studies showing that hypermetabolism is an early determinant of cancer 284 cachexia(10,26) and may partly explain the relation of hypermetabolism to survival. These 285 metabolic alterations induce chronic inflammation, with the production of cytokines such as 286 287 tumor necrosis factor and interleukin-6, and hormonal response, which in turn induce muscle proteolysis, glucose consumption from the liver, and lipid consumption from fat tissues, 288 leading to high REE(11, 12, 28). 289

290 However, our results raise the question of underlying mechanisms regardless of variations in body composition or inflammatory state. First, there was no significant differences in BMI 291 292 and LBM between hypermetabolic and normometabolic patients in our cohort, even after 293 adjustment on sex (data not shown). Second, hypermetabolism was also observed in patients with apparently good medical condition: 30% of patients with PS 0-1, 26% of patients with 294 normal CRP (< 10 mg/L) and 25% of patients with less than 5% weight loss showed 295 mREE/pREE ratio > 120%. Finally, hypermetabolism was an independent prognostic factor 296 in multivariable analysis including pre-cachexia features. 297

It should be noted that hypermetabolism may also be considered in terms of the metabolic contribution of cancer cells, independently of the cachexia process. A recent study has evaluated the energetic consumption of tumor in vivo using mathematical models and estimated that tumor-related energy cost can increase the energy expenditure from 100 to 302 1400 kcal/day(27), considering increased glucose turnover and variable proportions of
303 oxidative and glycolytic metabolism in cancer cells.

Limitations of the current study include the methods used for determining REE and LBM. 304 305 REE was measured using Fitmate® indirect calorimeter with face-mask, a recent and compact (20 x 24 cm) metabolic analyzer, which demonstrates good accuracy and reliability for 306 measuring REE in adults(29,30). In the specific setting of cancer patients, a recent study 307 suggests rather a low accuracy of the Fitmate® device, compared with REE measurement 308 from VO2 and VCO2 by a metabolic cart(31). One possible explanation was that respiratory 309 quotient determined by metabolic cart was variable (0.69 to 0.92) and in average lower (0.80) 310 311 than the fixed quotient of 0.85 assumed by the Fitmate® calorimeter. However, these results were obtained in a small series of patients (n=26) and the variation of VO2 during 312 measurement was not reported. Moreover, in another small series, the respiratory quotient 313 314 was much less variable and no difference was observed between lung cancer patients and healthy controls(12). 315

LBM was determined from CT-scan, using Mourtzakis formula(24). Although Dual-energy absorptiometry is the reference method to quantify body composition, CT-scan appears as an acceptable surrogate in cancer patients. Indeed, lumbar–skeletal muscle cross-sectional area is linearly related to the whole-body muscle(24,32). Moreover, CT-scans are performed in routine diagnosis and follow-up work-up in cancer patients, and thus offer a convenient solution for determining LBM in this population.

Missing data in LBM assessment are another limitation of the current study. However, the reasons for missing data, i.e. CT-images not available in medical records or not including L3 vertrebra- are not related to energy expenditure, and in the subgroup analysis, mREE/LBM showed good agreement with mREE/pREE ratio.

The number of lost to follow-up patients (9%) represents another limitation of our study. However, reasons for lost to follow-up did not depend from REE. Indeed, no significant differences in mREE/pREE ratio were found between lost to follow-up patients and the rest of the cohort. Thus, lost to follow-up patients were unlikely to impact the interaction of REE with survival and with other prognostic factors. Furthermore, our study included a relatively large number of death events (N=98, 68%), so that lost to follow-up patients had only limited effects on the statistical power for survival analyses.

333

In the current context of personalized medicine, routine REE determination in cancer patients 334 335 could help to adjust their nutritional management. REE measurement may be considered as a point of care tool in lung cancer treatment. In particular, sufficient protein and energy 336 administration is critical to prevent weight loss, which is a major prognostic factor in this 337 338 population. In addition, targeting hypermetabolism may represent a novel therapeutic approach in the prevention of cancer cachexia. Inflammatory and adrenergic mediators are 339 340 important determinants behind elevated REE in weight-losing patients(11,33) and can be targeted by non-steroidal anti-inflammatory drugs or beta-blockers. Recently, a randomized 341 phase II trial in advanced colorectal cancer or NSCLC patients showed that beta-blocker 342 espindolol reverses weight loss and improves fat-free mass(34), but not survival. Since 343 cancer-associated weight loss is a multifactorial process, resulting from decreased food 344 intake, increased energy expenditure or both(8), multimodal and individualized approaches, 345 including anti-inflammatory drugs, beta-blockers, ghrelin agonists, exercise and nutritional 346 management are possibly required to reverse weight loss and improve survival. 347

348

In conclusion, hypermetabolism at the time of diagnosis is an independent prognostic factor
of survival in metastatic NSCLC patients. Future trials of multimodal intervention for cancer

- 351 cachexia should include REE measurement, adapt nutritional support and offer dedicated
- 352 treatment to hypermetabolic patients.

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356

### 357 Statement of Authorship

358 The authors' responsibilities were as follow: AJ analyzed data and wrote paper; AJ and FG

designed the research and had primary responsibility for final content of the manuscript; all

360 authors conducted research, interpreted the data, revised, read and approved the final

361 manuscript.

362

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364 All authors declare that they have no conflict of interest related to this work.

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469		controlled, international multicentre phase II study (the ACT-ONE trial). J Cachexia
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471		

## **Tables**

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## 474 Table 1. Population characteristics

Variable	N	Total	mREE/pREE ≤ 120%	mREE/pREE > 120%	p-value
		N=144	N=87 (60%)	N=57 (40%)	
Age	144				0.08
		64.2 (11.8)	62.8 (12.6)	66.2 (10.4)	
Sex	144				0.008
Female		53 (37%)	40 (46%)	13 (23%)	
Male		91 (63%)	47 (54%)	44 (77%)	
Smoking habit	143				0.63
Non-smoker		24 (17%)	16 (19%)	8 (14%)	
Smoker or former smoker		119 (83%)	70 (81%)	49 (86%)	
Histo-molecular subtype	144				0.29
squamous		15 (10%)	10 (11%)	5 (9%)	
non-squamous					
ALK/EGFR wild-type		88 (61%)	48 (55%)	40 (70%)	

ALK/EGFR undetermined		17 (12%)	11 (13%)	6 (10%)	
ALK/EGFR alteration		24 (17%)	18 (21%)	6 (10%)	
Number of metastatic sites	144				0.02
≤2		93 (65%)	63 (72%)	30 (53%)	
> 2		51 (35%)	24 (28%)	27 (47%)	
Performance status	144				0.009
0-1		81 (56%)	57 (66%)	24 (42%)	
$\geq 2$		63 (44%)	30 (34%)	33 (58%)	
BMI	144				0.16
$\leq 25 \text{ kg/m}^2$		95 (66%)	53 (61%)	42 (74%)	
> 25 kg/m <sup>2</sup>		49 (34%)	34 (39%)	15 (26%)	
Weight loss in the last 6 months	143				<10 <sup>-3</sup>
$\leq 5\%$		83 (58%)	62 (71%)	21 (38%)	
> 5%		60 (42%)	25 (29%)	35 (62%)	
Albumin	142				0.01
< 35 g/L		38 (27%)	16 (19%)	22 (39%)	
$\geq$ 35 g/L		104 (73%)	70 (81%)	34 (61%)	
					1

CRP	144				0.07
< 10 mg/L		52 (36%)	37 (43%)	15 (26%)	
$\geq 10 \text{ mg/L}$		92 (64%)	50 (57%)	42 (74%)	
LBM (kg)	81				
		43.5 (9.0)	42.7 (9.8)	44.6 (7.6)	0.33
mREE (kcal/d)	144				
		1652.9 (440.9)	1468.6 (389.5)	1934.4 (360.4)	<10 <sup>-9</sup>
mREE/pREE ratio (%)	144				
		116.3 (23.8)	102.0 (17.0)	138.2 (14.2)	<10 <sup>-26</sup>
mREE/LBM (kcal/kg/d)	81				
		38.5 (8.2)	34.8 (6.5)	43.7 (7.5)	<10 <sup>-6</sup>

475

476 Values are expressed in N(%) for qualitative variables and in mean (sd) for quantitative variables, and compared with chi-square and t-test

477 respectively. Significant p-values are indicated in bold.

BMI, body mass index; CRP, C-reactive protein; LBM, lean body mass estimated from L2 body CT; mREE, measured resting energy

479 expenditure; pREE, predicted resting energy expenditure, using Harris and Benedict equations

# 481 Table 2. Univariate analysis of overall survival

Variable	HR [95% CI]	p-value
Age		
/ year increase	1.01 [0.99-1.03]	0.26
Sex		
Male vs Female	1.41 [0.91-2.17]	0.12
Smoking habit		
Smoker or former smoker vs Non-smoker	2.40 [1.28-4.52]	0.007
Histo-molecular subtype		
non-squamous ALK/EGFR wild-type or undetermined vs	0.58 [0.31-1.11]	0.10
squamous		
non-squamous ALK/EGFR altered vs squamous	0.19 [0.08-0.46]	<10 <sup>-3</sup>
Number of metastatic sites		
$\geq$ 3 vs 1-2	1.21 [0.80-1.83]	0.37
Performance status		
$\geq 2 \text{ vs } 0-1$	1.50 [1.01-2.24]	0.04
BMI		
> 25 vs $\leq$ 25 kg/m <sup>2</sup>	0.81 [0.53-1.24]	0.34
Weight loss in the last 6 months		
$\geq$ 5 vs < 5%	2.27 [1.52-3.40]	<10 <sup>-4</sup>
Albumin		
≥ 35 vs < 35 g/L	0.42 [0.27-0.64]	<10-4
CRP		
$\geq 10 \text{ vs} \leq 10 \text{ mg/L}$	2.05 [1.33-3.17]	0.001
LBM		
/ kg increase	0.99 [0.97-1.02]	0.71
mREE/pREE ratio		

High versus low*	1.60 [0.95-2.70]	
mREE/LBM		0.07
> 120 vs $\le$ 120 %	2.16 [1.45-3.21]	<10 <sup>-3</sup>
> 115 vs $\leq$ 115 %	1.54 [1.03-2.31]	0.04
> 110 vs ≤ 110 %	1.52 [0.99-2.33]	0.05
/ 10% increase	1.12 [1.03-1.21]	0.007

482

\*High and low mREE/LBM were defined by values above or below the median, respectively

484 The hazard ratio (HR) for death and the 95% confidence intervals (CI) are based on Cox

485 proportional-hazards regression models. Significant p-values are indicated in bold.

BMI, body mass index; CRP, C-reactive protein; LBM, lean body mass; mREE, measured

487 resting energy expenditure; pREE, predicted resting energy expenditure, using Harris and

488 Benedict equations

489 Table 3. Multivariable analysis of overall survival

Variable	HR [95% CI]	p-value
Smoking habit		
Smoker or former smoker vs Non-smoker	1.73 [0.83-3.62]	0.14
Histo-molecular subtype		
non-squamous ALK/EGFR wild-type or undetermined vs	0.61 [0.30-1.22]	0.16
squamous		
non-squamous ALK/EGFR altered vs squamous	0.25 [0.09-0.67]	0.006
Performance status		
$\geq 2 \text{ vs } 0-1$	0.98 [0.61-1.58]	0.95
Weight loss		
$\geq$ 5 vs < 5%	1.98 [1.25-3.14]	0.004
Albumin (g/L)		
$\geq$ 35 vs < 35 g/L	0.56 [0.35-0.90]	0.02
CRP (mg/L)		
$\geq$ 10 vs < 10 mg/L	1.52 [0.95-2.43]	0.08
mREE/pREE ratio		
> vs $\leq 120 \%$	1.90 [1.22-2.93]	0.004

490

491 The hazard ratio (HR) for death and the 95% confidence intervals (CI) are based on Cox

492 proportional-hazards regression model. Significant p-values are indicated in bold.

493 CRP, C-reactive protein; mREE, measured resting energy expenditure; pREE, predicted

494 resting energy expenditure, using Harris and Benedict equations

- 496 Figure Legends
- 497 Figure 1. Patients' selection for analysis
- 498 Figure 2. Kaplan-Meier estimates of overall survival according to REE





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- 24 absence of REE measurement:
  - 1 refusal
  - 11 calorimeter failure
  - 12 not achieving steady state measurement
- 1 concomitant malignancy
- 1 missing anthropometric data

144 patients included in the final analysis

