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Artificial nutrition in patients with cancer has no impact on tumour glucose metabolism: Results of the PETANC Study

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26 **Abstract**

27 ***Background and Aims***

28 Nutrition support is recommended in cachexic patients with cancer. However, there is no clear
29 evidence about its impact on tumour growth. Glycolysis, which is usually higher in cancer than normal
30 cells, can be monitored by ^{18}F -fluorodeoxyglucose positron emission tomography/computed
31 tomography (^{18}F -FDG PET/CT) imaging that is widely used for cancer staging and therapy efficacy
32 assessment. Here, we used ^{18}F -FDG PET/CT imaging to investigate whether artificial nutrition has an
33 impact on tumour glucose metabolism in patients with cancer and cachexia.

34 ***Methods***

35 This prospective study included ten patients with histologically proven head and neck or oesophageal
36 cancer. All patients underwent ^{18}F -FDG PET/CT imaging at baseline and after (parenteral and/or
37 enteral) nutrition support on average for 7 days. Tumour glucose metabolism changes were evaluated
38 using static (SUV_{max} , SUV_{mean} and SUL_{peak}) and dynamic (glucose metabolic rate and transport
39 constant rates, k) parameters computed from the ^{18}F -FDG PET/CT data.

40 ***Results***

41 Artificial nutrition (median energy intake of 21.83 kcal/kg/day [13.16-45.90], protein intake of 0.84
42 g/kg/day [0.56-1.64]) was administered. Eight patients (80%) received enteral nutrition and two
43 patients (20%) parenteral support. Comparison of ^{18}F -FDG PET/CT parameters did not highlight any
44 significant difference in tumour glucose metabolism before and after the period of nutrition support.

45 ***Conclusions***

46 In cachexic patients with head and neck or oesophageal cancer, nutrition support administered
47 according to the current guidelines shows no impact on tumour glucose metabolism, assessed by ^{18}F -
48 FDG PET/CT.

49 **Keywords:** Nutritional support; tumour growth; ^{18}F -FDG PET/CT; cancer; cachexia; supportive care

50 INTRODUCTION

51 Cachexia is a common problem in patients with advanced cancer, especially oesophageal and
52 head and neck cancer. In these patients, cachexia is correlated with an increase in therapy-related side
53 effects and poorer response to treatment (cancer relapse, lower survival). European and national
54 evidence-based guidelines have been published about nutritional support therapy in patients with
55 cancer [1, 2]. Nutritional support, administered as recommended by these guidelines, has an impact on
56 the patient outcome. However, it is not known whether artificial nutrition could “feed” the tumour and
57 accelerate its growth. According to the European and French learned societies, the available proofs of
58 a positive effect of artificial nutrition on tumour growth are not sufficient to recommend the
59 suppression or delay of this therapy in cachectic patients with cancer. However, these
60 recommendations are based on very few and quite old studies. Specifically, in 1991, Rossi-Fanelli *et*
61 *al.* determined the thymidine labelling index in tumour samples collected before and after 14 days of
62 glucose-based or lipid-based parenteral nutrition formula, or isocaloric oral diet (n=27 patients). They
63 did not find a positive effect of glucose (or a negative effect of lipids) on cancer cell proliferation [3].
64 Jin *et al.* assessed tumour cell growth (percentage of cells in S phase and DNA index) and sensitivity
65 to chemotherapy in tumour samples from 91 patients with gastrointestinal cancer and malnutrition
66 after 7 days of various preoperative interventions (parenteral nutrition alone, parenteral nutrition plus
67 chemotherapy, chemotherapy alone, and no treatment) [4]. They found that the nutrition support and
68 chemotherapy combination improved the patients’ short-term nutritional status without increasing
69 tumour cell proliferation and prevented some adverse events observed in the group with chemotherapy
70 alone. They also suggested, but without evidence, that parenteral nutrition improves chemotherapy
71 effectiveness.

72 Recent imaging technologies allows investigating this crucial question in a non-invasive
73 manner, by performing serial ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography/computed
74 tomography (^{18}F -FDG PET/CT). ^{18}F -FDG PET/CT imaging data are used to compute static and
75 dynamic FDG parameters. Several studies have shown than dynamic FDG uptake measurements are
76 more accurate than the standardized uptake value (SUV) to assess differences between benign and

77 tumour tissues and to highlight changes in tumour metabolism after treatment [5, 6]. Moreover, ¹⁸F-
78 FDG PET-based quantification of glucose metabolism is reproducible with a coefficient of variation
79 of approximately 10% (test-retest studies for repeated scans of the same patients) [7]. Since glucose
80 transport is the rate-limiting step of glycolysis in tumours, if artificial nutrition would have an effect
81 on tumor activity, it would be by modifying tumor expression of glucose transporters (GLUTs) and
82 hexokinases. Tumour mass changes are of a quite long duration and could not be detected
83 quantitatively using the available methods (CT scan for example) in a short time period, contrary to
84 tumour glucose metabolism which may be modified very quickly after treatment induction.

85 Therefore, we designed a prospective clinical study to determine whether artificial nutrition
86 has an impact on tumour glucose metabolism in cachectic patients with cancer by comparing ¹⁸F-FDG
87 PET/CT static and dynamic imaging parameters before and after a period of nutrition support.

88

89 **METHODS**

90 *Study design and patients*

91 Inclusion criteria for this prospective study were: patients with histologically-proven head and
92 neck or oesophageal cancer and cachexia (weight loss >5%) and eligible for artificial (enteral or
93 parenteral) nutrition supplementation; availability of one ¹⁸F-FDG PET/CT exam performed at our
94 centre before inclusion (standard procedure, outside this study); ≥18 years of age, and WHO (ECOG)
95 performance status ≤2. The main exclusion criteria were: administration of a cancer treatment
96 (chemotherapy, targeted therapy or surgery) in the past 2 months, or radiotherapy in the past 4 months;
97 capillary blood glucose >12mmol/L at the first ¹⁸F-FDG PET/CT evaluation; current treatment for
98 diabetes (insulin or oral treatment); and contra-indication to ¹⁸F-FDG PET/CT, such as pregnancy or
99 breastfeeding, or psychological disorders. All patients signed a written informed consent prior to
100 inclusion. The study was conducted in accordance with the Good Clinical Practice requirements
101 (Helsinki Declaration), and was approved by local and national review boards. It was also registered
102 on clinical.trials.gov.

103 ***Nutritional intervention***

104 Nutrition support therapy was administered in accordance with the French Clinical Nutrition
105 and Metabolism Society guidelines [8]. Enteral and parenteral nutrition was adapted to the patient's
106 current oral intake that was deduced from the 30-35cal/kg/day objective. Enteral nutrition was
107 administered with a nasogastric probe. If enteral nutrition was not possible, parenteral nutrition was
108 administered through a central venous catheter.

109 ***Assessment***

110 The intra-tumour metabolic glucose activity was evaluated using ^{18}F -FDG PET/CT imaging at
111 baseline (standard procedure) and after a minimum of 5 days of artificial nutrition. During this time,
112 patients did not receive any cancer treatment. However, treatment initiation (*i.e.* chemotherapy) could
113 not be delayed by the study. The patient food intake was measured using a visual analogue scale (food
114 intake VAS) at baseline and at the second ^{18}F -FDG PET/CT exam.

115 ***Glucose metabolism***

116 Glucose metabolism differs in normal and cancer cells. Specifically, normal cells produce
117 energy from glucose mainly through the mitochondrial oxidative phosphorylation pathway.
118 Conversely, cancer cells preferentially produce energy through conversion of glucose into lactate,
119 even in aerobic conditions [9] (*i.e.*, aerobic glycolysis, also known as the "Warburg effect") [10]. To
120 compensate for the poor energy production yield through the lactate pathway, glycolysis is increased
121 in tumour cells through upregulation of GLUTs and glucose hexokinase. These transporters are not
122 insulin-sensitive (unlike muscles) and therefore are not altered by glycaemia or a fasting period [11].

123 ^{18}F -FDG is a glucose analogue used as a PET radiotracer. Its uptake by tumour cells is directly
124 related to their glucose consumption. Like glucose, it is transported into the cells, phosphorylated to
125 ^{18}F -FDG-6-phosphate (^{18}F -FDG-6-P), and trapped within the cells. Therefore, ^{18}F -FDG-PET imaging
126 allows the direct estimation of the cancer cell glucose concentration and glycolytic activity. ^{18}F -FDG-

127 PET is routinely used in oncology for the initial tumour detection, characterization and staging and for
128 monitoring the therapeutic response in several cancer types [12].

129 ***Imaging***

130 Both ^{18}F -FDG-PET and CT exams were performed using the same apparatus (Discovery
131 PET/CT 690 scan, GE Healthcare, Milwaukee, Wisconsin, USA) [13], in the same conditions, and
132 approximately (± 2 hours) at the same time of the day. Patients were asked to strictly fast during the
133 6 hours before ^{18}F -FDG injection and artificial nutrition was also stopped. After intravenous injection
134 of 3.5MBq/kg ^{18}F -FDG, dynamic PET images centred on the tumour were acquired for 40 minutes,
135 followed by static whole-body images at 60 minutes after ^{18}F -FDG injection. Images were acquired
136 using the *List Mode*, corrected (for normalization, dead time, activity decay, random coincidence,
137 attenuation and scatter) and then reconstructed in a 256 \times 256 image matrix. The acquired field of view
138 size was 70 cm. Image analysis was performed using the PMOD software. For all patients, the region
139 of interest (ROI) was drawn around the primary tumour by the same experimented nuclear medicine
140 physician to calculate the imaging parameters. SUV is the most commonly used parameter for glucose
141 metabolism quantification, and represents the FDG concentration in a volume of interest (*i.e.*, the
142 tumour or part of the tumour) normalized to the patient's weight and total injected activity:

$$143 \quad \text{SUV} = \frac{\text{activity concentration in tissue}}{(\text{injected activity} / \text{body weight})}$$

144 On static 3D PET images (acquired 60 minutes after ^{18}F -FDG injection), the following parameters
145 were extracted from the ROI within the tumour:

- 146 - **SUV_{max}**: the voxel with the highest radioactivity within the ROI; is the most widely used
147 parameters with good inter-observer reproducibility;
- 148 - **SUV_{mean}**: reflects the metabolic activity within the whole tumour; however, it is sensitive to
149 the tumour volume delineation;
- 150 - **SUL_{peak}** (SUL = SUV normalized to the lean body mass): represents the average activity in a
151 small fixed-size ROI that includes the maximum voxel; this is considered to be the best
152 parameter for the assessment of solid cancer response to treatment [12].

153 SUV_{mean} and SUV_{max} were also assessed in peritumoral healthy tissue.

154 To reflect variations over time, the dynamic PET (dPET) images acquired just after ^{18}F -FDG injection

155 were used to calculate the following parameters. The glucose metabolic rate (**MRGlu**, expressed in

156 $\mu\text{mol}\cdot\text{min}^{-1}\cdot 100\text{g}^{-1}$ of tumour tissue) was calculated using the “MRGlu Patlack” mode of the PMOD

157 software, as previously described [14]. The vascular input function was set on an artery found in the

158 view field, and the lump constant (LC) was set to 1. Another PMOD mode (“the two-compartment”

159 mode) allowed calculating **the transport constant rates (k)** of the two-compartment model

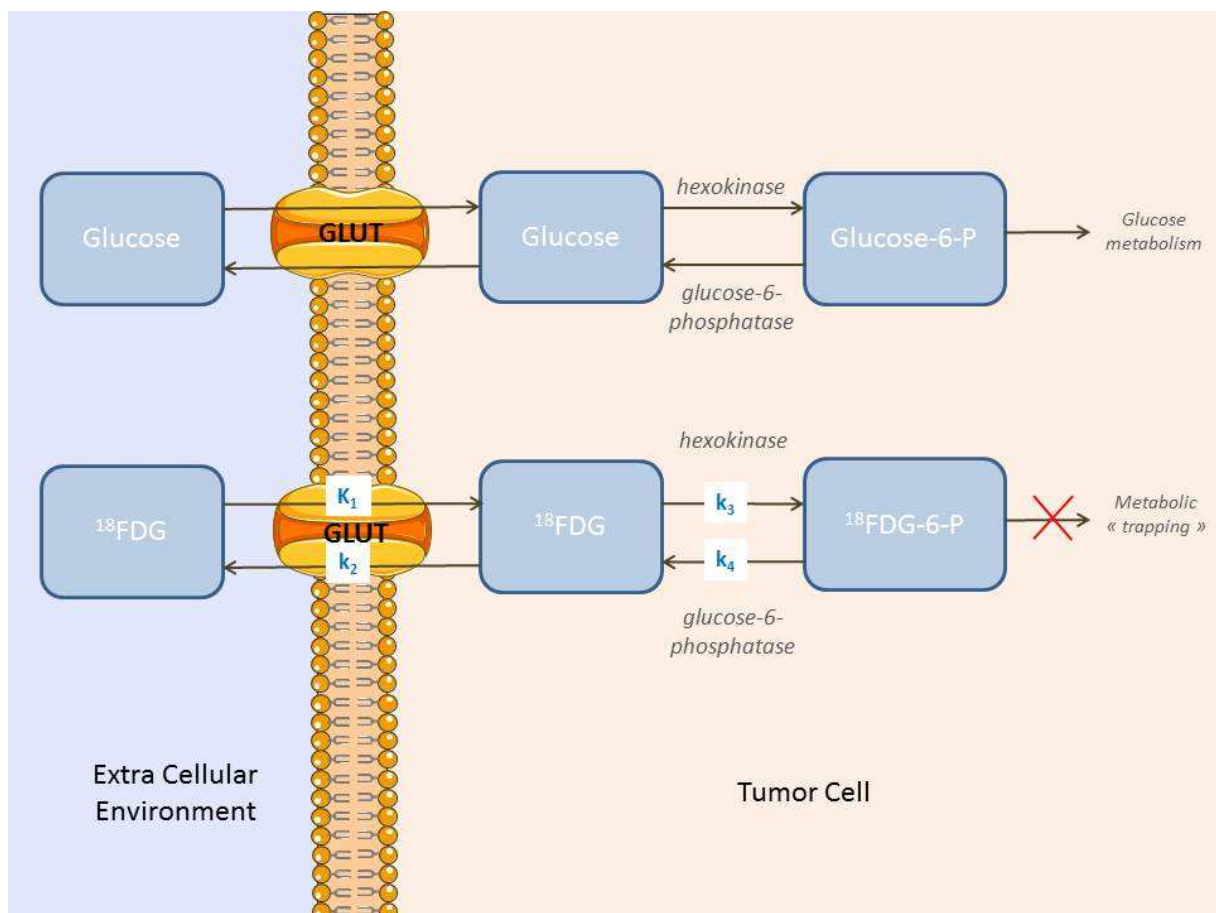
160 (Figure 1): k_1 , k_2 , k_3 , k_4 (expressed in h^{-1}). These variables are associated with molecular biological

161 processes, such as GLUT (k_1 - k_2) and hexokinase activities (k_3 - k_4). The PET/CT device quantitative

162 accuracy was assessed following the European guidelines for ^{18}F -FDG PET/CT tumour imaging [15],

163 and the device was accredited for tumour imaging by the European Association of Nuclear Medicine

164 Research Ltd (EARL).



165

166 **Figure 1:** Two-compartment model of FDG kinetics in tumour cells

167 ***Endpoints***

168 The primary endpoint was the difference between pre- and post-artificial nutrition intra-
169 tumour SUV_{max} values. Secondary endpoints were the pre- and post-artificial nutrition variations of the
170 static parameters SUV_{mean} and SUL_{peak}, and of the dynamic parameters MRGlu, k₁, k₂, k₃, and k₄.

171 ***Statistical analysis***

172 Continuous variables were described using medians and ranges, and categorical variables
173 with frequencies and percentages. The Wilcoxon Rank-Sum test was used to compare the distribution
174 of continuous variables between the first and second ¹⁸F-FDG PET/CT exam. All tests were two-sided
175 and a *p*-value <0.05 was considered as statistically significant. Statistical analyses were performed
176 using STATA 13.0 (StataCorp, College Station, TX, USA).

177

178 **RESULTS**

179 ***Patients***

180 Eleven patients were included in our prospective monocentric study (Table 1). Among them, 9
181 (81.8%) were men. The median age was 61 years [range: 52-74], and the WHO (ECOG) performance
182 status score ranged between 0 (n=4, 36.4%) and 1 (n=7, 63.6%). Three patients (27.3%) had head and
183 neck, and eight (72.7%) oesophageal cancers. None of the patients received any cancer treatment prior
184 to inclusion in this study, but all patients were intended to be curatively treated. The median duration
185 between cancer diagnosis and inclusion in the trial was 19.5 days [7-46].

186 The patients' median weight loss was 4.05% (0.6-6.1) at 1 month and 10.8% (7.3-34) at 6
187 months post-diagnosis. One patient was excluded from the study after the first ¹⁸F-FDG PET/CT
188 because he required oesophageal dilatation and stent that could induce inflammation and, thus, bias the
189 analysis results.

Baseline characteristics	n=11
Sex, n (%)	
Men	9 (81.8)
Women	2 (18.2)
Age (years), median [range]	61 [52-74]
WHO performance status	
0	4 (36.4)
1	7 (63.6)
Weight loss at 1 month (%), median [range]	4.05 [0.6-6.1]
Weight loss at 6 months (%), median [range]	10.8 [7.3-34]
Body mass index (kg/m ²)	21 [16-27.8]
Previous treatment	None
Primary tumour localization, n (%)	
Head and neck	3 (27.3)
Oesophagus	8 (72.7)
Nutritional status	
Baseline Food intake VAS (/10), median [range]	3 [0-6]
Artificial nutrition	
Yes	10 (100)
Missing	1
Artificial energy intake (kcal/kg/day), median [range]	21.83 [13.16-45.90]
Including proteins (g/kg/day), median [range]	0.84 [0.56-1.64]
Artificial nutrition type	
Enteral	8 (80)
Parenteral	2 (20)
Missing	1
Duration of artificial nutrition (days), median [range]	7 [5-9]
Oral nutrition	
Yes	10 (100)
Missing	1
Oral energy intake (kcal/kg/day), median [range]	19.44 [5.37-25.95]
Including proteins (g/kg/day), median [range]	0.63 [0.11-3.64]
Food intake VAS (/10) at PET2, median [range]	5 [1-10]

WHO: World Health Organization; VAS: Visual Analogue Scale; kcal: kilocalories

191 ***Nutritional status***

192 The baseline median food intake VAS score was 3 [0-6]. Artificial nutrition was administered
 193 to 10 patients (median energy intake: 21.83 kcal/kg/day [13.16-45.90], with a median protein intake of
 194 0.84 g/kg/day [0.56-1.64]) (Table 1). Artificial nutrition (enteral for eight patients, 80%, and
 195 parenteral for two patients, 20%) was used to complement oral nutrition (median oral energy intake:
 196 19.44 kCal/kg/day [5.37-25.95]). On average, patients received artificial nutrition for 7 days ([5-9])
 197 before the second ¹⁸F-FDG PET/CT exam. The food uptake VAS score was 5 [1-10] at second
 198 PET/CT, higher than that at baseline evaluation, although it was not significant ($p=0.13$).

199 ***Metabolic ¹⁸F-FDG PET/CT data***

200 The values of all the tumour glucose metabolism parameters (static and dynamic) were not
 201 significantly different between first and second ¹⁸F-FDG PET/CT (Table 2 and Figure 2). Specifically,
 202 the pre- and post-artificial nutrition mean SUV_{max} scores (primary outcome) were comparable (11.0
 203 [7.8-22.2] and 10.2 [7.3-20.6]). There was also no significant difference in SUV_{mean} and SUV_{max} in
 204 peritumoral tissue between the first and second ¹⁸F-FDG PET/CT (Table 2).

205

	PET/CT 1	PET/CT 2	<i>p</i> -value
Body weight just before ¹⁸ F-FDG injection (kg), median [range]	65.9 [30-83]	66.0 [31-83]	1
Blood glucose level (g.L ⁻¹) just before ¹⁸ F-FDG injection, median [range]	1 [0.7-1.1]	1.1 [0.9-1.3]	1
Median time between nutrition delivery and PET/CT (hours)		8.37 [6.50-15.12]	
Tumoral FDG uptake			
SUV _{max} (g/mL), median [range]	11.0 [7.8-22.2]	10.2 [7.3-20.6]	0.7
SUV _{mean} (g/mL), median [range]	6.4 [4.3-12.9]	6.1 [3.9-12.2]	1
SUL _{peak} (g/mL), median [range]	8.8 [6.8-18.8]	8.6 [5.5-17.4]	0.76
MRGlu (μmol.min ⁻¹ .100g ⁻¹), median [range]	32.2 [10.3-77.1]	35 [11.6-88.5]	0.63
k ₁ (h ⁻¹), median [range]	0.4 [0.19-0.67]	0.4 [0.1-0.95]	0.82

k_2 (h^{-1}), median [range]	0.6 [0.42-0.78]	0.5 [0.18-0.78]	0.5
k_3 (h^{-1}), median [range]	0.1 [0.03-0.21]	0.1 [0.03-0.17]	0.4
k_4 (h^{-1}), median [range]	0 [0-0]	0 [0-0.06]	0.69

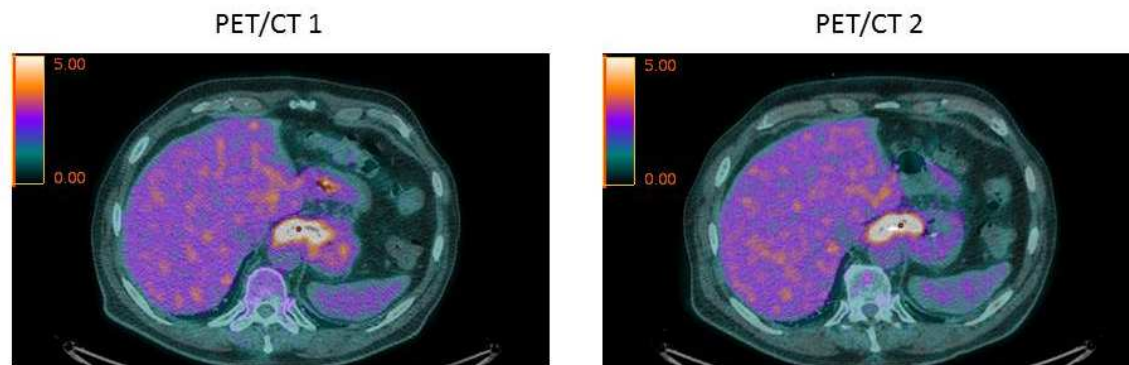
Peritumoral FDG uptake

SUV _{mean} (g/mL), median [range]	1.5 [0.8-2.7]
SUV _{max} (g/mL), median [range]	2 [1.3-3.8]

FDG: ^{18}F -Fluorodeoxyglucose, SUV: Standardized Uptake Value; SUL: Standardized Uptake Value corrected for Lean Body Mass, MRGlu: Metabolic Rate of Glucose

206

207 **Table 2:** Glucose metabolism parameters at the first and second ^{18}F -FDG PET/CT



208

209 **Figure 2:** Representative ^{18}F -FDG PET/CT images centred on the oesophageal cancer at baseline
 210 (PET/CT 1) and after 9 days of artificial nutrition (PET/CT 2) showing the absence of visual
 211 differences in ^{18}F -FDG uptake (images acquired 60 minutes after ^{18}F -FDG injection)

212

213 DISCUSSION

214 In this study we show that artificial nutrition in patients with head and neck and oesophageal
 215 cancer has no impact on tumour glucose metabolism, assessed by ^{18}F -FDG PET/CT (both static
 216 dynamic PET parameters). This is, to our knowledge, the first clinical study that studied the impact of
 217 standard nutritional support (for a mean of 7 days) using non-invasive visualization of tumour glucose
 218 metabolism by ^{18}F -FDG PET.

219 In 2004, Bozetti *et al.* performed a study with ^{18}F -FDG PET/CT in 12 patients with liver
220 metastases from colorectal cancer [16]. They investigated the effect of the administration of glucose-
221 or lipid-based total parenteral nutrition (4 mg/kg/min glucose, or 2 mg/kg/min lipids and 0.7
222 mg/kg/min amino acids) for three hours before ^{18}F -FDG PET/CT, compared with control (fasting
223 without glucose/lipid infusion). They did not find any significant change in the SUV score of liver
224 metastases. However, this study assessed the immediate effect of a short load of glucose or lipid [16],
225 whereas our present work evaluated the impact of a longer nutritional support (at least 5 days). The
226 reviews by Bozetti *et al.* and by Bossola *et al.* [17, 18] identified only few studies (controlled or not)
227 on the impact of nutritional interventions on tumour growth. In all these studies, the number of
228 patients was small (n=10 to 20), and the definition of malnutrition and of cachexia heterogeneous.
229 Moreover, in most of them, tumour growth was assessed based on cancer cell cycle kinetic parameters
230 (DNA index, DNA distribution by flow cytometry, labelling index with tritiated thymidine or
231 bromodeoxyuridine). Among the five controlled and randomized studies (nutritional support for 6 to
232 18 days) [4, 19-22], only two reported an increase in tumour cell proliferation following artificial
233 nutrition [4, 19]. These reviews concluded that there is no evidence for an effect of nutritional support
234 on tumour growth. In agreement, the European guidelines state that "theoretical arguments that
235 nutrients "feed the tumour" are not supported by evidence related to clinical outcome and should not
236 be used to refuse, diminish or stop feeding". Since the studies by Rossi-Fanelli [3] and Jin [4] quoted
237 in the European guidelines, imaging techniques and nutritional support guidelines have changed.
238 Nevertheless, we found surprising that studies on this topic are quite rare, especially now when
239 dieticians and nutritionists are involved in the management of patients with cancer. On the other hand,
240 recent publications have evaluated the link between fasting and tumour cell sensitivity to
241 chemotherapy [23]. A recent comprehensive review of all literature data (many animal studies and few
242 epidemiological and clinical studies) ([https://www6.inra.fr/nacre/Le-reseau-NACRe/Publications/
243 Rapport-NACRe-jeune-regimes-restrictifs-cancer-2017](https://www6.inra.fr/nacre/Le-reseau-NACRe/Publications/Rapport-NACRe-jeune-regimes-restrictifs-cancer-2017)) concluded that there is no evidence that
244 fasting and restrictive diets (i.e., intermittent fasting, caloric restriction and ketogenic diets) have any
245 effect (beneficial or deleterious) on cancer prevention and treatment. FDG tumour uptake may be
246 influenced by lactate levels in tumours ([24]), and Schroeder *et al.* showed that a ketogenic diet (which

247 differs in terms of carbohydrate intake from the artificial nutrition delivered in our study) decreased
248 tumour lactate levels in patients with head and neck cancer [25]. A difference in our outcome
249 parameters could have been linked to the tumour lactate levels. Plasma glucose levels were identical
250 for PET1 and PET2. However, as tumours are not insulin-dependent tissues, a difference in plasma
251 glucose level at PET1 and PET2 would probably have no impact on our results.

252 The small number of patients, although in the range of the previously published studies, is a
253 limitation of our study. The lack of significant differences between PET1 and PET2 may be caused by
254 the small size of the studied cohort. We had planned to include 20 patients, but accrual was difficult
255 mainly due to the protocol requirements: (i) organizing in a very short time both nutritional support
256 and a second ^{18}F -FDG PET/CT to ensure no delay in treatment initiation; and (ii) most potentially
257 eligible patients had already undergone ^{18}F -FDG PET/CT imaging before arrival in our centre.
258 Performing three ^{18}F -FDG PET/CT scans, which would have allowed patient inclusion, was not
259 acceptable. Other limitations are the relatively short period of nutritional support (median = 7 days)
260 before the second ^{18}F -FDG PET/CT (due to the organizational constraints described above and
261 because it was not acceptable to delay patients cancer therapy initiation), and the inclusion only of
262 patients with head and neck or oesophageal cancer only because ^{18}F -FDG PET/CT is performed at
263 diagnosis as standard practice.

264 In conclusion, our clinical study did not find any effect of artificial nutrition on tumour
265 metabolism assessed with ^{18}F -FDG PET/CT in cachectic patients with head and neck or oesophageal
266 cancer. Patients all received artificial nutrition according to the current guidelines in order to ensure
267 the best support to reduce side-effects, and to satisfy the nutritional requirements of patients with
268 cancer.

269

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275

276 **STATEMENT OF AUTHORSHIP**

277 All persons who meet authorship criteria are listed as authors, and all authors certify that they have
278 participated sufficiently in the work to take public responsibility for the content, including
279 participation in the concept, design, analysis, writing, or revision of the manuscript.

280

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283 the design and conduct of the study; collection, management, analysis, and interpretation of the data;
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286

287 **COMPETING INTERESTS STATEMENT**

288 The authors have no conflict of interest to disclose regarding the present study.

289

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349 **FIGURE AND TABLE LEGENDS**

350 **Table 1:** Patients' characteristics at baseline and nutritional status

351 **Table 2:** Glucose metabolism parameters at the first and second ^{18}F -FDG PET/CT

352 **Figure 1:** Two-compartment model of FDG kinetics in tumour cells

353 **Figure 2:** Representative ^{18}F -FDG PET/CT images centred on the oesophageal cancer at baseline
354 (PET/CT 1) and after 9 days of artificial nutrition (PET/CT 2) showing the absence of visual
355 differences in ^{18}F -FDG uptake (images acquired 60 minutes after ^{18}F -FDG injection)