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Abstract

Background and Aims

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

Methods

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

Results

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

Conclusions

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

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

INTRODUCTION

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

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

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

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

METHODS

Study design and patients

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

Nutritional intervention

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

Assessment

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

Glucose metabolism

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

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

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

Imaging

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

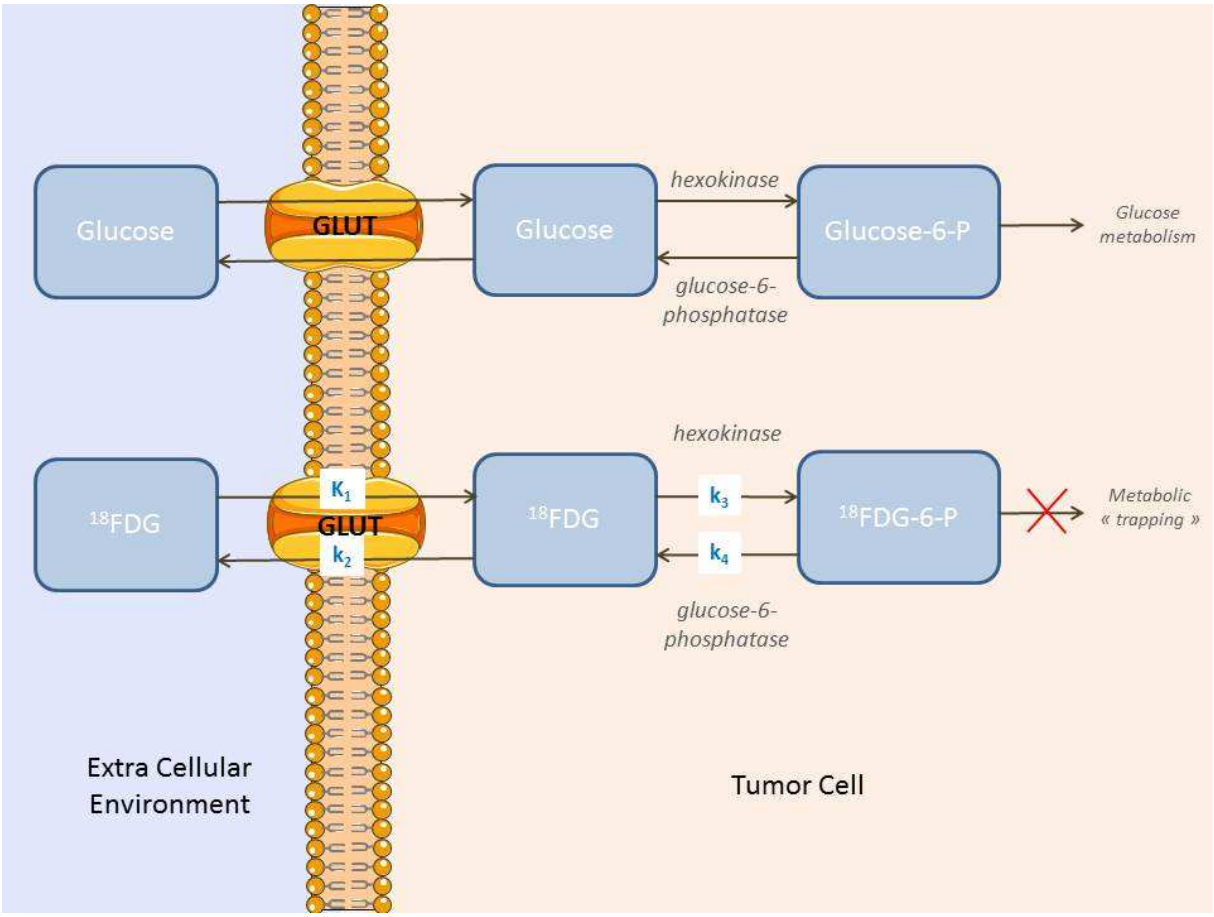
$$\mathrm{SUV} = \frac{\text{activity concentration in tissue}}{(\text{injected activity}/\ \text{body weight})}$$

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

- **SUV_{max}**: the voxel with the highest radioactivity within the ROI; is the most widely used parameters with good inter-observer reproducibility;
- **$SUV_{mean:}$** reflects the metabolic activity within the whole tumour; however, it is sensitive to the tumour volume delineation;
- **SUL_{peak}** (SUL = SUV normalized to the lean body mass): represents the average activity in a small fixed-size ROI that includes the maximum voxel; this is considered to be the best 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 µmol.min^{-1}.100g^{-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): $\mathbf{k_1}$, $\mathbf{k_2}$, $\mathbf{k_3}$, $\mathbf{k_4}$ (expressed in h^{-1}). These variables are associated with molecular biological
161 processes, such as GLUT (k1-k2) and hexokinase activities (k3-k4). 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).



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

Endpoints

The primary endpoint was the difference between pre- and post-artificial nutrition intra-tumour SUV_{max} values. Secondary endpoints were the pre- and post-artificial nutrition variations of the static parameters SUV_{mean} and SUL_{peak}, and of the dynamic parameters MRGlu, k_1, k_2, k_3, and k_4.

Statistical analysis

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

RESULTS

Patients

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

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

Table 1: Patients' characteristics at baseline and nutritional status

Nutritional status

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

Metabolic ^{18}F-FDG PET/CT data

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

	PET/CT 1	PET/CT 2	p-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

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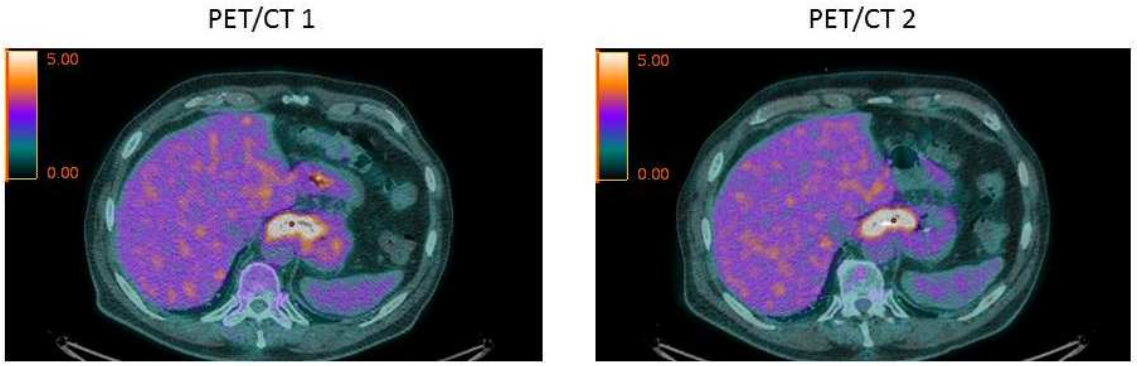
207 **Table 2:** Glucose metabolism parameters at the first and second ^{18}F-FDG PET/CT



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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.

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

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

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

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

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STATEMENT OF AUTHORSHIP

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

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COMPETING INTERESTS STATEMENT

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

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FIGURE AND TABLE LEGENDS

Table 1: Patients' characteristics at baseline and nutritional status

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

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

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