Role of 18F-PET-CT to Predict Pathological Response After Neoadjuvant Treatment of Rectal Cancer

Riccardo Caruso (ricaruso2@gmail.com)
Hospital Universitario HM Sanchinarro

Emilio Vicente
Hospital Universitario HM Sanchinarro

Yolanda Quijano
Hospital Universitario HM Sanchinarro

Hipolito Duran
Hospital Universitario HM Sanchinarro

Isabel Fabra
Hospital Universitario HM Sanchinarro

Eduardo Diaz
Hospital Universitario HM Sanchinarro

Luis Malave
Hospital Universitario HM Sanchinarro

Ruben Agresott
Hospital Universitario HM Sanchinarro

Lina Garcia Cañamaque
Hospital Universitario HM Sanchinarro

Benedetto Ielpo
Hospital Del Mar

Valentina Ferri
Hospital Universitario HM Sanchinarro

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Abstract

Objectives:

Neoadjuvant radiochemotherapy (nCRT) is universally considered to be a valid treatment to achieve downstaging, improve local disease control and obtain better resectability in locally advanced rectal cancer (LARC). The aim of this study is to correlate the change in tumor 18^{F} -FDG PET-CT standardized uptake value (SUV) before and after nCRT, in order to obtain an early prediction of pathologic response (pR) achieved in patients with LARC.

Data description:

We performed a retrospective analysis of patients with LARC diagnosis who underwent curative resection. All patients received nCRT and surgical treatment was carried after $8/12^{th}$. All patients underwent a baseline 18^{F} -FDG PET-CT scan within the week prior to the initiation of the treatment (PET-CT SUV1) and a second scan (PET-C T SUV2) within six weeks of the completion of nCRT. Furthermore, we evaluated the prognostic value of 18^{F} -FDG PET-CT in terms of disease free survival (DFS) and overall survival (OS) in patients with LARC.

A total of 133 patients with LARC were included in the study. Patients were divided in two groups according to the TRG (tumor regression grade): 107 (80%) as Responders group (TRG0-TRG1) and 26 (25%) as the No-Responders group (TRG2-TRG3). We obtained a significant difference in Δ%SUV between the two different groups responders vs no responders ($p<0.012$).

The results of this analysis have shown that 18F-FDG PET-CT may be an indicator in order to evaluate the pR to nCRT in patients with LARC. The decrease in 18F-FDG PET-CT uptake in the primary tumor may offer primary information in order to early identify those patients more likely to obtain a pCR to nCRT and predict those unlikely to regress significantly.

Introduction

Nowadays neoadjuvant radiochemotherapy (nCRT) is universally considered to be a valid treatment to achieve downstaging, to improve local disease control and to obtain better resectability in locally advanced rectal cancer (LARC) [1]. Currently, about 15-30% of patients undergoing neoadjuvant treatment achieves a pathologic complete response (pCR) with improved oncological outcomes [2]. A major challenge for the surgeon is to determine the course of treatment for those patients with pCR after nCRT [3-5]. In fact, the difficult choice between surgery (radical rectal resection or transanal local excision of residual scar) and the wait-and-see strategy does not provide a definitive answer. The pCR is defined through endoscopy with biopsy and through the radiological studies. However, a more reable histopathologic response is obtained only after the resected specimen analysis [6,7]. For this reason, it is important to develop methods that help identify an early prediction of histopathological response in patients with LARC after nCRT. The early determination of pathological response to nCRT is important not

only for prognostic value but also to change or adapt the standard nCRT strategy for those patients with a suboptimal pathologic response [8]. Currently, 18^F -FDG PET-CT is one of the most powerful tools in cancer diagnosis and staging. It combines a positron emission tomography scanner (PET) and an x-ray computed tomography (CT) scanner, so that images acquired from both devices can be taken sequentially. The spatial distribution of metabolic or biochemical activity in the body can be more precisely aligned or correlated with anatomic imaging obtained by CT scanning. It is well known that nCRT induces changes in tumor metabolism that influence the 18^F -FDG PET-CT tumor uptake [9].

The aim of this study is to correlate the change in tumor 18^F -FDG PET-CT standardized uptake value (SUV) before and after nRCT in patients with LARC, in order to differentiate between those who responded to treatment (the Responders) and those who did not respond (the No-Responders).

Materials And Methods

Patient population

The study was carried out at the General Surgery Department of Sanchinarro University Hospital, Madrid recruiting prospectively patients from October 2011 and February 2020 with LARC. The LARC patients are defined if with radiological staging T3-4 e/o N+ rectal tumor with a distance from the anal verge ≤ 10 cm. Patients age younger than 18 years, with concomitant metastases, perforated tumors, with peritoneal carcinomatosis or with comorbidities precluding surgery and neoadjuvant therapy, with rectal stent have been excluded from the analysis. All included patients received nCRT and surgical treatment was carried out within the 8/12th week after completing neoadjuvant treatment. The preoperative study included a colonoscopy with biopsy to confirm rectal adenocarcinoma. Trans-anal endorectal ultrasound, pelvic MRI (Magnetic resonance imaging), total body CT scan, and PET-CT scan were used as diagnostic and staging procedures. For the tumoral stage, the TNM staging system was used (American Joint Committee on Cancer) [10].

The histopathological examination was performed by expert colorectal pathologists. Pathologic tumor staging of the specimen after nCRT (ypTNM) and tumor regression grade (TRG) scores of the surgical specimens were established with the seventh guidelines of the American Joint Committee on Cancer [11]. TRG0 indicates a pathological complete response, TRG1 (moderate response) consists of single cells or small groups of cancer cells, TRG2 (minimal response) indicates residual cancer outgrown by fibrosis, and TRG3 (poor response) shows extensive residual cancer. Circumferential resection margin (CRM) is considered negative if the distance between the tumor and CRM is more than 1 mm (6). Patients were divided in two groups according to the TRG: Responders group (TRG0-TRG1) and the No-Responders group (TRG2-TRG3). Furthermore, we evaluated the prognostic value of 18^F -FDG PET-CT in terms of disease free survival (DFS) and overall survival (OS) in patients with LARC. Following nCRT, patients were reassessed to evaluate the tumor's response 6 weeks after finishing the treatment. The reevaluation study included a full physical examination, MRI, CTscan, and PET-CT scan. All resected specimens were examined by an experienced team of gastrointestinal pathologists.

Preoperative Radiochemotherapy (nCRT)

All patients were treated with preoperative intensity-modulated radiotherapy (IMRT) and an integrated-boost chemoradiation scheme. The planning target volume (PTV) included the presacral node, the tumor, complete mesorectal fascia, and common and internal iliac lymph nodes. Radiation therapy was completed in four to five weeks, with a total of 23 fractions. The dose for the first PTV was 46 Gy in 23 fractions, and the concomitant boost (PTV2) was 57.5 Gy in 23 fractions (BED=71.8 Gy[α/β=10] & Eq2 Gy/f=70 Gy). All patients received concurrent standard capecitabien-based chemotherapy (825 mg/m^2, in bid) and blood count was performed every 14 days. All patients underwent a surgical procedure including a low anterior resection or abdominoperineal excision six to eight weeks after the completion of treatment. All patients were operated on by the same team of surgeons and with mechanical bowel preparation.

18^F-FDG PET-CT analysis

All patients underwent a baseline 18^F -FDG PET-CT scan within the week prior to the initiation of the nCRT (PET-CT SUV1) and a second scan (PET-C T SUV2) within six weeks of the completion of nCRT. The 18^F-FDG PET-CT was performed with the Advance whole-body PET scanner in 3D mode, with axial spatial resolution of 4.7 mm. CT-based attenuation and decay correction were done. Patients were fasting six hours before underwent PET-CT, although water intake was encouraged. Before entering the scanner, patients were invited to drink water (1lt) and void their bladder. Fasting serum glucose levels were checked 15 minutes before FDG injection according to protocol. All patients received an intravenous injection of 18^F-FDG. The exact time of injection of 10 to 15 mCi of 18^F-FDG was recorded and imaging commenced no earlier than 45 minutes after the injection. Total body, caudo-cranial 18^F -FDG PET-CT images were acquired 70 minutes after the injection of18^F –FDG. PET-CT images were reconstructed from the acquired data, using the ordered subset expectation maximum iterative reconstruction algorithm. Maximum uptake value of the primary tumor was registered in all studies (baseline and after n weeks). The metabolic parameters were calculated as: SUVmax and SUVmean, and the response indices (Δ%, the percentage difference between two different PET/CT scans for SUVmax and SUVmean). SUVmax and SUVmean were calculated using the maximum and mean activity values with the highest radioactivity concentration in accordance with the injected dose and patient's body weight. Changes in SUVmax values were analyzed as the percentage difference from 18^F -FDG PET-CT 1 (before nCRT) and 18^F -FDG PET-CT 2 (after nCRT) (Δ% SUV). It was evaluated in relation to the pathologic response, defined as the TRG [6].

Statistical Analysis

Sensitivity, specificity, accuracy, positive predictive value (p-PV), and negative predictive value (n-PV) of post n-CRT 18^F -FDG PET-CT were assessed. To compare the correlation between the quantitative (numerical) variables, when these followed a normal distribution, a variance analysis and a t-Student were used. Categorical variables were assessed using a Chi-square test. The Mann-Whitney U-Test and

the Kruskal-Wallis test were performed for numerical variables. A receiver-operating characteristic (ROC) curve and logistic regression techniques were used to obtain the predictive model and the inflection point. DFS and OS were calculated with the Kaplan-Meier method and log-rank test. A multivariate survival analysis for disease-free survival or overall survival was performed using the Cox proportional-hazard regression model. All variables related to the risk of disease-free survival, or overall survival with a P value of less than 0.2 in univariate analysis, were included in the multivariate analysis. For the statistical analysis, SPSS software (version 10, IBM SPSS, Chicago, IL, USA) was used and all tests were considered statistically significant if value of $p \leq 0.05$.

Ethics

The study was approved by the institutional ethical committee of Sanchinarro University Hospital and all patients included were informed about the treatment and provided written informed consent. The study was conducted in agreement with the Declaration of Helsinki for studies in humans.

Results

A total of 137 patients with LARC were included and 4 were lost during the follow-up as they underwent surgery in another center and data couldn't been gathered. Therefore, 133 cases have been analyzed (STROBE flowchart figure 1). The demographic data of the patients are summarized in Table 1. A total of 29 (22%) patients underwent abdominal perineal resection (APR), 90 (68 %) underwent a low anterior resection (LAR) with protective stoma and 14 (10 %) underwent a LAR without protective stoma as shown in table 2. Patients were divided in two groups according to the TRG: 107 (80%) as Responders group (TRG0-TRG1) and 26 (25%) as the No-Responders group (TRG2-TRG3) (STROBE flowchart figure). Evaluation of the tumor response to nCRT according to TRG score is shown in table 3. We found a primary tumor down-staging in T classification after nCRT in 85 patients (65%). Therefore, nodal down-staging after nCRT was achieved in 55 patients (42%). In our series the pathological complete response (cpR) rate was about 19%. A logistic regression analysis was performed in order to obtain a prediction model of tumor pathological response (pR). Clinical prognostic factors (age, sex, TNM variables, Tumoral Markers, and FDG-PET values) were separately tested. From our statistical analysis, we obtained a significant difference in Δ%SUV between the two different groups responders vs no responders ($p<0.012$) as shown in Figure 2. ROC curve preliminary cut-off value of 70% of the $\Delta\%\ \mathrm{SUV}\ (\frac{SUVpre-SUVpost}{\mathrm{SUVpre}}100\%)$ was individuate as depicted in Figure 3. This showed that Δ%SUV media was a stronger discriminator between the two groups with a high accuracy of 81% (34/42), with a sensitivity of 84.4%, a specificity of 80%, a positive predictive value of 81.4% (p-PV), and a negative predictive value of 84.2% (n-PV).

The median follow-up period was 60,54 months (range, 9 to 103 months). Patients with overall recurrence were 25 (18,8%) (3 locoregional and 22 metastatic): 17 (12,8%) patients with delta Δ% SUV < 70% and 8 (6%) patients with Δ% SUV >70% with a significant correlation between recurrence and Δ SUV (p=0.037)

The median 5-years DFS was 55.3 months (range, 9 to 92 months). In the group of patient with delta SUV <70% DFS was 56,3% mean while in patient with with delta SUV >70% DFS resulted 85.7%, showing a statistically significance (p<0,05) (Figure 4)

In multivariate analysis, DSUV resulted and independent risk factors associated with local recurrence-free survival, as well pTN stage and preoperative ASA (Table 4).

Five-years OS (overall survival) rate resulted 60% in patients Δ% SUV <70% and 86,4% in patients Δ% SUV >70% showing a statistically significance (p<0,05) (Figure 5). The unadjusted Cox-proportional hazards regression revealed that delta SUV and pTN were associated with worse overall survival (Table 5).

Discussion

Radical surgery with TME (total mesorectal excision) remains the main curative treatment for patients affected by LARC [12]. The TME associated with nCRT improve outcomes by increasing 5-year survival rate [9]. Several previous studies have demonstrated that, compared with adjuvant treatment, preoperative nCRT significantly improves loco-regional tumor recurrence and reduces toxicity compared with postoperative strategies [10]. The early identification of pR after nCRT in rectal cancer remains an important challenge, and it could avoid surgical overtreatment without compromising local control and long-term survival [12]. It could considerably reduce the number of surgical procedures required in the future allowing less invasive procedures, such as TAMIS (Transanal minimally invasive surgery), to be performed for initially LARC [16]. This latter approach could also reduce rates of mortality, morbidity and other unsatisfactory functional outcomes that may occur after rectal resection. Furthermore, an early prediction in the No Responders group could provide the clinician the opportunity to evaluate the possibility of reorientation of the standard treatment by increasing number of chemotherapy cycles and radiotherapy, as well. The current conventional radiology, such as endorectal ultrasound (EU), CT scan and MRI for monitoring the tumor response, shows several limitations to assess the pR after nCRT. This is mainly due to the difficulties in discerning between disease persistence and radiation induced inflammation and fibrosis after nCRT [13]. ^{18}F -FDG PET-CT has a recognized validity for monitoring nCRT effects [14].

There are several studied that have investigated the predictive value of 18^{F}-FDG PET-CT in the LARC and in recurrent rectal cancer, and more are likely to be produced using collaborative, international research platforms [18-27]. However, these studies have some limits mainly due to the methodological heterogeneity secondary to their multicentric nature in terms of preoperative studies, chemoradiotherapy, patients' characteristics and PET study method (timing, technique and analysis of images). Despite these limits, it is important to observe that almost all these previous studies identify a significant correlation between tumor 18^{F}-FDG uptake and pR, also showing correlation between OS and DFS [13,15-18].

A recent study by Niccoli-Asabella et al. was able to evaluate the prognostic value of 18F-FDG PET-CT in terms of survival in patients with LARC who have undergone surgery after nCRT. This work showed a high

percentage of patients with TRG complete response (39.7%) with longer OS and DFS in responders group but without statistically significant differences [13].

The strength of our study relies on being one of the largest studies evaluating 18F-FDG PET-CT related to histopathological response (TRG score) at two time-points, before nCRT (early PET-CT) and after finishing CRT (late PET/CT). We found the optimal cut-off to distinguish responders patients (TRG3-TRG4) from no-responders patients (TRG0-TRG2) at of 70% of the Δ%SUV. Furthermore, our analysis showed that Δ%SUV was a stronger discriminator between the two groups with a high accuracy of 81% (34/42), with a sensitivity of 84.4%, a specificity of 80%, a positive predictive value of 81.4% and a negative predictive value of 84.2%. We were able to found correlation between Δ%SUV and OS and DFS showing a statistically significance (p<0,05), as well.

Another similar study by Leccisotti et al., found similar results They found the optimal cut-off to distinguish no-responders patients from responders patients on the early PET-CT scan as a reduction in tumor SUVmax of 61.2 % (85.4 % sensitivity, 65.2 % specificity) [18].

An important issue still uncleared remains the PET-CT study method (timing, technique and qualitative analysis of images). Most studies report inaccurate results due to heterogeneous methods for ^{18}F-FDG PET-CT quantification, the correct time to perform the study and the metabolic criteria [19,20]. It is important to standardize the criteria for the correct use of ^{18}F-FDG PET-CT in order to achieve a correct interpretation of the result. In the current literature, there is no standardized data that indicates the proper timing by which to perform the ^{18}F-FDG PET-CT. It is well known that chemotherapy produces an inflammatory reaction that lasts one week after the beginning of treatment, while radiotherapy inflammatory reaction may last up to 6 months. Therefore, it is important choose or indicate the right time to perform 18F-FDG PET-CT after nCRT in order to standardize the correct interval being a potential source of false-positive findings on the late 18F-FDG PET-CT. The World Health Organization recommends 18F-FDG PET-CT seven weeks after nCRT and surgery one week later [28]. This is mainly based after the trial performed by R.O Perez et al., showing a proper restaging with 18^{F}-FDG PET-CT at 6 and 12 weeks after the completion of therapy [15]. The present study was concomitant with this recommendation as all patients underwent FDG PET-CT six to seven weeks after the end of nCRT and surgery was performed eight weeks from the end of neoadjuvant treatment.

The main limitations are the relatively small number of patients in our cohort due to a single center enrollment. However, the unicentric nature represents also a guarantee for more homogenous data.

We believe that more technically advanced tools are important to accurately measure tumour change. Nowadays the use of quantitative analysis of PET/MRI to assess pCR following nRCT in LARC could improve outcome prediction and open the era of adaptive therapy for cancer patients [29,30].

In conclusion, the results of this analysis are promising and shown that 18F-FDG PET-CT may be an indicator in order to evaluate the pR to nCRT in patients with LARC. The decrease in 18F-FDG PET-CT uptake in the primary tumor may offer primary information in order to early identify those patients more

likely to obtain a pCR to nCRT and predict those unlikely to regress significantly. Rigorous follow up and future larger prospective studies are necessary to confirm these results.

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Tables

Table 1: Patients and tumor characteristics

Median age (range)	62,8 (33-79)
Sex	
Male	70 (53%)
Female	63 (47%)
ASA	
I	19 (14%)
II	76 (57%)
III	38 (29%)
Clinical T stage	
cT3	100 (75%)
cT4	33 (25%)
Clinical N stage	
cN0	47 (36%)
cN1	67 (50%)
cN2	19 (14%)
Location of the tumor	
Upper third	21 (16%)
Middle third	77 (58%)
Lower third	35 (26%)

Table 2-Operative data

Type of resection	
APR	29 (22%)
LAR	14 (10%)
LAR with stoma	90 (68%)
Mean Operative time (min) (SD)	280 ± 38
Intraoperative blood (ml) (SD)	205 ± 26
Hospital stay (days) (SD)	12.42 ± 7.77

APR: Abdominoperineal resection

LAR: Low anterior resection

SD: standard deviation

Table 3- Evaluation of the tumor response (TRG score)

	TRG				
	TRG 3	TRG 2	TRG 1	TRG 0	Total
Responders 107(80%)	0 (0)	0 (0)	75 (56)	32 (24)	107 (80)
No Responders 26(25%)	22 (17)	4 (8)	0 (0)	(0)	26 (25)

TRG: Tumor regression grading

Table 4: Univariate and Multivariate analysis DFS (disease free survival)

	Univariate analysis		Multivariate analysis	
Variable	Hazard ratio	p values	Hazard ratio	p values
Age (years, SD)		0,224		
<60				
>60	1			
	2,509 (0,531-11,855)			
Sex		0,795		
F	1			
M	0,850 (0,246-2,941)			
ASA		0.064		0.39
I-II	1		1	
III	3,328 (0.931-11,892)		5,074 (1,086-23,710)	
CEA		0,724		
>5	1			
<5	1,706 (0,340-4,067)			
Tumor		0.914		
localization				
>10 cm	1			
<10 cm	1,007 (0,278-14,172)			
Approch		0,293		
Laparoscopic	1			
Robotic	2,297 (0,487-10,830)			
pTNM		0.098		0.20
0- I	1		1	
II-II	3,717(0,786-17,569)		11,088 (1,451-84,720)	
TRG		0,268		
0-1	1			
2-3	2,801 (0,537-8,056)			
Lymphonodal ratio		0,961		
0	1			

<0,24	0,737 (0,89-6,097)			
>0,25	0,717 (0,64-8,064)			
Blood trasfusion		82		0.077
No	1		1	
yes	3,120(0,866-11,239)		3,830 (0,866-16,932)	
Dindo-Clavien ≥3		0.542		
no	1			
yes	1,594 (0,409-6,211)			
SUV pre		0,572		
<8	1			
>8	1,806 (0,222-14,702)			
SUV post		0,271		
<8	1			
>8	2,090 (0,535-8,166)			
Δ SUV		0.043		0.047
<70%	1		1	
>70%	4,078 (1,046-15,900)		4,793 (1,019-22,553)	

Table 5: Univariate and Multivariate analysis OS (overall survival)

	Univariate analysis		Multivariate analysis	
Variable	Hazard ratio	p values	Hazard ratio	p values
Age (years, SD)		0,261		
<60				
>60	1			
	2,464 (0,511-11,878)			
Sex		0,565		
F	1			
M	1,472 (0,395-5,486)			
ASA		0.175		0.097
I-II	1		1	
III	2,611 (0.652-10,448)		4,851 (0,752-21,283)	
CEA		0,908		
>5	1			
<5	1,102 (0,296-4,107)			
Tumor		0.860		
localization				
>10 cm	1			
<10 cm	1,133 (0,283-4,533)			
Approch		0,133		0.127
Laparoscopic	1		1	
Robotic	4,921 (0,615-39,385)		5,217/0,624-43,650)	
pTNM		0.048		0.20
0- I	1		1	
II-II	8,158(1,017-64,437)		15,315 (1,550-151,339)	
TRG		0,286		
0-1	1			
2-3	2,126 (0,531-8,504)			
Lymphoonodal ratio		0,898		
0	1			

<0,24	0,606 (0,73-5,042)			
>0,25	0,634 (0,57-7,000)			
Blood trasfusion		0.306		
No	1			
yes	2,065 (0,515-8,280)			
Dindo-Clavien>3		0.911		
no	1			
yes	1,093 (0,227-5,268)			
SUV pre		0,609		
<8	1			
>8	1,728 (0,212-14,056)			
SUV post		0,271		
<8	1			
>8	2,514 (0,514-10,086)			
Δ SUV		0.048		0.033
<70%	1		1	
>70%	4,060 (1,010-16,319)		7,629(1,174-49,591)	

Figures

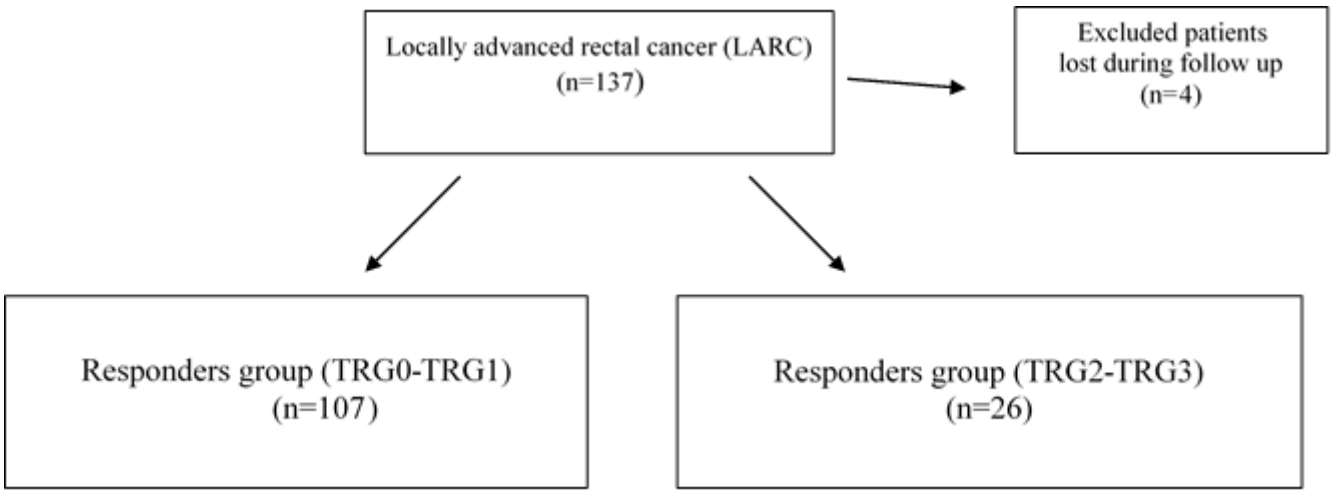

Figure 1

Flowchart

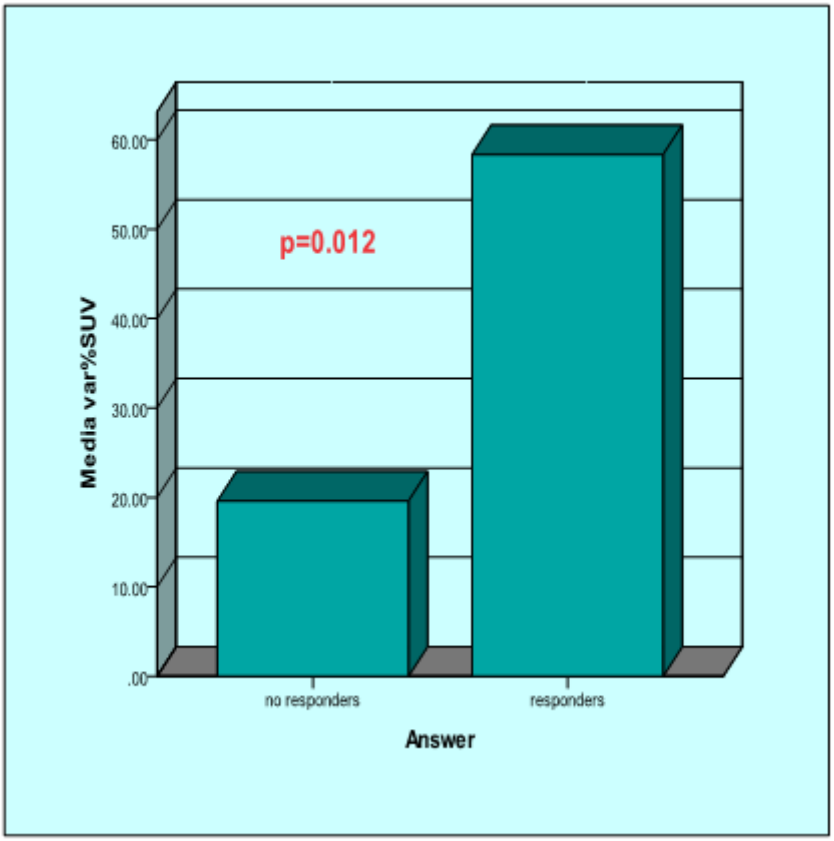

Figure 2

Difference in Δ%SUV between the responders and no responders group.

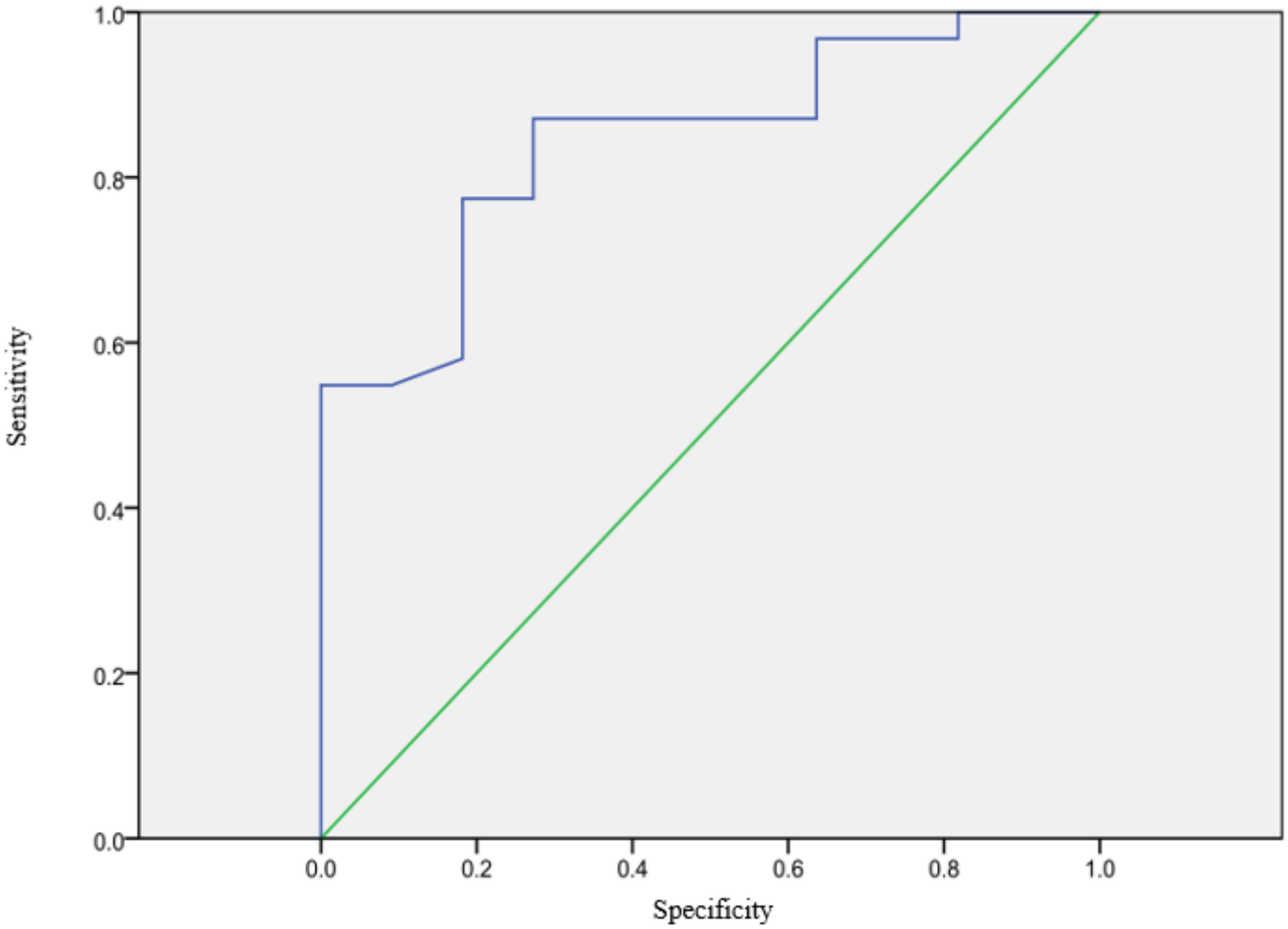

Figure 3

ROC (receiver operating characteristic) curve

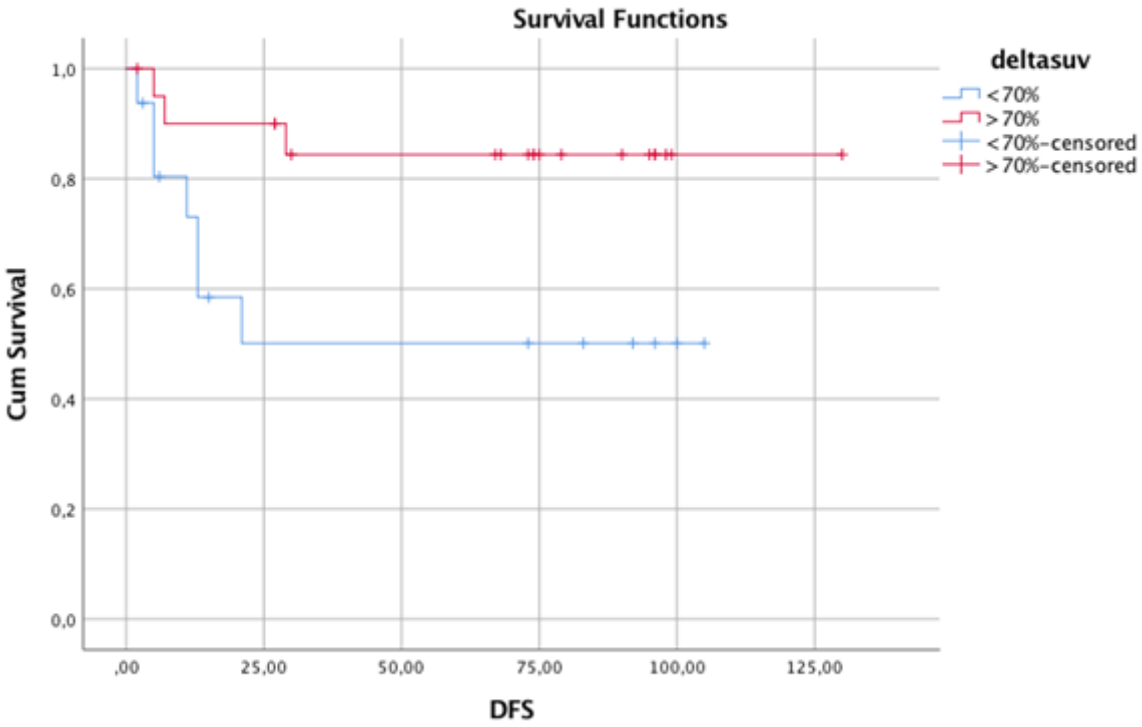

Figure 4

DFS (disease free survival) curve depending on the Δ SUV

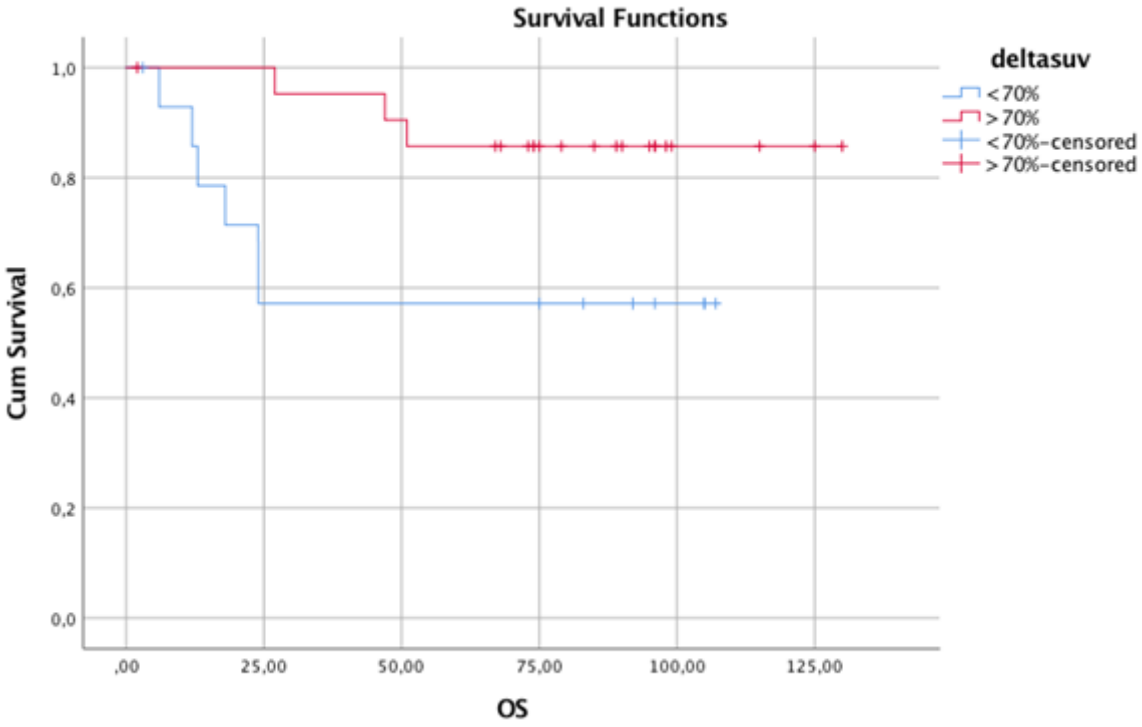

Figure 5

OS (overall survival) curve depending on the Δ SUV