Predictive value of ¹⁸F-FDG PET/CT on survival in locally advanced rectal cancer after neoadjuvant chemoradiation

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Abstract. – **OBJECTIVE:** To evaluate the prognostic value of ¹⁸F-FDG PET/CT in terms of survival in patients with locally advanced rectal cancer (LARC) who had undergone surgery preceded by neoadjuvant chemoradiotherapy (nCRT). Moreover, the existence of correlation between Overall Survival (OS) and Disease Free Survival (DFS) with pathological staging ((y)pT-NM and TRG) was evaluated.

PATIENTS AND METHODS: A total of 58 patients with biopsy-proven of LARC were included. All patients underwent conventional diagnostic/staging procedures to characterize the rectal lesion. The first whole-body ¹⁸F-FDG PET/CT was performed 1 week before the beginning of nCRT (baseline scan). The second ¹⁸F-FDG PET/CT was scheduled at 5-6 weeks from nCRT completion (post-nCRT scan). Survival was evaluated in 3 different restaging classification systems, based on focusing only on primary lesion (TRG), loco-regional evaluation (ypTNM) and whole-body ¹⁸F-FDG PET/CT evaluation (VRA).

RESULTS: Among the 58 patients at the end of the observation, 46/58 patients (79.3%) were alive and 12/58 (20.7%) were dead. This work demonstrated a higher percentage of patients with TRG complete response (39.7%) compared to literature (24.6%), with longer Overall Survival (OS) and Disease Free Survival (DFS) in responders even if without statistically significant differences.

CONCLUSIONS: The present study highlights the predictive and prognostic potential role of ¹⁸F-FDG PET/CT in assisting physicians on personalized decision in the selective risk-adapted treatment strategy, and to schedule the correct follow-up approach.

Introduction

The management of locally advanced rectal cancer (LARC) includes surgery preceded by neoadjuvant chemoradiotherapy (nCRT). The treatment strategy has been implemented by less invasive procedures such as total mesorectal excision (TME) that allows sphincter preservation.

This strategy is possible thanks to a reliable evaluation of tumor response assessment. The evaluation's methods of the response to nCRT reported in literature are very diversified, without any agreement of its benefits or efficacy; in fact, only in few studies[1,2] complete remission is reached. Nevertheless, 5-year survival of LARC patients undergoing nCRT can vary from 83 to 90%, but it is not defined whether post-therapy restaging has predictive survival role[2]. Consequently, it is not established whether whole body clinical restaging with imaging technique, or pathological assessment by (y)pTNM or local response Tumor Regression Grade (TRG) is more useful for survival prediction. Molecular imaging with positron emission tomography/computed tomography (PET/CT) using [¹⁸F] 2-fluoro-2-deoxy-D-glu-

cose (^{18}F-FDG) is a hybrid imaging modality that allows assessing molecular and morphologic information at the same time[3]. ^{18}F-FDG PET/CT has gained wide acceptance in oncology with many clinical applications because it represents an efficient tool for whole body staging and re-staging and there is increasing evidence that can significantly contribute to therapy response assessment, influencing therapeutic management and treatment planning, and to prediction of prognosis in oncologic patients[3]. ^{18}F-FDG PET/CT has proven efficacy with special emphasis for the staging of rectal carcinomas and some studies have also shown its validity in the evaluation of the response to therapies [1,3]. The aim of our study was to evaluate the prognostic value of ^{18}F-FDG PET/CT in terms of survival in patients with LARC who had undergone nCRT. We also evaluated the existence of correlation between Overall Survival (OS) and Disease Free Survival (DFS) with pathological staging ((y)pTNM and TRG).

Patients and Methods

Patients

58 patients with biopsy-proven of LARC were included. All patients underwent conventional diagnostic/staging procedures to characterize the rectal lesion. The following exclusion criteria were applied: pregnancy, aged younger than 18 years, previous rectal treatment (chemotherapy, radiotherapy or surgery), presence of distant metastases at the time of diagnosis, neoadjuvant therapy contraindications. Written informed consent was obtained from all patients. Characteristics of patients and disease at the initial staging are reported in Table I. Patients were followed for at least 5 years.

Treatments

Neoadjuvant chemotherapy, consisting of 5-fluorouracil (435 mg/m^2/d) and leucovorin (20 mg/m^2/d) for 32-34 days, was intravenously administered. The whole pelvic field received 25 fractions of 180 cGy/d over over 5 weeks, for a total of 5040 cGy, using a 4-field box technique. Neoadjuvant chemotherapy was started concurrently on the first day of radiotherapy. All patients were scheduled to TME 8 weeks after completion of the nCRT. The same surgical team with improved experience (M.S. and R. D. L.) operated all patients.

^{18}F-FDG PET/CT

The first whole-body ^{18}F-FDG PET/CT was performed 1 week before the beginning of nCRT (baseline scan). The second ^{18}F-FDG PET/CT was scheduled at 5-6 weeks from nCRT completion (post-nCRT scan). Images were acquired with a discovery LSA PET/CT device (GE Healthcare, Waukesha, WI, USA) that integrates a PET (advance nxI) with 16-slice CT scanner (light speed plus). All patients, before ^{18}F-FDG (Sparkle srl, Casarano (LE), Italy) administration fasted for at least 8 h and had a capillary blood glucose <160 mg/mL. The image acquisition was obtained 50 min after the intravenous injection of 3.7 MBq/kg of ^{18}F-FDG. The CT scan was carried out from the external acoustic meatus to the root of the thigh with patients lying on their back with hands above their head. The CT acquisition parameters were: 340 mA (auto), 120 kV, slice thickness 3.75 mm, tube rotation time 0.8 ms, collimation field of view (FOV) of 50 cm. The CT data were used for attenuation correction of PET scanning, which was performed immediately after the acquisition of CT images. The CT scans were performed without administration of contrast medium. The PET acquisition was obtained in caudal-cranial direction; PET was reconstructed with a matrix of 128x128, ordered subset expectation maximum iterative reconstruction algorithm (two iterations, 28 subsets), 8 mm Gaussian filter and 50 cm field of view.

Image Analysis

Two nuclear medicine physicians with at least 8 years of experience (C.A. and C.F.) blindly and independently analyzed data using a dedicated Advantage™ Workstation (version 3.2; GE Healthcare, Waukesha, WI, USA). Baseline and post-nCRT ^{18}F-FDG PET/CT scans were analyzed by "MultiVol CONF PETCT" program that allows the simultaneous observation of both scans. Qualitative analysis was performed by visual response assessment (VRA) and patients were then classified into the following categories: Complete Response (CR) if there was complete absence of pathological ^{18}F-FDG uptake sites, Partial Response (PR) if there was a remarkable reduction of ^{18}F-FDG uptake, Stable Disease (SD) if there were no changes from the baseline ^{18}F-FDG PET/CT and Progressive Disease (PD) in case of increased uptake of ^{18}F-FDG or onset of new ^{18}F-FDG uptake areas from the baseline ^{18}F-FDG PET/CT. CR and PR were considered "VRA responders" while SD and PD were considered "VRA

non responders". Volumes of interest (VOIs) were drawn ssemiautomatically on the rectal area of the abnormal ^{18}F-FDG uptake corresponding to the tumor in the baseline scan. Semiquantitative analysis was performed calculating Standardized Uptake Values (SUV_{max} and SUV_{mean}), using the maximum and mean activity values within each VOI with the highest radioactivity concentration, normalized to the injected dose and patient's body weight. Metabolic Tumor Value (MTV) and Total Lesion Glycolysis (TLG) were evaluated using a fixed threshold of 40% of SUV_{max}, both for baseline ($MTV_{baseline}$, $TLG_{baseline}$) and for post-nCRT scan ($MTV_{post-nCRT}$, $TLG_{post-nCRT}$)[4-7]. The SUV_{max} and SUV_{mean} values of the baseline scan ($SUV_{baseline}$) and the post-nCRT scan ($SUV_{post-nCRT}$) were used to calculate response index (RI%) with the formula $[(SUV_{baseline} - SUV_{post-nCRT})/SUV_{baseline}]$ x100. ΔMTV and ΔTLG were also calculated as the difference between baseline and post-nCRT scan values.

Response Evaluation and Follow Up

The assessment of the tumor response to nCRT was performed according to Mandard's Tumor Regression grade (TRG score)[8] and by the evaluation of the (y)pTNM categories according to the International Union against Cancer[4]. According to the TRG, the patients were divided into two groups: "TRG responders" (TRG I) and "TRG non-responders" (TRG II to V). According to (y)pTNM patients CR, PR, SD and PD were assigned comparing with the TNM initial staging; patients were then divided into "(y)pTNM responders" and "(y)pTNM non-responders". The clinical follow up was performed by expert gastrointestinal surgeons (M.S. and R.D.) who collected all the data about the instrumental procedures from the third month after surgery to the end of the study.

Statistical Analysis

All semiquantitative data were expressed as medians and compared by the Mann-Whitney U test.

Overall survival (OS) was defined as the time from surgery until death for any cause or to the last follow-up. Disease-free survival (DFS) was defined as the time from surgery to the documented local or distant recurrence (whichever occurred first) or last follow-up. OS and DFS rates were estimated with their 95% CI using the Kaplan-Meier method and compared with the log-rank test. Hazard ratios (HR) were derived from Cox regression analysis. A univariate analysis assessed the correlation of pre- and post-surgical cha-

racteristics (considered as dichotomous variables) with DFS and OS. A *p*-value ≤0.05 was considered statistically significant. Statistical evaluations were carried out using SPSS 20.0 for Mac (IBM Corp., IBM SPSS Statistics for Windows, Armonk, NY, USA).

Results

Metabolic ^{18}F-FDG PET/CT Response Evaluation

According the VRA, 12/58 patients (20.7%) were considered CR, 36/58 patients (62.1%) PR, 4/58 patients (6.9%) PD and 6/58 patients (10.3%) SD. Then, 48/58 patients (17.2%) were considered "VRA Responders" and 10/58 patients (82.8%) "VRA Non-responders". Description of the semiquantitative parameters in the whole population and in subgroups are reported on Table II. There were no differences statistically significant for semiquantitative parameters among CR, PR, SD and PD and between "VRA Responders" and "VRA Non-responders" (*p*> 0.05). An exemplar case of a PR patient is showed on Figure 1.

Pathological Response Evaluation

According to the TRG criterion, the surgical specimen showed 23/58 "TRG responders" (39.7%) and 35/58 "TRG non-responders" (60.3%). According the (y)pTNM 10/58 patients (17.2%) were considered CR, 17/58 patients (29.3%) PR, 10/58 patients (17.2%) PD and 21/58 patients (36.3%) SD. Next, 27/58 patients (46.6%) resulted "(y)pTNM responders", while 31/58 (53.4%) resulted "(y)pTNM non-responders". All the pathological characteristics are described in Table III.

Survival Characteristics

Among the 58 patients at the end of the observation, 46/58 patients (79.3%) were alive and 12/58 (20.7%) were death. Furthermore 33/58 patients (56.9%) had relapse: 22/33 patients had relapse at the 3 month follow up (at rectal anastomosis in 7 patients, liver in 5, lungs in 7, lymph nodes, bones and peritoneum in 1 patient respectively); 2/33 at the 6 month follow up (rectal anastomosis); 5/33 at the 12 month follow up (rectal anastomosis in 3, liver and lungs in 1 patient respectively); 4/33 at the 24 month follow up (rectal anastomosis, liver, lungs and lymph nodes in 1 patient respectively).

Exemplar cases of patients with rectal relapses and distant metastases onset in follow up are reported in Figure 2 and 3. Median follow up was
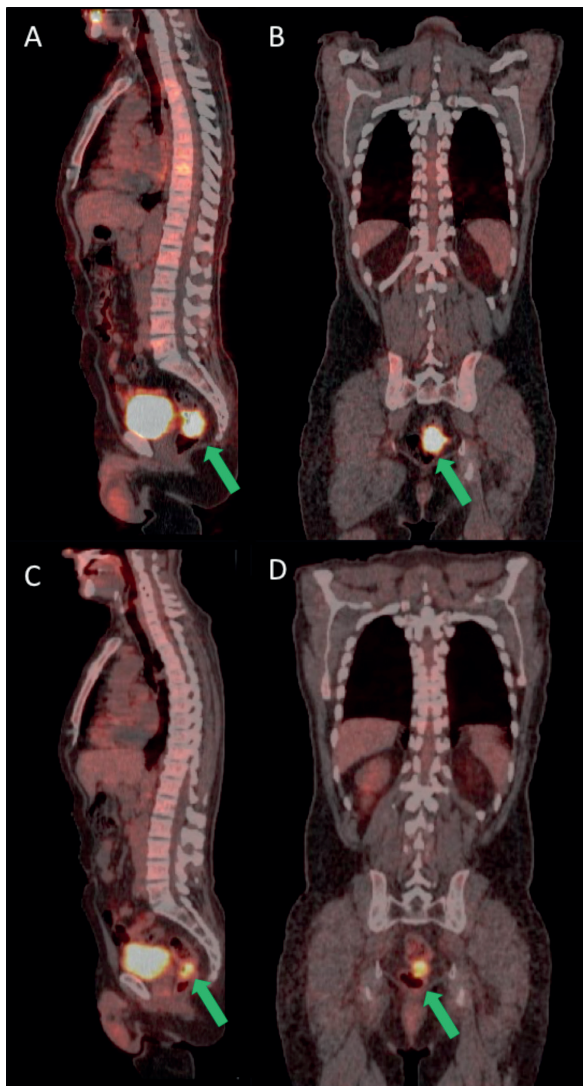
Figure 1. 70-year-old male with a vegetans lesion at 7 cm from the anal verge. Baseline ^{18}F-FDG PET/CT sagittal *(A)* and coronal *(B)* images show the rectal lesion, SUVmax: 17.2 (green arrows). The post nCRT ^{18}F-FDG PET/CT sagittal *(C)* and coronal *(D)* images show reduction of rectal lesion size and pathological uptake, SUVmax: 10.6 (green arrows). Patient was classified as PR and his OS was 80 months and a liver lesion onset at the 24-month follow up.

Table I. Baseline characteristics of study population.

No. of patients	58
Sex	
Male	39 (67.2%)
Female	19 (32.8%)
Age (years old)	Mean 66 (range: 38-89)
Clinical staging	
II	33 (56.9%)
III	25 (43.1%)

the distinction in "VRA responders" and "VRA non-responders", neither for the distinction in CR, PD, PR and SD. Results are reported in Table IV. In relation to pathological Response Evaluation by TRG, log rank test did not show statistical difference for OS and DFS for the distinction in "TRG responders" and "TRG non-responders". Results are reported in Table V.

About pathological response evaluation by (y) pTNM, log rank test showed statistical difference for OS both for the distinction in "(y)pTNM responders" and "(y)pTNM non-responders" and for the distinction in CR, PD, PR and SD (p=0.030). For DFS no statistical significance was found in difference between "(y)pTNM responders" and "(y)pTNM non-responders" and among CR, PD, PR and SD. The survival curves are showed in Figure 4 and results are reported in Table VI.

Discussion

The nCRT treatment led to a better outcome of patients with LARC with increased 5-year survival rate; the most recent and wide study with 336 LARC patients showed 73.5% survivors followed for a mean of 60.4 months[9]. Survival seems to be related to the response to therapy, in particular it is greater if the therapy has led to complete tumor eradication then the lack of any pathological change or even tumor progression despite the nCRT[10]. The tumor response to nCRT varies considerably among patients, the complete disappearance of the tumor is reached in about 20% of cases[11]. In our work, 17.2% of patients achieved a complete pathological response (ypT0N0M0). Assessment of disease parameters as potential predictors of the long-term outcome of patients with LARC undergoing nCRT can help in identifying patients to whom conservative surgery might be offered[11]. Despite various attempts at
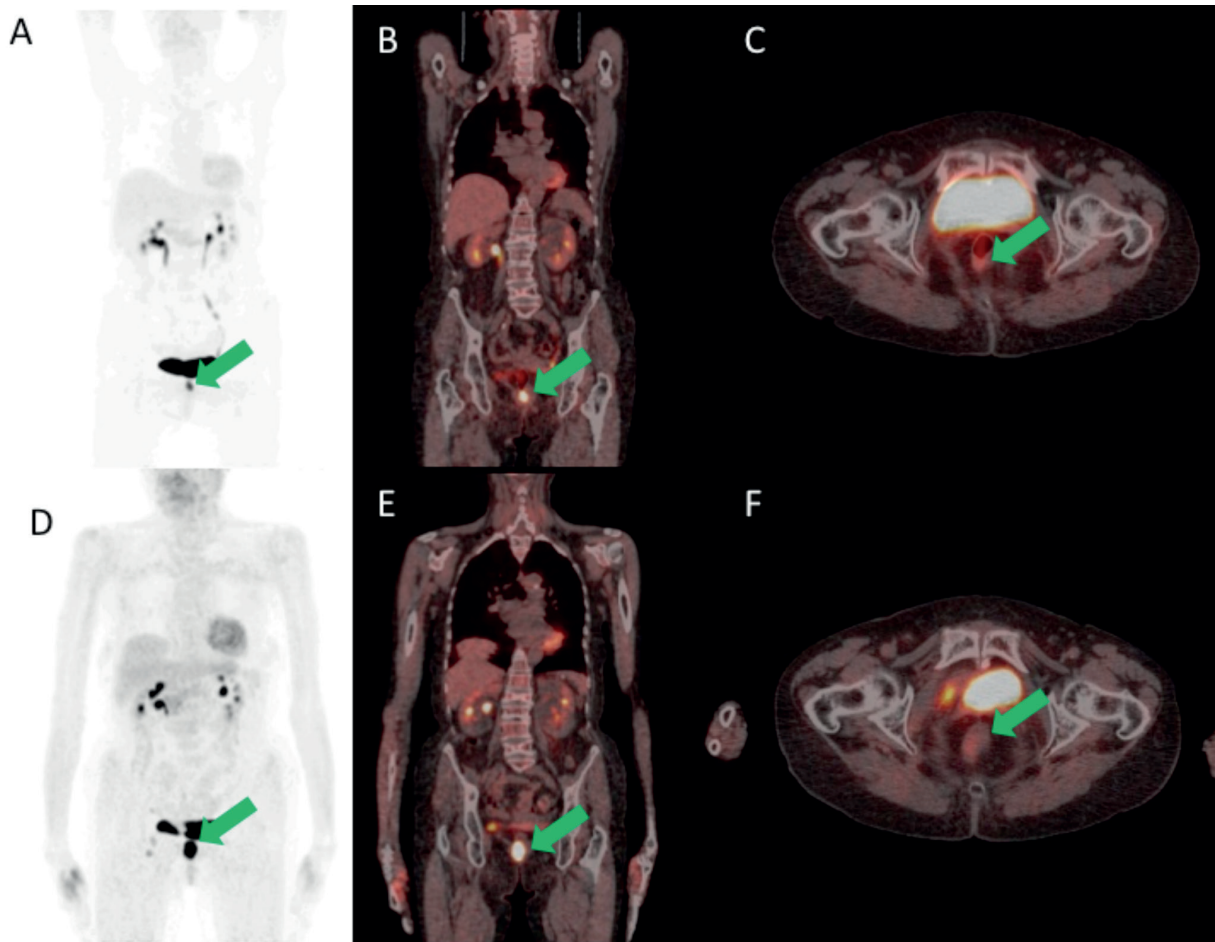
63 months (range 3-96). Kaplan Meier curves showed a global OS of 83.51 months (SD 3.30) and DSF of 45.72 months (SD 5.79). About the semiquantive parameters, only age is significantly related to the OS (OR=1.123 p=0.007). All the remnant parameters are not related neither to the OS and DSF. Cox test showed neither of variables and semiquantitative parameters have significant correlation. Regarding metabolic ^{18}F-FDG PET/CT response evaluation, log rank test did not show statistical difference for OS and DFS neither for

Figure 2. 65-year-old female VRA classified as PR; TRG was II and ypTNM was I. ¹⁸F-FDG PET/CT MIP *(A)*, coronal *(B)* and axial *(C)* images performed after nCRT showed a small rectal lesion with SUVmax of 5.4. Follow up at 3 months ¹⁸F-FDG PET/CT MIP *(D)*, coronal *(E)* and axial *(F)* images show local-regional relapse with SUVmax: 21.7 (green arrows). OS was 68 months.

Table II. ¹⁸F-FDG PET/CT semi-quantitative parameters.

	Mean (±SD)						
	All patients	**VRA responders**	**VRA non-responders**	**CR**	**PR**	**SD**	**PD**
SUV max$_{baseline}$	18.37 (±8.91)	20.17 (±8.57)	9.72 (±4.27)	22.37 (±9.53)	19.44(±8.24)	9.65(±3.32)	9.82 (±6.04)
SUV mean$_{baseline}$	9.35 (±4.3)	10.30 (±4.05)	4.76 (±2.10)	11.64(±4.67)	9.86(±3.79)	4.73(±1.79)	4.80 (±2.80)
MTV$_{baseline}$	24.81 (±13.7)	26.12 (±13.80)	18.50 (±11.83)	26.93 (±16.39)	25.85(±13.08)	19.48(±6.61)	17.04 (±18.49)
TLG$_{baseline}$	247.23 (±221.20)	20.17 (±8.57)	100.80 (±110.41)	356.64 (±306.30)	251.43(±191.88)	90.89(±48.73)	115.67 (±179.24)
SUV max$_{post-nCRT}$	6.75 (±3.1)	6.28(±2.88)	8.99(±3.47)	3.30 (±1.75)	7.28(±2.48)	7.58(±3.90)	11.10 (±0.90)
SUV mean$_{post-nCRT}$	3.11 (±1.53)	2.88 (±1.39)	4.24(±1.75)	1.51 (±0.81)	3.33(±1.24)	3.48(±1.89)	5.37 (±0.61)
MTV$_{post-nCRT}$	23.17 (±15.20)	23.43 (±16.44)	21.92 (±6.99)	34.19 (±23.31)	19.84(±11.80)	21.88(±6.68)	21.98 (±8.49)
TLG$_{post-nCRT}$	70.54 (±57.42)	70.84 (±61.05)	69.08 (±37.62)	80.55 (±63.73)	67.61(±60.71)	76.05(±43.23)	58.63 (±29.80)
RI max%	58.02 (±22.07)	63.55 (±17.71)	31.45 (±22.36)	73.80 (±11.67)	60.13(±18.17)	26.76(±23.67)	38.48 (±21.36)
RI mean%	61.05 (±24.17)	66.96 (±19.42)	32.65 (±25.44)	78.33 (±9.63)	63.17(±20.45)	29.45(±26.70)	37.44 (±26.51)
ΔMTV	26.23 (±31.48)	65.58 (±31.95)	12.21 (±26.09)	24.13 (±34.72)	30.83(±31.32)	8.67(±21.24)	17.52 (±35.05)
ΔTLG	53.18 (±34.61)	59.99 (±13.80)	20.50 (±29.28)	57.16 (±36.48)	60.94(±30.65)	18.36(±23.49)	23.70 (±40.36)

predicting response and long-term outcome based on molecular profiling of tumors, there are no markers adequately validated about such as probiotics and bioactive molecules for this pur-
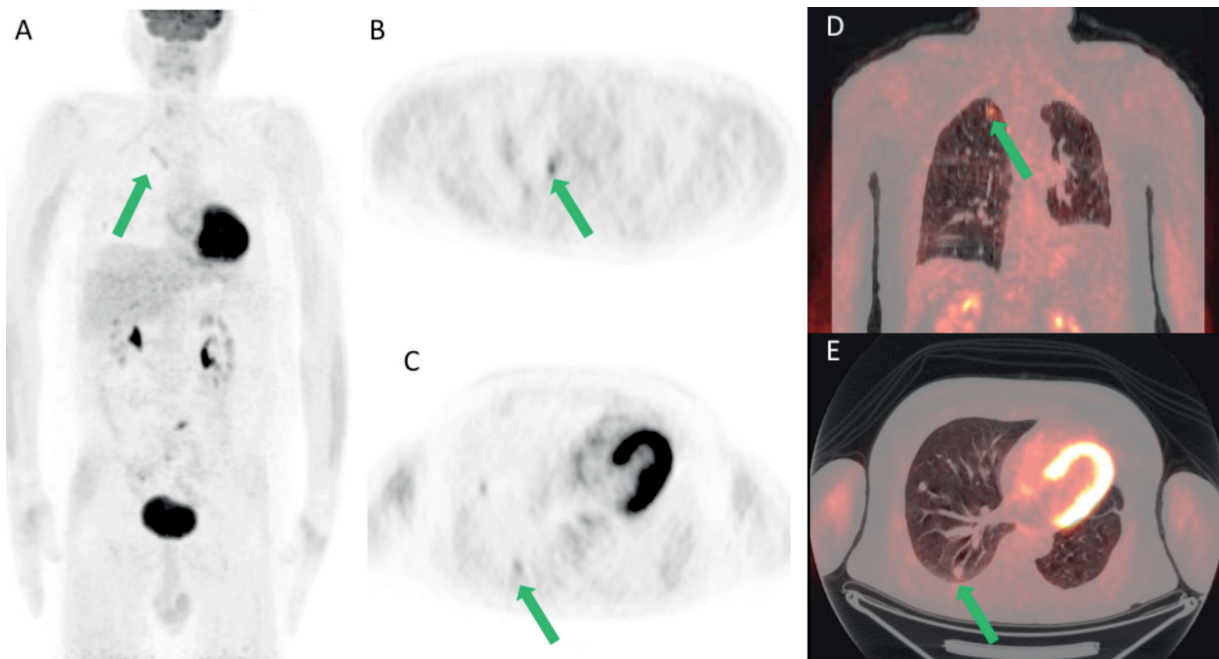
Figure 3. 70-year-old male, VRA classified as CR. Follow up ^{18}F-FDG PET/CT at 3 months: MIP *(A)*, axial *(B, C, E)* and coronal *(D)* images show two metastatic lesions of right lung. SUV max: 5.2 (*green arrows*). OS was 71 months.

pose[12,13]. Purely morphological diagnostic techniques are not able to predict treatment response because anatomical changes onset lately than functional tissues modifications[14-16]. It is well known the role of ^{18}F-FDG PET/CT in the management of oncological patients and there is also a growing consensus in its usefulness in evaluating the response to therapies in several oncological diseases[17]. Furthermore, there is a growing number of studies[18-20] that have investigated the prognostic value of ^{18}F-FDG PET/CT. About LARC, since there is a certain degree of heterogeneity in the applied methodology, literature reports different results, not directly comparable[1]. This difference is also observed because the qualitative assessment of ^{18}F-FDG PET/CT images can be associated with the analysis of semiquantitative parameters. To date these parameters include not only SUVs, that are related to increased tumor aggressiveness and poor long-term prognosis, but also MTV and TLG, which are more representative of the entire tumor burden[7,21]. Their role in predicting outcome is still under discussion and we did not relate them to OS and DFS because we did not find significant statistical differences among the different groups. de Geus-Oei et al[22] showed that the chemotherapy-induced changes in glucose metabolism of the lesion are highly predictive for patient outcome: an increase in ra-

tes death and progression is associated with an increased ^{18}F-FDG uptake. A recent systematic review[23] including five studies demonstrated that a CR on ^{18}F-FDG PET/CT after nRCT is predi-

Table III. Pathological characteristics of the study population.

N (%)	
Yp Staging	
0	11 (19%)
I	17 (29.3%)
II	10 (17.2%)
III	20 (34.5%)
Mandard's TRG	
1	13 (22.4%)
2	10 (17.2%)
3	11 (19%)
4	19 (32.8%)
5	5 (8.6%)
R	
R0	50 (86.2%)
R1	7 (12.1%)
R2	1 (1.7%)
Grading	
G1	4 (6.9%)
G2	29 (50%)
G3	16 (27.5%)
GX	9 (15.5%)

Table VI. Survival according VRA evaluation.

	Overall survival			Disease free survival		
	MEAN (months)	SD		MEAN (months)	SD	
CR	69.91	5.81	Log Rank = 8.594	33.00	9.14	Log Rank = 1.776
PR	92.54	3.30	*p* > 0.05	58.50	10.74	*p* > 0.05
SD	69.95	5.72		39.13	8.72	
PD	91.17	3.50		30.00	11.55	
Responders	90.74	3.67	Log Rank =4.698	51.67	7.52	Log Rank = 0,938
No-responders	76.92	4.86	*p* > 0.030	38.61	8.32	*p* > 0.05

Table V. Survival according TRG evaluation.

	Overall survival			Disease free survival		
	MEAN (months)	SD		MEAN (months)	SD	
Responders	72.51	4.08	Log Rank = 0.049	47.35	7.44	Log Rank = 1.727
No-responders	83.36	4.10	*p* > 0.05	39.5	7.39	*p* > 0.05

Table IV. Survival according VRA evaluation.

	Overall survival			Disease free survival		
	MEAN (months)	SD		MEAN (months)	SD	
CR	66.56	6.63	Log Rank = 2.872	39	10.45	Log Rank = 3.802
PR	86.30	3.75	*p* > 0.05	46.5	7.4	*p* > 0.05
SD	72.96	10.74		61.66	16.93	
PD	59.50	6.02		10.5	4.97	
Responders	83.44	3.64	Log Rank =0.00	46.25	6.38	Log Rank = 0,037
No-responders	79.35	7.38	*p* > 0.05	41.2	13.002	*p* > 0.05

ctive of OS, but not of DFS. In our analysis, CR patients had a better OS and DFS only compared with PD patients, but this difference was not statistically significant, even when we compare OS and DFS in "VRA Responders" and "VRA Non-responders". However, we must keep in mind the limited number of events (cancer deaths) observed in this small patient population that likely restrict the statistical power of these data. Literature reports that the pathologic stage ((y) pTNM) and the extent of residual cancer (TRG) at completion of nCRT better correlate with prognosis than the clinical stage[11,24]. For this reason, we chose to evaluate survival in the 3 different restaging classification systems, based on focusing only on primary lesion (TRG), loco-regional evaluation (ypTNM) and whole-body ^{18}F-FDG PET/CT evaluation (VRA). Our work demon-

strated a higher percentage of patients with TRG complete response (39.7%) compared to literature (24.6%), with longer OS and DFS in responders even if without statistically significant differences. The rate of (y)pTNM CR of our study was lower than literature (17.2% *vs.* 22.6%), and OS and DFS in CR patients was shorter than the other groups; otherwise, OS and DFS in PR patients were the longest. These results show that (y)pTNM, not providing total body information, is not a complete evaluation system for predicting outcome. The statistically significant difference in OS between "(y)pTNM responders" and "(y) pTNM non-responders" is a further confirm [24]. The difference in OS and DFS between responders and non-responder groups was higher according to TRG and (y)pTNM compared to VRA, this is probably due to the inserting of PR pa-
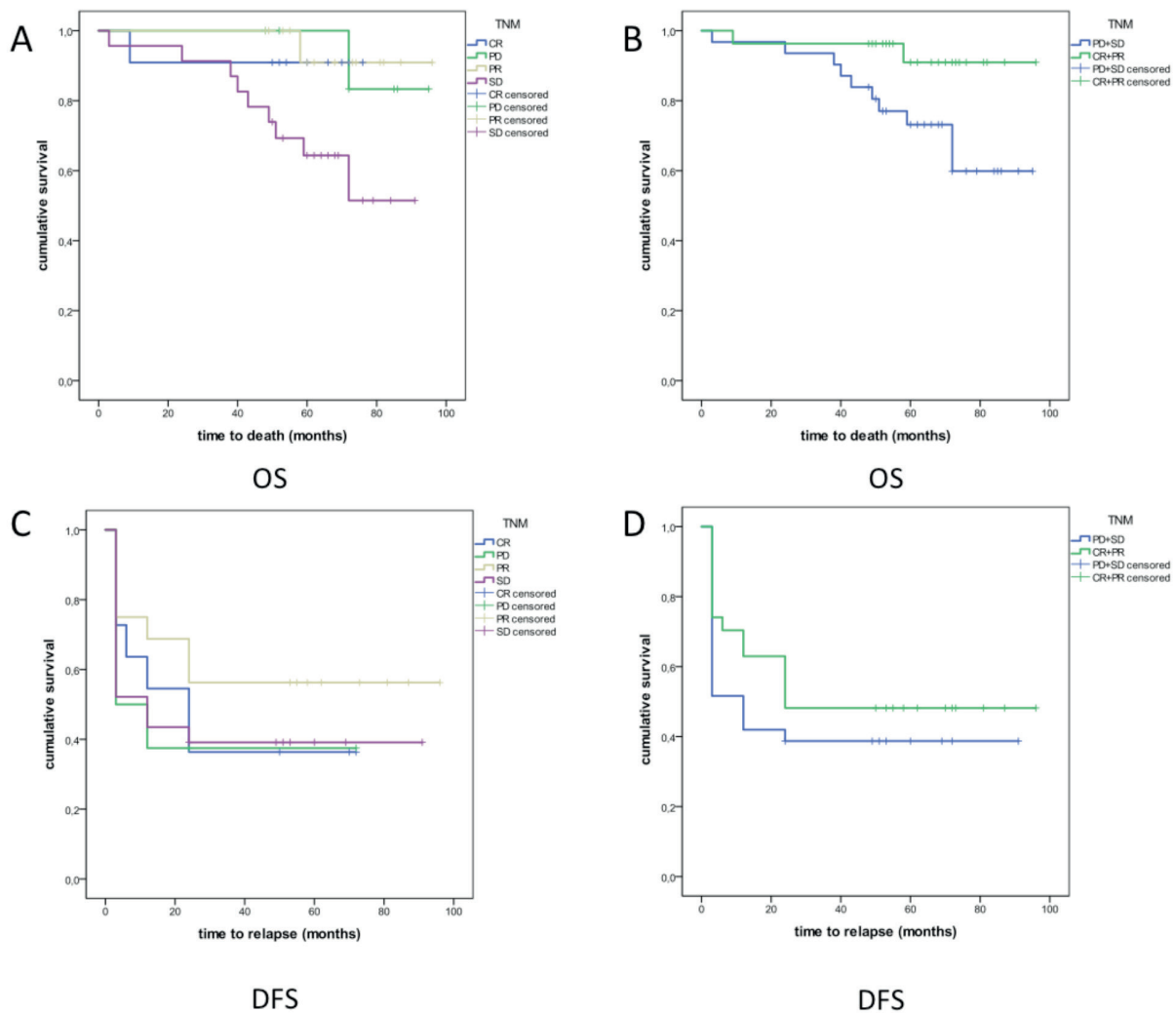
Figure 4. Survival curves for (y)pTNM evaluation. *(A)* OS in CR, PR, SD and PD; *(B)* OS in "(y)pTNM responders" and "(y)pTNM non-responders"; *(C)* DFS in CR, PR, SD and PD; *(D)* DFS in "(y)pTNM responders" and "(y)pTNM non-responders".

tients in "VRA responders"; this choice is related to the possibility of fibrotic tissue keeping weak ^{18}F-FDG uptake for long time. The small number of our sample is a limit of the study, but the extended patient follow-up (median 91 months) is a feature rarely found in other reports and strength of our study.

Conclusions

We highlight the potential role of ^{18}F-FDG in assisting physicians on personalized decision. The predictive and prognostic value of ^{18}F-FDG PET/CT may be pivotal in the selective risk-adapted treatment strategy and to schedule the correct follow-up approach.

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