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Surveillance of clinically complete responders using serial ^{18}F-FDG PET/CT scans in patients with esophageal cancer after neoadjuvant chemoradiotherapy

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ABSTRACT

Active surveillance for patients with esophageal cancer with a clinically complete response (cCR) after neoadjuvant chemoradiotherapy (nCRT) is being studied. Active surveillance requires accurate clinical response evaluations (CREs). ^{18}F-FDG PET/CT might be able to detect local tumor recurrence after nCRT as soon as the esophagus recovers from radiation-induced esophagitis. The aims of this study were to assess the value of serial ^{18}F-FDG PET/CT to detect local recurrence in patients beyond 3 months after nCRT and to determine when radiation-induced esophagitis has resolved.

Methods This retrospective multicenter study selected patients with a cCR after nCRT, who initially declined surgery and subsequently underwent active surveillance. CREs included ^{18}F-FDG PET/CT, endoscopic biopsies and endoscopic ultrasound with fine-needle aspiration at regular intervals. Maximum standardized uptake values normalized for lean body mass (SUL_{max}) were measured at the primary tumor site. The percentage change in SUL_{max} ($\Delta\%SUL_{max}$) between the last follow-up scan and the scan 3 months post-nCRT was calculated. Tumor recurrence was defined as biopsy-proven vital tumor at the initial tumor site.

Results Of forty-one eligible patients, 24 patients had recurrent disease at a median of 6.5 months post-nCRT and 17 patients remained cancer-free during a median follow-up of 24 months post-nCRT. Five of 24 patients with tumor recurrence had sudden intense SUL_{max}-increases of >180%. In 19 of 24 patients with tumor recurrence, SUL_{max} gradually increased (median $\Delta\%SUL_{max}$ +18%), whereas SUL_{max} decreased (median $\Delta\%SUL_{max}$ -12%) in patients with ongoing cCR ($P < 0.001$, independent-samples *t* test). In patients with ongoing cCR, SUL_{max} was lowest at 11 months post-nCRT.

Conclusion Serial ^{18}F-FDG PET/CT might be a useful tool to detect tumor recurrence during active surveillance. In patients with ongoing cCR, lowest-SUL_{max} is reached at 11 months post-nCRT, suggesting that radiation-induced esophagitis has mostly resolved by that time. These findings warrant further evaluation in a larger cohort.

Keywords: Esophageal neoplasms; neoadjuvant therapy; watchful waiting; positron-emission tomography; local neoplasm recurrence

INTRODUCTION

Neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy is emerging as a standard treatment for locally advanced esophageal cancer. This approach is largely based on results of the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study, that showed improved survival with multimodality treatment compared to surgery alone (*1, 2*). In this trial, the surgical resection specimen of 29% of patients treated with nCRT showed no evidence of residual tumor (*1*). These patients may not have benefitted from surgery, since surgery is tied to an increased risk of mortality, postoperative morbidity and decreased quality of life (*1, 3, 4*). For this reason, the feasibility and efficacy of active surveillance for patients with a clinically complete response (cCR) to nCRT are being investigated (*5*). Active surveillance implies that surgery is offered only when locoregional tumor is detected in absence of distant metastases. Clinical response evaluations (CREs) are needed to select patients who can safely undergo active surveillance and to monitor disease recurrence. The optimal set of diagnostics has been investigated previously and comprises endoscopy with bite-on-bite biopsies, endoscopic ultrasound with fine-needle aspiration of suspected lymph nodes and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) (*6*).

Detection of local residual tumor by qualitative and quantitative assessment of a single ^{18}F-FDG PET/CT at 3 months after nCRT alone is inaccurate, because of persistent ^{18}F-FDG uptake probably due to post-radiation esophagitis (*7*). Thus, after nCRT, ^{18}F-FDG PET/CT is primarily being performed to detect regional lymph node metastases and hematogenous metastases (*6*). In the context of an active surveillance strategy, however, the efficacy of ^{18}F-FDG PET/CT for the detection of local tumor recurrence is unclear.

We hypothesize that the inflammatory response in the esophagus will diminish beyond 3 months after nCRT as the esophagus continues to recover from radiotherapy (*7*). Accordingly, increasing ^{18}F-FDG uptake over time could well be a sensitive parameter to detect local residual tumor regrowth during active surveillance. The standardized uptake value corrected for lean body mass (SUL_{max}), a quantification of ^{18}F-FDG uptake, could possibly

serve as an imaging biomarker to monitor disease recurrence from the lowest value observed, which is defined as the so-called “nadir” (*8*).

The primary aim of this retrospective study was to assess the value of serial ^{18}F-FDG PET/CT scans to identify local tumor recurrence in patients undergoing active surveillance beyond 3 months after nCRT. The secondary aim was to determine a lowest value of SUL_{max} (nadir-SUL_{max}) during follow-up of patients with ongoing cCR, to determine the time point at which radiation-induced esophagitis has mostly resolved.

MATERIALS AND METHODS

Study design

The present study is a retrospective observational cohort study using data obtained from the prospective diagnostic pre- *S*urgery *A*s *N*eeded in *O*esophageal cancer (preSANO) trial (www.trialregister.nl: NTR4834), a local prospectively maintained database and the surgery arm of the ongoing therapeutic SANO trial (NTR6803) (*5, 6, 9*). The multicenter preSANO trial assessed the accuracy of a set of diagnostic modalities to detect substantial residual tumor (>10% residual tumor). The multicenter SANO trial has been initiated to assess the effectiveness and cost-effectiveness of active surveillance compared to immediate surgery. All patients included in the present study underwent nCRT with the intention to undergo immediate surgery after nCRT. The data in the present study have been obtained from three Dutch hospitals: the Erasmus University Medical Center, the Zuyderland Medical Center and the Catharina Hospital Eindhoven. The trials have been approved by the medical–ethical committee of the Erasmus University Medical Center (MEC-2013-211 and MEC-2017-392). All patients provided informed consent.

Patients

Patients had been diagnosed with potentially curable esophageal cancer and received neoadjuvant treatment consisting of five weekly cycles of carboplatin (AUC 2 mg/mL/min) and paclitaxel (50 mg/m^2) on day 1 in combination with a total radiotherapy dose of 41.4 Gy delivered in 23 daily fractions of 1.8 Gy, 5 days per week. At 1.5 month after nCRT, the first clinical response evaluation (CRE-1) was performed with endoscopy and biopsies of the primary tumor site. If no histological evidence of vital tumor was detected, a second CRE (CRE-2) took place at 3 months after nCRT. To exclude disseminated disease prior to the scheduled surgery, at CRE-2 also an ^{18}F-FDG PET/CT scan was performed. Moreover, patients underwent endoscopy with biopsies and endoscopic ultrasound with fine-needle aspiration of suspected lymph nodes.

Patients were eligible for this study if they had a cCR without signs of distant metastases at CRE-2, but had declined surgery for various reasons or had become unfit for surgery due to a deteriorating physical condition. cCR at CRE-2 was defined as absence of residual tumor on biopsies and negative fine-needle aspiration of suspected lymph nodes. Instead of surgery, patients were offered an active surveillance protocol with frequent CREs similar to the active surveillance arm of the SANO trial (*5*). After CRE-2, the following CREs (*i.e.* CRE-3, CRE-4, and so on) were scheduled every 3 months in the first year, every 4 months in the second year, every 6 months in the third year, and yearly thereafter, up to a five-year follow-up period in total (Fig. 1). If during active surveillance regrowth of tumor was histologically proven or highly suspected (*e.g.* because of non-traversable tumor at endoscopy), patients were referred to either immediate surgery or palliative care (Fig. 1). Patients with ^{18}F-FDG non-avid tumors before start of nCRT were excluded from analysis.

Definition of tumor recurrence

Local tumor recurrence was defined as histologically proven vital tumor located at the initial tumor site. This definition ignores the locoregional lymph node status, since this study relates changes in ^{18}F-FDG uptake in the esophagus – at the primary tumor site – to corresponding histopathology. Histopathological assessment was performed on tissue from biopsies or on the resection specimen. Assessment of the primary tumor in the resection specimen was by means of the modified tumor regression grade (TRG) system according to Chirieac et al.: TRG1 (0% residual carcinoma), TRG2 (1-10% residual carcinoma), TRG3 (11-50% residual carcinoma) and TRG4 (>50% residual carcinoma) (*10*). Ongoing cCR was defined as no histological evidence of recurrence of tumor at the initial tumor site at the time of analysis.

^{18}F-FDG PET/CT acquisition and processing

^{18}F-FDG PET/CT scans were acquired in three different centers that applied the scanning protocol similar to the SANO trial (*5*). In brief, scanning was performed according to European Association Research Limited (EARL)

qualifications for qualitative standardized uptake value (SUV) measurements (*11*). Start of ^{18}F-FDG PET/CT acquisition was 60 ± 5 minutes after injection of 2.3 MBq/kg ^{18}F-FDG. All follow-up scans were performed on the same scanners under the same conditions.

^{18}F-FDG PET/CT analysis

On every follow-up ^{18}F-FDG PET/CT scan, regions of interest were manually drawn over the primary tumor site determined from the baseline ^{18}F-FDG PET/CT scan (OsiriX MD v.7.5, Pixmeo SARL, Bernex, Switzerland). The placement of regions of interest was independently reviewed by an experienced nuclear medicine physician (R.V.). If this investigator disagreed with the placement of the region of interest of the first investigator, a consensus was established between the two investigators. Regions of interest were also placed at the normal esophagus, blood pool and liver to obtain internal reference measurements. At the regions of interest, standardized uptake values corrected for lean body mass (SUL) were measured. Lean body mass was calculated according to the James equation (*11*).

The percentage change in maximum SUL during active surveillance ($\Delta\%SUL_{max}$) was calculated with the SUL_{max} values of the scan at 3 months after nCRT and the last follow-up scan in active surveillance. In patients who developed local tumor recurrence, the last follow-up scan corresponded to the moment that local recurrence was histologically proven. In patients with ongoing cCR, the last follow-up scan corresponded to the most recent scan performed during active surveillance at the moment of analysis. If active surveillance had been stopped in patients with ongoing cCR at the primary tumor site because of distant or lymph node metastases, the last follow-up scan corresponded to the moment of the last histopathological evaluation of the initial tumor with biopsies.

In patients with ongoing cCR, the nadir-SUL_{max} was determined (*8*). Nadir-SUL_{max} was defined as the lowest SUL_{max} measurement obtained during follow-up. This nadir-SUL_{max} served to determine the moment when ^{18}F-FDG uptake caused by radiation-induced esophagitis is supposed to have normalized.

Statistical analysis

Continuous data are presented with a median value and interquartile range (IQR). Values of ΔSUL_{max} were analyzed between groups using the parametric independent-samples *t* test for normally distributed data or the non-parametric Mann-Whitney U test for non-normally distributed data. Extreme outliers of $\Delta\%SUL_{max}$ were identified by data visualization with boxplots and are described separately. The extreme outliers were removed from the statistical tests for comparison of means and medians, because we expect that these outliers distort the assessment of clinically relevant subtle differences in ΔSUL_{max} between patients with and without local tumor recurrence. To indicate precision of results, 95% confidence intervals (95% CI) were used. A two-sided *P*-value of < 0.05 was considered statistically significant. Since this is an explorative study, sample size calculation was not performed. Statistical analysis was performed using R-3.6.1 for MacOS (R: A language for statistical computing version; Vienna, Austria).

RESULTS

Study group

Between March 2013 and July 2019, 43 patients with FDG-avid tumors who had cCR at CRE-2, declined planned surgery and underwent active surveillance off-protocol were identified from the prospective database of 278 patients (15%) who underwent nCRT with the intention to undergo immediate surgery thereafter. Baseline characteristics are shown in Table 1. The ^{18}F-FDG PET/CT scan at CRE-2 was performed at a median of 11.6 weeks (IQR 10.4 – 12.3) after completion of nCRT.

The flowchart of the study is shown in Fig. 2. Two of the 43 patients had clinically manifest distant metastases at 3 months after nCRT and did not undergo further analysis of the primary tumor with endoscopy and biopsies. Since the histological status of the primary tumor was therefore unknown, these patients were excluded from further analysis. Thus, data of 41 patients were eligible for analysis of serial ^{18}F-FDG PET/CT scans during active surveillance.

At a median follow-up of 6.5 months after completion of nCRT (IQR 5.9 – 11), the primary tumor had recurred in 24 of 41 (59%) patients. In most cases of local tumor recurrence, this was at CRE-3 (15/24, 63%). Esophagectomy was performed in 21 of 24 patients; 20 of them had biopsy-proven local tumor recurrence and one patient had non-traversable tumor at endoscopy with TRG4 in the resection specimen. Three of 24 patients did not undergo esophagectomy for the following reasons respectively: unfit for surgery; definitely declined surgery; unresectable tumor (Fig. 2).

During a median follow-up of 24 months after nCRT (IQR 12 – 25), no biopsy-proven recurrence of the primary tumor was found in 17 of 41 (41%) patients (*i.e.* ongoing cCR). Ten of these 17 patients were in active surveillance at time of analysis. Active surveillance had been ended for 7 of 17 patients with cCR at time of analysis: one patient underwent esophagectomy because of a solitary lymph node recurrence without biopsy-proven tumor at the primary tumor site (ypT0N3, TRG1); two patients definitely declined surgery after CRE-3; one patient was

conditionally inoperable at CRE-3; one patient died due to cardiovascular disease; and two patients had distant metastases after CRE-3 and CRE-4 respectively (Fig. 2).

For all patients with either local tumor recurrence or ongoing cCR, the individual courses of SUL_{max} at the primary tumor site and the SUL values at the reference regions are shown in Supplemental Tables 1 and 2.

SUL_{max} in patients with local tumor recurrence

Two different patterns of ^{18}F-FDG uptake were observed indicative of local recurrence. Five of 24 patients had sudden intense increases in SUL_{max}, all >180% (*i.e.* extreme outliers). In these patients, median $\Delta\%SUL_{max}$ was +283% (IQR 262 – 316) and absolute ΔSUL_{max} was +6.1 (IQR 5.6 – 8.3). These increases took place at the following time-moments after nCRT: between 3 and 6 months (n=2); between 6 and 9 months (n=1); between 12 and 16 months (n=1); and between 24 and 30 months, after a first increase between 20 and 24 months (n=1, Fig.3).

In the remaining 19 of 24 patients with local tumor recurrence, a gradual increase of median $\Delta\%SUL_{max}$ of +18% (IQR 14 – 43) was seen. By contrast, median $\Delta\%SUL_{max}$ was -12% (IQR -36 – 1.4) in the 17 patients with ongoing cCR. The mean difference of $\Delta\%SUL_{max}$ between these groups was statistically significant ($P < 0.001$, 95% CI 21 – 58%, independent-samples *t* test) (Fig. 4). In patients with local tumor recurrence, the median absolute ΔSUL_{max} was +0.69 (IQR 0.35 – 1.0); in patients with ongoing cCR this was -0.28 (IQR -1.1 – 0.30; $P < 0.001$, 95% CI 0.65 – 1.69, Mann-Whitney U test) (Fig. 4).

Patients' tumor characteristics, separated for the different ^{18}F-FDG uptake patterns, are shown in Supplemental Table 3.

SUL_{max} in patients with ongoing cCR

In patients with ongoing cCR, the nadir-SUL_{max} was found at a median time of 11 months (IQR 5.9 – 18) after nCRT. The median value of nadir-SUL_{max} was 1.80 (IQR 1.4 – 2.1). At CRE-2, median SUL_{max} was 2.6 (IQR 2.1 – 3.2), at CRE-3 this was 2.1 (IQR 1.8 – 2.4), at CRE-4 2.2 (IQR 1.7 – 2.4) and at CRE-5 2.2 (IQR 1.8 – 2.5) (Fig. 5).

In Fig. 6, ^{18}F-FDG PET/CT scans are shown of a patient with ongoing cCR of the distal esophagus, illustrating a pattern of SUL_{max} increase at a location different from the location of the primary tumor. Approximately a year after nCRT, linear ^{18}F-FDG uptake develops cranially to the initial tumor site, of unknown cause. At the primary tumor site in the distal esophagus, SUL_{max} remains comparable to the background ^{18}F-FDG-activity level. No histologically proven recurrence of tumor was found during all CREs.

DISCUSSION

This study identified two patterns of SUL_{max} increases ($\Delta\%SUL_{max}$) in patients with local tumor regrowth beyond 3 months after nCRT. Some patients showed a pattern of sudden increase in FDG-metabolism ($\Delta\%SUL_{max}$ >180%), which was indicative of residual disease in all. Most patients with local tumor regrowth, however, had an insidious gradual increase in $\Delta\%SUL_{max}$. In contrast, patients with ongoing cCR had stable or decreasing $\Delta\%SUL_{max}$. These findings suggest that ^{18}F-FDG PET/CT can be used during active surveillance after nCRT, not only to detect distant metastases or to guide endoscopic ultrasound with fine-needle aspiration of suspected lymph nodes, but also to monitor local tumor recurrence. These findings apply to patients with cCR who, like in the present cohort, choose to refrain from surgery after nCRT. This would also become relevant for patients who will undergo active surveillance if that strategy becomes a standard alternative treatment to immediate surgery in patients with cCR (*5, 9, 12-14*). This policy is currently being investigated in the ongoing therapeutic Dutch SANO trial and the French ESOSTRATE trial (*5, 15*).

To our knowledge, this is the first study that describes repeated ^{18}F-FDG PET/CT in an active surveillance setting for esophageal cancer patients with cCR. For rectal carcinoma, serial ^{18}F-FDG PET/CT was used in a watch-and-wait protocol in patients with cCR after nCRT (*16*). In that study, complete responses on ^{18}F-FDG PET/CT corresponded with negative clinical and endoscopic examinations. Moreover, for squamous cell head-and-neck cancer, surveillance with ^{18}F-FDG PET/CT was shown cost-effective to guide the decision to perform surgery after nCRT (*17*).

Response assessment with a single ^{18}F-FDG PET/CT scan at 3 months after completion of nCRT is not accurate, partly because of persisting post-radiation inflammation (*7*). In the present study, ^{18}F-FDG uptake decreased after 3 months post-nCRT and further normalized at 6 months post-nCRT and onwards, supported by a median nadir-SUL_{max} of 1.80 (IQR 1.4 – 2.1) at 11 months (IQR 5.9 – 18) post-nCRT. These findings indicate an ongoing recovery of esophagitis beyond 3 months after nCRT, presumably reaching stability within a year.

Increased ^{18}F-FDG uptake after completion of nCRT, as shown in Fig. 6, should be interpreted carefully with respect to its distribution and location. A linear pattern of ^{18}F-FDG uptake located outside the initial tumor site suggests benign inflammatory conditions such as Candida esophagitis or gastro-esophageal reflux disease, whereas focal ^{18}F-FDG uptake at the initial tumor site suggests recurrent tumor (*18*).

A major strength of the present study is that ^{18}F-FDG PET/CT data were prospectively and systematically obtained. This allowed comparison of serial SUL_{max} measurements with histological biopsies at all CREs. Nevertheless, several limitations need to be addressed. First, the cohort size was too small to define a cut-off value for ΔSUL_{max} that reliably discriminates between a clinically manifest recurrence and ongoing cCR. Hypothetically, a cut-off value for ΔSUL_{max} could be formulated similarly to the definition of biochemical failure in prostate cancer based on prostate-specific antigen. This is defined as a certain increase higher than the nadir prostate-specific antigen value (*8*). Such a cut-off value incorporates the information of the course of SUL_{max} over time, rather than of one moment in time. Second, the nadir-SUL_{max} for defining the moment at which radiation-induced esophagitis has extinguished, may change when a larger number of patients is analyzed than in the present study. Third, regions of interest were manually placed on the initial tumor site. An automatic registration of regions of interest at multiple scans might possibly improve robustness of serial SUL_{max} measurements. Fourth, this cohort of patients might be a highly-selected group, imposing selection bias to the results. This may be reflected by for example the median age of 70 years in this cohort, as opposed to a median of 66 years of patients in the preSANO trial, although the other baseline characteristics are relatively similar (*6*). Fifth, in order to optimize sensitivity in SUL_{max}-changes with serial ^{18}F-FDG PET/CT, adherence to scanning protocols should become even more strict. Fluctuations of SUL_{max} in patients with ongoing cCR (Supplemental Table 2) may partially be attributed to variations in scanning parameters apart from physiologic causes. By performing scanning exactly under the same circumstances every time, the signal-to-noise ratio might be further improved.

Results of the present study have potential implications for clinical decision-making. As shown in Fig. 3, an increase in SUL_{max} at the initial tumor site after a relatively stable signal at more than two years in active surveillance

might be more suspect of residual tumor than of physiological fluctuations or other benign causes such as reflux-esophagitis. If such a deviation takes place without confirmation by biopsy-proven recurrence, shortening the interval to the next CRE should be considered. Alternatively, one could even decide to proceed to surgery without further delay.

Before such clinical implications can be accepted, these results require validation in a larger group of patients randomly allocated to active surveillance, e.g. in the experimental active surveillance arm of the ongoing SANO trial (*5*). Furthermore, new techniques for response assessment should be explored as well. Integrated PET/MRI seems promising, since it could provide additional anatomical and functional value over PET/CT (*19, 20*). Visualization of the esophagus with PET/MRI however is still challenging because of the cardiorespiratory motion in the mediastinum (*21*). Additionally, complex imaging features could be explored by radiomics. Radiomic features are able to describe, for instance, shape characteristics or heterogeneity of the tumor (*22*). Theoretically, change in radiomic features may reveal early tissue changes within an active surveillance setting.

CONCLUSION

Results of this explorative study show that serial ^{18}F-FDG PET/CT might be a useful tool to distinguish recurrence of tumor from physiological SUL_{max} fluctuations in complete responders during active surveillance. A steep increase in FDG-activity over a short period of time should be a warning sign for recurrent local tumor. Furthermore, a gradual increase in FDG-activity over the course of time should also alert to recurrence of tumor. Radiotherapy-induced esophagitis will usually have dissolved at eleven months after completion of chemoradiotherapy.

DISCLOSURE

The preSANO trial was funded by the Dutch Cancer Foundation (project number EMCR-2014-7430). The SANO trial is currently funded by ZonMW (project number 843004104) and the Dutch Cancer Foundation (project number 10825). No other potential conflicts of interest relevant to this article exist.

KEY POINTS

Question: Is serial ^{18}F-FDG PET/CT a valuable tool in monitoring local esophageal cancer recurrence in patients who undergo active surveillance after neoadjuvant chemoradiotherapy (nCRT)?

Pertinent findings: This retrospective cohort study demonstrated increasing SUL_{max} at the primary tumor site compared to start of active surveillance in 24 patients who developed biopsy-proven tumor during active surveillance. Most patients had a gradual increase pattern, while 5 patients had sudden SUL_{max}-increases of >180%. In contrast, SUL_{max} decreased in 17 patients without local tumor recurrence, in whom lowest-SUL_{max} was observed at 11 months after nCRT.

Implications for patient care: These initial results should be confirmed in a prospective manner. Increasing SUL_{max} on ^{18}F-FDG PET/CT during active surveillance should alert to local tumor recurrence, especially when the increase is steep (>180%) or occurs when radiation-esophagitis has mostly dissolved.

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TABLE 1 Baseline patient and tumor characteristics

Variable	**Data *n* (%) (total of 43 patients)**
Male	33 (77)
Age in years (median, interquartile range)	70 (62 – 74)
Histology	
Squamous cell carcinoma	11 (26)
Adenocarcinoma	31 (72)
Adenosquamous carcinoma	1 (2)
cT*	
cT1	0 (0)
cT2	11 (26)
cT3	28 (65)
cT4	1 (2)
cTx	1 (2)
Missing	2 (5)
cN*	
cN0	17 (41)
cN1	11 (26)
cN2	12 (28)
cNx	1 (2)
Missing	2 (5)
Differentiation grade	
Good-moderate	16 (37)
Poor	10 (23)
Missing	17 (40)

*Clinical tumor staging was according to the 7th edition of the International Union against Cancer's TNM classification.

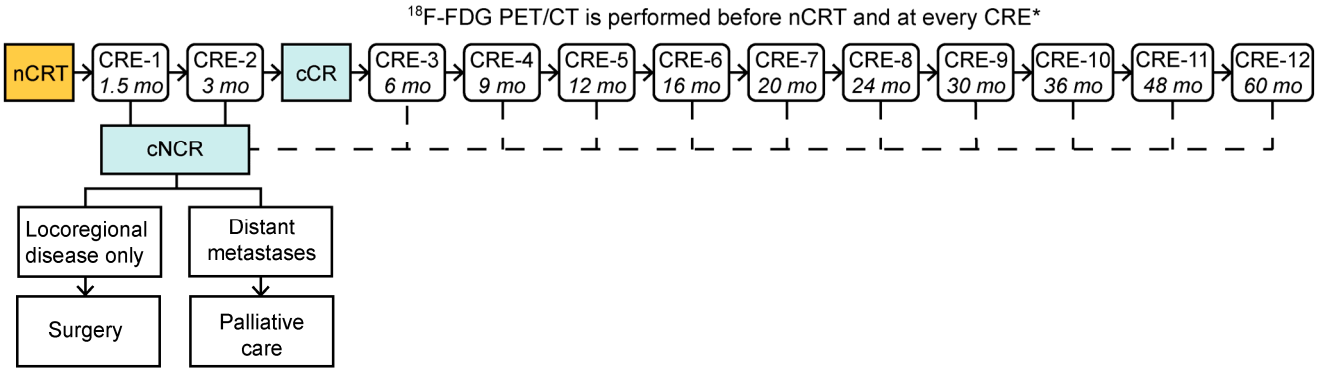


FIGURE 1. Timeline of CREs during active surveillance according to the SANO trial protocol.

*At CRE-1 ^{18}F-FDG PET/CT is performed in case of cNCR to exclude distant metastases.

nCRT = neoadjuvant chemoradiotherapy; CRE = clinical response evaluation; mo = months after nCRT; cCR = clinically complete response; cNCR = clinically non-complete response

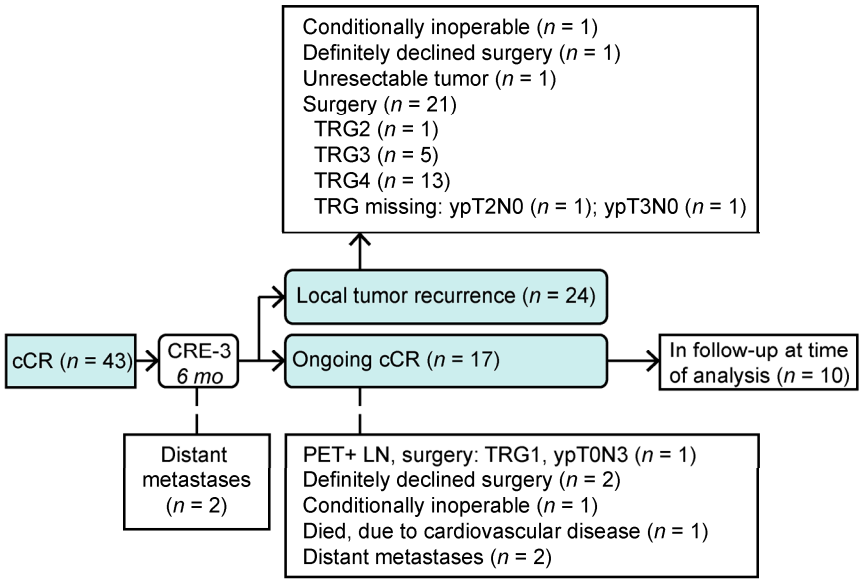


FIGURE 2. Flowchart of study patients with cCR at 3 months after nCRT.

cCR = clinically complete response; CRE = clinical response evaluation; mo = months after neoadjuvant chemoradiotherapy; TRG = tumor regression grade; PET+ LN = positive lymph nodes detected with ^{18}F-FDG PET/CT

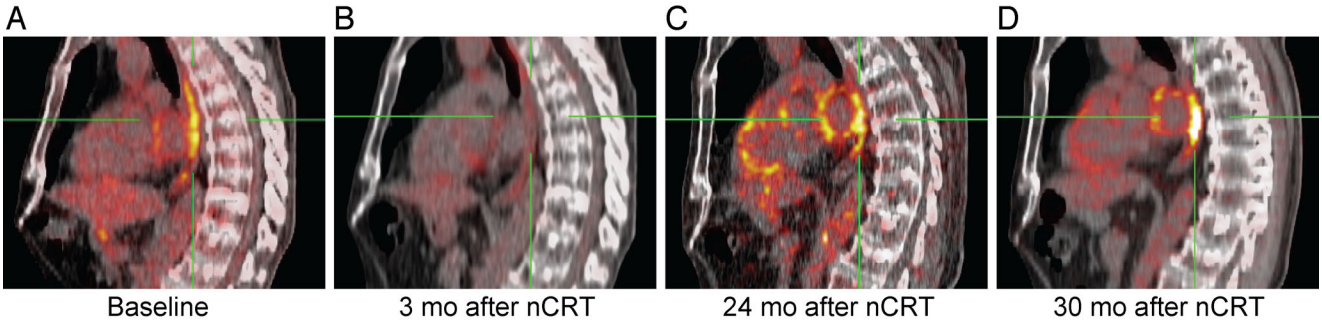


FIGURE 3. Sagittal view of a patient who developed local tumor recurrence during active surveillance. (A) Baseline scan. (B) Normalized ^{18}F-FDG uptake in the esophagus at 3 months after nCRT. (C) From 20 to 24 months after nCRT, SUL_{max} increases with 20% without histological evidence for recurrence of tumor. (D) From 24 to 30 months after nCRT, SUL_{max} increases with 51% and local tumor recurrence is diagnosed with biopsies. Esophagectomy at 30 months after nCRT was performed (TRG3, ypT1bN0).

mo = months; nCRT = neoadjuvant chemoradiotherapy

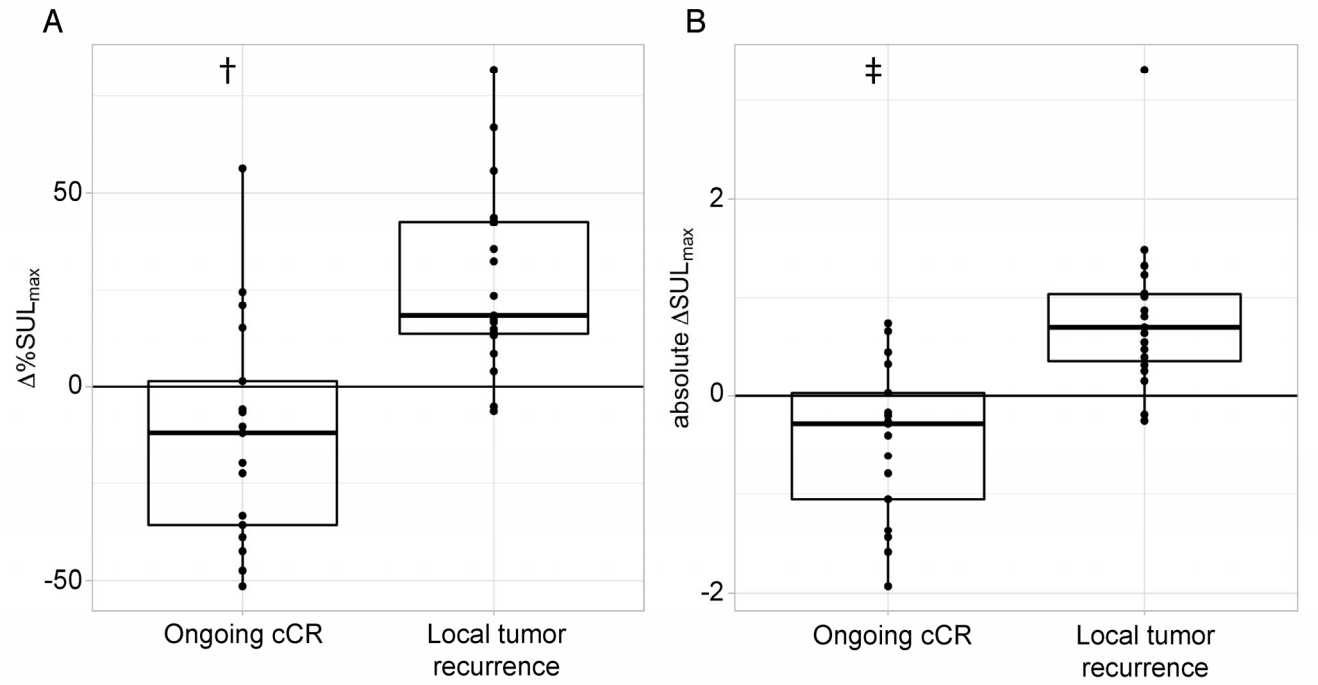


FIGURE 4. Boxplots of (A) $\Delta\%SUL_{max}$ and (B) absolute ΔSUL_{max} of the primary tumor site in patients with ongoing cCR versus patients who developed local tumor recurrence. Five outliers with extreme high $\Delta\%SUL_{max}$-values of >180% are not shown and are described separately in the Results (see Statistical Analysis).

† $P < 0.001$ (independent-samples *t* test).

‡ $P < 0.001$ (Mann Whitney U-test).

cCR = clinically complete response

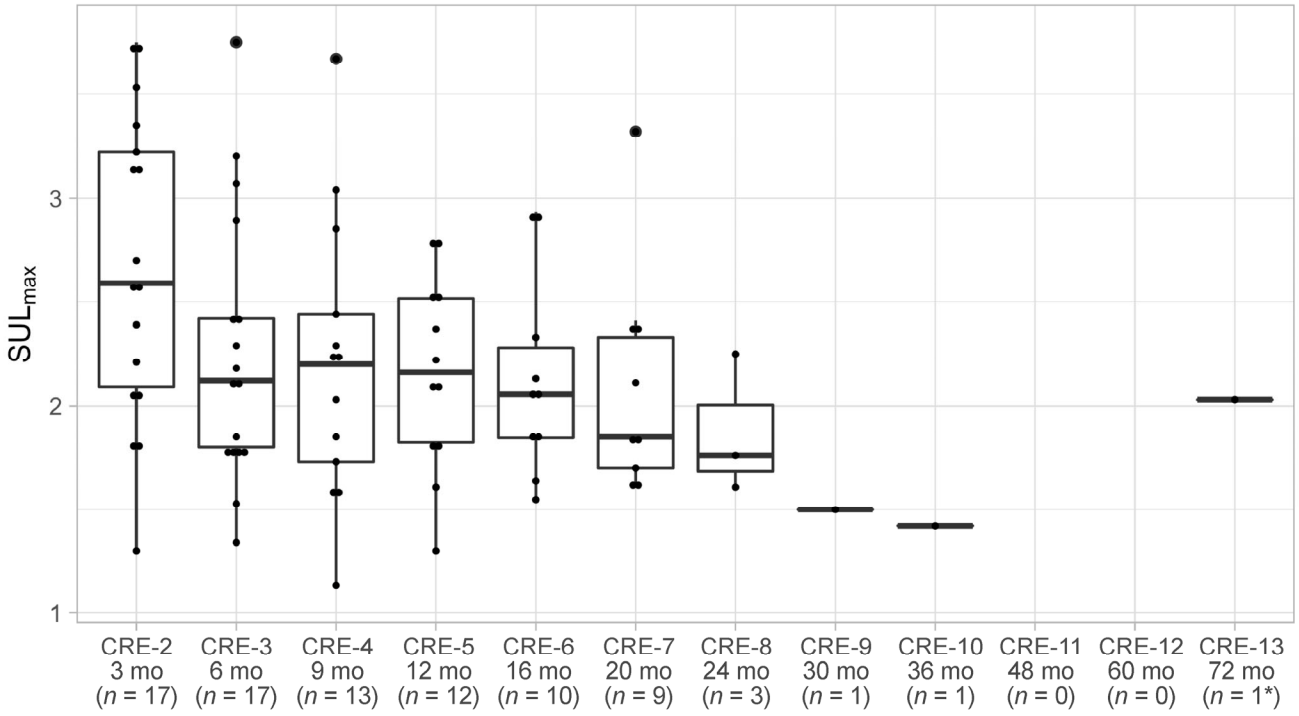


FIGURE 5. Boxplots representing median and interquartile range of SUL_{max} in patients with ongoing cCR.

* This patient had no scans performed between CRE-6 and CRE-13.

CRE = clinical response evaluation; mo = months after nCRT

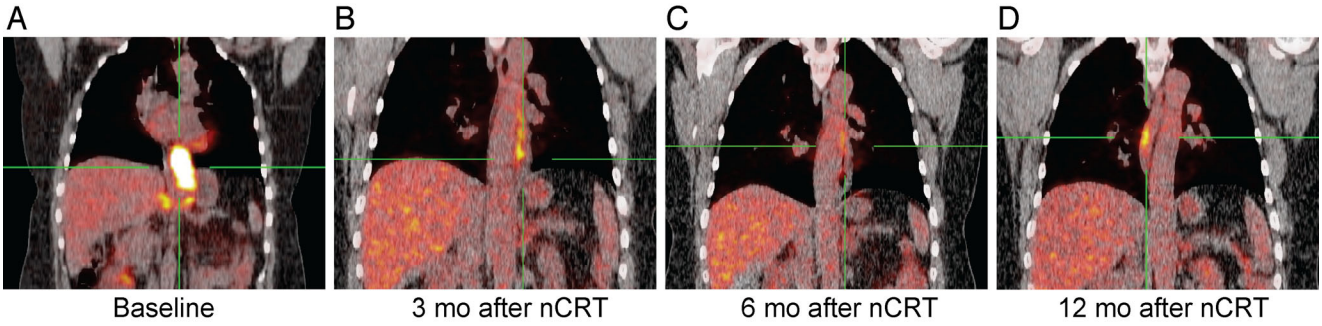
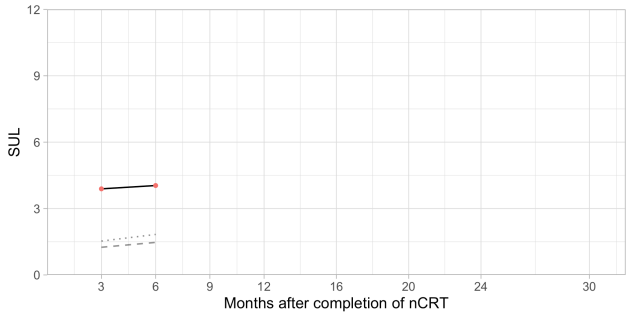
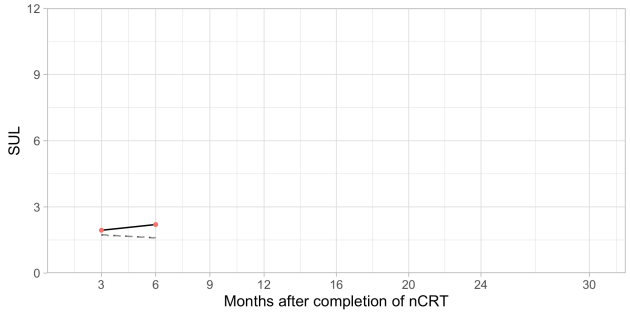
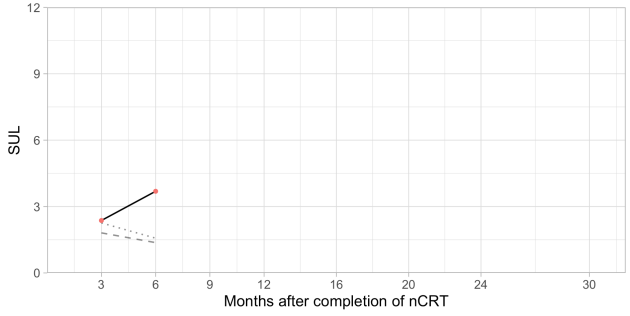


FIGURE 6. Coronal view of a patient with ongoing cCR. (A) Baseline scan. (B, C) Normalization of ^{18}F-FDG uptake in the esophagus until 6 months after nCRT. (D) Development of linear ^{18}F-FDG uptake at 12 months after nCRT cranially to the initial tumor site, of unknown cause. No histologically proven recurrence of tumor was found during all CREs.

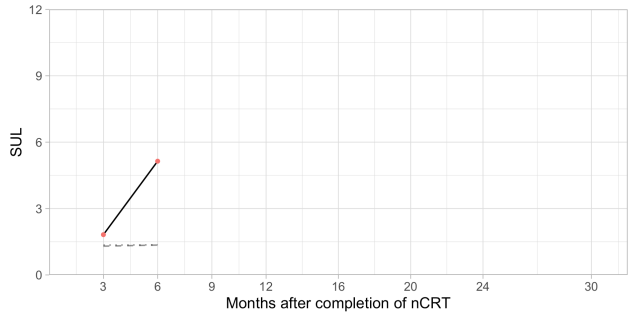
mo = months; nCRT = neoadjuvant chemoradiotherapy,

Supplemental Data

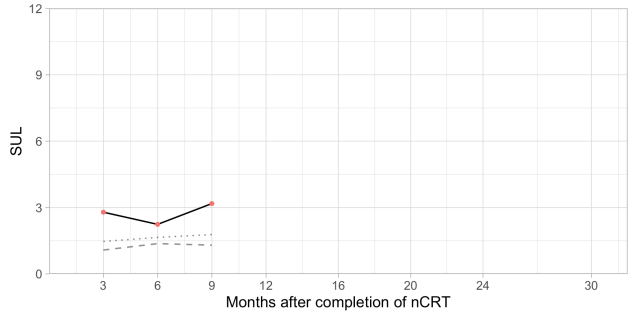
Supplemental Table 1. Patients with histologically proven recurrence of primary tumor at latest response evaluation in active surveillance

Patient	CRE	$SUL_{max, tumor}$	$SUV_{max, tumor}$	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	$SUL_{mean, blood pool}$	$SUL_{mean, liver}$	$SUL_{max, oes}$	Lines in graph: $SUL_{max, tumor}$; $SUL_{mean, blood pool}$; $SUL_{max, oes}$
1	2	3.89	4.94	75	59	5.2	63	1.25	1.86	1.53	
	3	4.04	5.19	77	60	missing	61	1.47	1.93	1.83	
2	2	1.94	2.49	81	63	9.3	57	1.74	2.13	1.72	
	3	2.20	2.83	82	64	9.1	64	1.59	2.13	1.61	
3	2	2.37	2.96	74	59	8.0	59	1.81	2.21	2.26	
	3	3.69	4.52	70	57	7.1	54	1.37	1.67	1.57	

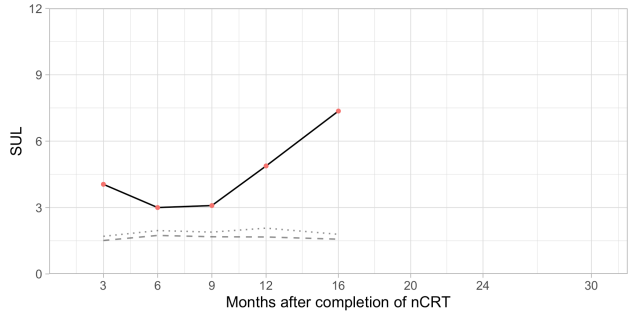
4	2	1.82	2.75	68	45	6.5	67	1.3	2.04	1.35
	3	5.14	7.77	68	45	6.2	50	1.35	1.99	1.36



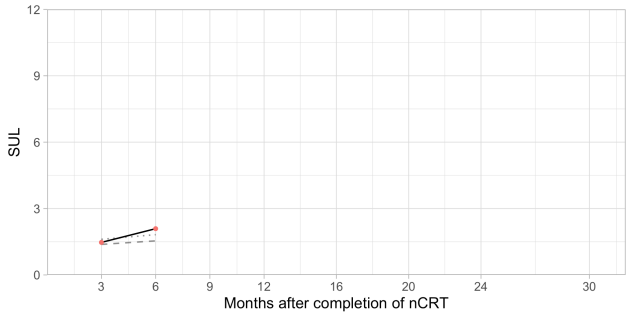
5	2	2.79	3.54	70	55	6.4	72	1.08	1.70	1.47
	3	2.24	2.84	70	55	6.1	58	1.37	1.68	1.65
	4	3.18	4.07	72	56	5.9	61	1.30	1.78	1.78



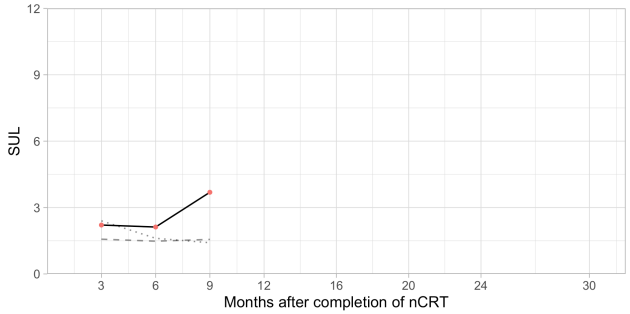
6	2	4.05	5.30	85	65	7.4	59	1.51	1.88	1.70
	3	3.00	3.93	85	65	7.2	55	1.74	2.06	1.96
	4	3.09	4.04	85	65	6.7	55	1.68	2.18	1.89
	5	4.88	6.41	86	65	6.4	58	1.67	2.05	2.07
	6	7.36	9.39	80	63	5.2	62	1.57	2.03	1.79



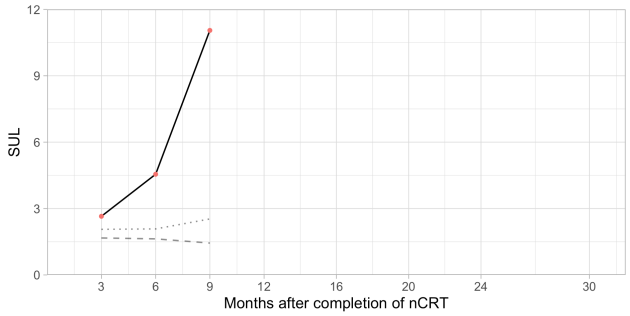
7	2	1.47	1.82	80	64	7.7	59	1.38	1.61	1.61
	3	2.09	2.63	82	65	9.7	56	1.54	1.84	1.82



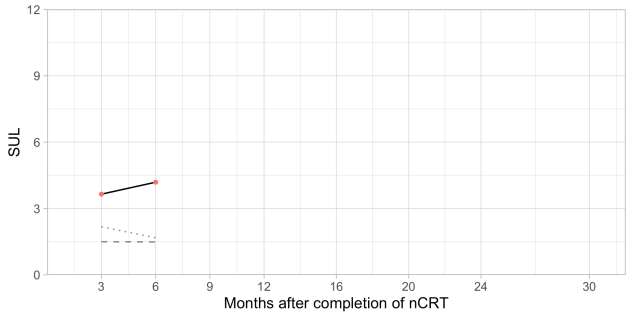
8	2	2.21	3.04	93	68	7.6	44	1.57	2.02	2.40
	3	2.12	2.87	90	67	7.2	59	1.48	1.89	1.61
	4	3.69	5.10	94	68	8.0	51	1.56	2.10	1.41



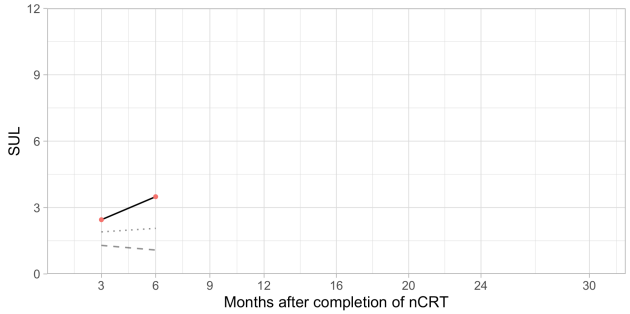
9	2	2.65	3.01	58	51	5.9	50	1.67	2.02	2.06
	3	4.55	5.27	63	54	5.4	50	1.63	2.14	2.08
	4	11.05	12.90	65	56	4.8	59	1.44	1.79	2.53



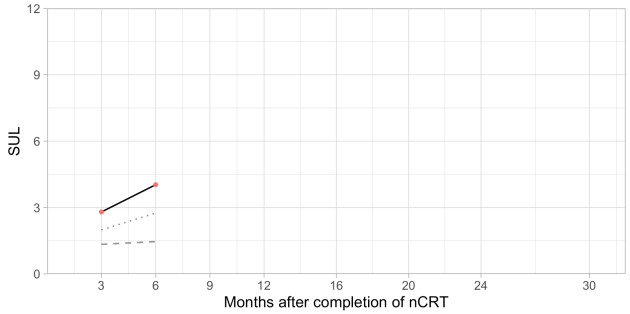
10	2	3.65	5.28	107	74	5.5	60	1.50	2.46	2.18
	3	4.19	6.06	107	74	6.0	58	1.49	2.43	1.68



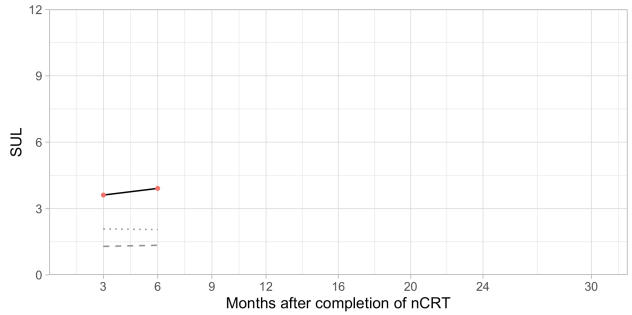
11	2	2.45	3.73	76	50	5.4	55	1.29	1.53	1.90
	3	3.49	5.31	76	50	5.7	66	1.08	1.60	2.06



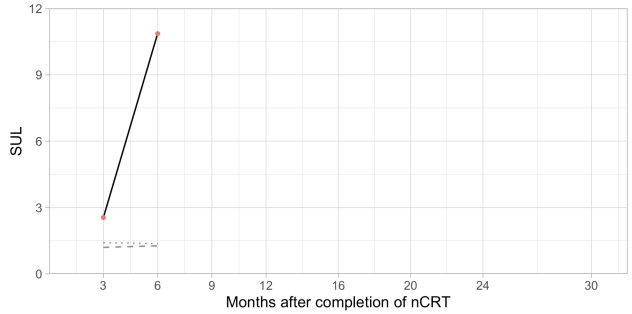
12	2	2.8	3.31	56	47	6.9	61	1.34	1.68	1.99
	3	4.03	4.81	58	49	7.7	60	1.46	1.87	2.75



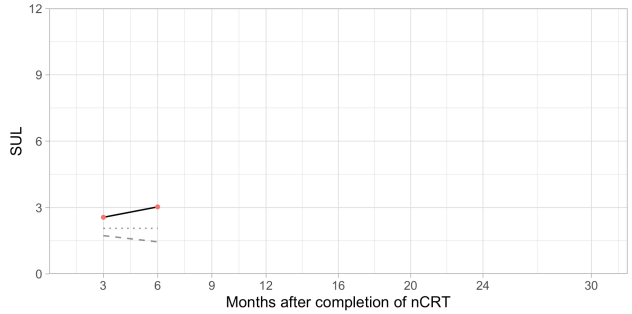
13	2	3.61	4.85	88	66	5.0	40	1.29	1.78	2.08
	3	3.91	5.26	88	66	5.2	60	1.34	1.88	2.05



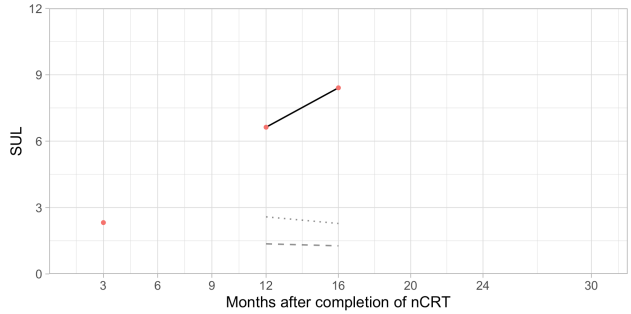
14	2	2.55	3.96	108	69	6.1	61	1.2	1.65	1.41
	3	10.86	17.00	109	70	6.0	55	1.27	1.93	1.37



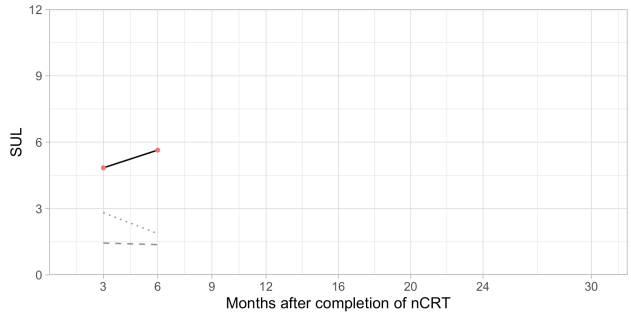
15	2	2.56	3.33	81	62	5.7	55	1.73	2.08	2.06
	3	3.03	3.88	78	61	5.1	54	1.45	1.78	2.06



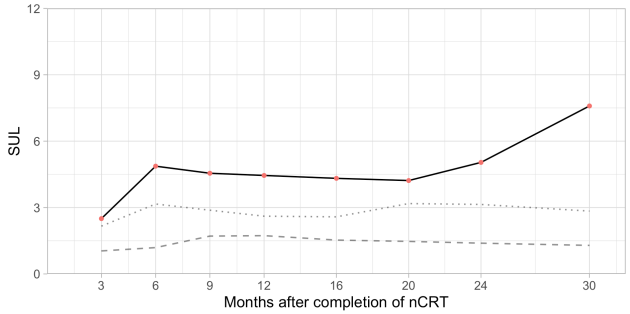
16	2	2.32	2.83	73	60	5.8	62	1.34	1.82	1.65
	No scans performed at CRE-3 or CRE-4									
	5	6.63	8.46	75	59	missing	50	1.36	1.92	2.58
	6	8.41	10.69	74	58	5.8	54	1.27	1.87	2.28



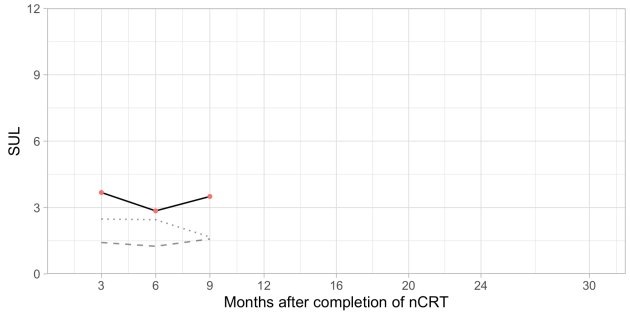
17	2	4.84	6.88	112	79	8.4	53	1.44	2.13	2.81
	3	5.64	8.33	112	76	8.0	52	1.37	2.00	1.87



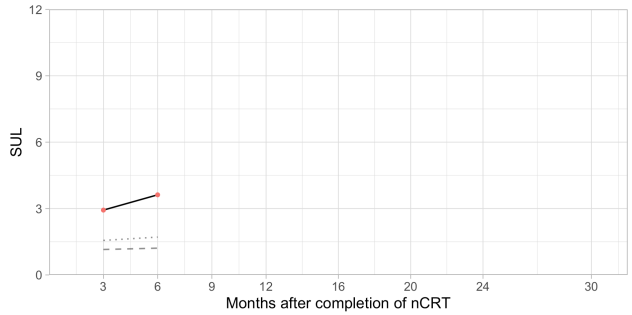
18	2	1.98	2.48	76	61	4.3	69	1.05	1.34	1.74
	3	4.87	6.09	76	61	5.7	67	1.19	1.74	3.16
	4	4.55	5.80	80	63	5.1	51	1.71	1.96	2.88
	5	4.45	5.57	76	61	5.3	51	1.73	2.04	2.61
	6	4.32	5.40	76	61	5.0	53	1.53	1.85	2.58
	7	4.22	5.33	78	62	6.2	55	1.47	1.86	3.18
	8	5.04	6.37	78	62	5.3	59	1.39	1.85	3.14
	9	7.59	9.49	76	61	missing	57	1.29	1.71	2.84



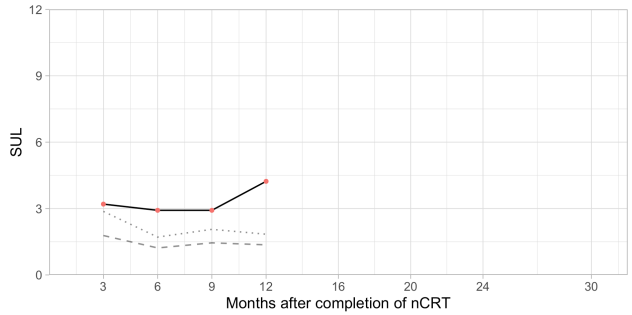
19	2	3.68	5.52	67	45	5.6	50	1.42	1.90	2.48
	3	2.85	4.23	66	44	6.3	59	1.25	1.82	2.45
	4	3.50	5.11	65	45	4.9	60	1.58	1.98	1.67



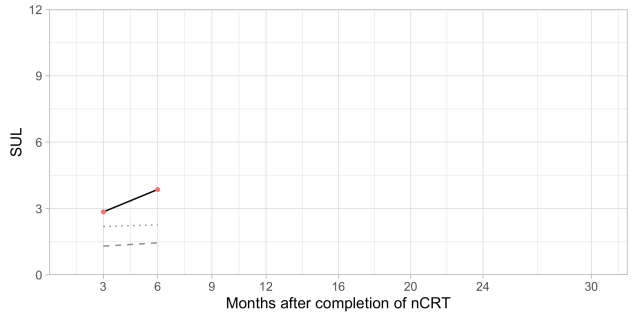
20	2	2.93	3.66	79	63	4.9	65	1.15	1.53	1.56
	3	3.62	4.60	83	65	5.1	65	1.21	1.57	1.71



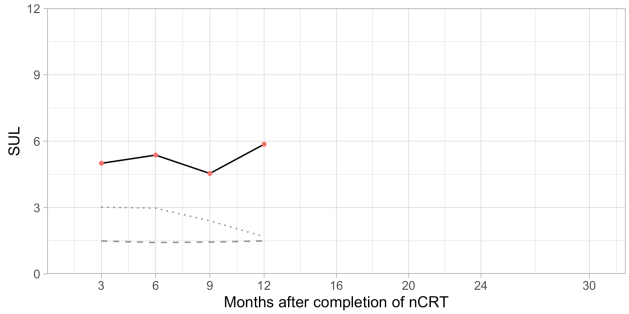
21	2	3.20	3.98	62	50	5.4	52	1.78	2.11	2.87
	3	2.92	3.73	65	51	5.2	63	1.22	1.56	1.71
	4	2.92	3.62	62	50	4.7	55	1.45	2.85	2.06
	5	4.23	5.39	63	49	5.2	56	1.36	1.68	1.84



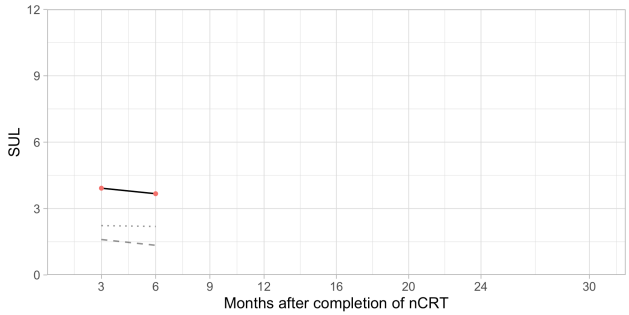
22	2	2.85	3.62	67	53	5.1	60	1.30	1.78	2.19
	3	3.86	4.86	67	53	4.9	56	1.45	1.90	2.26



23	2	5.00	7.44	122	82	6.7	50	1.49	2.01	3.02
	3	5.37	7.98	122	82	7.0	50	1.42	2.17	2.97
	4	4.54	7.32	128	80	8.0	58	1.44	2.00	2.40
	5	5.86	9.55	130	80	8.8	63	1.49	2.00	1.68



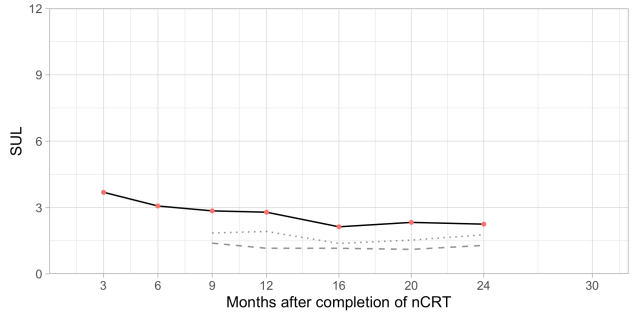
24	2	3.92	4.60	64	55	5.3	50	1.60	1.83	2.23
	3	3.67	4.39	64	53	4.9	50	1.34	1.78	2.19

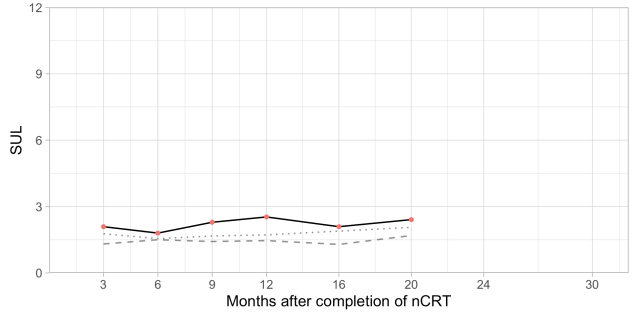


LBM = lean body mass; SUL_{max} = maximum standardized uptake value corrected for lean body mass; $SUL_{max, oes}$ = SUL_{max} in the physiological esophagus; nCRT = neoadjuvant chemoradiotherapy.

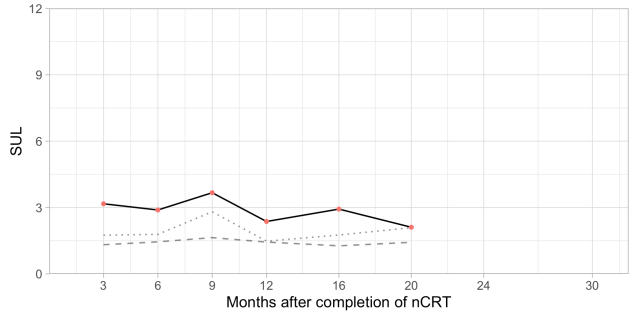
Supplemental Table 2. Patients with ongoing clinically complete response of primary tumor during active surveillance

Patient	CRE	$SUL_{max, tumor}$	$SUV_{max, tumor}$	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	$SUL_{mean, blood pool}$	$SUL_{mean, liver}$	$SUL_{max, oes}$	Lines in graph: $SUL_{max, tumor}$; $SUL_{mean, blood pool}$; $SUL_{max, oes}$
25	2	3.69	5.45	90	61	6.4	51	1.15	1.53	1.89	
	3	3.07	4.60	92	61	6.0	67	missing	missing	missing	
	4	2.85	4.11	97	67	5.8	62	1.39	1.62	1.85	
	5	2.79	4.46	101	63	6.6	59	1.16	1.59	1.92	
	6	2.13	3.40	101	63	5.8	62	1.16	1.60	1.38	
	7	2.33	3.84	105	64	5.7	63	1.11	1.43	1.53	
	8	2.25	3.71	105	64	6.4	68	1.29	1.41	1.77	
26	2	2.09	3.05	98	67	4.9	59	1.31	1.80	1.77	
	3	1.8	2.61	97	67	5.1	59	1.5	1.77	1.55	
	4	2.29	3.32	97	67	5.1	56	1.42	1.95	1.67	
	5	2.53	3.67	97	67	5.1	61	1.46	1.74	1.72	
	6	2.09	3.03	97	67	4.6	59	1.29	1.72	1.89	
	7	2.41	3.44	95	66	5.2	58	1.69	1.97	2.06	

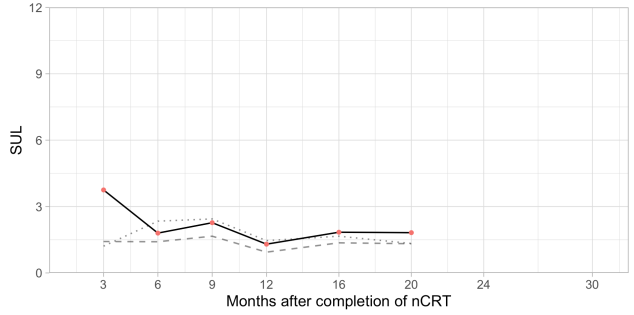




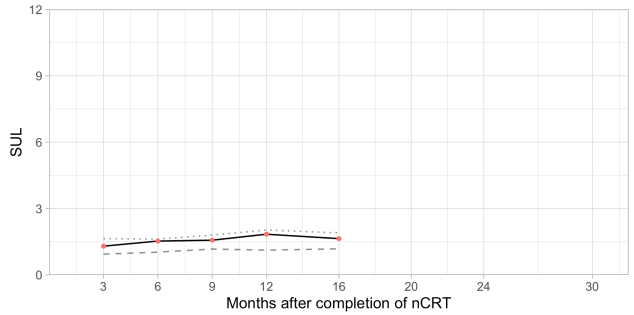
27	2	3.17	4.07	77	60	5.2	57	1.32	1.68	1.75
	3	2.89	3.71	77	60	5.9	64	1.45	1.75	1.79
	4	3.67	4.71	77	60	4.7	56	1.64	1.96	2.81
	5	2.37	3.13	82	62	6.1	61	1.44	1.71	1.48
	6	2.93	3.73	75	59	5.8	68	1.27	1.60	1.76
	7	2.11	2.69	75	59	5.3	59	1.43	1.74	2.09



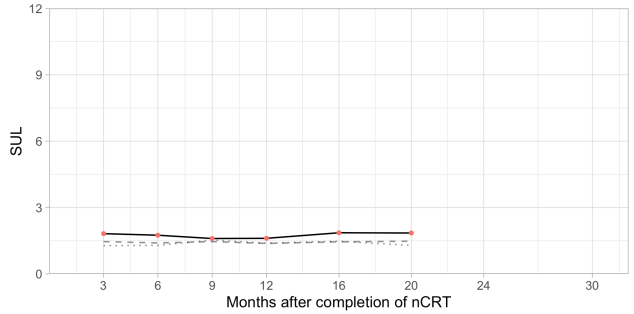
28	2	3.75	4.65	73	59	7.0	66	1.42	1.95	1.21
	3	1.80	2.26	76	61	4.3	73	1.41	2.08	2.34
	4	2.27	2.90	79	62	5.0	59	1.66	2.37	2.44
	5	1.30	1.65	78	62	5.5	63	0.94	1.51	1.46
	6	1.84	2.34	78	62	4.7	64	1.36	1.79	1.66
	7	1.82	2.72	98	66	6.6	63	1.32	1.51	1.33



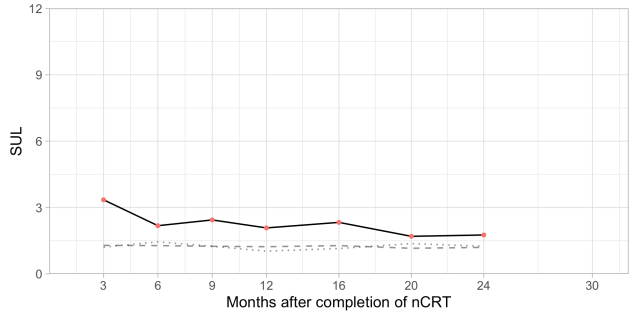
29	2	1.30	1.63	47	38	5.8	63	0.94	1.38	1.64
	3	1.53	1.91	47	38	5.6	56	1.03	1.42	1.62
	4	1.57	1.93	45	37	5.4	66	1.17	1.39	1.80
	5	1.84	2.27	45	37	5.4	65	1.12	1.47	2.03
	6	1.64	2.01	45	37	4.8	61	1.18	1.47	1.90
	no scans performed between CRE-6 and CRE-13									
	13	2.03	2.46	42	35	5.7	65	1.11	1.44	2.31



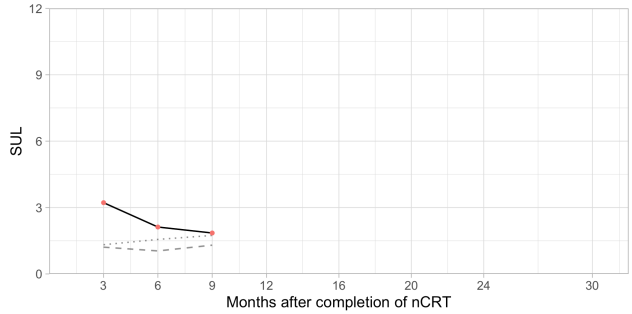
30	2	1.82	2.80	78	51	7.9	60	1.46	1.95	1.28
	3	1.75	2.70	78	51	7.7	58	1.40	2.47	1.29
	4	1.60	2.46	78	51	8.9	58	1.46	1.93	1.53
	5	1.61	2.45	77	51	8.3	58	1.38	1.90	1.39
	6	1.86	2.74	73	49	7.8	61	1.45	2.07	1.48
	7	1.85	2.66	70	49	8.7	56	1.48	2.05	1.29



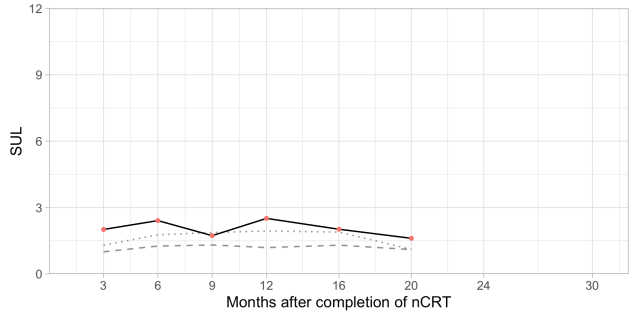
31	2	3.35	4.17	42	34	4.5	62	1.29	1.58	1.21
	3	2.18	2.71	42	34	5.1	59	1.28	1.65	1.45
	4	2.44	2.96	39	32	4.7	58	1.25	1.60	1.25
	5	2.08	2.48	37	31	5.2	60	1.23	1.61	1.03
	6	2.33	2.79	37	31	4.9	59	1.28	1.60	1.15
	7	1.70	2.02	37	31	5.7	63	1.16	1.55	1.37
	8	1.76	2.11	38	32	4.8	63	1.2	1.71	1.25



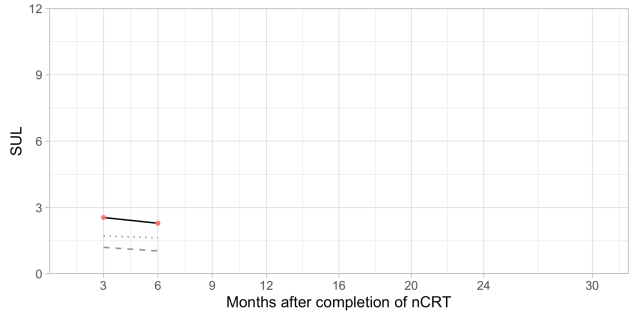
32	2	3.22	4.92	83	54	5.6	60	1.21	1.92	1.32
	3	2.12	3.29	85	55	5.6	56	1.04	1.85	1.56
	4	1.85	2.87	85	55	5.4	58	1.3	1.61	1.74



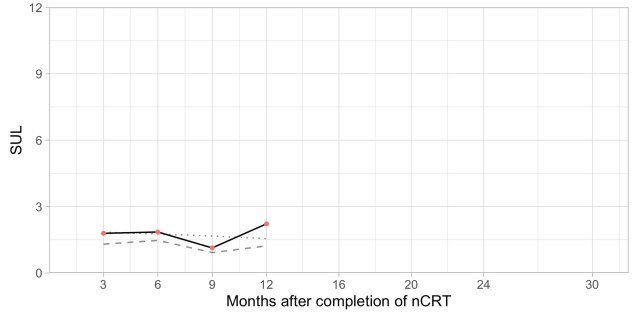
33	2	2.01	2.50	55	44	5.9	60	1.00	1.20	1.30
	3	2.41	3.01	56	45	6.1	62	1.26	1.47	1.77
	4	1.73	2.19	58	46	5.1	55	1.31	1.61	1.87
	5	2.51	3.18	58	46	5.5	60	1.19	1.44	1.94
	6	2.02	2.56	58	46	5.2	58	1.30	1.51	1.89
	7	1.61	1.99	54	44	4.8	58	1.10	1.31	1.11



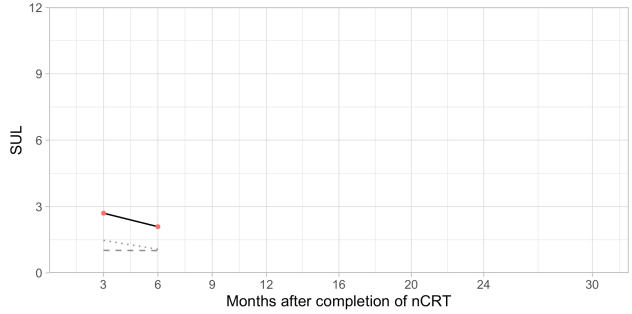
34	2	2.55	3.27	72	56	4.8	55	1.20	1.47	1.72
	3	2.29	2.97	74	57	5.5	64	1.04	1.41	1.63



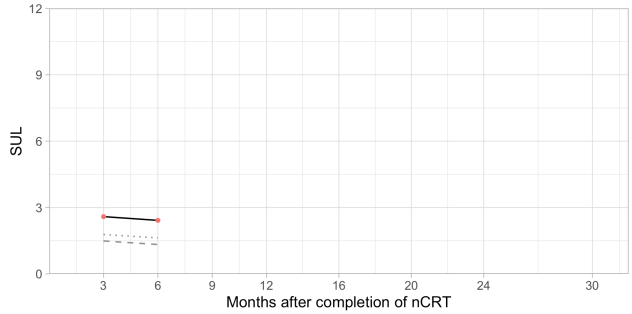
35	2	1.79	2.25	73	58	5.5	60	1.30	1.6	1.84
	3	1.85	2.33	73	58	6.7	56	1.47	1.72	1.76
	4	1.13	1.42	73	58	7.3	68	0.92	1.23	1.67
	5	2.22	2.81	74	59	7.3	65	1.22	1.51	1.55



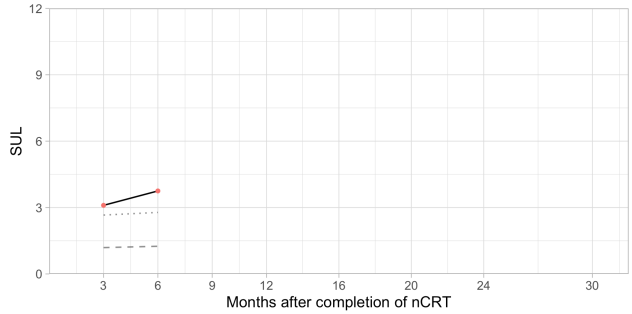
36	2	2.70	4.28	85	54	6.3	60	1.02	1.50	1.47
	3	2.09	3.41	88	54	5.9	60	1.01	1.53	1.07



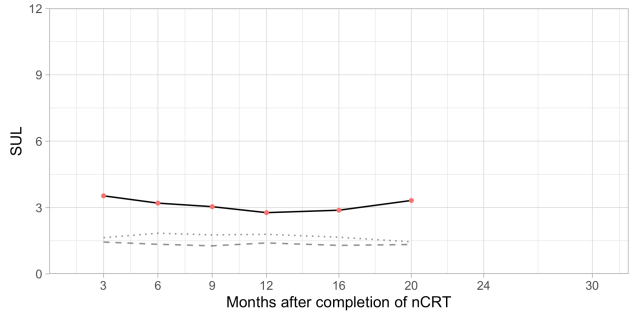
37	2	2.59	3.33	77	60	8.0	61	1.49	1.71	1.78
	3	2.42	3.06	77	61	8.5	65	1.33	1.61	1.63



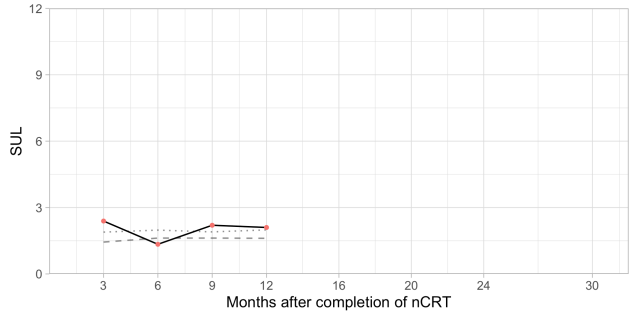
38	2	3.10	5.06	82	50	5.6	64	1.19	1.46	2.66
	3	3.75	5.84	76	49	5.2	76	1.25	1.53	2.78



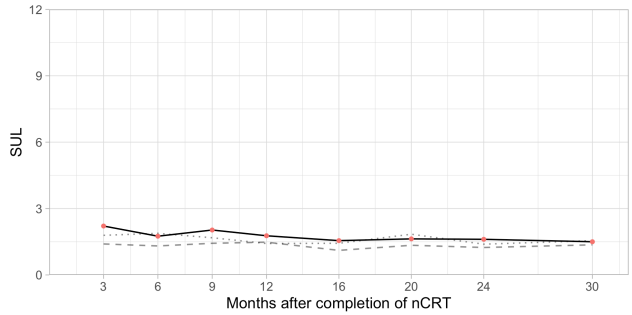
39	2	3.53	4.37	73	59	5.3	55	1.44	2.60	1.64
	3	3.20	4.00	75	60	5.2	58	1.34	1.76	1.84
	4	3.04	3.86	74	58	5.5	64	1.27	1.80	1.76
	5	2.77	3.54	75	59	5.3	58	1.40	1.88	1.79
	6	2.88	3.70	75	58	5.9	56	1.29	1.68	1.66
	7	3.32	4.31	77	59	5.6	59	1.33	1.78	1.45



40	2	2.39	3.43	102	71	6.2	59	1.44	2.31	1.89
	3	1.34	1.87	98	70	6.3	64	1.62	2.15	1.98
	4	2.20	3.11	100	71	5.5	60	1.62	2.03	1.90
	5	2.10	3.07	106	73	6.7	57	1.61	2.05	1.99



41	2	2.21	2.83	89	70	5.2	60	1.40	1.85	1.79
	3	1.75	2.29	94	72	5.7	61	1.31	1.70	1.88
	4	2.03	2.76	95	70	5.2	64	1.43	1.92	1.68
	5	1.77	2.43	97	71	5.7	55	1.48	1.76	1.42
	6	1.55	2.14	98	71	5.4	59	1.11	1.62	1.43
	7	1.63	2.25	98	71	5.2	60	1.34	1.73	1.84
	8	1.61	2.22	98	71	5.6	65	1.24	1.64	1.39
	9	1.50	2.07	98	71	5.0	58	1.36	2.29	1.55
	10	1.42	1.94	96	70	5.6	58	1.36	1.65	1.52



LBM = lean body mass; SUL_{max} = maximum standardized uptake value corrected for lean body mass; $SUL_{max, oes}$ = SUL_{max} in the physiological esophagus; nCRT = neoadjuvant chemoradiotherapy.

Supplemental Table 3. Tumor characteristics of patients who developed local tumor recurrence, shown separately for different patterns of SUL_{max} increases, and of patients with ongoing clinically complete response

	Local tumor recurrence (*n* = 24)			**Ongoing cCR (*n* = 17)**
	Gradual SUL_{max} increase (*n* = 19)	Steep (>180%) SUL_{max} increase (*n* = 5)	Total (*n* = 24)	
Histology				
Squamous cell carcinoma	2	2	4	6
Adenocarcinoma	17	3	20	10
Adenoscquamous carcinoma	0	0	0	1
cT*				
cT1	0	0	0	0
cT2	7	1	8	3
cT3	12	4	16	11
cT4	0	0	0	1
cTx	0	0	0	1
Missing	0	0	0	1
cN*				
cN0	8	2	10	7
cN1	5	0	5	6
cN2	6	3	9	2
cNx	0	0	0	1
Missing	0	0	0	1
Differentiation grade				
Good-moderate	7	3	10	6
Poor	6	0	6	4
Missing	6	2	8	7

Data represent number of patients.

*Clinical tumor staging was according to the 7th edition of the International Union against Cancer's TNM classification.

cCR = clinically complete response