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18F-FDG PET/CT as Predictive of Response after Chemoradiation in Esophageal Cancer Patients

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Abstract

Introduction—The purpose of this study was to evaluate if a baseline, an interim or a post-chemoradiation (CTRT) 18F-FDGPET/CT studies could provide information on pathologic response to CTRT and overall survival (OS).

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Conflict of Interest: None

Materials and Methods—Thirty-one patients with histologically proven adenocarcinoma or squamous cell carcinoma of the esophagus, fit for trimodality therapy were prospectively enrolled. Most were men (93.5%), and had a stage III cancer (74.2%). Chemotherapy consisted of oxaliplatin/5-fluorouracil (45.2%) and taxane/5-fluorouracil (54.8%). All patients underwent a baseline, an interim (performed 12+/-2 days after onset of CTRT) and a post-CTRT 18F-FDGPET/CT study. The 18F-FDGPET/CT variables evaluated were at baseline, interim and post-CTRT studies maximum standardized uptake value (SUVmax) and total lesion glycolysis (TLG). Clinical and 18F-FDGPET/CT parameters were correlated with pathologic complete response (pathCR) and OS.

Results—Among the 31 patients studied, 61.3% achieved a clinical complete response (cCR) and 87.1% had surgery. The median OS was 35.1 months (95% CI: 19.9 – NA). PathCR rate was 22.2%. There was only a marginal association between cCR and pathCR ($p=0.06$). None of the other variables was predictive of pCR. There was association between OS and baseline TLG ($p=0.03$) at the optimal cutoff TLG value of 75.15. Additionally, TLG and TLG post-CTRT were also associated with OS ($p = 0.01$ and 0.03 , respectively).

Conclusion—None of the PET parameters are predictive of pCR but TLG at baseline and post-CTRT are prognostic of OS.

Keywords

Gastroesophageal cancer; 18F-FDG PET/CT; chemoradiation; pathologic response; Early response evaluation

INTRODUCTION

Gastroesophageal cancer is the eighth most common malignancy worldwide.[1, 2] In the United States an estimated 18,170 new cases and 15,450 deaths are expected in 2014[3]. In North America and the western world the incidence of esophageal squamous cell carcinoma (SCC) has been decreasing, however the incidence of adenocarcinoma has been steadily climbing over the past four decades.[4-6]

CTRT followed by surgery (trimodality therapy) is the generally recommended treatment for localized gastroesophageal carcinoma because it improves OS and cure rates. [7-11] Surgery alone leads to a poor prognosis, even though it is a key component of treatment for esophageal cancer (EC).[12] Most patients (with stage II or III disease) are treated empirically and using a similar approach, since clinical parameters (clinical stage, gender, location of the cancer within the thorax, histology, age, or baseline conventional imaging) cannot predict response to CTRT.[13-15] The exception is whole-body metabolic imaging with 18-fluorodeoxy-glucose positron emission computed tomography (18F-FDG PET/CT) because changes in 18F-FDG uptake have been shown to have prognostic value and correspond to therapy response [16-21] However, 18F-FDG PET/CT has not been correlated to pathological response in gastroesophageal cancer patients who have undergone CTRT nor have there been studies showing the optimal timing to perform 18F-FDG PET/CT to predict response.

EC patients when treated with preoperative therapy have divergent and unpredictable outcomes. At least three subgroups can be based on pathologic response outcome as judged in the surgical specimen: (1) (P0) no residual cancer, i.e., pathological complete response (pathCR) (2) (P1) 1% to 50% of residual cancer (some response), and (3) (P2) >50% residual cancer (no response). The median survival and metastatic potential depends on the degree of residual cancer.[13-15, 22, 23]

Berger et al[22] and Rohatgi et al,[14] among many others, have demonstrated that patients with a pathCR live significantly longer than those who have < pathCR. Approximately 25% of patients achieve a pathCR and ~25% have >50% residual cancer.[13] Type of cytotoxics with radiation and dose of radiation prior to surgery do not seem to predict these subgroups. [13, 24-26] Since CTRT and esophageal surgery are associated with considerable morbidity and unpredictable outcome,[27-31] it would be important to develop tools that identify these subgroups either before any therapy or at least before surgery. Availability of such tools might spur new strategies in the clinic.

The purpose of this study was to evaluate if an interim 18F-FDG PET/CT and novel measurements of tumor metabolism could provide more information on pathological complete response and OS in EC.

METHODS

Patient Selection

Patients with histologically proven adenocarcinoma or squamous cell carcinoma of the esophagus, age 18 years old, with clinical II or III stage cancer deemed to be fit for trimodality therapy (TMT) were included in this study (NCT00833625).

Initial staging of all patients consisted of a baseline esophagealgastroduodenoscopy (EGD) with biopsy, endoscopic ultrasonography and a baseline 18F-FDG PET/CT, among other tests. Additionally all patients underwent an interim and a post-CTRT 18F-FDG PET/CT after the start of CTRT.

Patients were excluded if the baseline 18F-FDG PET/CT demonstrated that the primary tumor had a SUVmax below 4.0 or if the patients received induction chemotherapy prior to CTRT. Patients with baseline T1N0 or T4anyN tumors were also excluded.

Statistical Considerations

The primary end point was pathologic response. The secondary end point was OS in 90 prospectively accrued patients. These end points were correlated to the clinical 18F-FDG PET/CT parameters. These parameters were measured in terms of absolute values and changes in these parameters (from the baseline to interim or from baseline to post-CTRT 18F-FDG PET/CT).

18F-FDG PET/CT Image Acquisition and Processing

All patients underwent whole-body 18F-FDG PET/CT studies. These studies were performed at initial staging (baseline 18F-FDG PET/CT), 12+/-2 day from the start of

CTRT (interim 18F-FDG PET/CT) and approximately 12 weeks from the start of CTRT (post-CTRT 18F-FDG PET/CT).

All patients were required to fast for 6 h prior to the injection of 18F-FDG, be well hydrated prior to imaging and instructed to empty their bladder immediately before image acquisition. Blood glucose was below 140 mg/dl in all patients. All patients received a dose of 7.0 MBq/kg (0.2 mCi/kg) of 18F-FDG and rested in a dark, quiet room. Whole-body images from the orbit to the upper thigh were acquired 90 min after the 18F-FDG injection, on an integrated PET/CT scanner (GE Medical Systems, Milwaukee, WI or Siemens Medical Systems, Nashville, TN). Whole-body non-contrast CT scans were used for attenuation correction. Images were reconstructed iteratively and displayed in 2.5 mm slices in the transverse, coronal and sagittal planes.

18F-FDG PET/CT Interpretation and Quantification

All 18F-FDG PET/CT images were subjected to visual and quantitative analyses and performed by two experienced board-certified nuclear medicine physicians with over 20 years of experience.

Quantitative interpretation was performed on all 18F-FDG PET/CT images and consisted of generating volumetric data using a semi-automatic volume of interest (VOI) drawn in the primary tumor of the patient. This VOI was automatically copied to the interim and post-CTRT studies and submitted to manual inspection for excluding from the analyses any uptake not related to the primary tumor, such as esophagitis.

The following 18F-FDG PET/CT parameters of the primary tumor were obtained: SUV_{max}, the TLG (total lesion glycolysis of the tumor), the difference in SUV_{max} (SUV_{max}) and the difference in TLG (TLG) from baseline to interim and the SUV_{max} and TLG from baseline to post-CTRT 18F-FDG PET/CT. Below are the equations to calculate the SUV, TLG, TLG and SUV_{max}.

$$\text{SUV} = \frac{\text{Radioactivity concentration}}{\text{Injected activity of } ^{18}\text{F-FDG/body weight}}$$

$$\text{TLG} = \text{MTV (metabolic tumor volume in ml)} \times \text{SUVmean}$$

$$\text{Interim } \Delta\text{SUVmax} = \frac{\text{Interim TLG} - \text{Baseline TLG}}{\text{Baseline TLG}}$$

$$\text{Interim } \Delta\text{TLG} = \frac{\text{Interim TLG} - \text{Baseline TLG}}{\text{Baseline TLG}}$$

$$\text{Post-CTRT } \Delta\text{TLG} = \frac{\text{Post-CTRT TLG} - \text{Baseline TLG}}{\text{Baseline TLG}}$$

$$\text{Post-CTRT } \Delta\text{TLG} = \frac{\text{Post-CTRT TLG} - \text{Baseline TLG}}{\text{Baseline TLG}}$$

Statistical Analysis

In this prospective study, with a total sample size of 90 patients and assuming that 25% of these patients will achieve pathCR, we will have an 84% power to test the null hypothesis of H_0 : AUC = 0.6 (ie, poor discrimination) against the alternative hypothesis of H_1 : AUC = 0.8 (ie, good discrimination), using the two-sided asymptotic Z-test and at 0.05 significance level. The SAS macro, %ROCPOWER, was used for power computation (Zepp, 1995).^[32] Patients who had cancer progression before undergoing the planned surgery were included in the analysis as non-responders.

Patient characteristics are summarized using frequency (%) for categorical variables and median (range) for continuous variables. OS is defined as the time interval between enrollment date and the date of death due to any cause. Patients who were alive were censored at the last follow-up date. Univariate logistic regression models were fit to assess the association between pathCR and patient characteristics. The probabilities of OS were estimated using the method of Kaplan and Meier[33]. Univariate Cox[34] proportional hazards models were fit to assess the association between OS and patient characteristics. The association between clinical CR and path CR was assessed through Fisher's exact test. All statistical analyses were conducted in SAS and Splus.

RESULTS

We were able to recruit only 31 of 90 planned patients between March 2009 and February 2012 due to limited funding for interim ^{18}F -FDG PET/CTs.

Patient characteristics are summarized in Table 1. Most patients were men (93.5%), white (90.3%), had an excellent ECOG PS 0-1 (100%), and had baseline stage III disease (74.2%). Roughly half were treated with oxaliplatin/5-fluorouracil (45.2%) while the other half received a taxane/5-fluorouracil (54.8%). 61.3% of patients achieved a clinical CR (cCR).

87.1 % of patients were able to undergo surgery, while 12.9% did not mostly because of the development/finding of metastatic disease.

18F-FDG PET/CT Analyses

All 31 patients performed three 18F-FDG PET/CT studies (baseline, interim and post-CTRT), therefore 93 studies were evaluated to calculate the quantitative parameters. These characteristics are summarized in Table 2.

PathCR

Patholgy analysis was classified as P0 when there was no residual cancer, i.e., pathological complete response (pathCR); P1 when 1% to 50% of residual cancer was present (some response to therapy) and P2 when there was >50% residual cancer (no response).

Twenty-seven patients underwent surgery and six (22.2%) had a pathCR. Univariate logistic regression models for pathCR, which suggests that none of the 18F-FDG PET/CT parameters were associated with pathCR (Table 3). There was a marginal association between cCR and pathCR ($p=0.06$) (Data not shown). All six patients with pathCR also had a cCR.

Overall Survival (OS)

Among the total 31 patients studied, 19 (61.3%) died. The median OS was 35.1 months (95% CI: 19.9 – NA). Table 4 shows the fitted univariate Cox proportional hazards models, which suggest that on 18F-FDG PET/CT, the post-CTRT TLG and post-CTRT TLG were the only variables significantly associated with OS. The analysis also suggests that on 18F-FDG PET/CT, the baseline TLG, when dichotomized at the optimal cutoff value of 75.15, shows a significant association with OS (i.e., patients with baseline TLG value 73.7 had a longer median OS; $p=0.03$) (Table 5). None of the other clinical or 18F-FDG PET/CT parameters (SUVmax and SUVmax) were significantly associated with OS.

DISCUSSION

Given that EC is a highly heterogenous cancer, tools are needed to individualize therapy and allow for response prediction. It has previously been reported that the baseline 18F-FDG PET/CT and changes in 18F-FDG PET/CT post-CTRT are the most accurate noninvasive tools to predict long-term survival after preoperative CTRT, although it did not correlate well with pathologic response [18].

We attempted to identify indicators of pathCR and OS. None of the clinical characteristics evaluated (clinical response, tumor size, presence of lymph nodes, TNM stage, use of chemotherapy and Barrett's disease) correlated to pathCR or OS. Among the clinical parameters evaluated, only cCR was marginally associated with pathCR ($p=0.06$).

We thus tried in our prospective phase II trial to evaluate if 18F-FDG PET/CT parameters (SUVmax and TLG) performed at baseline, interim and post-CTRT scans could provide more information on OS and pathologic subtypes of EC.

Since CTRT is the standard treatment in North America and leads to more dramatic pathologic responses we hypothesized that an interim PET could be predictive of pathCR. We planned to enroll a total of 90 patients, however were successful in enrolling only 31. Our data strongly suggest that metabolic imaging cannot be used to predict pathCR. The differentiation between pathCR and minimal microscopic residual cancer may not be possible due to many factors: PET/CT resolution; the esophagitis that occurs after CTRT (which leads to increase in 18F-FDG uptake); the histological type [it has previously been shown that SUVmax is not as predictive in adenocarcinomas] [35]. What if we could enroll 90 patients? Based on the statistical simulation we carried out, even with 90 patients, it appears highly unlikely that a significant correlation would emerge between pathCR and the 18F-FDG PET/CT parameters and the probability of reaching a significant correlation between baseline SUVmax and pathCR would be only 0.48.

The most common 18F-FDG PET/CT parameter used in response prediction is SUVmax. The SUVmax measured on a baseline 18F-FDG PET/CT has been shown to be prognostic. For example, a baseline SUVmax above 12 is associated with a poorer OS in patients with EC treated with definitive CTRT.[36] SUVmax may have some use when preoperative chemotherapy is used. A study composed of only 15 patients with adenocarcinoma of the esophagogastric junction, performed 18F-FDG PET at baseline and interim (14 days after neoadjuvant chemotherapy). The SUV discriminated responders from non-responders. [37] However these parameters are not prognostic in the same manner after CTRT. In a number reports, baseline SUVmax was not prognostic of treatment outcome in EC [38-40]. For example, in one study comprising of SUV (baseline and interim) measured on 18F-FDG PET (interim performed 14 days after the start of CTRT) in patients with EC demonstrated that the SUVmean decrease was 30.9% in histopathologic responders (defined as having less than 10% residual cancer cells) and 1.7% in non-responders ($p=0.001$). However, the accuracy was too low to justify early discontinuation of CTRT [41].

TLG is a relatively new 18F-FDG PET/CT parameter that takes into account the tumor volume (in ml) identified on the metabolic images and the mean SUV value within the region of interest drawn surrounding the tumor. Therefore, TLG reflects the volume of metabolically active tumor and intensity of abnormal tumor metabolism. In patients with SCC, the correlation of pathologic response was higher with TLG (AUC 0.93) than with SUVmax (AUC 0.71) [42]. However, we were not able to reproduce these findings in our patients as TLG was not associated with pathCR. Although the TLG equation is pre-defined and may not differ among investigators or centers, there may be variability of TLG measurements among observers. This variation is more pronounced than the SUVmax values (because the latter are less dependent on delineation of regions of interest). However, TLG is precisely measured by PET/CT (as opposed to PET without CT) due to the CT component, provides delineation of the tumor and it is, reliable and reproducible. On the other hand, studies addressing TLG (baseline to post-CTRT) in EC patients have shown an even stronger correlation with OS than with solely SUVmax values [43], even in patients with adenocarcinomas.

Our report is the first to demonstrate as a part of a prospective Phase II study that baseline TLG was significantly associated with OS ($p=0.03$). Interestingly, we found that both post-

CTRT TLG and post-CTRT TLG were significantly associated with OS ($p=0.01$ and $p=0.03$, respectively). Similarly, in a recent report, Foley et al. analyzed 103 EC patients who had PET performed between Sept 2010 and Nov 2011 (74% adenocarcinomas) and found that baseline TLG was independently associated with OS ($p=0.018$) [44]. To that effect, it would be worthwhile to calculate TLG as well as SUVmax in 18F-FDG PET/CTs and to further investigate their role in guiding treatment of EC patients. We conclude that SUVmax may not be as reliable as TLG for prognostication in EC and TLG parameters warrant further investigation.

In summary, this study adds to the evidence that 18F-FDG PET/CT parameters (SUVmax and TLG) are not predictive of pathCR in EC patients treated with CTRT. On the other hand, 18F-FDG PET/CT is a powerful prognostic tool capable of evaluating OS in EC patients treated with CTRT. Using a cut off baseline TLG value of 75, it is possible to stratify stage II/III patients that will undergo CTRT in terms of OS and possibly guide future treatment strategies.

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REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA: a cancer journal for clinicians*. 2011; 61:69–90. [PubMed: 21296855]
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International journal of cancer Journal international du cancer*. 2010; 127:2893–917. [PubMed: 21351269]
3. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA: a cancer journal for clinicians*. 2014; 64:9–29. [PubMed: 24399786]
4. Brown LM, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. *Journal of the National Cancer Institute*. 2008; 100:1184–7. [PubMed: 18695138]
5. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *Journal of the National Cancer Institute*. 2005; 97:142–6. [PubMed: 15657344]
6. Engel LS, Chow WH, Vaughan TL, Gammon MD, Risch HA, Stanford JL, et al. Population attributable risks of esophageal and gastric cancers. *Journal of the National Cancer Institute*. 2003; 95:1404–13. [PubMed: 13130116]
7. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *The New England journal of medicine*. 2012; 366:2074–84. [PubMed: 22646630]
8. Ajani JA, Barthel JS, Bentrem DJ, D'Amico TA, Das P, Denlinger CS, et al. Esophageal and esophagogastric junction cancers. *Journal of the National Comprehensive Cancer Network : JNCCN*. 2011; 9:830–87. [PubMed: 21900218]
9. Donahue JM, Nichols FC, Li Z, Schomas DA, Allen MS, Cassivi SD, et al. Complete pathologic response after neoadjuvant chemoradiotherapy for esophageal cancer is associated with enhanced survival. *The Annals of thoracic surgery*. 2009; 87:392–8. discussion 8-9. [PubMed: 19161745]

10. Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2008; 26:1086–92. [PubMed: 18309943]
11. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2001; 19:305–13. [PubMed: 11208820]
12. Rice TW, Rusch VW, Apperson-Hansen C, Allen MS, Chen LQ, Hunter JG, et al. Worldwide esophageal cancer collaboration. *Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE*. 2009; 22:1–8.
13. Chirieac LR, Swisher SG, Ajani JA, Komaki RR, Correa AM, Morris JS, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer*. 2005; 103:1347–55. [PubMed: 15719440]
14. Rohatgi P, Swisher SG, Correa AM, Wu TT, Liao Z, Komaki R, et al. Characterization of pathologic complete response after preoperative chemoradiotherapy in carcinoma of the esophagus and outcome after pathologic complete response. *Cancer*. 2005; 104:2365–72. [PubMed: 16245310]
15. Rohatgi PR, Swisher SG, Correa AM, Wu TT, Liao Z, Komaki R, et al. Failure patterns correlate with the proportion of residual carcinoma after preoperative chemoradiotherapy for carcinoma of the esophagus. *Cancer*. 2005; 104:1349–55. [PubMed: 16130133]
16. Flamen P, Van Cutsem E, Lerut A, Cambier JP, Haustermans K, Bormans G, et al. Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2002; 13:361–8. [PubMed: 11996465]
17. Levine EA, Farmer MR, Clark P, Mishra G, Ho C, Geisinger KR, et al. Predictive value of 18-fluoro-deoxy-glucose-positron emission tomography (18F-FDG-PET) in the identification of responders to chemoradiation therapy for the treatment of locally advanced esophageal cancer. *Annals of surgery*. 2006; 243:472–8. [PubMed: 16552197]
18. Swisher SG, Maish M, Erasmus JJ, Correa AM, Ajani JA, Bresalier R, et al. Utility of PET, CT, and EUS to identify pathologic responders in esophageal cancer. *The Annals of thoracic surgery*. 2004; 78:1152–60. discussion -60. [PubMed: 15464463]
19. Ott K, Weber W, Siewert JR. The importance of PET in the diagnosis and response evaluation of esophageal cancer. *Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE*. 2006; 19:433–42.
20. Wieder HA, Ott K, Lordick F, Becker K, Stahl A, Herrmann K, et al. Prediction of tumor response by FDG-PET: comparison of the accuracy of single and sequential studies in patients with adenocarcinomas of the esophagogastric junction. *European journal of nuclear medicine and molecular imaging*. 2007; 34:1925–32. [PubMed: 17680242]
21. Stahl A, Stollfuss J, Ott K, Wieder H, Fink U, Schwaiger M, et al. FDG PET and CT in locally advanced adenocarcinomas of the distal oesophagus. Clinical relevance of a discordant PET finding. *Nuklearmedizin*. 2005; 44:249–55. quiz N55-6. [PubMed: 16400385]
22. Berger AC, Farma J, Scott WJ, Freedman G, Weiner L, Cheng JD, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2005; 23:4330–7. [PubMed: 15781882]
23. Rizk NP, Venkatraman E, Bains MS, Park B, Flores R, Tang L, et al. American Joint Committee on Cancer staging system does not accurately predict survival in patients receiving multimodality therapy for esophageal adenocarcinoma. *J Clin Oncol*. 2007; 25:507–12. [PubMed: 17290058]
24. Javeri H, Xiao L, Rohren E, Komaki R, Hofstetter W, Lee JH, Maru D, Bhutani MS, Swisher SG, Wang X, Ajani JA. Influence of the Baseline FDG Positron Emission Tomography Results on Survival and Pathologic Response in Patients with Gastroesophageal Cancer Undergoing Chemoradiation Cancer. 2008 In Press.

25. Kelsey CR, Chino JP, Willett CG, Clough RW, Hurwitz HI, Morse MA, et al. Paclitaxel-based chemoradiotherapy in the treatment of patients with operable esophageal cancer. *International journal of radiation oncology, biology, physics*. 2007; 69:770–6.
26. Bader FG, Lordick F, Fink U, Becker K, Hofler H, Busch R, et al. Paclitaxel in the neoadjuvant treatment for adeno carcinoma of the distal esophagus (AEG I). A comparison of two phase II trials with long-term follow-up. *Onkologie*. 2008; 31:366–72. [PubMed: 18596383]
27. Griffin SM, Shaw IH, Dresner SM. Early complications after Ivor Lewis subtotal esophagectomy with two-field lymphadenectomy: risk factors and management. *Journal of the American College of Surgeons*. 2002; 194:285–97. [PubMed: 11893132]
28. Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG, Gunderson L, Mortimer J, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *The New England journal of medicine*. 1998; 339:1979–84. [PubMed: 9869669]
29. Moskovitz AH, Rizk NP, Venkatraman E, Bains MS, Flores RM, Park BJ, et al. Mortality increases for octogenarians undergoing esophagogastrectomy for esophageal cancer. *The Annals of thoracic surgery*. 2006; 82:2031–6. discussion 6. [PubMed: 17126106]
30. Bains MS. Complications of abdominal right-thoracic (Ivor Lewis) esophagectomy. *Chest Surg Clin N Am*. 1997; 7:587–98. discussion 98-9. [PubMed: 9246404]
31. Ajani JA, Winter K, Komaki R, Kelsen DP, Minsky BD, Liao Z, et al. Phase II Randomized Trial of Two Nonoperative Regimens of Induction Chemotherapy Followed by Chemoradiation in Patients With Localized Carcinoma of the Esophagus: RTOG 0113. *J Clin Oncol*. 2008
32. Zep RC. A SAS macro for estimating power for ROC curves in one-sample and two-sample cases. *Proceedings of the 20th SAS Users Group International Conference (SUGI)*. 1995:223.
33. Kaplan EL, Meier P. Nonparametric estimator from incomplete observations. *J Am Stat Assoc*. 1958; 53:457–81.
34. Cox DR. *Regression Models and Life-Tables*. *J R Stat Soc B*. 1972; 34:187.
35. Smithers BM, Couper GC, Thomas JM, Wong D, Gotley DC, Martin I, et al. Positron emission tomography and pathological evidence of response to neoadjuvant therapy in adenocarcinoma of the esophagus. *Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE*. 2008; 21:151–8.
36. Suzuki A, Xiao L, Hayashi Y, Macapinlac HA, Welsh J, Lin SH, et al. Prognostic significance of baseline positron emission tomography and importance of clinical complete response in patients with esophageal or gastroesophageal junction cancer treated with definitive chemoradiotherapy. *Cancer*. 2011; 117:4823–33. [PubMed: 21456015]
37. Weber MA, Bender K, von Gall CC, Stange A, Grunberg K, Ott K, et al. Assessment of diffusion-weighted MRI and 18F-fluoro-deoxyglucose PET/CT in monitoring early response to neoadjuvant chemotherapy in adenocarcinoma of the esophagogastric junction. *Journal of gastrointestinal and liver diseases : JGLD*. 2013; 22:45–52. [PubMed: 23539390]
38. Tan S, Kligerman S, Chen W, Lu M, Kim G, Feigenberg S, et al. Spatial-temporal [(1)(8)F]FDG-PET features for predicting pathologic response of esophageal cancer to neoadjuvant chemoradiation therapy. *International journal of radiation oncology, biology, physics*. 2013; 85:1375–82.
39. Hatt M, Visvikis D, Albarghach NM, Tixier F, Pradier O, Cheze-le Rest C. Prognostic value of 18F-FDG PET image-based parameters in oesophageal cancer and impact of tumour delineation methodology. *European journal of nuclear medicine and molecular imaging*. 2011; 38:1191–202. [PubMed: 21365252]
40. Cuenca X, Hennequin C, Hindie E, Rivera S, Vercellino L, Baruch-Hennequin V, et al. Evaluation of early response to concomitant chemoradiotherapy by interim 18F FDG PET/CT imaging in patients with locally advanced oesophageal carcinomas. *European journal of nuclear medicine and molecular imaging*. 2013; 40:477–85. [PubMed: 23371374]
41. van Heijl M, Omluo JM, van Berge Henegouwen MI, Hoekstra OS, Boellaard R, Bossuyt PM, et al. Fluorodeoxyglucose positron emission tomography for evaluating early response during neoadjuvant chemoradiotherapy in patients with potentially curable esophageal cancer. *Annals of surgery*. 2011; 253:56–63. [PubMed: 21233607]

42. Roedl JB, Halpern EF, Colen RR, Sahani DV, Fischman AJ, Blake MA. Metabolic tumor width parameters as determined on PET/CT predict disease-free survival and treatment response in squamous cell carcinoma of the esophagus. *Molecular imaging and biology : MIB : the official publication of the Academy of Molecular Imaging*. 2009; 11:54–60. [PubMed: 18769974]
43. Jayachandran P, Pai RK, Quon A, Graves E, Krakow TE, La T, et al. Postchemoradiotherapy positron emission tomography predicts pathologic response and survival in patients with esophageal cancer. *International journal of radiation oncology, biology, physics*. 2012; 84:471–7.
44. Foley KG, Fielding P, Lewis WG, Karran A, Chan D, Blake P, et al. Prognostic significance of novel (1)(8)F-FDG PET/CT defined tumour variables in patients with oesophageal cancer. *European journal of radiology*. 2014; 83:1069–73. [PubMed: 24794862]

Highlights

- Phase II study
- evaluate if baseline, interim or post-CTRT PET provide information on pathCR or OS
- None of the PET parameters (TLG, Suv_{max}) are predictive of pathCR
- TLG at baseline and post-CTRT are prognostic of OS

Table 1

Patient's characteristics (N=31).

Characteristics		Number of patients (%)
Tumor type	Adenocarcinoma	29 (93.5%)
	SCC	2 (6.5%)
Gender	Female	2 (6.5%)
	Male	29 (93.5%)
Race	Asian-indian	1 (3.2%)
	Hispanic	2 (6.4%)
	White	28 (90.3%)
Alcohol	Frequent	13 (42.0%)
	Never	7 (22.6%)
	Occasional	6 (19.4%)
	Past	5 (16.1%)
Smoking	Nonsmoker	12 (38.7%)
	Nonsmoker quit	13 (41.9%)
	Smoker	6 (19.4%)
ECOG__PS	0	16 (51.6%)
	1	15 (48.4%)
Barretts	None	26(83.9%)
	LS>=3cm	4(12.9%)
	SS<3cm	1 (3.2%)
Baseline_Stage	IIA	8 (25.8%)
	III	23 (74.2%)
Treatment	Oxaliplatin + 5 FU	14 (45.2%)
	Taxane + 5 FU	17 (54.8%)
Clinical_CR	No	12 (38.7%)
	Yes	19 (61.3%)
Surgery	No	4 (12.9%)
	Yes	27 (87.1%)
Path_Stage	P0	6 (22.2%)
	P1	19 (70.4%)
	P2	2 (7.4%)
Residual_Cancer	0	6 (22.2%)
	1-5	14 (51.8%)
	5-10%	1 (3.7%)
	20-30	4 (14.8%)
	70-80	2 (7.4%)

SCC = Squamous cell carcinoma; P0 = No residual cancer, i.e., pathological complete response (pathCR); P1 = 1% to 50% of residual cancer (some response); P2 = >50% residual cancer (no response).

Table 2

18F-FDG PET/CT quantitative parameters (n = 93 PET/CT studies).

18F-FDG PET/CT	Quantitative parameters	N	Mean +/- SD	Median (range)
Baseline	SUVmax	31	14.3 +/- 11	11.3 (4.6, 59.8)
	TLG	31	168.4 +/- 265	97.1 (14.9, 1430.1)
Interim	SUVmax	31	8.6 +/- 6.1	8 (2.6, 37.8)
	SUVmax	31	-32.1 +/- 27.2	-33 (-82, 34.3)
	TLG	31	88.2 +/- 156.2	56.3 (1.9, 888)
	TLG	31	-43 +/- 31.2	-51.6 (-89.9, 33)
Post-CTRT	SUVmax	31	4.4 +/- 1.8	3.9 (1.8, 11.1)
	SUVmax	31	-59.3 +/- 24.4	-66.5 (-94.6, 14.2)
	TLG	31	17.6 +/- 26.9	10.3 (0.4, 144.1)
	TLG	31	-82.2 +/- 20.1	-91.2 (-99.3, -7.7)

SD = standard deviation; TLG = total lesion Glycolysis; SUVmax = maximum standardized uptake value.

Table 3

Association between 18F-FDG PET/CT and pathCR (N=27 patients; N pathCR = 6).

18F-FDG PET/CT	Variable	Coefficient	SE	p-value	OR
Baseline	SUVmax	0.08	0.06	0.20	1.08
	TLG	0.0008	0.003	0.81	1.001
Interim	SUVmax	-0.13	0.17	0.44	0.88
	SUVmax	-0.01	0.02	0.45	0.99
	TLG	-0.02	0.02	0.20	0.98
	TLG	-0.01	0.02	0.55	0.99
Post-CTRT	SUVmax	-0.37	0.38	0.33	0.69
	SUVmax	-0.003	0.02	0.89	1.00
	TLG	-0.07	0.07	0.26	0.93
	TLG	-0.008	0.02	0.75	0.99

SE = standard error; OR = odds ratio; TLG = total lesion glycolysis; SUVmax = maximum standardized uptake value.

Table 4

Univariate Cox regression model for OS.

	covariate	HR	95% CI		p-value
Tumor Characteristics	Length of Tumor (cm)	1.13	0.90	1.41	0.28
	Barretts ND (vs. LS ≥ 3 cm or SS < 3cm)	0.80	0.26	2.46	0.70
Lymph nodes (LN)	Number of positive LN	1.10	0.88	1.37	0.41
	Total number of LN	1.00	0.94	1.05	0.87
	% positive LN	1.04	0.97	1.11	0.31
TNM Stage	III vs. IIA	1.20	0.40	3.67	0.74
Chemotherapy	Taxane (vs. Oxaliplatin)	0.64	0.26	1.61	0.35
Baseline 18F-FDG PET/CT	SUVmax	1.01	0.97	1.05	0.71
	TLG	1.001	0.999	1.002	0.32
Interim 18F-FDG PET/CT	SUVmax	1.03	0.95	1.11	0.46
	SUVmax	1.00	0.98	1.01	0.70
	TLG	1.00	1.00	1.00	0.34
	TLG	0.99	0.98	1.01	0.40
Post-CTRT 18F-FDG PET/CT	SUVmax	1.20	0.95	1.52	0.13
	SUVmax	1.01	0.99	1.03	0.47
	TLG	1.02	1.00	1.03	0.01
	TLG	1.02	1.00	1.05	0.03

ND = no dysplasia; LS = long segment; SS = short segment; NA = not applicable; TLG = total lesion glycolysis; SUVmax = maximum standardized uptake value.

Table 5

Association of baseline and interim 18F-FDG PET/CT parameters (SUV and TLG) with OS.

		Variable	N_death	Median OS (months)	95% CI	P-value
Baseline 18F-FDG PET/CT						
SUVmax	7.74	7	2	Not reached	15.4 - NA	0.18
	> 7.74	24	17	33.5	16.8 - 44.8	
TLG	75.15	11	3	Not reached	15.4 - NA	0.03
	> 75.15	20	16	33.5	16.8 - 44.8	
Interim 18F-FDG PET/CT						
SUVmax	−33	16	10	35.1	14.3 - NA	0.86
	> −33	15	9	33.5	19.9 - NA	
TLG	−51.6	15	9	35.1	14.3 - NA	0.83
	> −51.6	16	10	33.5	16.8 - NA	

NA = not applicable; TLG = total lesion Glycolysis; SUVmax = maximum standardized uptake value.