Initial Standardized Uptake Value of Positron Emission Tomography Influences the Prognosis of Patients with Localized Gastric Adenocarcinoma Treated Preoperatively

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Key Words

Localized gastric adenocarcinoma · Preoperative chemoradiation · Initial standardized uptake value of positron emission tomography · Signet ring cells · Prognostic role

Abstract

Background: In patients with localized gastric adenocarcinoma (LGAC) who receive preoperative therapy, tools to predict response or prognosticate outcome before therapy are lacking. We used initial standardized uptake value (iSUV) of positron emission tomography (PET) to evaluate its association with overall survival (OS). **Methods:** We identified 60 patients with confirmed LGAC who were treated with preoperative chemoradiation and had a baseline PET in addition to other routine staging. Fisher's exact test and Wilcoxon's rank sum test were used to determine the association between iSUV and other variables, and the log-rank test and Cox proportional hazards model were used for survival anal-

ysis. **Results:** The median iSUV was 6 (range, 0–28). The presence of signet ring cells in pretreatment biopsies correlated highly with low iSUV (≤ 6 ; $p = 0.0017$). Patients with a high iSUV (> 6) had a longer OS compared to those with a low iSUV (≤ 6 ; $p = 0.0344$). iSUV was not an independent predictor ($p = 0.12$); however, the risk of death was reduced for patients with an iSUV > 6 (hazard ratio = 0.26). **Conclusion:** Our novel findings show that among LGAC patients treated with preoperative chemoradiation and surgery, those with a high iSUV have longer OS than patients with a low iSUV. iSUV appears to have a predictive role in patients with LGAC when treated with preoperative chemoradiation.

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Introduction

Gastric adenocarcinoma (GAC), a common malignancy with a poor prognosis, is listed as the third leading cause of cancer-related mortality worldwide [1]. In the

USA, 24,590 new cases are estimated to be diagnosed and 10,720 patients to succumb to GAC in 2015 [2]. Surgical resection plays a major part in the cure of patients with localized GAC (LGAC); however, 5-year survival rates after surgery alone are 20–50%, and adjunctive therapy must be offered [3]. Multimodality treatment options for GAC include postoperative chemoradiation, perioperative chemotherapy and postoperative chemotherapy. In addition, multiple phase II trials have evaluated the role of preoperative chemoradiation for GAC [4]. With preoperative chemoradiation, the rates of pathologic complete response (no residual tumor cells in the resected surgical specimen) range from 20 to 25%, and 70–78% of patients are able to undergo an R0 resection [5–7].

Patients with LGAC, when treated with preoperative therapy, tend to have heterogeneous and unpredictable outcomes. Heterogeneity in patients' outcomes is frequently noted even if similarly staged patients receive the same therapy. This heterogeneity is most likely related to the differing molecular biology of individual GAC, responsible for different levels of sensitivity to chemotherapy and radiotherapy and its metastatic potential [8].

In addition to improving outcomes by identifying novel agents, there is a need to customize preoperative therapy of LGAC patients based on GAC biology. Evidence suggests that imaging modalities such as positron emission tomography (PET), using [^{18}F]-fluorodeoxyglucose (FDG) as a tracer and integrating with computed tomography (CT) (PET/CT) for anatomic localization, seem to be an effective noninvasive tool to predict biological aggressiveness and the prognosis of patients with LGAC. However, its role in defining biology is debatable, as other variables can play roles as well.

Prior studies are conflicting. Initial standardized uptake value (iSUV) has been correlated with overall survival (OS) after surgery. Other studies either found a correlation between low iSUV and OS or a lack of such a correlation [9–13]. Two studies have addressed iSUV and histopathologic subtypes of GAC [12, 13]. To our knowledge, ours is the first study examining iSUV as a predictor in LGAC patients who received preoperative chemoradiation, and we provide compelling reasons for our results.

Materials and Methods

Patient Selection

We identified patients from our prospectively assembled and maintained GAC database in the Department of Gastrointestinal Medical Oncology at the University of Texas MD Anderson Cancer Center (UTMDACC). The Institutional Review Board of the UTMDACC approved the analysis. We studied 60 consecutive pa-

tients with confirmed LGAC who received preoperative therapy and surgery between 2002 and 2013. All had a baseline PET/CT. All patients were staged with upper endoscopy as well as endoscopic ultrasound. They had a negative peritoneal staging by laparoscopy or laparotomy. Clinical staging was based on the American Joint Committee on Cancer (AJCC) Classification, 6th edition [14].

Trimodality Therapy

All patients had concurrent chemotherapy with radiation. They received fluoropyrimidine (intravenously or orally) with or without either a taxane or a platinum compound during radiotherapy. The total radiation dose delivered was either 45 Gy in 25 fractions or 50.4 Gy in 28 fractions, at 1.8 Gy per fraction delivered once daily, 5 days per week, prescribed to cover 95% of a clinical target volume encompassing the primary tumor, the mucosal margin and regional lymphatic regions. Prior to chemoradiation, 53 patients (88%) had received up to 8 weeks of induction chemotherapy.

Approximately 5–7 weeks after the completion of chemoradiation, all patients underwent preoperative upper endoscopy with biopsies and a PET/CT or CT scan of the chest and abdomen. They then proceeded to surgery. Surgical procedures included extensive lymph node dissection, and specimens were staged by using the AJCC Classification, 7th edition [15].

Follow-Up and Survival

Patients were monitored periodically until 5 years after surgery or until death. Follow-up survival data were obtained from the hospital records, patient follow-up data, death records (Social Security Database) and the UTMDACC tumor registry. The estimated median follow-up time was 2.64 years (95% CI, 2.34–4.36).

FDG-PET/CT Scans

PET/CT scans were performed on a dedicated PET/CT system (Discovery ST-8; GE Medical Systems, Milwaukee, Wis., USA). Details of PET scanning and SUV calculations have been described by our group elsewhere [16–19]. At our institution, we follow the NCI guidelines for image preparation, acquisition and analysis [20–22].

Statistical Methods

Fisher's exact test and Wilcoxon's rank sum test were used to determine the association between iSUV and other variables. The log-rank test and Cox proportional hazards model were used for survival analysis. For the purpose of exploratory analysis, a multivariate Cox model was fitted to evaluate whether iSUV was significantly associated with OS after adjusting for the effects of the Eastern Cooperative Oncology Group Performance Status (ECOG PS), baseline lymph node status, histologic grade and the presence of signet ring cells (SRCs). Variables with a p value <0.05 were considered statistically significant. SAS software 9.3 (SAS institute, Cary, N.C., USA) and Splint software 8.2 (TIBCO, Palo Alto, Calif., USA) were used for the analyses.

Results

Patient and Tumor Characteristics

The baseline and posttreatment patient characteristics are shown in table 1. Patients were primarily male (63%)

Table 1. Summary of baseline characteristics

Covariate	Frequency
Race	
Caucasian	40 (66.7%)
Other	20 (33.3%)
Gender	
Female	22 (36.7%)
Male	38 (63.3%)
ECOG PS	
0	16 (26.7%)
1	42 (70%)
2	2 (3.3%)
Siewert classification	
Type 3 GEJ	29 (48.3%)
Gastric	31 (51.7%)
Baseline EUS T	
T2	5 (8.3%)
T3/T4	55 (91.7%)
Baseline EUS N	
N0	27 (45%)
N1/N2	33 (55%)
Baseline M	
M0	60 (100%)
Baseline clinical stage	
I/II	26 (43.3%)
III/IV	34 (56.7%)
Presence of SRCs	
Yes	31 (51.6%)
No	29 (48.3%)
Histologic grade	
G2 – moderately differentiated	17 (28.3%)
G3 – poorly differentiated	43 (71.7%)
iSUV	
≤6	30 (50%)
>6	30 (50%)
Tumor size	
N/A	18 (30%)
<5	18 (30%)
≥5	24 (40%)

GEJ = Gastroesophageal junction; EUS = endoscopic ultrasound; N/A = not available.

and Caucasian (67%), with a median age of 60 years (range, 26–82 years). Twenty-nine had type 3 gastroesophageal junction adenocarcinoma according to the Siewert classification, and 31 had GAC elsewhere.

Table 2. Comparison of continuous variables between the patient groups with iSUV ≤6 and >6

Covariate	Mean ± SD, median (range)	Wilcoxon rank sum test, p value
Age at presentation at UTMDACC, years		0.4987
iSUV >6 (n = 30)	57.9 ± 12, 59 (26–82)	
iSUV ≤6 (n = 30)	60 ± 10.9, 60.5 (36–78)	
Tumor size, cm		0.0120
iSUV >6 (n = 25)	6.5 ± 3.3, 6 (1.2–18)	
iSUV ≤6 (n = 17)	4.4 ± 2.6, 4 (1.4–12)	
Baseline BMI		0.5732
iSUV >6 (n = 11)	28.6 ± 13.4, 25.7 (0–48.3)	
iSUV ≤6 (n = 15)	26.5 ± 6.5, 29.7 (17.3–34.5)	
SUV of primary tumor		<0.0001
iSUV >6 (n = 30)	13 ± 5.6, 11.8 (6.4–28.2)	
iSUV ≤6 (n = 30)	2.8 ± 2.2, 3.4 (0–6)	

iSUV and Patient Characteristics

For the analysis, iSUV was dichotomized by 6, which was the median iSUV. Fisher's exact test was used to evaluate the association between iSUV and other variables. The presence of SRCs correlated highly with low iSUV ($p = 0.0017$). Fisher's exact test suggested that patients with type 3 LGACs (69%) were more likely to have a higher iSUV (>6) compared to those with a tumor located elsewhere in the stomach (32%; $p = 0.0092$). Also, larger tumors (≥5 cm) were more likely to have a high iSUV ($p = 0.0043$). There was a nonsignificant trend for an association between low iSUV and high histologic grade (G3; $p = 0.084$). iSUV could not predict pathologic complete response ($p = 0.1042$).

Table 2 shows the results of Wilcoxon's rank sum test to compare continuous variables with iSUV >6 and iSUV ≤6. LGACs were larger in patients with an iSUV >6 compared to those with an iSUV ≤6 ($p = 0.012$).

iSUV and Survival

The log-rank test was used to compare OS between subgroups of patients. Patients with a high iSUV (>6) had longer OS compared to those with a low iSUV (≤6; $p = 0.0344$). The only other factor strongly associated with a shorter OS in the log-rank test was poor performance status (ECOG PS = 2; $p = 0.0002$).

In the exploratory multivariate analysis, iSUV was not independently prognostic ($p = 0.12$) after adjusting for

Table 3. Studies assessing the influence of iSUV of PET/CT in the LGAC setting

Ref.	Patients, n	Type of treatment	Findings
Stahl et al. [9]	40	Preoperative chemotherapy	No significant correlation with prognosis
Vallböhmer et al. [23]	42	Preoperative chemotherapy	No significant correlation with prognosis
Mochiki et al. [11]	85	Primary surgery	High iSUV → worse OS
Pak et al. [13]	41 (with SRC histology)	Primary surgery	High iSUV → worse aggressive clinical course, although iSUV not independently prognostic
Lee et al. [12]	271 (with subgroup analysis according to histopathologic subtypes)	Primary surgery	High iSUV → predictive factor for tumor recurrence for patients with TAC or PAC, not for SRC and MAC

TAC = Tubular adenocarcinoma; PAC = poorly differentiated adenocarcinoma; MAC = mucinous adenocarcinoma.

the effects of EGOCS, baseline lymph node status, histologic grade and the presence of SRC (data not shown). However, the risk of death was reduced for patients with a high iSUV (hazard ratio for death = 0.26). Patients with a low iSUV, G3 histology and SRCs had a tendency for a shorter OS.

Discussion

The SUV of PET reflects the biology of cancer and possibly the metabolic rate. Prior studies have reported poor OS and high recurrence rates in patients with high iSUV, but these patients had primary surgery [11, 12]. Stahl et al. [9] reported that OS was not different in patients with a high or low iSUV after preoperative chemotherapy. Similar results in a later study by Vallböhmer et al. [23] showed that iSUV did not correlate with OS after preoperative chemotherapy. Table 3 shows all the studies evaluating the potential of iSUV for the assessment of prognosis in the LGAC setting. In our study of patients that received preoperative chemoradiation, those with a high iSUV tended to do better.

Our study sheds light on histologic subtypes and SRCs displaying a significant association with iSUV. Prior reports using the Lauren classification have shown that FDG-PET/CT had significantly lower sensitivity in detecting diffuse type, SRC and mucinous GACs than in detecting intestinal-type adenocarcinomas [9, 24–27]. The poor predictive value of low iSUV may be due to a

lack of avidity in the diffuse type of GAC [9, 28] and a low expression of glucose transporter 1 (GLUT1) [9, 25, 29].

GLUT1, the human erythrocyte glucose transporter, is a member of the facultative glucose transporter family, which currently is composed of 14 members. A previous study demonstrated the role of overexpression of facultative glucose transporter genes in human cancer [30]. GLUT1, as a glucose metabolism-related protein, is responsible for FDG SUV uptake in various tumors. Overexpression of GLUT1 has been described in tumors of the esophagus [31], colon [32], pancreas [33], lung [34], brain [35], ovary [36] and breast [37].

Rapid cancer growth induces a hypoxic environment in tumors. Hypoxia-inducible factor 1 acts as a sensor for hypoxic stress, upregulating angiogenic factors and activating the transcription of genes encoding glucose transporters, such as GLUT1. Thus, overexpression of GLUT1 may play an important role in tumor survival by promoting an adequate energy supply through the glycolytic pathway, supporting their high metabolic rate in a not so ideal hypoxic environment [38].

In gastric cancer, frequencies and levels of GLUT1 expression do not appear to be very high; approximately only 30% of the cases examined in the study of Kawamura et al. [29] were positive. These differences in GLUT1 expression may be attributed to histological variations. SRCs and mucinous GACs, which are characterized by low cellularity and/or high mucinous content, present a very low FDG uptake due to low GLUT1 expression [29, 39, 40]. One possible reason why high FDG SUV uptake

by GAC does not reflect tumor aggressiveness as in other neoplasms came from a more recent study that implied that glutamine metabolism may be upregulated in GAC [41]. Thus, GAC cells could eliminate the necessity for glucose transport, as they use glutamine as an energy source in a hypoxic tumor microenvironment. This malignant transformation has been reported in other cancers [42] as well, and interestingly an ongoing glutamine-based phase I PET study is currently recruiting patients with a history of histologically confirmed solid malignancies and/or lymphomas (NCT01697930).

The positive association between high SUV and lower histologic grade found in our study is not necessarily unexpected. Contrary to other tumors, G2 GACs accumulated FDG more intensely than G3 GACs. Therefore, histologic grade may not represent biological aggressiveness in this tumor. A plausible reason explaining the high SUV of G2 tumors in our study is the absence of SRCs and a mucinous component in these low-grade tumors (0 out of 17 patients had SRCs in their pretreatment biopsies), a finding shown also in the study of Stahl et al. [9].

Essentially, in our study, a low iSUV indicates SRCs or G3 histology and, therefore, poor outcome in LGAC. On the other hand, a high iSUV is associated with no SRCs, lower (G2) grade and more sensitivity to chemoradiation, therefore predicting good outcome and prolonged OS. Finally, our data suggest that in our population of LGAC patients who received preoperative chemoradiation, a high iSUV is associated with a prolonged OS. In contrast, when a single modality such as surgery or surgery with preoperative chemotherapy is used, a high iSUV leads to poor patient outcomes and is not a good predictor of OS, as shown in previous studies [9, 11–13, 23]; however, we are aware of the difficulty of comparing such data between different studies. A possible explanation for this is that tumors with a high iSUV (no SRCs and a low grade) are more sensitive to chemoradiation. A high iSUV may indicate a group of patients presenting with LGAC with

a favorable prognosis when treated with preoperative chemoradiation.

Our study, being retrospective, has some shortcomings: (1) it is a single high-volume center experience, (2) the total denominator is relatively small, and since the number of events was also small, the analysis was not powered enough to detect differences in survival, and (3) clear and reproducible cutoff values are still lacking and prospective multicenter studies need to be carried out with centralized SUV assessment. However, our data have strengths that can contribute to the management of patients with LGAC, as they involve a uniformly treated population.

In conclusion, our novel findings show that among LGAC patients treated with preoperative chemoradiation and surgery, those with no SRCs and/or G2 histology have a high iSUV (>6) and longer OS, whereas patients with SRCs and/or G3 histology have a low iSUV (≤ 6) and shorter OS. Thus, iSUV appears to have a prognostic role in patients with LGAC when treated with preoperative chemoradiation.

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Disclosure Statement

The authors declare that there is no conflict of interest.

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