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RETROSPECTIVE STUDY

Prognostic value of baseline FDG uptake on PET-CT in esophageal carcinoma

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Abstract

AIM: To evaluate the influence of baseline maximum standardized uptake value (SUV_{max}) on survival in a cohort of patients, undergoing positron emission tomography-computed tomography (PET-CT) scan for esophageal carcinoma.

METHODS: The pre-treatment SUV_{max} numeric reading was determined in patients with confirmed esophageal or junctional cancer having PET-CT scan during the time period 1st January 2007 until 31st July 2012. A minimum follow up of 12 mo was required. Patients were subdivided into quartiles according to SUV_{max} value and the influence of SUV_{max} on survival was assessed using univariate and multivariate analysis. The following pre-treatment factors were investigated: patient characteristics, tumor characteristics and planned treatment.

RESULTS: The study population was 271 patients (191 male) with esophageal or junctional carcinoma. The median age was 65 years (range 40-85) and histologic subtype was adenocarcinoma in 197 patients and squamous carcinoma in 74 patients. The treatment intent was radical in 182 and palliative in 89 patients. SUV_{max} was linked to histologic subtype (P = 0.008), tumor site (P = 0.01) and Union for International Cancer Control (UICC) stage (P < 0.001). On univariate analysis, prognosis was significantly associated with SUV_{max} (P = 0.001), T-stage (P < 0.001) and UICC stage (P < 0.001). On multivariate analysis, only T-stage and UICC stage remained significant.

CONCLUSION: Pretreatment SUV_{max} was not a useful marker in isolation for determining prognosis of patients with esophageal carcinoma.

Key words: Esophageal neoplasms; Fluorodeoxyglucose F18; Positron emission tomography; Positron emission tomography-computed tomography; Prognosis

Core tip: Positron emission tomography-computed tomography (PET-CT) is integral to the staging of esophageal cancer. It is unclear whether the value of PET-CT extends beyond the identification of metastatic disease. The influence of PET-CT maximum standardized uptake value (SUV_{max}) on prognosis was determined for 271 patients. Although SUV_{max} was closely linked to disease stage, it did not exert an independent effect and was not a useful prognostic marker.

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INTRODUCTION

Positron emission tomography (PET) is an important component in the staging algorithm for patients with cancers of the esophagus and gastroesophageal junction[1,2]. At some centers, it is employed early in the staging pathway with all patients being assessed by this modality. In other centers, it features later in the staging pathway, only being utilized if computed tomography (CT) and endoscopic ultrasound demonstrate potentially resectable tumor characteristics[1,2].

Its principal application is in the identification of occult metastatic disease, not identified on CT imaging, or in the confirmation of high fluorodeoxyglucose (FDG) uptake in suspicious areas on CT imaging[1].

We have previously shown that PET-CT influences the treatment decision overall for 10% of patients with esophageal cancer, and for 26% of patients free of definite metastatic disease after initial CT imaging[2].

The maximum standardized uptake value (SUV_{max}) is a measure of the relative metabolic activity of the cancer. A recent meta-analysis confirmed the close link between the SUV_{max} and both tumor stage and prognosis[3]. Whether the SUV_{max} exerted an independent effect, unrelated to known clinical prognostic markers was unclear.

The majority of studies have assessed selected patient groups, typically only those receiving one form of treatment such as chemoradiotherapy, palliative chemotherapy or surgery (with or without neoadjuvant chemotherapy)[4-24]. It is likely that this has resulted in clustering of SUV_{max} values. Only four smaller studies have assessed the influence of SUV_{max} in unselected patients undergoing PET-CT[8,14,21,24]. Those studies concluded that SUV_{max} was significantly associated with prognosis but that this was not independent of existing clinical markers such as Union for International Cancer Control (UICC) stage.

The aim of the current study was to assess whether the SUV_{max} provided additional prognostic information, over and above the UICC stage and known clinical prognostic markers in a large cohort of unselected patients.

MATERIALS AND METHODS

The use of anonymized patient information was approved by the Institutional Clinical Audit and Effectiveness Board. Individual patient consent was not required as no change in patient management was effected for the purposes of this audit.

The study was a retrospective review of all patients undergoing PET-CT during the time period 1st January 2007 to 31st July 2012. At our institution, PET-CT became incorporated into the staging algorithm of routine clinical practice in November 2006. Patients undergoing PET-CT after 31st July 2012 were not included, so that a minimum patient follow up time of 12 mo would be obtained.

All patients with a diagnosis of esophageal or gastric cancer are discussed at a weekly multi-disciplinary meeting and treatment intention and schedule determined. The staging algorithm has previously been published[2].

The 7th edition of the UICC stage was determined by consensus decision at the multi-disciplinary meeting based upon pre-treatment imaging.

PET-CT

During the years 2006-2008 coregistered PET-CT was performed using a General Electric Discovery ST PET-CT scanner with eight-slice CT scan, producing fused single image scans. Since 2008, imaging has been performed using a Siemens Biograph TruePoint PET-CT scanner. Half-body PET acquisition was obtained (from eyes to knees). Patients were fasted for 6 h prior to injection with 350-420 MBq of ^{18}F-FDG (4.5 MBq/kg) that was administered to patients lying supine in a quiet and warm environment. Whole-body two-dimensional image acquisition was obtained 60 min after injection of 18F-FDG using a 128 × 128 matrix. Fused PET-CT images were single reported with quality assurance validation of 10% of scans. The diagnostic CT and previous imaging was available at the time of reporting. The threshold for the diagnosis of metastatic disease on PET-CT was a standardized uptake value in excess of 2.5.

The influence of patient characteristics (age and sex), tumor characteristics (tumor location, histologic subtype, T stage, N stage and UICC stage), planned treatment strategy and baseline SUV_{max} on PET-CT were investigated using univariate analysis. Significant variables were then investigated using Cox regression analysis.

Parametric data were analyzed using the unpaired *t*-test and non-parametric data were analyzed using the Mann-Whitney and Kruskal-Wallis test. Statistical analysis was performed using SPSS software version 15 (SPSS, Chicago, IL, United States). Significance was assumed at the 5% level.

RESULTS

The study population comprised 271 patients (191 males) of median age 65 years (range 40-85). Primary tumor location was upper esophagus in 13 patients, middle esophagus in 50 patients, lower esophagus in 136 patients and gastroesophageal junction in 72 patients. Histologic subtype was adenocarcinoma in 197 patients and squamous cell carcinoma in 74 patients.

Distribution of UICC stage was as follows: Stage 0 or 1 (45 patients), Stage 2 (50 patients), Stage 3 (99 patients) and Stage 4 (77 patients). Stage 4 disease was defined on the basis of distant metastatic disease in 31 patients and on the basis of celiac axis lymphadenopathy in 46 patients. Lymphadenopathy anterior to the left gastric pedicle was defined as locoregional disease as this would be routinely within the field of surgical resection. Lymphadenopathy posterior to the left gastric pedicle was defined as celiac axis lymphadenopathy and would not be included in the field of surgical resection.

Of note, there was no significant difference in the SUV_{max} readings obtained during the two time periods,

Table 1 Influence of patient characteristics on maximum standardized uptake value and survival

Factor	Mean SUV_{max} (95%CI)	Median survival in days (95%CI)
Sex		
Male (n = 191)	11.4 (10.5, 12.3)	566 (491, 641)
Female (n = 80)	12.1 (10.2, 14.0)	884 (403, 1364)
	P = 0.950	P = 0.05
Age in years		
Age ⩽ 65 (n = 136)	11.5 (10.5, 12.5)	575 (456, 694)
Age > 65 (n = 135)	11.7 (10.4, 13.1)	586 (418, 754)
	P = 0.770	P = 0.25
Histology		
Adenocarcinoma (n = 197)	11.3 (10.2, 12.4)	570 (483, 657)
Squamous carcinoma (n = 74)	12.4 (11.3, 13.6)	629 (445, 813)
	P = 0.008	P = 0.75
Tumor location		
Upper esophagus (n = 13)	15.6 (11.4, 19.8)	973 (142,1804)
Mid esophagus (n = 50)	12.8 (11.0, 14.6)	425 (252, 598)
Lower esophagus (n = 136)	10.8 (9.6, 12.0)	586 (464, 708)
Junctional (n = 72)	11.6 (10.0, 13.1)	684 (430, 938)
	P = 0.010	P = 0.14

SUV_{max}: Maximum standardized uptake value.

Table 2 Influence of cancer stage on maximum standardized uptake value and survival

Factor	Mean SUV_{max} (95%CI)	Median survival in days (95%CI)
T stage		
T0 or T1 (n = 15)	3.1 (1.5, 4.7)	Not reached
T2 (n = 49)	8.7 (7.0, 10.4)	1225 (742, 1708)
T3 (n = 183)	12.7 (11.7, 13.7)	495 (413, 577)
T4 (n = 24)	14.1 (11.6, 16.7)	390 (186, 594)
	P < 0.001	P < 0.001
N stage		
N0 (n = 107)	9.1 (8.1, 10.2)	1094 (835, 1352)
N1 (n = 89)	12.9 (11.4, 14.5)	466 (371, 561)
N2 (n = 61)	13.4 (11.6, 15.1)	477 (307, 646)
N3 (n = 14)	14.4 (8.8, 19.9)	530 (350, 710)
	P < 0.001	P < 0.001
UICC stage		
Stage 0 or 1 (n = 45)	5.6 (4.2, 7.0)	2092 (1060, 3124)
Stage 2 (n = 50)	12.1 (10.6, 13.6)	780 (195,1365)
Stage 3 (n = 99)	11.9 (10.7, 13.2)	594 (473, 715)
Stage 4 (n = 77)	14.4 (12.6, 16.1)	349 (280, 418)
	P < 0.001	P < 0.001

SUV_{max}: Maximum standardized uptake value; UICC: Union for International Cancer Control.

when the two PET-CT scanners were employed. Specifically, with the study population divided into quintiles, there was no significant difference between successive quintiles of SUV_{max} (P = 0.55).

According to the multi-disciplinary panel, the treatment intention was radical (curative) for 182 patients and palliative for 89 patients. For the 182 patients treated with radical intent, principal treatment modality was surgery with or without neoadjuvant chemotherapy (114 patients), chemoradiotherapy (63 patients) and endoscopic mucosal resection (5 patients). Nineteen of the surgically

Table 3 Influence of treatment intent and modality on maximum standardized uptake value and survival

Factor	Mean SUV_{max} (95%CI)	Median survival in days (95%CI)
Treatment intention		
Curative (n = 182)	10.6 (9.7, 11.5)	984 (699, 1269)
Palliative (n = 89)	13.6 (11.9, 15.2)	370 (332, 408)
	P = 0.001	P < 0.001
Treatment type		
Endoscopic resection (n = 5)	1.3 (-1.0, 3.6)	Not reached
Surgical resection (n = 95)	10.7 (9.5, 11.9)	1285 (962, 1608)
Chemoradiotherapy (n = 63)	11.6 (10.0, 13.1)	700 (411, 988)
Palliative (n = 89)	13.8 (12.1, 15.5)	370 (349, 390)
Exploratory surgery (n = 19)	8.8 (6.6, 11.0)	340 (280, 400)
	P < 0.001	P < 0.001

SUV_{max}: Maximum standardized uptake value.

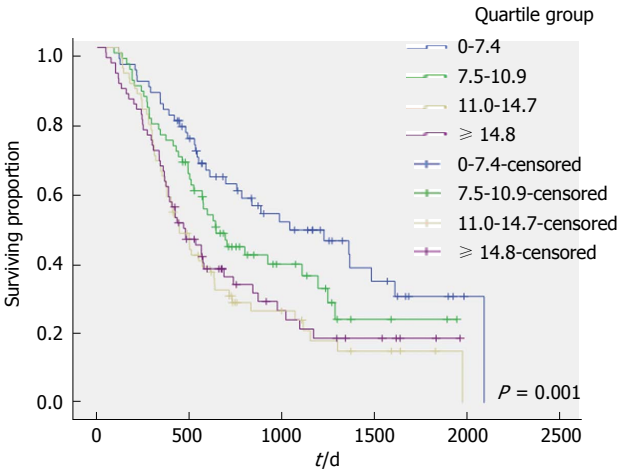

Figure 1 Survival of patients stratified into quartiles of maximum standardized uptake value.

treated patients underwent exploratory surgery because of the identification of unresectable T4 disease or peritoneal disease (19/114, 17%).

Analysis of SUV_{max} and survival

The outcome of univariate analysis comparing associations between patients factors (Table 1), tumor factors (Table 2) and treatment factors (Table 3) and SUV_{max} is shown. These show that SUV_{max} increased as disease burden (T stage, N stage and UICC stage) increased. Figure 1 plots survival for patients when stratified into quartiles of SUV_{max} (1st quartile 0-7.4, 2nd quartile 7.5-10.9, 3rd quartile 11.0-14.7, 4th quartile > 14.7). The strong link between SUV_{max} and survival is evident. The significance of SUV_{max} was lost on multivariate analysis. Using Cox regression analysis, the only factors significantly associated with survival were T-stage (P < 0.001) and UICC stage (P < 0.001). The same findings were evident when both the complete cohort was analyzed and when subgroup analy-

Table 4 Summary of literature reporting on prognostic value of maximum standardized uptake value in patients with esophageal carcinoma

Ref.	Patients (*n*)	Adeno-carcinoma (%)	Treatment intention of studied group	Median (or mean) SUV_{max}	SUV_{max} significant on univariate analysis	SUV_{max} significant on multivariate analysis	Other significant associations on multivariate analysis
Fukunaga *et al*[4], 1998	48	Not stated	Curative	7	Yes	Not assessed	Not assessed
Choi *et al*[5], 2004	69	0%	Curative	6.3/13.7 (thresholds)	Yes	No	UICC stage
Hong *et al*[6], 2005	47	87%	Curative	Not stated	No	No	Number of abnormalities on PET-CT
Stahl *et al*[7], 2005	40	100%	Curative	10.5	No	Not assessed	
van Westreenen *et al*[8], 2005	40	70%	Curative and palliative	6.7	Yes	No	Treatment
Cerfolio *et al*[9], 2006	89	53%	Curative	6.6	Yes	Yes	UICC stage
Choi *et al*[10], 2006	51	0%	Curative	Not stated	Yes	No	UICC stage, N1 status (on PET-CT), immunohistochemical markers
Westerterp *et al*[11], 2008	26	100%	Curative	0.26	Yes	Not assessed	
Omloo *et al*[12], 2008	125	85%	Curative	0.27	Yes	No	UICC stage
Cheze-Le Rest *et al*[13], 2008	47	77%	Curative	9	Yes	Yes	Treatment, number of abnormalities on PET-CT
Chatterton *et al*[14], 2008	129	19%	Curative and palliative	8.2	No	Not assessed	Not assessed
Makino *et al*[15], 2008	38	100%	Curative	11.1	Yes	No	N1 status (on PET-CT)
Javeri *et al*[16], 2009	161	100%	Curative	10.1	No	No	
Kato *et al*[17], 2009	184	0%	Curative	4.5	Yes	Yes	N1 status
Rizk *et al*[18], 2009	189	100%	Curative	4.5 (preset threshold)	Yes	Not assessed	Not assessed
Sepesi *et al*[19], 2009	72	83%	Curative	6.2	Yes	Yes	
Shenfine *et al*[20], 2009	45	100%	Curative	5.7	Yes	No	UICC stage
Hyun *et al*[21], 2010	151	3%	Curative and palliative	17.2	Yes	No	UICC stage, metabolic tumor volume
Brown *et al*[22], 2012	103	80%	Curative	6.4 (early)/8.8 (later scans)	Yes	No	N1 status, age
Gillies *et al*[23], 2012	121	100%	Curative	8.5	Yes	No	N1 status (on PET-CT)
Chan *et al*[24], 2013	185	75%	Curative and palliative	8.9	Yes	No	N1 status, tumor volume on EUS

SUV_{max}: Maximum standardized uptake value; UICC: Union for International Cancer Control; PET-CT: Positron emission tomography-computed tomography.

sis of individual treatment groups (chemoradiotherapy, surgery, palliative chemotherapy) and histologic subtype (adenocarcinoma, squamous carcinoma) was performed.

DISCUSSION

Twenty-one studies published to date have assessed the influence of pretreatment SUV_{max} on the prognosis of cancer of the esophagus in 1960 patients (Table 4)[4-24]. By cancer subtype, the proportion of patients with adenocarcinoma in the studies has ranged from 0% to 100%, with a median of 78%. As was noted in the current study, squamous carcinoma is associated with higher FDG uptake than adenocarcinoma. Sixteen of the studies assessed only patients being treated with radical intent, either surgery (with or without neoadjuvant chemotherapy) or chemoradiotherapy. Only four studies assessed patients treated with both radical and palliative intent. The current study represents the largest unselected study to date.

There were wide variations in the median, mean and threshold SUV_{max} noted in the published studies. The median value of 10.9 identified in the current study was higher than the majority of the studies and likely reflects the unselected population evaluated. Of note, the scans obtained in this study were obtained using two PET-CT machines, although there was no evidence that this had any influence on the measurements.

Pan *et al*[3], in a meta-analysis of the literature published up to 2009 identified SUV_{max} to be associated with a hazard ratio of 1.86 for overall survival, with higher values reflecting poorer survival. The authors however assessed the link between uptake and survival using univariate analysis. In the current study, a significant link between SUV_{max} and prognosis was noted on univariate analysis, but this effect disappeared on multivariate analysis. Table 4 indicates that 17 of the 21 studies (81%) identified a significant association between SUV_{max} and prognosis on univariate analysis, but only four of 16 studies (25%) found that this effect persisted on multivariate analysis.

The reason for this is likely to be the close relationship between SUVmax and UICC stage, and the overriding effect of UICC stage on all other prognostic markers. The literature taken en masse report similar themes.

Other factors that have been identified as being of prognostic value indirectly relate to cancer stage such as PET-CT N stage, the absolute number of abnormalities on PET-CT and the endoscopic ultrasound derived tumor node metastasis stage or tumor volume.

The current study has assessed the influence of a single pretreatment uptake value on cancer outcome, although other studies have suggested that serial PET-CT scanning may yield additional information by comparing pre- and post-treatment values[25,26]. At our institution, it is not standard practice to perform serial PET-CT. Patients undergo only one pretreatment examination.

We have previously shown that PET-CT alters the cancer stage in 26% of patients and that this translates into a change in management for 18%[2]. The implications of the current study are that the value of the PET-CT remains in the diagnosis of "occult" metastatic disease or confirming suspicious abnormalities on initial CT imaging. Its role is purely in triangulating with other information in order to predict pretreatment stage. The pretreatment SUV_{max} measurement, while closely linked to prognosis does not provide additional meaningful information that can be used in clinical decision making.

Several studies have noted that FDG uptake in regional lymph nodes may provide additional prognostic information[10,15,22-24]. At our institution, no attempt has been made to stage local peritumoral lymphadenopathy on the basis of PET-CT. We have considered the spatial resolution of the imaging insufficient to allow distinction between primary tumor and local lymphadenopathy. Local nodal staging is assessed by endoscopic ultrasound.

In conclusion, this study did not demonstrate the utility of PET-CT scanning, over and above determination of UICC stage. Pre-treatment SUV_{max} did not yield additional useful information.

COMMENTS

Background

Positron emission tomography-computed tomography (PET-CT) imaging is routinely employed in the staging of esophageal cancer. Its principal role is in the identification of metastatic disease. Some previous reports have suggested that the fluorodeoxyglucose (FDG) uptake [maximum standardized uptake value (SUV_{max})] may afford additional prognostic information.

Research frontiers

The research hotspot is to determine whether or not the effect of SUV_{max} on prognosis is independent of known prognostic markers, such as Union for International Cancer Control (UICC) stage

Innovations and breakthroughs

Univariate analysis identified that prognosis was linked to baseline pre-treatment) SUV_{max} in patients with esophageal cancer. However, this effect did not persist on regression analysis, with conventional prognostic markers (UICC stage and tumor stage) assuming significance.

Applications

The principal value of PET-CT in this patient group remains the identification of distant metastatic disease.

Peer review

The authors are to be congratulated on their effort. Although a retrospective study, it is well written and the authors have experience in this technology. They have addressed the clinical question about the independent effect of the prognostic information that maximum PET-CT FDG uptake could provide.

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