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Value of complete metabolic response by ^{18}F-fluorodeoxyglucose-positron emission tomography in oesophageal cancer for prediction of pathologic response and survival after preoperative chemoradiotherapy

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ABSTRACT

We aimed to assess the ability of ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan to predict pathologic complete response (CR) and survival in patients with oesophageal cancer treated with preoperative chemoradiotherapy (CRT). The study cohort consisted of 62 consecutive patients with operable oesophageal cancer who were treated with preoperative CRT followed by oesophagectomy. Endoscopy, computed tomography (CT) and PET were performed before and after CRT.

Of the 62 patients, 56 (90%) patients responded to preoperative CRT. FDG-PET-determined complete metabolic response (CMR) was achieved by 33 patients (54.1%), whereas pathologic CR was achieved by 28 patients (45.2%). Compared with endoscopic biopsy or CT scan, CMR by FDG-PET showed the highest correlation with pathologic CR (concordance, 71%). At a median follow-up of 19.3 months (range, 3.9–57.1 months), median overall survival (OS) was not reached in patients with CMR compared to 22.4 months in patients who did not achieve CMR. Median disease free survival (DFS) was not reached in patients with CMR compared to 17.4 months in patients who did not achieve CMR. By multivariate analysis, CMR by FDG-PET was significantly associated with better DFS and OS ($P = 0.006$, $P = 0.033$, respectively). The variables associated with pre-CRT PET scan were not predictive of survival.

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In conclusion, CMR by FDG-PET has a significant correlation with pathologic CR and can predict the long-term outcome in oesophageal cancer patients undergoing CRT. Although surgery is standard treatment for respectable oesophageal cancer, currently even in patients with CMR, the addition of ^{18}F-FDG-PET could be used to select the patient subgroup not requiring surgery.

1. Introduction

Despite conflicting results from randomised trials, concurrent chemoradiotherapy (CRT) followed by oesophagectomy has become the standard treatment option, with about 70% of patients receiving preoperative CRT undergoing esophagectomy.[1–4] Of resected patients, 11–56% achieve pathologic complete response (CR), and patients who achieve pathologic CR survive longer than those who do not.[5–7] In spite of improvements in surgical techniques, however, the postoperative mortality rate from oesophagectomy has been reported to be about 5–9%.[8] Furthermore, a recent European trial found no overall survival (OS) benefit when oesophagectomy was added to CRT, particularly for patients who responded to chemoradiotherapy.[9] This finding, in combination with the postoperative mortality rate from oesophagectomy, suggests that surgery may be detrimental for patients who have achieved pathologic CR after preoperative CRT. In addition, the increased rate of pathologic CR after preoperative CRT indicates a need for a surrogate marker that can predict pathologic CR in response to preoperative therapy.

Conventional structure-based imaging techniques, such as computed tomography (CT), endoscopy and endoscopic ultrasonography (EUS), are generally considered inaccurate in predicting response to CRT, primarily because these modalities cannot differentiate between viable tumours and inflammatory reactions, oedema, and fibrosis.[10,11] [^{18}F]-fluorodeoxyglucose (FDG)-positron emission tomography (PET), however, is a functional imaging modality that can detect changes in tissue metabolism that usually precede structural imaging response.[12,13] Current evidence suggests that ^{18}F-FDG PET can identify patients who achieve a pathologic response to neoadjuvant treatment prior to surgical resection, as well as being able to predict long-term survival.[14–16] We previously showed that the pathologic response of initially highly metabolic tumour after preoperative CRT could correlate with the metabolic response.[17] However, it is not clear whether complete metabolic response (CMR), as assessed by FDG-PET, reflects pathologic CR.

We therefore evaluated the accuracy of CMR assessed by FDG PET in predicting pathologic CR in patients with operable oesophageal cancer who underwent neoadjuvant CRT, as well as the ability of ^{18}F-FDG PET to predict long-term survival after preoperative CRT followed by surgery.

2. Patients and methods

2.1. *Eligibility*

Beginning in March 1999, we have performed prospective phase II and phase III clinical trials in locally advanced but resectable oesophageal cancer.[4,6] FDG-PET was introduced as a diagnostic tool in March 2001, and patients were evaluated with FDG-PET before and after CRT. Of the 89 consecutive patients who underwent FDG PET before and after CRT, 27 did not undergo oesophagectomy due to patient refusal, disease progression or poor general condition. Because the aim of this study was to evaluate the ability of FDG-PET to predict pathologic CR and long-term survival after preoperative CRT and surgery, only those patients who underwent preoperative CRT, two sessions of FDG-PET and subsequent oesophagectomy were included ($n = 62$). This prospective study was approved by the Institutional Review Board for Human Research of Asian Medical Centre, and all participants provided written informed consent.

2.2. *Pretreatment evaluation*

Patients underwent conventional evaluation (endoscopic biopsy, EUS, oesophagography and chest CT scan, plus abdominal CT in patients with lower oesophageal cancer) and FDG-PET before preoperative CRT. The clinical stage of each tumour was determined using the TNM staging system.

2.2.1. *Chest CT imaging*

Spiral CT scans were performed with contrast enhancement, and each slice had a 5-mm spatial thickness. Chest CT scans encompassed contiguous slices from the cricoid cartilage and included the lower neck to the upper abdomen, which, in turn, included the perigastric and mesenteric root lymph nodes. Each patient was evaluated by one of four experienced chest radiologists. Radiologic responses to CRT were determined by measuring the maximum tumour length and maximum wall thickness before and after treatment.

2.2.2. *FDG-PET acquisition and processing*

All patients fasted for at least 6 h, and glucose levels did not exceed 130 mg/dL in any patient. At 1 h after intravenous injection of about 550 MBq of ^{18}F-FDG, whole body PET scans from skull base to upper thigh were performed using PET or PET-CT scanners (ECAT HR^{+} or Biograph Sensation 16, SIEMENS, Knoxville, TN). Using PET scanner, emission and transmission images were acquired at each bed position for 6 and 4 min, respectively. Using PET-CT scanner, CT scans were acquired with a tube voltage of 120 kV, 110 mAs and a slice width of 5 mm, and PET emission data were acquired for 2 min per bed position. The PET images were reconstructed iteratively on a 128×128 matrix using an ordered-subsets expectation maximisation algorithm. For semiquantitative analysis of each lesion showing increased FDG uptake, the maximal standardised uptake value (SUV) based on patient's lean body mass

(LBM) was measured. LBM was calculated using the following formula: LBM = 1.07 height – 148 (weight/height).[2]

2.3. Preoperative CRT

Chemotherapy was begun on day 1 of radiotherapy. Until December 2002, cisplatin was given as a single intravenous (i.v.) bolus (60 mg/m^2) on days 1 and 29 with hydration, and fluorouracil (5-FU, 1000 mg/m^2/day) was administered as a continuous infusion for 4 days on days 2–5.[4] Beginning in January 2003, 5-FU was replaced by capecitabine, and patients received induction cisplatin (60 mg/m^2 i.v.) on day 1 and capecitabine (2000 mg/m^2/day p.o.) on days 1–14, followed by 1 week of rest. This was followed by cisplatin (30 mg/m^2 i.v.) on days 22, 29, 36, and 43, plus capecitabine (1600 mg/m^2/day p.o.), 5 days per week, concurrent with radiotherapy.[6] Radiotherapy was performed with 15-MV X-rays from a linear accelerator (Varian Clinac 1800, 2100CD, or 21EX; Varian Medical Systems, Palo Alto, CA). Until December 2002, 38 fractions of 1.2 Gy were delivered twice daily for a total dose of 45.6 Gy, with a minimum interval between fractions of 6 h. Radiotherapy was delivered 5 days a week and covered every radiation field.[4] The overall treatment time was 4 weeks. Beginning in January 2003, the fraction schedule was modified to 46 Gy in 23 fractions over 4 weeks (2 Gy per fraction per day, 5 days a week).

2.4. Treatment monitoring, restaging and follow-up evaluation

Patients were interviewed and examined weekly during CRT for evaluation of treatment safety and compliance. Acute toxicity was assessed according to the NCI-CTC version 2.0. For restaging, endoscopy with biopsy, oesophagography, chest CT, abdomen CT and FDG-PET were repeated after CRT prior to surgery. Evaluations after preoperative CRT were carried out at least 2–3 weeks after the end of CRT as a rule. After surgical treatment, all patients were evaluated with history, physical examination, chest and abdominal CT scans every 3 months for the first 2 years, and every 6 months for the next 3 years.

2.5. Assessment of response to CRT

2.5.1. Assessment of response by conventional modality

Endoscopy with biopsy was performed in all patients after preoperative CRT. CT results were reported independent of PET results, but as part of routine clinical practice by an experienced radiologist. Because most patients had radiation oesophagitis after CRT, additional information about mucosal irregularity were determined by oesophagography to assess response. Results of endoscopy, CT and PET scan were discussed by the investigators before surgery, and clinical response was defined by consensus. Responses were classified as CR, partial response (PR), minimal response/no change (MR), or progressive disease (PD) according to WHO criteria. In addition, patients were dichotomised into CR and residual disease (RD) groups.

2.5.2. Assessment of response by FDG-PET scan

All PET and PET/CT images were reviewed and interpreted by an experienced nuclear physician. Metabolic response on FDG-PET was classified into four groups as complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SD) and progressive metabolic disease (PMD) according to EORTC criteria.[18] Then, patients were dichotomised into CMR and residual metabolic disease groups. A PET scan was considered positive when a focal abnormal accumulation of FDG was observed. It was regarded as negative when a normal distribution of FDG tracer was observed, even if the CT was abnormal at this site. The diffuse increased activity in oesophagus on the field of radiation treatment was considered a benign oesophagitis. For semiquantitative analysis, when no visible lesion was evident on preoperative FDG-PET, the SUV was uniformly designated as 0.5 of the baseline or background FDG uptake level.

2.6. Surgery and assessment of pathologic response

All patients underwent oesophagectomy after completion of restaging workups. The surgeon dissected and tagged the regional lymph nodes using guidelines for lymph node mapping of oesophageal cancer.[19] In each case, the entire lesion was serially sliced into 4-mm-thick sections, each of which was examined for degree of local tumour spread and lymph node metastases. Patients with no residual viable tumour cells in the surgical specimen (pT0N0M0) were classified as having achieved pathologic CR. Patients with macroscopic or microscopic foci of residual tumours were considered to have pathologic RD.

2.7. Statistical analysis

The sensitivity, specificity, positive predictive value and negative predictive value of FDG-PET were calculated after comparison with pathologic findings, and the results were compared with those of conventional reevaluation workup. Survival probability analyses were performed using the Kaplan–Meier method. Survival was calculated from the date of surgery to the date of death or most recent follow-up. Statistical significance was assessed by the log-rank test. Independent predictive factors for survival were determined using Cox-regression analysis. Variables for univariate survival analysis included age, sex, location of primary site, histologic grade, clinical stage, maximum SUV of primary tumour, pre- and post-CRT SUV change, and CR/RD by CT and FDG-PET. Variables significant by univariate analysis ($P < 0.1$) were included in multivariate survival analysis. Data analysis were performed with SPSS version 12.0 (SPSS, Chicago, IL) and SigmaPlot 9.0 software. Statistical significance was defined as $P < 0.05$.

3. Results

3.1. Patient characteristics

The characteristics of the 62 patients are summarised in Table 1. Histologically, all primary tumours were squamous cell carcinomas.

3.2. Tumour response post-CRT

All patients underwent pre- and post-CRT endoscopy, oesophagography, CT scan and FDG-PET scan. The median time

Table 1 – Baseline demographic and clinical characteristics

	No. of patients (*N* = 62)	%
Age (years)		
Median (range)	63 (45–74)	
Sex		
Male	54	
Female	8	
Preoperative chemotherapy		
FP #1 & 45.6 Gy/38fr	9	
XP #1 → wXP & 46 Gy/23fr	53	
Dysphagia		
No dysphagia	13	21.0
Dysphagia to solid food	34	54.9
Dysphagia to liquid food	15	24.2
Weight loss (within 6 months)		
No weight loss	36	58.1
Weight loss <10%	17	27.4
Weight loss ⩾10%	9	9.6
Location of primary tumour		
Upper 1/3	3	4.8
Middle 1/3	25	40.3
Lower 1/3	34	54.8
Clinical stage		
Stage IIA	15	24.2
Stage IIB	18	29.0
Stage III	29	46.8
Tumour type, squamous carcinoma		
Well differentiated	6	9.7
Moderate differentiated	45	72.6
Poorly differentiated	11	17.7

Abbreviations: FP, 5FU and cisplatin; XP, capecitabine and cisplatin; wXP, weekly XP.

Table 2 – Results of serial FDG-PET scan, surgery and pathologic response

	No. of patients (*N* = 62)	%
Time from CRT to PET (median, range)	25 (15–59)	
Initial tumour length by PET (median, range)	4 (0–8)	
Initial max-SUV of primary tumour (median, range)	7 (0.5–15.1)	
Initial number of PET-positive lymph node	1 (0–9)	
SUV decrease % of primary tumour	83.3 (0–100)	
PET response		
CMR (complete metabolic response)	33	54.1
Not CMR	28	45.9
Clinical response (GFS/CT/PET)		
Response	56	90.3
Complete response	31	50.0
Partial response	25	40.3
No response	6	9.7
Time from CRT to surgery (median, range)	45 (30–79)	
Type of surgery		
Ivor-Lewis	51	82.3
McKeown	10	16.1
Transhiatal oesophagectomy	1	1.6
Complete resection		
R_0	60	96.8
R_1	2	3.2
Pathologic response		
Complete response	28	45.2
Residual disease	34	54.8
Pathologic staging		
Stage 0	28	45.2
Stage I	5	8.1
Stage II	15	24.2
Stage III	6	9.7
Stage IVA	2	3.2
T0N1	6	9.7

Abbreviation: SUV, standardised uptake value.

interval between the end of preoperative CRT and post-CRT PET scan was 25 days (range, 15–59 days). Fusion PET/CT imaging was performed in 27 patients (43.5%). Clinically, 56 patients (90.3%) were considered as responders after preoperative CRT. After the completion of CRT, 33 patients (53.2%) achieved CMR by PET criteria, whereas only nine patients (14.5%) achieved CR by CT criteria (Table 2).

3.3. *Results of oesophagectomy*

The results of surgical treatments are summarised in Table 2. The median time interval between the end of preoperative CRT and surgery was 45 days (range, 30–79 days). The median number of dissected lymph nodes per patient was 41 (range, 14–69).

3.4. *Comparisons of clinical response with pathologic results*

The results of response evaluation using endoscopic biopsy, CT scan and FDG-PET were compared with the results of pathologic response (Table 3). The results of post-CRT endoscopic biopsy were compared with pathologic T stage. The accuracies of endoscopic biopsy, CT scan and FDG-PET were 71%, 58%, and 71%, respectively, for distinguishing pathologic CR from RD. Clinical CR accurately predicted pathologic CR in 79% of patients.

3.5. *Survival and prognostic significance of PET response assessment*

Median patient follow-up period was 19.3 months (range, 3.9–57.1 months). At the time of analysis, 20 of the 58 patients were known to have died. Four patients died postoperatively, three of whom had achieved pathologic CR. Analysis of survival excluded patients who died of postoperative complication. We found that 82.4% of patients survived 1 year and 62.8% of patients survived 2 years. Median overall survival (OS) time was not reached, whereas median disease free survival (DFS) was 27.5 months (95% CI, 15.3–39.8 months). Uni-

Table 3 – Accuracy of post-CRT examinations for detection of residual disease ($n = 62$)

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Kappa coefficient, P
Endoscopic biopsy	30.4	100.0	100.0	66.7	70.9	$\kappa = 0.337$, $P = 0.001$
CT scan	84.8	16.7	58.3	44.4	57.9	$\kappa = 0.081$, $P = 0.485$
FDG-PET scan	51.2	66.7	78.6	63.6	70.5	$\kappa = 0.415$, $P = 0.001$
Clinical response	76.4	82.1	83.9	74.2	79.0	$\kappa = 0.583$, $P = 0.000$

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

Table 4 – Results of multivariate analysis for predicting disease free survival and overall survival

	Disease free survival			Overall survival		
	Months	HR	P	Months	HR	P
SUV decrease, %			0.025			0.64
<80%	17.09	1		24.23	1	
⩾80%	31.42	0.25		Not reached	0.52	
PET response			0.006			0.033
CMR	Not reached	1		Not reached	1	
Not CMR	17.38	3.58		22.38	3.09	

Abbreviations: SUV, standardised uptake value; CMR, complete metabolic response.

variate analysis showed that patients with an SUV decrease in FDG uptake of <80% had significantly shorter DFS ($P = 0.016$) and OS ($P = 0.023$) times than did patients with an SUV decrease of 80% or more. Patients with CMR had a significantly longer median survival time (Table 4). Multivariate analysis showed that an SUV decrease ⩾80% was an independent prognostic factor for DFS ($P = 0.025$), and that CMR was an independent prognostic factor for DFS ($P = 0.006$) and OS ($P = 0.033$) (Figs. 1 and 2).

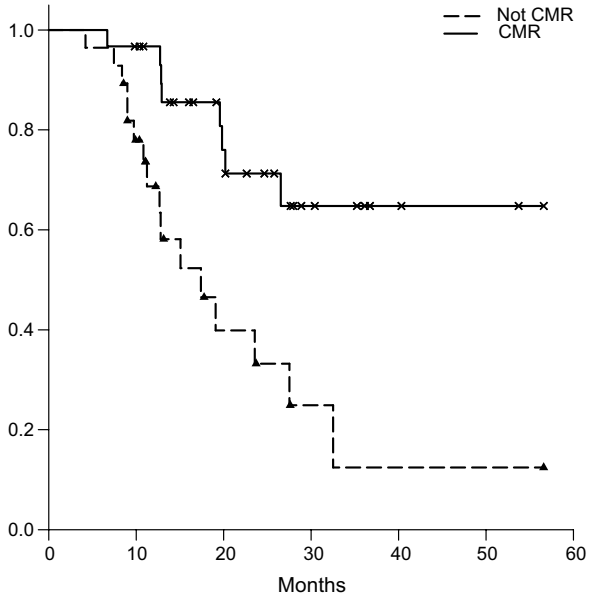

Fig. 1 – Disease free survival according to metabolic response (CMR versus not CMR, $P = 0.006$).

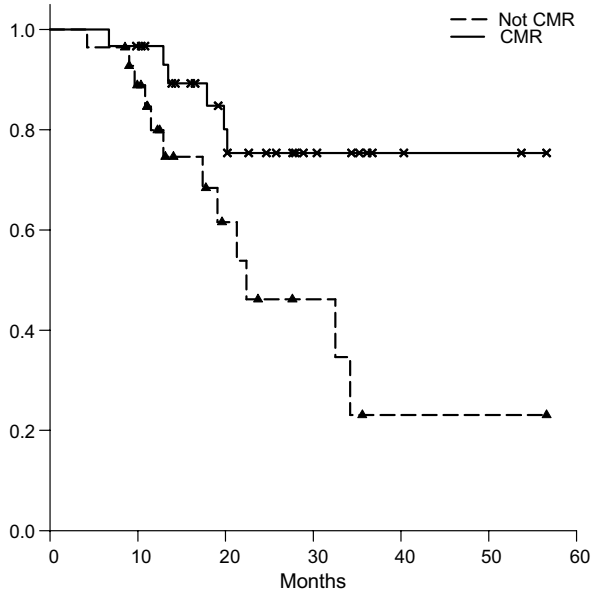

Fig. 2 – Overall survival according to metabolic response (CMR versus not CMR, $P = 0.033$).

3.6. *Patients with discordant results by FDG-PET and pathology*

Twelve patients showed a CMR by PET scan but did not attain pathologic CR. Six of these patients had pathological T0N1 disease, and five of these had only one regional lymph node metastasis each. Of the other six patients, one was stage I (pT1N0), two were stage IIA (pT2N0), two were stage IIB (pT2N1) and one was stage IVA (pT1N0M1a) with one celiac node metastasis. Each patient had a primary tumour <1 cm. At a median follow-up of 24 months (range, 5.5–54.2 months), three patients had died, one each of operative mortality,

pneumonia and disease progression. Three patients (25%) showed disease recurrence, one with locoregional and two with lung metastases. To date, seven of these patients remain alive without disease.

4. Discussion

Up to 40% of these patients have been reported to achieve pathologic CR after preoperative CRT, with the proportion being higher in patients with squamous cell carcinoma than in those with adenocarcinoma. In addition, the authors had experienced in previous studies that about 50% of patients who received preoperative CRT achieved pathologic CR.[4,6] Considering the morbidity of oesophagectomy and adverse effects for quality of life, if it is possible to predict whether patients will achieve pathologic CR, some patients are able to avoid oesophagectomy and the associated complications.

In the current study, we analysed CMR by FDG-PET as a marker for predicting pathologic CR and survival. Although, we found that CMR by FDG-PET showed the highest correlation with pathologic CR, the correlation was only 71%. False positives were due to radiation oesophagitis and reactive mediastinal lymphadenopathy. Small residual disease, particularly in single regional lymph nodes, was falsely negative by FDG-PET scan. Our results are in agreement with those of a study in 36 patients assessed before and 1 month after CRT, in which the concordance between serial FDG-PET and histology was 78% and PET had a similar accuracy for adenocarcinoma as for squamous cell carcinoma.[15] In another study, a post-CRT PET SUV $\leqslant$4 was observed to have the highest accuracy for pathologic response (76%).[20] At present, the gold standard for evaluating the response to preoperative CRT is surgery; FDG-PET is unsuitable for use as the sole criterion to determine the need for oesophagectomy.

PET/CT has been reported to improve the accuracy of FDG imaging in oesophageal cancer.[21] Although we performed FDG PET/CT in 27 patients (43.5%), its accuracy was not superior to that of FDG-PET scan alone. The optimal time at which to evaluate the response to CRT has not yet been determined, although FDG-PET performed 2 weeks after the initiation of preoperative chemotherapy for oesophageal carcinoma had a much lower false-positive rate.[22] Although we performed post-CRT PET scan at least 2 weeks after the end of radiotherapy, we found that 26% of patients had radiation oesophagitis by PET (data not shown).

We observed that endoscopic biopsy had sensitivity for detecting residual disease of only 30.4%, whereas it had a false negative rate for predicting residual primary tumours of 58.2%. Thus, endoscopic biopsy provided little benefit for the evaluation of pathologic response before surgery. The accuracy of endoscopic ultrasound restaging after preoperative CRT has been reported to be <50% in oesophageal cancer, especially in T-stage, because of inflammatory changes.[11,23,24] Although its accuracy was higher for squamous cell carcinomas, disease free endoscopic biopsy could not predict complete response to preoperative CRT.

We found that patients who attained CMR by post-CRT FDG-PET had significantly better OS and DFS than those who did not attain CMR. Twelve patients who achieved CMR by FDG-PET, however, had residual pathologic disease; of these, five had a single lymph node metastasis each. Although a SUV decrease of the primary tumour $\geqslant$80% was also associated with better DFS, the results of initial FDG-PET could not predict patient outcome. Baseline number of PET abnormalities (NPA) >1, a marker of regional node metastases, has been reported to be an independent predictor of OS.[25] In the current study, 33 of our patients (56.9%) were found to have node metastases by FDG-PET. When we compared patient survival according to the number of positive lymph nodes, we found no survival differences, consistent with reports that baseline clinical stage is not a predictor of survival.[26] The usefulness of baseline PET scan for predicting long-term outcome remains unclear.

Although the follow-up period was relatively short, with median OS not reached, this clinical study is the first to evaluate the predictive value of FDG-PET CMR criteria for pathologic CR and survival after preoperative CRT in operable oesophageal cancer.

In conclusion, we found that FDG-PET scan is a useful tool for predicting pathologic response and long-term outcome in the preoperative CRT setting. Our study emphasises the importance of developing biomarkers that can accurately predict pathologic response.

Conflict of interest statement

None declared.

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