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Early metabolic change after induction chemotherapy predicts histologic response and prognosis in patients with esophageal cancer: Secondary analysis of a randomized trial

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Abstract

Background—Early metabolic response after preoperative induction chemotherapy (IC) appears to predict histologic response and prognosis in esophageal cancer (EC), but the usefulness of this approach needs further development.

Objective—We evaluated metabolic response after one cycle of IC using positron emission tomography (PET) to correlate PET response and outcomes.

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Patients and Methods—We retrospectively analyzed PET data from a randomized phase 2 trial (NCT00525915) of chemoradiation and surgery with or without IC for the treatment of EC. PET was performed at baseline, after one cycle of IC, and 5–7 weeks after chemoradiation. The relationship between PET response (≥35% reduction in standardized uptake value [SUV]) after IC and treatment response was analyzed.

Results—In 63 patients who received IC, the mean initial SUV_{max} prior to treatment was 11.9 ± 8.04 and mean SUV_{max} after one cycle of IC was 6.47 ± 4.45 . The mean SUV reduction after IC was 39.3%. Eleven of 37 PET responders achieved a pathologic complete response (pCR), but only two of 22 PET non-responders did (univariate logistic regression; odds ratio: 4.25, 95% confidence interval: 0.83–21.77; $p = 0.08$). PET responders to IC had significantly longer overall survival (OS) than PET nonresponders (log-rank $p = 0.009$). PET response after chemoradiation did not correlated with OS (log-rank $p = 0.15$).

Conclusion—Early PET response after IC is prognostic but subsequent PET changes (for example, after chemoradiation) are not prognostic. Early PET response might have a potential to predict pCR.

1 Introduction

Esophageal cancer (EC) is estimated to be the eighth most common cause of cancer (456,000 yearly cases worldwide) and the sixth most common cause of cancer-related death (400,000 yearly deaths) [1]. Preoperative chemoradiation followed by surgery is currently the standard therapy for resectable advanced EC [2, 3]. Approximately 25% of patients achieve a pathologic complete response (pCR) in the surgical specimen after preoperative chemoradiation [3]. If pCR can be predicted before surgery, a selective surgical resection strategy can be used, which can help preserve the esophagus [4].

Positron emission tomography (PET) has been used for the staging of EC, as well as restaging after preoperative treatment [5]. In addition, because metabolic response after preoperative therapy was shown not to correlate with pCR, further evaluation of this strategy is warranted [6–10]. The MUNICON I trial showed that EC patients with early metabolic response to preoperative chemotherapy had a better prognosis [11]. In contrast, metabolic nonresponders had poor prognosis even if therapy was changed to chemoradiation [12]. However, there is an ongoing desire to associate PET response to pCR as it can change the therapeutic landscape.

Our group reported a phase II randomized trial (NCT00525915) of induction chemotherapy (IC) followed by preoperative chemoradiation, or preoperative chemoradiation without IC, in which PET was performed before treatment, after one cycle of IC, and before surgery [13]. Here, we performed an ad hoc secondary analysis to determine whether early PET response is predictive and prognostic. We also had an opportunity to review the value of late PET changes (after chemoradiation) and correlation these with outcomes.

2 Patients and Methods

2.1 Patients

We analyzed patients who had participated in a prospective phase 2 study conducted at UT MD Anderson Cancer Center from 2005 to 2011 (NCT00525915) [13]. The study enrolled trimodality eligible patients who were younger than 76 years and had adequate organ function, Eastern Cooperative Oncology Group performance status of 0 or 1, and T1N+ or T2/3 with any N baseline clinical stage. Patients were followed with imaging studies and endoscopic evaluations every 3 months for 1 year, then every 6 months for two additional years, and finally once per year for up to 5 years or until death. The Institutional Review Board approved this analysis. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients included in the study.

2.2 Treatment Groups

Patients were randomized to either chemoradiation followed by surgery or IC followed by chemoradiation and then surgery. All preoperative treatments were carried out in the outpatient setting.

Patients in the non-IC group received 50.4 Gy of intensity-modulated proton or photon radiation in 28 fractions and concurrent fluorouracil (250 mg/m² daily as a 24-hour infusion from Monday to Friday for 5 weeks) and oxaliplatin (40 mg/m² intravenously once per week for 5 weeks). Patients in the IC group received up to two cycles (8 weeks) of IC consisting of a 4-week cycle of 2200 mg/m² fluorouracil infused over 48 hours starting on days 1 and 15 and 100 mg/m² oxaliplatin on days 1 and 15. After one cycle of IC, PET or endoscopic evaluation was performed. Patients who did not have any progression or adverse events after the first cycle of IC received a second cycle of IC and then the same chemoradiation as in the non-IC group.

After recovering from the chemoradiation for 4 to 7 weeks, all patients underwent preoperative staging and surgical evaluation. Patients then underwent minimally invasive esophagectomy or three-field approach, transhiatal, or transthoracic esophagectomy as determined by the operating team.

2.3 PET Evaluation

PET was performed at baseline, after one cycle of IC (median: day 26, range: 22–31), and after chemoradiation (median: 4.86 weeks, range: 3.29–13). The reduction in standardized uptake value (SUV) in the post-IC and post-chemoradiation PET studies was calculated relative to the SUV in the pretreatment PET study. PET responders were defined as those who had a ≥35% SUV reduction, as in the MUNICON trial [11, 12]. SUV reduction could not be calculated in one patient in the IC group, who had no FDG uptake in the pretreatment PET study.

2.4 Statistical Analysis

All statistical analyses were conducted in SAS and Splus. All p values were two-sided and the statistical significance cutoff was $p = 0.05$. The Chi-squared test was used to assess differences in categorical variables and the Wilcoxon rank-sum test was used to assess differences in continuous variables. Overall survival (OS) was defined as the time from randomization to the date of death due to any cause. OS probabilities were estimated using the Kaplan-Meier method. Univariate logistic regression analysis was performed to identify predictors of pCR, and odds ratios with 95% confidence intervals were calculated.

3 Results

3.1 Patient Characteristics

A total of 126 patients participated in the study (Figure 1). Patient characteristics are listed in Table 1. The groups were well balanced except for performance status; more patients who received IC had a performance status of 0 than did patients who did not undergo IC (44% compared with 25%, $p = 0.02$).

3.2 PET Response after One Cycle of IC

In the IC group, the mean ($\pm$ standard deviation) SUV_{max} prior to treatment was 11.9 ± 8.04 and the mean SUV_{max} after one cycle of IC was 6.47 ± 4.45 . The mean SUV reduction after IC was 39.3%. Of those patients who underwent a PET evaluation and did not have any progression after the first cycle of IC, 37 (63%) were PET responders (35% reduction) and 22 (37%) were PET nonresponders. Having a poorly differentiated tumor was associated with PET nonresponse ($p = 0.007$). In addition, the median SUV of the baseline PET study was significantly higher in PET responders than in nonresponders ($p = 0.005$). No other characteristics differed significantly between the PET responders and the PET nonresponders (Table 2).

3.3 PET Response and pCR

Of 126 patients, 109 underwent surgery (54 in the IC group and 55 in the non-IC group) and 21 of these (19%) achieved pCR. In the IC group, 14 patients (26%) achieved pCR, and in the non-IC group, 7 (13%) achieved pCR. Among the 37 PET responders to IC, 11 patients achieved pCR. In contrast, only two of the 22 PET nonresponders achieved pCR (odds ratio: 4.25, 95% confidence interval (CI): 0.83 – 21.77; $p = 0.08$) (Table 3). In the entire cohort, 18 of the 80 PET responders after chemoradiation and 2 of the 27 PET nonresponders achieved a pCR (odds ratio: 3.63, 95% CI: 0.78–16.81; $p = 0.10$).

3.4 PET Response and Survival

Of 126 patients, 76 (60%) have died. The median OS was 3.8 years (95% CI: 2.7–7.4 years). As shown in Figure 2A, PET responders after IC had significantly better OS (median OS not reached) than did PET nonresponders (median OS = 2.1 years; $p = 0.009$). In contrast, PET response after chemoradiation was not significantly correlated with OS in the IC group ($p = 0.15$; Figure 2B). Moreover, even among all patients, PET response after chemoradiation was not correlated with OS ($p = 0.40$; Figure 2C).

4 Discussion

Our results show that PET response after IC, but not after chemoradiation, is associated with favorable prognosis in patients with esophageal cancer. While not statistically significant, PET response to IC results in a trend for achieving a pCR.

Early PET response has previously been shown to be predictive of response to preoperative chemotherapy and could serve as a potential tool in personalized therapy. The MUNICON I trial showed that early PET responders to preoperative chemotherapy had a favorable prognosis and major histologic response [11]. Then, the MUNICON II trial revealed that PET nonresponders had poor prognosis even after radiation was added to chemotherapy [12]. These findings are consistent with our results that early PET response after IC is prognostic. However, in the MUNICON trials, treatment was changed according to PET response, whereas in our study, the planned preoperative treatment was administered regardless of response to IC. The MUNICON II trial showed that adding radiation to preoperative chemotherapy did not improve prognosis in nonresponders [12]. The PET nonresponder underwent a total dose of 32 Gy of radiation with concurrent chemotherapy consisting of monotherapy cisplatin or 5-fluorouracil, if renal function did not allow cisplatin therapy. However, this regimen and radiation seem suboptimal.

The CALGB 80803 study has evaluated another strategy, in which the chemotherapy regimen (FOLFOX or carboplatin/paclitaxel) is determined by PET response after IC [14]. In this study, 257 patients with EC first received FOLFOX or carboplatin/paclitaxel during IC and then those with PET nonresponse were switched to the alternative regimen during chemoradiation. The pCR rate of PET responder was 26% and that of PET nonresponder was 18%, which satisfied the primary study endpoint of improving pCR for PET nonresponder. This pCR rate of PET nonresponder to IC is higher than that of our current study (9%) and a previous report (4%) [15], which suggests that crossing over to alternative regimen in chemoradiation might increase the pCR rate. However, the design of this study did not include a head-to-head comparison of the PET non-responder continuing on the same regimen, and crossing over to alternative regimen. Ideally, the PET non-responder should be compared in two cohorts: one cohort receiving the same chemotherapy with radiation and the other cohort receiving an alternate chemotherapy. Survival results of the CALGB 80803 study have not yet been reported. Further studies are needed to overcome primary resistance.

The strategy of making decisions based on PET response is under evolution and much work remains to be done. Interestingly, three PET responders who declined surgery in this study have not had a recurrence in five years.

There are several unclear issues regarding the practical usefulness of PET. First, the definition of PET response remains unclear. The PET response criteria in solid tumors recommend 30% SUV reduction as a cutoff value, but this is for all solid tumors [16]. We defined PET response as >35% reduction in SUV because this cutoff was used in a previous study of patients with EC [11, 14, 17, 18]. We analyzed survival and pCR outcomes by using both a >30% and >35% cutoff level, but there were no differences. Second, reported results

of PET response have varied. Consistent with our results, several studies reported that SUV changes after preoperative chemotherapy might be associated with histologic response and survival [11, 17–19]. A recent meta-analysis by Zhu et al. showed that early metabolic changes could predict treatment outcomes [20]. After chemoradiation, complete metabolic response has been identified as a predictive marker [21]. However, when cut-off values were used, varying results have been reported [9, 8, 22, 23]. In our study, PET response after chemoradiation was not prognostic or predictive of pathological response.

Our study has limitations. First, the patient population consisted of those participating in a phase 2 randomized clinical trial, but the analysis was retrospectively performed. Second, the number of patients was limited. Especially, the small patient numbers in the subgroups limit the statistical analysis. Third, there is missing PET in some patients and these were not included. Finally, some patients declined surgery after preoperative chemoradiation. The strength of our study is that data were derived from a prospectively conducted trial, it shows that the first PET response (after IC) is prognostic but second PET response (after chemoradiation) has no prognostic or predictive value. PET cannot predict for pCR and finally, patients who have an EC with high baseline SUV are likely to be PET responders.

In conclusion, our results suggest that early PET response after IC could be prognostic and has a potential to be predictive for pCR, but has considerable practical limitations. Further refining of PET data and approach might prove useful. Combining PET response to biomarker assays might be productive as well.

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Key Points

- PET response after induction chemotherapy in esophageal cancer patients who are treated with trimodality treatment is associated with favorable prognosis.
- Early PET response has the potential to be predictive of pathological complete response.
- Early PET response appears prognostic rather than predictive of response to chemoradiation.

Figure 1.
CONSORT diagram for the phase 2 study, from which the current data was derived. IC, induction chemotherapy; PET, positron emission tomography.

Figure 2.

Kaplan-Meier analysis of overall survival. (A) Kaplan-Meier curves for responders (standardized uptake value [SUV] reduction $\geq 35\%$) and nonresponders (SUV reduction $< 35\%$) to induction chemotherapy (IC). (B) Kaplan-Meier curves for responders and nonresponders after chemoradiation among those who received IC. (C) Kaplan-Meier curves for responders and nonresponders to chemoradiation among all patients who underwent chemoradiation in the study.

Table 1

Demographic and clinical characteristics of patients who participated in the phase 2 study, from which the current data was derived.

Variable	No. (%)			p
	All Patients n = 126	No IC n = 63	IC n = 63	
Median age (range)	60 (27–75)	60 (29–74)	60 (27–75)	0.73
Race/ethnicity				0.84
White	118 (94)	58 (92)	60 (95)	
Hispanic	6 (5)	3 (5)	3 (5)	
Black	1 (1)	1 (2)	0 (0)	
Asian	1 (1)	1 (2)	0 (0)	
Sex				>0.99
Male	117 (93)	59 (94)	59 (94)	
Female	9 (7)	4 (6)	4 (6)	
ECOG performance status				0.02
0	44 (35)	16 (25)	28 (44)	
1	82 (65)	47 (75)	35 (56)	
Tumor histologic characteristics				>0.99
Adenocarcinoma	122 (97)	61 (97)	61 (97)	
Squamous cell carcinoma	4 (3)	2 (3)	2 (3)	
Location of tumor				>0.99
Siewert type I	81 (64)	41 (65)	40 (63)	
Siewert type II	41 (33)	20 (32)	21 (33)	
Esophagus	4 (3)	2 (3)	2 (3)	
Baseline T stage				0.63
T2	20 (16)	9 (14)	11 (17)	
T3	106 (84)	54 (86)	52 (83)	
Baseline N stage				0.39
N0	44 (35)	22 (35)	22 (35)	
N1	53 (42)	23 (37)	30 (48)	
N2	27 (21)	17 (27)	10 (16)	
N3	2 (2)	1 (2)	1 (2)	
Baseline clinical stage				0.70
IB	7 (6)	4 (6)	3 (5)	
IIA	5 (4)	1 (2)	4 (6)	
IIB	38 (30)	19 (30)	19 (30)	
IIIA	49 (39)	23 (37)	26 (41)	
IIIB	25 (20)	15 (24)	10 (16)	
IIIC	2 (2)	1 (2)	1 (2)	
Tumor differentiation				0.72
Well differentiated	1 (1)	0 (0)	1 (2)	
Moderately differentiated	58 (46)	28 (44)	30 (48)	

Variable	No. (%)			p
	All Patients n = 126	No IC n = 63	IC n = 63	
Poorly differentiated	67 (53)	35 (56)	32 (51)	
Median tumor length (range)	5 (1.4–13)	5 (1.4–13)	5 (2–9)	0.87
Median initial PET SUV (range)	10.1 (7.0–15.4)	10.1 (3.2–39.6)	10.1 (0–45)	0.62
Median PET SUV after chemoradiation (range)	4.4 (0–12)	4.45 (0–12)	4.2 (0–12)	0.27

IC, induction chemotherapy; ECOG, Eastern Cooperative Oncology Group; PET, positron emission tomography; SUV, standardized uptake value.

Table 2

Patient characteristics by response to induction chemotherapy (35% decrease in SUV on PET after one cycle compared with pretreatment PET SUV value; n = 59).

Variable	Responders, n = 37	Nonresponders, n = 22	p
Median age (range)	62 (43–75)	55.5 (27–70)	0.07
Race/ethnicity			0.88
White	35 (95)	21 (95)	
Hispanic	2 (5)	1 (5)	
Sex			0.59
Male	34 (92)	21 (95)	
Female	3 (8)	1 (5)	
ECOG performance status			0.40
0	16 (43)	12 (55)	
1	21 (57)	10 (45)	
Tumor histologic characteristics			0.71
Adenocarcinoma	36 (97)	21 (95)	
Squamous cell carcinoma	1 (3)	1 (5)	
Location of tumor			0.68
AEG I	22 (59)	15 (68)	
AEG II	14 (38)	6 (27)	
Esophagus	1 (3)	1 (5)	
Baseline T Stage			0.15
T2	9 (24)	2 (9)	
T3	28 (76)	20 (91)	
Baseline N stage			0.49
N0	12 (32)	9 (41)	
N1	20 (54)	9 (41)	
N2	5 (14)	3 (14)	
N3	0 (0)	1 (5)	
Baseline clinical stage			0.58
IB	3 (8)	0 (0)	
IIA	2 (5)	2 (9)	
IIB	11 (30)	7 (32)	
IIIA	16 (43)	9 (41)	
IIIB	5 (14)	3 (14)	
IIIC	0 (0)	1 (5)	
Tumor differentiation			0.007
Well differentiated	1 (3)	0 (0)	
Moderately differentiated	23 (62)	5 (23)	
Poorly differentiated	13 (35)	17 (77)	
Median tumor length (range)	5 cm (2–9 cm)	6 cm (2–9 cm)	0.30
Median initial PET SUV (range)	10.9 (4.9–45)	7.85 (3–14.9)	0.005

Variable	Responders, n = 37	Nonresponders, n = 22	p
Median PET SUV after chemoradiation (range)	4.2 (0–12)	3.9 (0–10.6)	0.86
Median PET SUV after one cycle of induction chemotherapy (range)	5.3 (0–18.5)	6.7 (2.8–18.4)	0.048

PET, positron emission tomography; SUV, standardized uptake value; ECOG, Eastern Cooperative Oncology Group.

Table 3

Univariate logistic regression analysis of factors associated with pathologic complete response.

Factor	Odds ratio (95% confidence interval)	p
ECOG performance status		0.79
0	1 (reference)	
1	1.14 (0.42 3.13)	
Tumor differentiation		0.70
Moderately or well differentiated	1 (reference)	
Poorly differentiated	0.83 (0.32 2.15)	
Tumor depth		0.58
IB, IIA, IIB	1 (reference)	
IIIA, IIIB	0.76 (0.29 1.98)	
SUV reduction after IC		0.08
<35%	1 (reference)	
35%	4.25 (0.83 21.77)	
SUV reduction after chemoradiation		0.10
<35%	1 (reference)	
35%	3.63 (0.78 16.81)	

ECOG, Eastern Cooperative Oncology Group; SUV, standardized uptake value; IC, induction chemotherapy.