



# Metabolic assessment by PET in the treatment of esophageal cancer

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*Comment on:* Harada K, Wang X, Shimodaira Y, *et al.* Early Metabolic Change after Induction Chemotherapy Predicts Histologic Response and Prognosis in Patients with Esophageal Cancer: Secondary Analysis of a Randomized Trial. *Target Oncol* 2018;13:99-106.

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The use of [<sup>18</sup>F]-2-fluoro-deoxy-D-glucose positron emission tomography (FDG-PET) imaging is emerging as an important tool in the treatment of esophageal cancer. Over a decade ago, the MUNICON investigators first incorporated metabolic assessment by PET into clinical trial design and evaluated the strategy of taking patients with locally advanced gastroesophageal junction (GEJ) adenocarcinomas, who had a suboptimal response to two weeks of induction chemotherapy with 5-fluorouracil (FU)/cisplatin directly to surgery (1). Patients with a metabolic response (defined as  $\geq 35\%$  reduction in standard uptake value (SUV) between baseline and repeat PET) continued with an additional 12 weeks of chemotherapy prior to surgery. PET responders had significantly improved outcomes when compared to PET non-responders. Compared to a prior prospective study where all patients received pre-operative therapy irrespective of PET response, the results suggested no worsening of outcomes with early discontinuation of inactive pre-operative therapy in PET non-responders (2).

In the article accompanying this editorial, Harada and colleagues report results of an ad hoc secondary analysis of PET data from 63 patients who were treated in a randomized phase II trial evaluating chemoradiation and surgery with or without induction chemotherapy for the treatment of esophageal cancer. The majority of patients were male and had adenocarcinoma histology. Additionally, most patients had GEJ tumors and locally advanced (T3/node positive) disease. They found that early PET response after induction chemotherapy was associated with favorable

prognosis (median OS not reached in PET responders *vs.* 2.1 years in non-responders;  $P=0.009$ ) and observed a trend towards improvement in pathologic complete response (pCR) rate (odds ratio 4.25, 95% confidence interval: 0.83–21.77,  $P=0.08$ ). However, PET response after chemoradiation was not predictive of pathologic response and did not correlate with overall survival (OS). This is in keeping with recent studies which have suggested that PET may not be helpful as a predictive marker of response to pre-operative chemoradiation (3,4). This study also found that the median SUV of the baseline PET was significantly higher in PET responders than non-responders, which has also been shown previously (5).

In this study, the planned preoperative therapy was administered regardless of metabolic response to induction chemotherapy. A number of studies have now evaluated if suboptimal metabolic response can be countered with a change in planned treatment. The MUNICON 2 trial attempted to improve outcomes in patients with GEJ adenocarcinoma who were PET non-responders to 5-FU/cisplatin by treating them with “salvage” chemoradiation with cisplatin prior to surgery (6). Despite this, PET non-responders continued to have inferior 2-year progression-free survival (PFS) and a trend toward inferior 2-year OS suggesting that these patients may have underlying unfavorable biology. However, cisplatin was administered as a single-agent with a low dose of radiation (32 Gy) and was already associated with sub-optimal PET response when administered as induction therapy in combination with 5-FU in these patients.

A strategy of changing to alternative non-cross-resistant chemotherapy has also been evaluated. Our group previously reported long-term disease-free survival in patients who had progressed on induction chemotherapy and were changed to alternative chemotherapy during chemoradiation (7). We also retrospectively reviewed our experience of changing to alternative chemotherapy during radiation in patients with esophageal/GEJ adenocarcinomas who were PET non-responders to induction chemotherapy (8). Results suggested that improvements in pCR rate and PFS were possible. Furthermore, a trend toward improved OS in patients who switched to alternative chemotherapy during radiation was observed.

A similar approach was then evaluated prospectively in the Cancer and Leukemia Group B 80803 study, a randomized phase II trial which enrolled patients with locally advanced esophageal and GEJ adenocarcinoma (9). Following a baseline PET, 257 patients received induction FOLFOX (bolus and infusional 5-FU/leucovorin/oxaliplatin) or carboplatin/paclitaxel. PET responders continued with the same regimen during radiation prior to surgery, while PET non-responders received the alternative regimen with radiation, followed by surgery. The primary endpoint of the study was to improve the pCR rate from a historical control rate of 3%. Patients who were PET non-responders had pCR rates of 17–19%, meeting the primary endpoint of the study (1,6,8). Survival data was recently presented (10). Median OS was 47.3 months in PET responders *vs.* 28.9 months in PET non-responders ( $P=0.09$ ). Based on comparison with historical controls, changing chemotherapy in PET non-responders appeared to improve outcomes in this patient population (6) and also compares favorably with the OS observed in PET non-responders in the study reported here by Harada and colleagues (2.1 years).

Intriguingly, the pCR rate in patients who were PET responders to induction FOLFOX and continued this regimen with radiation was 37.5% compared to 12.5% in those who were PET responders to induction carboplatin/paclitaxel. Furthermore, OS in patients who received FOLFOX during induction and radiation was 50.3 months representing the longest OS of all 4 patient groups while patients who received carboplatin/paclitaxel during induction and radiation had an OS of 39.6 months. While this study was not designed to detect a difference in outcome between induction regimens, these results are hypothesis-generating. Finally, patients who were PET non-responders to induction FOLFOX and were switched

to carboplatin/paclitaxel during radiation had a median OS of 30.9 months which also compares favorably to the 2.1 years reported in this study and again suggests that there may be a benefit from the use of PET in individualizing treatment by guiding appropriate chemotherapy during radiation.

There are also emerging data regarding the role of metabolic assessment by PET in esophageal squamous cell carcinoma (SCC). Recent data from our group showed that PET imaging after induction chemotherapy was predictive of outcomes in 111 patients with localized esophageal SCC who received chemoradiation with or without surgery (11). Median PFS (70.1 *vs.* 7.1 months;  $P<0.01$ ) and median OS (84.8 *vs.* 17.2 months;  $P<0.01$ ) were improved in PET responders *vs.* non-responders. However, in contrast to results observed in adenocarcinoma, our data suggest that patients who are PET non-responders after induction do not derive benefit from a strategy of changing chemotherapy during radiation. Of 41 PET non-responders, 16 continued with the same chemotherapy and 25 changed to alternative chemotherapy with radiation. Median PFS and OS in PET non-responders who changed chemotherapy *vs.* those who did not were 6.4 *vs.* 8.3 months ( $P=0.556$ ) and 14.1 *vs.* 17.2 months ( $P=0.81$ ) respectively.

The SCOPE2 trial (NCT02741856) is prospectively evaluating radiotherapy dose escalation in a randomized phase II/III trial in patients with esophageal adenocarcinoma and SCC receiving definitive chemoradiation. Patients are randomized to standard or high dose radiation and those who are PET non-responders to initial therapy with cisplatin/capecitabine will also be eligible to be randomized to alternative chemotherapy with carboplatin/paclitaxel along with either standard or high dose radiation.

However, the efficacy of a higher radiation dose is called into question by the results of a Chinese study evaluating the optimal radiation dose during definitive chemoradiation for 305 inoperable esophageal SCC. These data have been presented in poster form and demonstrated no difference in locoregional PFS, PFS or OS in patients treated with 60 Gy radiation versus standard dose radiation (50 Gy) in combination with cisplatin/docetaxel (12). In addition, in our SCC data, the majority of PET non-responders (70%) experienced distant failure. Taken together, this suggests that intensification of locoregional therapy is unlikely to be a successful approach.

Instead, the addition of novel agents is urgently needed. Increasing knowledge of the molecular characteristics of esophageal carcinoma and pathway networks and

their interactions may provide a framework to develop new therapies, including targeted therapies and immunotherapeutic strategies. Molecular analysis is also required in both PET responders and non-responders to uncover markers of response and potential mechanisms of chemoresistance. Future trials should enroll by single histology and stratify patients by PET response to help advance our knowledge in this area.

The results of the study by Harada *et al.* further endorse the role of metabolic assessment by PET in predicting outcomes following subsequent chemoradiation and surgery in patients with esophageal carcinoma. The results of the CALGB 80803 study suggest that PET response following induction chemotherapy may be clinically actionable by allowing consideration of a change to alternate chemotherapy during radiation in patients with esophageal adenocarcinoma who are PET non-responders. This may allow us to narrow the divide in survival outcomes between PET responders and non-responders. Going forward, PET imaging may have a role in identifying patients likely to experience poor outcomes who can then be considered for experimental approaches, such as the addition of immune checkpoint inhibitors to treatment regimens.

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