Editorial

Editorial on "Can CT-PET and endoscopic assessment post-neoadjuvant chemoradiotherapy predict residual disease in esophageal cancer"

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Neoadjuvant chemoradiation (nCRT) followed by surgery is the most common treatment modality for resectable esophageal cancer nowadays (1). Esophagectomy and gastrointestinal continuity reconstruction are extensive and challenging procedures (2). Some studies had shown that patients achieved pathologic complete response (pCR) may not benefit from subsequent surgery (3,4). However, the assumption of sparing the surgery is based on the pathologically disease free of patients. The main question arise that, can the clinical complete response (cCR) assessed by positron emission tomography (PET)/computed tomography (CT) and endoscope truly represent the microscopic complete response on pathologic examination?

In the article "Can CT-PET and endoscopic assessment post-neoadjuvant chemoradiotherapy predict residual disease in esophageal cancer" recently published in *Annals of Surgery* (5), Heneghan *et al.* tried to answer the question. The authors performed a retrospective analysis on consecutive patients with stage I–III locally advanced esophageal cancer (LAEC) between 2006 and 2014. All 138 patients [103 adenocarcinomas and 35 squamous cell carcinomas (SCC)] had nCRT followed by surgery. Both endoscopy and F-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT evaluations were performed at the initial staging and at restaging 4–6 weeks after nCRT. Authors investigated the ability of the restaging PET/CT and endoscope in identification of patients with pCR.

Complete metabolic response (cMR), defined by SUVmax <4 and no nodal uptake on PET/CT, showed poor sensitivity (55.9%) and poor positive predictive value (PPV, 30.2%) for pCR. Among the 63 patients with cMR, only 30% had actually achieved pCR, while many of them had minimal residual disease (32%) or nodal positive disease (25%). The change in tumor SUVmax (%ΔSUVmax, 63.3%±24.7%) was a significant predictor of pCR in univariate analysis but was not significant in multivariate analysis. Complete response on endoscopy (cER) also had poor sensitivity (40.7%) and PPV (24.4%) for pCR. Although endoscopic ultrasound and systematic biopsy were not performed in this study, the low sensitivity of endoscopy in detection of pCR is consistent with other studies (6-8). The complete responder groups defined by PET/CT and endoscope seem not consistent with each other (Spearman correlation coefficient =0.07, P=0.48). This discrepancy between the two modalities may be explained by the basic difference between anatomic and molecular imaging. Unlike the direct visualization of morphologic changes of esophageal mucosa on endoscope, the metabolic changes on PET may precede detectable morphologic changes on endoscope (9). However, both modalities are suboptimal in detection of pCR when the mucosal changes or glycolytic activity of minimal tumor burden is beyond their resolutions. The cCR, defined as combination of both cMR

and cER, was limited by low sensitivity of both modalities and had the worst sensitivity (32.4%) and poor PPV (35.5%) for pCR. No matter using cMR, cER or cCR, the sensitivity and PPV for pCR were worse on patients with adenocarcinoma than SCC. In multivariate analysis, only histological subtype and lymph node status were significant predictors of pCR. None of the imaging assessments was independent predictor of pCR. However, both cMR and cCR demonstrated prognostic significance in survival cox regression analysis. Of interest, in patients with pCR, those with cMR had additional survival benefit. The importance of PET/CT in post-nCRT risk stratification had been well known (10,11).

The intention to avoid surgery for LAEC is not only because of the reduction of surgical risks but also the improved quality of life. Reliable assessment tool that could identify pCR is the assumption of this personalized strategy for LAEC. Although the definition of cMR using SUVmax <4 is debatable, the findings in this study were consistent with others. The accuracy of PET/CT to predict pCR was suboptimal and could not justify the omission of esophagectomy (12-15). The results were not surprised and showed consistency with our clinic experience. The resolution of PET/CT and endoscope cannot detect residual tumor cells or micrometastases and thus has falsely classified patients as complete resolution. This was manifested as low specificity of PET/CT for pCR in Heneghan's work (5) and (12). Interestingly, in Heneghan et al., the accuracy of PET/CT was limited in sensitivity as well as in specificity. Low sensitivity and thus high false negative rate of cMR meant that patients with pCR might have not been revealed as cMR. Despite the adequate 4 to 6 weeks waiting time before restaging PET/CT, FDG uptake caused by radiation-induced inflammation could possibly have not subsided yet. Furthermore, the difficulty in differentiating gastric uptake from residual adenocarcinoma located at esophagogastric junction could have contributed to the falsely residual FDG uptake. It is not uncommon that SUVmax could be higher than four in both scenarios. The definition of cMR may be further adjusted in future studies.

The %ΔSUVmax was a significant predictor of pCR in univariate analysis [odds ratio 1.03 (1.01–1.06), P<0.01]. Although it was not significant in multivariate analysis, it is worth of noticing that PET parameters quantifying the changes between pre-nCRT and post-nCRT might be more predictive than those based solely on post-nCRT PET. Radiomics, which uses computerized tools to extract a large number of image features, is an emerging quantitative imaging biomarker in oncology (16). Several studies applied radiomics for esophageal cancer, especially for prediction of treatment response and prognosis (17,18). PET texture features outperformed SUVmax in identification of partial or complete responder to nCRT, defined by RECIST criteria (19), with sensitivity of each feature ranged from 76% to 92%. We found features derived from PET intensity and texture had equal or better accuracy than %ΔSUVmax for the prediction of pathologic tumor response to nCRT (18). The post-nCRT PET of responder tended to be more homogenous on texture features. For better prediction, the radiomics features were combined to construct a multivariate regression model or machine learning models (20-22). We constructed a support vector machine model with radiomics features and clinical parameters, which achieved a sensitivity higher than 90% for predicting partial or complete pathologic response to nCRT (20). It would be more challenging when the task is restricted to predict complete pathologic response only. Nevertheless, Tixier *et al.* showed that some texture features can identify complete pathologic response better than SUV-based parameters (17). Recently, Desbordes *et al.* built a random forest classifier for cCR with sensitivity 82%±9% and specificity 91%±12% (21). For prediction of pCR, van Rossum *et al.* found that the incorporation of texture and geometry features could improve the performance of prediction models with clinical factors and conventional PET parameters (23). Though many issues in radiomics are still needed to be investigated (24), it is one of the most promising tools in the era of precision medicine considering its potential and relative low additional cost.

^{18}F-FDG PET/CT has been a valuable imaging tool in the prognosis and response evaluation of esophageal cancer. However, the complete resolution of tumor on PET/CT after nCRT is of prognostic significance but is not sufficiently reliable to serve as the decision maker for avoiding complex surgery for LAEC. Heneghan's recent work highlighted the low sensitivity and positive predict value of PET/CT for identifying pathologic complete resolution after nCRT. Other prediction tool or quantification techniques like radiomics should be investigated before the application of surgery-as-needed strategy for esophageal cancer.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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