

# On predicting clinical response to chemoradiotherapy in esophageal squamous cell carcinoma: additional evaluation by magnetic resonance imaging may help

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The current standard treatment options for locally advanced esophageal squamous cell carcinoma (ESCC) include neoadjuvant chemoradiotherapy (CRT) followed by esophagectomy and definitive CRT (1-4). For patients who receive neoadjuvant CRT, pathologic tumor response, including pathologic complete response (pCR) and tumor regression grade, is predictive of patients' survival (5,6). For patients who receive definitive CRT, clinical complete tumor response has also been shown to associate with patients' survival (7). However, the clinical tumor response evaluation for locally advanced esophageal cancer is limited by inferior sensitivity and specificity of conventional imaging modalities (8). For example, although endoscopy can evaluate the response of intraluminal esophageal tumor and can confirm the suspicious lesions by biopsy, it could not detect residual tumor deep in muscular layer and adventitia of esophageal wall. The application of computed tomography (CT) to evaluate esophageal tumor response is frequently hampered by consequences of CRT, such as edema, fibrosis, and necrosis. A better clinical tumor response evaluation is warranted to help prognosis prediction in patients of locally advanced ESCC receiving definitive CRT.

High resolution T2-weighted magnetic resonance imaging (MRI) has been studied for staging of esophageal

cancer (9,10). Compared with CT, T2-weighted MRI can show clear layers of esophageal wall, the surrounding structure, and the depth of tumor invasion. Diffusion-weighted MRI (DWI), a functional imaging, has also been investigated in esophageal cancer (11). Apparent diffusion coefficient (ADC), a parameter calculated from DWI, represents the level of free diffusion of water. A retrospective study of ESCC patients demonstrated that lower ADC measured in their tumors, meaning restricted diffusion of water in higher cellularity, was associated with worse prognosis (12). ADC has also been studied in evaluating tumor response to CRT in several cancer types, including esophageal cancer (13,14). However, MRI is less sensitive than endoscopy in detecting intraluminal esophageal tumors and less sensitive than CT in detecting small lung metastases. Therefore, it has been hypothesized that adding MRI studies to the conventional CT and endoscopy would improve the predictive accuracy of the clinical tumor response evaluation in ESCC patients treated with CRT.

Qiu and colleagues recently published a clinical study evaluating the prognosis prediction performance of combining MRI, endoscopy and CT in patients with loco-regional ESCC treated with definitive CRT (15). The study enrolled 67 patients with clinical stages II to

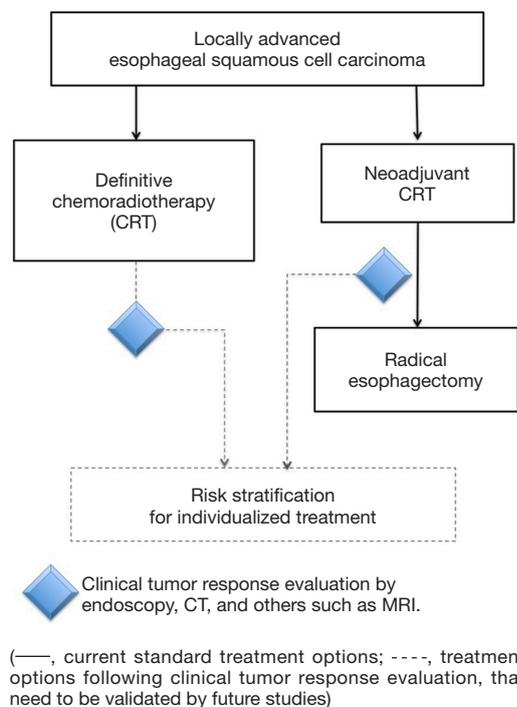
IVb ESCC according to American Joint Committee on Cancer (AJCC) 6<sup>th</sup> edition, and compared the traditional criteria using CT and endoscopy with the new criteria using additional T2-weighted and diffusion-weighted MRI studies in evaluating the clinical response to definitive CRT. The complete response defined by the traditional criteria comprised disappearance of primary tumor at endoscopy and CT (esophageal wall thickness <10 mm) and pathologic lymph nodes at CT (short axis <10 mm); and the complete response defined by the new criteria comprised no intraluminal tumor at endoscopy, no new metastasis at CT, normalization or subtle hypo-dense thickness of esophageal wall and no involved lymph nodes at T2-weighted MRI, and ADC<sub>post</sub> of primary tumor  $\geq 2.64 \times 10^{-3}$  mm<sup>2</sup>/s. Among 67 enrolled patients, 10 (14.9%) were classified as complete responders by the traditional criteria, whereas 37 (55.2%) were classified as complete responders by the new criteria incorporating MRI studies. Using 12-month progression-free survival (PFS) as a surrogate of treatment efficacy, the sensitivity was much higher for the new criteria than the traditional criteria (82.4% vs. 20.6%) and the specificity for the two criteria was very similar (88.9% vs. 92.6%). Complete response defined by the new criteria, rather than that by the traditional criteria, was an independent prognostic factor for PFS (hazard ratio: 0.114, P<0.0001). The authors concluded that tumor responses evaluated by the new criteria combining MRI, endoscopy and CT is highly predictive of the prognosis for ESCC patients treated with definitive CRT.

Qiu and colleagues are congratulated for publishing the data supporting the superiority of combining MRI studies with conventional endoscopy and CT as the evaluation of clinical tumor response to CRT in ESCC patients. However, caution needs be exercised when interpreting their results. The report was based on a single-institute cohort study and its analysis was likely performed retrospectively. The finding of improved prediction of PFS by the new criteria was not validated by independent patient cohorts. According to the authors, histologically diagnosed ESCC patients with stage I–IVb disease who underwent definitive CRT were enrolled between 2011 and 2015. However, it was not clearly mentioned in the report what criteria were used to select patients for definitive CRT, but not other treatment options such as neoadjuvant CRT or radical surgery. The way patients were selected may lead to certain bias. Patients enrolled received two different chemotherapy regimens, nedaplatin plus S-1 and nedaplatin plus docetaxel, both of which are not commonly used in

most parts of the world. Further, it is not clear why the authors used AJCC TNM system 6<sup>th</sup> version to stage their patients enrolled between 2011 and 2015 since the AJCC TNM 7<sup>th</sup> edition was launched in 2009. Lastly, the authors used 12-month PFS as a surrogate of treatment efficacy and for the primary analysis in this study. Although this may seem to be reasonable because the median follow-up period for the entire cohort was relatively short (only 15.3 months), survival endpoints with longer periods are preferred to truly reflect the efficacy of definitive CRT and the prognosis of loco-regional ESCC.

Despite the aforementioned limitations, the study does provide important information that may have significant clinical implications. The addition of MRI to the clinical tumor response evaluation could help detect patients with good prognosis who might be missed by the traditional criteria due to the low ability of CT to differentiate post-CRT wall thickness from the presence of residual cancer cells. In the new criteria, MRI evaluates not only wall thickness of the primary tumor site, but also the normalization of esophageal wall layers (by T2-weighted imaging) and the tumor cellularity (by diffusion-weighted imaging). Further studies using a larger patient population and a longer period of follow-up are warranted to validate the findings of this report.

The results of the study may be further investigated to improve our care of patients with locally advanced ESCC. First, according to this study, patients who were categorized as non-complete responders according to the new criteria incorporating MRI studies had a median PFS of 7.8 months and a 2-year PFS of 16%, which were significantly worse than those of complete responders. These non-responders are a potential group of patients indicated for adjuvant or additional therapy to improve their outcome (*Figure 1*). Second, other imaging modalities such as <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (PET) and endoscopic ultrasonography (EUS), that have been widely used for staging ESCC, were not included in the study by Qiu *et al.* (10). Some studies revealed that the timing of response evaluation by PET may influence the accuracy of survival prediction (16,17). Whether adding PET and EUS to the response evaluation will further improve the predictive accuracy of the new criteria will be an interesting topic of future studies. Third, it is currently unknown whether the new criteria incorporating MRI studies would be helpful in predicting pCR and patients' outcome in ESCC patients receiving neoadjuvant CRT. Predictive biomarkers of pCR could potentially help



**Figure 1** The potential application of clinical tumor response evaluation in improving the treatment of locally advanced esophageal squamous cell carcinoma. MRI, magnetic resonance imaging.

stratify patients with different risks for different treatment strategies (*Figure 1*). For example, those with high probability of pCR after neoadjuvant CRT may consider avoiding esophagectomy and continuing additional CRT as a definitive treatment. Finally, studies have been undergoing to explore molecular and genetic markers, in tumor tissues or in peripheral blood, in order to establish potentially predictive or prognostic biomarkers in ESCC patients treated with CRT.

Overall, continuing efforts to refine the clinical tumor response criteria are important to implement risk-stratification and personalized therapy for patients with locally advanced ESCC.

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### Footnote

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

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