Endoscopic biopsy and EUS for the detection of pathologic complete response after neoadjuvant chemoradiotherapy in esophageal cancer: a systematic review and meta-analysis CME

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Background and Aims: Accurate determination of residual cancer status after neoadjuvant chemoradiotherapy (nCRT) for esophageal cancer could assist in selecting the optimal treatment strategy. The aim of this study was to review the evidence on the diagnostic accuracy of endoscopic biopsy and EUS after nCRT for detecting residual cancer at the primary tumor site (ypT+) and regional lymph nodes (ypN+) as opposed to a pathologic complete response (ypT0 and ypN0).

Methods: PubMed/Medline, Embase, and the Cochrane library were systematically searched. The analysis included diagnostic studies reporting on the accuracy of endoscopic biopsy or EUS in detecting residual cancer versus complete response after nCRT for esophageal cancer with histopathology as the reference standard. Bivariate random-effects models were used to estimate pooled sensitivities and specificities and examine sources of heterogeneity.

Results: Twenty-three studies comprising 12 endoscopic biopsy studies (1281 patients), 11 EUS studies reporting on ypT status (593 patients), and 10 EUS studies reporting on ypN status (602 patients), were included. Pooled estimates for sensitivity of endoscopic biopsy after nCRT for predicting ypT+ were 34.5% (95% confidence interval [CI], 26.0%-44.1%) and for specificity 91.0% (95% CI, 85.6%-94.5%). Pooled estimates for sensitivity of EUS after nCRT were 96.4% (95% CI, 91.7%-98.5%) and for specificity were 10.9% (95% CI, 3.5%-29.0%) for detecting ypT+, and 62.0% (95% CI, 46.0%-75.7%) and 56.7% (95% CI, 41.8%-70.5%) for detecting ypN+, respectively.

Conclusions: Endoscopic biopsy after nCRT is a specific but not sensitive method for detecting residual esophageal cancer. Although EUS after nCRT yields a high sensitivity, only a limited number of patients will have negative findings at EUS with still a substantial false-negative rate. Furthermore, EUS provides only moderate accuracy for detecting residual lymph node involvement. Based on these findings, these endoscopic modalities cannot be used to withhold surgical treatment in test-negative patients after nCRT. (Clinical trial registration number: CRD42015016527.) (Gastrointest Endosc 2016;83:866-79.)

Esophageal cancer continues to affect more than 450,000 people worldwide, and its incidence is rapidly increasing.[1] In patients with resectable nonmetastatic esophageal cancer, neoadjuvant chemoradiotherapy (nCRT) followed by surgery is increasingly applied as standard treatment with curative intent.[2,3] A pathologic complete response to nCRT is observed in approximately 25% to 30% of patients.[3-6] Many studies have reported that this absence of viable tumor cells at both the primary tumor site and regional lymph nodes (ie, ypT0N0) is associated with favorable overall survival rates of approximately 60% to 70%.[4-6] Several investigators have speculated that surgery (with accompanying morbidity and mortality) may be safely omitted in patients who achieve ypT0N0, but accurately identifying these patients is challenging.[7] A reliable diagnosis of residual cancer before surgery would enable investigators to study the feasibility and outcome of a tailored treatment algorithm in which complete responders after nCRT

Abbreviations: nCRT, neoadjuvant chemoradiotherapy; NPV, negative predictive value; QUADAS, quality assessment of diagnostic accuracy studies; ypN, final pathologic N-stage after chemoradiotherapy; ypT, final pathologic T-stage after chemoradiotherapy; ypT+, pathologic residual primary tumor; ypT0, pathologic complete response primary tumor; yN+, pathologic residual lymph node involvement; yN0, pathologic absence of residual lymph node involvement.

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TABLE 1. Search strategy and results as of July 14, 2015

No.	Search query	PubMed	Embase	Cochrane
1	eus OR endoscopic ultrasound OR endoscopic ultrasonography OR endoscopic biopsy OR endoscopic biopsies OR gastroscopy OR endosonography OR endoscopic sonography OR endoscopic OR endoscopy	146,403	212,825	13,058
2	esophageal OR esophagus OR oesophageal OR oesophagus OR gastro-esophageal OR gastro-oesophageal OR gastroesophageal OR oesophagogastric OR esophagogastric	131,842	172,871	8868
3	cancer OR cancers OR tumor OR tumour OR tumors OR tumours OR neoplasm OR neoplasms OR malignancy OR malignancies OR adenocarcinoma OR adenocarcinomas OR carcinoma OR carcinomas	2,289,820	2,934,415	99,870
4	response OR neoadjuvant OR chemotherapy OR chemoradiotherapy OR chemoradiation OR preoperative	1,927,724	2,406,894	177,055
5	1 and 2 and 3 and 4	1730	2949	83

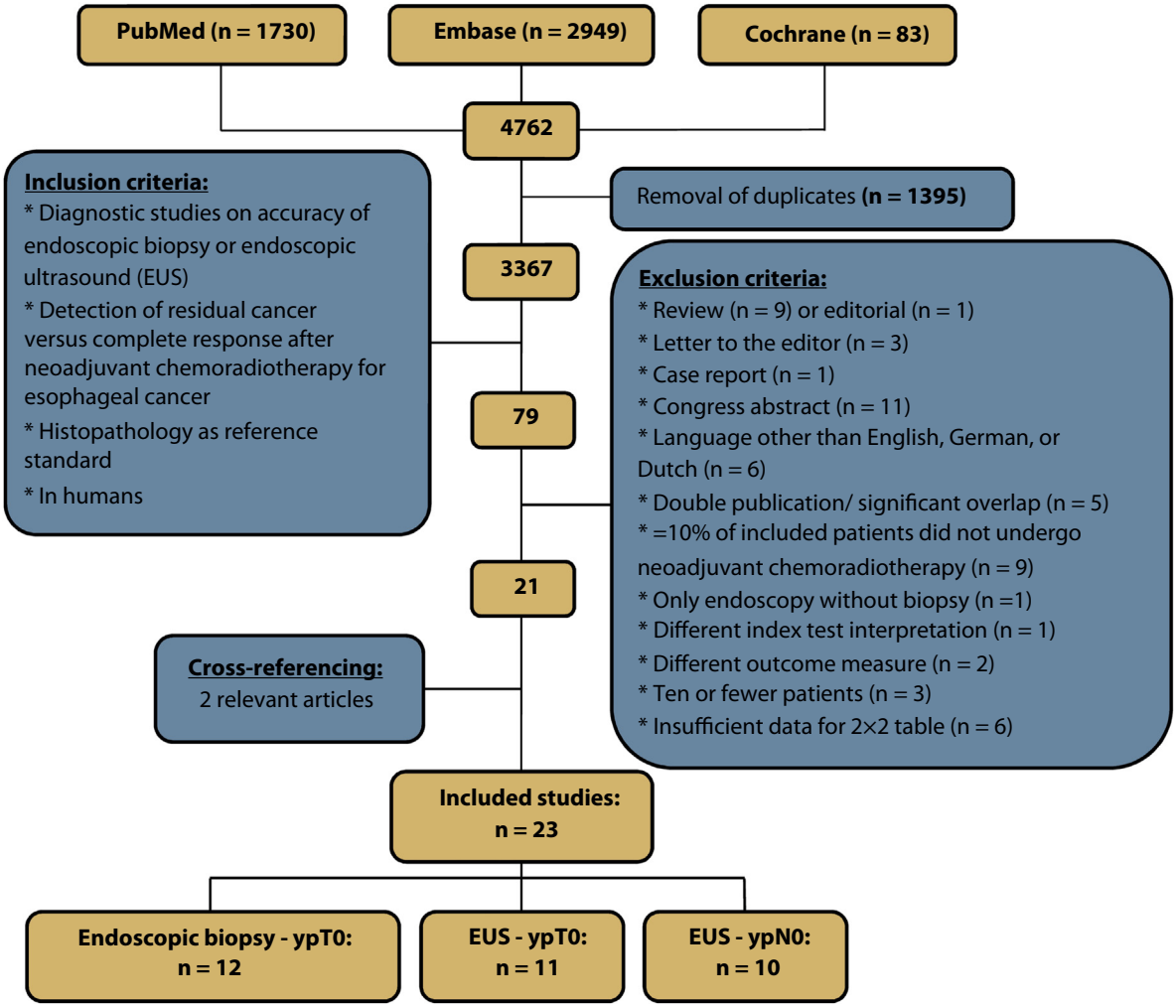

Figure 1. Flowchart summarizing search results and study selection. *ypT0,* pathologic complete response of primary tumor; *ypN0,* no residual lymph node involvement.

could be offered close clinical follow-up instead of esophagectomy.[8]

Endoscopy with biopsy is widely accepted as the standard initial procedure to provide a histologic diagnosis for esophageal cancer with high accuracy.[9] The role of EUS before treatment is well-established for assessing depth of tumor invasion and regional lymph node involvement of esophageal tumors.[10,11] By its unique visualization of the esophageal wall and surrounding tissues, EUS provides an accuracy of >80% for initial T-staging and >70% for initial N-staging in patients who underwent surgical resection without neoadjuvant treatment.[11-13] However, the accuracy of the endoscopic modalities after nCRT is thought to be impeded by difficulties of endoscopic biopsy