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Association between clinical complete response and pathological complete response after preoperative chemoradiation in patients with gastroesophageal cancer: analysis in a large cohort

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Background: Chemoradiation followed by surgery is the preferred treatment of localized gastroesophageal cancer (GEC). Surgery causes considerable life-altering consequences and achievement of clinical complete response (clinCR; defined as postchemoradiation [but presurgery] endoscopic biopsy negative for cancer and positron emission tomographic (PET) scan showing physiologic uptake) is an enticement to avoid/delay surgery. We examined the association between clinCR and pathologic complete response (pathCR).

Patients and methods: Two hundred eighty-four patients with GEC underwent chemoradiation and esophagectomy. The chi-square test, Fisher exact test, *t*-test, Kaplan–Meier method, and log-rank test were used.

Results: Of 284 patients, 218 (77%) achieved clinCR. However, only 67 (31%) of the 218 achieved pathCR. The sensitivity of clinCR for pathCR was 97.1% (67/69), but the specificity was low (29.8%; 64/215). Of the 66 patients who had less than a clinCR, only 2 (3%) had a pathCR. Thus, the rate of pathCR was significantly different in patients with clinCR than in those with less than a clinCR ($P < 0.001$).

Conclusions: clinCR is not highly associated with pathCR; the specificity of clinCR for pathCR is too low to be used for clinical decision making on delaying/avoiding surgery. Surgery-eligible GEC patients should be encouraged to undergo surgery following chemoradiation despite achieving a clinCR.

Key words: clinical complete response, esophageal cancer, multimodality therapy, pathologic complete response, prediction

introduction

Gastroesophageal cancer (GEC, those originating in the esophagus and gastroesophageal junction) is the eighth most common cancer worldwide [1, 2]. Approximately 482 000 new cases and 407 000 deaths were estimated globally by GLOBOCAN 2008 [1, 2]. In the United States, an estimated 16 640 new cases were diagnosed in 2010, and 14 500 deaths were expected during the same period [3]. In the western world, the incidence of gastroesophageal squamous cell carcinoma has been declining, but the incidence of adenocarcinoma has been climbing over the past four decades [4–6]. Obesity, high body mass index, smoking, gastroesophageal reflux disease, and Barrett esophagus are frequently associated with adenocarcinoma [7, 8]. Surgery is a major component of therapy for localized GEC, but primary surgery is linked to poor prognosis [9]. In the United States, chemoradiation followed by surgery (trimodality) is the most frequently recommended strategy for thoracic GEC [10–14].

When discussing prognosis and treatments, most patients with newly diagnosed GEC and their families are dismayed by the prevailing statistics and often disappointed to learn the potential consequences of surgery. Patients typically request repeated discussions to justify the need for surgery and frequently seek alternatives. Most patients and their families remain thoroughly engaged in the discussions of results of elaborate staging at various time points during (baseline and following chemoradiation) and after therapy. Even when a

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long-term strategy (chemoradiation followed by surgery) has been established, it is often reassessed and challenged at the postchemoradiation (i.e. preoperative) staging. Patients often feel the temptation to avoid surgery, and sometimes the treating team decides to delay the planned surgery. These clinical challenges will need to be addressed by developing reliable predictive models.

The inherent heterogeneity in treatment outcome remains an ongoing challenge. In this context, we reviewed our data on patients with GEC, particularly focusing on postchemoradiation staging, where the achievement of clinical complete response (clinCR; defined as endoscopic biopsies without cancer cells and positron emission tomographic (PET) scan with only physiologic uptake) reignites the debate about surgery and casts considerable doubts on its necessity.

Rates of pathologic complete response [pathCR; defined as the absence of cancer cells in the resected specimen (primary and nodes)] after chemoradiation have been low traditionally, and no individual or combination of variables can reliably predict pathCR. In the absence of a pathCR predictive model, the question is whether clinCR is highly associated with pathCR and, if so, whether the sensitivity and specificity of this association are adequate to inform clinical decision making on whether to avoid/delay surgery in any GEC patient.

methods and patients

study objective

The primary objective was to assess whether clinCR is correlated highly with pathCR and, if so, whether the sensitivity and specificity of clinCR for pathCR are high enough to be further developed for clinical implementation as a predictive variable in GEC.

patients

We retrospectively reviewed data on patients treated for GEC between 2002 and 2010 from a prospectively assembled database of the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center. The Institutional Review Board approved the database and the analysis.

We identified all patients with biopsy-proven GEC who underwent chemoradiation followed by surgery (trimodality therapy). Trimodality therapy was recommended after a multidisciplinary evaluation of each patient by a team that included medical oncologists, gastroenterologists, pathologists, radiologists, radiation oncologists, and thoracic oncologic surgeons. Every patient underwent full disease staging at baseline that included PET-computed tomographic (CT) scans, endoscopic ultrasonography, blood tests, and endoscopic biopsies. Patients who received salvage surgery were not included. No other selection criteria were implemented.

preoperative chemoradiotherapy

All patients received concurrent chemotherapy with radiotherapy. The total radiation dose delivered was either 45 grays (Gy) in 25 fractions or 50.4 Gy in 28 fractions, at 1.8 Gy per fraction delivered once a day. All patients received a fluoropyrimidine agent (i.v. or oral) and either a taxane or a platinum compound as the second cytotoxic agent during radiation treatment. Five to six weeks after completion of chemoradiation, all patients underwent a comprehensive restaging evaluation that included complete blood count, measurement of serum electrolytes, upper gastroesophageal endoscopy with biopsies, and PET-CT imaging.

CT and PET imaging

PET-CT imaging was carried out before and after chemoradiation in all patients. PET-CT images were acquired with an integrated PET-CT device (Discovery ST-8; GE Medical System, Milwaukee, WI), and the whole-body mode was implemented as the standard software. The patient fasted for at least 6 h before PET. All patients were tested to confirm that their glucose level was within the normal range (80–120 mg/dl) before administration of fluorodeoxyglucose (FDG). Before PET, unenhanced CT was carried out from the base of the skull to the upper thigh according to a standardized protocol carried out with the following settings: transverse 3.75-mm section thickness, 140 kVp, 120 mA, and 13.5-mm table speed. Emission scans were obtained 60 min after i.v. administration of FDG (mean dose, 555 MBq). The acquisition time was 3 min per bed position in the two-dimensional mode. Images were reconstructed with attenuation-weighted ordered-subset expectation maximization with and without attenuation correction [15, 16].

response assessment

After a review of all postchemoradiation staging results, each patient was assigned to one of two categories: (i) clinCR or (ii) less than clinCR. clinCR was defined as postchemoradiation endoscopic biopsies negative for cancer cells and no evidence of distant metastasis by PET as well as a maximum standardized uptake value (SUV_{max}) in the primary region at a physiologic level (or, when SUV_{max} was higher than normal, it was distributed in the esophagitis pattern) [17, 18].

surgery

Approximately 6–8 weeks after completion of chemoradiation, all patients underwent esophagectomy and lymph node dissection with curative intent. Surgical procedures included Ivor-Lewis, transthoracic, transhiatal, and three-field or minimally invasive esophagectomy.

follow-up and survival

Patients were monitored periodically until 5 years after surgery or until death. Follow-up data were obtained from the MD Anderson tumor registry and hospital records or the Social Security database.

statistical analysis

Patient characteristics are summarized in tabular form for categorical data and as averages and standard deviations for continuous variables. Categorical variables were compared by chi-square analysis or Fisher exact test and continuous variables by *t*-test. Survival analysis was done using the Kaplan–Meier method, and survival compared by the log-rank test. We used standard OS and DFS calculations.

results

patient and tumor characteristics

The baseline characteristics of 284 GEC patients who received preoperative chemoradiation followed by planned surgery are shown in Table 1. The average age was 58.5 ± 10.2 years, and the majority of patients were men (87.3%) and Caucasian (91.2%). Adenocarcinoma was the dominant cancer type (91.9%). Before treatment, most of the patients had stage cII or cIII disease (using the sixth edition of AJCC criteria [19]), but 14 (4.9%) patients had stage IVa disease, advanced localized tumor with regional lymph node metastasis or T4a [resectable T4 lesion]) [19, 20].

Baseline PET was carried out in 257 patients and postchemoradiation PET was carried out in 265 patients. The median iSUV was 10.1 (range: 0–58) and the median postchemoradiation SUV was 4.5 (range: 0–18).

survival and relapse

Median follow-up interval was 40.3 months [95% confidence interval (CI) 33.0–47.6 months]. The estimated median overall survival (OS) duration for all 284 patients was 67.4 months (95% CI 38.1–96.7 months) and median relapse-free survival (RFS) interval was 37.0 months (95% CI 12.9–61.1 months). The estimated OS and RFS rates at 5 years were 51.7% (95% CI 43.7% to 59.7%) and 46.4% (95% CI 39.4% to 53.4%), respectively. As of this writing, 100 (35.2%) patients have died.

Table 1. Baseline patient and tumor characteristics ($n = 284$)

Covariate	Frequency (%)
Sex	
Male	248
Female	36
Age (years)	
Average	58.5
SD	10.2
Race	
Asian	4
Black	5
Hispanic	16
White	259
Primary tumor site	
Esophagus	23
AEG I	159
AEG II	102
Tumor stage [19]	
I	1
II	117
III	152
IV	14
Histology	
Adenocarcinoma	261
Adenosquamous cell carcinoma	2
Squamous cell carcinoma	20
Undetermined	1
Tumor grade	
G1 well differentiated	2
G2 moderately differentiated	127
G3 poorly differentiated	155
Length of tumor	
Average (cm)	5.4
SD	2.4

AEG, adenocarcinoma of the esophagogastric junction; SD, standard deviation.

clinical complete response and pathological complete response

After preoperative chemoradiation, 218 of 284 (76.8%) patients achieved clinCR, and 69 (24%) patients achieved pathCR. Of the 218 patients who had a clinCR, only 67 (30.7%) had a pathCR. Among 66 patients with less than a clinCR, 2 (3%) achieved a pathCR. This difference in percentage of patients with pathCR was statistically significant ($P < 0.001$). These results indicate that 151 (69.3%) of 218 patients with a clinCR did not achieve a pathCR. The sensitivity of clinCR for pathCR

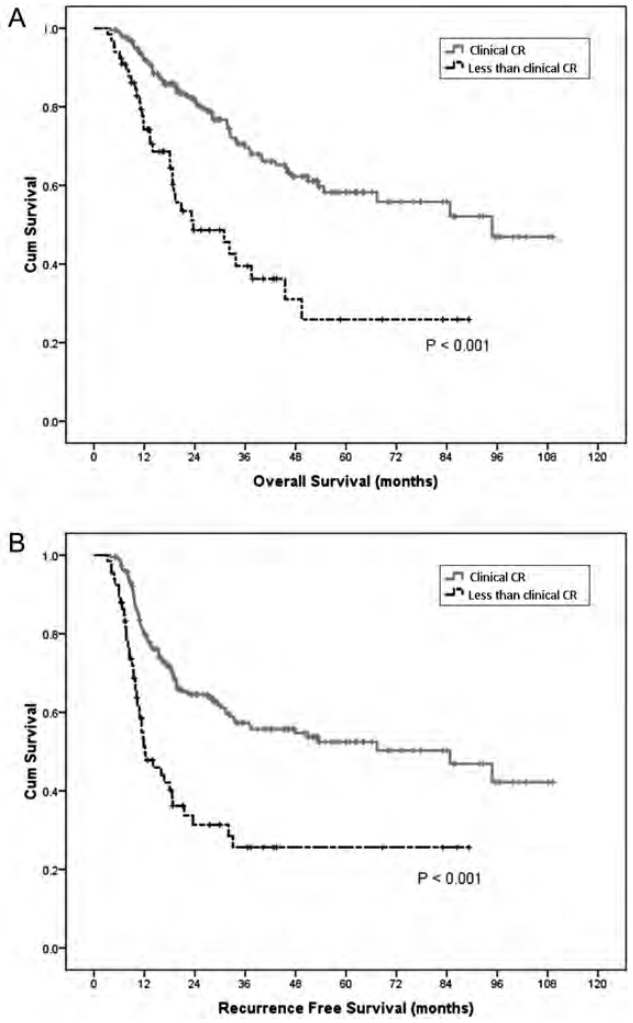

Figure 1. (A). Kaplan–Meier survival plots comparing overall survival of patients who achieved clinical complete response and those who did not achieve a clinical complete response. (B). Kaplan–Meier survival plots comparing recurrence-free interval of patients who achieved clinical complete response and those who did not achieve a clinical complete response.

was 97.1%, but the specificity was only 29.8%. The positive predictive value (67/218) is 30.7% and the negative predictive value is 96.7%.

Of the 284 patients, 129 (45.4%) received induction chemotherapy for as long as 8 weeks before preoperative chemoradiation. Among these 129 patients, the clinCR rate was 81.4%, while it was 72.9% in the 155 patients who did not have induction chemotherapy ($P = 0.12$; odds ratio of 1.63; 95% CI 0.92–2.87). The difference in pathCR rate in these two groups also was not significant.

survival of ClinCR and PathCR patients

The estimated median OS duration was 94.8 months (95% CI NA–NA) for clinCR patients and 23.6 months (95% CI 10.0–37.2) for those with less than a clinCR. The estimated median RFS duration was 84.8 months (95% CI 41.2–128.3) for those with a clinCR and 12.2 months (95% CI 7.7–16.7 months) for those with less than a clinCR (Figure 1A and B).

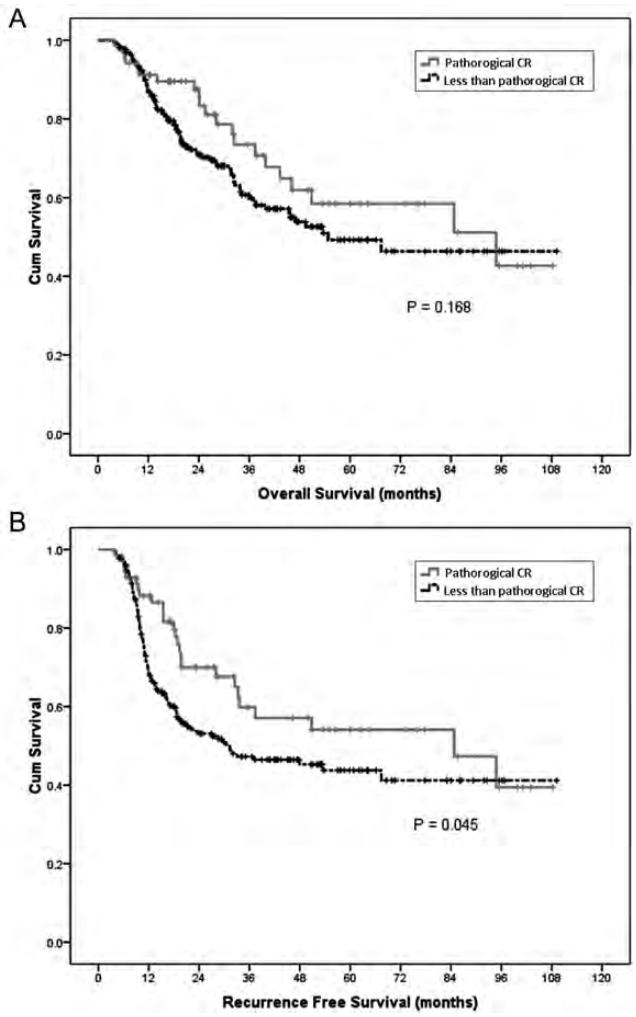

Figure 2. (A). Kaplan–Meier survival plots comparing overall survival of patients who achieved pathologic complete response and those who did not achieve a pathologic complete response. (B). Kaplan–Meier survival plots comparing recurrence-free interval of patients who achieved pathologic complete response and those who did not achieve a pathologic complete response.

The estimated median OS duration was 94.8 months (95% CI 33.7–156) for those with a pathCR and 54.8 months (95% CI NA–NA) for those with less than a pathCR. The estimated median RFS duration was 84.8 months (95% CI 27.1–142) for those with a pathCR and 31.3 months (95% CI 10.5–52.1) for those with less than a pathCR (Figure 2A and B).

discussion

The management of localized GEC presents numerous challenges. Because there is no early detection strategy for this disease, these tumors often are eusT2 or T3 and long (median length is often 6 cm) at the time they are diagnosed. Nodal involvement at diagnosis is also frequent. Chemoradiation followed by surgery is the most frequently recommended treatment regimen, on the basis of level-1 evidence [14], but each component of this therapy is associated with considerable morbidity and or complications. Long-term surgical consequences include weight loss, significant gastroesophageal reflux disease (with or without microaspirations), dumping syndrome, and disconnect between brain center for hunger and limited reservoir, leading to significant postprandial pain and mental distress.

Although patients cannot grasp the long-term consequences of surgery before actually experiencing them, every patient is very anxious about surgery and requires several sessions to discuss its advisability. The most stressful moment in the treatment process is the discussion of postchemoradiation staging results before surgery. At this juncture, the risk is high that a long-term plan that included surgery will be jeopardized. Patients and family are deeply engaged at this time, and PET and endoscopic biopsy results are discussed several times by different members of the multidisciplinary team. Patients sometimes get different messages from different team members, and they may ask whether surgery is necessary if the biopsy result is negative and PET has 'normalized'. There is little guidance in the literature for decision making at this juncture.

Other groups have reported clinCR rates (although their definitions of clinCR were not as stringent as used by our group) after chemoradiation varying from 28% to 86% and pathCR rates varying from 10% to 43% [21–26]. However, these previous reports are on small numbers of patients. In our cohort, largest yet reported, the clinCR rate was 76.8% and the pathCR rate 24.0%. Disease staging was more thorough in our cohort than in any other reported group. Our data on 218 patients who achieved clinCR after chemoradiation provide definite information regarding positive and negative predictive values of clinCR for pathCR, and will benefit clinicians facing challenges in advising patients to undergo surgery. As all 218 patients had surgery, we can say with certainty that the achievement of a clinCR had little correlation with the achievement of a pathCR. Therefore, delaying surgery in this group of patients on the basis of clinCR alone could put many individuals at risk of some degree of local relapse, particularly an unresectable situation later on. It would be desirable to avoid surgery in patients who are destined to achieve a pathCR, but neither clinCR nor any other known variable provides sufficient confidence (or high enough specificity) to recommend avoidance or delay of surgery. On the other hand, the decision is quite simple in patients who have less than a

clinCR, since 97% of these patients have residual cancer in the surgical specimen. It may be that before postchemoradiation staging, a thorough education of the patient, family, and treating team would reduce the stress of plans to proceed with surgery. Patients who achieve clinCR but do not wish to undergo surgery have poor relapse-free survival [27], but this group cannot be directly compared with those who are initially assigned to definitive chemoradiation (based on the extent of their cancer or comorbidities).

The weakness of our report is that it is a retrospective analysis, but the strengths include an analysis of a large number of patients with uniformly and thoroughly staged (that included baseline PET-CT, baseline EUS, postchemoradiation PET, and postchemoradiation endoscopic biopsies, among others) disease. Our report also puts these results into a clinical practice context.

In conclusion, our data suggest that the achievement of clinCR does not correlate with the achievement of pathCR. Therefore, all surgery-eligible GEC patients should be encouraged to proceed to resection/lymphadenectomy after recovery from chemoradiation.

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disclosure

The authors have declared no conflicts of interest.

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