ORIGINAL PAPER

Surg. Gastroenterol. Oncol. 2021 eCollection July 20 DOI: 10.21614/sgo-eC-300

Defining Clinical Complete Response Using Endoscopy and Computed Tomography in Esophageal Cancer Patients Undergoing Chemoradiotherapy

Navarat Tangbumrungtham[1], Nuttapong Ngamphaiboon[2], Chuleeporn Jiarpinitnun[3], Poompis Pattaranutaporn[3], Suriya Chakkaphak[4], Kanpat Visutjindapon[4], Papawee Paisan[4], Kornkanok Somboonpun[5], Pitichote Hiranyatheb[4*]

[1]Department of Otolaryngology, Ramathibodi Hospital, Faculty of Medicine, Mahidol University, Bangkok, Thailand
[2]Division of Medical Oncology, Department of Medicine, Ramathibodi Hospital Faculty of Medicine, Mahidol University, Bangkok, Thailand
[3]Division of Radiation Oncology, Department of Radiology, Ramathibodi Hospital Faculty of Medicine, Mahidol University, Bangkok, Thailand
[4]Division of General Surgery, Department of Surgery, Ramathibodi Hospital Faculty of Medicine, Mahidol University, Bangkok, Thailand
[5]Surgical Research Unit, Department of Surgery Ramathibodi Hospital, Faculty of Medicine, Mahidol University, Bangkok, Thailand

***Corresponding author:**
Pitichote Hiranyatheb, MD
Department of Surgery
Faculty of Medicine
Ramathibodi Hospital
270 Rama VI road, Ratchatewe,
Bangkok 10400, Thailand
Telephone: 662-201-1527
Fax: 662-201-1527, extension 214
E-mail: pitichoteh@yahoo.com

ABSTRACT

Background: The validity of a clinical complete response (cCR) for predicting pathological complete response (pCR) and oncologic outcomes in esophageal cancer patients undergoing chemoradiotherapy (CRT) remains unclear. The aim of this study was to assess the outcomes of post-CRT patients with cCR using our available combined tools.
Methods: Locally advanced esophageal cancer patients who received neoadjuvant or definitive CRT at our institution were retrospectively reviewed. After completing CRT, combined endoscopy and CT findings were used to define cCR, and the correlation between cCR and treatment outcomes was analyzed.
Results: We identified 79 patients. cCR was observed in 13/41 (32%) and 10/38 (26%) patients treated with a trimodality approach and definitive CRT (DCRT), respectively. Esophageal cancer-specific survival was significantly better in cCR patients in the trimodality group ($p < 0.05$). In the DCRT group, the OS and DFS of cCR patients were significantly greater than patients with non-cCR ($p < 0.05$). Non-cCR patients in both groups had higher rates of disease recurrence compared with cCR patients ($p < 0.05$).
Conclusion: cCR in this study correlated well with pCR and survival outcomes in esophageal cancer patients undergoing CRT. A larger prospective study is warranted to confirm these results.
Key words: esophageal cancer, chemo-radiotherapy, clinical complete response, pathological complete response

Received: 01.01.2021
Accepted: 05.03.2021

INTRODUCTION

Esophageal cancer is an aggressive disease, ranked as the sixth most

common cause of cancer deaths worldwide (1). The prognosis is poor, with a 5-year overall survival of 15%–25% (2). A contributing factor to the poor survival rate is that the disease is associated with a high incidence of lymph node and distant metastasis once it is diagnosed. Consequently, esophagectomy alone may not be a curative option (3). Chemo-radiotherapy (CRT) has become a crucial part of treatment for patients with locally advanced disease. Studies have shown that either definitive treatment or neoadjuvant therapy followed by esophagectomy is the accepted standard of care, with comparable overall survival (OS) (4,5). In patients receiving trimodality therapy, the potential benefits over nonoperative treatment are better local tumor control (6,7) and more accurate staging can be obtained from histopathologic study of the resected specimen. Favorable oncologic outcomes are found in patients without viable tumor cells detected in the resected tissue (8), termed pathological complete response (pCR), which was achieved in up to 29% of patients (23% with adenocarcinoma and 49% with squamous cell carcinoma) according to the CROSS study (9). However, the addition of esophagectomy to CRT is also associated with a substantial risk of treatment-related consequences (10,11). The high CRT response rate and high surgical risk have encouraged a trend toward an esophagus-preserving approach to treating this disease (12). The key element in this approach is an accurate measure for assessing clinical response to define the group achieving a clinical complete response (cCR) as a reliable predictor for pCR (13). In fact, when dysphagia symptoms improve, and the lesion grossly disappears or decreases in size, some patients are reluctant to proceed with esophagectomy, even when the initial management plan was a trimodality approach, because of the fear of this major surgery and the possibility of developing complications. However, until recently, without surgery, there were no other methods or investigative tools to precisely evaluate tumor cell disappearance after CRT. Although cCR has been reported to be associated with a good prognosis (14), many studies still reported a high rate of tumor cell detection in the resected specimen after esophagectomy in patients with cCR (15-17). The most recent prospective study (preSANO trial) demonstrated that combining endoscopy, with bite-on-bite biopsies, and endoscopic ultrasonography (EUS), with fine needle aspiration (FNA), and computed tomography (CT)-positron emission tomography (PET) can increase the yield of residual tumor and interval metastasis detection in post-CRT patients (18). Other authors reported using magnetic resonance imaging (MRI) with promising results (19). However, using these combined modalities requires numerous resources and results in very high costs, which many patients cannot afford, especially in Thailand.

Another point of concern is the criteria used to assess clinical response. Traditionally, the response evaluation criteria in solid tumors (RECIST) have been used as a guide to elucidate the status of patients with cCR. The definition of cCR according to the RECIST criteria is the "disappearance of all target lesions" (20). The difficulty confirming the absence of all target lesions is that, in addition to CT providing an anatomic unidimensional measurement, there are no stringent details regarding what other tools or tumor characteristics should be considered. Consequently, different methods for assessing cCR appear in the literature (15,16,21-23). Unfortunately, in many countries, resources such as EUS or CT-PET are limited due to accessibility, reimbursement policies, and patients' financial restraints. Therefore, we aimed to evaluate the outcome of cCR assessed using available tools, such as endoscopy with biopsy and CT, in patients who completed CRT, in both pre-operative and definitive settings.

MATERIAL AND METHODS

Study populations

Locally advanced esophageal cancer patients who received CRT either pre-operatively or definitively at Ramathibodi Hospital, Mahidol University, Thailand between 2008 and 2019 were retrospectively reviewed. Esophageal cancer patients, namely cervical, thoracic, and Siewert type 1 esophagogastric junction (EGJ) cancer patients, were identified from the Ramathibodi Hospital database. Patients with Siewert type 2–3 EGJ cancer, distant metastasis, unavailable medical records, or who were treated with chemotherapy or radiotherapy alone were excluded. The treatment plan was guided by the hospital's tumor care team, which consisted of medical oncologists, radiation oncologists, radiologists, upper gastrointestinal surgeons, and other subspecialties, as needed. Pretreatment staging involved history taking, physical examination, routine laboratory tests, esophagogastroduodenoscopy (EGD) with tissue biopsy, and CT. EUS and/or CT-PET were used only in a few cases and only for pretreatment staging because of patients' financial constraints. Therefore, the results of these modalities were not included in the analysis. Tumor staging was performed according to the American Joint Committee

on Cancer Staging Manual, eighth edition (24). This study was approved by the Ethics Committee of Ramathibodi Hospital, Mahidol University.

CRT

All patients were treated according to the standard of care at the time of diagnosis at the treating physician's discretion. RT was performed using high-energy photon external-beam RT delivered by three-dimensional conformal radiotherapy, or intensity-modulated radiotherapy or combined techniques. The dose of neoadjuvant radiotherapy was 40–50 Gy in 23–28 fractions, at 1.8–2.0 Gy per fraction, whereas the dose in definitive treatment was 50–70 Gy in 25–35 fractions. Locally advanced esophageal cancer patients were treated with either platinum-based therapies and 5-fluorouracil (5-FU) or carboplatin and paclitaxel regimens concurrently with RT. Carboplatin and paclitaxel were administered intravenously at doses of AUC 2 and 50 mg/m2, respectively, weekly for five cycles. In the platinum-based and 5-FU regimen, the dose of carboplatin ranged from AUC 4 to 6 or cisplatin ranged from 60 to 100 mg/m2 on day 1, with a 5-FU dose of 750–1000 mg/m2 on days 1–4, every 3–4 weeks.

Clinical response assessment

Each patient underwent clinical assessment approximately 4–8 weeks after the end of treatment (either chemotherapy or radiotherapy) consisting of clinical examination, EGD, and CT. EGD was performed using a standard endoscope (GIF H-180; Olympus Corp., Tokyo, Japan) with a diameter of 9.8 mm. If the scope could not be passed through the lesion, the lesion was classified as a stricture. We used a smaller EGD scope (such as the GIF XP 160; Olympus Corp.) in some of the stricture cases to examine the lesion and the remainder of the esophagus. The endoscopic findings were recorded and classified similar to the method described by Chao et al. (25) as one of the following: stricture, tumor, ulcer, other findings, or normal. The finding of stricture was classified and recorded separately. Three to four-bite random biopsies were performed at the suspected lesion sites in most cases.

CT of the chest, whole abdomen, and neck in cases with cervical and upper thoracic lesions were performed using a 64-slice (128-slice after 2017) multi-detector CT scanner with a 3-mm slice thickness. Non-enhanced scans followed by enhanced scans were performed using a water-soluble contrast agent. The CT findings were reported by the radiologists and retrospectively reviewed by the authors. The CT parameters were retrospectively reviewed and measured as maximal wall thickness of the esophagus/tumor, maximal tumor length, and short axis diameter, with the lymph node characteristics. The maximal tumor thickness and short axis diameter of the lymph nodes were obtained on an axial view. These parameters were measured using picture archiving and communication system (PACS) software (Synapse; Fujifilm Medical Systems, Valhalla, NY, USA).

Response assessment criteria

After completing CRT, patients were categorized into a cCR or non-cCR group according to the RECIST criteria (20). Thresholds from post-treatment variables obtained from each modality showing significant correlation with pCR were incorporated into the criteria to differentiate cCR from other types of treatment response. cCR was then defined by the presence of all of the following parameters:

1) endoscopy: 1.1) no visible tumor; 1.2) negative endoscopic biopsy;
2) CT scan: 2.1) post-treatment maximal esophageal wall thickness < 10 mm; 2.2) short axis of the intrathoracic and intraabdominal lymph nodes < 10 mm and < 5 mm for the supraclavicular lymph nodes; 2.3) no other abnormal lymph node findings, such as heterogeneous enhancement, central necrosis, or round shape; and 2.4) no other distant metastasis or other tumors detected.

Esophagectomy

Patients with planned trimodality treatment ideally underwent esophagectomy within 8–10 weeks after completing neoadjuvant therapy. The duration was extended to 12 weeks or longer until the patient was fit to undergo surgery, if necessary. Surgical techniques and approaches were dependent upon the surgeon's preference and tumor location.

Follow-up

All patients were followed-up regularly with a clinical examination every 3–4 months, upper endoscopy every 4–6 months, and CT of the chest and abdomen every 6 months for the first 2 years. Thereafter, endoscopy and CT were performed every 6 months for 3 years, and then annually thereafter until

recurrent or metastatic disease was detected. Other modalities, such as bone scan or PET-CT were performed in some patients, if clinically indicated.

Statistical analysis

Patients' demographic data were reported as median and standard deviation. Categorical variables were compared using the chi-square test. Continuous variables were analyzed using Student's t test and the Wilcoxon rank sum test. Survival analysis was performed using the Kaplan–Meier method and the log-rank test. All p-values were two-tailed, and p-values < 0.05 were considered significant. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of cCR for predicting pCR were assessed. Data calculation and analysis were performed using Stata Statistical Software, release 14.1 (StataCorp, 2015; College Station, TX, USA).

RESULTS

General patients' characteristics

A total of 79 patients were eligible and were included in the analysis and divided into a trimodality treatment group (41 patients) and definitive CRT (DCRT) group (38 patients). Patients' characteristics are summarized in *table 1*. The mean age of the tri-modality and DCRT groups was 59 years and 63 years,

Table 1 - Demographic data

Variables	Trimodality group (n=41), (%)	DCRT group (n=38), (%)	P value
Age: Median ±SD	59.05 ±8.50	62.13 ±9.42	0.133
Sex			
- Male	38 (93)	36 (95)	0.537
- Female	3 (7)	2 (5)	
ECOG performance status			
- 0	33 (80)	25 (66)	0.190
- 1	8 (20)	12 (32)	
- 2	0 (0.00)	1 (2)	
Underlying diseases			
- None	18 (44)	18 (47)	0.466
- Chronic obstructive pulmonary disease	4 (10)	2 (5)	0.118
- Diabetes mellitus	4 (10)	3 (8)	1.000
- Hypertension	9 (22)	7 (19)	0.215
- Chronic kidney disease	1 (2)	1 (3)	1.000
- Cerebrovascular accident	0 (0)	2 (5)	-
- Atrial fibrillation	2 (5)	2 (5)	-
- Others	3 (7)	3 (8)	0.233
Tumor location			
- Cervical	0 (0)	1 (3)	0.481
- Upper thoracic	1 (2)	11 (29)	0.002
- Middle thoracic	21 (51)	15 (39)	0.405
- Lower thoracic	17 (42)	10 (26)	0.1
- Esophagogastric junction	2 (5)	1 (3)	0.529
Histology			
- Squamous cell carcinoma	40 (98)	37 (97)	1.000
- Adenocarcinoma	1 (2)	1 (3)	
Clinical stage (TNM)			
- I	0	0	0.136
- II	7 (17)	7 (18)	
- III	25 (61)	15 (40)	
- IVA	9 (22)	16 (42)	
Regimens of chemotherapy			
- Carboplatin and paclitaxel	28 (68)	26 (68)	0.060
- Cisplatin and 5-fluorouracil	13 (32)	12 (32)	
Total dose of radiation (Gray)			
- 40 - 49	11 (27)	9 (24)	0.050
- 50 – 59	30 (73)	24 (63)	
- 60 – 70	0 (0.00)	5 (13)	#
Clinical response assessment			
- cCR	13 (32)	10 (26)	0.598
- Non-cCR	28 (68)	28 (74)	

cCR, clinical complete response; DCRT, definitive chemo-radiotherapy; ECOG, Eastern Cooperative Oncology Group

respectively. Most of the patients in both groups were male (93% and 94%, trimodality and DCRT groups, respectively). According to the Eastern Co-operative Oncology Group (ECOG), nearly all patients in both groups were assigned an ECOG score of 0 or 1 (78/79 patients). The underlying diseases of the patients in both groups were comparable, and the majority of the tumors in both groups were located at the mid-esophagus. Tumors at the upper thoracic esophagus were seen more frequently in the DCRT group, and squamous cell carcinoma was the most frequent histopathologic subtype in both groups. No significant difference was found in the clinical stage of the tumor and the chemotherapy regimens between the groups. All eligible patients received chemotherapy with either a carboplatin/paclitaxel regimen (n=53), or a combination of (5-FU) and cisplatin (n=24). Esophagectomy was performed using McKeown's technique in 28 cases (68.29%), Ivor–Lewis technique in 11 cases (26.82%), and trans-hiatal technique in 1 case (2.4%), depending on the tumor location. Two-field lymphadenectomy was performed in 26/41 cases (63.41%). The reasons for choosing nonoperative treatment were: 1) unresectable lesion (n=13); 2) unfit for surgery (n=10); 3) the patient declined surgery (n=9); 4) disease progression after CRT (n=3); 5) tracheoesophageal fistula after CRT (n = 2); and 6) cervical lesion (n=1). The median radiation dose did not differ between the groups (50.4 Gy in both groups), but five patients in the DCRT group received a radiation dose of more than 60 Gy. There were 13/41 (31.71%) and 10/38 (26.31%) patients in the trimodality and DCRT groups, respectively, classified as cCR.

Table 2 - Correlation between pCR and assessment variables

Variables	pCR (n=16)	Non-pCR (n=25)	P-value
Endoscopic findings			
- Tumor	0	9	0.014
- Stricture	3	11	0.102
- Normal	1	0	1.000
- Scar	8	4	0.474
- Mucosal thickening	1	3	0.434
- Ulcer	5	7	0.637
- Others	0	1	1.000
Endoscopic biopsy results			
- Cancer	0	1	0.115
- Atypical/dysplasia	1	2	
- Scar or mucosal inflammation	11	17	
- Others	0	3	
- No biopsy	4	2	
CT scan parameters			
Pre CRT maximal wall thickness			
- < 10 mm	4	0	0.018
- ≥ 10	12	24	
Post CRT maximal wall thickness			
- < 10 mm	13	7	0.043
- ≥ 10 mm	3	18	
% Decrease (%)			
- <30	5	10	0.165
- 30 - 50	4	10	
- >50	7	4	
Post CRT lymph node status			
- Positive	2	11	0.034
- Negative	14	14	
Tumor length (cm)			
- Pretreatment	6.4 (5,8:3)	6.0 (4,8:4)	0.442
- Post treatment	5.0 (4.2,5:0.8)	5.3 (3.6,7:3.4)	0.765
Clinical response assessment			
- cCR	12	1	< 0.001
- Non-cCR	4	24	

cCR, clinical complete response; cm, centimeter; CRT, chemo-radiotherapy; CT, computed tomography; pCR, pathological complete response

Correlation between the variables and pCR

Of 41 patients in the trimodality group, 16 (39.02%) achieved pCR. We investigated the and pCR after completing preoperative CRT (*table 2*). Three main parameters were included in the analysis: 1) endoscopic characteristics of the lesion, 2) results of endoscopic biopsy, and 3) CT findings. The results showed that endoscopic findings related to the tumor, pre- and post-CRT maximal thickness < 10 mm, and the presence of positive lymph nodes on CT was significantly related to pCR. Only those post-CRT assessment parameters showing a significant association with pCR were incorporated into the RECIST criteria to evaluate clinical response. Using the criteria mentioned above, we found that cCR was associated with pCR. However, among 16 patients with pCR, only 12 achieved cCR (75%). The sensitivity, specificity, PPV, and NPV of cCR for predicting pCR was 75%, 96%, 92.30%, and 85.71%, respectively.

Correlation between the assessment variables and histopathology

With regard to histopathology of the specimen, there were 19 patients with ypT0, 4 with ypT1, 8 with ypT2, 6 with ypT3, and 4 with ypT4. For lymph node metastasis, there were 30 patients with ypN0, 9 with ypN1 and 2 with ypN2. The relation between these ypT and ypN stages and those assessment parameters from endoscopy and CT scan was analyzed. It was shown that endoscopic findings of tumor and post-CRT maximal thickness < 10 mm was significantly correlated with ypT0 ($p< 0.01$), and the presence of negative lymph nodes on CT scan was significantly correlated with ypN0 ($p < 0.05$).

Survival

Survival duration was calculated from the date of the first diagnosis to the date of confirmed tumor recurrence, progression, or death from any cause. With a median follow-up interval of 27 months (95% confidence interval (CI): 13–37 months) in both groups (30 months in the trimodality group and 22 months in the DCRT group), overall 2- and 5-year survival in the trimodality group was 56.09% and 39.02%, respectively, compared with 42.10% and 28.94%, respectively, for the DCRT group. Median OS in the trimodality group was 28 months (95% CI: 17–57 months), whereas the median OS in the DCRT group was 16 months (95% CI: 14–26 months). The causes of death in the 41 patients receiving trimodality treatment were cancer (n=17), post-operative complication (n=3), pneumonia (n=2), tracheoesophageal (TE) fistula (n=1), myocardial infarction (n=1), and renal cell carcinoma (n=1). Of the 38 patients in the DCRT group, the causes of death were cancer (n=22), TE fistula (n=1), and unknown (n=4). The median disease-free survival (DFS) in the trimodality group was 19 months (95% CI: 11–53 months) and 11 months (95% CI: 7–19 months) in the DCRT group. No statistically significant difference was found between the trimodality and DCRT groups for OS and DFS (OS: p=0.258, DFS: p=0.213).

Correlation between post-CRT clinical response and survival

In patients receiving trimodality treatment, the median OS was 99 months (95% CI: 11– not estimable months) for cCR patients and 20 months (95% CI: 17–38 months) for non-cCR patients with 2-year OS rates of 69.23% and 50%, respectively. The median DFS was 99 months (95% CI: 7–not estimable months) for cCR patients and 16 months (95% CI: 9–53 months) for non-cCR patients with 2-year DFS of 69.23% versus 35.71%. There were trends toward better OS and DFS in favor of the cCR group, but the differences were not statistically significant (p = 0.08 for OS and p = 0.10 for DFS; *fig. 1* and *fig. 2*). However, after excluding patients who died of other causes, the difference in median esophageal cancer-specific survival between the cCR and non-cCR groups was statistically significant (not reached vs 27 months, p < 0.05).

In patients undergoing DCRT, the median OS in cCR patients was not reached (95% CI: 13–not estimable months) with 2-year OS rates of 80% compared with a median OS of 15 months (95% CI: 11–21 months) with 2-year OS rates of 28.57% in non-cCR patients. The

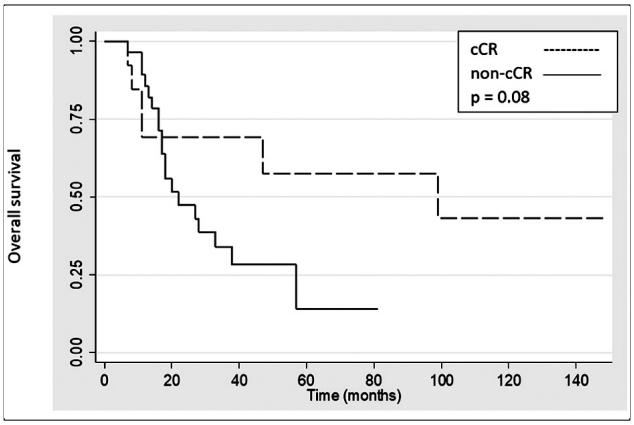

Figure 1 - Overall survival curve of patients in trimodality group comparing cCR versus non-cCR
cCR: clinical complete response

median DFS was not reached (95% CI: 7–not estimable months) with 2-year DFS rates of 80% for cCR patients and 8 months (95% CI: 6–12 months) with 2-year DFS rates of 17.85% for non-cCR patients. A statistically significant difference was found between cCR and non-cCR groups regarding OS and DFS (p < 0.05 and p < 0.01, respectively), as shown in *fig. 3* and *fig. 4*.

Recurrence patterns

Twenty-four (58.53%) patients in the trimodality group and 23 (60.52%) patients in the DCRT group developed disease recurrence. Patients achieving cCR after treatment vs non-cCR, respectively, in both groups, had a lower frequency of recurrence (23.07% vs 75% in the trimodality group, and 20% vs 75% in the DCRT group), lower incidence of distant and combined metastasis (15.38% vs 62.93% in the trimodality group and 10% vs 46.42% in the DCRT group), and longer duration until recurrence (recurrence diagnosed in the first year after completing treatment: 7.69% vs 53.57%

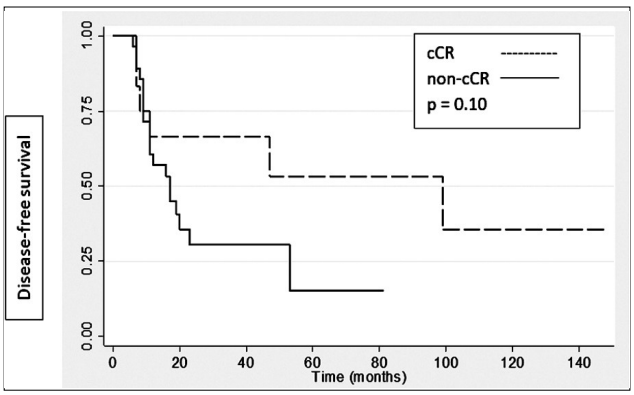

Figure 2 - Disease-free survival curve of patients in trimodality group comparing cCR versus non-cCR
cCR: clinical complete response

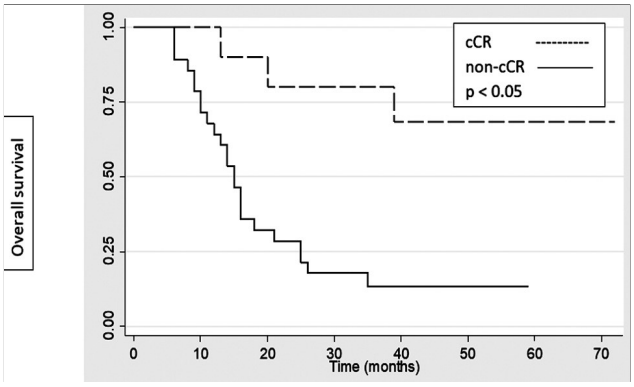

Figure 3 - Overall survival curve of patients in DCRT group comparing cCR versus non-cCR
cCR: clinical complete response; DCRT, definitive chemo-radiotherapy

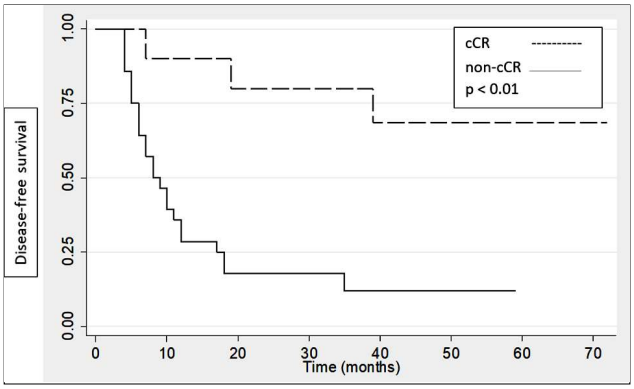

Figure 4 - Disease-free survival curve of patients in DCRT group comparing cCR versus non-cCR
cCR: clinical complete response

in the trimodality group and 10% vs 64.28% in the DCRT group). The most common pattern of recurrence was distant metastasis, and these metastases were commonly detected with locoregional recurrence, as shown in *table 3*. In cCR patients, three patients in the trimodality group and two patients in the DCRT group developed disease recurrence. One of three cCR patients in the trimodality group developed disease recurrence in the superior mediastinum, lungs, and bone only 1 month after surgery, and another cCR patient in the DCRT group developed tumor recurrence in the liver, lungs, bone, and intraabdominal lymph nodes 5 months after the last CRT.

DISCUSSION

The results of this study demonstrated that patients achieving cCR in both treatment groups had, or showed a trend toward, better OS and DFS and lower recurrence rates compared with non-cCR patients. Moreover, a correlation between cCR and pCR was also seen, with a sensitivity of 75% and a specificity of 96%. Each assessment modality was evaluated for efficacy and limitations regarding its use for post-CRT evaluation. Endoscopy with biopsy is usually used for this purpose. Endoscopic biopsy results may predict pathological tumor regression and clinical response in esophageal cancer patients achieving CRT (26). However, several studies reported that the accuracy of endoscopic biopsy alone was low, with pCR detected in only 24%–36% of patients with negative biopsy results (26-28). The findings in these studies are similar to the results of our study, with pCR observed in only 34% of patients with negative biopsy. One possible reason for this issue is that after CRT, there were still residual cancer cells located in scar and inflamed tissue in the mucosal and submucosal layers, and it may be difficult to obtain malignant cells in these tissues with standard endoscopic biopsies (29,30). To increase the cancer-cell yield in this situation, the results from the preSANO study showed that more aggressive tissue sampling with bite-on-bite biopsy technique, can increase the sensitivity and specificity of the detection rate of residual cancer (18).

In addition to tissue biopsy, the endoscopic characteristics of the lesion were found to be associated with the endoscopic biopsy results and postsurgical pathology (25,28). It is generally accepted that finding a tumor

Table 3 - Pattern of recurrence

Pattern of recurrence new	Trimodality			DCRT		
	cCR (n = 13)	Non-cCR (n = 28)	p value	cCR (n = 10)	Non-cCR (n = 28)	p value
Total number of recurrences	3 (23%)	21 (75%)	0.001	2 (20%)	21 (75%)	0.006
Pattern of recurrence						
- Local (Tumor/anastomosis)	0	1		0	3	
- Local and regional	1	2		1	3	
- Distant metastasis	1	7		0	2	
- Combined distant metastasis and loco-regional	1	11		1	13	

cCR, clinical complete response; DCRT, definitive chemo-radiotherapy

during endoscopic examination in post-CRT patients correlates highly with the presence of residual cancer (31). Moreover, other endoscopic findings, such as ulcer, scar, granular protruded lesion, Lugol-voiding lesion, or erosion were associated with false negative endoscopic biopsy results (25) and an increased local recurrence in patients receiving neoadjuvant CRT without surgery (22). According to the Japanese classification of esophageal cancer, erosion, irregular mucosa, ulcer, or protruded changes should be interpreted as the persistence of malignant cells (32). However, except for finding a tumor, no correlation was identified between endoscopic findings and pCR, or survival, in our study. This difference may be the result of the small number of patients in our study.

CT has been the main investigative tool for evaluation according to the RECIST criteria. However, it may be challenging in terms of reproducibility to measure an esophageal lesion, especially in a radiated esophagus (20,33). Despite this difficulty, several studies reported parameters measured or derived from the CT scan that may be associated with pCR and/or survival in post-CRT esophageal cancer patients. Swisher et al. (34) found a correlation between post-CRT esophageal maximal wall thickness and survival using multivariate analysis. However, the authors concluded that this result might be a statistical abnormality because the univariate analysis did not show a significant association. Another study, by Li et al. (35), revealed that both pre- and post-CRT maximal esophageal wall thickness in patients with T3–4 squamous cell carcinoma was associated with pCR, but that only pre-CRT maximal wall thickness ≥ 20 mm was significantly associated with poor survival outcomes. A similar result for the association between pCR and post-treatment esophageal wall thickness was also observed in a study by Molena and colleagues (36). These results are similar to our results indicating that maximal esophageal thickness, either pre- or post-CRT, was associated with pCR. The contrary result was observed in a study by Qiu and colleagues (37). Although the criteria for diagnosing cCR and the tools used in the study were similar to those in our study, the authors found no significant correlation between cCR and progression-free survival in their univariate analysis. The small number of patients recruited in both studies, differences in the proportions of the tumor sites, and differences in the CRT treatment regimen may have contributed to this discrepancy.

There is increasing data supporting the additional use of other modalities with endoscopy and or CT to improve the accuracy of residual tumor detection. EUS with or without FNA, and or dynamic contrast-enhanced and functional diffusion-weighted MRI to assess residual locoregional disease, and CT-PET to diagnose interval distant metastasis can help increase the accuracy of the post-treatment evaluation (18,19,37,38). Several ongoing trials are determining the optimal combined tools and criteria for more accurate clinical response prediction. The randomized, phase 3 SANO trial (39), using the same combination of diagnostic modalities as the preSANO trial is one of these studies. Additionally, the multicenter observational preoperative image-guided identification of response to neoadjuvant CRT in esophageal cancer (PRIDE) study has begun and focuses on clinical response assessment using combined endoscopy, EUS, PET-CT, dynamic contrast-enhanced MRI, and circulating tumor cells and DNA analysis (40).

The results in our study should be interpreted cautiously while considering the following limitations: 1) this was a retrospective study; 2) the number of patients in the study was small; 3) interpretations and measurement of endoscopic and CT results were performed by general radiologists and gastroenterologists; thus observer bias cannot be excluded; 4) researchers were not blinded during the data recording, which may have impacted the data analysis; and 5) pCR in this study may not represent the true status of absence of tumor cells because detecting distant metastasis depended only on clinical examination and CT. As shown in our study, two patients with cCR developed recurrent tumors shortly after the end of the last treatment. Metastases may have been present post-CRT, but were not detected during assessment. Using additional and more accurate tools, such as PET, could address this problem and avoid unnecessary surgical resection (41).

We believe that our study regarding the clinical assessment after chemoradiotherapy using our criteria may be able to use to predict the treatment response and prognosis after CRT in esophageal cancer patients. Because cCR is not equal to nonexistence of cancer cells, esophagectomy is still a preferred choice for all eligible patients after receiving preoperative CRT. Avoidance of or postponed esophagectomy with active surveillance may be an alternative option in high risk patients who had cCR after undergoing CRT. However, if surgery is postponed, the patient must be informed the risk of existence of occult cancer, and the risk of tumor progression that can become unresectable during surveillance (13). More studies regarding the positive and negative effect of active surveillance as well as the effective protocol and tools used are

required before considering this as a standard of esophageal cancer care.

CONCLUSION

This study demonstrated that cCR assessed by combined endoscopy with biopsy and CT in post-CRT esophageal cancer patients showed a higher rate of pCR and better survival outcomes in cCR patients than in non-cCR patients. These clinical response variables may be used to predict treatment response after completing CRT. However, due to the limitations of this study, our results do not provide sufficient evidence to ensure the absence of residual cancer cells, using these assessment modalities. Further studies with greater numbers of patients and ideal methodology are required to validate our results.

Author's contributions

Conception and design: NN, CJ and PH. Administrative support: SC. Provision of study materials or patients: NN, CJ, PPat, KV, PPai, and PH. Collection and assembly of data: KV, PPai, and PH. Data analysis and interpretation: NT, KS, and PH. Manuscript writing: All authors. Final approval of manuscript: All authors.

Acknowledgments

The authors wish to thank Dr Panuwat Lertsithichai, MD, and Dr Napaphat Seraphim, PhD, from the Department of Surgery for their invaluable recommendations regarding research methodology.

Sources of support: None

Conflict of interest: None Declared

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ethics approval was obtained through the ethics committee at the Ramathibodi hospitals, Mahidol university, and all patient information was de-identified. The Ramathibodi Ethic Committee approved a waiver of consent for this study as a retrospective chart review. The research involves no more than minimal risk to the patients and is not adversely affect the rights and welfare of the patients. All patient identifications were protected according to the GCP guideline and not published in the manuscript. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration (as revised in 2013).

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet 2013; 381:400-12.
3. Hiranyatheb P, Osugi H. Radical lymphadenectomy in esophageal cancer: from the past to the present. Dis Esophagus 2015;28:68-77.
4. Voeten DM, den Bakker CM, Heineman DJ, Ket JCF, Daams F, van der Peet DL. Definitive chemoradiotherapy versus trimodality therapy for resectable oesophageal carcinoma: meta-analyses and systematic review of literature. World J Surg 2019; 43:1271-85.
5. Münch S, Pigorsch SU, Deve□ka M, Dapper H, Feith M, Friess H, et al. Neoadjuvant versus definitive chemoradiation in patients with squamous cell carcinoma of the esophagus. Radiat Oncol 2019;14:66.
6. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 2005; 23:2310-7.
7. Bedenne L, Michel P, Bouché O, Milan C, Mariette C, Conroy T, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007; 25:1160-8.
8. Berger AC, Farma J, Scott WJ, Freedman G, Weiner L, Cheng JD, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. J Clin Oncol 2005; 23:4330-7.
9. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
10. Low DE, Kuppusamy MK, Alderson D, Cecconello I, Chang AC, Darling G, et al. Benchmarking complications associated with esophagectomy. Ann Surg 2019; 269:291-8.
11. Altorki NK, Lee PC, Liss Y, Meherally D, Korst RJ, Christos P, et al. Multifocal neoplasia and nodal metastases in T1 esophageal carcinoma: implications for endoscopic treatment. Ann Surg 2008; 247:434-9.
12. van der Wilk BJ, Eyck BM, Spaander MCW, Valkema R, Lagarde SM, Wijnhoven BPL, et al. Towards an organ-sparing approach for locally advanced esophageal cancer. Dig Surg 2019; 36:462-9.
13. Ferri L. Clinical complete response after neoadjuvant therapy for esophageal cancer: What's lurking under the surface? Ann Surg Oncol 2018; 25:2120-1.
14. Monjazeb AM, Riedlinger G, Aklilu M, Geisinger KR, Mishra G, Isom S, et al. Outcomes of patients with esophageal cancer staged with (18F) fluorodeoxyglucose positron emission tomography (FDG-PET): can postchemoradiotherapy FDG-PET predict the utility of resection? J Clin Oncol 2010; 28:4714- 21.
15. Piessen G, Messager M, Mirabel X, Briez N, Robb WB, Adenis A, et al. Is there a role for surgery for patients with a complete clinical response after chemoradiation for esophageal cancer? An intention-to-treat case–control study. Ann Surg 2013; 258:793-800.
16. Cheedella NK, Suzuki A, Xiao L, Hofstetter WL, Maru DM, Taketa T, et al. Association between clinical complete response and pathological complete response after preoperative chemoradiation in patients with gastroesophageal cancer: analysis in a large cohort.

Ann Oncol 2013; 24:1262-6.
17. van Rossum PSN, Goense L, Meziani J, Reitsma JB, Siersema PD, Vleggaar FP, et al. Endoscopic biopsy and EUS for the detection of pathologic complete response after neoadjuvant chemoradiotherapy in esophageal cancer: a systematic review and meta-analysis. Gastrointest Endosc 2016; 83:866-879.
18. Noordman BJ, Spaander MCW, Valkema R, Wijnhoven BPL, van Berge Henegouwen MI, Shapiro J, et al. Detection of residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (preSANO): a prospective multicentre, diagnostic cohort study. Lancet Oncol 2018; 19:965-974.
19. Vollenbrock SE, Voncken FEM, van Dieren JM, Lambregts DMJ, Maas M, Meijer GJ, et al. Diagnostic performance of MRI for assessment of response to neoadjuvant chemoradiotherapy in oesophageal cancer. Br J Surg 2019; 106:596-605.
20. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45: 228-47.
21. Castoro C, Scarpa M, Cagol M, Alfieri R, Ruol A, Cavallin F, et al. Complete clinical response after neoadjuvant chemoradiotherapy for squamous cell cancer of the thoracic oesophagus: is surgery always necessary? J Gastrointest Surg 2013; 17:1375-81.
22. Fang HY, Chao YK, Chang HK, Tseng CK, Liu YH. Survival outcomes of consolidation chemoradiotherapy in esophageal cancer patients who achieve clinical complete response but refuse surgery after neoadjuvant chemoradiotherapy. Dis Esophagus 2017; 30:1-8.
23. Heneghan HM, Donohoe C, Elliot J, Ahmed Z, Malik V, Ravi N, et al. Can CT-PET and endoscopic assessment post-neoadjuvant chemoradiotherapy predict residual disease in esophageal cancer? Ann Surg 2016;264:831-8.
24. Amin MB, Edge SB, Greene F, Byrd DR, Brookland RK, Washington MK, et al. AJCC Cancer Staging Manual. 8th Ed. New York: Springer, 2017.
25. Chao YK, Yeh CJ, Lee MH, Wen YW, Chang HK, Tseng CK, et al. Factors associated with false-negative endoscopic biopsy results after neoadjuvant chemoradiotherapy in patients with esophageal squamous cell carcinoma. Medicine (Baltimore) 2015;94:e588.
26. Miyata H, Yamasaki M, Takiguchi S, Nakajima K, Fujiwara Y, Konishi K, et al. Prognostic value of endoscopic biopsy findings after induction chemoradiotherapy with and without surgery for esophageal cancer. Ann Surg 2011; 253:279-84.
27. Schneider PM, Metzger R, Schaefer H, Baumgarten F, Vallbohmer D, Brabender J, et al. Response evaluation by endoscopy, rebiopsy, and endoscopic ultrasound does not accurately predict histopathologic regression after neoadjuvant chemoradiation for esophageal cancer. Ann Surg 2008; 248:902-8.
28. Sarkaria IS, Rizk NP, Bains MS, Tang LH, Ilson DH, Minsky BI, et al. Post-treatment endoscopic biopsy is a poor-predictor of pathologic response in patients undergoing chemoradiation therapy for esophageal cancer. Ann Surg 2009; 249:764-7.
29. Chao YK, Tsai CY, Chang HK, Tseng CK, Liu YH, Yeh CJ. A pathological study of residual cancer in the esophageal wall following neoadjuvant chemoradiotherapy: Focus on esophageal squamous cell carcinoma patients with false negative preoperative endoscopic biopsies. Ann Surg Oncol 2015; 22:3647-52.
30. Shapiro J, ten Kate FJ, van Hagen P, Biermann K, Wijnhoven BP, van Lanschot JJB. Residual esophageal cancer after neoadjuvant chemoradiotherapy frequently involves the mucosa and submucosa. Ann Surg 2013; 258:678-89.
31. Brown WA, Thomas J, Gotley D, Burmeister BH, Lim KH, Martin I, et al. Use of oesophagogastroscopy to assess the response of oesophageal carcinoma to neoadjuvant therapy. Brit J Surg 2004; 91:199-204.
32. Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: part II and III. Esophagus 2017;14:37-65.
33. Kurokawa Y, Shibata T, Ando N, Seki S, Mukaida H, Fukuda H. Which is the optimal response criteria for evaluating preoperative treatment in esophageal cancer: RECIST or histology? Ann Surg Oncol 2013; 20:3009-14.
34. Swisher SG, Maish M, Erasmus JJ, Correa AM, Ajani JA, Bresalier R, et al. Utility of PET, CT, and EUS to identify pathologic responders in esophageal cancer. Ann Thorac Surg 2004; 78:1152-1160.
35. Li SH, Rau KM, Lu HI, Wang YM, Tien WY, Liang JL, et al. Pretreatment maximal oesophageal wall thickness is independently associated with response to chemoradiotherapy in patients with T3-4 oesophageal squamous cell carcinoma. Eur J Cardiothorac Surg 2012; 42:958-64.
36. Molena D, Sun HH, Badr AS, Mungo B, Sarkaria IS, Adusumilli PS, et al. Clinical tools do not predict pathological complete response in patients with esophageal squamous cell cancer treated with definitive chemoradiotherapy. Dis Esophagus 2014; 27:355-9.
37. Qiu B, Wang D, Yang H, Xie W, Liang Y, Cai P, et al. Combined modalities of magnetic resonance imaging, endoscopy and computed tomography in the evaluation of tumor responses to definitive chemoradiotherapy in esophageal squamous cell carcinoma. Radiother Oncol 2016; 121:239-45.
38. Chang WL, Wang WL, Chung TJ, Lin FC, Yen CJ, Lai WW, et al. Response evaluation with endoscopic ultrasound and computed tomography in esophageal squamous cell carcinoma treated by definitive chemoradiotherapy. J Gastroenterol Hepatol 2015; 30:463-9.
39. Noordman BJ, Wijnhoven BPL, Lagarde SM, Boonstra JJ, Coene PPLO, Dekker JWT, et al. Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: a stepped-wedge cluster randomised trial. BMC Cancer 2018;18:142.
40. Borggreve AS, Mook S, Verheij M, Mul VEM, Bergman JJ, Bartels-Rutten A, et al. Preoperative image-guided identification of response to neoadjuvant chemoradiotherapy in esophageal cancer (PRIDE): a multicenter observational study. BMC Cancer 2018;18:1006.
41. Findlay JM, Gillies RS, Franklin JM, Teoh EJ, Jones GE, di Carlo S, et al. Restaging oesophageal cancer after neoadjuvant therapy with (18)F-FDG PET-CT: identifying interval metastases and predicting incurable disease at surgery. Eur Radiol 2016; 26:3519-33.