

Survival benefit of surgery in patients with clinical T4 esophageal cancer who achieved complete or partial response after neoadjuvant chemoradiotherapy or radiotherapy

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Abstract

Objective: This study aimed to determine the long-term survival of patients with cT4 esophageal cancer (EC) and whether neoadjuvant chemoradiotherapy/radiotherapy plus surgery (nCRT/RT + S) is superior to definitive CRT(dCRT)/RT in terms of survival in cT4 EC downstaged after nCRT/RT.

Summary background data: Treatment options for cT4 EC include dCRT/RT and nCRT/RT + S, but it is not clear whether the latter provides survival benefit in patients downstaged after nCRT/RT.

Methods: From 2002 to 2017, 726 patients with cT4 esophageal squamous cell carcinoma (ESCC) were retrospectively analyzed. Patients achieving clinical complete response (cCR) or partial response (PR) after 4-week RT (median dose, 40.7 Gy) and considered fit for surgery were offered esophagectomy. Of the 726 patients, 308 (42.4%) achieved cCR/PR, while 74 patients received subsequent surgery (nCRT/RT + S group), 234 patients received dCRT/RT.

Results: Median follow-up was 58 months. The 3-year overall survival (OS) and progression-free survival (PFS) rates for all patients were 33.3% and 35.6%, respectively. The corresponding OS and PFS rates were 54.8% and 48.5% in the nCRT/RT + S group *versus* 30.0% and 22.1% in the dCRT/RT group (both $p < 0.0001$). After adjusting the confounding variables with inverse probability of treatment weighting, the adjusted 3-year OS rates were 50.4% in the nCRT/RT + S group *versus* 50.8% in the dCRT/RT group ($p = 0.15$). However, the adjusted 3-year PFS rates were significantly different between the two groups (49.0% and *versus* 38.3%, $p = 0.004$). Postoperative complications occurred in 18 (24.3%) patients.

Conclusion: The long-term survival of cT4 ESCC was improved after the use of three-dimensional CRT. In cT4, EC responded to nCRT/RT, surgery improves PFS but not OS.

Keywords: clinical T4 stage, definitive chemoradiotherapy/radiotherapy, esophageal squamous cell carcinoma, neoadjuvant treatment, surgery

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Introduction

Esophageal cancer (EC) and esophagogastric-junction cancer (EGJC) kill more than 375,000 people each year in China, making this malignancy the fourth most common cause of cancer-related death in the country.¹ The proportion of patients

with locally advanced disease is high in China. In one large cohort study of 8156 patients with clinically staged esophageal squamous cell carcinoma (ESCC), 16% of patients had clinical T4a (cT4a) stage.² In the multicenter 3JECROG survey, cT4 ESCC accounted for 44.3% of all cases.³ On

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account of the large number of patients, treatment efficiency of cT4 stage disease needs to be concerned.

The NEOCRTEC5010 study shows that neoadjuvant chemoradiotherapy (nCRT) plus surgery improves survival over surgery alone among patients with locally advanced ESCC.⁴ The National Comprehensive Cancer Network guidelines recommend either neoadjuvant treatment followed by surgery or definitive CRT (dCRT) for cT4a ESCC and dCRT for unresectable T4b ESCC. While the recommendation remains controversial because the proportion of cT4 patients in the clinical trials cited was less than 10%, and survival of cT4 EC patients was not separately examined.⁵⁻⁷ Therefore, the best treatment mode for this group remains to be established.

Since the 1960s, planned preoperative radiotherapy (RT) has been used for unresectable ESCC in our hospital – Cancer Hospital, Chinese Academy of Medicine Sciences (CAMS); this approach has yielded much better survival rates than surgery alone.^{8,9} Currently, a multidisciplinary team evaluates images for downstaging of the tumor and decides whether radical excision is possible after patients have completed 4-week nCRT/RT. Esophagectomy is recommended if R0 resection is considered possible for the patient who is willing to undergo surgery. However, it is not clear whether survival is better in patients opting for surgery than in those opting for completing dCRT.^{10,11}

The aim of this retrospective study was to compare the long-term results between cT4 ESCC patients treated with dCRT/RT *versus* nCRT/RT followed by surgery (nCRT/RT + S).

Methods

Eligibility

The medical records of 1030 patients with cT4 ESCC who were treated at the Cancer Hospital, CAMS from October 2002 to December 2017, were retrospectively reviewed (Figure 1(a)). Patients were eligible for inclusion if they (1) had locally advanced or cT4 stage ESCC [celiac or supraclavicular nodal involvement, i.e. M1-Lym stage by 2002 *Union Internationale Contre le Cancer* (UICC) classification, was not a disqualification] and (2) had undergone esophageal resection after CRT/RT or had completed dCRT/RT. Patients

were excluded if they (1) had any other malignancy; (2) had been treated with two-dimensional conformal RT; (3) had been diagnosed with non-squamous cell carcinoma; (4) had metastasis before the start of RT or palliation therapy; (5) had not received RT for any reason; (6) had been lost to follow-up or had been followed up for <3 months (if survived); or (8) had undergone salvage surgery. The Independent Ethics Committee of CAMS approved the project (No. 21/095-2766) and waived the need for informed consent because of the deidentification of the patient data.

Clinical workflow and criteria for response

Pretreatment staging evaluation included physical examination; contrast esophagography; esophagoscopy, with or without endoscopic ultrasonography (EUS); endoscopy; computed tomography (CT) of the neck, chest, and upper abdomen; magnetic resonance imaging (MRI) of the chest and abdomen; bone scintigraphy; ultrasonography; positron-emission tomography (PET)-CT (if necessary), and bronchoscopy (for patients with suspected tracheobronchial invasion on CT). On bronchoscopy, the tracheobronchial tree was considered to be involved if the tumor extended into the lumen and confirmed by definite pathological diagnosis. On CT scan, adjacent thoracic aorta was considered to be involved if the tumor was attached to the artery at a contact angle of $\geq 90^\circ$.^{10,11} Diagnosis of metastasis to lymph nodes was based on CT, EUS, and ultrasonography findings.

The decision on whether CRT or RT should be used was based on the stage of the tumor, range of the radiation field, patient's age, and Karnofsky performance score (KPS). The effect of RT was evaluated after about 21–23 fractionations^{10,12} (Figure 1(b)). Clinical complete response (cCR) was defined as a complete disappearance of the tumor, without the evidence of erosion on contrast esophagography, CT, endoscopy, and EUS. On contrast esophagography, cCR was diagnosed if there was a complete disappearance of the tumor, with a smooth esophagus outline and smooth passage of barium. Partial response (PR) was defined as a decrease in the longest diameter of the tumor by at least 30% on CT or EUS; disappearance of most of the lesions on contrast esophagography, with no obvious distortion or angulation of the esophagus, no extra cavity ulcers, and smooth passage of barium (even if the edges were not smooth, or there were small defects and small niches, or if the edges were

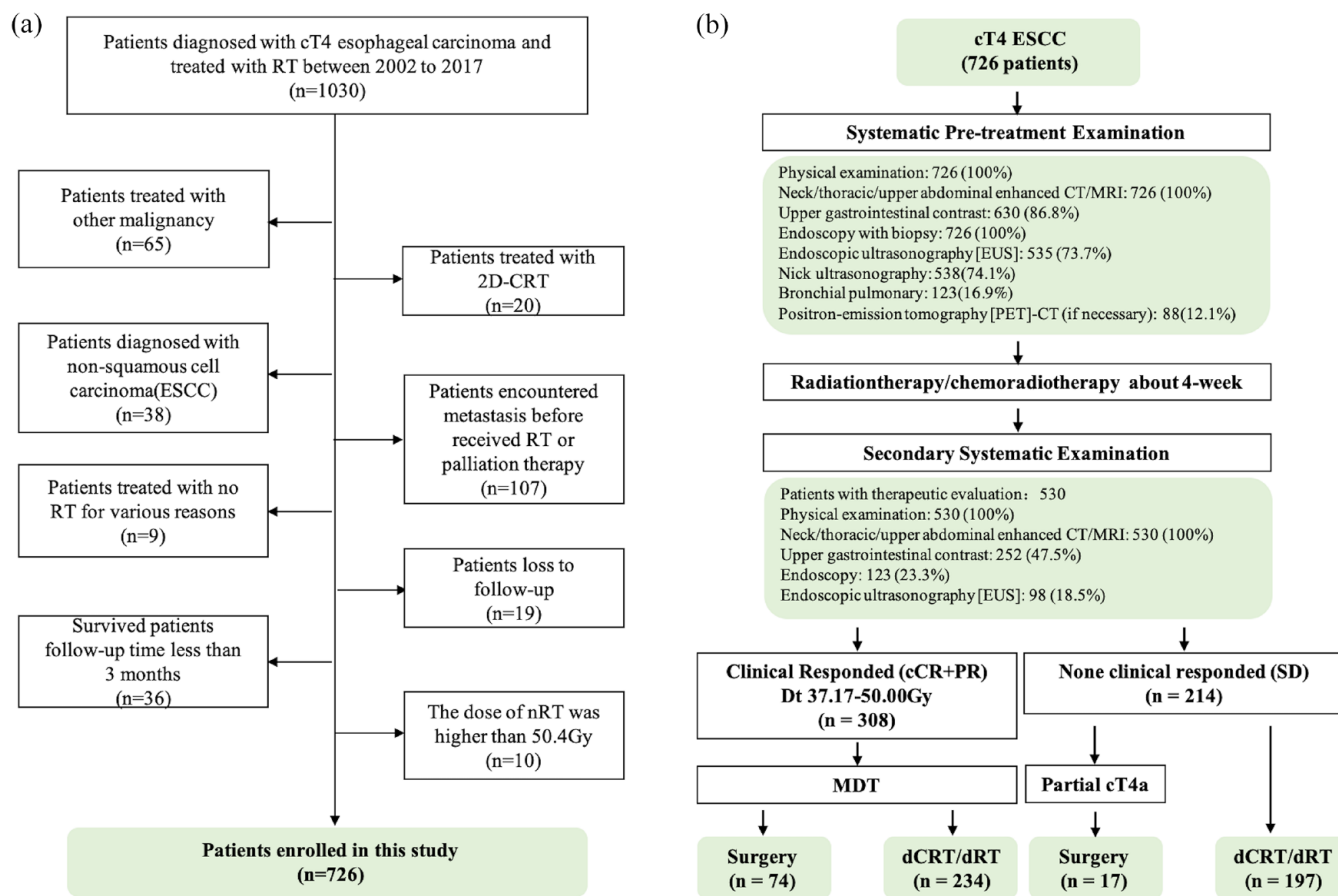


Figure 1. Patient selection: (a) STROBE guidelines showing patient selection and (b) clinical workflow.

smooth but the lumen was obviously narrow). cCR and PR were classified as responders (Supplemental Figure S1(A1)–(A7), (C1)–(C7)). Progressive disease was defined as at least 20% absolute increase in tumor burden (compared with nadir) or appearance of new lesions. All other cases were defined as stable disease (SD, Supplemental Figure S1(B1)–(B7), (D1)–(D7)); obvious filling defects, niche shadows, twisted angles, or lumen stenosis on contrast esophagography were classified as SD.

Lymph node evaluation was performed according to the Response Evaluation Criteria in Solid Tumors 1.1. After resection, pathological complete response (pCR) was defined as the absence of residual tumor at the primary site and in nodal tissue.

If cCR or PR was achieved, multidisciplinary consultation determined whether surgery was considered feasible and the patient was willing. Then, esophagectomy was performed. If complete tumor and lymph nodes resection was not

considered feasible or the patient was unwilling for surgery, follow-up RT was continued. Thus, patients having cCR/PR after initial treatment could be divided into two groups: those treated with nCRT/RT followed by surgery (nCRT/RT + S group) and those continuing with CRT or RT (dCRT/RT group).

Radiotherapy

Enhanced CT was performed for positioning and outlining the target area. The dose to be prescribed was determined and submitted to the physician for formulation of the RT plan. RT was started only after the plan had been approved by the chief physician. Cone-beam CT-guided RT was administered at least three times in the first week and once a week thereafter.

Primary gross tumor volume (GTV) and possibly GTV of metastatic lymph nodes were determined by imaging or clinical examinations. Clinical target volume (CTV) was defined as follows: for the

cervical and upper thoracic esophagus, the upper boundary was the cricothyroid, and the lower boundary was 3 cm below the tracheal carina; for the middle and lower thoracic esophagus, the upper boundary was the first thoracic vertebrae and the lower boundary was 3 cm below the tumor (for the middle thoracic esophagus) or at the level of the abdominal trunk (for the lower thoracic esophagus), including partial lower cervical, supraclavicular region and mediastinal stations 1R/L, 2R/L, 3p, 4R/L, 7, 8, and corresponding lymphatic drainage area around the stomach. The planning target volume was the CTV plus a uniform 0.5-cm margin.

All patients received three-dimensional (3D) conformal RT, intensity-modulated RT or volumetric intensity-modulated arc therapy once a day for 5 days per week. For nCRT/RT, the total dose ranged from 37.2 to 50.0 Gy (EQD2 or equivalent dose in 2-Gy fractions, with each fraction ranging from 1.80 to 2.14 Gy; median dose, 40.7 Gy). For dCRT/RT, 90% patients received a total radiation dose of 50–64 Gy (EQD2, with each fraction ranging from 1.80 to 2.14 Gy; median dose, 60 Gy).

Chemotherapy

The concurrent intravenous chemotherapy ($n=332$) regimens included TP (paclitaxel combined and platinum, $n=308$) regimen, PF [fluorouracil (FU) and platinum, $n=42$] regimen, and platinum only ($n=9$) or paclitaxel only ($n=2$). The TP regimen comprised paclitaxel 50 mg/m², and nedaplatin or cisplatin 20–25 mg/m², administered as intravenous drip on the first day, and repeated weekly for a total of 4–5 cycles. The PF regimen comprised FU 500 mg/m² intravenous infusion on days 1–5; nedaplatin or cisplatin 75 mg/m², intravenous infusion on the first day, and then repeated every 21 days or 28 days, for a total of 1–2 cycles. Oral chemotherapy regimens included S-1 ($n=18$), capecitabine ($n=11$), and capecitabine ($n=4$), taken twice daily orally (or through nasal feeding tube for patients on enteral nutrition) within half an hour after meals during treatment days. It was not taken during weekends or whenever RT was interrupted or stopped.

Surgery

For nCRT/RT + S patients, esophagectomy was performed at 4–8 weeks (median, 6 weeks) after the end of nCRT/RT. Only in one patient was the

interval prolonged to 19 weeks (due to grade 3 radiation pneumonitis). Enhanced CT of neck/thorax/upper abdomen was repeated to confirm that the tumor and metastatic lymph node could be resected completely. The surgical approach and procedure were determined by the tumor's location and the surgeon's preference. The characteristics of surgery are listed in Supplemental Table S1. Generally, the right thoracotomy (Ivor Lewis or McKeown) with extended lymphadenectomy (the resection of lymph nodes along the bilateral recurrent nerves and those resected during standard lymphadenectomy) was performed for patients with upper thoracic lesions, whereas left thoracotomy with standard lymphadenectomy (the resection of all lymph nodes in the middle and lower periesophageal portion, subcarinal region, perigastric region, and along the left gastric artery) for patients with middle and lower lesions. Endoscopy surgery included minimally invasive Ivor Lewis and Minimally invasive McKeown. A gastric tube passed through the posterior mediastinal route served as a substitute for the resected esophagus. The anastomotic site was determined according to the tumor location: cervical anastomosis for upper thoracic lesions, and intrathoracic anastomosis for middle and lower thoracic lesions.

Follow-up

Acute and late toxicities were scored according to the Common Toxicity Criteria, version 2.0 (before 2003) and the Common Toxicity Criteria for Adverse Events, version 3.0 (after 2003). Patients were assessed weekly during treatment, every 3–6 months during the first 2 years after treatment, every 6–12 months in the next 3 years, and annually thereafter. Assessment was made with detailed history (for symptoms of cough, fever, hoarseness, dysphagia or chest tightness, and so on); blood examination (blood routine, basic metabolic panel, tumor markers, and so on); contrast-enhanced CT of neck, thorax, and abdomen; ultrasound of neck and abdomen; upper gastrointestinal contrast study; bone scan (in case of bone pain or abnormally elevated alkaline phosphatase); CT or MRI of brain (in case of any symptoms related to central nervous system). Endoscopy, EUS, PET-CT, and fine-needle aspiration cytology were performed if needed. Survival status, disease progression, other treatments received, nutrition, life quality, late toxic effects, and so on were documented at each follow-up.

Statistical analysis

Overall survival (OS) was defined as the time from the beginning of RT to death from any cause, and progression-free survival (PFS) from the beginning of RT to disease progression, relapse, or death from any cause. Inverse probability of treatment weighting (IPTW) was used to adjust for differences in clinical characteristics between the nCRT/RT + S group and the dCRT/RT group.¹³ IPTW aims to simulate a cohort in which treatments are randomly assigned to patients. Standardized mean difference was used to assess the balance of covariates between the two treatment groups before and after weighting.

The Kaplan–Meier method was adopted to calculate the survival rate, and the log-rank method was used to compare survival curves between groups. A Cox regression model with stepwise selection was used to perform multivariate analyses of the effect of covariates on OS and PFS. The significance level was set as $p < 0.05$. SPSS 25.0 (IBM Corp., Armonk, NY, USA) and R 3.3.3 (<https://cran.r-project.org/>) were used for statistical analysis.

Results

Patient characteristics

Table 1 lists the characteristics of the study population. Of the 726 patients, 567 (78.1%) were <70 years old and 159 (21.9%) were ≥ 70 years old. There were 661 (91.0%) patients with KPS of 80–100. Primary tumor length was <5 cm in 140 (19.3%) patients, 5–7 cm in 276 (38.0%) patients, and ≥ 7 cm in 310 (42.7%) patients. TNM staging was according to American Joint Committee on Cancer (AJCC) 6th edition criteria. In all, 340 (46.8%) patients had invasion of pleura, pericardium, and/or diaphragm and 386 (53.2%) had invasion of aorta, heart, lung parenchyma, or other adjacent structure. Primary lesion volume (volume of primary tumor and metastatic lymph nodes outlined by the physician in the 3D-RT planning system) was ≤ 46 cm³ in 230 (32.3%) patients and > 46 cm³ in 482 (67.7%) patients.

Survival

Median follow-up was 58 months (range, 1–147 months); it was 44 months (3–147 months) in the nCRT/RT + S group and 59 months (1–141 months) in the dCRT/RT group. In the total

study cohort, the 1-year, 3-year, and 5-year OS rates were 64.8%, 33.3%, and 26.6%, respectively, and the PFS rates were 50.2%, 35.6%, and 20.1%, respectively (Figure 2(a)).

Log-rank analysis is shown in Table 1. The multivariate analysis (Supplemental Figure S2) showed that KPS, primary tumor length, M stage, primary lesion volume, response to initial CRT/RT, surgery, and perforation were independently associated with OS.

The 1-year, 3-year, and 5-year OS rates were 85.6%, 54.8%, and 46.0%, respectively, in the nCRT/RT + S group *versus* 61.6%, 30.0%, and 24.1%, respectively, in the dCRT/RT group. The 1-year, 3-year, and 5-year PFS rates were 76.7%, 48.5%, and 42.5%, respectively, in the nCRT/RT + S group *versus* 46.2%, 22.1%, and 16.8%, respectively, in the dCRT/RT group. The differences between the groups were significant (both $p < 0.0001$, Figure 2(b) and (c)).

Of the 726 patients, 308 (42.4%) achieved cCR/PR. While 74 patients received subsequent surgery (nCRT/RT + S group), 234 patients received definitive radiotherapy (dCRT/RT group). The 1-year, 3-year, and 5-year OS rates were 85.1%, 53.0%, and 47.4%, respectively, in the nCRT/RT + S group [median survival time (MST), 46.4 months] *versus* 83.1%, 49.0%, and 44.0%, respectively, in the dCRT/RT group (MST, 32.9 months); the difference was not statistically significant ($p = 0.15$; Figure 3(a)). The 1-year, 3-year, and 5-year PFS rates were 74.3%, 46.3%, and 43.7%, respectively, in the nCRT/RT + S group *versus* 64.6%, 36.8%, and 26.2%, respectively, in the dCRT/RT group; the difference was statistically significant ($p = 0.005$; Figure 3). After adjusting the confounding variables with IPTW (Supplemental Table S2), the adjusted 1-year, 3-year, and 5-year OS rates, and MST were 86.2%, 54.0%, 47.7%, and 46.4 months, respectively, in the nCRT/RT + S group *versus* 83.7%, 50.8%, 41.9%, and 36.9 months, respectively, in the dCRT/RT group; the difference was not statistically significant ($p = 0.15$, Figure 3(c)); however, the adjusted 1-year, 3-year, and 5-year PFS rates were significantly different between the two groups (74.7%, 49.0%, and 46.2% *versus* 65.1%, 38.3%, and 27.6%, respectively; $p = 0.004$; Figure 3(d)). In multivariable analysis, surgery resulted in better PFS than dCRT/RT, without significant difference in OS (Supplemental Table S3).

Table 1. Characteristics of patients, tumors, and treatments.

	No. of patients	%	OS	PFS
			p Value	p Value
Total patients	726			
Age (years)			0.051	0.042*
<70	567	78.1		
≥70	159	21.9		
KPS			0.001*	0.004*
<80	65	9.0		
≥80	661	91.0		
Length			0.022*	0.008*
<5 cm	140	19.3		
≥5 and <7 cm	276	38.0		
≥7 cm	310	43.7		
Location			0.677	0.802
Upper	264	36.4		
Middle	354	48.7		
Middle	108	14.9		
Tumor invasion			0.014*	0.019*
I*	340	46.8		
II [§]	386	53.2		
N stage (AJCC 6th)			0.062	0.026*
N0	82	11.3		
N1	644	88.7		
M stage (AJCC 6th)			<0.001*	<0.001*
M0	570	78.5		
M1a	67	9.2		
M1b	89	12.3		
Radiation technology			0.832	0.905
CRT	102	14.0		
IMRT	587	80.9		
VMAT	37	5.1		
Concurrent chemotherapy			<0.001*	<0.001*

(Continued)

Table 1. (Continued)

	No. of patients	%	OS	PFS
			<i>p</i> Value	<i>p</i> Value
No chemotherapy	332	45.7		
Doublet chemotherapy	350	48.2		
Other chemotherapy	44	6.1		
Primary lesion volume			<0.001*	<0.001*
≤46 cm ³	230	32.3		
>46 cm ³	482	67.7		
Response to initial CRT/RT			<0.001*	<0.001*
cCR/PR	308	42.5		
SD	214	29.5		
PD	8	1.1	<0.001*	<0.001*
None evaluation	196	27.0		
Surgery			<0.001*	<0.001*
Yes	91	12.5		
No	635	87.5		
Perforation			<0.001*	<0.001*
Yes	40	5.5		
No	686	94.5		

*Tumor invasion: pleura, pericardium, and diaphragm.

‡Tumor invasion: aorta, heart, lung parenchyma, or other adjacent structure.

AJCC, American Joint Committee on Cancer; cCR, clinical complete response; CRT, chemoradiotherapy; KPS, Karnofsky performance score; IMRT, intensity-modulated radiotherapy; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RT, radiotherapy; SD, stable disease; VMAT, volumetric intensity-modulated arc therapy.

Among the 386 patients in tumor invasion II⁺ group, the 5-year OS rate was 43.0% (MST, 25.9 months) in the nCRT/RT + S group *versus* 21.7% (MST, 15.3 months) in the dCRT/RT group ($p=0.003$; Supplemental Figure S3(a)). Of them, 167 (43.3%) patients achieved cCR/PR after 4-week RT and 39 (10.1%) patients received subsequent surgery. Among the responders, the 5-year OS and PFS rates were 45.2% (MST, 25.8 months) and 40.2% in the nCRT/RT + S group *versus* 45.6% (MST, 49.8 months) and 28.3% in the dCRT/RT group ($p=0.99$ and $p=0.22$; Supplemental Figure S3(e) and (f)).

Among the 214 non-responders with SD, the 1-year, 3-year, and 5-year OS rates were 81.1%, 47.9%, and 47.9% in nCRT/RT group, compared with 48.4%, 16.1%, and 9.3% in dCRT/RT group ($p<0.0001$; Supplemental Figure S4).

Moreover, among the 91 patients in the nCRT/RT + S group, postoperative pathology showed ypT0-2N0 in 48.4% (44/91) patients. The 5-year OS rate in this subgroup was 62.0% (MST, 62.0 months) *versus* 3.2% (MST, 17.7 months) in patients with ypT3-4N⁺ ($p<0.0001$; Supplemental Figure S5).

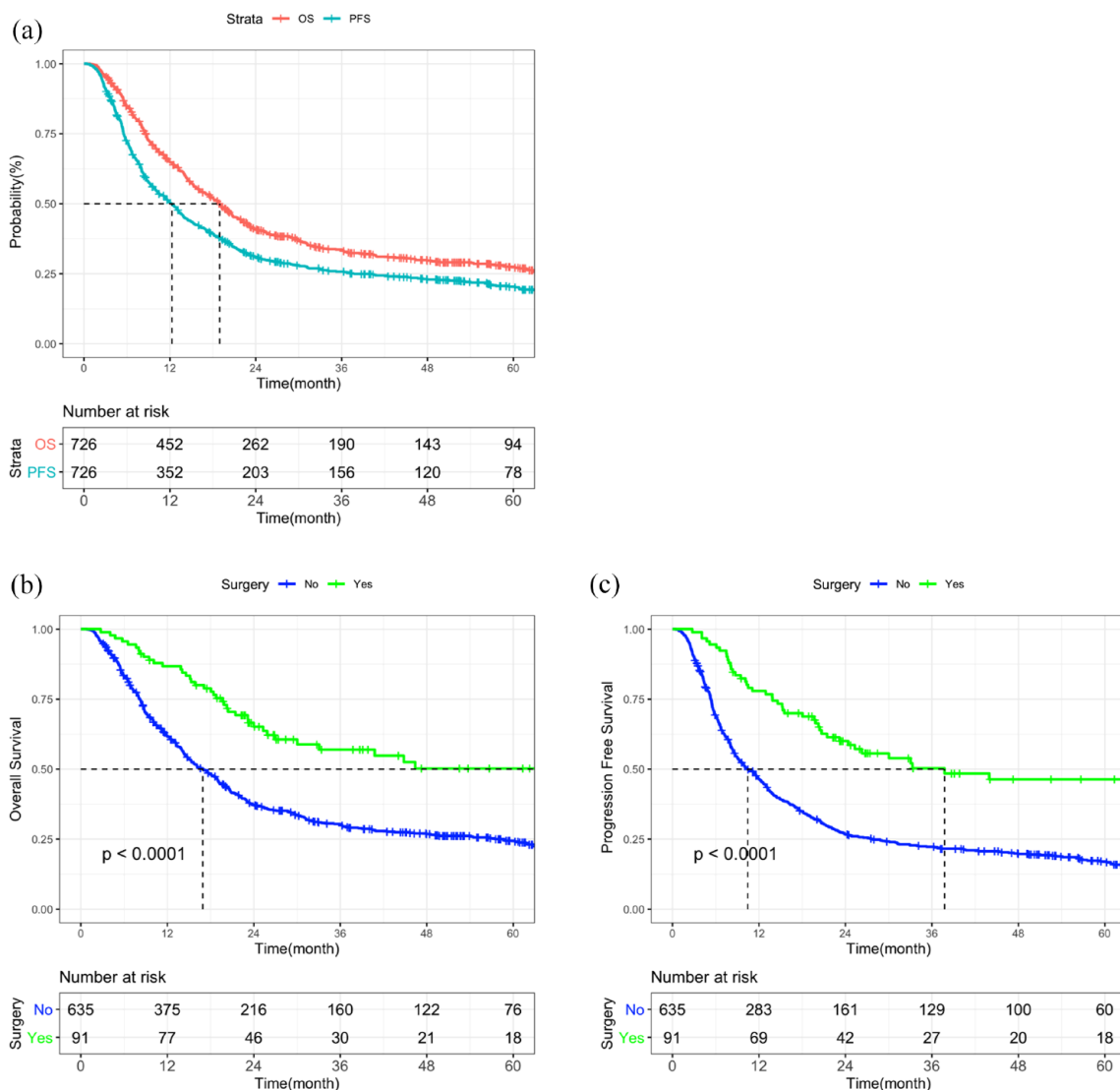


Figure 2. Kaplan–Meier curves for OS and PFS in the whole cohort (a) and for dCRT/RT group and nCRT/RT + S group (b and c). dCRT/RT, definitive chemoradiotherapy/radiotherapy; nCRT/RT + S, neoadjuvant chemoradiotherapy/radiotherapy plus surgery; OS, overall survival; PFS, progression-free survival.

Resection rate and toxicities

Among the 91 patients who underwent surgery, 74 patients had a response evaluation of cCR/PR after RT. Among the responders, three (4.1%) patients had R2 resection and 71 (95.9%) had curative resection. Details of treatment-related toxicities are listed in Figure 4. Postoperative complications occurred in 18 (24.3%) patients; five (7.1%) patients had postoperative respiratory failure, four (5.7%) had anastomotic stenosis, eight (11.4%) had anastomotic fistula, and six (8.6%) had other complications (pneumonia, pleural effusion, and bleeding). Two (2.9%) patients died within

30 days of surgery due to severe complications such as respiratory failure and anastomotic stenosis (Figure 4). All patients were evaluated for acute toxicity: 36 (11.7%) patients had grade 3–4 leukopenia and 11 patients (3.6%) had grade 3–4 skin reaction in dCRT/RT group (Table 2). No patient had grade 5 radiation-related toxicity.

Discussion

This is the largest cohort study to have reported the long-term survival and addressed the survival benefit of surgery in cT4 ESCC. Our study

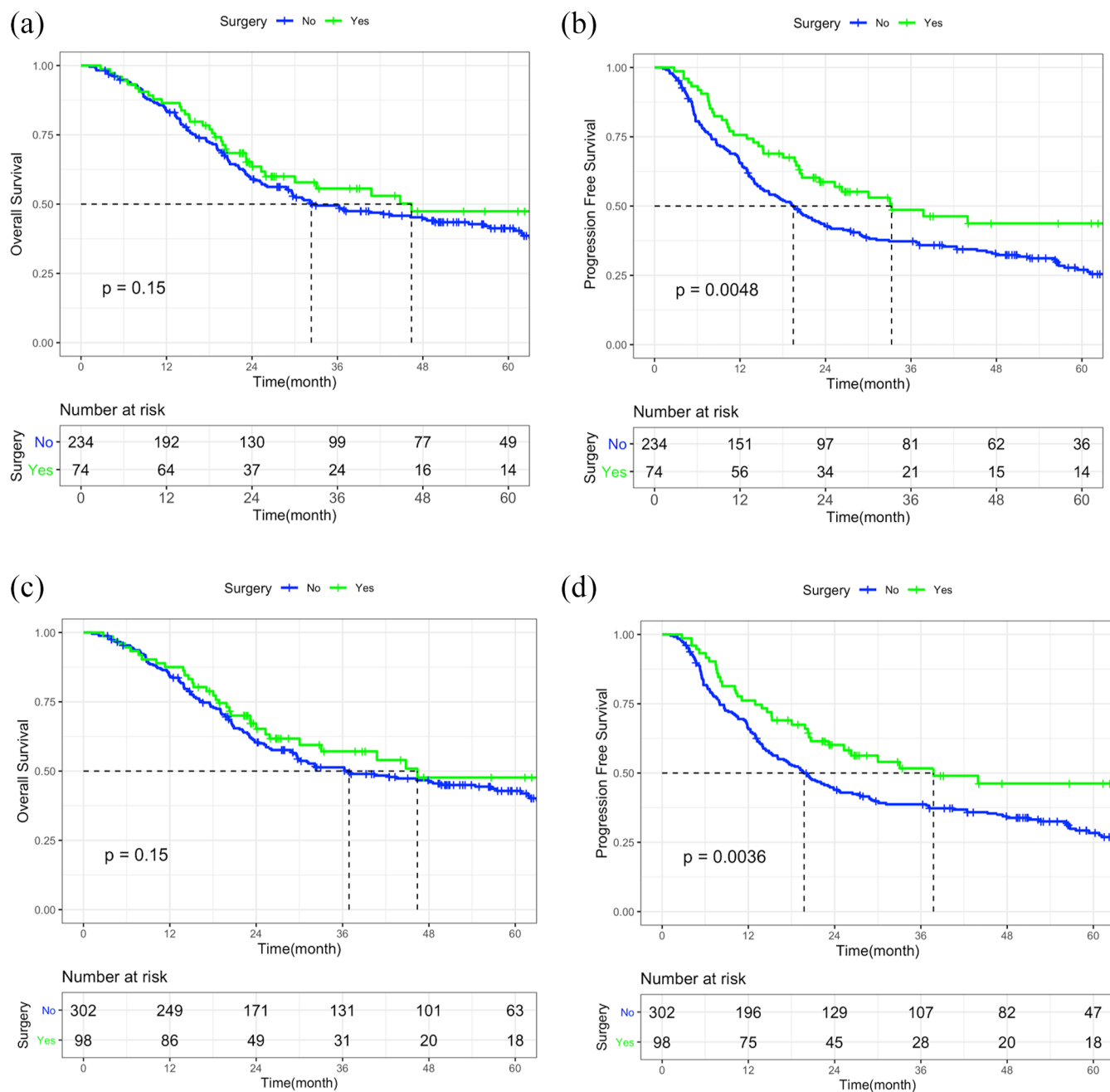


Figure 3. Before IPTW: OS (a) and PFS (b) of responders. IPTW analysis: OS (c) and PFS (d) of responders. IPTW, inverse probability of treatment weighting; OS, overall survival; PFS, progression-free survival.

demonstrated the long-term OS and corresponding PFS for cT4 ESCC were improved after the use of 3D-CRT. In cT4 EC patients who were responded to nCRT/RT, surgery improved PFS but not OS. For non-responders eligible for surgery, esophagectomy may improve survival.

With advances in RT technology and the application of concurrent chemotherapy, OS after dCRT

for ESCC has been improved. In a recent report, the 5-year OS rate after dCRT was 26.0–44.3%.^{14–16} Even in stage III–IV ESCC, the 5-year OS rate is 23.5–27.7%.¹⁷ All patients in this study had cT4 stage; in addition, the proportion of patients with primary lesion volume $\geq 46 \text{ cm}^3$ (67.7%) and with lymph node metastasis (88%) were higher than in previous studies (64.5% and 86.5%, respectively).^{4,5} The survival rate after

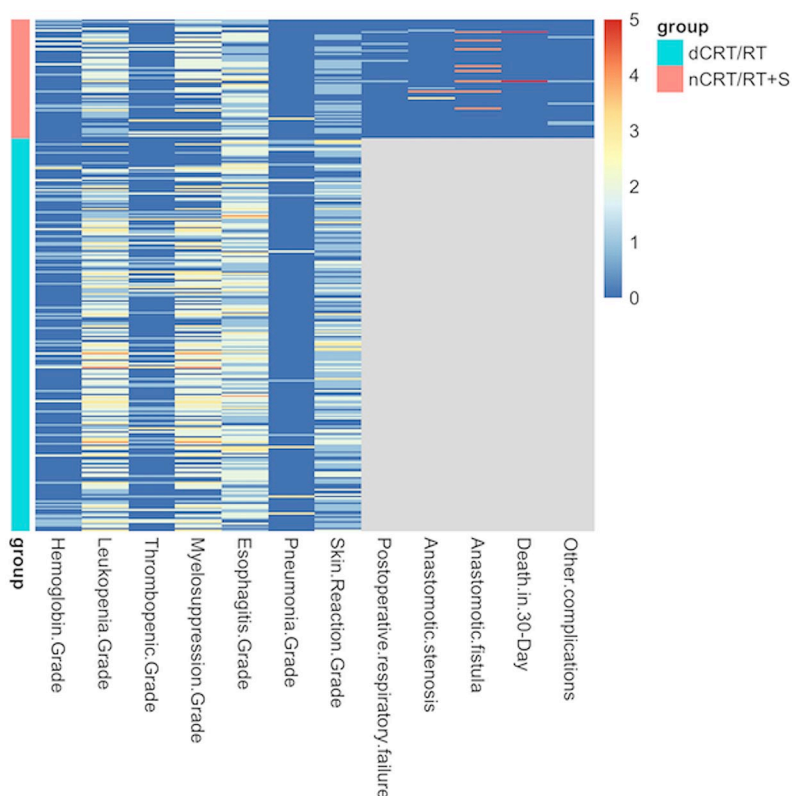


Figure 4. The severity of individual toxicities in dCRT/RT group and nCRT/RT + S group among responders. dCRT/RT, definitive chemoradiotherapy/radiotherapy; nCRT/RT + S, neoadjuvant chemoradiotherapy/radiotherapy plus surgery.

3D-CRT is better than with conventional RT of earlier years. In our study cohort, the 1-year, 3-year, and 5-year OS rates were 64.8%, 33.3%, and 26.6%, respectively. Though some patients were not considered for surgery, their 1-year, 3-year, and 5-year OS rates after dCRT/RT were 61.6%, 30.0%, and 24.1%, respectively. Thus, dCRT/RT alone also appears to be effective treatment for locally advanced cT4 EC.

It remains unclear whether surgical resection can provide additional survival benefit in cT4 ESCC with tumors downstaged after nCRT/RT. Among responders (cCR + PR), IPTW analysis showed that OS rates were not significantly different between patients receiving dCRT/RT and patients receiving nCRT/RT + S (5-year OS, 47.7% versus 41.9%; MST, 46.4 months versus 36.9 months, $p=0.15$); however, PFS was significantly improved by the addition of surgery (5-year PFS, 46.2% versus 27.6%, $p=0.0036$). Subgroup analysis showed that for the patients achieving cCR/PR whose tumor had invasion of aorta, heart, lung parenchyma, or other adjacent

structure, surgery had no benefit on OS and PFS. These results are not consistent with two studies from other countries. In the randomized FFCD9102 trial ($n=259$), which compared the efficacy of dCRT versus nCRT + S for patients with resectable locally advanced ESCC, no survival benefit was demonstrated with nCRT + S among responders to CRT (MST, 17.7 months versus 19.3 months; 2-year OS, 34% versus 40%).¹⁸ However, propensity-score matched analysis in a European multicenter retrospective study on operable EC patients with cCR after CRT ($n=222$) found that survival is better in patients receiving surgery than in patients receiving only surveillance (MST, 83.0 versus 31.0 month; 5-year OS, 58.9% versus 33.4%, $p=0.001$).¹⁹ There are several possible reasons for the different results. First, precise assessment of the efficacy of CRT is necessary to identify the improvement in outcomes in downstaged cases receiving surgery,^{20,21} but the evaluation of cCR by the current clinical imaging examinations is not accurate. In the FFCD9102 trial¹⁸ and the European study,¹⁹ pathological examination

Table 2. Protocol-defined toxicities and postoperative complications.

Event	nCRT/RT + S (%)	dCRT/RT (%)	χ^2	p Value
Toxicities				
Hemoglobin grade			-	>0.999
0-2 Level	74 (24.0%)	233 (75.6%)		
3-4 Level	0 (0.0%)	1 (0.4%)		
Leukopenia grade			6.527	0.011*
0-2 Level	71 (23.1%)	198 (64.3%)		
3-4 Level	3 (0.9%)	36 (11.7%)		
Thrombopenia grade			-	>0.999
0-2 Level	73 (23.7%)	229 (74.4%)		
3-4 Level	1 (0.3%)	5 (1.6%)		
Myelosuppression grade			5.936	0.019*
0-2 Level	70 (22.7%)	195 (63.3%)		
3-4 Level	4 (1.3%)	39 (12.7%)		
Esophagitis grade			2.156	0.155
0-2 Level	71 (23.1%)	212 (68.8%)		
3-4 Level	3 (0.9%)	22 (7.1%)		
Pneumonia grade			-	>0.999
0-2 Level	73 (23.7%)	231 (75.0%)		
3-4 Level	1 (0.3%)	3 (1.0%)		
Skin reaction grade			-	0.072
0-2 Level	74 (24.0%)	223 (72.4%)		
3-4 Level	0 (0.0%)	11 (3.6%)		
Postoperative complications				
Postoperative respiratory failure	5 (6.8%)	-		
Anastomotic stenosis	4 (5.4%)	-		
Anastomotic fistula	8 (10.8%)	-		
Other complications	5 (6.8%)	-		
Death in 30 days	2 (2.7%)	-		
Total	18 (24.3%)			
Numbers listed refer to the number of events and not the number of patients because patients could have experienced more than one event. dCRT/RT, definitive chemoradiotherapy/radiotherapy; nCRT/RT + S, neoadjuvant chemoradiotherapy/radiotherapy plus surgery.				

showed residual tumor in 35–77% of patients. In our cohort, postoperative pathology showed ypT0–2N0 in 48.4% patients; OS was much higher in these patients than in patients achieving ypT3–4/N⁺ (5-year OS, 62.0% *versus* 3.2%). Furthermore, in the European multicenter study, the doses of dCRT and nCRT were 50.4 Gy and 45 Gy, respectively, which were not too different. Our previous study has shown that the incidence of major pathological response increases with increase in RT dose.²² Other authors have shown that OS is significantly better in patients with major pathological response than in patients showing only minor response.²³ In one retrospective study, ESCC patients receiving high-dose irradiation (≥ 60 Gy) had better OS and local control rate than patients receiving conventional dose (50.4 Gy).²⁴ In the present study, 70.9% (450/635) patients in the dCRT/RT group received radiation dose >60 Gy. Third, the sample size was small. Further studies are needed on methods to improve the accuracy of imaging evaluation.

Analysis of previous data from our center also showed that, among patients with operable EC, the 5-year OS rate was 60% for those with major pathological response²³; the OS rate of patients with minor response was significantly lower than that of patients with major/moderate pathological response and of patients receiving surgery alone. Postoperative response is related to OS, as was also demonstrated in our study where patients with ypT0–2N0 had better OS than patients with ypT3–4/N⁺ (5-year OS, 62.0% *versus* 3.2%; Supplemental Figure S5). Besides, only 25.3% (23 patients) with cT4 EC achieved pCR after surgery, which is much lower than the pCR of 43.2% reported in NEOCRTEC5010.⁴ The possible reasons for the lower pCR in our cohort might be related to the larger primary lesion volume, more extensive lymph node metastasis, and lack of chemotherapy or the use of nonstandard chemotherapy.

Treatment-related toxicity is an important factor that is considered during treatment selection. In the FFCD9102 trial, 97 (75.0%) patients had R0 resection, and 6 (4.7%) patients died during the first 3 months after registration due to surgical complications.¹⁸ In our cohort, among the 74 responders, 71 (95.9%) patients had curative resection, and 24.3% (18/74) had postoperative complications; the most common complication was anastomotic fistula (11.4%, 8/74). Two

(2.9%) patients died within 30 days of surgery due to severe complications. These data suggest that the addition of surgery might increase risks, but it can be controlled. Thus, among patients with potentially resectable cT4 before treatment, even if evaluation after 4-week RT shows SD, surgery can markedly improve 5-year survival (47.9% *versus* 9.3%; Supplemental Figure S3). None R0 resection and not low rate of postoperative complications might be accounted for the result that higher PFS rate of surgery group cannot be transformed into higher OS rate. Meanwhile, for unresectable lesions that are insensitive to treatment, the prognosis is obviously poor (5-year OS, 9.3%; Supplemental Figure S3). More follow-up studies on adjuvant therapy are needed to enhance the life quality and prolong survival. In the CheckMate 577 trial, conducted among patients with resected EC or EGJC who had received nCRT, disease-free survival was significantly longer among those who received nivolumab adjuvant therapy than among those who received placebo (median disease-free survival, 22.4 months *versus* 11.0 months, $p < 0.001$).²⁵ Thus, immunotherapy has the potential to improve outcomes in unresectable and radiation-insensitive cT4. Recently, in another JCOG1109 trial for locally advanced [clinical stage IB, II, III (excluding T4) (UICC 7th)] ESCC with neoadjuvant treatment, the reported 3-year OS rate was 62.6% for CF (cisplatin plus 5-FU), compared with 72.1% for DCF (docetaxel, cisplatin plus 5-FU; $p = 0.006$), and 68.3% for CF-RT (cisplatin plus 5-FU, radiation 41.4 Gy/23 fractions; $p = 0.12$).^{26,27} Neoadjuvant therapy with DCF significantly improved OS compared with CF, with a manageable toxicity profile. Though this study excluded T4 tumors, it also provides a new potential neoadjuvant treatment for ESCC.

This study has several limitations. In our cohort, 45.7% of patients had RT only without concurrent chemotherapy, probably due to the low ability of tolerability of concurrent CRT in Chinese population. However, our retrospective study did not show a significant difference in 5-year OS between CRT and RT alone (median dose, 60 Gy; 34.7% *versus* 27.7%).¹⁷ To determine whether RT alone is a suitable secondary treatment option for EC patients who cannot tolerate chemotherapy, we conducted a prospective randomized study.²⁸ Furthermore, although statistical methods were applied to reduce bias, the low surgery rates may have underestimated the benefit of

surgery. Third, due to the retrospective nature, several confounding variables were not included in this study (i.e. comorbidities, nutritional status, eating situation, and quality of life). The relatively long-time span and the fact that this was a single-center retrospective study could also have biased the results.

In conclusion, for cT4 ESCC patients who achieved downstage after 4-week CRT or RT, surgery appears to improve PFS. A prospective stratified study is needed to determine the efficacy of nCRT followed by surgery so that the most appropriate treatment can be chosen.

Declarations

Ethics approval and consent to participate

The Independent Ethics Committee of CAMS approved the project (No. 21/095-2766) and waived the need for informed consent because of the deidentification of the patient data.

Consent for Publication

Not applicable.

Author contributions

Lin-Rui Gao: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Writing – original draft.

Chen Li: Data curation; Investigation.

Weiming Han: Data curation; Investigation; Methodology.

Wenjie Ni: Data curation; Investigation.

Wei Deng: Data curation; Investigation.

Lijun Tan: Data curation; Investigation.

Zongmei Zhou: Investigation.

Dongfu Chen: Investigation.

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Jun Liang: Investigation.

Jima Lv: Investigation.

Wenqing Wang: Investigation.

Wenyang Liu: Investigation.

Lei Deng: Investigation.

Xin Wang: Investigation.

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Jianyang Wang: Investigation.

Yirui Zhai: Investigation.

Nan Bi: Investigation.

Lvhua Wang: Investigation.

Zhouguang Hui: Investigation.

Ye-Xiong Li: Investigation; Project administration; Supervision; Validation; Writing – review & editing.

Zefen Xiao: Conceptualization; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – review & editing.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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