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Simultaneous integrated boost for mediastinal lymph node recurrence after radical surgery for esophageal cancer: Interim results from a phase I/II prospective study

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Abstract

Background: This was a single institute, phase I/II study of salvage chemoradiotherapy (CRT) with simultaneous integrated boost in patients with mediastinal lymph node (LN) recurrence after esophagectomy.

Methods: Patients who presented with a clinical diagnosis of ≤5 mediastinal LN recurrence received three consecutive levels of radiotherapy dose for the recurrences. Level 1: 58.8 Gy/2.1 Gy/28 fractions, Level 2: 64.4 Gy/2.3 Gy/28 fractions and Level 3: 70 Gy/2.5 Gy/28 fractions.

Results: A total of 17 patients (10 patients in phase I and 7 patients in phase II) were enrolled in the present study between June 2019 and July 2020. The median duration from surgery to initial recurrence was four months (range: 3–43 months). The most common site of recurrence according to JES was 106recR, accounting for 35%. Dose-limiting toxicity was not observed during three-month follow-up after completion of irradiation. The most common hematological toxicities were leukocytopenia and anemia. The most common nonhematological toxicity was esophagitis. The ORR according to RECIST was 58.8% (CR: seven patients; PR: three patients). With a median follow-up of 15 months (95% CI: 7–16 months), all patients were still alive. Among them, two patients who received a level 1 dose and one patient who received a level III dose developed multiple lung metastases after salvage CRT, and another patient who received a level 1 dose developed an out-of-field recurrence in the left cervical lymph node area. Another patient who received a level III dose developed chest wall recurrence after salvage CRT.

Conclusions: The regimen of salvage CRT using the simultaneous integrated boost (SIB) technique (70 Gy/2.5 Gy/28F) for mediastinal lymph node recurrence in ESCC patients after esophagectomy is feasible and well tolerated.

KEYWORDS
clinical trial, esophageal cancer, recurrence, salvage chemoradiotherapy

INTRODUCTION

Esophageal cancer is one of the most common causes of cancer-related death in China, with 477 900 newly diagnosed cases, and about 375 000 related deaths annually.[1] The histological type of esophageal cancer in China is significantly different from that in western countries, and more than 90% of esophageal cancer cases have been classified as esophageal squamous cell carcinoma (ESCC) in China. Currently, curative surgery is the preferred treatment for resectable ESCC. However, locoregional recurrences remain the most frequent patterns of recurrence after esophagectomy, which account for 23.8%–58.0% of cases of recurrence,[2–4] while 5.5%–33% of cases develop distant metastasis.[5,6] For patients with isolated cervical lymph node recurrence, two retrospective studies have demonstrated that cervical

lymphadenectomy might be the main treatment for esophageal carcinoma patients who develop cervical lymph node recurrence after curative esophagectomy when compared with salvage radiotherapy/radiochemotherapy.[7,8] However, for patients with mediastinal lymph node recurrence, salvage surgery is associated with a high risk of perioperative morbidity and mortality.[9–11] According to the National Comprehensive Cancer Network (NCCN) guidelines, salvage chemoradiotherapy is preferably recommended for such patients with recurrence. However, this recommendation is based on only a few retrospective studies with small sample sizes.[8,12] In addition, the optimal radiotherapy dose remains undetermined. As a result, in the present study, we performed a prospective phase I/II study of salvage chemoradiotherapy (CRT) with simultaneous integrated boost (SIB) for mediastinal lymph node recurrence after esophagectomy. The phase I portion of this study aimed to identify the optimal dose of salvage radiotherapy dose for the treatment of mediastinal lymph node recurrence with acceptable toxicity. The phase II portion aimed to assess the efficacy and toxicity of the recommended dose of salvage CRT for the treatment of esophageal cancer.

METHODS

Inclusion criteria

The inclusion criteria were as follows: (a) Histopathologically proven diagnosis of thoracic esophageal squamous cell carcinoma. (ii) Age ≥ 18 and ≤ 80 ECOG performance status 0–1. (iii) Diagnosis of ≤5 mediastinal lymph node recurrence after esophagectomy. Diagnosis of lymph node recurrence: (a) lymph node recurrences were pathologically confirmed, (b) pathological confirmation unavailable, and patients needed to fulfill one of the following criteria: (a) two consecutive computed tomography (CT) scans at an interval of one month or more showed lymph nodes had continued to increase, with a short diameter greater than 0.5 cm, (b) positron emission tomography (PET)/CT scan showed lymph nodes with FDG uptake, and (c) CT scan detected newly enlarged lymph nodes after surgery; patients without pathological diagnosis were discussed at department meetings before treatment. (iv) Patients without distant metastasis and life expectancy ≥3 months. (v) Adequate hematological function (white blood cell count ≧ 3.0×10^9/L; platelets ≧50 × 109/L; hemoglobin ≥90 g/L). (vi) Adequate liver and kidney function (creatinine <110 gmol/L; urea nitrogen <7.1 mmol/L; bilirubin <1.5 x ULN, ALT and AST ≤2.5 x ULN). (vii) Patients provided their written, signed informed consent

Exclusion criteria

The exclusion criteria were as follows: (i) Prior radiotherapy to site of recurrence of esophageal cancer. (ii) Other coexisting malignancies or malignancies diagnosed within the last five years. (iii) Pregnant women. (iv) Women who were breastfeeding.

(v) Patients with uncontrolled serious medical or mental illnesses.

Pretreatment evaluation

Before enrollment in the present study, all potentially eligible patients were evaluated by history-taking, physical examination, electrocardiogram, bone marrow, renal, hepatic and pulmonary function. A CT of the neck, chest and abdomen would be performed. PET/CT was recommended but not mandatory for patients enrolled in the study.

Radiation technique

Treatment-planning CT scans using intravenous contrast were performed for all patients in the supine position with both arms straight beside the body. Gross tumor volume (GTV-N), defined as any visible mediastinal lymph node recurrence, was delineated by physicians using all possible resources (CT, endoscopic ultrasonography [EUS] and F18-fluorodeoxyglucose [F18-FDG] PET/CT, etc). Planning gross target volume (PGTV) was created by expanding GTV-N using a 0.5 cm expansion around GTV-N. Elective nodal irradiation (ENI) was adopted for all patients, meaning that all patients had their prophylactic lymph node regions irradiated: (i) For patients with recurrence within one year after surgery: clinical target volume (CTV) included the mediastinal lymphatic drainage area (1R, 1 L, 2R, 2 L, 4R, 4 L, 7) and the primary tumor bed with pT3/pT4; (ii) for patients with recurrence more than one year after surgery, CTV included the mediastinal lymphatic drainage area (1R, 1 L, 2R, 2 L, 4R, 4 L, 7). The typical contouring of CTVs for lymph node recurrence according to the interval from surgery to recurrence are described in Figure 1 and Figure 2. PTV was generated using a uniform 0.5 cm expansion around CTV.

Follow-up

All patients were assessed at three-month intervals for the first two years after treatment, at six-month intervals for the next three years, and annually thereafter. Computed tomography of the neck, thorax, and upper abdomen using contrast, ultrasonography of the neck and upper abdomen, nuclear bone scanning, conventional blood studies and biochemistry studies were performed at each follow-up, in addition to gastric endoscopy, or PET/CT, as required.

Toxicity evaluation

Acute treatment related toxicities were defined as acute when they occurred within 90 days from the start of

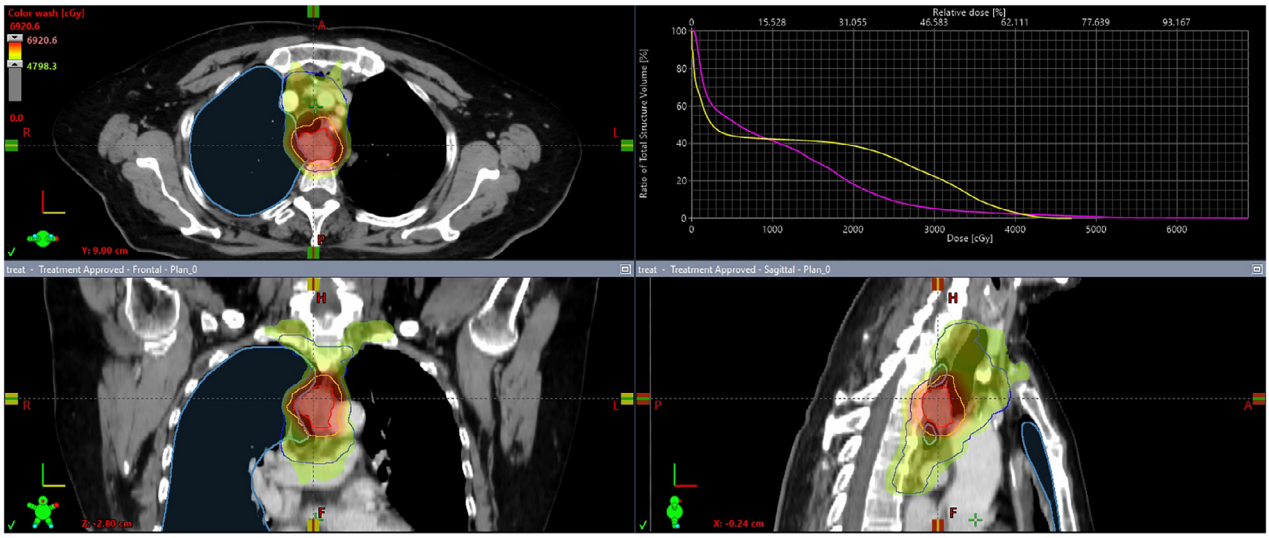

FIGURE 1 Target contouring and planning design for elective field radiotherapy after recurrence without tumor bed irradiation. GTVnd (red line), PGTVnd (yellow line), PTV (blue line). The prescribed dose (SIB-IMRT) for 95% PTV was 50.4 Gy/1.8 Gy/28F, and for 95% PGTVnd was 64.4 Gy/2.3 Gy/28F

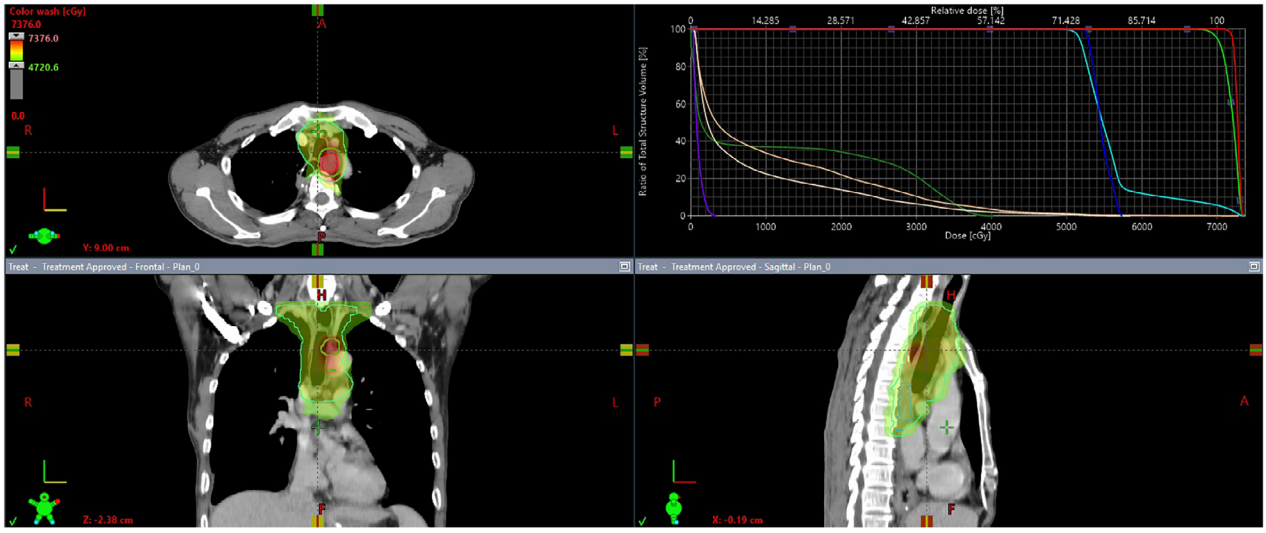

FIGURE 2 Target contouring and planning design for elective field radiotherapy after recurrence with tumor bed irradiation. GTVnd (red line), PGTVnd (green line), CTV-TB (blue line), PTV (light green). The prescribed dose (SIB-IMRT) for 95% PTV was 50.4 Gy/1.8 Gy/28F, and for 95% PGTVnd was 70 Gy/2.5 Gy/28F

radiotherapy using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The dose-limited toxicity (DLT) was defined as grade 4 or higher hematological toxicities and/or grade 3 or higher nonhematological toxicities (including radiation-induced esophagitis, pneumonitis, etc). The dose escalation started with dose level 1. After radiotherapy three patients were followed up for three months, starting from the first day of radiotherapy. If no patients developed DLT, the next dose level was started until intolerable, or up to the highest dose level (70 Gy/28F). If one patient developed DLT, a further three patients would be enrolled into the study. If only one out of six patients had DLT, the dose escalation was continued. The dose escalation was terminated when ≥1 of three patients (≥33%), or ≥2 of six patients developed DLT, and the previous lower dose level was considered the maximum tolerated dose (MTD). In addition, all patients received prophylactic irradiation of the mediastinal lymphatic drainage area at a dose of 50.4 Gy/28F. Radiotherapy plans were generated by the Varian Eclipse: External Beam Planning system (version 15.6). Irradiation was delivered with 6-MV photon energy using a linear accelerator. Dose coverage required that 95% of PTVs receive the prescribed dose. Concurrent chemotherapy (S-1 alone or cisplatin combined with paclitaxel) was recommended for all enrolled patients.

TABLE 1 Baseline characteristics of patients included in the study

Characteristics	Number of patients	%
Age (years; median, range)	64 (46–77)	
Gender		
Male	14	82.4
Female	3	17.6
ECOG score		
0	13	76.5
1	4	23.5
Tumor location (AJCC eighth edition)		
Upper thoracic	6	35.3
Middle thoracic	6	35.3
Lower thoracic	5	29.5
pT stage		
pT1	1	5.9
pT2	5	29.4
pT3	11	64.7
pN stage		
pN0	8	47.1
pN1	7	41.2
pN2	2	11.8
pStage (AJCC eighth edition)		
IB	1	5.9
IIA	5	29.4
IIB	2	11.8
IIIA	1	5.9
IIIB	8	47.1
Volume of recurrence		
Median (cm^3, range)	5.0 (0.77–26.5) cm^3	
Concurrent regimens		
S-1	14	82.4
DDP + PTX	3	17.6
Duration from surgery to recurrence, months	4 (3–43) months	
Dose-escalating regimen		
58.8 Gy/28F	4	23.5
64.4 Gy/28F	3	17.6
70 Gy/28F	10	58.5

Abbreviations: DDP, cisplatin; PTX, paclitaxel.

Sample size

In the phase I stage, the sample size was calculated as "3 + 3" protocol. In the phase II stage, sample size estimation was performed based on the Simon's optimal two-stage design.[13] Initially, we hypothesized that the one-year survival could be increased from 56% to 76%. With a unilateral alpha error of 5% and a statistical power of 80%, a planned 37 subjects were needed. However, the one-year survival in the phase I study was 100%, and we modified the hypothesis that the one-year survival could be increased from 56%[14] to 97%, thus a total of seven patients were needed in the phase II study.

Statistical analysis

The post-recurrence survival and overall survival (OS) was calculated by the Kaplan–Meier method and analyzed using the log-rank test. All tests were two-sided, and p-values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the Statistical Package for Social Sciences 23.0 software (SPSS Inc).

Ethical issues

All patients signed a written informed consent before enrolment. This trial was approved by the local review board (Ruijin Hospital Ethics Committee) and was in accordance with the Helsinki Declaration. The study is registered in an international public registry (ClinicalTrials.gov: NCT03990532).

Trial registration: NCT03990532. Registered 19 June 2019, https://clinicaltrials.gov/ct2/show/NCT03990532?term=salvage+radiotherapy&cond=Esophageal+Cancer&draw=2&rank=1

RESULTS

Patient characteristics

From June 2019 to July 2020, 17 patients were enrolled into the study. Of these, there were 10 patients in the phase I dose escalating study, four patients in level I and three in two other levels. Seven patients were enrolled in the phase II study. Patient characteristics are summarized in Table 1. There were 14 males and three females with a median age of 64 years (range: 46 to 77 years). 64.7% had T3, 29.4% had T2 and 5.9% had T1. As for LN stage, 47.1% had N0, 41.2% had N1 and 11.8% had N2. Approximately 47.1% of the patients presented with stage IIIB. Median volume of recurrence were 5.0 (0.77–26.5) cm^3. All patients received concurrent chemotherapy. Of these, 14 patients were treated with S-1 alone, twice a day, on RT day, from Monday to Friday, and the other three patients were treated with doublet chemotherapy of cisplatin and paclitaxel on a weekly basis.

Distribution of LN recurrence

The specific sites of recurrence of each patient according to the Japan Esophageal Society (JES) are listed in Table 2. A total of 30 sites of recurrence were identified in the present study. The most common site of recurrence according to JES was 106recR, accounting for 43.3%, followed by 106recL (16.7%).

TABLE 2 Sites of recurrence according to the Japan Esophageal Society (JES)

Patients	Number of recurrences	Sites of recurrence according to JES
No.1	3	106recR (2 sites), 114
No.2	2	107106tbl
No.3	1	106recR
No.4	2	106recR, 106recL
No.5	5	104R(2 sites),104 L(2 sites),114
No.6	1	106tbl
No.7	1	105
No.8	1	105
No.9	3	106recR(2 sites), 114
No.10	1	106recR
No.11	2	106recR (2 sites)
No.12	1	105
N0.13	1	106tbl
No.14	1	104R
No.15	1	106recR
No.16	5	104R, 106recR, 106recL(2 sites),113
No.17	1	106tbR

Toxicity and tolerance

The last follow-up was done in November 2020, and a median follow-up was 15 months (95% confidence interval, 7–16). During the phase I dose escalating study, all 10 patients tolerated RT very well. None of the 10 patients stopped or delayed treatment due to treatment related toxicities. No DLT was observed and the dose escalation was terminated at the highest dose level (70 Gy/28F) without reaching the MTD. During the phase II study, a total of seven patients received the recommended dose from phase I trial, and no DLT was observed. For the 17 patients available for acute toxicity assessment, the most common hematological toxicities were leukocytopenia and anemia (Table 3). The most common nonhematological toxicity was esophagitis (grade 1: 64.7% and grade 2: 11.8%).

Tumor control and survival

At the last follow-up, all the enrolled patients were still alive. Of the 17 patients available for tumor response analysis, the overall response rate (ORR) according to the RECIST criteria was 58.8% and the local regional control rate was 100%. Of the 10 patients in the phase I study with minimal follow-up of 13 months, the one-year OS rate and local-regional control rate was 100%, and median progression-free survival (PFS) was 16 months (95% CI: 6–16 months). Among them, two patients who received a level 1 dose and one patient who received a level III dose developed multiple lung metastases after salvage CRT, and another patient who received a level 1 dose developed an out-of-field recurrence in the left cervical lymph node area.

DISCUSSION

Until now, esophagectomy has been the main treatment option for resectable esophageal cancer according to NCCN guidelines. However, approximately 50% of these cases develop recurrence, which is a major reason for treatment failure. Prior to the present study, several retrospective studies have investigated the common sites of recurrence after radical surgery, and determined that supraclavicular (25.8%) and mediastinal LN (44.4%) recurrence are the most common.[6,15] Two retrospective studies demonstrated that cervical lymphadenectomy might be superior than that of chemoradiotherapy for patients with cervical LN recurrence.[7,8] However, almost half the patients with mediastinal LNs develop recurrence, and salvage surgery is associated with a high risk of perioperative morbidity and mortality.

TABLE 3 Hematological and nonhematological toxicity (NCI-CTC version 4.0)

	NCI-CTC grade (n = 10)											
	0		1		2		3		4		5	
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hematological												
Leukocytopenia	5	29.4	5	29.4	5	29.4	2	11.8	0	0	0	0
Neutropenia	12	70.6	2	11.8	3	17.6	0	0	0	0	0	0
Anemia	6	35.3	9	52.9	2	11.8	0	0	0	0	0	0
Thrombocytopenia	12	70.6	4	23.5	1	5.9	0	0	0	0	0	0
Nonhematological												
Esophagitis	4	23.5	11	64.7	2	11.8	0	0	0	0	0	0
Fatigue	14	82.4	3	17.6	0	0	0	0	0	0	0	0
Pneumonitis	12	70.6	5	29.4	0	0	0	0	0	0	0	0

Therefore, the optimal treatment options remains controversial. In addition, recent clinical studies have demonstrated that simultaneous integrated boost intensity-modulated radiation therapy (SIB-IMRT) is the optimal irradiation technology to increase the dose to regions at high risk, while simultaneously reducing the dose to organs at risk and the total treatment times.[16,17] Therefore, we performed this prospective phase I/II study to clearly determine the optimal radiotherapy dosage for recurrences by using SIB-IMRT technology and to assess the overall efficacy and toxicity of the recommended treatment regimen.

To the best of our knowledge, no prospective trials have been performed to define the optimal radiotherapy dosage for recurrence after esophagectomy. Most of these publications are retrospective studies, thus the specific salvage radiation dose significantly differs among various studies. Shioyama et al.[18] compared the survival outcomes of 66 patients receiving a dose of ≥50 Gy with 16 patients receiving a dose of <50 Gy, and observed improved two-year and five-year OS rates (26.0% vs. 10.0%, and 13.0 vs. 0.0%, respectively). Therefore, the researchers recommended that 50 Gy was the best radiation dose for salvage treatment. Subsequently, Zhang and colleagues[14] found that an irradiation dose of ≥60 Gy could improve the OS (16.3 months vs. 11.3 months, $p < 0.05$) and PFS (10.6 months vs. 8.7 months, $p < 0.05$) among patients with recurrent esophageal cancer after esophagectomy. In a recent large retrospective study, Ni et al.[6] also found that the five-year OS was significantly improved in the ≥60 Gy group as compared to that in the <60 Gy group (25.3% vs. 13.9%, $p = 0.026$). The conclusion of these studies was that a salvage dose of at least 60 Gy might be more reasonable and effective for local regional recurrence. Based on these publications, we commenced the phase I study which consisted of three consecutive levels of radiotherapy dose for the recurrences. If the original linear-quadratic model was used to convert 59.4 Gy in 33 fractions to a biological equivalent dose (BED) with α/β of 10 Gy, the BED_{10} was 70.1 Gy. Thus, our first dose level started with level 1: 58.8 Gy/28F, and the BED_{10} was 71.1 Gy. No DLT was observed in the phase I study. The most common hematological toxicities were leukocytopenia and anemia (grade 2). The most common nonhematological toxicity was esophagitis (grade 1: 80%). Therefore, SIB-IMRT for mediastinal LN recurrence at 70 Gy/2.5 Gy/28F was tolerable and could be recommended for the phase II study.

The outcomes of esophageal carcinoma patients who develop recurrence after curative esophagectomy has been reported to be poor. The one- and three-year OS rates were approximately 45.9%–53.5% and 10.6%–22.7%, respectively in several studies.[9,19,20] However, in the present study, at the time of the last follow-up, all the enrolled patients were still alive. The ORR according to RECIST criteria is 58.8% and the local regional control rate is 100%. For 10 patients in the phase I study with minimal follow-up of 13 months, the one-year OS was 100%, with a median PFS of 16 months. The following reasons might explain this difference. First, the median time from initial surgery to recurrence was 4.0 months in our study, compared to 7.0–15.0 months in the abovementioned studies. Therefore, early recurrence detection is the main focus for improving the salvage treatment effect. Second, only patients with isolated LN recurrences (number of recurrences ≤5) were included in the present study, while the OS of these cases was significantly higher than that of cases with multiple recurrences. Finally, all the enrolled patients were treated with fluorouracil-based concurrent chemotherapy, and it has been reported that salvage CRT could significantly improve survival when compared to salvage radiotherapy alone.

In conclusion, our study showed that salvage CRT by implementing SIB for mediastinal lymph node recurrence to a dose of 70 Gy/2.5 Gy/28F with concurrent chemotherapy is safe and feasible. No DLT was observed. Our treatment regimen archives a satisfactory completion rate and disease control rate with acceptable toxicity profile.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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