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LETTER

Effectiveness of postoperative adjuvant radiochemotherapy *versus* radiotherapy in thoracic esophageal squamous cell carcinoma with lymph node metastasis: a multicenter randomized study

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Esophageal cancer (EC) is a malignant tumor originating from esophageal epithelium and remains a leading cause of cancer incidence and mortality worldwide[1,2]. According to the 2020 World Health Organization statistics, there were approximately 604,000 new EC cases and 544,000 EC-related deaths globally with China reporting approximately 320,000 new cases and 300,000 deaths, mainly from esophageal squamous cell carcinoma (ESCC)[3]. Although there has been progress in the treatment of EC, the long-term prognosis of patients with R0 resection and lymph node-positive disease continues to be suboptimal[4]. A retrospective analysis performed by our center suggested that the median overall survival (OS) of lymph node-positive patients with EC who received postoperative adjuvant radiotherapy (PART) was 29 months compared to 21 months for surgery alone with 3-year survival rates of 43% and 36%, respectively, indicating a potential survival benefit of PART[5]. However, whether adding concurrent chemotherapy to PART confers additional survival benefit has not been established. To answer this clinical question, we initiated the ZTOG-1401 trial, a prospective, multicenter, randomized phase III clinical study aimed at comparing the efficacy and safety of postoperative adjuvant concurrent chemoradiotherapy (PACRT) *versus* PART alone in lymph node-positive resectable thoracic squamous cell carcinoma patients after R0 resection. Herein we report the study design and preliminary outcomes with a follow-up period of 36 months to provide evidence guiding postoperative adjuvant therapy selection.

From May 2015 to October 2017, 113 lymph node-positive resectable thoracic ESCC patients between 18 and 70 years of age with R0 resection and pathologic stage T1-4N1-3M0 were recruited from 9 centers; the detailed participant recruitment process is illustrated in **Figure S1**. The subjects were centrally randomized using a random grouping table generated by SAS software and assigned to the short-course concurrent chemoradiation (SCRT) (n = 39) or stereotactic radiotherapy (SRT) group (n = 74). Inclusion criteria included an expected survival >6 months, peripheral blood counts within normal limits (WBC ≥ 4.0 × 10^9/L, ANC ≥ 1.5 × 10^9/L, platelets ≥100.0 × 10^9/L, and hemoglobin ≥90 g/L) and adequate liver and renal function. Patients who had received anti-tumor treatment in the past were excluded. The SCRT group received concurrent chemoradiotherapy with 50.4 Gy delivered in 28 fractions and chemotherapy consisting of paclitaxel (150 mg/m^2) plus carboplatin (AUC = 5). Dose adjustment and toxicity management were carried out according to the CTCAE v4.0 standard during the treatment process. The SRT group received

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radiotherapy alone with the same fractionation and dose. All subjects underwent baseline assessment and collected perioperative specimens, followed by standardized follow-up every 3 months for 3 years. The primary endpoint of the study was OS, while secondary endpoints included disease-free survival (DFS), treatment-related adverse events (graded according to CTCAE v4.0), and patient-reported quality of life (using the FACT-E scale). The study was approved by the Ethics Committees of all participating centers (Approval No. 2025-03-137) and conducted in accordance with the Declaration of Helsinki and CONSORT guidelines.

Among the 113 enrolled patients, 100 were male (88.5%) and 13 were female (11.5%). The patients were randomized to the SCRT (n = 39) or SRT group (n = 74). The baseline demographic and clinical characteristics were balanced between the 2 groups with a median age of 61.0 years [interquartile range (IQR): 56.0–65.0 years for the SCRT group and 57.0–65.0 years for the SRT group] and a median BMI of 20.8 kg/m^2 (IQR: 19.5–22.8 kg/m^2 for the SCRT group and 18.0–23.0 kg/m^2 for the SRT group; **Table 1**). Most patients had T4 tumors (70.9% in the SCRT group and 60.8% in SRT group) and N1 lymph node involvement (66.7% in SCRT group and 70.3% in the SRT group). The median number of resected lymph nodes was 24 in both groups (IQR: 18.0–31.0 for the SCRT group and 18.0–30.8 for the SRT group) and the distribution of ECOG physical status was comparable. As of 31 October 2017, the overall median follow-up time was 36.0 months (range, 5.4–59.8 months) with 36.9 months (range, 11.8–41.2 months) for the SCRT group and 36.0 months (range, 5.4–59.8 months) for the SRT group. During the follow-up period, a total of 45 deaths (39.8%) occurred, including 15 cases (38.4%) in the SCRT group and 30 cases (40.5%) in the SRT group. The 36-month mortality rates were 42.4% and 39.7% in the SCRT and SRT groups, respectively (no significant difference).

Survival analysis revealed no significant differences between the two groups with respect to OS (P = 0.93) or DFS (P = 0.69; **Figure 1**). The 1- and 3-year OS rates were 94.7% and 57.6% for the SCRT group and 90.5% and 60.4% for the SRT group, respectively. The 1- and 3-year DFS rates were 71.0% and 45.5% for the SCRT group and 72.9% and 53.9% for the SRT group, respectively. Subgroup analysis indicated that age, gender, BMI, tumor location, number of resected lymph nodes, and clinical stage did not significantly influence OS (**Figure S2 and Table S1**) or DFS (**Figure S3 and Table S2**). Patient-reported outcomes were comparable between the two groups with postoperative FACT-E mean scores of 75.0 ± 9.899 for the SCRT group and 68.583 ± 8.129 for the SRT group (P = 0.33) and post-radiotherapy scores of 75.5 ± 9.192 and 63.25 ± 15.398 (P = 0.30), respectively. The results indicated that there

Table 1 Baseline demographics and clinical characteristics (n = 113)

Characteristics	SCRT	SRT	*P*
All patients	39	74	
Gender (%)			1
Females	4 (10.26)	9 (12.16)	
Males	35 (89.74)	65 (87.84)	
Age [median (IQR)]	61.000 [56.500, 65.000]	61.000 [57.000, 65.000]	0.8041
Tumor location (%)			0.1219
Middle thoracic	12 (30.77)	20 (27.03)	
Thoracic	25 (64.10)	54 (72.97)	
Upper thoracic	2 (5.13)	0 (0.00)	
BMI [median (IQR)]	20.760 [19.510, 22.770]	20.846 [17.968, 23.001]	0.6946
Clinical stage (%)			0.4481
I	6 (15.38)	16 (21.62)	
II	15 (38.46)	32 (43.24)	
III	12 (30.77)	21 (28.38)	
IV	6 (15.38)	5 (6.76)	
Clinical T stage (%)			0.3596
1	1 (2.56)	4 (5.41)	
2	3 (7.69)	7 (9.46)	
3	5 (12.82)	18 (24.32)	
4	30 (76.92)	45 (60.81)	
Clinical N stage (%)			0.4266
1	26 (66.67)	52 (70.27)	
2	9 (23.08)	19 (25.68)	
3	4 (10.26)	3 (4.05)	
Number of lymph nodes resected [median (IQR)]	24.000 [18.000, 31.000]	25.000 [18.000, 30.750]	0.7601
ECOG performance status (%)			0.7735
1	4 (10.26)	5 (6.76)	
2	35 (89.74)	69 (93.24)	

IQR, interquartile range; SCRT, short-course concurrent chemoradiation; SRT, stereotactic radiotherapy.

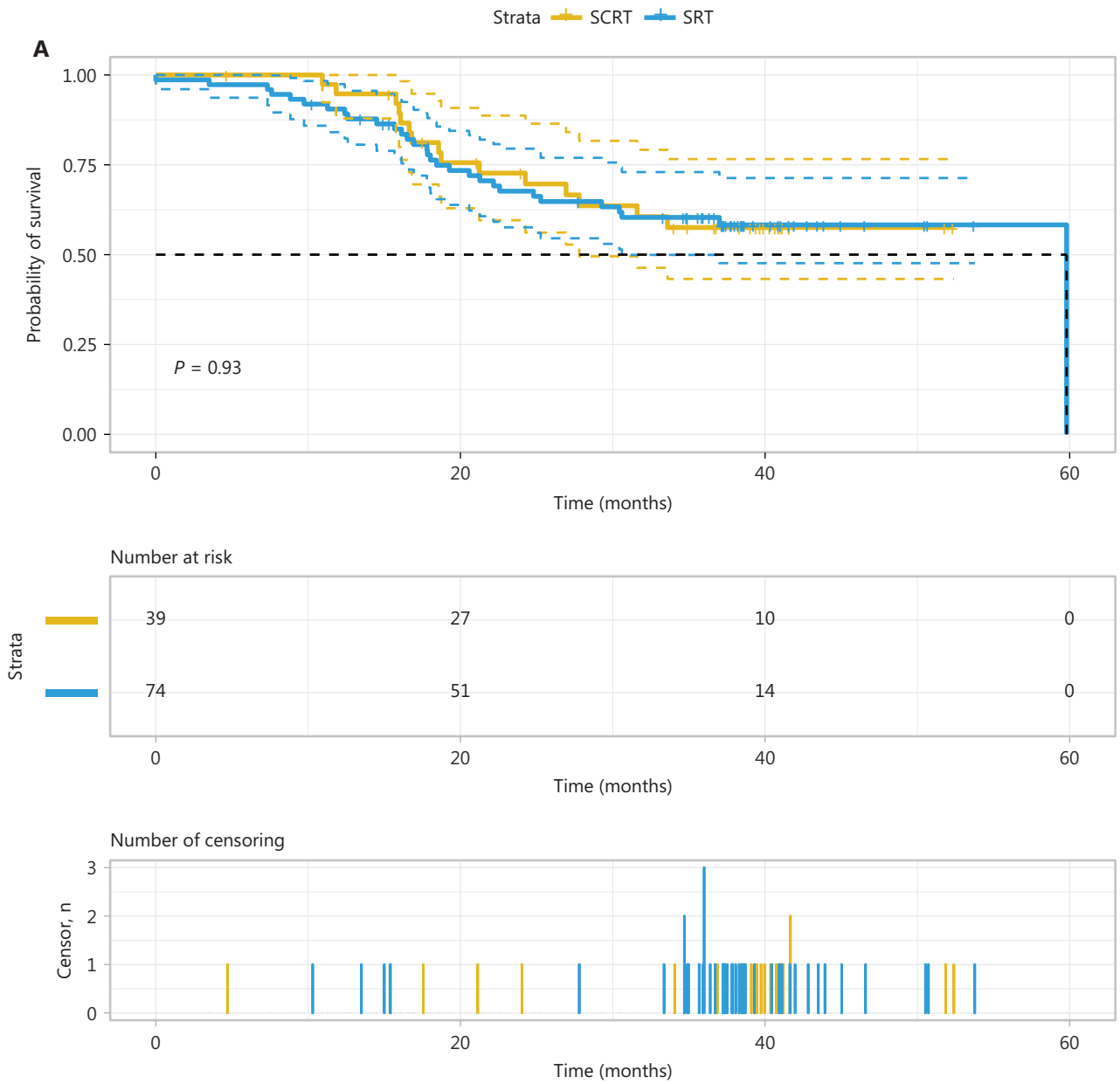

Figure 1 Continued

was no significant difference in survival outcomes and quality of life between PACRT and radiotherapy alone.

No significant differences in OS or DFS were detected between postoperative concurrent chemoradiotherapy (PCRT) and postoperative concurrent radiotherapy (PRT) in patients with R0-resected, lymph node-positive thoracic ESCC at the 36-month follow-up visit. These findings are consistent with previous phase III randomized trials, which showed improved survival with both adjuvant modalities compared to surgery alone but no significant intergroup differences[6-8].

Subgroup analysis of OS and PFS based on Cox regression models revealed no significant interactions for conventional clinical parameters. Notably, the subgroup with <20 dissected lymph nodes showed an elevated point estimate, suggesting a potential differential treatment trend warranting further validation. Limited sample sizes precluded reliable estimation in some subgroups. Although violations of the proportional hazards assumption were observed for some covariates, sensitivity analyses confirmed the robustness of the subgroup findings. While no significant beneficiary subgroups were identified,

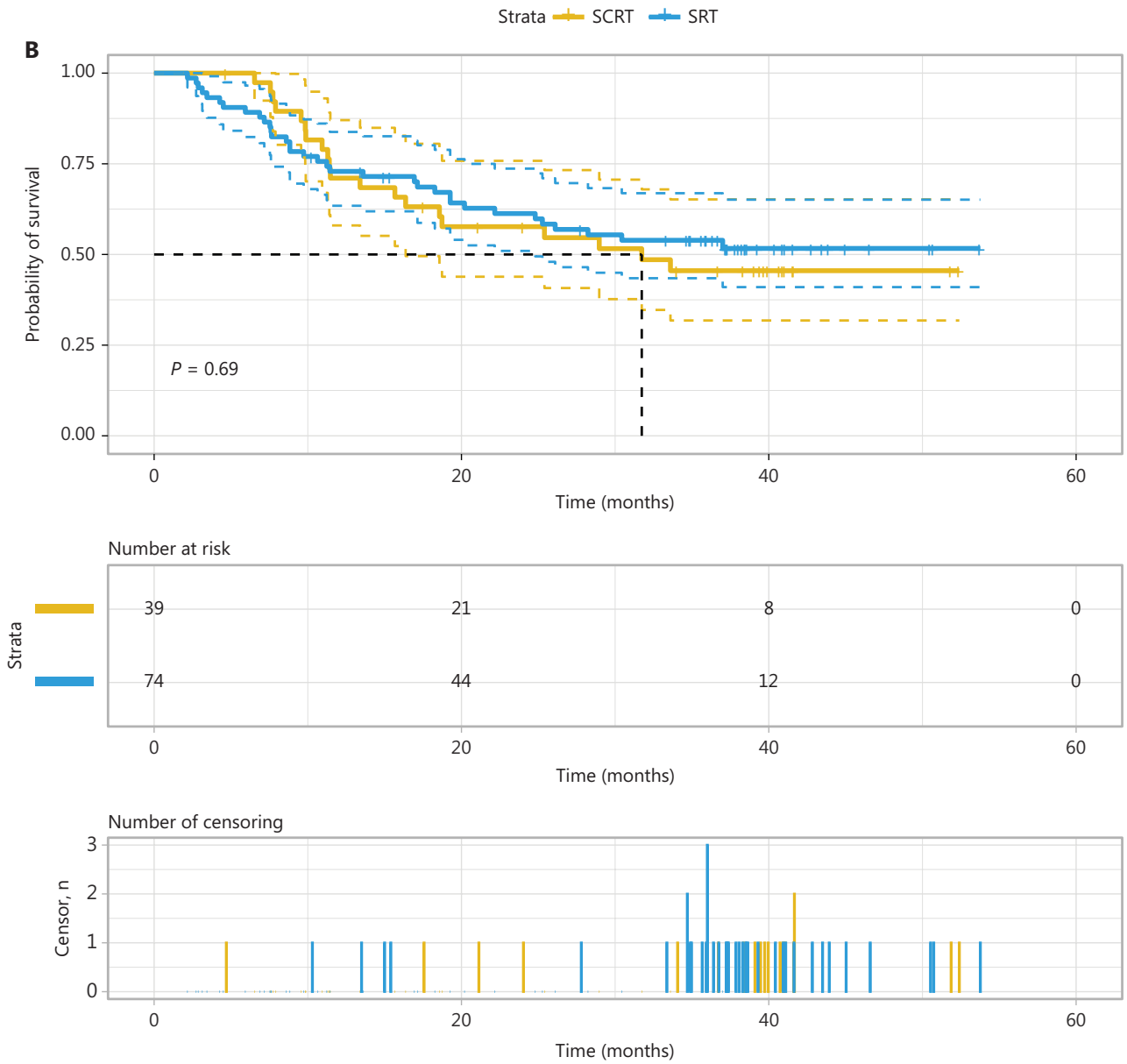

Figure 1 (A) Overall survival in the SCRT and SRT groups. (B) Disease-free survival in the SCRT and SRT groups. SCRT, short-course concurrent chemoradiation; SRT, stereotactic radiotherapy.

some patient characteristics may have modulated the treatment response.

From a mechanistic perspective, while PCRT theoretically enhances efficacy through chemoradiation synergy, the additive advantage may be attenuated in R0-resected, node-positive patients due to reduced tumor burden and compromised postoperative tolerance, providing a plausible explanation for the neutral findings[9,10].

Based on this evidence, clinical decision-making should emphasize individualized treatment strategies. PRT offers comparable survival outcomes with reduced treatment-related toxicity for elderly patients with significant co-morbidities or delayed postoperative recovery. PCRT remains a reasonable option following multidisciplinary evaluation for patients with good performance status and high-risk pathologic features. Therefore, postoperative adjuvant therapy should be determined through comprehensive assessment of functional status, recovery capacity, and treatment tolerance. Future research should focus on identifying predictive biomarkers to guide more precise treatment selection.

The present study had several limitations. First, the small sample size and unequal group allocation may have undermined statistical power. Second, the patient population was predominantly comprised of males with advanced-stage disease and primarily recruited from specific regions, which restricts the generalizability of findings. Furthermore, potential differences in treatment protocols across multiple centers could affect the consistency of the outcomes. Larger, more representative, and standardized multicenter trials are warranted to validate these findings.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Jiangfeng Wang, Weimin Mao.
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Analyzed data: Ding Wang.
Wrote the paper: Jiangfeng Wang, Wenhui Shen.

Data availability statement

All relevant data are included in the article and its supplementary materials. The raw imaging data and statistical analysis files can be found in **Figures S1 and S2**.

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