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Real-World Role of Adjuvant Radiotherapy after Neoadjuvant Treatment for Thoracic Esophageal Cancer

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Abstract

Background

Patients with locally advanced esophageal squamous cell carcinoma (ESCC) undergoing surgery after neoadjuvant chemotherapy (NCT) or neoadjuvant chemoimmunotherapy (NICT) remain at risk of disease progression. Currently, adjuvant radiotherapy (ART) is not recommended following these treatment sequences due to a lack of high-level evidence supporting its efficacy. This real-world study preliminarily evaluates the potential role of ART in this clinical setting.

Methods

A sum of 324 ESCC patients who had surgery following NCT or NICT were included and divided into two groups: the neoadjuvant therapy with surgery (NA+S) group and the neoadjuvant therapy with surgery followed by adjuvant radiotherapy (NA+S+RT) group. The primary outcomes assessed were the two-year recurrence free survival (RFS) and overall survival (OS). The Kaplan-Meier method was utilized for survival analysis, while the Cox regression model was applied to determine the clinical factors linked to prognosis.

Results

The NA+S group (n=180) and the NA+S+RT group (n=144) showed no statistically significant differences in 2-year RFS (71.8% vs 68.8%, P=0.661, 95% CI: 55.52-63.95) or 2-year OS (80.7% vs 74.3%, P=0.162, 95% CI: 60.44-68.17), indicating that ART did not provide a survival benefit. Subgroup analysis showed no significant survival difference between patients with major pathological response (MPR) and those without (non-MPR). However, among ypN+ patients, RFS was significantly improved in the NA+S+RT group (60.6% vs 41.8%, P=0.005, 95% CI: 37.65-50.90). Similarly, ypT3-4 patients showed a survival benefit in 2-year RFS after ART (65% vs 44.4%, P<0.05, 95% CI: 38.42-52.33). The incidence of distant metastasis, especially to the lung, bone, and pleura, was notably greater in the NA+S+RT group than in the NA+S group (P<0.05). The results of the multivariate analysis identified ypN+ and non-MPR as independent risk factors for both RFS and OS.

Conclusion

ART did not improve survival outcomes in the entire neoadjuvant therapy cohort; however, it conferred a survival benefit in patients with ypN+ disease or ypT3-4 tumors.

Introduction

Esophageal cancer (EC) is a type of cancer that occurs frequently worldwide[1], with China exhibiting a notably elevated occurrence of esophageal squamous cell carcinoma (ESCC)[2, 3]. Different combinations of surgery, chemotherapy, immunotherapy, and radiotherapy have improved outcomes in locally advanced EC[4–6]. Nonetheless, data from follow-up of the CROSS and NEOCRTEC5010 trials indicate that 40%–50% of patients still experience disease progression[4, 5], and a retrospective study from our center reported local-regional recurrence in approximately 30% of patients[7].

Recent studies on neoadjuvant chemoimmunotherapy (NICT) have demonstrated acceptable toxicity and pathological complete response rates that are not inferior to those achieved with neoadjuvant chemoradiotherapy (NCRT) in locally advanced ESCC[8–10]. Furthermore, multiple reports indicate that the most common sites of recurrence after esophagectomy—with or without prior neoadjuvant therapy—are the supraclavicular and upper mediastinal lymph nodes[11–14]. Thus, it is crucial to create more efficient adjuvant strategies aimed at slowing down disease progression. Given these findings, adjuvant radiotherapy (ART) represents a promising approach to control locoregional recurrence and potentially improve survival.

The CheckMate 577 trial established a landmark advance in adjuvant therapy for EC after surgery[15]. However, no survival benefit was observed in the Asian ESCC population, underscoring the need for further evidence and research to define appropriate indications for adjuvant therapy. Although radiotherapy can reduce locoregional recurrence and improve survival in EC[16, 17], the role of ART in patients undergoing surgery after neoadjuvant chemotherapy (NCT) or NICT remains unclear. In real-world practice, a proportion of patients receiving NCT or NICT experience local recurrence during follow-up. Salvage radiotherapy for these recurrences is often limited by dose constraints for organs at risks and by challenges in target delineation. Consequently, this research intends to explore the impact of ART in ESCC patients following NCT or NICT.

Patients and Materials

Patients with EC who underwent surgery following NCT or NICT at the Affiliated Cancer Hospital of Nanjing Medical University from January 2018 to December 2023 were included. The inclusion criteria included were: (1) age 18–80 years; (2) receipt of NCT or NICT followed by surgery; (3) histologically or cytologically confirmed SCC. Exclusion criteria included were: (1) non-thoracic EC; (2) multiple primary tumors; (3) non-R0 resection; (4) loss to follow-up or missing data; (5) receipt of preoperative radiotherapy.

Treatment Protocols

All patients underwent a minimum of one treatment cycle. The NCT protocols incorporated taxane in combination with platinum-based agents (cisplatin, carboplatin, or nedaplatin), with some regimens additionally including tegafur (S-1) or fluorouracil. The immune checkpoint inhibitors used included: sintilimab, toripalimab, tislelizumab, camrelizumab, pembrolizumab, serplulimab, and nivolumab. ART was administered concurrently with chemotherapy in some patients. The median dose of ART was calculated at 47.8 Gy (with a range of 40.0–50.4 Gy), delivered via conventional fractionation five times weekly. The clinical target volume (CTV) predominantly included the lymphatic drainage regions in the bilateral supraclavicular and mediastinal areas, along with the tumor bed. Following multidisciplinary discussion, the CTV for tumors situated in the lower thoracic EC was also extended to include the left gastric lymphatic drainage region.

Surgical Approach and Pathological Response Criteria

All patients had surgery performed 4 to 6 weeks after finishing neoadjuvant therapy, following confirmation of no disease progression by contrast-enhanced CT scans of the chest and abdomen. The primary surgical approaches were Ivor-Lewis or McKeown esophagectomy, with a minority of patients undergoing open thoracotomy. A routine lymphadenectomy involving two or three fields was conducted for all patients. Additionally, cervical lymph node dissection was included when the surgeon suspected cervical nodal involvement.

Pathological evaluation comprised assessment of histologic type, tumor grade, proximal/distal surgical margins, the count of affected lymph nodes, and the extent of tumor regression. The post-neoadjuvant pathological staging, referred to as ypTNM was methodically defined in accordance with the criteria set forth in the 8th edition of the TNM classification[18]. All pathological examinations were performed jointly by two senior pathologists from our center. The surgically excised tumor tissue showed no residual tumor cells under a microscope, indicating pathological complete remission (pCR). The tumor regression grade (TRG) was categorized in accordance with the 8th edition TNM standards: no viable tumor cells (TRG 0); denoted isolated single cancer cells or small clusters (TRG 1); residual tumor with evident regression (TRG 2); and minimal or no regression (TRG 3)[18]. TRG 0 and TRG 1 were defined as a major pathological response (MPR).

Follow-up and Endpoints

Post-treatment patient monitoring involves assessments every three months during the initial one to two years, followed by evaluations every six months in the third to fifth years after treatment. Post-treatment surveillance included a comprehensive physical examination, upper gastrointestinal barium study, neck ultrasonography, and enhanced CT scan of chest and abdomen and/or MRI. Where necessary, Positron emission tomography–computed tomography (PET-CT) scans and endoscopic pathological tissue biopsies shall be performed.

This study's main objectives were to evaluate the two-year recurrence-free survival (RFS), which is the duration from the surgical procedure to the locoregional tumor reappearance, and overall survival (OS), which refers to the period from surgery until death from any cause. Local recurrence was characterized as a relapse occurring at the anastomotic location and/or in the cervical, mediastinal, or abdominal lymphatic nodes. Distant metastasis referred to hematogenous spread to other solid organs or structures.

Statistical Analysis

Categorical variables are expressed in terms of counts and percentages. A comparison of baseline characteristics between the neoadjuvant therapy combined with surgery (NA + S) group and the neoadjuvant therapy followed by surgery and then ART (NA + S+RT) group was performed utilizing the

chi-square test. Differences in survival were analyzed using the Kaplan-Meier method, with significance assessed through the log-rank test. To identify risk factors for RFS and OS, Cox proportional hazards regression was applied. Variables that yielded a P value of less than 0.2 in univariate analysis were incorporated into the multivariate model that followed. All statistical analyses were carried out using SPSS software (version 27.0), with a statistically significant threshold set at $P < 0.05$.

Results

Patient Characteristics

A total of 324 ESCC patients who met the eligibility criteria and underwent NCT or NICT were enrolled. Based on the receipt of ART, they were divided into the NA+S group (n=180) and the NA+S+RT group (n=144). Comparisons of baseline clinical characteristics revealed that the administration of ART was significantly associated with age, pretreatment clinical stage, neoadjuvant regimen, pathological differentiation grade, TRG grade, ypT stage, and ypN stage (all $P < 0.05$). In the NA+S+RT group, a greater percentage of ypN+ patients was observed, with figures of 65.67% compared to 34.33% in other groups. Additionally, 47.84% of the patients had 15 or more lymph node dissections (see Table 1).
The overall median follow-up duration for the cohort reached 46 months (95% CI: 42.67–49.33).

Survival

The 2-year RFS rates for the non-ART cohort and the ART cohort were recorded at 71.8% and 68.8%, respectively (P=0.661, 95% CI: 55.52-63.95). In terms of OS rates after 2 years, the figures were 80.7% for the ART group and 74.3% for the non-ART group (P=0.162, 95% CI: 60.44-68.17) (Figure 1). While these variations did not reach statistical significance, the ART cohort exhibited a greater RFS rate at the 1-year mark (85.3% vs. 78.0%). Subgroup analysis based on pathological response showed that among non-MPR patients, ART was associated with a higher 2-year RFS rate (64.7% vs. 52.7%; P = 0.076; 95% CI: 43.57–55.29), though this did not reach statistical significance. No improvement was observed in 2-year OS (65.7% vs. 67.0%; P = 0.931; 95% CI: 49.92–60.72). For the MPR subgroup, ART provided no benefit in either RFS or OS (Figure 2).

Stratified by ypT stage, subgroup analysis indicated that neither RFS nor OS differed significantly between the treatment groups for patients with ypT0 or ypT1–2 disease (all P > 0.05; Figure 3). In patients presenting with ypT3–4 tumors, the OS difference between the NA+S+RT group and the NA+S group did not reach statistical significance (P = 0.051; 95% CI: 47.04–60.20). However, a notable trend indicating a higher 2-year OS was observed in the NA+S+RT group (67.5%) in comparison to the NA+S group (52.7%). Additionally, the NA+S+RT group showed a significant improvement in 2-year RFS rate compared to the NA+S group (65% vs. 44.4%; P < 0.05; 95% CI: 38.42–52.33) (Figure 3). For patients with ypN0 disease, ART did not provide a significant benefit in either RFS or OS. In contrast, among ypN+ patients, ART was associated with a significantly better RFS (60.6% vs. 41.8%; P = 0.005; 95% CI: 37.65–50.90) (Figure 4).

Multivariate analysis revealed that ypN+ and Non-MPR correlated with reduced RFS and OS, whereas having fewer than 15 lymph nodes dissected served as a negative prognostic indicator for RFS (Table 2).

Recurrence Pattern

The NA+S group predominantly experienced locoregional recurrence (n=52, 28.89%), including 7 cases of anastomotic recurrence. In contrast, Distant metastases were more common in the NA+S+RT group (30.56% vs. 11.11%; P < 0.001). Moreover, metastases to the lung, bone, and pleura occurred more frequently in patients who received ART (P<0.05) (Table 3).

Discussion

To date, guidelines still recommend surgery following NCRT for the treatment of locally advanced EC. However, with the publication of several phase II clinical trials of NICT demonstrating favorable tumor regression and manageable toxicity[8, 9], as well as the recent results of the REVO[10] and ESCORT-NEO[19] trials, the use of NICT has become increasingly widespread in clinical practice for EC in China. Among ESCC patients undergoing neoadjuvant therapy and subsequent surgery, locoregional recurrence rates remain as high as 25%–30%, with mediastinal lymph nodes representing the most common sites of regional failure[7, 11, 12, 20]. The addition of radiotherapy—particularly ART—to systemic therapy to improved local tumor control has been rarely reported. Therefore, this study explores the value of adjuvant radiotherapy by analyzing the survival of ESCC patients receiving NCT or NCT in the real world, with the goal of clarifying its clinical value and better informing post-neoadjuvant therapeutic decision-making.

Previous research, including the CheckMate 577 trial[15] and several retrospective studies[21, 22] suggest that ART can improve the prognosis of patients with high risk of metastasis. Additionally, a phase II clinical trial demonstrated that adjuvant chemoradiotherapy (ACRT) could enhance RFS in locally advanced ESCC patients with involved or close (≤ 1 mm) margins, extranodal extension (ENE), or ypN2–3 disease[23]. Our study found that ART did not improve 2-year RFS or OS in ESCC patients who received NCT or NICT. However, the 1-year RFS results suggest a potential short-term delay in recurrence. Furthermore, ART may still confer survival benefits in patients with residual tumor or ypN+ disease.

The poorer survival observed in patients receiving adjuvant radiotherapy may be attributable to their higher baseline tumor burden. This is supported by a greater proportion of ypStage II-IV disease in the ART group compared to the NA + S group (36.11% vs. 21.60%), and more ypN+ patients (27.16% vs. 14.20%). Moreover, a previous meta-analysis indicated that postoperative ART following NCRT was associated with significantly increased mortality[24]. Another study also reported that ART after NCT did not improve—and might even reduce—overall survival in EC patients[25].

In EC patients with T2–3 disease, ART or ACRT is associated with a reduction in locoregional failure and an improvement in survival outcomes[26–28]. Therefore, we conducted a subgroup analysis based on

ypT stage. Despite the absence of a significant RFS or OS benefit in the ypT0 or ypT1–2 subgroups, patients with ypT3–4 disease experienced a statistically significant improvement in 2-year RFS following ART ($P < 0.05$). Despite the lack of a significant difference in 2-year OS for the ypT3-4 subgroup, the ART group demonstrated a promising trend toward improved long-term survival outcomes.

Multivariate analysis results suggest that ypN + and Non-MPR are associated with poor RFS and OS. Although the difference in RFS between treatment groups among non-MPR patients was not statistically significant, the NA + S+RT group showed a numerically higher RFS than the NA + S group, suggesting a potential benefit. Furthermore, ypN+ patients in the NA + S+RT group experienced a significant improvement in RFS ($P < 0.05$). While our survival analysis indicated that ART did not improve RFS or OS in ypN0 patients, it should be noted that another ongoing retrospective study at our center suggests a potential RFS benefit trend in ypT2–4N0 patients receiving ART. These results suggest that ART has potential value in patients with high ypTNM and lymph node involvement after neoadjuvant therapy.

While radiotherapy is established to reduce locoregional recurrence[16, 17], the present study did not demonstrate a significant reduction in local recurrence—including nodal and anastomotic failures—with ART ($P > 0.05$). Conversely, distant metastasis occurred at a higher incidence rate in the ART group ($P < 0.05$), with lung metastases representing the most common site of distant spread (14.58%). Several factors may explain these observations. First, the tolerability of adjuvant therapy is generally lower than that of neoadjuvant treatment[29]. Second, high-dose radiotherapy may induce "detrimental distant effect"[30], potentially increasing the risk of secondary thoracic malignancies in irradiated ESCC patients[31]. Finally, The proportion of patients with high tumor burden was high in the ART group, which is associated with poorer prognosis. This may further explain the increased incidence of thoracic metastases (e.g., lung and pleural) observed in the NA + S+RT group.

Several limitations should be considered in this study. First, as a retrospective analysis, the data are subject to inherent potential biases. Factors such as postoperative complications and adverse effects of ART could not be fully accounted for. Second, the neoadjuvant treatment regimens were not uniform, and because pCR rates differ between NCT and NICT, these two groups were not analyzed separately, which may have introduced confounding factors. Third, detailed data regarding chemoradiation regimens, radiation doses, and treatment cycles were not available, precluding a comparative effectiveness analysis across different treatment protocols. Finally, the recurrence patterns observed here may not be generalizable to all ESCC patients. To precisely delineate recurrence patterns and confirm the survival outcomes observed here, future multicenter studies with larger cohorts are warranted.

Conclusion

Although ART did not improve overall survival in the entire cohort of locally advanced ESCC patients after neoadjuvant therapy and surgery, it may offer a survival benefit specifically for those with ypN+ disease or ypT3-4 tumors, irrespective of nodal status. The confirmation of these results will require further validation through large-scale, prospective studies.

Abbreviations

ESCC Esophageal squamous cell carcinoma

EC Esophageal cancer

NCT Neoadjuvant chemotherapy

NICT Neoadjuvant chemoimmunotherapy

NCRT Neoadjuvant chemoradiotherapy

ART Adjuvant radiotherapy

NA+S Neoadjuvant therapy with surgery

NA+S+RT Neoadjuvant therapy with surgery followed by adjuvant radiotherapy

CTV Clinical target volume

ypTNM Post-neoadjuvant pathological stage

ypT Post-neoadjuvant pathological tumor stage

ypN Post-neoadjuvant pathological node staging

pCR Pathological complete remission

TRG Tumor regression grade

MPR Major pathological response

RFS Recurrence free survival

OS overall survival

Declarations

Author contributions

LYX, WXJ: Collected data, Performed analysis, Drafting of the manuscript. NZX,LYT: Collected data. QPD: Conceived and designed the analysis. LYT: Conceived and designed the analysis, Review the manuscript, Obtained funding. All authors approved the submitted manuscript.

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Availability of data and materials

The data from the study is available from the corresponding author on reasonable request.

Ethics approval and constant to participate

This study was approved by the Ethics Committee of Jiangsu Cancer Hospital (approval number: KY-2024-108). The requirement for informed consent from participants was waived by the Ethics Committee in accordance with the ethical principles outlined in the Declaration of Helsinki.

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Publication consent

Not Applicable.

Competing interests

The authors declare no competing interests.

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Tables

Tables 1 to 3 are available in the supplementary files section

Figures

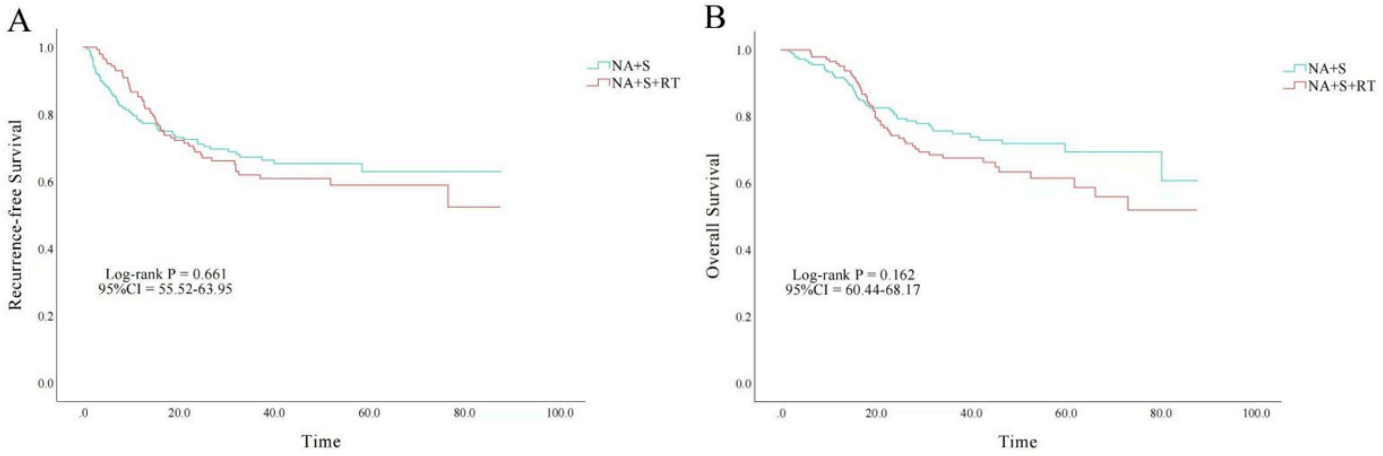


Figure 1

Kaplan–Meier Analysis Comparing the NA+S and NA+S+RT Groups for Recurrence-Free Survival (A) and Overall Survival (B) in All Patients.

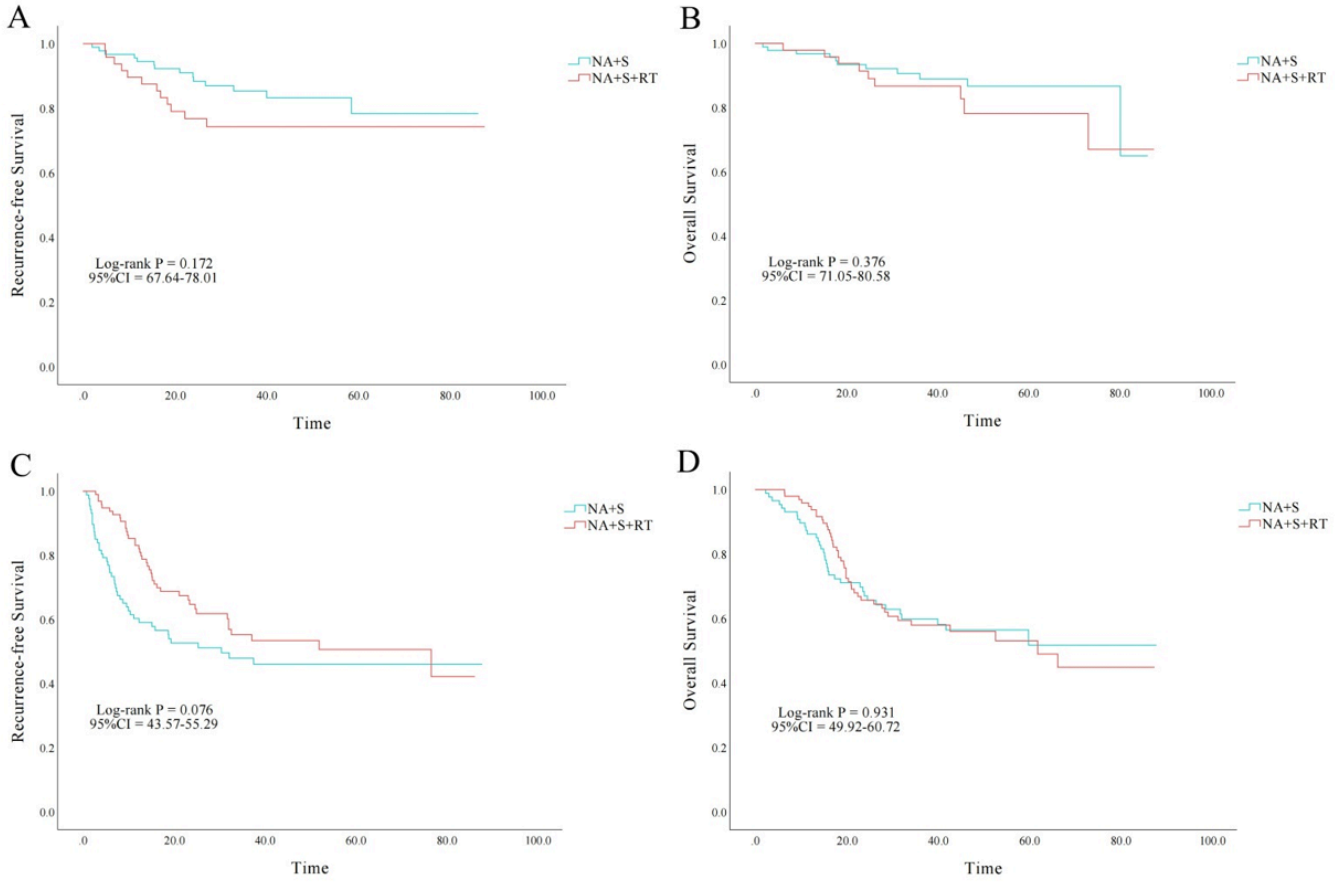


Figure 2

Recurrence-Free Survival (RFS) and Overall Survival (OS) for the NA+S vs. NA+S+RT Groups in MPR and Non-MPR Patients. MPR: (A) RFS, (B) OS. non-MPR: (C) RFS, (D) OS.

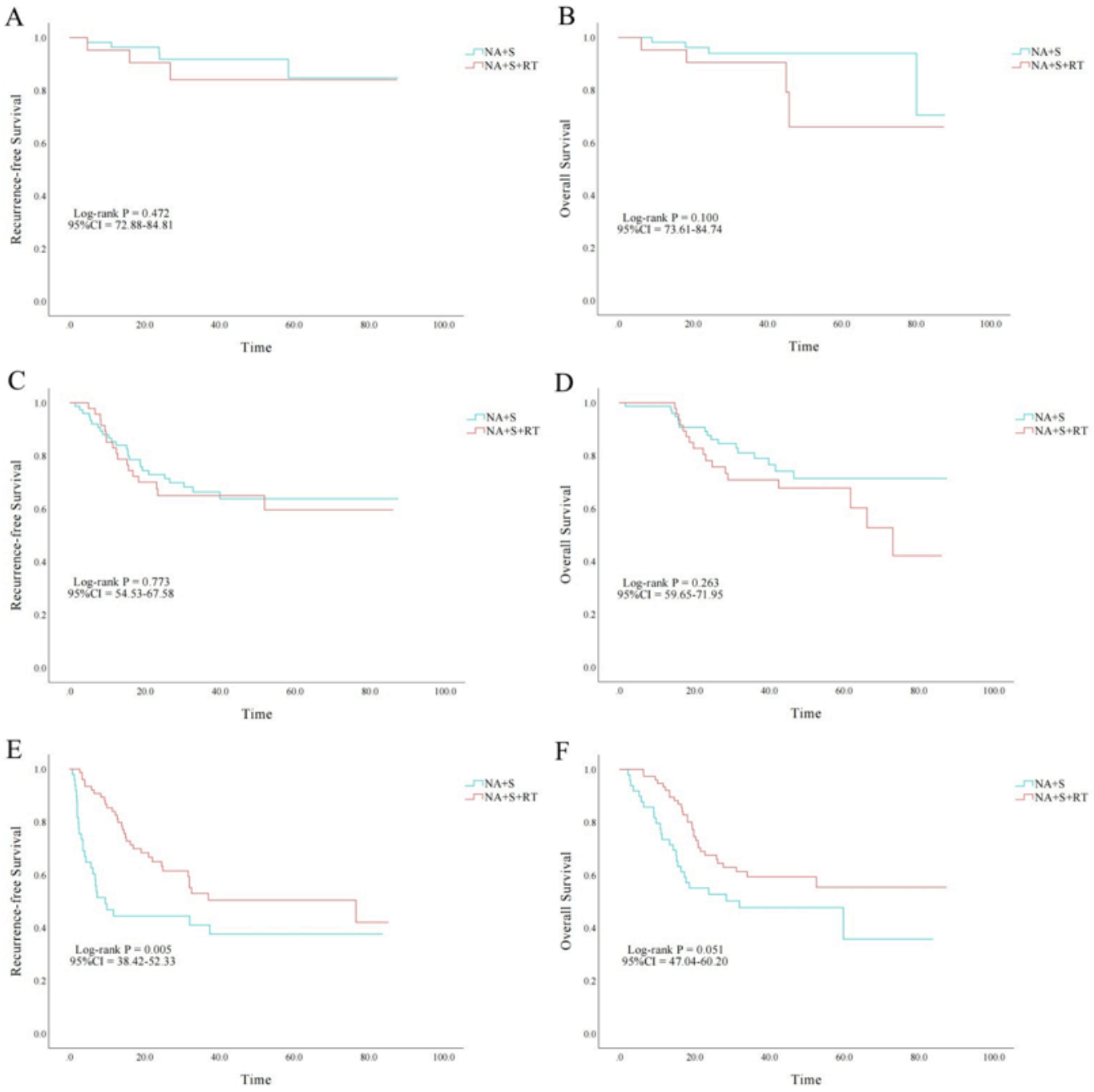


Figure 3

Recurrence-Free Survival (RFS) and Overall Survival (OS) for the NA+S vs. NA+S+RT Groups Across ypT Stages. ypT0: (A) RFS, (B) OS. ypT1-2: (C) RFS, (D) OS. ypT3-4: (E) RFS, (F) OS.

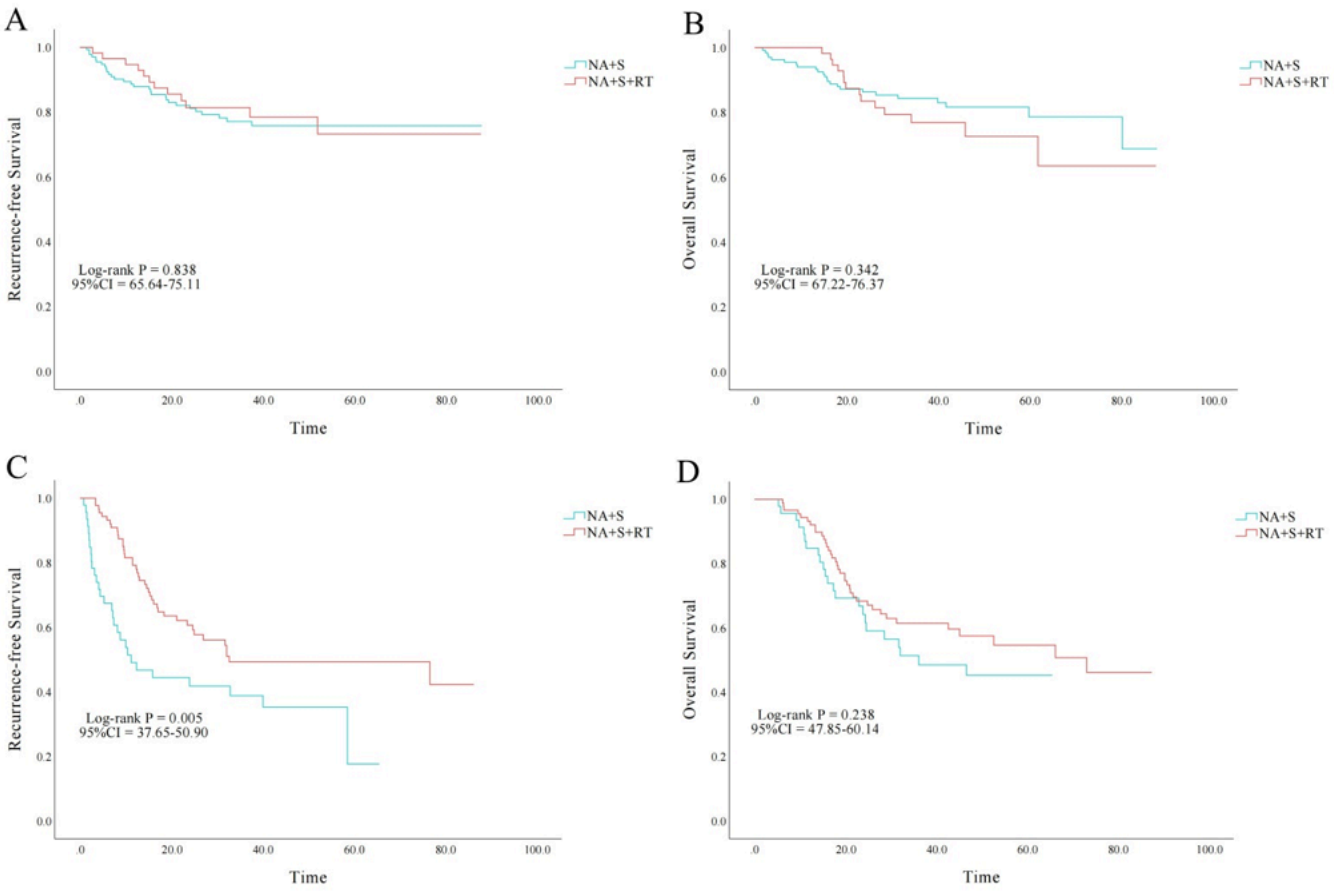


Figure 4

Recurrence-Free Survival (RFS) and Overall Survival (OS) for the NA+S vs. NA+S+RT Groups in ypN0 and ypN+ Patients. ypN0: (A) RFS, (B) OS. ypN+: (C) RFS, (D) OS.

Supplementary Files

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