Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Real-World Deliverability of Adjuvant Nivolumab After Esophagectomy: Treatment Initiation, Completion, and Postoperative Complications

Takeshi Matsubara

nanadai@med.shimane-u.ac.jp

Shimane University

Shunsuke Kaji
Shimane University

Hiroki Okamura
Shimane University

Koki Kawakami
Shimane University

Yohei Sasaki
Shimane University

Kosuke Nakamura
Shimane University

Kazunari Ishitobi
Shimane University

Takahito Taniura
Shimane University

Takayuki Tanaka
Shimane University

Tetsu Yamamoto
Shimane University

Masaaki Hidaka
Shimane University

Research Article

Keywords: adjuvant therapy, esophageal cancer, esophagectomy, nivolumab, postoperative complications

Posted Date: November 10th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11411853/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Purpose

Evidence on the practical delivery of adjuvant nivolumab after neoadjuvant chemotherapy and esophagectomy remains limited. We described treatment initiation and completion in routine practice and explored their associations with postoperative complications.

Methods

This single-center retrospective study included 25 patients who initiated adjuvant nivolumab after neoadjuvant treatment and R0 esophagectomy in 2022–2025. Twenty patients treated with postoperative S-1 in 2011–2023 constituted a nonconcurrent, descriptive reference cohort. The outcomes were time from surgery to treatment initiation, 1-year treatment completion, reasons for discontinuation, and adverse events. Survival analyses were exploratory.

Results

Median time to treatment initiation was 77 days with nivolumab and 67 days with S-1. Among nivolumab recipients, the median interval was longer in patients with Clavien–Dindo grade ≥II complications than in those without (113.0 vs 69.5 days; p = 0.008), and in those with grade ≥III complications than in those without (132.0 vs 74.5 days; p = 0.027). Ten of 25 patients (40.0%) completed 1 year of nivolumab; one was still receiving treatment at the cutoff. Recurrence and adverse events each led to discontinuation in six patients (24.0%). Grade ≥3 immune-related adverse events occurred in six patients (24.0%).

Conclusion

Among patients who started adjuvant nivolumab, postoperative complications were associated with later treatment initiation, and recurrence and adverse events frequently prevented completion. These descriptive findings require confirmation in larger multicenter cohorts and do not establish the impact of treatment timing on survival.

Introduction

Esophageal cancer remains associated with a high risk of recurrence after curative surgery. In Japan, neoadjuvant chemotherapy (NAC) followed by esophagectomy is the standard treatment for locally advanced esophageal squamous cell carcinoma (ESCC). The JCOG9907 trial established preoperative cisplatin plus 5-fluorouracil (CF) as the standard strategy [1], and the subsequent JCOG1109 (NExT) trial demonstrated an overall survival benefit of docetaxel, cisplatin, and 5-fluorouracil (DCF) over CF [2]. Despite these advances, patients with residual pathological disease after NAC remain at high risk of recurrence.

The CheckMate 577 trial demonstrated that adjuvant nivolumab prolonged disease-free survival compared with placebo in patients with residual pathological disease after neoadjuvant chemoradiotherapy and R0 resection (median, 22.4 vs. 11.0 months; hazard ratio, 0.69; 95% confidence interval, 0.56–0.86) [3]. However, CheckMate 577 evaluated nivolumab after chemoradiotherapy,

whereas NAC, particularly DCF, is commonly used for ESCC in Japan [2, 3]. Thus, evidence for adjuvant nivolumab after NAC and esophagectomy remains limited.

More recently, a nationwide real-world matched study from the Netherlands reported improved overall survival with adjuvant nivolumab after neoadjuvant chemoradiotherapy and resection. After propensity score matching, 308 patients were included in each group; the 2-year OS rate was 66.8% with nivolumab and 58.8% without adjuvant nivolumab (hazard ratio, 0.75; 95% confidence interval, 0.60–0.97) [4]. These data support the effectiveness of adjuvant nivolumab in routine clinical practice after chemoradiotherapy, but evidence regarding treatment deliverability after NAC remains limited.

S-1 has also been investigated as postoperative therapy after NAC. The phase II PIECE trial reported 3-year recurrence-free survival (RFS) and overall survival (OS) rates of 72.3% and 85.0%, respectively [5]. We previously reported the feasibility of postoperative S-1, with a 12-month treatment continuation rate of 80% and a median relative dose intensity of 100% among patients who received NAC [6]. The ongoing phase III JCOG2206 (SUNRISE) trial is comparing observation, adjuvant nivolumab, and adjuvant S-1 after NAC and curative esophagectomy [7].

Beyond efficacy, whether adjuvant therapy can be initiated and sustained after esophagectomy is an important clinical issue. Postoperative complications may delay treatment initiation, while adverse events and early recurrence may limit treatment continuation. Real-world data on the deliverability of adjuvant nivolumab after NAC remain scarce. We therefore evaluated adjuvant nivolumab after neoadjuvant therapy and curative esophagectomy, focusing on the impact of postoperative complications on treatment initiation and completion. A historical S-1 cohort was included as an exploratory reference.

Materials and Methods

Study Design and Patients

This single-center retrospective cohort study was conducted at the study institution. We reviewed patients with esophageal cancer who underwent curative esophagectomy after neoadjuvant therapy and subsequently received adjuvant therapy.

The nivolumab cohort included 25 consecutive patients with residual pathological disease who received adjuvant nivolumab between January 2022 and December 2025. The historical S-1 cohort was selected from 41 patients who received postoperative S-1 between January 2011 and December 2023. Of the 41 patients, 16 patients who had not received NAC and five patients who achieved a pathological complete response (pCR) after NAC were excluded, leaving 20 patients with residual pathological disease after NAC and curative resection for the present analysis. This cohort differed from that in our previous S-1 feasibility study [6].

The study was approved by the Institutional Review Board of the institutional ethics committee (approval nos. 1120 and 2023-001) and conducted in accordance with the Declaration of Helsinki. Because this was a retrospective study using existing clinical data, the requirement for written informed consent was waived, and patients were provided the opportunity to opt out of the study.

Neoadjuvant Treatment and Surgery

Neoadjuvant regimens included docetaxel, cisplatin, and 5-fluorouracil (DCF); cisplatin and 5-fluorouracil (CF); and chemoradiotherapy.

All patients underwent curative esophagectomy with regional lymphadenectomy and achieved R0 resection. The thoracic procedure was performed by robot-assisted minimally invasive esophagectomy (RAMIE) or video-assisted thoracoscopic esophagectomy (VATS) in the nivolumab cohort and by VATS in the S-1 cohort.

Postoperative Adjuvant Therapy

Adjuvant nivolumab was initiated after postoperative recovery and administered at 480 mg every 4 weeks for up to 1 year unless discontinued because of recurrence, adverse events, patient preference, or other clinical reasons.

Postoperative S-1 was administered orally and was planned to be continued for 1 year according to the treatment strategy used during the historical study period.

Postoperative Complications

Postoperative complications before adjuvant therapy initiation were classified according to the Clavien–Dindo (CD) classification. CD grade ≥ II complications were defined as clinically relevant and CD grade ≥ III complications as severe.

The interval from surgery to adjuvant therapy initiation was compared according to the presence or absence of CD grade ≥ II and ≥ III complications within each cohort.

Treatment Deliverability and Safety

Treatment deliverability was assessed by the interval from surgery to adjuvant therapy initiation, completion of the planned 1-year treatment, and reasons for discontinuation.

For nivolumab, reasons for discontinuation included adverse events, recurrence, and patient preference. Immune-related adverse events (irAEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, and evaluated as any grade and grade ≥ 3.

Oncological Outcomes and Follow-up

Recurrence-free survival (RFS) was defined as the interval from surgery to recurrence or death from any cause, whichever occurred first. Overall survival (OS) was defined as the interval from surgery to death from any cause. Patients without an event were censored at the date of their last follow-up. Clinical outcomes were assessed through March 31, 2026.

Comparisons between the nivolumab and historical S-1 cohorts were exploratory because of the retrospective design, small sample size, and differences in treatment era and baseline characteristics.

Statistical Analysis

Continuous variables are presented as medians with interquartile ranges or ranges and categorical variables as numbers and percentages. Continuous and categorical variables were compared using the Mann–Whitney U test and Fisher's exact test, respectively.

RFS and OS were estimated using the Kaplan–Meier method and compared using the log-rank test. All tests were two-sided, with $p < 0.05$ considered statistically significant. No adjustment for multiple comparisons was performed. Analyses were performed using JMP (SAS Institute Inc., Cary, NC, USA).

Results

Patient Characteristics

A total of 45 patients were included in the present analysis: 25 in the nivolumab cohort and 20 in the historical S-1 cohort. The median age was 70 years (range, 50–79) in the nivolumab cohort and 68.5 years (range, 51–78) in the S-1 cohort. Men accounted for 96.0% (24/25) and 85.0% (17/20) of the respective cohorts.

In the nivolumab cohort, neoadjuvant treatment consisted of DCF in 17 patients (68.0%), CF in one (4.0%), chemoradiotherapy in two (8.0%), and other regimens in five (20.0%). Other neoadjuvant regimens included docetaxel, oxaliplatin, and S-1 (DOS) and 5-fluorouracil plus oxaliplatin (FOLFOX). RAMIE was performed in 14 patients (56.0%) and VATS in 11 (44.0%). Pathological lymph node metastases (pN+) were present in 21 patients (84.0%), and 15 (60.0%) had pathological stage III–IV disease. In the historical S-1 cohort, pN+ disease was present in 16 patients (80.0%), and nine (45.0%) had pathological stage III–IV disease.

The median interval from surgery to adjuvant therapy initiation was 77 days (IQR, 71–132) in the nivolumab cohort and 67 days (IQR, 56–90) in the S-1 cohort. Baseline clinicopathological characteristics are summarized in Table 1.

Table 1
Baseline clinicopathological characteristics

Characteristic	Nivolumab (n = 25)	Historical S-1 (n = 20)
Age, years, median (range)	70 (50–79)	68.5 (51–78)
Male sex, n (%)	24 (96.0)	17 (85.0)
Neoadjuvant treatment, n (%)		
DCF	17 (68.0)	6 (30.0)
CF	1 (4.0)	10 (50.0)
Chemoradiotherapy	2 (8.0)	4 (20.0)
Other	5 (20.0)	0
Surgical approach, n (%)		
RAMIE	14 (56.0)	0
VATS	11 (44.0)	20 (100)
pN+, n (%)	21 (84.0)	16 (80.0)
pStage III–IV, n (%)	15 (60.0)	9 (45.0)
CD grade ≥ II complications, n (%)	17 (68.0)	10 (50.0)
CD grade ≥ III complications, n (%)	9 (36.0)	2 (10.0)
Surgery-to-adjuvant interval, days, median (IQR)	77 (71–132)	67 (56–90)

Abbreviations: CF, cisplatin plus 5-fluorouracil; CD, Clavien–Dindo; DCF, docetaxel, cisplatin, and 5-fluorouracil; IQR, interquartile range; RAMIE, robot-assisted minimally invasive esophagectomy; VATS, video-assisted thoracoscopic esophagectomy.

Postoperative Complications and Timing of Adjuvant Therapy

CD grade ≥ II complications occurred in 17 of 25 patients (68.0%) in the nivolumab cohort and 10 of 20 patients (50.0%) in the S-1 cohort.

In the nivolumab cohort, patients with CD grade ≥ II complications had a significantly longer interval from surgery to adjuvant therapy initiation than those with CD grade < II complications (median, 113.0 vs. 69.5 days; $p = 0.008$). In the S-1 cohort, the corresponding intervals were 78.5 and 64.0 days, respectively, with no significant difference ($p = 0.198$).

CD grade ≥ III complications occurred in nine of 25 patients (36.0%) in the nivolumab cohort and two of 20 patients (10.0%) in the S-1 cohort. In the nivolumab cohort, the interval to treatment initiation was significantly longer in patients with CD grade ≥ III complications than in those with CD grade < III

complications (median, 132.0 vs. 74.5 days; $p = 0.027$). In the S-1 cohort, the corresponding intervals were 115.5 days (IQR, 103.25–127.75) and 65.0 days (IQR, 55.25–89.0), respectively ($p = 0.0885$). This comparison should be interpreted cautiously because only two patients in the S-1 cohort had CD grade ≥ III complications.

The associations between postoperative complications and the timing of adjuvant therapy initiation are summarized in Table 2 and Fig. 1.

Table 2
Association between postoperative complications and time to initiation of adjuvant therapy

Cohort	Postoperative complications	n	Surgery-to-treatment interval, days, median (IQR)	*p* value
Nivolumab	CD < II	8	69.5 (57–76.25)	
	CD ≥ II	17	113.0 (76–141)	**0.008**
Historical S-1	CD < II	10	64.0 (51.5–85.75)	
	CD ≥ II	10	78.5 (63–97)	0.198
Nivolumab	CD < III	16	74.5 (66.5–113.75)	
	CD ≥ III	9	132.0 (77–150)	**0.027**
Historical S-1	CD < III	18	65.0 (55.25–89.0)	
	CD ≥ III	2	115.5 (103.25–127.75)	0.0885

Footnote: Comparisons were performed using the Mann–Whitney U test. The CD grade ≥III analysis was secondary and should be interpreted cautiously, particularly in the historical S-1 cohort, in which only two patients experienced CD grade ≥III complications.

Deliverability and Safety of Adjuvant Nivolumab

Among the 25 patients who initiated adjuvant nivolumab, 10 (40.0%) completed the planned 1-year treatment, one (4.0%) remained on treatment at the data cutoff, and 14 (56.0%) discontinued treatment.

The reasons for discontinuation were disease recurrence in six patients (24.0%), adverse events in six (24.0%), and patient preference in two (8.0%). Thus, disease recurrence and adverse events were the two most frequent reasons for failure to complete the planned treatment.

Any-grade irAEs occurred in 12 patients (48.0%), including grade ≥ 3 irAEs in six (24.0%). Treatment deliverability and safety outcomes are summarized in Table 3.

Table 3
Deliverability and safety of adjuvant nivolumab

Outcome	Nivolumab (n = 25)
Completed planned 1-year treatment	10 (40.0%)
Treatment ongoing at evaluation	1 (4.0%)
Treatment discontinued	14 (56.0%)
└ Disease recurrence	6 (24.0%)
└ Adverse events	6 (24.0%)
└ Patient preference	2 (8.0%)
Any-grade irAE	12 (48.0%)
Grade ≥ 3 irAE	6 (24.0%)

Abbreviation: irAE, immune-related adverse event.

Recurrence-Free Survival

During follow-up, RFS events occurred in 10 of 25 patients (40.0%) in the nivolumab cohort and eight of 20 patients (40.0%) in the historical S-1 cohort.

The estimated 1- and 2-year RFS rates were 75.6% and 63.8%, respectively, in the nivolumab cohort and 80.0% and 70.0%, respectively, in the S-1 cohort. No statistically significant difference in RFS was observed between the cohorts (log-rank $p = 0.454$). Kaplan–Meier curves are shown in Fig. 2.

Overall Survival

Nine deaths occurred in the nivolumab cohort and eight in the historical S-1 cohort. The estimated 1- and 2-year OS rates were 88.0% and 72.6%, respectively, in the nivolumab cohort and 95.0% and 85.0%, respectively, in the S-1 cohort.

No statistically significant difference in OS was observed between the cohorts (log-rank $p = 0.249$). Kaplan–Meier curves are shown in Online Resource 1 (Supplementary Figure S1).

Discussion

The present study evaluated the real-world deliverability of adjuvant nivolumab after neoadjuvant therapy and curative esophagectomy. Postoperative complications were associated with delayed treatment initiation. At the data cutoff, 40% of patients had completed the planned 1-year course, while one patient remained on treatment. Adverse events and recurrence were the main reasons for discontinuation. These findings suggest that treatment deliverability after esophagectomy has two components: timely initiation after postoperative recovery and sustained treatment after initiation.

Postoperative complications have been associated with poor long-term outcomes after esophagectomy [8–10], although their prognostic impact remains controversial. In an exploratory analysis of JCOG1109, grade ≥ 2 complications were not significantly associated with OS in any treatment arm [11]. Our findings suggest another clinically relevant consequence of postoperative morbidity: delayed transition to adjuvant therapy. The median interval to nivolumab initiation increased from 69.5 to 113.0 days with CD grade ≥ II complications and from 74.5 to 132.0 days with CD grade ≥ III complications. Thus, postoperative morbidity may affect subsequent treatment even when its direct impact on long-term survival is uncertain.

Evidence regarding the optimal timing of postoperative systemic therapy after esophagectomy remains limited. Rhodin et al. reported a median interval of 59 days to adjuvant therapy, although their population largely preceded the current era of neoadjuvant therapy and immune checkpoint inhibition [12]. More relevant to the Japanese setting, the PENTAGON trial of adjuvant nivolumab after preoperative DCF specifies treatment initiation within 4–16 weeks after surgery [13]. In our cohort, patients with CD grade ≥ III complications initiated nivolumab at a median of 132 days, exceeding this 16-week window. Our study cannot determine whether this delay compromises efficacy, but it demonstrates that severe postoperative complications may prevent treatment from being delivered within the intended timeframe.

This issue is particularly relevant in Japan. CheckMate 577 established adjuvant nivolumab after neoadjuvant chemoradiotherapy and R0 resection [3], whereas NAC, particularly DCF, is widely used for locally advanced ESCC in Japan [2]. Recent Japanese retrospective studies have suggested favorable outcomes with adjuvant nivolumab after NAC [14, 15]. However, these studies primarily focused on oncological efficacy. Our study addresses a complementary question: whether adjuvant nivolumab can be initiated and sustained after NAC and esophagectomy in routine practice.

The recent nationwide Dutch analysis further strengthens the real-world evidence base for adjuvant nivolumab: in a propensity score-matched comparison after neoadjuvant chemoradiotherapy and resection, 2-year OS was 66.8% with nivolumab and 58.8% without adjuvant nivolumab [4]. Notably, postoperative complications were included among the variables used for treatment-group matching, but the study did not specifically evaluate how postoperative morbidity affected the timing of nivolumab initiation or subsequent treatment completion. Our study therefore complements these efficacy-focused data by examining the perioperative pathway required to deliver postoperative nivolumab, particularly in the Japanese NAC setting.

Treatment continuation represents the second component of deliverability. At the data cutoff, 40% of patients had completed 1 year of nivolumab, while one patient remained on treatment. Any-grade and grade ≥ 3 irAEs occurred in 48% and 24%, respectively, and adverse events led to discontinuation in 24%. In CheckMate 577, treatment-related grade 3–4 adverse events occurred in 13%, and 9% discontinued nivolumab because of treatment-related adverse events [3]. A multicenter real-world study reported grade 3–5 irAEs in 15% and early discontinuation due to irAEs in 24% [16]. Sugase et al. prospectively evaluated adjuvant nivolumab after esophagectomy and reported a 1-year completion rate of 52%;

recurrence, nivolumab-related adverse events, and patient preference accounted for discontinuation in 30%, 10%, and 8%, respectively [17]. Although direct comparisons across studies are limited by differences in patient selection and adverse-event definitions, these findings indicate that completion of the planned 1-year treatment is challenging in routine practice.

Importantly, incomplete treatment should not be attributed solely to toxicity. In our cohort, six patients (24%) discontinued nivolumab because of recurrence, similar to the 30% reported by Sugase et al. [17]. Patients receiving adjuvant nivolumab have residual disease after neoadjuvant treatment and remain at substantial risk of early recurrence. Thus, completion of 1 year of nivolumab reflects both treatment tolerability and disease control. This distinction is important when treatment completion is used as a measure of real-world deliverability.

S-1 provides a useful historical reference for postoperative therapy after NAC in Japan. Our previous study showed a 12-month S-1 continuation rate of 80% among patients who received NAC [6], while the phase II PIECE trial reported 3-year RFS and OS rates of 72.3% and 85.0%, respectively [5]. In the present study, the 1- and 2-year RFS rates were 75.6% and 63.8% with nivolumab and 80.0% and 70.0% with historical S-1; the corresponding OS rates were 88.0% and 72.6% versus 95.0% and 85.0%. Neither comparison was statistically significant. However, these findings should not be interpreted as evidence of equivalent efficacy because the cohorts were small, nonrandomized, and treated during different periods. The ongoing JCOG2206 (SUNRISE) trial will provide prospective comparative evidence for nivolumab and S-1 after NAC and esophagectomy [7].

The present findings also emphasize that postoperative systemic therapy should not be considered independently of surgical treatment. The ability to deliver adjuvant therapy begins with postoperative recovery. Complications may delay treatment initiation, while toxicity and recurrence may subsequently prevent completion. Thus, surgical recovery, treatment initiation, and treatment continuation represent successive steps in a single multidisciplinary treatment pathway. This perspective may be particularly relevant as postoperative systemic therapy becomes increasingly integrated into the treatment of locally advanced ESCC.

This study has important limitations. It was a single-center, retrospective analysis of only 25 nivolumab recipients, so estimates are imprecise and the analyses are susceptible to confounding. Patients who never initiated nivolumab were not included, creating selection bias and precluding estimation of treatment initiation at the level of all potentially eligible surgical patients. The S-1 cohort was nonconcurrent and differed in treatment era and clinical characteristics; its outcomes should not be interpreted as evidence of comparative efficacy or safety. Complication subgroup analyses were small, particularly for severe complications in the S-1 cohort, and multiple tests were conducted without multiplicity adjustment. Furthermore, one nivolumab recipient remained on treatment at the cutoff, so the 40% completion proportion is a data-cutoff status, not a mature estimate of eventual completion. Finally, this study cannot establish a causal effect of complications or treatment timing on oncological

outcomes. Larger multicenter studies that include all potentially eligible postoperative patients are needed.

Conclusion

In this small, selected cohort of patients who initiated adjuvant nivolumab following esophagectomy, postoperative complications were associated with a longer interval to treatment initiation. At the data cutoff, 10 of 25 patients (40.0%) had completed 1 year of treatment, and one remained on treatment; recurrence and adverse events were frequent reasons for discontinuation. These observations describe important practical barriers to adjuvant treatment delivery but do not demonstrate causal effects or comparative treatment efficacy.

Declarations

Data availability statement

The data underlying this article are available from the corresponding author on reasonable request, subject to institutional and ethical restrictions.

Generative AI assistance

Use of AI tools: ChatGPT (OpenAI) was used to assist with language editing, manuscript organization, and preparation of submission documents. All scientific content, analyses, and editorial decisions remain the responsibility of the authors, who reviewed the final manuscript.

Competing interests: The authors declare no competing interests.

Ethics approval and consent

Approval of the research protocol: The protocol for this research project was approved by the Institutional Review Board of the institutional ethics committee (Approval Nos. 1120 and 2023-001) and conformed to the provisions of the Declaration of Helsinki.

Informed consent: The requirement for written informed consent was waived by the Institutional Review Board because of the retrospective nature of the study. Patients were provided the opportunity to opt out of the study.

Registry and registration number: N/A (retrospective observational study).

Animal studies: N/A.

Funding: No specific funding was received for this study.

References

1. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol. 2012;19:68–74.
2. Kato K, Machida R, Ito Y, et al. Doublet chemotherapy, triplet chemotherapy, or doublet chemotherapy combined with radiotherapy as neoadjuvant treatment for locally advanced oesophageal cancer (JCOG1109 NExT): a randomised, controlled, open-label, phase 3 trial. Lancet. 2024;404:55–66.
3. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med. 2021;384:1191–1203.
4. Verhoeven RHA, Kuijper SC, Slingerland M, et al. Adjuvant nivolumab after chemoradiotherapy and resection for patients with esophageal cancer: a real-world matched comparison of overall survival. Int J Cancer. 2026;158:1292–1301. doi:10.1002/ijc.70168.
5. Nomura M, Yamaguchi T, Chin K, et al. Phase II trial of adjuvant S-1 following neoadjuvant chemotherapy and surgery in patients with locally advanced esophageal squamous cell carcinoma: the PIECE trial. Ann Surg Oncol. 2025;32:302–311.
6. Hirahara N, Matsubara T, Kaji S, et al. Feasibility study of adjuvant chemotherapy with S-1 after curative esophagectomy following neoadjuvant chemotherapy for esophageal cancer. BMC Cancer. 2022;22:718.
7. Kita R, Matsuda S, Nomura M, et al. Protocol digest of a randomized controlled Phase III study comparing surgery alone versus adjuvant nivolumab versus adjuvant S-1 for locally advanced oesophageal squamous cell carcinoma with no pathological complete response after neoadjuvant chemotherapy followed by curative esophagectomy: Japan Clinical Oncology Group study JCOG2206 (SUNRISE Trial). Jpn J Clin Oncol. 2024;54:212–216.
8. Booka E, Takeuchi H, Suda K, et al. Meta-analysis of the impact of postoperative complications on survival after oesophagectomy for cancer. BJS Open. 2018;2:276–284.
9. Saeki H, Tsutsumi S, Tajiri H, et al. The impact of postoperative complications on survivals after esophagectomy for esophageal cancer. Medicine (Baltimore). 2015;94:e1369.
10. Yang Y, Han C, Xing X, Qin Z, Wang Q, Lan L, Zhu H. Effects of postoperative complications on overall survival following esophagectomy: a meta-analysis using the restricted mean survival time analysis. Thorac Cancer. 2025;16:e70011.
11. Booka E, Kato K, Ito Y, et al. Prognostic impact of postoperative complications after neoadjuvant therapy followed by esophagectomy for esophageal cancer: an exploratory analysis of phase III trial JCOG1109. Ann Surg. 2026.
12. Rhodin KE, Raman V, Jawitz OK, Tong BC, Harpole DH, D'Amico TA. The effect of timing of adjuvant therapy on survival after esophagectomy. Ann Thorac Surg. 2020;110:1023–1029.
13. Goto H, Oshikiri T, Kato T, et al. Protocol for a phase II study to evaluate the efficacy and safety of nivolumab as a postoperative adjuvant therapy for patients with esophageal cancer treated with

preoperative docetaxel, cisplatin plus 5-fluorouracil treatment (PENTAGON trial). PLoS One. 2024;19:e0299742.

14. Koga N, Kimura Y, Yokomizo R, et al. Clinical outcomes of adjuvant nivolumab following neoadjuvant chemotherapy and esophagectomy in patients with esophageal cancer: a single-center retrospective cohort study. Surg Today. 2026;56:896–905.
15. Sugase T, Kanemura T, Matsuura N, et al. Survival impact of adjuvant nivolumab therapy for locally advanced esophageal squamous cell carcinoma treated with neoadjuvant chemotherapy with docetaxel plus 5-fluorouracil and cisplatin. Ann Surg Oncol. 2025;32:5887–5897.
16. Koops van 't Jagt M, Strijdhorst A, Huizer TJ, et al. Tolerability of adjuvant nivolumab in esophageal or gastroesophageal junction cancer: a real-world study. Int J Cancer. 2026. doi:10.1002/ijc.70686.
17. Sugase T, Kanemura T, Matsuura N, et al. Safety and short-term outcomes of adjuvant nivolumab therapy at 480 mg dose every four weeks in resected esophageal cancer: a prospective cohort study. Esophagus. 2025;22:565–573.

Figures

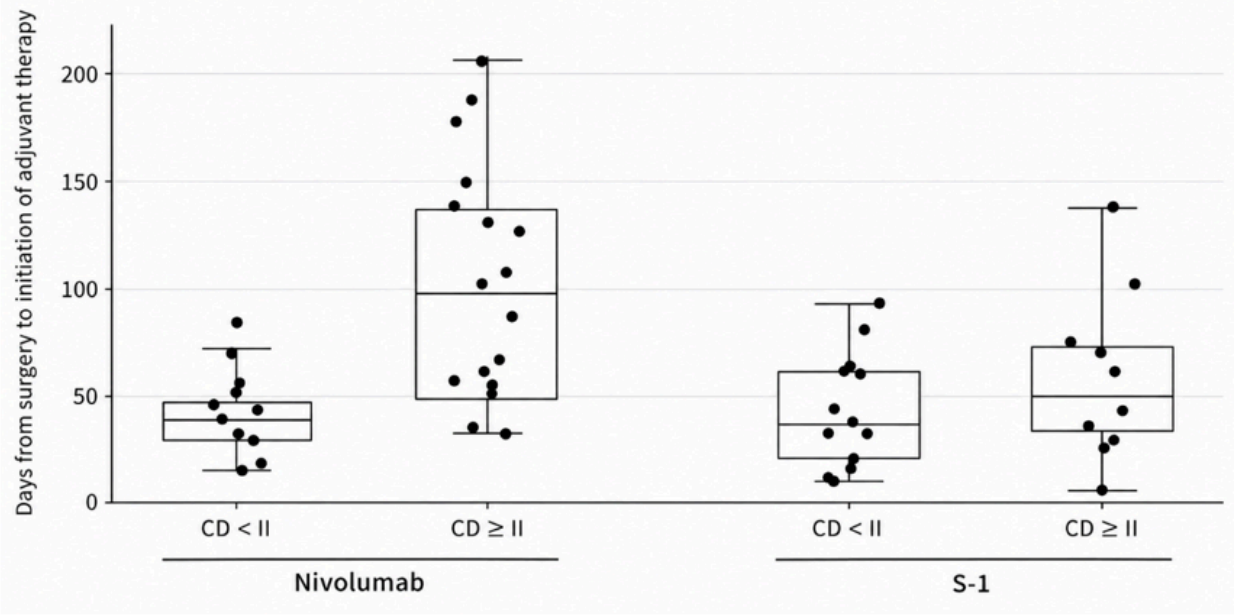


Figure 1

Association between postoperative complications and the interval from esophagectomy to initiation of adjuvant therapy. Individual patient data and box plots show the interval from surgery to initiation of adjuvant therapy according to the presence or absence of Clavien–Dindo (CD) grade ≥II postoperative complications. In the nivolumab cohort, the median interval was 69.5 days in patients with CD <II

complications and 113.0 days in those with CD ≥II complications (median difference, 43.5 days; p = 0.008). In the historical S-1 cohort, the corresponding median intervals were 64.0 and 78.5 days, respectively (median difference, 14.5 days; p = 0.198). Comparisons were performed using the Mann–Whitney U test. Horizontal lines within boxes indicate medians, and boxes indicate interquartile ranges. CD, Clavien–Dindo.

Alt text: Box plots with individual patient points show longer surgery-to-adjuvant-therapy intervals with Clavien-Dindo grade II or higher complications, especially in the nivolumab cohort.

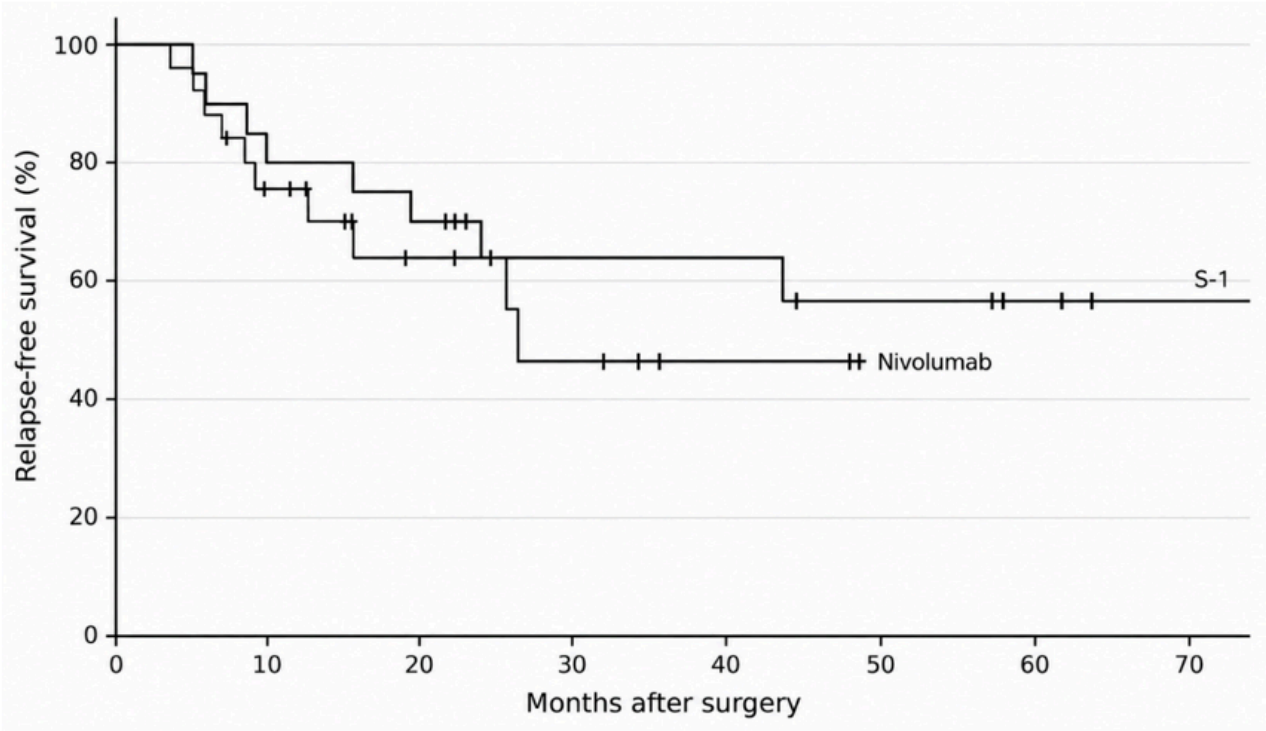


Figure 2

Recurrence-free survival according to postoperative adjuvant therapy.
Kaplan–Meier curves for recurrence-free survival in patients receiving adjuvant nivolumab and those in the historical S-1 cohort. The estimated 1- and 2-year RFS rates were 75.6% and 63.8%, respectively, in the nivolumab cohort and 80.0% and 70.0%, respectively, in the historical S-1 cohort. No statistically significant difference was observed between the groups (log-rank p = 0.454). RFS, recurrence-free survival.

Alt text: Kaplan-Meier curves compare recurrence-free survival after adjuvant nivolumab and historical S-1; the curves are similar through 2 years and the log-rank comparison is not significant.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigureS1.png
- 04SupplementaryFigureLegend.docx