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Early Initiation of Adjuvant Nivolumab After Esophagectomy Is Associated With Immune-related Liver Injury

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Abstract

Background/Aim: Adjuvant nivolumab after esophagectomy is increasingly being adopted for patients with esophageal cancer. However, its safety and efficacy following neoadjuvant docetaxel, cisplatin, and 5-fluorouracil (DCF) remain unclear. At our institution, we observed a high incidence of immunerelated liver injury (irLI). In this study, we evaluated the short-term outcomes of adjuvant nivolumab therapy and investigated the risk factors associated with irLI development.

Patients and Methods: This single-center study included 34 patients with thoracic esophageal squamous cell carcinoma who received neoadjuvant DCF, underwent esophagectomy, and were administered adjuvant nivolumab between 2022 and 2024. Patient demographics, details of adverse events, including irLI, and short-term survival data were retrospectively collected from medical records. Clinicopathological features associated with irLI were evaluated using univariate and multivariate analyses.

Results: Adverse events related to adjuvant nivolumab occurred in 22 of 34 patients (64.7%), and irLI developed in 14 of 34 patients (41.2%); all irLI cases were Common Terminology Criteria for Adverse Events Grade ≥3. The median interval from surgery to nivolumab initiation was 28 days in the patients who developed irLI. IrLI occurred in 13 of 22 patients (59.1%) who initiated nivolumab <8 weeks postoperatively *versus* 1 of 12 patients (8.3%) who initiated at ≥8 weeks after surgery. In multivariate analysis, early initiation of nivolumab (<8 weeks) was the only independent predictor of irLI.

Conclusion: Early initiation of adjuvant nivolumab therapy after neoadjuvant DCF and esophagectomy is associated with a higher incidence of irLI.

Keywords: Esophageal cancer, DCF, adjuvant nivolumab, irAE, liver injury.

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Introduction

Nivolumab, an immune checkpoint inhibitor (ICI), blocks the interaction between programmed death-1 and its ligands, thereby reactivating antigen-specific T cells that have been rendered unresponsive by tumor cells and exerting antitumor effects (1, 2). Nivolumab is a key agent in the systemic therapy for esophageal cancer (3, 4). However, ICIs cause immune-related adverse events (irAEs), which result from the activation of self-reactive T-cells, causing immune-mediated damage to normal cells and tissues. IrAEs have been reported in nearly every organ but are relatively common in barrier tissues including the skin, gastrointestinal tract, respiratory epithelium, and liver (2, 5).

For esophageal cancer, treatment outcomes with surgery alone remain suboptimal, and multimodal treatment combining systemic chemotherapy and radiation therapy is the key to improving prognosis (6, 7). Following the results of the CheckMate 577 trial, adjuvant nivolumab after esophagectomy improved long-term outcomes in patients who did not achieve a pathological complete response (pCR) following neoadjuvant chemoradiotherapy (8). However, in Japan, the standard treatment for locally advanced esophageal cancer is radical esophagectomy performed after administration of neoadjuvant docetaxel, cisplatin, and 5-fluorouracil (DCF) (9). Evidence regarding the safety and efficacy of adjuvant nivolumab in patients undergoing esophagectomy after neoadjuvant DCF remains limited. Only two retrospective studies to date have reported that adjuvant nivolumab is feasible and safe in this setting (10, 11); therefore, further studies are warranted.

We observed a high incidence of irAEs, particularly immune-related liver injury (irLI), during adjuvant nivolumab therapy in patients with esophageal cancer who underwent esophagectomy after neoadjuvant DCF. In this study, we aimed to evaluate the short-term outcomes of adjuvant nivolumab in this cohort and identify the clinicopathological factors associated with the development of irLI.

Patients and Methods

Patient eligibility and data collection. This was a single-center retrospective analysis conducted at Niigata City General Hospital. The eligibility criteria for this study were as follows: squamous cell carcinoma of the thoracic esophagus, neoadjuvant DCF followed by esophagectomy, nivolumab as postoperative adjuvant therapy, and treated from 2022 to 2024. The exclusion criteria were R1 or R2 resection and requirement for pharyngolaryngoesophagectomy. The clinicopathological features of the included patients were retrospectively extracted from their medical records. Pretreatment comorbidities were evaluated using the Charlson Comorbidity Index (CCI) (12).

Neoadjuvant chemotherapy. Eligibility for neoadjuvant chemotherapy was defined as stage II-III disease according to the 12th edition of the Japanese Classification of Esophageal Cancer (13). This included cT1N1 cStage I and cStage IVB cases with supraclavicular lymph node metastasis, as classified by the 8th edition of the Tumor Node Metastasis System of the International Union Against Cancer (UICC-TNM). Additional criteria included an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0-1 and absence of severe comorbidities or organ dysfunction. The neoadjuvant chemotherapy regimen consisted of docetaxel 70 mg/m^2 and cisplatin 70 mg/m^2 administered as a 1-h intravenous infusion, and 5-FU 750 mg/m^2/day as a continuous intravenous infusion for five consecutive days. Three courses of neoadjuvant DCF were administered at 3-week intervals.

Surgical procedure. The surgical procedure was performed using either robot-assisted minimally invasive esophagectomy (RAMIE) or video-assisted minimally invasive esophagectomy (VAMIE). The extent of lymphadenectomy was either a two-field (mediastinal and abdominal lymph nodes) or three-field (cervical, mediastinal, and abdominal lymph nodes) dissection. Two-field lymphadenectomy was considered when the

tumor was located in the lower third of the esophagus. Surgery was scheduled approximately 4-6 weeks after the completion of neoadjuvant DCF.

Tumor stage and histopathological examination. The tumor stage was evaluated according to the 8th edition of the UICC-TNM classification. The histological response to neoadjuvant DCF was assessed based on the proportion of viable tumor cells in the primary tumor tissues and classified as follows: Grade 3 (G3), complete disappearance of viable cancer cells; Grade 2 (G2), less than one-third of viable cancer cells remaining; Grade 1b (G1b), one-third to two-thirds of viable cancer cells remaining; Grade 1a (G1a), more than two-thirds of viable cancer cells remaining; or Grade 0 (G0), no significant pathological response (14).

Adjuvant nivolumab therapy. Adjuvant nivolumab was considered for patients who underwent surgery after DCF and did not achieve a Grade 3 histological response, equivalent to a pCR. However, patients with severe postoperative complications or an ECOG-PS of ≥2 were excluded from adjuvant therapy. Patients considered eligible for nivolumab were informed of alternative treatment options, including observation alone, and nivolumab treatment was started after obtaining informed consent. Nivolumab was administered either as 240 mg intravenous infusion every two weeks (Q2W) or 480 mg every four weeks (Q4W), at the discretion of the attending physician. The treatment duration was set to one year from the initiation of therapy. Regarding the timing of nivolumab initiation, in the early period (January 2022 to December 2023), the policy was to initiate nivolumab therapy as early as possible after surgery. However, considering the occurrence rates of adverse events, the policy in the late period (January to December 2024) was to initiate nivolumab at least eight weeks after surgery. Adverse events associated with adjuvant nivolumab were recorded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Immune-related liver injury associated with adjuvant nivolumab therapy. Diagnosis and management of irLI were conducted in accordance with the guidelines of the American Society of Clinical Oncology (ASCO) and the Japan Society of Hepatology (15, 16). During nivolumab therapy, all patients underwent regular blood tests. If hepatobiliary enzyme elevations were detected, nivolumab was temporarily withheld and patients were referred to a hepatologist. A careful evaluation was performed to distinguish irLI from other hepatic diseases and from druginduced liver injury (DILI) due to agents other than nivolumab. To increase diagnostic certainty of irLI, liver biopsy was considered in principle. The severity of irLI was graded according to CTCAE version 5.0. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin were compared with the upper limit of normal (ULN). As with typical DILI, the type of liver injury was classified using the R value, defined as (ALT/ULN)/(ALP/ULN). Cases were categorized as hepatocellular (R ≥5), mixed (2 < R < 5), or cholestatic (R ≤2) types (17).

Statistical analysis. The differences in patient characteristics and clinicopathological factors were evaluated. Categorical variables were compared using Fisher's exact test or the chi-squared test, as appropriate, and continuous variables were analyzed using Student's *t*-test or the Mann–Whitney *U*-test, based on distribution. Variables with $p<0.1$ in univariate analysis were entered into a multivariate logistic regression model to calculate odds ratios (ORs) with 95% confidence intervals (CIs). Overall survival (OS) was defined as the time from surgery to death from any cause or last follow-up. Recurrence-free survival (RFS) was defined as the time from surgery to the first documented recurrence, death from any cause, or the last follow-up. All statistical analyses were performed using EZR version 1.68 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria) (18). All tests were two-sided, and $p<0.05$ was considered statistically significant.

Ethical statement. This study protocol was approved by the Human Ethics Review Committee of the Niigata City General Hospital (25-043). All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation, the Helsinki Declaration, and its later versions.

Results

Patient characteristics. A total of 40 patients with esophageal squamous cell carcinoma who underwent esophagectomy following neoadjuvant DCF and received adjuvant nivolumab were identified. After excluding five patients with R1 or R2 resection margins and one patient who underwent pharyngolaryngoesophagectomy, 34 patients were included in the analysis. The median length of follow-up time was 26.4 months (range=12.3-48.1 months). A summary of patient characteristics is presented in Table I. The median age of the 34 patients was 71 years, and 24 were men. The median CCI score was 3. Alcoholic liver disease and chronic hepatitis virus infection were observed in three patients (8.8%). During neoadjuvant DCF, eight patients (23.5%) experienced liver injury. Fifteen (44.1%) patients were regular users of proton pump inhibitors (PPIs). Except for one case of VAMIE, all surgical procedures were performed using RAMIE. Twenty-two patients (64.7%) underwent a three-field lymphadenectomy, including bilateral cervical lymph node dissection. Prophylactic thoracic duct ligation was performed in 15 (44.1%) patients to prevent postoperative chylothorax. Seven patients were classified as ypM1; among them, four had supraclavicular lymph node metastasis. The histological response was Grade 0 in three cases (8.8%), Grade 1a in 17 cases (50.0%), Grade 1b in 10 cases (29.4%), and Grade 2 in four cases (11.8%). The adjuvant nivolumab dosing regimen was 240 mg Q2W in 21 patients (61.8%) and 480 mg Q4W in 13 patients (38.2%). The median body mass index (BMI) at nivolumab initiation was 19.7 kg/m^2. The median interval from surgery to nivolumab initiation was 40 days (range=25-167 days).

Adverse events associated with adjuvant nivolumab. A summary of the adverse events associated with adjuvant nivolumab is presented in Table II. Of the 34 patients, 22 (64.7%) experienced adverse events. The details of non-irAEs were as follows: fatigue in four patients, decreased appetite in three patients, diarrhea in two patients, arthralgia in one patient, and rash in one patient. IrAEs occurred in 16 patients (47.1%), with irLI being the most common (14 patients, 41.2%). Interstitial pneumonia, adrenal insufficiency, and hypothyroidism were observed in one patient (2.9%). Fourteen patients (41.2%) completed one year of adjuvant nivolumab treatment, whereas nivolumab was discontinued within one year in 15 patients (44.1%) owing to adverse events.

Summary of cases with irLI. Table III shows the patient backgrounds and treatment details for 14 patients who developed irLI. The median age was 71 years and the male-to-female ratio was 10:4. The interval from surgery to nivolumab initiation was a median of 34 days (range=27-57 days). The nivolumab dosing regimens were 480 mg Q4W in eight patients and 240 mg Q2W in six patients. The interval from nivolumab initiation to onset of irLI was a median of 28 days (range=12-112 days). In all 14 patients, clinical findings, imaging studies, and laboratory results excluded liver injury due to other drugs, acute exacerbation of viral or alcoholic hepatitis, hepatic metastases, and autoimmune hepatitis. Except for one patient, liver biopsy was performed in all cases and irLI was histologically confirmed. IrLI typically presented as acute hepatitis, most commonly as panlobular hepatitis with necrosis (19, 20). CD8-positive T-cell infiltration on immunohistochemistry was a key diagnostic feature of irLI (21). No cases showed histopathological findings suggestive of immune-related cholangitis or immune-related sclerosing cholangitis (22, 23). Based on the R value, the types of liver injury were hepatocellular in 13 patients (92.9%) and mixed in one patient (7.1%). The severity of irLI was CTCAE Grade 3 in eight patients, Grade 4 in five patients, and Grade 5 in one patient. In this study cohort, no cases of irLI of Grade 1-2 were observed;

Table I. *Clinicopathologic features of the included patients.*

Variables	All patients (n=34)
Age	
Median age, years (range)	71 (51-79)
Sex, n (%)	
Female	10 (29.4)
Male	24 (70.6)
BMI	
Median BMI, kg/m^2 (range)	19.7 (15.4-27.6)
CCI score, n (%)	
1	2 (5.9)
2	9 (26.5)
3	18 (52.9)
4	4 (11.8)
5	0
6	1 (2.9)
Alcoholic liver disease, n (%)	
Absence	31 (91.2)
Presence	3 (8.8)
Chronic hepatitis virus infection, n (%)	
Absence	31 (91.2)
Presence	3 (8.8)
PPIs use, n (%)	
Absence	19 (55.9)
Presence	15 (44.1)
Tumor location, n (%)	
Upper	8 (23.6)
Middle	13 (38.2)
Lower	13 (38.2)
Treatment courses of DCF, n (%)	
Two courses	3 (8.8)
Three courses	31 (91.2)
Adverse events during DCF, n (%)	
None	0
CTCAE Grade <3	6 (17.6)
CTCAE Grade ≥3	28 (82.4)
Liver injury during DCF, n (%)	
Absence	26 (76.5)
Presence	8 (23.5)
Surgical procedures, n (%)	
RAMIE	33 (97.1)
VAMIE	1 (2.9)
Extent of lymphadenectomy, n (%)	
Two-field	12 (35.3)
Three-field	22 (64.7)
Prophylactic thoracic duct ligation, n (%)	
Not performed	19 (55.9)
Performed	15 (44.1)

Variables	All patients (n=34)
Operative time	
Median operative time, min (range)	522 (449-710)
Blood loss during surgery	
Median blood loss, ml (range)	91 (5-1,580)
Postoperative complications, n (%)	
Total	13 (38.2)
Recurrent nerve palsy	8 (23.5)
Anastomotic leakage	2 (5.9)
Pneumothorax	2 (5.9)
Pneumonia	1 (2.9)
Others	4 (11.8)
Clavien-Dindo Grade <3	10 (29.4)
Clavien-Dindo Grade ≥3	3 (8.8)
ypT, n (%)	
T1	10 (29.4)
T2	8 (23.5)
T3	15 (44.1)
T4	1 (2.9)
ypN, n (%)	
N0	12 (35.3)
N1	15 (44.1)
N2	4 (11.8)
N3	3 (8.8)
ypM, n (%)	
M0	27 (79.4)
M1	7 (20.6)
ypStage, n (%)	
Stage I	5 (14.7)
Stage II	8 (23.5)
Stage III	14 (41.2)
Stage IV	7 (20.6)
Histological response, n (%)	
Grade 0	3 (8.8)
Grade 1a	17 (50.0)
Grade 1b	10 (29.4)
Grade 2	4 (11.8)
Dosing regimen of nivolumab, n (%)	
240 mg Q2W	21 (61.8)
480 mg Q4W	13 (38.2)
Interval from surgery to nivolumab initiation	
Median interval from surgery to nivolumab initiation, days (range)	40 (25-167)

BMI: Body mass index; CCI: Charlson comorbidity index; PPIs: proton pump inhibitors; DCF: docetaxel, cisplatin and 5-fluorouracil; CTCAE: Common Terminology Criteria for Adverse Events; RAMIE: robot-assisted minimally invasive esophagectomy; VAMIE: video-assisted minimally invasive esophagectomy; Q2W: every two weeks; Q4W: every four weeks.

all cases were classified as Grade ≥3. Nivolumab cessation alone led to improvement in some patients; however, 11 patients (78.6%) required prednisolone (PSL). For Grade 3 toxicities, PSL was initiated at 1.0-1.5 mg/kg/day, and for Grade 4 toxicities PSL was initiated at 1.5-2.0 mg/kg/day. A reduction in hepatobiliary enzyme levels to Grade

Table II. *Adverse events related to adjuvant nivolumab.*

Events, n (%)	n=34	
	All grades	Grade ≥3
At least one AE, n (%)	22 (64.7)	16 (47.1)
Fatigue	4 (11.8)	1 (2.9)
Decreased appetite	3 (8.8)	0
Diarrhea	2 (5.9)	0
Arthralgia	1 (2.9)	0
Rash	1 (2.9)	0
IrAEs	16 (47.1)	15 (44.1)
Immune-related liver injury (irLI)	14 (41.2)	14 (41.2)
Interstitial pneumonia	1 (2.9)	1 (2.9)
Adrenal insufficiency	1 (2.9)	0
Hypothyroidism	1 (2.9)	0

AE: Adverse event; IrAEs: immune-related adverse events.

2 or lower was considered improvement, after which the PSL dose was carefully tapered over 4-6 weeks. Median time from the peak hepatobiliary enzyme level to improvement to Grade 2 or lower was 14 days. For severe cases at risk of progression to liver failure, intravenous methylprednisolone 1,000 mg/day was administered for three days as steroid pulse therapy. Mycophenolate mofetil was used for refractory cases. One patient died from liver failure despite treatment. Two additional deaths occurred: one from sepsis and one from respiratory failure due to aspiration pneumonia, both in patients whose liver injury had been improving. Regarding rechallenge of nivolumab after improvement of liver injury, the ASCO Clinical Practice Guideline does not recommend in cases of Grade ≥3 irLI (15), and no patients in this study underwent readministration of nivolumab.

Correlation between clinicopathologic features and irLI. The clinicopathological features associated with irLI were evaluated, and the results are summarized in Table IV. No significant relationships were observed between irLI and patient age, sex, BMI, CCI score, history alcoholic liver disease, chronic hepatitis virus infection, or PPIs use. The incidence of irLI was higher in patients who underwent two-field lymphadenectomy than in those who underwent three-field lymphadenectomy (61.5% *vs*. 28.6%; p=0.080). Although patients who underwent prophylactic thoracic duct ligation also showed a higher incidence of irLI than those who did not (60.0% *vs*. 26.3%; p=0.080), the difference was not statistically significant. Pathological factors, including ypStage and histological response, were not associated with irLI. The incidence of irLI tended to be higher in patients treated with nivolumab 480 mg Q4W than in those treated with 240 mg Q2W, although the difference was not statistically significant (61.5% *vs*. 28.6%; p=0.080). In contrast, when the timing of nivolumab initiation was examined, 13 of 22 patients (59.1%) who started nivolumab within eight weeks postoperatively (early-initiation group) developed irLI compared to only one of 12 patients (8.3%) who started nivolumab at eight weeks or later after surgery (delayed-initiation group). The incidence of irLI was significantly higher in the early-initiation group than in the delayed-initiation group (p=0.009).

Independent risk factors for irLI. Multivariate analysis with a logistic regression model was performed to identify clinicopathologic factors associated with the development of irLI, including the extent of lymphadenectomy, prophylactic thoracic duct ligation status, dosing regimen of nivolumab, and timing of nivolumab initiation as factors with p-value <0.1 in univariate analysis (Table V). Among these, only an early initiation (<8 weeks) of adjuvant nivolumab was identified as an independent risk factor for irLI [odds ratio (OR)=14.00, 95%CI=1.33-147.00; p=0.028). No statistically significant association was observed between the timing of nivolumab initiation and short-term survival. However, the earlyinitiation group showed numerically worse 2year OS (100% *vs*. 77.3%, p=0.076) and 2year RFS (66.7% *vs*. 50.0%, p=0.287) than the delayedinitiation group (Figure 1).

Discussion

Herein, we evaluated the short-term outcomes of adjuvant nivolumab after esophagectomy following neoadjuvant DCF for patients with esophageal cancer. irLI occurred in

Table III. *Summary of cases with immune-related liver injury (irLI).*

Case	Age	Sex	ypStage	Interval from surgery to nivolumab initiation	Dose of nivolumab	Interval from nivolumab initiation to onset of irLI	Liver biopsy	Type of liver injury
1	68 y/o	Male	Stage 3B	57 days	480 mg Q4W	35 days	Performed	Hepatocellular
2	73 y/o	Female	Stage 3B	34 days	480 mg Q4W	28 days	Not performed	Hepatocellular
3	72 y/o	Male	Stage 3B	29 days	480 mg Q4W	112 days	Performed	Hepatocellular
4	70 y/o	Male	Stage 3A	43 days	240 mg Q2W	28 days	Performed	Mixed
5	68 y/o	Female	Stage 1B	31 days	480 mg Q4W	56 days	Performed	Hepatocellular
6	73 y/o	Male	Stage 3B	34 days	240 mg Q2W	14 days	Performed	Hepatocellular
7	70 y/o	Male	Stage 2A	27 days	240 mg Q2W	14 days	Performed	Hepatocellular
8	78 y/o	Male	Stage 4B	32 days	240 mg Q2W	49 days	Performed	Hepatocellular
9	71 y/o	Male	Stage 3B	43 days	240 mg Q2W	14 days	Performed	Hepatocellular
10	71 y/o	Male	Stage 2A	38 days	480 mg Q4W	56 days	Performed	Hepatocellular
11	65 y/o	Male	Stage 1B	34 days	240 mg Q2W	27 days	Performed	Hepatocellular
12	78 y/o	Female	Stage 2A	39 days	480 mg Q4W	28 days	Performed	Hepatocellular
13	79 y/o	Male	Stage 2B	29 days	480 mg Q4W	28 days	Performed	Hepatocellular
14	71 y/o	Female	Stage 3B	48 days	480 mg Q4W	12 days	Performed	Hepatocellular

Case	Peak AST level (U/l)	Peak ALT level (U/l)	Peak ALP level (U/l)	Severity of irLI (CTCAE)	Treatment of irLI	Time to improvement of liver injury	Prognosis	Follow-up time from onset of irLI
1	397	550	122	Grade 3	Nivolumab cessation alone	21 days	AWD	9.3 months
2	245	390	125	Grade 3	Nivolumab cessation alone	14 days	AWD	31.1 months
3	324	380	164	Grade 3	Nivolumab cessation alone	25 days	NED	32.2 months
4	247	352	380	Grade 3	PSL 1.0 mg/kg/day	9 days	NED	45.8 months
5	245	377	107	Grade 3	PSL 1.0 mg/kg/day	6 days	NED	34.0 months
6	273	379	109	Grade 3	PSL 1.0 mg/kg/day	4 days	NED	24.8 months
7	501	730	74	Grade 3	PSL 1.0 mg/kg/day	14 days	NED	22.4 months
8	507	634	235	Grade 3	PSL 1.5 mg/kg/day	14 days	DOD	6.4 months
9	774	1,359	327	Grade 4	PSL 1.5 mg/kg/day	28 days	NED	38.9 months
10	727	847	175	Grade 4	PSL 1.5 mg/kg/day	10 days	NED	28.0 months
11	1,216	1,726	272	Grade 4	mPSL 1,000 mg/day, PSL 1.5 mg/kg/day, MMF	18 days	AWD	21.5 months
12	3,992	2,054	254	Grade 4	mPSL 1,000 mg/day, PSL 2.0 mg/kg/day	13 days	DOC (sepsis)	2.1 months
13	1,946	2,050	126	Grade 4	mPSL 1,000 mg/day, PSL 1.5 mg/kg/day	13 days	DOC (respiratory failure)	0.5 months (14 days)
14	2,011	2,063	141	Grade 5	PSL 2.0 mg/kg/day	Not improved	DOC (liver failure)	0.4 months (12 days)

irLI: Immune-related liver injury; Q2W: every two weeks; Q4W: every four weeks; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; CTCAE: Common Terminology Criteria for Adverse Events; PSL: prednisolone; mPSL: methylprednisolone; MMF: mycophenolate mofetil; AWD: alive with disease; NED: no evidence of disease; DOD: death from disease; DOC: death from other causes.

41.2% of patients, and all cases had Grade 3 or higher toxicity. By contrast, the CheckMate 577 trial reported any-grade AST elevation in approximately 5% of patients and Grade ≥3 AST elevation in less than 1% (8). Sugase *et al.* (10) reported that, in patients who received adjuvant nivolumab after esophagectomy following neoadjuvant DCF, similar to the present study, AST elevation occurred in 20% of patients, with Grade 3 or higher events in 6%. Koga *et al.* (11) reported outcomes for 15 patients who received adjuvant nivolumab; eight patients developed irAEs, which were predominantly colitis and interstitial pneumonia, and no cases of liver injury were observed.

Table IV. *Correlation between clinicopathologic features and immune-related liver injury (irLI).*

Variables		IrLI		*p*-Value
		Absence n=20	Presence n=14	
Age, n (%)	<75 years	16 (59.3)	11 (40.7)	1.000
	≥75 years	4 (57.1)	3 (42.9)	
Sex, n (%)	Female	6 (60.0)	4 (40.0)	1.000
	Male	14 (58.3)	10 (41.7)	
BMI, n (%)	<20	11 (56.2)	7 (43.8)	1.000
	≥20	9 (61.1)	7 (38.9)	
CCI score, n (%)	<4	19 (65.5)	10 (34.5)	0.135
	≥4	1 (20.0)	4 (80.0)	
Alcoholic liver disease, n (%)	Absence	18 (58.1)	13 (41.9)	1.000
	Presence	2 (66.7)	1 (33.3)	
Chronic hepatitis virus infection, n (%)	Absence	18 (58.1)	13 (41.9)	1.000
	Presence	2 (66.7)	1 (33.3)	
PPIs use, n (%)	Absence	10 (52.6)	9 (47.4)	0.495
	Presence	10 (66.7)	5 (33.3)	
Severe AE during DCF, n (%)	Absence	2 (33.3)	4 (66.7)	0.202
	Presence	18 (64.3)	10 (35.7)	
Liver injury during DCF, n (%)	Absence	15 (57.7)	11 (42.3)	1.000
	Presence	5 (62.5)	3 (37.5)	
Extent of lymphadenectomy, n (%)	Three-field	15 (71.4)	6 (28.6)	0.080
	Two-field	5 (38.5)	8 (61.5)	
Prophylactic thoracic duct ligation, n (%)	Not performed	14 (73.7)	5 (26.3)	0.080
	Performed	6 (40.0)	9 (60.0)	
Operative time, n (%)	<500 min	6 (54.5)	5 (45.5)	1.000
	≥500 min	14 (60.9)	9 (39.1)	
Blood loss during surgery, n (%)	<100 ml	19 (59.1)	9 (40.9)	1.000
	≥100 ml	7 (58.3)	5 (41.7)	
Postoperative complications, n (%)	Absence	13 (61.9)	8 (38.1)	0.728
	Presence	7 (53.8)	6 (46.2)	
ypStage, n (%)	Stage I-II	7 (53.8)	6 (46.2)	0.728
	Stage III-IV	13 (61.9)	8 (38.1)	
Histological response, n (%)	Grade 0-1a	8 (57.1)	6 (42.9)	1.000
	Grade 1b-2	12 (60.0)	8 (40.0)	
Dosing regimen of nivolumab, n (%)	240 mg Q2W	15 (71.4)	6 (28.6)	0.080
	480 mg Q4W	5 (38.5)	8 (61.5)	
Interval from surgery to nivolumab initiation, n (%)	<8 weeks (early-initiation group)	9 (40.9)	13 (59.1)	0.009
	≥8 weeks (delayed-initiation group)	11 (91.7)	1 (8.3)	

IrLI: Immune-related liver injury; BMI: body mass index; CCI: Charlson comorbidity index; PPIs: proton pump inhibitors; AE: adverse events; DCF: Docetaxel, cisplatin, and 5-fluorouracil; Q2W: every two weeks; Q4W: every four weeks.

These results reveal a markedly higher frequency and severity of irLI in our cohort and highlight the need for caution when considering adjuvant nivolumab in patients who have undergone esophagectomy following neoadjuvant chemotherapy.

Delayed initiation of adjuvant chemotherapy adversely affects the long-term survival of patients with various malignancies. In a previous meta-analysis, delayed initiation of adjuvant chemotherapy beyond eight weeks after surgery was associated with a 27% increased risk of death from colorectal cancer and a 20% increased risk of death from gastric cancer (24). However, the optimal timing for the initiation of adjuvant chemotherapy after esophageal cancer surgery has not yet been established. Furthermore, the optimal timing for initiating ICIs as adjuvant therapy has not been adequately investigated. At

Table V. *Factors related to immune-related liver injury (irLI) in multivariate analysis.*

Variables	Reference	OR	95%CI	*p*-Value
Two-field lymphadenectomy	*vs.* Three-field	1.78	0.27-11.60	0.549
Prophylactic thoracic duct ligation	*vs.* No ligation	4.28	0.66-27.70	0.127
480 mg Q4W regimen of nivolumab	*vs.* 240 mg Q2W	3.55	0.54-23.50	0.189
Early initiation (<8 W) of nivolumab	*vs.* Delayed initiation (≥8 W)	14.00	1.33-147.00	0.028

OR: Odds ratio; 95%CI: 95% confidence intervals; Q4W: Every 4 weeks; Q2W: Every 2 weeks; 8 W: eight weeks after surgery.

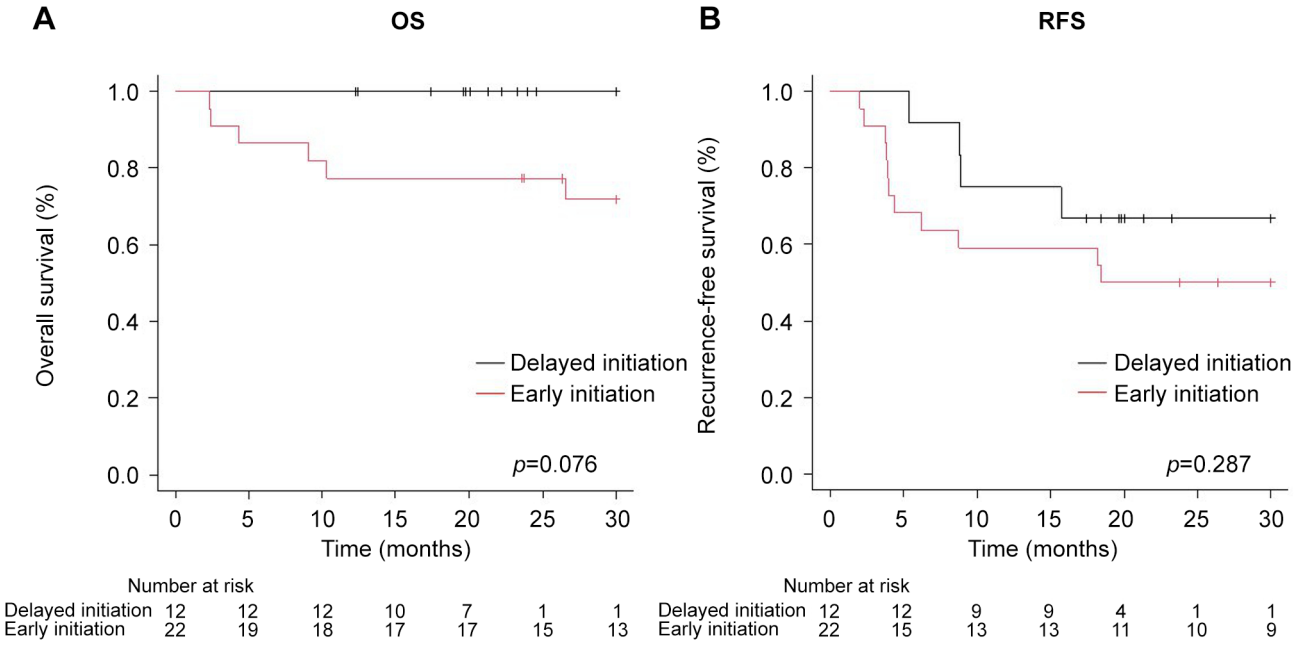

Figure 1. *Kaplan–Meier survival curves stratified by adjuvant nivolumab initiation timing. Early-initiation group had numerically lower 2-year overall survival (OS) (100% vs. 77.3%, p=0.076) (A) and 2-year recurrence-free survival (RFS) (66.7% vs. 50.0%, p=0.287) (B); differences were not statistically significant.*

our institution, we adopted the same approach as conventional adjuvant chemotherapy and initiated adjuvant nivolumab as early as possible after esophagectomy; however, we subsequently observed a high frequency of irLI. Multivariate analysis showed that nivolumab initiation within eight weeks after surgery was an independent risk factor for the development of irLI and was associated with a trend toward worse short-term survival. In two prior studies that examined the efficacy and safety of adjuvant nivolumab in patients with esophageal cancer who underwent esophagectomy after preoperative DCF therapy, the incidence of irLI was lower than in our study (10, 11). Although none of the prior studies examined the relationship between the interval from surgery to nivolumab initiation and irAE occurrence in detail, Sugase *et al.* (10) reported that 55% of their patients began nivolumab 10 weeks or more after surgery. In the series by Koga *et al.* (11), nivolumab was started within 4-6 months after surgery. The median time from surgery to nivolumab initiation in our cohort was only 40 days, substantially shorter than in the two prior studies.

Esophagectomy is more invasive than most other gastrointestinal cancer surgeries, and preoperative triplet chemotherapy further increases physiological stress.

Restoration of immune regulatory mechanisms may require a prolonged recovery period. In a previous study on perioperative systemic immunity in patients with esophageal cancer who underwent surgery after neoadjuvant chemoradiotherapy, circulating lymphocytes decreased immediately after surgery, and circulating $CD8^+$ lymphocytes increased up to postoperative week six (25). In a separate study examining the relationship between irAEs and peripheral blood lymphocyte counts in patients receiving ICIs for several malignancies, patients who developed severe irAEs showed a significant decrease in lymphocyte counts (26). Consistent with these observations, Takahashi *et al.* (27) demonstrated that peripheral immune cell profiles, including circulating eosinophils, were associated with prognosis after esophagectomy, suggesting that individual immunologic backgrounds may influence susceptibility to immune related toxicities. In cases of highly invasive surgery and intensive neoadjuvant therapy, administering ICIs early after surgery, while immune regulatory mechanisms remain inadequately recovered, may promote the development of irAEs. A study on patients with melanoma reported that initiation of ICIs within six weeks after surgery was associated with worse RFS than later initiation (28). Additionally, in the CheckMate 577 trial, patients who began adjuvant nivolumab 10 weeks or later after surgery demonstrated a better prognosis (8). When ICIs are administered as a postoperative adjuvant therapy, initiating treatment too early after surgery may increase the risk of irAEs and reduce the likelihood of achieving adequate antitumor efficacy.

One possible factor contributing to the high frequency of irAEs observed with adjuvant nivolumab in this study is the timing of treatment initiation, as noted above; however, other potential contributors also warrant investigation. Previous studies have shown that baseline patient characteristics can influence postoperative outcomes. For example, Shimada *et al.* (29) identified preoperative anemia as an independent prognostic factor in patients with esophageal cancer undergoing curative treatment, underscoring the importance of host-related factors in treatment tolerance and clinical outcomes. Systemic physiological stress may also increase vulnerability to immune-related toxicities. Aoyama *et al.* (30) demonstrated that body weight loss at recurrence was an independent prognostic factor in patients with recurrent esophageal cancer, indicating that compromised host status may predispose individuals to severe treatment related adverse events. Asian populations, including Japanese, generally have a smaller body habitus and lower BMI than the predominantly Western populations enrolled in many clinical trials, which may lead to relatively higher drug exposure; notably, the CheckMate 577 trial enrolled 69% of participants from North America or Europe and only 14% from Asia (8). The median BMI of the patient cohort in this study was relatively low (<20); however, univariate analysis showed no statistically significant association between BMI and the incidence of irAEs. Moreover, prior studies conducted in Japanese patient cohorts similar to ours have reported irAEs incidence rates comparable to those observed in the pivotal clinical trial (10, 11). Several reports have indicated that various concomitant medications increase the incidence of irAEs in patients treated with ICIs. PPIs are among the most widely prescribed medications worldwide; however, they have been reported to be risk factors for immune-related colitis owing to disturbances of the gut microbiota and damage to the intestinal mucosal barrier, and concomitant PPIs use has also been associated with an increased incidence of interstitial nephritis (31, 32). Disturbance of the gut microbiome has been implicated in the development and progression of various liver diseases, including nonalcoholic fatty liver disease and autoimmune hepatitis, and may also be associated with the onset of irLI (33). PPIs are frequently administered to patients with esophageal cancer for symptom relief or postoperative management, and the resulting high PPIs exposure may have contributed to PPIs being identified as a potential risk factor for irAEs. In this study, 15 of 34 patients (44.1%) received PPIs during nivolumab therapy. However, no statistically significant association was observed between PPIs use and the occurrence of irAEs in our cohort.

Table VI. *Comparison of clinicopathological baseline characteristics between the early and delayedinitiation groups.*

Variables		Interval from surgery to nivolumab initiation		*p*-Value
		<8 weeks (Early-initiation group) n=22	≥8 weeks (Delayed-initiation group) n=12	
Age	Median age, years (range)	71 (61-79)	67 (51-79)	0.112
Sex, n (%)	Female	6 (60.0)	4 (40.0)	0.714
	Male	16 (66.7)	8 (33.3)	
BMI, n (%)	<20	12 (66.7)	6 (33.3)	1.000
	≥20	10 (62.5)	6 (37.5)	
CCI score, n (%)	<4	17 (58.6)	12 (41.4)	0.137
	≥4	5 (100)	0 (0)	
Alcoholic liver disease, n (%)	Absence	20 (64.5)	11 (35.5)	1.000
	Presence	2 (66.7)	1 (33.3)	
Hepatitis virus infection, n (%)	Absence	21 (67.7)	10 (32.3)	0.279
	Presence	1 (33.3)	2 (66.7)	
Tumor location, n (%)	Upper	5 (62.5)	3 (37.5)	1.000
	Middle	8 (61.5)	5 (38.5)	
	Lower	9 (69.2)	4 (30.8)	
Treatment courses of DCF, n (%)	Two courses	1 (33.3)	2 (66.7)	0.279
	Three courses	21 (67.7)	10 (32.3)	
Adverse events of DCF, n (%)	None	0	0	0.389
	CTCAE Grade <3	5 (83.3)	1 (16.7)	
	CTCAE Grade ≥3	17 (60.7)	11 (39.3)	
Liver injury during DCF, n (%)	Absence	17 (65.4)	9 (34.6)	1.000
	Presence	5 (62.5)	3 (37.5)	
Surgical procedures, n (%)	RAMIE	21 (63.6)	12 (36.4)	1.000
	VAMIE	1 (100)	0	
Extent of lymphadenectomy, n (%)	Three-field	12 (57.1)	9 (42.9)	0.292
	Two-field	10 (76.9)	3 (23.1)	
Ligation of thoracic duct, n (%)	Not performed	11 (57.9)	8 (42.1)	0.476
	Performed	11 (73.3)	4 (26.7)	
Operative time	Median operative time, min (range)	508 (449-710)	539 (483-656)	0.166
Blood loss during surgery	Median blood loss, ml (range)	100 (5-1,580)	90 (5-334)	0.499
Postoperative complications, n (%)	None	15 (71.4)	6 (28.6)	0.367
	Clavien-Dindo Grade <3	6 (60.0)	4 (40.0)	
	Clavien-Dindo Grade ≥3	1 (33.3)	2 (66.7)	
ypStage, n (%)	Stage I	2 (40.0)	3 (60.0)	0.451
	Stage II	5 (62.5)	3 (37.5)	
	Stage III	11 (78.6)	3 (21.4)	
	Stage IV	4 (57.1)	3 (42.9)	
Histological response, n (%)	Grade 0	1 (33.3)	2 (66.7)	0.136
	Grade 1a	14 (82.4)	3 (17.6)	
	Grade 1b	5 (50.0)	5 (50.0)	
	Grade 2	2 (50.0)	2 (50.0)	
Dosing regimen of nivolumab, n (%)	240 mg Q2W	12 (57.1)	9 (42.9)	0.292
	480 mg Q4W	10 (76.9)	3 (23.1)	
Interval from surgery to nivolumab initiation	Median interval from surgery to nivolumab initiation, days (range)	34 (25-48)	68 (57-167)	<0.001

BMI: Body mass index; CCI: Charlson Comorbidity Index; DCF: docetaxel, cisplatin, 5-fluorouracil; CTCAE: Common Terminology Criteria for Adverse Events; RAMIE: robot-assisted minimally invasive esophagectomy; VAMIE: video-assisted minimally invasive esophagectomy; Q2W: every two weeks; Q4W: every four weeks.

Although irAEs can affect any organ system, the reason liver injury occurred at a disproportionately high frequency in this study remains unclear and warrants further investigation. Research on irLI caused by ICIs for esophageal cancer is limited; however, studies on other malignancies have reported several risk factors associated with irLI development. Female sex and prior ICI exposure have been reported as risk factors for irLI (34, 35); however, most patients in this study were men, and none had prior exposure to ICIs. In a meta-analysis of atezolizumab (ICI) recipients, Asian ancestry, including Japanese, was reported as a risk factor for irLI; notably, all patients included in the present study were Japanese (36). According to the cited meta-analysis, elevated baseline liver enzyme levels were associated with irLI. Alcoholic liver disease and hepatitis virus infection can elevate baseline liver enzyme levels. However, in this study, their prevalence was not significantly associated with the development of irLI. Chylothorax is a serious complication following esophagectomy, and prophylactic thoracic duct ligation reportedly reduces its incidence (37, 38). As the thoracic duct is the primary lymphatic pathway, its ligation can modify lymphatic flow and potentially stress the liver. Per a previous report, the alteration of lymphatic flow after thoracic duct ligation can decrease the proportion of circulating $CD4^+$ lymphocytes and increase the proportion of $CD8^+$ lymphocytes (39). As $CD8^+$ lymphocytes play a central role in irAEs, prophylactic thoracic duct ligation may increase the overall risk of irAEs.

Study limitations. First, as this was a single-center retrospective study with a small sample size, potential biases related to patient characteristics and treatment strategies could not be excluded. Second, the diagnosis of irLI relies on exclusion, and demonstrating that liver injury is truly an irAE caused by nivolumab is challenging. However, in this study, liver biopsy was performed in all but one patient who developed liver injury, and the pathologists judged the findings to be consistent with irLI. In addition, in the adjuvant nivolumab setting, no concomitant chemotherapy is administered and routine prophylactic antiemetics are not required, minimizing the likelihood of DILI from agents other than nivolumab. Third, the timing of initiation of adjuvant nivolumab differed between the early and late periods. Most patients in the early-initiation group were concentrated in the early period, whereas those in the delayed initiation group were concentrated in the late period. However, comparison of baseline characteristics between the early- and delayed-initiation groups revealed no statistically significant differences (Table VI).

Conclusion

Among patients with esophageal cancer who underwent esophagectomy following neoadjuvant chemotherapy, early postoperative initiation of adjuvant nivolumab may be associated with an increased incidence of irLI. ICIs, including nivolumab, represent an important therapeutic option for esophageal cancer; however, their use requires careful monitoring and rigorous attention to safety.

Conflicts of Interest

There are no financial or other interests regarding the submitted manuscript that might be construed as conflicts of interest.

Authors' Contributions

Conception and design: N.S., S.K.; Development of methodology: N.S., S.K.; Acquisition of data: Y.K., K.S., J.Y., M.N.; Analysis and interpretation of data: N.S., Y.K., K.S., J.Y., M.N.; Writing, review, and revision of the manuscript: N.S.; Study supervision: S.K.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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