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Adverse Events in Patients With Esophageal Cancer Treated With Nivolumab in Combination With Radiotherapy

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Abstract. *Background/Aim: When nivolumab is administered as second-line therapy for esophageal cancer, radiotherapy may also be provided in cases either concurrently or sequentially. The aim of this study was to retrospectively examine whether the incidence of adverse events increases in such cases. Patients and Methods: Twenty-two esophageal cancer patients [17 males and 5 females; mean age 71 years (range=58-87 years)] treated with nivolumab were included. Patients were divided into two treatment groups: nivolumab alone (N group) (12 patients) and nivolumab combined with radiotherapy (R group) (10 patients). All patients had squamous cell carcinoma. The primary outcomes measured were the severity and frequency of adverse events. Results: Adverse events were seen in 6 of the 12 patients in the N group and 8 of the 10 in the R group. There were significantly more adverse events in the R group (p=0.035), but no difference in Grade 3 or higher adverse events (p=0.781), indicating that the adverse events were controllable. There was no significant difference in treatment effect between the N and R groups. Conclusion: In this report, 50% of adverse events in the N group were grade 3-4, 25% of which were grade 4, as seen in previous reports. In the present study, the side effects were not enhanced by treatment with immune checkpoint inhibitors plus radiotherapy. Immune checkpoint inhibitors plus radiation therapy would be a relatively safe treatment and may become an option for esophageal cancer treatment in the future.*

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Esophageal cancer is one of the most common malignancies with over 500,000 new diagnoses and deaths in 2020 worldwide (1). Recurrent and advanced esophageal cancer is mainly treated with radiotherapy, and anticancer drug treatment.

As a result of the ATTRACTION-3 study (2), the efficacy of second-line treatment was confirmed, and immune checkpoint inhibitor therapy was introduced as an anticancer drug treatment. According to studies such as CheckMate648 (3) and KEYNOTE-181 (4), the use of immune checkpoint inhibitors plus chemotherapy is now recommended even in the first line. It is expected that this will improve future treatment results.

Adverse events with nivolumab plus chemotherapy increase, but the percentages of patients who reported tolerable treatment side effects over time with nivolumab plus chemotherapy were similar to those with chemotherapy alone, and adverse events were considered acceptable (3). In other words, when administering nivolumab, the concomitant use of chemotherapy does not increase the number of adverse events that make it difficult to continue treatment or reduce quality of life. It is not uncommon to experience recurrence during treatment for esophageal cancer, and its treatment is mostly chemotherapy and radiotherapy, although surgery is also performed if resectable. We have also administered chemotherapy to recurrent cases and non-resectable cases and nivolumab as second-line therapy.

Recently, the concept of oligometastases, that includes lesions in the lymph node, brain, lung, and liver, has become acceptable and reports on radiotherapy as a treatment method have been published (5). When nivolumab was administered as second-line therapy, radiation therapy was also performed if possible. In this study, we retrospectively examined whether the occurrence of adverse events increased in such cases.

Patients and Methods

Twenty-two cases of esophageal cancer were treated with nivolumab. The characteristics of the patients are shown in Table I.

The patients were divided into two groups according to treatment methods: Nivolumab single treatment (N Group) and nivolumab plus radiation therapy (R Group). The N Group had 12 cases; 8 cases were men, and the median age was 73 years (range=58-87 years). Six of 12 received esophagectomy and lymphadenectomy. The R Group had 10 cases (8 cases received nivolumab plus radiation therapy at the same time, 2 cases received nivolumab therapy immediately after radiation therapy); 9 were men and the median age was 70 years (range=62-81 years). Seven of 10 were subjected to esophagectomy and lymphadenectomy. The treatment targets were primary lesion and metastases (lymph nodes, lungs, liver, bones). The histologic type was only squamous cell carcinoma. The primary evaluation examined the degree and frequency of adverse events. The adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0. The secondary evaluation comprised response rate and overall survival period.

Statistical analyses were performed using the χ^2 test, Student's *t*-test, Kaplan-Meier method, and log-rank test with SPSS (v25; IBM, Armonk, NY, USA). *p*-Values ≤0.05 were considered significant.

Table I. *Patient characteristics*.

Variable	N group (n=12)	R group (n=10)	*p*-Value
Age			
<70	7	5	
≥70	5	5	0.515
Sex			
Male	8	9	
Female	4	1	0.218
Previous surgery			
Yes	6	7	
No	6	3	0.305
Target organ			
Primary tumor	6	3	
Lymph nodes	5	7	
Lung	3	3	
Liver	2	1	
Bone	0	2	
Previous radiation therapy	6	0	0.009

N group: Nivolumab single treatment; R group: nivolumab plus radiation therapy.

Results

The adverse events of the patients are shown in Table II. In the N group, 1 case of grade 3 liver damage, 1 case of grade 4 cerebral hemorrhage, 2 cases of grade 1 hypothyroidism, 2 cases of grade 2 hypertension, 1 case of grade 3 diarrhea, and 1 case of grade 1 pruritus were observed. In the R group, 1 case of grade 5 liver failure, 2 cases of grade 2 adrenal insufficiency, 1 case of grade 2 adrenal insufficiency, 3 cases of grade 1 hypothyroidism, 3 cases of grade 2 hypothyroidism, 1 case of grade 3 glucose intolerance, 1 case of grade 1 myocarditis, and 1 case of grade 2 hypertension were observed.

As described above, adverse events were observed in 6 out of 12 subjects in the N group and 8 out of 10 subjects in the R group, and adverse events were significantly more frequent in the R group. Adverse events were significantly more common in the R group (p=0.035). However, there was no difference in grade 3 or higher adverse events (p=0.781). Adverse events were predominantly controllable (Table III).

In the N group, there were 1 case of complete response (CR), 4 cases of partial response (PR), 4 cases of stable disease (SD), and 3 cases of progressive disease (PD) among the evaluable lesions. In the R group, there were 6 PR, 2 SD, and 2 PD. There was no significant difference in treatment effect (Table IV).

There was also no significant difference in overall survival between the groups (Figure 1).

Discussion

Even if esophageal cancer is resected, there is a high risk of recurrence. Although the treatment results after recurrence have improved with the advancement of chemotherapy, they are still not satisfactory. 5FU/CDDP combination therapy (6, 7) and taxanes (8, 9) were expected to be effective, but there were no follow-up treatments of 5FU/CDDP combination therapy and taxanes. The ATTRACTION-1 study (10) showed the usefulness of nivolumab, and the ATTRACTION-3 study (2) made nivolumab second-line regimen for esophageal cancer treatment. And the treatment results have improved. In addition, studies such as CheckMate648 (3) and KEYNOTE-181 (4) have made it possible to use immune checkpoint inhibitors plus chemotherapy even in the first line. These treatment methods are expected to improve treatment results. The CheckMate648 study (3) reported that nivolumab plus chemotherapy increased adverse events but that percentages of patients who reported tolerance of treatment side effects over time with nivolumab plus chemotherapy were like those with chemotherapy alone.

At our institution, nivolumab alone was used until immune checkpoint inhibitors plus chemotherapy were recommended, and there were some cases in which radiotherapy was used in combination. We experienced a grade 5 adverse event when nivolumab was combined with radiotherapy. Therefore, we decided to examine the adverse events when nivolumab and radiation therapy were combined, retrospectively. Adverse events in the ATTRACTION1 trial were 63.1%, of which 20% were grade 3-4 (10). In the ATTRACTION3 study, adverse events were 65%, of which 18% were grade 3-4 (2). In this report, adverse events in the N group accounted for 50%, of which 25% were grade 3-4. Also, in the CheckMate648 trial, nivolumab plus chemotherapy had 96% adverse events, 47% of which were grade 3-4 (3). In this

Table II. *Treatment-related adverse events of all cases and radiotherapy dose in group R.*

Cases	No adverse events	Hepatobiliary disorders	Nervous system disorders	Adrenal insufficiency	Hypo-thyroidism	Glucose intolerance	Myocarditis	Hypertension	Diarrhea	Pruritus	Radiation (Gy)
N group											
1									Grade 3	Grade 1	
2	Yes							Grade 2			
3					Grade 1						
4					Grade 1						
5	Yes										
6			Grade 4								
7											
8		Grade 3									
9	Yes										
10								Grade 2			
11	Yes										
12	Yes										
R group											
1		Grade 5									46
2								Grade 2			50
3				Grade 1							56
4					Grade 2						39
5	Yes										59.4
6				Grade 2							30
7	Yes										54
8						Grade 3	Grade 1				60
9		Grade 2		Grade 1	Grade 2						54
10		Grade 2		Grade 1	Grade 2						60

N group: Nivolumab single treatment; R group: nivolumab plus radiation therapy.

Table III. *Treatment-related adverse events.*

Variable	N group	R group	*p*-Value
Any grades	6	8	0.035
Grade 3-5	3	2	0.781
Grade			
1	3*	4*	
2	1	7*	
3	2*	1*	
4	1	0	
5	0	1	

*There are duplicate cases. N group: Nivolumab single treatment; R group: nivolumab plus radiation therapy.

Table IV. *Patients' response to treatment.*

Variable	N group	R group	*p*-Value
Objective response rate			
≥SD	75%	70%	0.583
Best overall response			
CR	1	0	
PR	4	6	
SD	4	1	
PD	3	2	
Not evaluable	0	1	0.387

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease. N group: Nivolumab single treatment; R group: nivolumab plus radiation therapy.

report, the incidence of adverse events in the R group was 80% and grade 3-5 was 20%, which was considered lower than the frequency of grade 3-4 in the CheckMate648 study. We experienced a grade 5 liver failure, but in the CheckMate648 trial, 2% of patients with nivolumab plus chemotherapy died (3), which is not acceptable.

An analysis of the treatment of esophageal cancer using the Comprehensive Registry of Esophageal Cancer in Japan reports that there is no difference between the therapeutic effects of chemoradiotherapy at doses of 50.4 Gy and 60 Gy. However, adverse events have not been reported (11). Although there is a report that radiation therapy is relatively safe and effective for oligometastases, details of adverse events have not been described. Radiation therapy itself seems to have few adverse events immediately after the start of treatment. However, it is necessary to pay attention to late

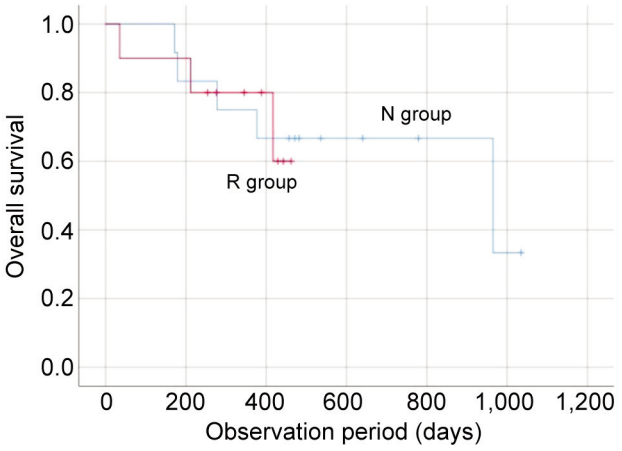

Figure 1. *There is no significant difference in overall survival between the Nivolumab single treatment (N) group and the Nivolumab plus radiation therapy (R) group (p=0.921).*

complications (5). Re-irradiation is an option of treatment for recurrent esophageal cancer patients with a history of radiotherapy. It has been reported that severe adverse events with grade 3 or higher were observed in 19.2% of patients who underwent re-radiotherapy for recurrence, and 7.7% of them had grade 5 adverse events (12). Although there were no cases of re-irradiation therapy in our case, late adverse events should be followed carefully.

The treatment effect of nivolumab monotherapy was reported in ATTRACTION-3, and the median survival time (MST), the primary endpoint, was 10.9 months (95%CI=9.2-13.3) in the Nivolumab group and 8.4 months in the chemotherapy group (95%CI=7.2-9.9), significantly prolonged in the nivolumab group (HR=0.77, 95%CI=0.62-0.96, p=0.019). The response rate in the nivolumab group was reported to be 1% for CR and 19% for PR, respectively (2). CheckMate648 compared the combination therapy of nivolumab and chemotherapy and reported CR and PR rates of 13% and 34% in combination therapy, respectively, for nivolumab and chemotherapy combination therapy (3). It can be observed that the combination therapy has a higher response rate compared to the nivolumab. The CR rate of chemoradiotherapy was reported to be 49.1% and 46.4%, respectively, in a comparative study with irradiation doses of 50.4 Gy and 60 Gy showing no difference (11). We hypothesize that the response rate may increase not only with the combination of nivolumab and chemotherapy, but also with the combination of radiotherapy.

In this study, the PR rate in the R group was higher than that in the N group, although there was no significant difference. It was expected that the combined use of immune checkpoint inhibitors and radiation therapy would have additive and synergistic effects, and we thought that additional effects could not be detected in a small number of cases. However, no survival benefit was obtained, but combination therapy has just begun and is currently being continued. We plan to investigate whether long-term treatment can extend the survival period.

This study has several limitations. First, this study had a small number of cases. Second, the present study is retrospective and was performed at a single institution. Third, the indication for nivolumab plus radiation depended on patient selection.

In conclusion, immune checkpoint inhibitors plus chemotherapy are now recommended. In this study, immune checkpoint inhibitors plus radiotherapy did not increase adverse events and, therefore, may be considered safe. They may become one of the options for the treatment of esophageal cancer in the future.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

Conception and design, and/or acquisition of data, and/or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of manuscript, accountable for all aspects of the work: All Authors.

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References

1 Sung H, Ferlay J, Siegel R, Laversanne M, Soerjomataram I, Jemal A, Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians 71(3): 209-249, 2021. DOI: 10.3322/caac.21660

2 Kato K, Cho B, Takahashi M, Okada M, Lin C, Chin K, Kadowaki S, Ahn M, Hamamoto Y, Doki Y, Yen C, Kubota Y, Kim S, Hsu C, Holtved E, Xynos I, Kodani M, Kitagawa Y: Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. The Lancet Oncology 20(11): 1506-1517, 2020. DOI: 10.1016/S1470-2045(19)30626-6

3 Doki Y, Ajani J, Kato K, Xu J, Wyrwicz L, Motoyama S, Ogata T, Kawakami H, Hsu C, Adenis A, El Hajbi F, Di Bartolomeo M, Braghiroli M, Holtved E, Ostoich S, Kim H, Ueno M, Mansoor W, Yang W, Liu T, Bridgewater J, Makino T, Xynos I, Liu X, Lei M, Kondo K, Patel A, Gricar J, Chau I, Kitagawa Y: Nivolumab combination therapy in advanced esophageal

squamous-cell carcinoma. New England Journal of Medicine 386(5): 449-462, 2022. DOI: 10.1056/NEJMoa2111380

4 Kojima T, Shah MA, Muro K, Francois E, Adenis A, Hsu CH, Doi T, Moriwaki T, Kim SB, Lee SH, Bennouna J, Kato K, Shen L, Enzinger P, Qin SK, Ferreira P, Chen J, Girotto G, de la Fouchardiere C, Senellart H, Al-Rajabi R, Lordick F, Wang R, Suryawanshi S, Bhagia P, Kang SP, Metges JP, KEYNOTE-181 Investigators: Randomized Phase III KEYNOTE-181 study of pembrolizumab *versus* chemotherapy in advanced esophageal cancer. J Clin Oncol 38(35): 4138-4148, 2020. DOI: 10.1200/JCO.20.01888

5 Matsushita H, Jingu K, Umezawa R, Yamamoto T, Ishikawa Y, Takahashi N, Katagiri Y, Kadoya N: Stereotactic radiotherapy for oligometastases in lymph nodes-a review. Technology in Cancer Research & Treatment 17: 153303381880359, 2020. DOI: 10.1177/1533033818803597

6 Takashima A, Shirao K, Hirashima Y, Takahari D, Okita N, Akatsuka S, Nakajima T, Matsubara J, Yasui H, Asakawa T, Kato K, Hamguchi T, Muro K, Yamada Y, Shimada Y: Chemosensitivity of patients with recurrent esophageal cancer receiving perioperative chemotherapy. Diseases of the Esophagus 21(7): 607-611, 2019. DOI: 10.1111/j.1442-2050.2008.00821.x

7 Okunaka M, Kotani D, Demachi K, Fujiwara H, Sakashita S, Yoshino T, Fujita T, Kojima T: Significance of chemotherapy-free interval and tumor regression grade in patients with recurrent esophageal squamous cell carcinoma receiving chemotherapy with fluorouracil and platinum after esophagectomy following preoperative chemotherapy. Esophagus 19(2): 240-249, 2022. DOI: 10.1007/s10388-021-00885-3

8 Shirakawa T, Kato K, Nagashima K, Nishikawa A, Sawada R, Takahashi N, Shoji H, Sasaki Y, Honma Y, Iwasa S, Takashima A, Okita N, Hamaguchi T, Yamada Y, Shimada Y: A retrospective study of docetaxel or paclitaxel in patients with advanced or recurrent esophageal squamous cell carcinoma who previously received fluoropyrimidine- and platinum-based chemotherapy. Cancer Chemotherapy and Pharmacology 74(6): 1207-1215, 2019. DOI: 10.1007/s00280-014-2597-3

9 Mizota A, Shitara K, Kondo C, Nomura M, Yokota T, Takahari D, Ura T, Muro K: A retrospective comparison of docetaxel and paclitaxel for patients with advanced or recurrent esophageal cancer who previously received platinum-based chemotherapy. Oncology 81(3-4): 237-242, 2022. DOI: 10.1159/000334057

10 Satoh T, Kato K, Ura T, Hamamoto Y, Kojima T, Tsushima T, Hironaka S, Hara H, Iwasa S, Muro K, Yasui H, Minashi K, Yamaguchi K, Ohtsu A, Doki Y, Matsumura Y, Kitagawa Y: Five-year follow-up of nivolumab treatment in Japanese patients with esophageal squamous-cell carcinoma (ATTRACTION-1/ONO-4538-07). Esophagus 18(4): 835-843, 2021. DOI: 10.1007/s10388-021-00850-0

11 Nemoto K, Kawashiro S, Toh Y, Numasaki H, Tachimori Y, Uno T, Jingu K, Matsubara H: Comparison of the effects of radiotherapy doses of 50.4Â Gy and 60Â Gy on outcomes of chemoradiotherapy for thoracic esophageal cancer: subgroup analysis based on the Comprehensive Registry of Esophageal Cancer in Japan from 2009 to 2011 by the Japan Esophageal Society. Esophagus 17(2): 122-126, 2021. DOI: 10.1007/s10388-019-00711-x

12 Takeda K, Matsushita H, Umezawa R, Yamamoto T, Ishikawa Y, Takahashi N, Suzuki Y, Jingu K: Hyperfractionated radiotherapy for re-irradiation of recurrent esophageal cancer. Radiation Oncology Journal 39(4): 265-269, 2021. DOI: 10.3857/roj.2021.00325

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