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Development of Second Primary Malignancies in Long-term Survivors of Unresectable Esophageal Cancer

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Abstract

Background/Aim: The recent advent of immunotherapy has improved long-term survival in patients with unresectable esophageal cancer. However, second primary malignancies (SPMs) are expected to develop in these patients. We investigated the incidence of SPMs in patients with unresectable advanced esophageal cancer.

Patients and Methods: We retrospectively reviewed the records of patients with unresectable esophageal cancer, including those with locally advanced and metastatic disease, who were treated at the Kindai University Hospital between 2016 and 2022. The incidence of SPMs was determined among long-term survivors. The cumulative incidence of SPMs was estimated using the Gray subdistribution method, treating death as a competing risk.

Results: Among the 211 patients with unresectable esophageal cancer, 45 (21%) met the criteria for long-term survival. Five (11%) were diagnosed with SPMs after a median follow-up of 3.7 years. The cumulative incidences of SPMs after 3, 5, and 8 years were 7, 10, and 14%, respectively. The types of SPMs included diffuse large B-cell lymphoma and urothelial, lung, prostate, and thyroid cancers. All SPMs were cured with definitive treatment, and no deaths were attributed to them.

Conclusion: Even among patients with unresectable esophageal cancer**,** long-term survivors had a measurable rate of SPMs. This highlights the importance of post-treatment surveillance for SPMs.

Keywords: Esophageal cancer, second primary malignancy, immune checkpoint inhibitors, long-term survivor.

Introduction

Esophageal cancer accounts for 3.1% of all cancers, and it is the eighth most frequently diagnosed cancer that affects 604,000 individuals globally. This number is expected to increase to >957,000 by 2040 due to population aging and changes in lifestyle habits (1). The two major histological subtypes of esophageal cancer are squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma predominates in East Asian countries, accounting for

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approximately 90% of esophageal cancer cases in the region, which includes Japan (2). The established risk factors for esophageal squamous cell carcinoma include excessive alcohol consumption and tobacco smoking, which are also associated with several other malignancies (2, 3). Multiple primary malignancies are often detected at the time of diagnosis of esophageal cancer, and thorough screening for multi-organ malignancies is recommended (4).

Beyond synchronous tumors, second primary malignancies (SPMs) that develop following definitive esophageal cancer treatment are a major concern, especially for patients with early-stage disease (5, 6). Previous reports have suggested that patients with early-stage cancer are more likely to develop SPMs (7, 8). The incidence of SPM among patients with stage 0-I disease was 9, 15, and 36% at 3, 5, and 10 years, respectively, in a prospective JCOG0502 trial comparing surgical resection with definitive chemoradiotherapy for clinical T1bN0 esophageal cancer (7). This finding suggests that patients with early-stage disease who survive long-term have an increased risk of developing SPMs during prolonged follow-up. Another study reported that the incidence of SPM among patients with stage IV disease was 0% due to poor prognosis, and the median survival duration was approximately one year (8).

The recent emergence of immune checkpoint inhibitors has led to a paradigm shift in the use of systemic chemotherapy for solid tumors. The KEYNOTE-590 trial demonstrated improved overall survival with the addition of pembrolizumab to conventional chemotherapy for metastatic esophageal cancer (9). In addition, the CheckMate-648 trial demonstrated the superiority of nivolumab plus ipilimumab and nivolumab plus chemotherapy to conventional chemotherapy (10). Tislelizumab, sintilimab, and camrelizumab have been shown to prolong survival (11-13). Immunotherapy provides a durable response that results in the long-term survival of patients with metastatic esophageal cancer. Ongoing trials are evaluating the potential of immunotherapy in patients with locally advanced disease (14, 15). Given the expanding therapeutic landscape and improved prognoses, patients with metastatic or locally advanced esophageal cancer and those with early-stage disease may have similar risks of developing SPMs. However, SPMs have not been investigated for this entity, likely due to the limited survival duration. This study aimed to clarify the incidence and clinicopathological characteristics of SPMs in patients with unresectable esophageal cancer and their implications for post-treatment monitoring and comprehensive cancer care. We hypothesized that the incidence of SPMs is elevated among patients with unresectable esophageal cancer, especially long-term cancer survivors.

Patients and Methods

Study population. We retrospectively reviewed a computerized database of patients with esophageal cancer treated at the Kindai University Hospital between 2016 and 2022. The inclusion criteria were as follows: i) histologically confirmed esophageal cancer (regardless of subtype), ii) locally advanced or metastatic disease that was determined to be unresectable by a multidisciplinary tumor board at the time of diagnosis, and iii) no history of primary or synchronous malignancies in other organs at the time of diagnosis.

In this study, we focused on patients who survived for >2 years following the initiation of treatment; they were designated as "long-term survivors". SPMs were defined as newly diagnosed primary malignancies arising at anatomical sites, other than the esophagus, that were histologically distinct from the initial esophageal cancer. Cancers diagnosed within six months of the initiation of treatment for esophageal cancer were excluded from the SPM analysis to rule out synchronous malignancies or preexisting lesions.

This study was conducted in accordance with the ethical standards of the Institutional and National Research Committee and the 1964 Helsinki Declaration and its later amendments. The study protocol was approved by the Institutional Review Board of Kindai

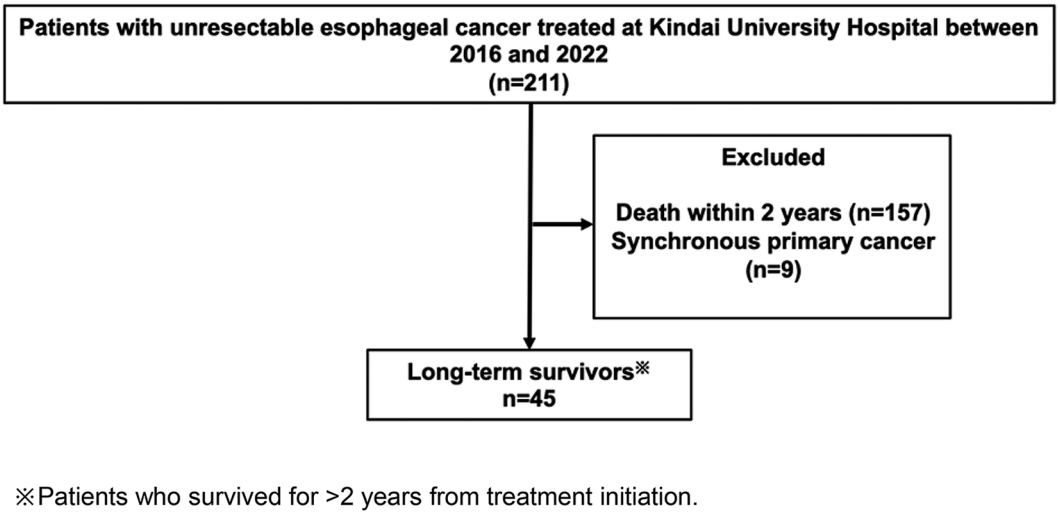

Figure 1. *Study flow chart.*

University Hospital (R07-082). All patients provided informed consent.

Data extraction. Patient characteristics were extracted from the medical records from the initial visit to our department. Brinkman Indices ≥100 indicated a history of smoking. Habitual alcohol consumption was defined as a daily intake of ≥60 g of ethanol. The clinical stage was determined according to the 8th edition of the Union for International Cancer Control. The follow-up duration was calculated from the date of esophageal cancer diagnosis to the date of death from any cause or the date of the last examination.

Statistical analysis. The primary outcome was the cumulative incidence of SPMs among long-term survivors. The cumulative incidence function was estimated using the Gray sub distribution framework, treating death as a competing risk. Analyses were performed using R version 4.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics. Initially, we enrolled 211 patients with metastatic or locally advanced esophageal cancer who were treated at the Kindai University Hospital. We excluded 157 patients who died or were lost to follow-up within two years and nine patients with synchronous primary cancer or a history of cancer at the time of initial diagnosis; 45 patients were retained as long-term survivors (Figure 1).

Table I summarizes the characteristics of long-term survivors. Men (71%), smokers (82%), habitual alcohol consumers (67%), and those with metastatic disease (69%) or squamous cell carcinoma (93%) were predominant. Chemotherapy, radiotherapy, and surgery were administered to 98, 69, and 27% of patients, respectively. Immune checkpoint inhibitors were used to treat 18% of the patients.

Cumulative incidence of SPMs. Five SPMs developed in five patients (11%) followed up for a median duration of 3.7 years (range=2.1-8.4). The clinical characteristics of the patients who developed SPMs are summarized in Table II. The types of SPMs included diffuse large B-cell lymphoma and urothelial, lung, prostate, and thyroid cancers. The median duration from the start of treatment to SPMs onset was 2.8 years (range=1.3-6.5). All patients with SPMs except for Case 2 were asymptomatic, and the SPMs were detected during routine follow-up for esophageal cancer. Case 2 presented with hematuria, and abdominal computed tomography (CT) revealed a ureteral lesion accompanied

Table I. *Characteristics of the 45 patients with metastatic or locally advanced esophageal cancer.*

Variable	n (%)
Age*, years	68 (47-80)
Sex	
Male	32 (71)
Female	13 (29)
Primary tumor location in the esophagus	
Ce	9 (20)
Ut	10 (22)
Mt	16 (36)
Lt	10 (22)
History of smoking	
Yes	37 (82)
No	8 (18)
History of habitual alcohol consumption	
Yes	30 (67)
No	15 (33)
Length of primary tumor	
<4 cm	8 (18)
≥4 cm	37 (82)
Disease status	
Locally advanced	14 (31)
Metastatic	31 (69)
Histology	
Squamous cell carcinoma	42 (93)
Adenocarcinoma	2 (4)
Neuroendocrine carcinoma	1 (2)
Treatment modality	
Chemotherapy	44 (98)
Surgery	12 (27)
Radiotherapy	31 (69)

Ce: Cervical esophagus; Ut: upper thoracic esophagus; Mt: middle thoracic esophagus; Lt: lower thoracic esophagus. *Values represent median (range).

by renal pelvic dilatation. Renal metastasis from esophageal cancer is rare. Therefore, surgical resection was performed, and histopathological examination confirmed urothelial carcinoma. For Case 3, a pulmonary nodule was identified and histologically confirmed as an adenocarcinoma distinct from the primary malignancy, leading to the diagnosis of SPMs. The cumulative incidences of SPMs for all organs after 3, 5, and 8 years were 7% [95% confidence interval (CI)=0.018-0.167], 10% (95% CI=0.030-0.207), and 14% (95% CI=0.048-0.273), respectively (Figure 2). All SPMs were cured with definitive treatment; however, three of the five patients (60%) died due to progression of the esophageal cancer.

Discussion

We determined the incidence and clinicopathological characteristics of SPMs in patients with unresectable esophageal cancer to inform post-treatment monitoring and comprehensive cancer care. The cumulative SPM incidences among the long-term survivors of unresectable esophageal cancer were 7, 10, and 14% at 3, 5, and 8 years, respectively.

Recent advances in systemic therapies for esophageal cancer have led to the long-term survival of more patients. However, this positive development has increased attention to the emergence of SPMs, which have become a significant clinical concern during extended follow-up. Cisplatin plus fluorouracil therapy is traditionally considered the standard treatment regimen, and several phase II trials have reported a median overall survival duration of 6.6-9.5 months (16-18). Immune checkpoint inhibitors have extended overall survival to 12.4-16.7 months. Overall survival has been further extended to 13.9-17.2 months for patients with PD-L1 expression or a combined positive score ≥10 (9-11). In addition to their attributed durable response, immune checkpoint inhibitors enhance tumor shrinkage when combined with chemotherapy. This can increase the likelihood of curative conversion surgery and contribute to the increasing long-term survivors (19, 20). The new therapeutic strategies of conversion surgery were used in two of the five patients who developed SPMs in the current study.

Sato *et al*. reported that SPMs were the most common causes of death in patients with esophageal cancer whose initial surgically resected lymph nodes histopathology revealed no malignancy (6). However, none of the patients in the present study died from SPMs. This outcome likely resulted from routine imaging (such as CT) performed to assess treatment efficacy, which facilitated the early detection of SPMs. However, a differential diagnosis of esophageal cancer metastasis and SPM was established in two cases (Cases 2 and 3). Surgical resection confirmed the diagnosis of SPM. The misdiagnosis of esophageal cancer metastasis may have worsened the prognosis in

Table II. *Characteristics of the patients who developed second primary malignancies.*

Case	Esophageal cancer stage	Pathological type	Treatment of esophageal cancer	Use of immuno-therapy	SPM type	SPM stage	Period from treatment initiation to SPM onset (years)	Treatment of SPM	Cause of death
1	IV A	SCC	Chemoradiotherapy	No	Diffuse large B-cell lymphoma	I*	6.5	Surgery	Esophageal cancer
2	IV B	Ad	Radiotherapy (palliative radiation to bone metastasis) Chemotherapy	Yes	Urothelial cancer	III	3.0	Surgery	Esophageal cancer
3	IV A	SCC	Chemoradiotherapy	No	Lung adenocarcinoma	I	2.8	Radiotherapy	Alive
4	IV A	SCC	Chemotherapy Surgery (conversion surgery) Chemoradiotherapy (definitive chemoradiotherapy to local recurrence)	No	Prostate cancer	III	1.3	Surgery	Alive
5	IV A	SCC	Chemotherapy Surgery (conversion surgery) Chemotherapy Radiotherapy (whole brain radiotherapy to brain metastasis)	Yes	Thyroid cancer	II	2.3	Surgery	Esophageal cancer

SCC: Squamous cell carcinoma; Ad: adenocarcinoma; SPM: second primary malignancy. *Lugano International Conference classification.

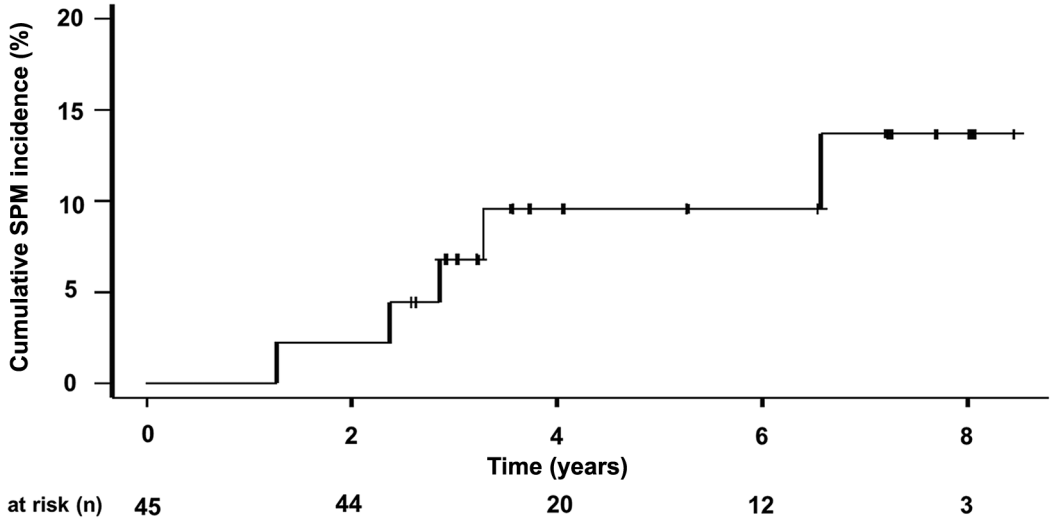

Figure 2. *Cumulative incidence of second primary malignancies (SPM).*

these two cases. This finding emphasizes the need for a histological diagnosis when considering worsening of unresectable primary esophageal cancer and SPM.

In our cohort, all patients who developed second primary malignancies had previously received radiotherapy as part of their treatment for esophageal cancer. Although

a causal relationship cannot be established, prior exposure to radiotherapy may have contributed to the development of SPMs in these patients. Previous studies have reported an increased risk of second primary malignancies following external beam radiotherapy, suggesting a potential association between radiation exposure and subsequent carcinogenesis (21, 22).

Several recent studies have reported increased incidences of hematological malignancies associated with immune checkpoint inhibitors (23, 24). However, hematological malignancy as an SPM developed in a patient who did not receive immune checkpoint inhibitors in our study. No association was observed between immunotherapy and hematological malignancies. However, further investigations of the incidence of SPMs after immunotherapy are warranted.

Limitations. First, it was a single-center retrospective study with a small sample size. Future prospective, multicenter studies with larger patient populations are warranted to validate our findings. Second, patients with squamous cell carcinoma were predominantly enrolled, which restricts the generalizability of our findings. Finally, the incidence of SPMs may have been underestimated due to limited surveillance. To date, SPMs in patients with advanced esophageal cancer have not attracted much attention, and the need for surveillance has not been fully recognized. As a result, surveillance may have been insufficient, leading to a possible underestimation of the incidence of SPMs. Indeed, previous reports have shown higher frequencies of head and neck cancer or gastric cancer as SPMs, suggesting that endoscopic examinations and otolaryngologic screening might not have been adequately performed in the current cohort. In addition, the progression of esophageal cancer may have precluded thorough evaluations for other malignancies. Despite these limitations, our study is the first to investigate the risk of SPMs in patients with unresectable esophageal cancer.

Conclusion

A relatively high proportion (11%) of long-term survivors of unresectable esophageal cancer in our cohort developed SPMs. Attention should be paid to the risk of development of SPMs among long-term survivors of esophageal cancer, even for unresectable cases with generally poor prognosis. Therefore, optimal surveillance strategies are needed.

Conflicts of Interest

Ryotaro Watanabe, Masaki Okura, and Tsutomu Iwasa declare that they have no conflict of interest. Seiichiro Mitani has received grants or contracts from Caris Life Sciences; payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Taiho Pharmaceutical Co., Ltd., MSD K.K., Ono Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Bristol-Myers Squibb Co. Ltd., and Daiichi Sankyo Co., Ltd.; and has participated on a Data Safety Monitoring Board or Advisory Board for Chugai Pharmaceutical Co., Ltd. Chiaki Inagaki has received personal honoraria as an invited speaker from Astellas Pharma Inc., Chugai Pharmaceutical Co., Ltd., MSD K.K., Ono Pharmaceutical Co., Ltd., and Taiho Pharmaceutical Co., Ltd.; holds personal stocks or shares in Daiichi Sankyo Co., Ltd. and Eisai Co., Ltd.; and has received institutional funding with no financial interest from Astellas Pharma Inc., Eisai Co., Ltd., and Ono Pharmaceutical Co., Ltd. Junko Tanizaki has received payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from AstraZeneca K.K., AbbVie GK, Boehringer Ingelheim Japan Inc., Bristol-Myers Squibb Co. Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eli Lilly Japan K.K., Janssen Pharmaceutical K.K., MSD K.K., Ono Pharmaceutical Co., Ltd., Pfizer Japan Inc., Taiho Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Co., Ltd.; and has participated on a Data Safety Monitoring Board or Advisory Board for AstraZeneca K.K., AbbVie GK, Chugai Pharmaceutical Co., Ltd., and Janssen Pharmaceutical K.K.

Kaoru Tanaka has received payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from AstraZeneca K.K., MSD K.K., Eisai Co., Ltd., Bristol-Myers Squibb Co. Ltd., Ono Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., Chugai

Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Novartis Pharma K.K., and Janssen Pharmaceutical K.K. Kimio Yonesaka has received grants or contracts from Daiichi Sankyo Co., Ltd. and Boehringer Ingelheim Japan Inc.; royalties or licenses from Daiichi Sankyo Co., Ltd.; consulting fees from Boehringer Ingelheim Japan Inc.; payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Amgen K.K., Chugai Pharmaceutical Co., Ltd., AstraZeneca K.K., Eli Lilly Japan K.K., Takeda Pharmaceutical Co., Ltd., MSD K.K., and Pfizer Japan Inc.; and holds patents planned, issued, or pending (US20200115467 and US20200061031).

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Authors' Contributions

All Authors contributed to the study conception and design. Material preparation and data collection were performed by Ryotaro Watanabe, Seiichiro Mitani, Masaki Okura, Chiaki Inagaki, Junko Tanizaki, Kaoru Tanaka, Tsutomu Iwasa, Kimio Yonesaka, and Hidetoshi Hayashi. Data analysis was conducted by Ryotaro Watanabe and Seiichiro Mitani. The first draft of the manuscript was written by Ryotaro Watanabe, and all authors commented on previous versions of the manuscript. All Authors read and approved the final manuscript.

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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