Second primary malignancies in patients with clinical T1bN0 esophageal squamous cell carcinoma after definitive therapies: supplementary analysis of the JCOG trial: JCOG0502

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Abstract

Background Previous studies have suggested that patients with esophageal squamous cell carcinoma (ESCC) are still at a high risk of developing second primary malignancies (SPMs) after definitive therapies. We evaluated the development of SPMs and explored its risk factors in patients with clinical T1bN0 ESCC.

Methods JCOG0502 prospectively compared esophagectomy with definitive chemo-radiotherapy for clinical T1bN0 ESCC. Here, we reviewed all JCOG0502 patients’ data for SPMs and investigated the risk factors for SPMs using uni-variable and multivariable analyses by Fine and Gray model.

Results Among 379 enrolled patients, 213 underwent esophagectomy and 166 received chemo-radiotherapy. Patient characteristics were male (85%); median age [63 (range 41–75) years; location of the primary tumor (upper/
middle/lower thoracic esophagus, 11%/63%/27%, respectively); alcohol consumption history (79%); smoking history (66%); prevalence of no/several/many/unknown Lugol-voiding lesions (LVLs) (45%/36%/8%/11%, respectively). In a median follow-up of 7.1 years, 118 SPMs occurred in 99 (26%) patients. Cumulative incidences of SPMs after 3, 5, and 10 years were 9%, 15%, and 36%, respectively. The most common primary tumor sites were the head and neck (35%), stomach (20%) and lungs (14%). In multivariable analyses, compared to no LVLs, several LVLs [hazard ratio (HR) 2.24, 95% confidential interval (CI) 1.32–3.81] and many LVLs (HR 2.88, 95% CI 1.27–6.52) were significantly associated with the development of SPMs. Sixteen patients died due to the SPMs. The presence of LVLs, which was a predictive factor for SPMs, may be useful for surveillance planning.

Keywords Esophageal cancer · Second malignancies · Esophagectomy · Definitive chemoradiotherapy

Introduction

Esophageal cancer is one of the most fatal diseases worldwide, mainly because of its high-grade malignancy [1]. In Asia, squamous cell carcinoma is the predominant histological type of esophageal cancer [2, 3]. Multiple squamous cell carcinomas frequently arise in the upper aero-digestive tract. The carcinogenic effects of tobacco and alcohol on the other parts of the aero-digestive tract, lead to the frequent occurrence of simultaneous or metachronous cancer development, particularly in the head and neck region and esophagus. This phenomenon is referred to as “field cancerization” [4, 5]. Thus, as recommended in guidelines, screening for double cancer should be performed during pretreatment examination of esophageal cancer [6]. In addition, several studies have suggested a remaining risk of second primary malignancies (SPMs) even after the completion of treatment for esophageal cancer. Several retrospective studies enrolled patients with esophageal cancer who underwent esophagectomy or received definitive chemo-radiotherapy, and demonstrated a high mortality following the development of SPMs [7–10]. Pooled analyses of multiple cancer registries and a population-based study surveying a large cohort of patients with esophageal cancer reported a significantly increased risk of developing metachronous SPMs [11–13].

We previously conducted a retrospective analysis of 758 patients with esophageal cancer and found an increased incidence of SPMs in patients with esophageal cancer even after definitive treatment [14]. Furthermore, early clinical stage was identified as a significant factor for the incidence of SPMs. This can be explained by the fact that SPMs can occur during a longer survival period in patients with early-stage cancers because recent advances in multimodal treatment strategies have contributed to the increased survival rate. Therefore, there is need for special attention regarding the possibility of SPMs developing in patients with early-stage esophageal cancer. However, the above-mentioned previous studies might have underestimated the incidence of SPMs due to the retrospective nature of the study. In addition, the risk of SPMs after treatment for early-stage esophageal cancer has not been fully investigated because most esophageal cancers are detected in the advanced stage. Smoking and alcohol consumption are well-known risk factors for the development of esophageal squamous cell carcinoma (ESCC) and head and neck cancers [15–17]. High-grade dysplasia and squamous cell carcinoma lack glycogen, are visible as void of Lugol staining in chromo-endoscopy, following iodine dye staining. The visible pattern of Lugol-voiding lesions (LVLs) can serve as an indicator of the risk of both esophageal cancer and head and neck cancers [18–20]. LVLs were also reported to be useful to predict the development of SPMs [19, 21]. We hypothesized that these risk factors are also associated with the incidence of SPMs.

JCOG0502, a multicenter phase III trial, compared esophagectomy with definitive chemoradiotherapy in clinical T1bN0 ESCC [22]. This trial enrolled and prospectively examined 379 patients, to show the non-inferiority of chemoradiotherapy compared with surgical resection. The objective of the present study was to evaluate the development of SPMs and explore its risk factors in patients with clinical T1bN0 ESCC using prospective data from JCOG0502.

Methods

Study design and patients

The details of JCOG0502 have been described elsewhere [22]. The main eligibility criteria were as follows: (1) histologically proven thoracic esophageal squamous cell, adeno-squamous or basaloid cell carcinoma; (2) clinical stage T1bN0M0 based on the 7th UICC-TNM classification; (3) age from 20 to 75 years; (4) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; (5) no prior therapy for esophageal cancer; (6) adequate organ function; and (7) without sever comorbidities. Screening tests for other active malignancies were conducted using upper endoscopy, computed tomography (CT) scans. Positron emission tomography or otolaryngological examination was not mandatory and performed according to investigator’s choice. All patients were informed of the randomized nature of the study. Only when patients refused...
randomization and consented to non-randomized parts of the trial, they were assigned to surgery or chemo-radiotherapy, as the patients and their oncology team decided. Esophagectomy with 2- or 3-field lymph node dissection was performed in the surgical arm. In the chemo-radiotherapy arm, cisplatin 70 mg/m² (days 1 and 29) and 5-fluorouracil 700 mg/m²/day (days 1–4, 29–32) combined with 60 Gy/30 fr radiotherapy were delivered. Written informed consent was obtained from all the patients prior to enrollment. The study protocol of the trial was approved by the institutional review boards of all institutions. The study was conducted in accordance with the principles of the Helsinki Declaration of 1964 and its later amendments and registered in the clinical trial database (UMIN000000551). Using data from all patients enrolled in JCOG0502, we performed additional analyses for SPMs.

**Follow-up protocol**

In the surgical arm, CT scans and tumor marker testing, such as carcinoembryonic antigen and squamous cell carcinoma antigen testing, were performed every 3 months in the first year, every 4 months in the second year, and every 6 months in the third, fourth, and fifth years after completion of surgical resection. Esophagogastroduodenoscopy was performed at the discretion of the investigators. In the chemo-radiotherapy arm, endoscopic examination was mandatory in addition to tumor marker testing, in similar time intervals as CT scan.

**Definitions and statistical considerations**

SPMs were defined as malignancies developing in organs other than the esophagus after enrollment in JCOG0502. SPMs in the esophagus were excluded from this study. Patient characteristics, such as age, body mass index (BMI), history of smoking, and alcohol use, were based on data at the time of enrollment in JCOG0502. LVLs were assessed in the noncancerous esophageal mucosa using electronic images of endoscopic examinations before the initiation of treatment. Three experienced endoscopists who were blinded to the clinical data reviewed the images centrally. Lugol-voiding pattern was graded according to the maximum number of small LVLs in at least one endoscopic field of view as follows: grades A, B, and C referred to no; several (1 to 9); and many (≥10) small LVLs, respectively [19].

The cumulative incidence function for SPMs was estimated using death as a competing risk. Since mortality affects the occurrence of SPMs and can be a competing risk, uni-variable and multivariable analyses using the Fine and Gray model were performed to investigate the risk factors for SPMs [23]. The hazard ratio (HR) and its 95% confidence interval (CI) were calculated. From a clinical standpoint, the following 10 variables were selected: age (≥65 vs. <65 years), sex (male vs. female), ECOG-PS (0 vs. 1), BMI (≥25 vs. <25 sq/m²), history of alcohol consumption (no vs. 0–25 mL of ethanol per day vs. vs. ≥25 mL of ethanol per day), history of smoking (no vs. 1–20 cigarette per day vs. ≥20 cigarette per day), LVLs (grade A vs. B vs. C), location of the primary tumor (upper thoracic esophagus vs. middle thoracic esophagus or lower thoracic esophagus), primary tumor length (≥4 vs. <4 cm), and study treatment arm (surgery vs. chemo-radiotherapy). The cut-off value of BMI was determined according to World Health Organization (WHO) criteria, and the cut-off values of alcohol consumption and smoking were set based on previous reports [24, 25]. All tests were two-sided, and a p value <0.05 was considered statistically significant. In the case of using a variable selection procedure, backward elimination method with a p value <0.10 was used in multivariable analyses. Statistical Analysis Software (SAS) version 9.4 (SAS Institute, Cary, NC) was used for all statistical analyses.

**Results**

**Patient characteristics**

A total of 379 patients were registered in the JCOG0502 between December 2006 and February 2013. The median observation time was 7.1 years (range 0.0–11.0 years). The patient backgrounds are summarized in Table 1. The median age was 63 years (range, 41–75 years), and 323 (85%) patients were male. Among the randomized patients, four were assigned to surgery (Cohort A) and seven to chemo-radiotherapy (Cohort B). Regarding the patient-preference arm, 209 and 159 underwent surgery (Cohort C) and chemo-radiotherapy (Cohort D), respectively. Information on history of alcohol or smoking, or prevalence of LVLs was not obtained from all patients since these were not mandatory investigational items at the time of enrollment.

**Incidences of SPMs**

A total of 118 SPMs were observed in 99 (26%) patients. Cumulative incidences after 3, 5, and 10 years were 9.0% (95% CI: 6.4–12.2); 14.7% (95% CI: 11.3–18.5); and 36.1% (95% CI: 28.9–43.5), respectively (Fig. 1). The most common primary tumor sites were the head and neck including five thyroid cancers (n = 41), stomach (n = 24), lung (n = 17), urinary tract (n = 10), colon and rectum (n = 9), pancreas (n = 3), liver (n = 3), and leukemia (n = 3) (Table 2). Cumulative incidences of head and neck...
cancers after 3, 5, and 10 years were 3.7% (95% CI 2.1–6.0), 5.3% (95% CI 3.4–7.9), and 11.5% (95% CI 7.9–15.8), respectively.

Among head and neck cancers (excluding thyroid cancer), 29 (81%), 4 (11%), and 2 (6%) were detected at endoscopic examination, CT scan, and regular otolaryngological examination, respectively. The development of tumor-related symptoms triggered the detection of only one case of head and neck cancer. Consequently, 26 (72%), 8 (22%), and 2 (6%) cancers were diagnosed with clinical stages 0–I, II–III, and IV, respectively. All stomach cancers were detected at endoscopic examination and with clinical stages 0–I. Among lung cancers, 14 (93%) were detected by CT scans. The remaining one (7%) developed symptoms and was diagnosed with lung cancer. Ten (67%), four (27%), and one (7%) cancer cases were diagnosed with clinical stages 0–I, II–III, and IV, respectively.

### Table 1 Patient characteristics

| Characteristics                                      | Patients (n = 379) |
|-------------------------------------------------------|--------------------|
| Age, years                                            | Median (range) 63 (41–75) |
| Sex                                                   | Male 323 (85%) |
|                                                       | Female 56 (15%) |
| Primary tumor location in the esophagus               | Upper thoracic esophagus 41 (11%) |
|                                                       | Middle thoracic esophagus 237 (63%) |
|                                                       | Lower thoracic esophagus 101 (27%) |
| Body mass index, sq/m²                                 | < 25 306 (81%) |
|                                                       | ≥ 25 73 (19%) |
| History of smoking                                    | Yes 251 (66%) |
|                                                       | No 119 (31%) |
|                                                       | Unknown 9 (2%) |
| History of alcohol consumption                         | Yes 300 (79%) |
|                                                       | No 48 (13%) |
|                                                       | Unknown 31 (8%) |
| LVLs                                                  | A 170 (45%) |
|                                                       | B 136 (36%) |
|                                                       | C 30 (8%) |
|                                                       | Unknown 43 (11%) |
| Length of primary tumor                                | < 4 cm 253 (67%) |
|                                                       | ≥ 4 cm 126 (33%) |
| Treatment modality                                    | Esophagectomy 213 (56%) |
|                                                       | Chemo-radiotherapy 166 (44%) |

### Table 2 Site of second primary malignancies

| Site of second primary malignancies | n (%)<sup>a</sup> |
|-------------------------------------|-------------------|
| Head and neck                       | 41 (35%)          |
| Stomach                             | 24 (20%)          |
| Lung                                | 17 (14%)          |
| Urinary tract                       | 10 (9%)           |
| Colorectal                          | 9 (8%)            |
| Pancreas                            | 3 (3%)            |
| Liver                               | 3 (3%)            |
| Leukemia                            | 3 (3%)            |
| Others                              | 8 (7%)            |

<sup>a</sup>Of the denominator was 118 sites (in 99 patients with second primary malignancies)

### Fig. 1 Cumulative incidence of second malignancies
Death due to SPMs

Sixteen patients died due to SPMs. Among the five most common types of SPMs, there were four and two deaths due to head and neck and lung cancers, respectively. However, there was no death following stomach cancer. Three, two, and one death occurred among patients with pancreatic cancer; leukemia; and myelodysplastic syndrome, colorectal cancer, tracheal cancer, breast cancer, and renal pelvis cancer, respectively.

Clinicopathological factors predicting the development of SPMs

The results of SPM risk analysis are presented in Table 3. Among 284 patients who had no missing data regarding the baseline background, both uni-variable and multivariable analyses revealed that the presence of LVLs was significantly associated with the development of SPMs. In the multivariable analysis, compared with no LVLs the HRs of several and many LVLs were 2.24 (95% CI 1.32–3.81) and 2.88 (95% CI 1.27–6.52), respectively. Multivariable analyses including all 379 patients were also conducted by analyzing missing data as a factor of missing value, which showed that compared to no LVLs, several (HR: 2.01, 95% CI 1.25–3.22) and many LVLs (HR: 2.44, 95% CI 1.13–5.25) were significant factors (Supplementary Table 1). Furthermore, a variable selection procedure also reproduced the results which revealed that the pattern of LVLs was significant (Supplementary Table 2). According to the grade of LVLs (A vs. B vs. C), the cumulative incidences of SPMs after 3, 5, and 10 years were 4.1% (95% CI 1.8–7.9) vs. 11.9% (95% CI 7.1–18.0) vs. 13.3% (95% CI 4.1–28.1); 7.2% (95% CI 3.9–11.7) vs. 20.0% (95% CI 13.7–27.2) vs. 26.7% (95% CI 12.3–43.4); and 31.2% (95% CI 19.7–43.4) vs. 41.2% (95% CI 31.0–51.1) vs. 33.9% (95% CI 17.4–51.2), respectively (Supplementary Fig. 1).

The association between SPMs and LVLs was observed in head and neck cancer (Supplementary Table 3). In the multivariable analysis including 284 patients whose baseline background data were not missing, compared to no LVLs, the HRs of several and many LVLs were 8.92 (95% CI 2.49–32.02) and 18.97 (95% CI 3.86–93.17), respectively. Meanwhile, the risk of other malignancies, such as gastric and lung cancers, did not increase in patients with LVLs (Supplementary Table 4). Interestingly, gastric cancer occurred more frequently in the chemo-radio-therapy arm (4% vs. 10%, HR 2.78, 95% CI 1.20–6.42).

Discussion

This study investigated the development of SPMs in patients with clinical T1bN0 ESCC who were enrolled in JCOG0502. To the best of our knowledge, this is the first study to evaluate a second cancer incidence in esophageal cancer patients who underwent surgery or chemo-radiotherapy using data from a study where the patients were prospectively followed up according to a protocol-specified schedule. Although the Japanese Esophageal Cohort (JEC) study also evaluated SPMs in a prospective setting, patients with esophageal cancer who were treated with endoscopic resection were included [19, 21]. Besides, our study had a larger sample size and longer follow-up period.

In our study, a high incidence of SPMs of 26% was observed, reinforcing the importance of SPMs detection in improving survival outcomes in patients with early-stage ESCC. Among the retrospective studies that assessed SPMs after treatment for esophageal cancer, Sato et al. reported SPM as the most common cause of death in patients with thoracic esophageal cancer whose initial surgically-resected lymph nodes tested negative [7]. In addition, the JCOG9708, a single-arm phase II clinical trial enrolled the same population as JCOG0502 and evaluated chemo-radiotherapy in patients with stage I ESCC [26]. In that study, the proportion of SPMs was reported to be 25%, which is quite similar to that of our study. The prevalence of SPMs was also comparable to those of previous reports, showing that the common primary tumor sites of SPMs are the aero-digestive tract organs, such as the head and neck, lung, and stomach [7–9, 14, 19]. In particular, the incidence of head and neck cancer was high, which supports the well-established “field cancerization” concept.

Seventeen of 99 (17%) patients who developed SPMs died. Given that the incidence of SPMs was high during the follow-up period, the survival of a considerable number of patients irrespective of SPM in the study population could be explained by the follow-up strategies. In JCOG0502, the protocol specified endoscopic examinations or CT scans during follow-up periods to enable early diagnosis of SPMs, with resultant relatively good prognosis. Of the three most common types of SPMs, 72%, 100%, and 93% were head and neck, stomach, and lung cancers, respectively, detected at clinical stages of 0–I. The rate of early detection in our study was comparable to or higher than that of the report by Yamaguchi, et al. showing 75%, 92%, and 60% were head and neck, stomach, and lung cancers, respectively, detected at clinical stages of 0–I [9]. A Japanese multicenter study including 77 specialized hospitals previously investigated the timing of follow-up for esophageal cancer patients after curative surgery or
definitive chemo-radiotherapy in clinical practice [27]. The outcome of this study demonstrated that most hospitals monitored their patients for at least 5 years in a routine follow-up, with an exceptionally high frequency of follow-up in the first 3 years after treatments, using upper gastrointestinal endoscopy or CT scan. Nonetheless, this study also showed a tendency toward a decreased follow-up frequency for the assessment of patients with clinical stages 0/I disease compared with patients with stages II–IV disease. Approximately 30–40% of patients with clinical stages 0/I underwent an annual or fewer numbers of upper gastrointestinal endoscopy and CT scan. This could be reasonable because patients with early-stage cancer are less likely to experience cancer recurrence. However, it is plausible to consider that particular attention need be paid not only to esophageal cancer recurrence but also to the high incidence of SPMs; thus, more intensive, and frequent follow-ups might also be critical in patients with stage I

| Factors | Univariable analysis | Multivariable analysis |
|---------|----------------------|-----------------------|
|         | HR       | 95% CI | p  | HR       | 95% CI | p  |
| Age, years vs. < 65 | | | | | |
| ≥ 65 | 1.05 | 0.67–1.63 | 0.84 | 0.98 | 0.59–1.61 | 0.92 |
| Gender vs. Female | | | | | |
| Male | 1.28 | 0.66–2.48 | 0.47 | 1.23 | 0.56–2.71 | 0.61 |
| ECOG-PS vs. 0 | | | | | |
| 1 | 1.07 | 0.12–9.83 | 0.95 | 1.00 | 0.10–10.48 | 1.00 |
| Body mass index, sq/m^2 vs. < 25 | | | | | |
| ≥ 25 | 0.75 | 0.39–1.44 | 0.38 | 0.77 | 0.40–1.50 | 0.44 |
| Smoking vs. 0 cigarette per day | | | | | |
| 1–20 | 1.15 | 0.68–1.95 | 0.61 | 1.30 | 0.72–2.34 | 0.38 |
| ≥ 20 | 1.46 | 0.81–2.64 | 0.21 | 1.92 | 0.99–3.75 | 0.06 |
| Alcohol consumption vs. 0 mL of ethanol per day | | | | | |
| 0–25 | 0.75 | 0.36–1.56 | 0.44 | 0.75 | 0.32–1.77 | 0.51 |
| ≥ 25 | 0.85 | 0.47–1.55 | 0.60 | 0.63 | 0.31–1.30 | 0.21 |
| Location of primary site vs. Ut | | | | | |
| Mt | 1.62 | 0.64–4.07 | 0.31 | 1.91 | 0.72–5.08 | 0.20 |
| Lt | 1.41 | 0.53–3.79 | 0.49 | 1.33 | 0.49–3.62 | 0.57 |
| LVLs vs. A | | | | | |
| B | 2.10 | 1.30–3.39 | 0.003 | 2.24 | 1.32–3.81 | 0.003 |
| C | 2.57 | 1.15–5.72 | 0.02 | 2.88 | 1.27–6.52 | 0.01 |
| Length of primary lesion vs. < 4 cm | | | | | |
| ≥ 4 cm | 1.38 | 0.88–2.17 | 0.16 | 1.25 | 0.77–2.03 | 0.37 |
| Treatment modality vs. Surgery | | | | | |
| CRT | 1.44 | 0.92–2.24 | 0.11 | 1.68 | 0.97–2.91 | 0.06 |

The patients included in these analyses had no missing data regarding the baseline background. 

HR hazard ratio, CI confidence interval, ECOG-PS Eastern Cooperative Oncology Group performance status, Ut upper thoracic esophagus, Mt middle thoracic esophagus, Lt lower thoracic esophagus, LVLs Lugol-voiding lesions, CRT chemo-radiotherapy.
esophageal cancer. In the JEC study, an otolaryngologist examined head and neck regions at 12 months of intervals in addition to upper gastrointestinal endoscopy at 6 months of intervals. As a result, 100% of second primary head and neck cancers, which were higher than that of our study, were detected as superficial cancer, and there was no death due to head and neck cancers [28].

Meanwhile, cancer screening requires efficient and cost-effective approaches. In this regard, the identification of risk factors is useful, and that motivated us to conduct this study. Multivariable analyses revealed an association between the development of SPMs and Lugol-voiding patterns. The high prevalence of LVLs has been linked to inactive aldehyde dehydrogenase type 2 (ALDH2) phenotypes [29]. ALDH2 plays a significant role in alcohol metabolism, especially in the degradation of carcinogenic acetaldehyde. Therefore, inactive ALDH2 phenotypes lead to the accumulation of acetaldehyde; and the direct exposure of acetaldehyde to esophageal or oral epithelium is one of the mechanisms accounting for carcinogenesis in the esophagus and head and neck regions [30]. TP53 mutations are frequently observed in the esophageal epithelium with high severity of LVLs grade [21]. Moreover, a recent study indicated that the replacement of normal esophageal mucosa with pathogenic mutant clones increased with age and was promoted by smoking and drinking [31]. These data are considered to support the concept of “field cancerization.” They could also explain the extremely high HR for the developments of head and neck cancers in patients with LVLs and contribute to the association between LVLs and the development of SPMs in this study. Meanwhile, the risk of SPMs other than head and neck cancers did not increase in patients with LVLs. This might suggest the requirement of intensive follow-up for head and neck regions especially in patients with LVLs. Additionally, since abstinence from drinking reportedly reduced cancer development even in patients with multiple LVLs, the identification of risk factors is vital in guiding patient education, particularly for those at a high risk [21].

In the analyses of prognostic factors, a higher incidence of SPMs in the chemo-radiotherapy arm was observed. However, in JCOG0502, most patients received the study treatment in a non-randomized patient-preference manner. Therefore, there was an imbalance in patient characteristics between the surgical and chemo-radiotherapy arms, which made it difficult to evaluate whether treatment modalities affected the occurrence of SPMs. Furthermore, esophagogastroduodenoscopy was not mandatory in the surgical arm, which could have contributed to differences in detecting gastric cancer. Compared with the surgical arm, more than double stomach cancer incidence rates were observed in the chemo-radiotherapy arm. Although data on the interval of esophagogastroduodenoscopy were not obtained in the present study, it was reported that approximately 10% or less of the hospitals continued follow-up after esophagectomy without using upper gastrointestinal endoscopy [27]. Our results may indicate the importance of regular upper gastrointestinal endoscopy to detect stomach cancer even when esophagectomy is performed. Previous studies have suggested an elevated risk of SPM in patients who received radiotherapy or chemotherapy [11, 12]. However, further research is warranted in this regard.

There are some limitations to the present study. First, the data on social history or LVLs were missing in some patients because the data were not mandatory at enrollment. Iodine staining is sometimes irritable and time-consuming. Since recent studies have reported that image-enhanced endoscopy can replace Lugol’s iodine staining, the optimal method should be determined in further research [32]. Moreover, alcohol consumption or smoking habit during the study treatments and follow-up periods was not analyzed. In addition, the median observation period of 7.1 years might not be long enough for the evaluation of late carcinogenic effects induced by chemotherapy or radiotherapy. However, despite these limitations, the present study contributes to follow-up strategies after curative treatments for early-stage esophageal cancer. SPMs, such as head and neck cancers and stomach cancer, developed with high cancer incidence, suggesting that regular otolaryngological examination or endoscopic examination is needed especially in patients at high risk to improve early detection rates of SPMs and prevent death due to SPMs.

In summary, our data show that the incidence of SPMs was high, indicating that careful attention to monitoring and management is crucial after treatment completion. However, the establishment of optimal surveillance planning is undoubtedly required. We plan to further study of SPMs using combined data with other studies, such as the JCOG0508 [33] and the JEC study [21], including patients with early-stage esophageal cancer.

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Author contributions SM, KK and SK contributed to the conception and interpretation of the results. SM and KK contributed to drafting the manuscript, and RM did especially on statistical considerations. TK, KS and RM performed the statistical analyses of collected data. HD, YY, IN, TK, MY, SN, MU, MW, ST, TA, SK, and
YK contributed to acquisition of data and revision of the manuscript. All authors read and approved the final manuscript.

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**Declarations**

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**References**

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65:87–108.
2. Abnet CC, Arnold M, Wei QW. Epidemiology of esophageal squamous cell carcinoma. Gastroenterology. 2018;154:360–73.
3. Tachimori Y, Ozawa S, Numasaki H, et al. Comprehensive registry of esophageal cancer in Japan. Esophagus. 2019;16:221–45.
4. Slaughter DP, Southwick HW, Smekal W. Field cancerization in oral stratified squamous epithelium: clinical implications of multicentric origin. Cancer. 1953;6:963–8.
5. Muto M, Nakane M, Katada C, et al. Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. Cancer. 2004;101:1375–81.
6. Muro K, Lordick F, Tsuchima T, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic esophageal cancer: a JSMO-ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS Ann Oncol. 2019;30:34–43.
7. Sato Y, Motoyama S, Maruyama K, et al. A second malignancy is the major cause of death among thoracic squamous cell esophageal cancer patients negative for lymph node involvement. J Am Coll Surg. 2005;201:188–93.
8. Matsubara T, Yamada K, Nakagawa A. Risk of second primary malignancy after esophagectomy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol. 2003;21:4336–41.
9. Yamaguchi T, Kato K, Nagashima K, et al. Type of second primary malignancy after achieving complete response by definitive chemoradiation therapy in patients with esophageal squamous cell carcinoma. Int J Clin Oncol. 2018;23:652–8.
10. Hu WS, Liu ZJ, Zhang JB, et al. Risk patterns of subsequent primary cancers following esophagectomy in early-stage thoracic esophageal squamous cell cancer patients. Tumori. 2015;101:328–33.
11. Zhu G, Chen Y, Zhu Z, et al. Risk of second primary cancer after treatment for esophageal cancer: a pooled analysis of nine cancer registries. Dis Esophagus. 2012;25:505–11.
12. Chen SC, Teng CJ, Hu YW, et al. Secondary primary malignancy risk among patients with esophageal cancer in Taiwan: a nationwide population-based study. PLoS ONE. 2015;10:e0116384.
13. Chuang SC, Hashibe M, Scelo G, et al. Risk of second primary cancer among esophageal cancer patients: a pooled analysis of 13 cancer registries. Cancer Epidemiol Biomarkers Prev. 2008;17:1543–9.
14. Mitani S, Kadokawa S, Oze I, et al. Risk of second primary malignancies after definitive treatment for esophageal cancer: a competing risk analysis. Cancer Med. 2020;9:394–400.
15. Steevens J, Schouten LJ, Goldbohm RA, et al. Alcohol consumption, cigarette smoking and risk of subtypes of oesophageal and gastric cancer: a prospective cohort study. Gut. 2010;59:39–48.
16. Yaegashi Y, Onoda T, Morioka S, et al. Joint effects of smoking and alcohol drinking on esophageal cancer mortality in Japanese men: findings from the Japan collaborative cohort study. Asian Pac J Cancer Prev. 2014;15:1023–9.
17. Oze I, Charvat H, Matsu K, et al. Revisit of an unanswered question by pooled analysis of eight cohort studies in Japan: does cigarette smoking and alcohol drinking have interaction for the risk of esophageal cancer? Cancer Med. 2019;8:6414–25.
18. Muto M, Hironaka S, Nakane M, et al. Association of multiple Lugol-voiding lesions with synchronous and metachronous esophageal squamous cell carcinoma in patients with head and neck cancer. Gastrointest Endosc. 2002;56:517–21.
19. Katada C, Yokoyama T, Yano T, et al. Association between the findings of metachronous secondary primary malignancies and the number of Lugol-voiding lesions. Dis Esophagus. 2020. https://doi.org/10.1093/dote/doz110.
20. Muto M, Takahashi M, Ohitsu A, et al. Risk of multiple squamous cell carcinomas both in the esophagus and the head and neck region. Carcinogenesis. 2005;26:1008–12.
21. Katada C, Yokoyama T, Yano T, et al. Alcohol consumption and multiple dysplastic lesions increase risk of squamous cell carcinoma in the esophagus, head, and neck. Gastroenterology. 2016;151:860-869.e7.
22. Kato K, Ito Y, Nozaki I, et al. Parallel-group controlled trial of surgery versus chemoradiotherapy in patients with stage I esophageal squamous cell carcinoma. Int J Clin Oncol. 2018;23:652–8.
23. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94:496–509.
24. Shitara K, Matsu K, Hatoaka S, et al. Heavy smoking history interacts with chemoradiotherapy for esophageal cancer prognosis: a retrospective study. Cancer Sci. 2010;101:1001–6.
25. Bagnardi V, Blangiardo M, La Vecchia C, et al. A meta-analysis of alcohol drinking and cancer risk. Br J Cancer. 2001;85:1700–5.
26. Kato H, Sato A, Fukuda H, et al. A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan
Clinical Oncology Group Study (JCOG9708). Jpn J Clin Oncol. 2009;39:638–43.

27. Toh Y, Kitagawa Y, Kuwano H, et al. A nation-wide survey of follow-up strategies for esophageal cancer patients after a curative esophagectomy or a complete response by definitive chemoradiotherapy in Japan. Esophagus. 2015;13:173–81.

28. Shinozaki T, Katada C, Shiga K, et al. Effectiveness of planned surveillance for detecting second primary head and neck cancers after endoscopic resection of esophageal squamous cell carcinoma. Jpn J Clin Oncol. 2020;50:1162–7.

29. Katada C, Muto M, Tanabe S, et al. Factors associated with the presence of multiple Lugol-voiding lesions in patients with esophageal squamous-cell carcinoma. Dis Esophagus. 2014;27:457–62.

30. Crabb DW, Edenberg HJ, Bosron WF, et al. Genotypes for aldehyde dehydrogenase deficiency and alcohol sensitivity. The inactive ALDH2(2) allele is dominant. J Clin Invest. 1989;83:314–6.

31. Yokoyama A, Kakiuchi N, Yoshizato T, et al. Age-related remodelling of oesophageal epithelia by mutated cancer drivers. Nature. 2019;565:312–7.

32. Morita FH, Bernardo WM, Ide E, et al. Narrow band imaging versus lugol chromoendoscopy to diagnose squamous cell carcinoma of the esophagus: a systematic review and meta-analysis. BMC Cancer. 2017;17:54.

33. Minashi K, Nihei K, Mizusawa J, et al. Efficacy of endoscopic resection and selective chemoradiotherapy for Stage I esophageal squamous cell carcinoma. Gastroenterology. 2019;157:382-390.e3.

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