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Original Articles

Efficacy of Intense Screening and Treatment for Synchronous Second Primary Cancers in Patients with Esophageal Cancer

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Background: The optimum management of esophageal cancers with synchronous second primary cancer (SPC) has not been determined. The aim of this study was to evaluate the efficacy of intense screening and treatment for esophageal cancers with synchronous SPC.
Methods: Between 1981 and 1997, 1479 patients with esophageal cancers were screened for synchronous SPC during the process of initial staging. Radical treatment was recommended for esophageal cancer and synchronous SPC in cases for whom both cancers were curable. Treatment results for esophageal cancer patients with or without synchronous SPC were compared.
Results: Among 1479 patients, 155 (10.5%) were found to have 166 synchronous SPC. Primary sites included the stomach in 65, the head and neck in 44, the colon/rectum in 27, the lung in 14 and other sites in 16 patients. Clinical stages of synchronous SPC were stage I in 41%, stage II in 20%, stage III in 25% and stage IV in 14%. The 5-year overall survival rates by clinical stages of esophageal cancers (stage 0, I, II, III, IV) in patients with synchronous SPC were 51% (95% CI, 23–78%), 43% (95% CI, 18–68%), 11% (95% CI, 0–22%), 14% (95% CI, 0–28%) and 12% (95% CI, 1–22%), respectively. The 5-year overall survival rate for patients with or without synchronous SPC were 20% (95% CI, 13–28%) and 32% (95% CI, 29–35%), respectively. No significant difference was observed between both groups ($p = 0.2562$).
Conclusions: Intense screening and treatment may be justifiable in the light of the high detection rate of curable SPC and the reasonable survival of patients with synchronous SPC. However, a prospective study including cost–benefit analysis is needed to provide the evidence to justify the intense screening and treatment.

Key words: esophageal cancer – multiple primary cancer – second primary cancer – screening

INTRODUCTION

The detection of esophageal cancer at a stage at which the disease may be curable, once a rare clinical event, has recently become commonplace. This is largely due to the liberal use of flexible endoscopy and the widespread adoption of a surveillance program for esophageal cancers. Nigro et al. (1) showed that 30% of patients with esophageal adenocarcinoma who had recently undergone esophageal resection at the University of Southern California were found to have tumors confined to the mucosa or submucosa. This trend does not differ between Western countries and the Far East where squamous cell carcinoma remains prevalent. The rising trend in curable esophageal cancers creates a new dilemma for the clinician. The incidence of multiple primary cancers (MPC) in patients with esophageal cancer is known to be high; it has been reported to be between 8.3 and 27.1% (2–7). The high incidence of MPC has been explained by the concept of field cancerization (8). In the past, esophageal cancer patients with synchronous second primary cancers (SPC) were thought to be candidates for palliative treatment. This was partly because surgical resection for the esophageal cancer and SPC was thought to be too radical and inappropriate for these patients and to offer only a small

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chance of cure (9). Screening for synchronous SPC was recommended to reduce unnecessary surgical resection for esophageal cancer. In recent years, in the light of the increased curability of esophageal cancers, this strategy may not be appropriate. However, there has been no major report about the outcome of intense screening and treatment for synchronous SPC in patients with esophageal cancer.

We performed intense screening and surveillance for SPC in patients with esophageal cancers who had been referred to one institution for the treatment of esophageal cancer. Radical treatment was recommended for esophageal cancer and synchronous SPC in cases in which both tumors were curable. In this study, we investigated the outcome of the intense screening and surveillance program and the treatment of esophageal cancer patients with synchronous SPC. The aim of this paper is to provide clinical data on the usefulness of intense screening and treatment for esophageal cancer patients with synchronous SPC.

METHODS

The subjects consisted of 1479 consecutive patients with esophageal cancers who were referred to and managed at a single cancer center between 1981 and 1997. Over this period, intense screening and surveillance to detect synchronous SPC were recommended for all patients with esophageal cancers before treatment for esophageal cancers. The patients in whom esophageal cancer was diagnosed immediately after the diagnosis of SPC were included in this study, because those patients also underwent screening to detect other SPC. In all patients, malignant esophageal tumor was confirmed histopathologically. Histopathological diagnosis was squamous cell carcinoma in 1369 (91%) and non-squamous cell carcinoma in 110 (9%) patients. Clinical and pathological restaging was retrospectively performed according to the staging system recommended by the International Union Against Cancer in 1997 using the clinical record, X-ray films and other available data.

The screening and surveillance were directed to detect cancers of the head and neck, lung, stomach and colon and rectum. The screening and surveillance procedure consisted of inspection and palpation of the head and neck region by head and neck surgeons; blood tests including tumor markers; chest/abdominal X-ray; barium swallow studies; endoscopic examinations for the larynx, pharynx, esophagus, stomach and colon/rectum; head and neck/chest/abdominal computed tomography (CT); and neck/abdominal ultrasound. If any symptoms and signs suggestive of cancers at other sites were found, examination was performed accordingly. As a general rule, the patients were followed up every 3 months over a 24-month period after surgery and every 6 months thereafter. Chest X-ray and computed tomography were recommended every 6 months and upper gastrointestinal endoscopy every 1 year after treatment.

MPC was defined according to Warren and Gates (10). Each of the tumors must be distinct and the probability of one being a metastasis of the other must be excluded. SPC was defined as synchronous if it occurred within 1 year of diagnosis of the esophageal cancer. Diagnosis of synchronous tumors was based on criteria outlined by Warren and Gates: (i) the tumor must be clearly malignant on histological examination, (ii) the tumor must be separated by normal mucosa and (iii) the possibility that the second tumor represents a metastasis must be excluded. If a patient had three or more primary cancers, he or she was classified according to the timing of the onset of the SPC.

The treatment policy for esophageal cancer was as described below. Surgical resection was recommended, if medically operable, except in the case of patients who were successfully treated with endoscopic mucosal resection (EMR). EMR was recommended for patients with mucosal esophageal carcinoma which was located within the epithelium and lamina propria. Indication criteria of surgical resection were the primary tumors not invading adjacent structures, no non-regional lymph node metastases and no distant metastases. The standard surgical technique for esophageal cancers was esophagectomy and nerve-sparing three-field lymphadenectomy. Details of the procedure have been described elsewhere (11). Patients who were suggested by the surgical specimen to have residual disease were recommended to receive post-operative radiotherapy or chemotherapy including 5-fluorouracil and/or platinum compound. The standard schedule of post-operative radiotherapy was 50–60 Gy, which was given in 20–24 fractions over 5–6 weeks. Since 1989, the clinical trial of intra-operative radiotherapy had been performed for patients with thoracic cancers undergoing radical surgical resection. Details of intra-operative radiotherapy have been described elsewhere (11). Radiotherapy with/without chemotherapy including 5-fluorouracil and/or platinum compound was considered when neither radical surgical resection nor EMR was indicated because of advanced disease, poor medical condition or the refusal of patients to undergo surgery. The standard schedule of radical radiotherapy was 65 Gy, which was given in 26 fractions over 7 weeks for patients treated with radical intent. Patients who were not suitable for EMR, radical surgical resection or radical radiotherapy were treated with palliative intent. The palliative therapy included bypass surgery, chemotherapy, palliative radiotherapy and palliative care.

Patients' characteristics including age, gender, smoking and drinking habits, pathological diagnosis, clinical staging and pathological staging were stored in a database. Smokers were classified into four categories according to accumulated amount of smoking, which was defined by number of cigarettes per day times number of years of smoking: 0 defined non-smokers, 1–600 defined mild smokers, 600–1200 defined moderate smokers and >1200 defined heavy smokers. Drinkers were also classified into four categories according to accumulated amount of drinking, which was defined by quantity of alcohol (ml) per day times number of years of drinking: 0 defined non-drinkers, 1–1000 defined mild drinkers, 1000–3000 defined moderate drinkers and >3000 defined heavy drinkers.

Table 1. Patients' characteristics and esophageal tumor classification

Factor	With synchronous SPC		Without synchronous SPC	
	No.	%	No.	%
Age (years)				
Median	65		63	
Range	42–85		34–97	
Gender				
Male	141	91	1156	87
Female	14	9	168	13
Smoking				
Non-smoker	34	22	350	26
Mild	45	29	372	28
Intermediate	47	30	390	30
Heavy	26	17	188	14
Unknown	3	2	24	2
Alcoholic drinking				
Non-drinker	39	25	353	27
Mild	15	10	221	17
Intermediate	43	28	372	28
Heavy	55	35	348	26
Unknown	3	2	30	2
Pathological diagnosis				
Squamous cell carcinoma	143	92	1228	93
Non-squamous cell carcinoma	12	8	96	7
Anatomical subsites				
Cervical esophagus	6	4	73	5
Upper thoracic esophagus	19	12	150	12
Middle thoracic esophagus	90	58	744	56
Lower thoracic esophagus	40	26	357	27
Clinical stage				
Stage 0	25	16	152	11
Stage I	16	10	114	9
Stage II	37	24	288	22
Stage III	28	18	358	27
Stage IV	40	26	338	25
Unknown	9	6	74	6
Pathological stage				
Stage 0	24	28	190	21
Stage I	6	7	77	9
Stage II	7	8	55	6
Stage III	15	17	225	25
Stage IV	34	40	345	38
Unknown	0	0	5	1
Period of treatment				
1981–92	55	35	676	51
1993–97	100	65	648	49

SPC, second primary cancer.

Table 2. Clinical stage of synchronous second primary cancers

Clinical stage	All patients*		Stomach		Head & neck		Colon & rectum		Lung		Others	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Stage I	63	41	43	66	6	14	11	41	5	36	1	6
Stage II	31	20	5	8	13	30	4	15	1	7	8	50
Stage III	39	25	12	18	16	37	6	22	5	36	6	38
Stage IV	22	14	5	8	8	19	6	22	3	21	1	6
Total	155	100	65	100	43	100	27	100	14	100	16	100

*More advanced stages were used for patients who had more than one cancer as a synchronous second primary cancer.

All patients received follow-up. Survival and cause-specific survival were calculated using the Kaplan–Meier method. When calculating cause-specific survival, patients who were alive at last follow-up or dead of causes other than esophageal cancers were censored. Statistical difference was compared with log-rank tests. The prognostic significance of selected factors to overall survival was evaluated using the Cox proportional hazards regression model. Comparisons between groups were performed using Student's *t*-test for numerical variables and the χ^2 test for nominal variables. A *P*-value of <0.05 was regarded as statistically significant. Because the period of observation was as long as 17 years, the detection rate might have been related to the time of treatment. Therefore, the detection rate according to the time of treatment was also investigated using χ^2 test. All statistical tests were two-sided.

RESULTS

Of the 1479 patients, 90% (1339) underwent all the procedure according to the protocol. The remaining 10% (140) did not undergo all the procedure because of limited life expectancy, patients' refusal, etc. Of the patients, 155 (11%) had synchronous SPC. In 120 (77%) of these 155 patients, synchronous SPC was detected by the screening procedure following the diagnosis of esophageal cancers. In the remaining 35 patients (23%), esophageal cancer was detected immediately after the diagnosis of SPC. Table 1 shows the patients' characteristics between the patients with or without synchronous SPC. Multiple significant testing demonstrated that there were no significant differences in patients' characteristics between the two groups except for period of treatment. We also evaluated the balance of patients' characteristics by grouping some categories together. The non-, mild and intermediate drinkers were grouped into one category. There were significantly more heavy drinkers in patients with synchronous SPC than in those without synchronous SPC (35 vs 26%, $P = 0.017$). Clinical stage was divided into two groups (stage 0–II vs III–IV). There were significantly more stage 0–II cases in patients with synchronous SPC than in those without synchronous SPC (50 vs 42%, $P = 0.036$). There were more cases with synchronous

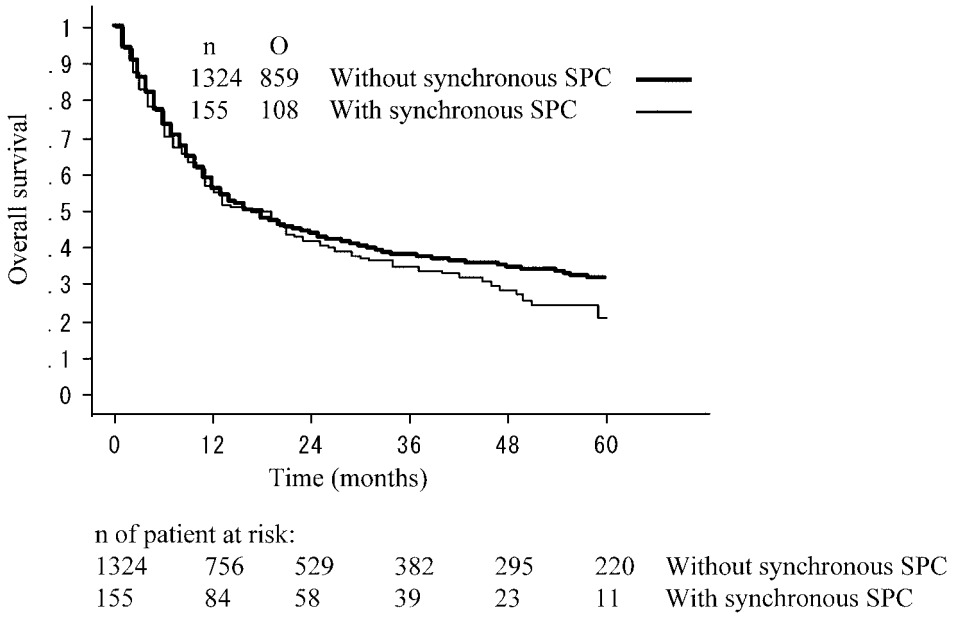

Figure 1. Overall survival (O = observed number of events and n = number of patients at risk at time 0).

Table 3. Overall survival rates at 5 years

	With synchronous SPC			Without synchronous SPC			*P*-value
	No.	Rate	(95% CI, %)	No.	Rate	(95% CI, %)	
All patients	155	20	(13–28)	1324	32	(29–35)	0.25
Type of treatment							
Surgical resection	86	26	(14–36)	897	38	(35–41)	0.34
EMR	15	38	(28–48)	56	86	(70–100)	0.001
Radiotherapy	44	8	(0–17)	295	4	(2–7)	0.29
Clinical stage							
Stage 0	25	51	(23–78)	152	84	(77–91)	0.003
Stage I	16	43	(18–68)	114	54	(43–64)	0.11
Stage II	37	11	(0–22)	288	37	(31–43)	0.009
Stage III	28	14	(0.2–28)	358	19	(14–23)	0.89
Stage IV	40	12	(1–22)	338	9	(5–12)	0.59
Pathological stage							
Stage 0	24	49	(28–72)	190	70	(63–77)	0.019
Stage I	6	0		77	52	(40–64)	0.027
Stage II	7	29	(0–62)	55	47	(34–61)	0.40
Stage III	15	23	(0–49)	225	34	(27–41)	0.98
Stage IV	34	21	(67–36)	345	17	(13–22)	0.53
Period of treatment							
1981–92	55	20	(9–31)	676	27	(24–31)	0.36
1983–97	100	23	(12–34)	648	33	(29–38)	0.23

SPC, second primary cancer; CI, confidence interval; EMR, endoscopic mucosal resection.

SPC in patients treated between 1993 and 1997 than in those treated between 1981 and 1992 (13 vs 8%, $P < 0.001$).

Eight patients had two synchronous SPC and one patient had three synchronous SPC. Thus, 166 synchronous SPC were identified. Primary sites of synchronous SPC were the aerodigestive tract in 90%, the stomach in 39%, the head and neck in 27%, the colon and rectum in 16% and the lung in 8%. The detection rates were 4.4% for stomach cancers, 3.0% for head and neck cancers, 1.8% for colon and rectum cancers, 0.95% for lung cancer and 1.1% for other cancers. Table 2 shows the clinical stage of synchronous SPC; 61% of synchronous SPC were stage I or II disease. In stomach cancers 66% were stage I disease, which was a significantly higher incidence than that in non-stomach cancers (66 vs 23%, $P < 0.001$).

Among the 1479 patients, 134 (9%) were found to have metachronous SPC in their medical history or the follow-up period. When an esophageal cancer was considered as the index tumor, 118 cancers were found in 108 (7%) patients more than 12 months prior to the detection of esophageal cancer and 28 were found in 27 (2%) patients more than 12 months subsequent to the detection of esophageal cancer. One out of the 138 patients with metachronous SPC had both antecedent and subsequent SPC. Six patients had both metachronous and synchronous SPC. Overall, 283 (19%) patients had metachronous and/or synchronous SPC.

The 5-year overall survival rates were 20% (95% CI, 13–28%) for patients with synchronous SPC and 32% (95% CI, 29–35%) for those without synchronous SPC (Fig. 1). No significant difference in overall survival was observed between the two groups ($P = 0.256$). Table 3 shows the 5-year overall survival rates according to the type of treatment for esophageal cancers, clinical stage, pathological stage and period of treatment. The overall survival rate was better in patients with synchronous SPC than in those without synchronous SPC among the group of patients with clinical stage 0 ($P = 0.012$), clinical stage II ($P = 0.009$), pathological stage 0 disease ($P = 0.019$), pathological stage I disease ($P = 0.027$) and in patients who received EMR ($P = 0.001$). In order to take the lead time bias into account, the patients were divided into those treated in 1981–1992 ($n = 731$) and in 1993–1997 ($n = 748$) and for each group the overall survival was compared between those with or without synchronous SPC. No significant differences in the overall survival were observed in the early period or in the late period. Multivariate analysis using the Cox proportional hazards regression model did not demonstrate that the existence of synchronous SPC influenced the overall survival (Table 4). Type of treatment, clinical stage and period at treatment were significant factors influencing the overall survival.

The 5-year overall survival rates were 19% (95% CI, 8–30%) for stomach cancer, 19% (95% CI, 7–37%) for head and

Table 4. Multivariate analysis for overall survival using the Cox proportional hazards regression model

Possible prognostic factor		Relative risk	*P*-value
Treatment	(Resection vs radiotherapy)	2.70 (2.338–3.135)	<0.0001
Clinical stage	(Stage 0–II vs III–IV)	2.48 (2.150–2.861)	<0.0001
Period at treatment	(1993–97 vs 1981–92)	1.46 (1.788–1.678)	<0.0001
Synchronous SPC	(Without vs with)	1.10 (0.888–1.361)	0.38

neck cancer, 41% (95% CI, 14–68%) for colon and rectum cancer, 0% for lung cancer and 21% (95% CI, 0–42%) for cancer at other sites. The 5-year overall survival rates by clinical stages of the synchronous SPC were 27% (95% CI, 13–41%) for clinical stage I, 32% (95% CI, 13–50%) for stage II, 9% (95% CI, 0–23%) for stage III and 0% for stage IV.

Type of treatment for esophageal cancers was classified into surgical resection, EMR, radiotherapy without resection, chemotherapy alone or no treatment. Table 5 shows treatment type between patients with or without synchronous SPC. More patients underwent surgical resection in those without synchronous SPC than in those with synchronous SPC (66 vs 37%, $P = 0.002$).

DISCUSSION

The Japanese national surveillance for esophageal cancer registration showed that 207 (11%) of 1979 patients registered in 1994 had synchronous SPC (7). This figure is consistent with the findings of the present series in a single institution showing 10% synchronous SPC. In the same previous study, stomach cancers accounted for 57%, head and neck cancers for 21%, colon and rectum cancers for 12% and lung cancers for 3% as the synchronous SPC. The proportion of each cancer in the present series was consistent with those findings. The consistency between the two studies suggests that the incidence of synchronous SPC depends on the characteristics of patients with esophageal cancers, but not on the institutional policy of screening and surveillance. The proportion of each cancer may differ among patients of different nationalities, considering the high incidence of stomach cancer in the present series of Japanese subjects (2–7). The significant increase in the detection rate of synchronous SPC after 1992 in this study may reflect improvements in diagnostic tools.

The detection rates of synchronous SPC for each site in this series were 4.4% for stomach, 3.0% for head and neck, 1.8% for colon and rectum and 1.0% for lung. Given that, in this study, synchronous SPC represent the annual incidence of SPC in esophageal cancer patients, the detection rate of synchronous SPC should be compatible with the estimated annual cancer incidence in the general population if there is no increase in SPC in patients with esophageal cancer. The estimated cancer incidence rates for Japanese populations in 1985 were reported as follows: 0.07% in men and 0.03% in women for stomach cancers; 0.007% in men and 0.002% in women for lip, oral, pharynx and larynx cancers; 0.02% in men and 0.02% in women for colon and rectal cancers; and 0.03% in men and 0.003% in women for lung cancers (12). From these findings, the detection rates of synchronous SPC in esophageal cancer were considered to be very high, although the detection rates in this study were not corrected for age, gender and calendar year. Some 61% of the synchronous SPC were stage I or II disease, suggesting that intense screening and surveillance resulted in high detection rates for early stage SPC, which have a chance of cure with radical treatment. Table 2 also shows that 66% of the synchronous stomach cancers were stage I. The higher incidence of stage I disease in stomach cancers than in the non-stomach cancers could be explained by the higher prevalence of stomach cancers in Japan and the usefulness of screening (13). However, the benefit of the intense screening could not be confirmed in Western countries, because of the lower incidence of gastric cancer and the difference in training and equipment. Although screening for synchronous SPC should be recommended before treatment for esophageal cancers in

Table 5. Treatment type for esophageal cancers between patients with or without synchronous SPC

	With synchronous SPC		Without synchronous SPC	
	No.	%	No.	%
Surgical resection	86	55	897	68
Endoscopic mucosal resection	15	10	56	4
Radiotherapy without resection	44	28	295	22
Chemotherapy alone	0	0	20	2
No treatment	10	7	56	4
Total	155	100	1324	100

SPC, second primary cancer.

terms of the higher detection rate of synchronous SPC, we cannot refer to the post-treatment surveillance for subsequent SPC in this paper, because a subsequent SPC was found in only 27 (2%) patients.

The effect of synchronous SPC on the survival of cancer patients is not well known. Robinson et al. (14) reported that patients with head and neck cancer without SPC showed a survival advantage in comparison with patients with head and neck cancer with SPC. This is probably an effect of the moderate prognosis of head and neck cancers. In the present series, the overall survival rate for patients with synchronous SPC was comparable to that of patients without synchronous SPC. This result is consistent with previous results reported by Poon et al., although stage distribution was not clarified in their series (6). Thus far, there has been no evidence of a comparatively better prognosis for esophageal cancer patients without SPC at any stage, indicating that the dismal prognosis of esophageal cancer overshadows the moderate effect of SPC on survival. However, the present study showed that the overall survival rate was better in patients without synchronous SPC than in patients with synchronous SPC among patients with clinical stage 0, clinical stage II, pathological stage 0 and pathological stage I disease. To our knowledge, the present study is the first to demonstrate that prognosis of patients without synchronous SPC was better than that of patients with synchronous SPC for early stage esophageal cancer. This result can be interpreted as a reasonable consequence of the moderate prognosis of patients with early stage esophageal cancer in this series. An alternative way of showing the efficacy of the screening was to compare the survival of patients undergoing the surveillance or not. In the future, such a study should be performed to obtain firm evidence.

In fact, the survival rates of patients with synchronous SPC in our series were compatible with or better than the standard survival rates reported in the literature for esophageal cancer patients without synchronous SPC who received radical surgery (15,16). The favorable outcome in this series is probably due to the shift of the disease population to the early curable stage by the screening and surveillance. It may be partly due to improved treatment techniques and perioperative management. Conflicting pathological diagnosis of high-grade dysplasia and carcinoma *in situ* may be linked to the better survival rates compared with those in a Western series (17). However, Peters (18) recently recommended treating high-grade dysplasia by esophagectomy as for adenocarcinoma of the esophagus even in Western countries because 43% of patients with high-grade dysplasia were found to be harboring occult carcinoma. Therefore, the best management policy for esophageal lesions would be the same in all countries despite the possible stage migration due to the difference in pathological diagnostic criteria for mucosal cancers. Cost–benefit analysis is outside the scope of this study in that it is strongly dependent on the socio-economic background in each community.

The schedule for treatment timing for both synchronous SPC and esophageal cancer is a challenging issue for physicians owing to technical complexity and biological considerations of tumor growth (19). The small but definite decrease in the incidence of surgery in patients with synchronous SPC may have been due to the difficulty of performing surgery for both diseases in time (i.e. before the disease is too advanced). However, the present study strongly suggests that patients with synchronous SPC should be treated in the same way as those without synchronous SPC, to the degree that this is possible. Molecular or biological data by which the doubling time of the tumor(s) and the metastatic potential of each tumor could be predicted would represent a landmark in determining an effective treatment schedule (20).

Several reports have demonstrated that smoking and/or drinking habits were significantly associated with the incidence of SPC in esophageal cancer patients (6,21). Many studies have shown that molecular instability exists in dysplasia and cancers in aerodigestive tract cancer patients (22,23). In this study, only drinking habit, especially heavy drinking, was associated with the incidence of synchronous SPC. It is not clear why the present study demonstrated no association of smoking habits with the incidence of SPC. In the present series, we found that 34 (9%) of 384 patients with no smoking habit had synchronous SPC and 39 (10%) of 392 patients with no drinking habit had synchronous SPC. We consider that the incidence of SPC in non-smokers and non-drinkers was sufficiently high to warrant a screening and surveillance procedure for all patients with esophageal cancers, irrespective of their smoking and drinking habits.

In conclusion, this study gave us basic data with which to consider the usefulness of screening and surveillance for SPC in patients with esophageal cancer. In our community, intense screening and surveillance to detect synchronous SPC are warranted, given the high detection rate of curable early stage SPC and the reasonable survival of patients with synchronous SPC. This study suggested that patients with esophageal cancer should be informed that having synchronous SPC does not necessarily shorten survival under an intense screening and surveillance program. However, no rigid conclusions can be drawn from this study, because it was a retrospective non-randomized study and did not address the cost–benefit analysis of the intense screening and treatment. A prospective study including cost–benefit analysis is needed to provide the evidence to justify the intense screening and treatment.

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