

Necessity of Screening for Multiple Primary Cancers in Patients with Esophageal Cancer

Tsuyoshi Noguchi, MD,¹ Tsuyoshi Kato, MD,¹ Shinsuke Takeno, MD,¹ Shinsuke Wada, MD,¹ Shigetaka Yanagisawa, MD,² Masashi Suzuki, MD,³ and Yuzo Uchida, MD¹

This study divided patients with esophageal cancer and multiple primary cancers into two groups, a head and neck cancer (HNC) group and a non-head and neck cancer (NHNC) group. These groups were then evaluated on the basis of clinical and pathological studies. Among 92 patients with esophageal cancer as one of multiple primary cancers, 38 (41.8%) were assigned to the HNC group. The following characteristics distinguished patients in the HNC group from those in the NHNC group: (1) younger age; (2) shorter interval between diagnosis of metachronous cancers; (3) many displayed superficial esophageal cancer. Among the cases in which esophageal cancer was discovered synchronously with head and neck cancer, head and neck cancers were discovered before esophageal cancer; and (4) many patients displayed esophageal dysplasia, and many had multiple esophageal cancers. In the present study, we demonstrated the necessity of screening for multiple primary cancers in patients with esophageal cancer. (*Ann Thorac Cardiovasc Surg* 2002; 8: 336–42)

Key words: screening, multiple primary cancers, esophageal cancer, head and neck cancer

Introduction

Esophageal cancer has been considered a disease with a poor prognosis. However, early detection by endoscopy using iodine dye^{1,2)} and extended lymph-node dissection (e.g., three-field lymph-node dissection) have contributed to improved prognosis. In Japan, Ide et al.³⁾ reported that among 2,903 patients with esophageal cancer, 829 (28.6%) displayed superficial esophageal cancer, and that the overall 2-year survival rate in patients with cancer invading the submucosal layer who underwent surgical excision was 88.5%, indicating a good prognosis.

One can predict that such improved prognosis will lead

From Department of Oncological Science (¹Surgery II), (²Oral and Maxillo-Facial Surgery) and Immunology and Allergy (³Otorhinolaryngology), Oita Medical University, Oita, Japan

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Address reprint requests to Tsuyoshi Noguchi, MD: Department of Oncological Science (Surgery II), Oita Medical University, Idaigaoka 1-1, Hasama-machi, Oita 879-5593, Japan.

to more frequent reports of multiple primary cancers. Numerous past studies have treated esophageal cancer as one of multiple primary cancers of the head and neck, from the perspective of field cancerization.⁴⁾ According to such reports, the incidence of esophageal cancer in patients with head and neck cancer was 1.7–7.4%.^{5–10)}

In addition, Gluckman et al.¹¹⁾ examined the prognosis of head and neck cancer accompanied by multiple primary cancers and noted the following reasons for poor prognosis: (1) a high incidence of a second cancer developing in the lung and esophagus, with a poor survival rate; (2) delayed diagnosis; (3) inability to use the optimal therapy for the second primary cancer due to the effects of previous radical therapies for the first primary cancer.¹¹⁾

Goodner et al. examined multiple primary cancers in patients with esophageal cancer, and reported that the incidence of head and neck cancer was 3.95%.¹²⁾ However, head and neck cancer was discovered earlier than esophageal cancer in all cases in their study. According to a report on conditions in Japan in 1997, 4.58% of the

Table 1. Relationship between first primary cancer and cause of death in patients with metachronous multiple primary carcinoma

	Cause of death		P value
	EC	MPC	
First primary cancer			
Esophageal cancer	2	6	
Multiple primary cancer	7	1	0.012
chi-square test			
EC: esophageal cancer			
MPC: multiple primary cancer			

patients with esophageal cancer displayed head and neck cancer.³⁾ Esophageal cancer was the primary cancer in five of 55 patients with metachronous head and neck cancer.

Increased discovery of multiple primary cancers after treatment of esophageal cancer should be expected as cases of esophageal cancer are detected earlier. The present study aimed to elucidate what types of cases are at high risk.

Patients and Methods

Patients

A total of 421 patients underwent surgical excision for esophageal cancer at the Department of Oncological Science, Surgery II, of Oita Medical University from January 1982 to December 2001. Among the 421 patients, 92 patients (21.9%) displayed multiple primary cancers. These 92 patients were divided into patients with head and neck cancer (HNC) group and patients with non-head and neck cancer (NHNC) group. The two groups were then compared.

If more than two primary cancers except esophageal cancer were present, patients were assigned to either the HNC or NHNC group based on the presence or absence of head and neck cancer. The head and neck cancer was defined as the index lesion. In cases in which more than two head and neck cancers were present (e.g., laryngeal cancer and pharyngeal cancer), or more than two cancers in separate organs were present (e.g., gastric cancer and colon cancer), the first primary cancer was defined as the index lesion, if the two cancers were discovered metachronously. If two cancers were discovered synchronously, the one that was symptomatic was defined as the index lesion.

If a second primary cancer was discovered within one

Table 2. Site of multiple primary cancers including synchronous and metachronous cancer in patients with esophageal cancer

Head and neck	38 (23)
Oral cavity	13 (8)
Pharynx	14 (10)
Larynx	11 (5)
Stomach	36 (10)
Colon and rectum	5 (3)
Lung	5 (2)
Liver	1 (1)
Kidney	1 (0)
Bladder	1 (0)
Prostate	2 (1)
Uterus	1 (0)
Malignant lymphoma	2 (1)
Total patients	92 (41)

() : number of patients with superficial esophageal cancer

year after the first primary cancer, the cancers were defined as synchronous. Fifty of the 92 cases were synchronous.

Statistical analysis

Gender, age, tumor size, tumor location, chronology, order of discovery, histology, number of metastatic nodes, UICC TNM classification of malignant tumors, presence or absence of esophageal dysplasia, and the presence or absence of multiple cancers were analyzed using the chi-square test, Mann-Whitney U-test, and Student t-test.

In addition, survival curves were calculated using the Kaplan-Meier method and data were analyzed using the log-rank test.

Results

Causes of death in patients with metachronous multiple primary cancers

Causes of death for patients with metachronous multiple primary cancers are shown in Table 1. Among cases in which esophageal cancer was the first primary cancer, two patients died from esophageal cancer, and six died from multiple primary cancers. In addition, among cases in which multiple primary cancers were the first primary cancer, one patient died from multiple primary cancers and seven patients died from esophageal cancer. These cases indicate that patients died from the second primary cancer.

Table 3a. The numbers of patients with the metachronous primary cancer combined with esophageal cancer diagnosed every year

	Number of patients
1986	1
1987	1
1988	0
1989	2
1990	0
1991	2
1992	3
1993	2
1994	5
1995	3
1996	3
1997	6
1998	6
1999	1
2000	3
2001	4
Total	42

Table 3b. The interval of metachronous multiple primary cancers between first and second primary cancer

Interval (year)	Number of patients
Unknown	2
1	5
2	4
3	8
4	5
5	2
7	3
8	1
9	1
10	2
11	1
12	2
15	2
17	1
18	1
22	1
29	1

Multiple primary cancers

Thirty-eight of 92 patients (41.3%) with esophageal cancer as one of multiple primary cancers displayed head and neck cancer, followed by 36 cases (39.1%) with gastric cancer. Head and neck cancers included 13 cases of oral cancer, 14 cases of pharyngeal cancer, and 11 cases of laryngeal cancer, indicating a high incidence of pharyngeal cancer (Table 2).

Table 3c. The interval between esophageal cancer and second primary cancer

Interval (year)	Number of patients
1	3
2	1
3	2
4	3
5	1
7	1
8	1

Of these patients, 50 were synchronous and the other 42 were metachronous multiple primary cancer.

The numbers of patients with the metachronous primary cancer combined with esophageal cancer diagnosed every year is shown in Table 3a. In the past 10 years, after cooperation with other departments was started, metachronous primary cancer has been detected in several patients every year.

The interval of metachronous multiple primary cancers ranged from 1-29 years (mean 6.9 years) in the patients whose interval could be informed. Second primary cancer was detected in 24 patients (60%) within five years (Table 3b).

Furthermore, of 12 patients whose first primary cancer arose in the esophagus, second primary cancer was detected in 10 patients (83.3%) within five years (Table 3c). The interval ranged from 1-8 years (mean 3.6 years).

In addition, among patients with superficial esophageal cancer, 23 of 41 cases (56.1%) displayed head and neck cancer, followed by 10 cases of gastric cancer (24.4%).

Clinical characteristics

Mean age in the HNC group was 62.4±1.7 years, which was less than that of the NHNC group, at 66.2±1.0 years. Regarding chronology, many metachronous multiple primary cancers were observed in the HNC group. Mean time interval to discovery of metachronous multiple primary cancers was 62.5±9.3 months, shorter than that of the NHNC group, at 122.1±25.8 months. In addition, among cases in the HNC group in which esophageal cancer was discovered synchronously with head and neck cancer, many cases were observed in which head and neck cancer was discovered before esophageal cancer (Table 4).

Histopathological characteristics

Regarding the depth of invasion of esophageal cancer, 19 cases (50%) in the HNC group were classified as T1. The

Table 4. Clinical characteristics according to multiple primary cancers in patients with esophageal cancer

cancer	HNC (n=38)	NHNC (n=54)	P value
Gender (M:F)			
Male	37	47	
Female	1	7	NS ⁽¹⁾
Age (years old, mean±SE)	62.4±1.7	66.2±1.0	0.045 ⁽²⁾
Size (mm, mean±SE)	37.5±4.2	44.3±3.5	NS ⁽²⁾
Location			
Cervical	2	3	
Upper third	4	7	
Middle third	24	25	
Lower third	7	13	
Abdominal	1	5	NS ⁽¹⁾
Chronology			
Synchronous	16	34	
Metachronous	22	20	0.048 ⁽¹⁾
Time interval (months, mean±SE)	62.5±9.3	122.1±25.8	0.024 ⁽²⁾
First primary cancer			
Synchronous			
EC	2	9	
MPC	14	5	0.003 ⁽¹⁾
Metachronous			
EC	8	4	
MPC	14	14	NS ⁽¹⁾

HNC: head and neck cancer group, NHNC: non-head and neck cancer group, EC: esophageal cancer, MPC: multiple primary cancers, NS: no significance

(1): chi-square test, (2): Student t-test

Table 5. Histopathological characteristics according to multiple primary cancers in patients with esophageal cancer

	HNC (n=38)	NHNC (n=54)	P value
Histology			
SCC	35	51	
ASC	1	0	
Unknown	2	1	NS ⁽¹⁾
UICC T			
is	4	0	
1	19	18	
2	2	7	
3	9	25	
4	4	2	
X	0	2	0.042 ⁽²⁾
UICC N			
0	23	22	
1	15	30	NS ⁽¹⁾
UICC M			
0	34	52	
1	4	0	
X	0	2	NS ⁽¹⁾
UICC stage			
0	4	0	
I	15	12	
IIA	4	10	
IIB	4	10	
III	7	20	
IV	4	0	
X	0	2	NS ⁽²⁾
Number of positive lymph nodes	1.47±0.44	1.88±0.4	NS ⁽³⁾
Dysplasia or multiple cancers of the esophagus			
Positive	23	20	
Negative	15	34	0.026 ⁽¹⁾

HNC: head and neck cancer group, NHNC: non-head and neck cancer group, SCC: squamous cell carcinoma, ASC: adenosquamous carcinoma, NS: no significance

(1): chi-square test, (2): Mann-Whitney U-test, (3): Student t-test

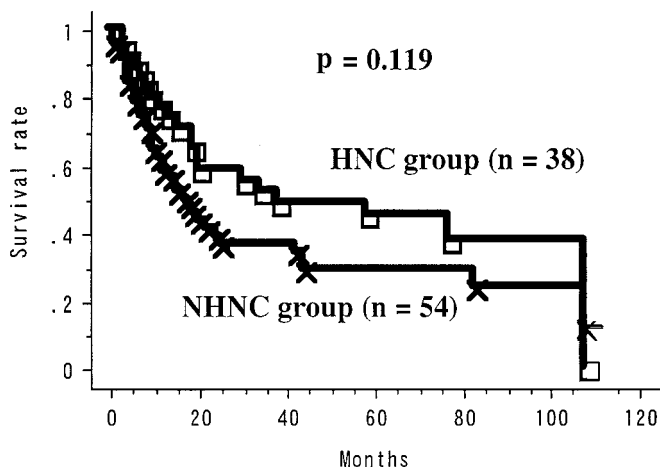


Fig. 1. Survival of patients with multiple primary cancers including esophageal cancer after esophagectomy. HNC: head and neck cancer group, NHNC: non-head and neck cancer group. No significant difference was demonstrated in survival after esophagectomy between the HNC and NHNC group.

HNC group displayed significantly more early cancers than the NHNC group. In addition, the HNC group included many cases of esophageal dysplasia associated with other abnormalities including multiple cancers (Table 5).

Survival

The five-year survival rate of 45.2% in the HNC group suggests a better prognosis than the NHNC group (28.9%). However, no significant differences were observed (p=0.119). (Fig. 1)

Discussion

Other researchers have reported second cancer as the factor determining prognosis in patients with multiple primary cancers.^{7,11)} Our study confirmed second primary cancer as the cause of death, providing support for these earlier studies. Surveillance of second primary cancer is important to improve prognosis.

Our department has been conducting surveillance of esophageal cancer among patients with head and neck cancer, and surveillance of head and neck cancer among patients with esophageal cancer by cooperation with other departments. As described in the result, cooperation with other departments such as otorhinolaryngology and oral

and maxillo-facial surgery is important and should be required for detecting metachronous primary cancer in patients with esophageal cancer. In addition, strict following should be required within five years after surgery since second primary cancer was detected in 60% of patients with metachronous multiple primary cancer and 80% of patients whose first primary cancer arose in the esophagus within five years. However, it was of interest that several second primary cancer was detected even after five years. Therefore, screening for second primary cancer may be required as long as possible. According to a report on conditions in Japan,³⁾ 4.58% of patients with esophageal cancer had head and neck cancer. Although our study only examined patients with esophageal cancer who underwent excision, a relatively high percentage, 9% (38 of 421) of patients with esophageal cancer had head and neck cancer. Of these patients, metachronous primary cancer was detected after esophagectomy for esophageal cancer in 2.9% (12 of 421). In addition, 56.1% of patients with esophageal cancer had head and neck cancer as the primary multiple cancer, indicating the importance of cooperation with other departments.

The HNC group had many cases of superficial esophageal cancer (T1 group). Among the patients with synchronous multiple primary cancers, there were many pa-

tients in whom head and neck cancer was discovered prior to esophageal cancer. This might have been due to the referral of such patients to us for screening by other departments.

Conversely, the finding that the HNC group had more cases of metachronous cancers compared with the NHNC group was attributed to the fact that the majority of the NHNC group had gastric cancer. That is, gastric cancer was detected synchronously by endoscopy. In addition, the concept of multiple primary cancers had not been established when older cases were being treated, and cooperation with other department had not been obtained.

Regarding methods of screening, Nino-Murcia et al. noted that esophagography and esophagoscopy may be complementary, and that esophagography is useful in patients for whom esophagoscopy cannot be performed.¹³⁾ Agrawal et al., however, noted that esophagoscopy may be superior to esophagography for early detection of esophageal cancer due to the benefit of iodine staining.¹⁴⁾

In addition, Sugimachi et al. noted that atypical esophageal epithelium has a high potential for malignancy, and should be treated as early cancer to improve prognosis.¹⁵⁾

At present, our group has also conducted surveillance using esophagoscopy, using iodine staining in all cases, to identify early cancer and dysplasia in patients with head and neck cancer who have not had treatment. When carcinoma in situ is found, endoscopic mucosal resection (EMR) is performed. When esophageal dysplasia are found, we conduct close follow-up.

With regard to follow-up, Shons et al. studied the time interval between discovery of metachronous multiple primary cancers and reported that 76.9% (40 of 52 cases) were found within an interval of five years.⁷⁾ Petit et al. noted that 60% (30 of 50 cases) were found within five years, and that the median interval was 47 months.⁹⁾ Our study also found that the mean time interval in the HNC group was 62.5 months, which was shorter than the NHNC group (122.1 months). In 13 of 22 cases (59.1%) the interval was less than five years, indicating the importance of follow-up in this period.

Since Slaughter proposed the concept of field cancerization in 1953,⁴⁾ numerous researchers have studied multiple primary cancers in patients with head and neck cancer. Based on the concept of field cancerization, Cowan et al. examined the loss of multiple chromosomal regions in patients with head and neck cancer,¹⁶⁾ and noted the possibility of tumor formation as a result of accumulations of its losses. Califano et al. performed microsatellite analysis in patients with head and neck cancer,¹⁷⁾ and noted that

chromosomal loss increased at each histological step from benign hyperplasia to dysplasia to carcinoma in situ to invasive cancer.

Recent studies have examined microsatellite instability in patients with cancer of both the head and neck and the esophagus.^{18,19)} These studies noted that microsatellite instability is helpful in predicting metachronous multiple primary cancers. Clinical applications are expected.

Conversely, our study indicates that many patients with esophageal cancer who also displayed head and neck cancer had dysplasia and multiple esophageal cancers. These results suggest that screening for head and neck cancer is particularly important for patients who undergo esophagectomy and have multiple abnormalities.

Conclusion

In this study, we divided patients with esophageal cancer into those with head and neck cancer and those with non-head and neck cancer, and compared them. Patients with head and neck cancer displayed the following characteristics:

1. Younger age
2. Shorter time interval between diagnosis of metachronous cancers
3. Many had superficial esophageal cancer. Among cases in which esophageal cancer was discovered synchronously with head and neck cancer, head and neck cancers were discovered before esophageal cancer.
4. Many patients displayed esophageal dysplasia, and many patients demonstrated multiple esophageal cancers.

The necessity of screening for head and neck cancers was suggested in the patients with aberrant epithelial lesion in esophagus.

Screening using endoscopy and identifying patients at high risk of multiple primary cancers using molecular-biological techniques is anticipated.

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