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Clinical outcomes of synchronous head and neck and esophageal cancer

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Purpose: To investigate clinical outcomes of synchronous head and neck and esophageal cancer (SHNEC).
Materials and Methods: We retrospectively reviewed 27 SHNEC patients treated with curative intent at a single institution. The treatment modality for individual cases was usually determined on a case by case basis.
Results: The median follow-up duration for the surviving patients was 28.2 months. The most common site of head and neck cancer was hypopharyngeal carcinoma (n = 21, 77.7%). The lower esophagus was the most common location of esophageal carcinoma (n = 16, 59.3%). The 2-year progression-free survival (PFS) and overall survival (OS) rates were 57.5% and 39.6%. Major pattern of failure was locoregional recurrence in the study patients. Esophageal cancer stage, the Eastern Cooperative Oncology Group (ECOG) performance status, and pretreatment weight loss were significant prognostic factors for OS in univariate analysis. Treatment-related death was observed in two patients, and one patient developed a grade 4 late treatment-related complication.
Conclusion: Although the survival outcome for SHNEC is poor, long-term survival might be achievable with aggressive treatment with stage I–II esophageal cancer and good performance.

Keywords: Synchronous cancer, Head and neck cancer, Esophageal cancer

Introduction

Patients with head and neck cancer sometimes develop esophageal cancer at the same time (synchronous) or after treatment (metachronous) because these cancers can arise via the same etiology and carcinogenesis. The "field cancerization theory" proposed in 1958 explains this possibility as being due to exposure to the same carcinogen, such as tobacco or alcohol, in multiple portions of the upper digestive tract [1,2]. In esophageal cancer, multiple primary cancers are frequently detected, and head-neck cancer is the second most common malignancy when multiple primary esophageal cancers are present [3-5]. The incidence of head and neck cancer combined with esophageal cancer is approximately 2%–24% [6-8]. Synchronous cancer is sometimes incidentally found in an [^{18}F]FDG-PET scan performed during a staging work-up. Recently, synchronous head and neck and esophageal cancer (SHNEC) has been shown to be more easily detectable, and the incidence of these two tumors has increased due to diagnostic advances in cancer detection [6,9-11].

Curative intent treatments for SHNEC are usually determined by the characteristics of each cancer lesion. Determining the optimal management in these cases is difficult because combined modality treatment for large amount of alimentary tract including extensive surgery, radiation therapy, and chemotherapy might sometimes be needed. For example,

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curative surgery involves resection via a pharyngo-laryngo-esophagectomy [12], and definitive radiation therapy (RT) is included for large head and neck and esophageal tumor volumes [13,14]. The treatment outcomes for SHNEC are not well-known due to the low incidence of this disease. Thus, we retrospectively reviewed the treatment results for SHNEC cases that presented in our institution.

Materials and Methods

The definition of SHNEC was a pharyngeal or laryngeal carcinoma combined with esophageal carcinoma at the time of initial treatment. A total of 40 SHNEC patients were found in electronic medical record of Asan Medical Center, Seoul, Korea from January 1999 to October 2013. The patients with distant metastasis (n = 3), transfer to other hospital (n = 6), and follow-up loss (n = 4) excluded. In the result, a total of 27 patients with SHNEC were included in this study. The staging and diagnostic procedure consisted of a computed tomography scan (chest and head and neck), endoscopy (laryngoscopy and esophagogastroscopy), endoscopic ultrasonography, and a [^{18}F]FDG-PET scan. Follow-up after treatment was usually performed at 1 month after treatment and every 3 to 6 months thereafter.

Treatment was usually determined by the status of each cancer. Definitive RT to the head and neck usually was given from 6,800 to 7,000 cGy divided into 30–35 fractions (daily doses from 200 to 220 cGy) for gross tumor. Postoperative RT was given at a total dose of approximately 5,000 to 5,800 cGy divided into 25–30 fractions. Bilateral whole neck including supraclavicular fossa was treated for elective nodal irradiation given from 4,400 to 4,600 cGy. RT planning was three-dimensional or intensity-modulated radiotherapy, and the energy selection was usually 6 MV photon. The total dosage for definitive and postoperative RT for esophageal cancer was about 5,400 cGy and 5,000 cGy, respectively. The RT field was included the mediastinum and esophagus within a cephalocaudal 5-cm margin from the gross tumor volume. The treatment usually given by anterior-posterior/posterior-anterior (AP/PA) with laryngeal block, with 15 MV photon energy. If both head and neck and esophageal RT were given concomitantly, we used the junction 2 cm above the manubrium, and junction change was performed two times.

The induction chemotherapy regimen was usually cisplatin-based with the addition of an antimetabolite as the concurrent chemoradiotherapy (CCRT) regimen which was conducted both with and without an antimetabolite. Surgery for head and neck cancer was performed on a case by case basis. An open thoracotomy for the esophageal cancer was performed via the Ivor-Lewis operation or McKeown procedure, and esophageal submucosal dissection (ESD) was performed for early superficial esophageal cancer.

Outcomes including local control and overall survival (OS) were measured from the start date of any cancer treatment (chemotherapy, surgery, or radiotherapy). The disease progression was judged by imaging study. The response rate of radiotherapy was evaluated by RECIST criteria 3.0. Kaplan-Meyer survival curves were used to assess actuarial local control and survival. A log-rank test for the univariate analysis was used to define the prognostic factors. A p-value less than 0.05 were considered significant. IBM SPSS ver. 21 (IBM Co., Armonk, NY, USA) was used for all statistical analysis.

Results

1. Patient characteristics

All 27 SHNEC patients included in our current analyses had a history of moderate alcohol intake, and 23 of these patients had a smoking history. The median age of the group was 64 years (range, 39 to 82 years). Nine patients experienced pretreatment weight loss >5% during the 6 months prior. At the pretreatment status evaluation, eight patients were unable to eat solid food. The median follow-up duration of the surviving patients was 28.2 months (range, 9.8 to 101.1 months). The Eastern Cooperative Oncology Group (ECOG) performance score for most patients was 0–1 (n = 22, 81.4%). The most common type of head and neck cancer was hypopharyngeal (n = 21, 77.7%), and moderately differentiated squamous cell carcinoma was the most common pathologic subtype (n = 19, 70.3%). Among the esophageal cancers in our study cohort, the median distance from the upper incisor was 30 cm (range, 18 to 38 cm), and most of these cases were of lower esophageal cancer (n = 16, 59.3%). The moderate differentiated type was the most common cancer subtype in our study cohort (n = 19, 70.3%), and 26 of our patients (96.3%) had squamous cell carcinomas with the remaining case being an adenocarcinoma. The esophageal cancer stage of the patients was 0 for 3 (11.1%), I for 14 (51.9%), II for 4 (14.8%), and III for 6 (22.2%) patients. Tables 1 and 2 summarizes the patient characteristics.

2. Treatment outcomes for the study patients

Ten patients experienced disease progression. Locoregional recurrence without distant metastasis was observed in seven

Table 1. Description of individual characteristics and treatment for all patients

No	Age (yr)	Gender	Site		Stage		Treatment				Status
			H&N	Esophagus	H&N	Esophagus	Ind. CT	H&N	Esophagus	Completion	
1	59	M	HPx.	Lower	T3N2c	TisN0	FP	RT alone	RT alone	Yes	NED
2	74	M	Lx.	Middle	T2N0	T1N3	FP	No Tx.	No Tx.	No	DOD
3	57	M	HPx.	Lower	T3N0	T1N0	FP	No Tx.	No Tx.	No	DOD
4	68	M	Lx.	Lower	T2N2c	T1N0	TS1 + P	No Tx.	No Tx.	No	DOD
5	67	M	Lx.	Lower	TisN0	T2N1	No	RT alone	Op.	Yes	DOD
6	64	M	HPx.	Middle	T2N1	T1N0	FP	CCRT	CCRT	No	DOD
7	66	M	HPx.	Upper	T4aN2b	T1N1	TS1 + P	CCRT	CCRT	Yes	DOD
8	64	M	HPx.	Lower	T1N0	T1N0	XP	RT alone	Op.	Yes	DWOD
9	39	F	OPx.	Lower	T1N2c	T2N0	XP	CCRT	Op.	Yes	NED
10	74	M	HPx.	Middle	T1N0	T1N0	No	RT alone	Op.	Yes	DWOD
11	52	M	HPx.	Lower	T3N0	T1N0	TS1 + P	CCRT	Op.	Yes	NED
12	82	M	HPx.	Lower	T3N2b	T1N0	No	RT alone	RT alone	Yes	DWOD
13	61	M	HPx.	Lower	T3N2b	T1N0	No	Op. + RT	CCRT	Yes	NED
14	75	M	HPx.	Lower	T1N3b	T3N3	TS1 + P	CCRT	CCRT	No	DWOD
15	49	M	OPx.	Middle	T2N2c	T1N0	No	Op.	Op.	Yes	DWOD
16	65	M	HPx.	Upper	T1N0	T2N2	XP	CCRT	CCRT	Yes	NED
17	56	M	HPx.	Lower	T4aN2c	T1N0	TS1 + P	CCRT	CCRT	Yes	DOD
18	52	M	HPx.	Upper	T2N2b	T1N0	XP	Op.	No Tx.	No	DOD
19	67	M	HPx.	Middle	T4aN1	TisN0	No	Op. + RT	ESD	Yes	NED
20	63	M	HPx.	Upper	T1N1	T4N3	XP	CCRT	CCRT	No	DWOD
21	82	M	HPx.	Lower	T3N2b	T1N2	No	BSC	BSC	No	DOD
22	60	M	HPx.	Lower	T4aN1	TisN0	No	Op. + RT	ESD	Yes	NED
23	73	M	HPx.	Lower	TisN0	T1N0	No	Op.	ESD	Yes	NED
24	71	M	HPx.	Middle	TisN0	T3N3	XP	CCRT	Op. + RT	Yes	DWOD
25	46	M	HPx.	Middle	T1N2b	T1N0	DFP	CCRT	CCRT	Yes	NED
26	70	M	OPx.	Lower	T3N0	T1N0	No	CCRT	ESD	Yes	NED
27	59	M	HPx.	Lower	T1N0	T1N0	No	Op. + RT	Op.	Yes	NED

H&N, head and neck; Ind. CT, induction chemotherapy; M, male; F, female, HPx., hypopharynx; Lx., larynx; OPx., oropharynx; FP, 5-fluorouracil + cisplatin; XP, Xeloda + cisplatin; TS1+P, TS-1 + cisplatin; DFP, docetaxel + 5-fluorouracil + cisplatin; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; Op., Operation; Tx., treatment; ESD, endoscopic submucosal dissection; BSC, best supportive care; NED, no evidence of disease; DOD, death of disease; DWOD, death without disease.

patients (Fig. 1). The 2-year, 5-year actuarial progression-free survival (PFS) rates, and median survival were 61.9%, 44.2% and 36 months, respectively (Fig. 2). Initial disease progression was seen mainly for head and neck cancers (n = 5) and all head and neck cancer recurrences arose in the hypopharyngeal cancer patients. Progression of esophageal cancer only involved two patients, and recurrence of both cancers only occurred in one patient. In two cases experienced distant metastasis without locoregional progression, it was difficult to define the primary cancer. Overall, 16 of our study patients died from various causes including disease progression (n = 7, 43.8%), tumor related cachexia during treatment (n = 4, 25%), treatment-related death (n = 2, 12.5%), another primary cancer (n = 1, 6.3%), and unknown causes (n = 2, 12.5%). The 2-year OS, 5-year OS, and median actuarial OS rates were 53.4%, 19.8%, and 34 months, respectively (Fig. 3). Seven patients had an incomplete treatment because of disease progression (n = 2), poor tolerance of the therapy (n = 4), and treatment refusal (n = 1). All of these seven patients who received an incomplete treatment died. In the univariate analysis, ECOG performance status (p = 0.031), pretreatment weight loss (p = 0.004), and esophageal cancer stage (p = 0.011) were significant prognostic factors for OS. ECOG performance status (p = 0.019) was also a prognostic factor for PFS (Table 3).

Twenty patients was received RT and median RT dose was 6,800 cGy (range, 5,200 to 7,000 cGy) of head and neck and 5,400 cGy (range, 4,500 to 6,800 cGy) of esophageal cancer. Definitive RT (with or without concurrent chemotherapy) to both tumor sites was performed in 9 patients (45%). Definitive RT to head and neck plus esophageal operation including ESD

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Table 2. Basic characteristics of all patients

Variable	No. (%)
Age (yr)	
≤60	10 (37.0)
>60	17 (63.0)
Sex	
Male	26 (96.3)
Female	1 (3.7)
ECOG	
0–1	21 (77.8)
2–3	6 (22.2)
Diet	
Hard	18 (66.7)
Soft–liquid	9 (33.3)
Wt. loss (%)	
<5	18 (66.7)
≥5	9 (33.3)
H&N stage	
I–III	13 (48.1)
IV	14 (51.9)
EC stage	
I–II	21 (77.8)
III	6 (22.2)

ECOG, Eastern Cooperative Oncology Group; Wt. loss, pretreatment weight loss; H&N, head and neck cancer; EC, esophageal cancer.

Table 3. Univariate analysis for OS and PFS in synchronous head and neck and esophageal cancer

Variable	No.	2-yr OS (%)	OS (p-value)	2-yr PFS (%)	PFS (p-value)
Age (yr)			0.135		0.460
≤60	10	44.4		53.3	
>60	17	37.1		68.1	
ECOG			0.031		0.019
0–1	21	47.4		68.2	
2–3	6	16.7		50.0	
Diet			0.276		0.156
Hard	18	44.9		71.4	
Soft–liquid	9	33.3		42.7	
Wt. loss (%)			0.004		0.232
<5	18	51.8		65.7	
≥5	9	22.2		62.5	
H&N stage			0.816		0.606
I–III	13	48.6		72.9	
IV	14	33.1		51.9	
EC stage			0.011		0.265
I–II	21	47.4		64.6	
III	6	16.7		60.0	

OS, overall survival; PFS, progression free survival; ECOG, Eastern Cooperative Oncology Group; Wt. loss, pretreatment weight loss; H&N, head and neck cancer; EC, esophageal cancer.

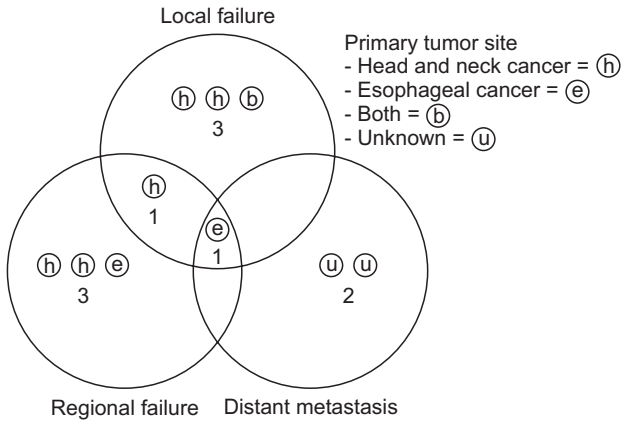

Fig. 1. Patterns of failure of all synchronous head and neck and esophageal cancer patients.

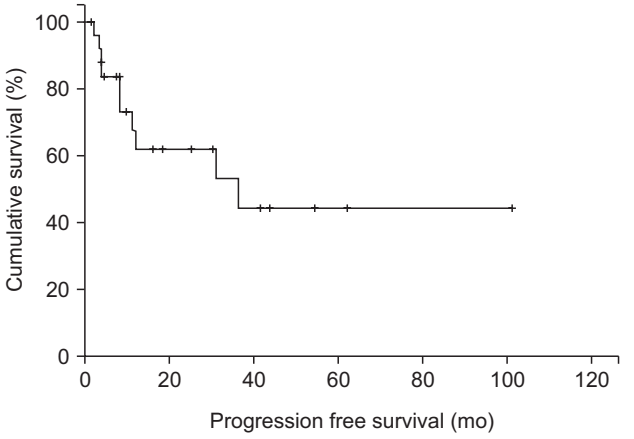

Fig. 2. Progression free survival of all synchronous head and neck and esophageal cancer patients.

was 7 patients (35%). Postoperative RT to head and neck plus esophageal operation was two patients (10%). Two patients (10%) received both definitive CCRT and postoperative RT. A patient received definitive CCRT to head and neck with postoperative RT to esophagus and other patients did postoperative radiotherapy to head and neck with definitive CCRT to esophagus. Overall response to definitive radiotherapy (n = 17) was 82.3%. Two-year PFS was 75.0% and two and median OS was 67.9% and 54 months.

3. Complications

The grade 3–4 acute hematologic, gastrointestinal and laryngeal toxicity was presented at 7 (25.9%), 6 (22.2%), and 8 (29.6%) patients and grade 3–4 chronic laryngeal and esophageal toxicity was 4 (14.8%) and 1 (3.7%) patients. Of these patients, serious complication was uncommon. One

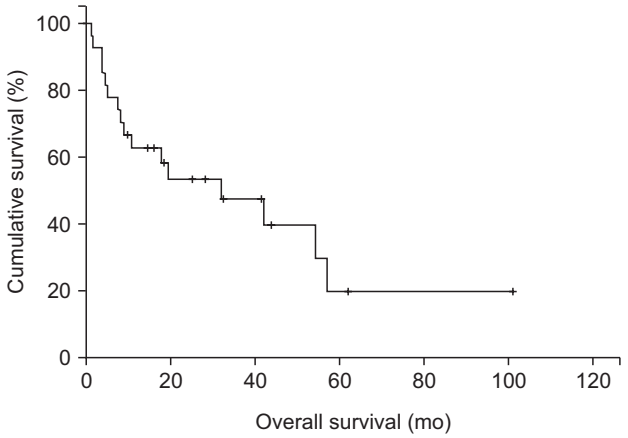

Fig. 3. Overall survival of all synchronous head and neck and esophageal cancer patients.

patient experienced radiation necrosis in the larynx and repeated aspiration. This patient received a total laryngectomy. There were no esophageal strictures or myelopathy in a survivor who received radical head and neck and esophageal RT. There were two treatment-related deaths; one patient died due to poor performance and pneumonia after definitive RT alone and the other due to peritonitis and adult respiratory distress syndrome (ARDS) after a transoral hypopharyngectomy and a McKeown procedure.

Discussion and Conclusion

In our current study, the survival rate and treatment-related serious complication rate were comparable to previous reports of SHNEC patients. Our analyses revealed a 2-year and median OS of 53.4% and 34 months, respectively and a 2-year and median PFS of 61.9% and 36 months. Serious adverse events only occurred in two cases. Welz et al. [15] reported a median survival in SHNEC patients of 37 months, and Shinoto et al. [13] reported a 2-year OS of 44% and no late grade 3 toxicity in a definitive chemoradiotherapy series of SHNEC patients. Because our current study included 7 patients who did not receive radiotherapy, direct comparison may not be difficult. Two-year PFS and OS in patients with radiotherapy was 75.0% and 67.9%. This result seems to be higher than previous study. This result may explain that current study included 55% superficial esophageal cancer (Tis or T1N0) in these patients.

The esophageal cancer stage was found to be an important prognostic factor whereas the head and neck cancer stage did not have prognostic significance by univariate analysis of our SHNEC cohort. Because esophageal cancer has a much poorer outcome than head and neck cancer, the prognosis would generally be determined by the esophageal cancer stage in SHNEC patients. Wind et al. [16] reported that there was no difference in survival between patients with esophageal cancer only and patients with SHNEC treated with esophagectomy. Shinoto et al. [13] also reported that advanced esophageal cancer was a negative prognostic indicator in SHNEC patients who received definitive chemoradiation treatment.

In our current study, the major patterns of recurrence were locoregional (8 of 10 total recurrences, 80%), and initial disease progression was mainly seen for head and neck cancer (5 of 8 local recurrences, 62.5%). Welz et al. [15] reported that 6 of 7 (85.7%) local recurrences in SHNEC patients involved head and neck cancer progression. Shinoto et al. [13] reported 16 locoregional recurrences, and that progression of head and neck cancer affected 13 of 22 (59.1%) total recurrences in their SHNEC series. Because hypopharyngeal cancer is the most commonly affected type of head and neck region, local recurrence may be relatively high. In this study, only hypopharyngeal cancer patients experienced local recurrence.

Our current study further showed that the pretreatment status such as weight loss and the ECOG performance status had prognostic significance in SHNEC. Because the treatment of SHNEC might involve an aggressive and high-volume regimen, determining whether patients can complete a radical treatment approach could be important. Six of nine patients in our current study with a pretreatment weight loss >5% did not complete their therapy, and three of five patients with an ECOG performance status ≥2 also did not. All long-term survivors in our current series completed their radical treatment regimen. Thus, a rigorous management approach is likely to be critical in SHNEC patients because treatment completion likely has a major impact on survival outcomes in these cases. Another reason that may explain why the pretreatment status is a known prognostic factor for esophageal cancer [17,18] is that tumor-related malnutrition may affect the treatment outcome.

The recorded incidence of SHNEC may increase in the future with advances in diagnostic techniques. Currently, [^{18}F]FDG-PET is widely used for cancer diagnosis and staging work-up [19], and its use for detecting double primary cancer may possibly have increased [11,20-24]. Recently, a higher incidence of synchronous esophageal cancer has been found through routine endoscopic screening of head and neck cancers [9]. Additionally, Wang et al. [6] have reported that routine screening with endoscopy in head and neck cancer patients might improve survival. Because the esophageal cancer stage

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is an important prognostic factor in SHNEC, routine endoscopy of head and neck cancers has led to a greater detection of earlier stage esophageal cancer when patients can receive adjunctive therapy.

Current study had several limitations. The study was retrospective study of very small number of patients. Thus, the prognostic analysis may have confounding factor because multivariate analysis was not performed. The characteristics of enrolled patients were very heterogeneous because this disease entity is uncommon. And treatment decision was performed on case by case. However, this study is largest series of SHNEC in the Korea with our knowledge and may be useful to understand this rare disease entity.

In summary, although the survival outcomes for SHNEC patients are poor, long-term survival might be achievable with aggressive treatments with a low rate of serious complications. Our present analyses have shown that the esophageal cancer stage has prognostic significance for SHNEC survival, but that the head and neck cancer stage does not. Identifying SHNEC patients with a pretreatment status that can tolerate aggressive treatment could be also important. In future studies, treatment outcomes and predictive factors should be investigated in trials with larger patient numbers because the incidence of SHNEC will likely be increased through detection by routine endoscopy and [^{18}F]FDG-PET scans.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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