JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010;40(10)938–943
doi:10.1093/jjco/hyq068
Advance Access Publication 12 May 2010

Significance of Endoscopic Screening and Endoscopic Resection for Esophageal Cancer in Patients with Hypopharyngeal Cancer

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Presented in part at the 49th Annual Meeting of the American Society for Therapeutic Radiology and Oncology (2007) in Los Angeles, CA, USA.

Received December 19, 2009; accepted April 7, 2010

Objective: The efficacy of endoscopic screening for esophageal cancer in patients with hypopharyngeal cancer remains controversial and its impact on prognosis has not been adequately discussed. We studied the use of endoscopic screening to detect esophageal cancer in hypopharyngeal cancer patients by analyzing the incidence, stage and prognosis.
Methods: We included 64 patients with hypopharyngeal cancer who received radical radiotherapy at our institute. Chromoendoscopic esophageal examinations with Lugol dye solution were routinely performed at and after treatment for hypopharyngeal cancer.
Results: Twenty-eight esophageal cancers were detected in 28 (41%) patients (18 synchronous and 10 metachronous cancers). Of the 28 cancers, 23 were stage 0 or I cancer and 15 of these were treated with endoscopic resection. Local control was achieved in all of these 23 stage 0 or I cancers. The 5-year overall survival rates with esophageal cancer were 83% in stage 0, 47% in stage I and 0% in stage IIA–IVB.
Conclusions: This study showed a strikingly high incidence of esophageal cancer in hypopharyngeal cancer patients. We suppose that the combination of early detection by chromoendoscopic examination and endoscopic resection for associated esophageal cancer in hypopharyngeal cancer patients improve prognosis and maintain quality of life.

Key words: hypopharyngeal cancer – esophageal cancer – endoscopic screening – endoscopic resection – prognosis

INTRODUCTION

The prognosis of hypopharyngeal cancer is relatively poor among head and neck cancers (1). The main reason is that hypopharyngeal cancer is often diagnosed at an advanced stage with cervical lymph node metastases. Furthermore, synchronous and metachronous double cancers affect the prognosis of hypopharyngeal cancer as well as the other head and neck cancers (2–6). Of the various double cancers, squamous cell carcinoma of the esophagus, which is

commonly caused by excessive tobacco and alcohol consumption, is one of the most frequently associated with hypopharyngeal cancer as well as the other head and neck cancers (7–15). The poor prognosis is likely because the second esophageal cancer is often found in an advanced stage.

Surgical and radiotherapy techniques have improved the prognosis of hypopharyngeal cancer. Chemoradiotherapy in particular has progressed significantly (16,17). Because this improvement in prognosis has made the implications of developing an associated esophageal cancer more important, endoscopic screening was introduced in Eastern Asia to detect the second esophageal cancer at an early stage and eliminate its adverse influence on the overall prognosis of hypopharyngeal cancer (9–11,18–24). Because the incidence of the second esophageal cancer is variable, the efficacy of endoscopic screening remains controversial and its impact on prognosis has not been adequately discussed.

We performed a chromoendoscopic screening of the esophagus to improve the prognosis in patients with hypopharyngeal cancer. In this study, we analyzed the results and discussed the significance of endoscopic screening.

PATIENTS AND METHODS

Seventy-three patients with hypopharyngeal cancer received radical radiotherapy at the Osaka Medical Center for Cancer and Cardiovascular Diseases from October 1999 to December 2006. Of these, nine patients had a history of esophageal cancer before treatment. The remaining 64 patients without a history of esophageal cancer were included in this study. With the exception of esophageal cancer, 16 patients had 20 combined cancers: 6 head and neck cancers, 5 gastric cancers, 3 lung cancers, 1 pancreatic cancer, 1 colon cancer, 1 rectal cancer, 1 bladder cancer, 1 renal cell carcinoma and 1 primary unknown cancer. These cancers occurred before or after the hypopharyngeal cancer diagnosis. Our treatment policy for hypopharyngeal cancer was as follows: conventional radiation therapy for T1, accelerated hyperfractionated or stereotactic radiation therapy for early T2, concurrent chemoradiation therapy (CCRT) for advanced T2 and early T3, surgical resection with or without neck resection for advanced T3 and T4. For patients that manifested lymphadenopathy of N2b or more and underwent radiotherapy, planned neck dissection was indicated prior to radiotherapy. During the study period, 134 patients with hypopharyngeal cancer received radical surgery, 27 patients received palliative therapy and 10 patients did not receive any therapy.

The patients were 58 men and 6 women with a median age of 62 years (range, 47–91 years). The median follow-up time for survivors was 43 months (range, 24–86 months). Histology confirmed the presence of squamous cell carcinoma of the hypopharynx in all patients. The stages of hypopharyngeal cancer are presented in Table 1 according to the International Union Against Cancer (UICC) Tumor-Node-Metastasis (TNM) classification (25). Forty-one patients (64%) were classified as having stage III or IV cancer.

Table 1. Stage of hypopharyngeal cancer

Stage	I	II	III	IVA	IVB	Total
Hypopharyngeal cancer with esophageal cancer	0	12	1	13	0	26
Hypopharyngeal cancer without esophageal cancer	2	9	8	17	2	38
Total	2	21	9	30	2	64

Patients received radical radiation therapy, which was completed in all cases. Around 70 Gy (range, 60–74 Gy) of radiation was delivered 5 days per week to the gross tumor volume in 4.5–7.5 weeks. The elective lymph node areas were irradiated with 39–46 Gy. The median dose per fraction was 2 Gy (range, 1–3 Gy). Five patients received CCRT (weekly docetaxel, 10 mg/m^2). Planned neck dissection was performed in 12 patients before radiation therapy (1 patient with N1, 2 with N2a, 8 with N2b and 1 with N3).

Chromoendoscopic screening was performed to detect esophageal cancer at treatment and annually during follow-up as follows: immediately after a standard endoscopy, 20–40 ml of a 1.5% iodine solution was directly inserted into the biopsy channel of the endoscope until the normal esophageal mucosa was evenly stained. The results of chromoendoscopy were considered abnormal if there were unstained lesions. If unstained lesions were observed, biopsy specimens were taken for histological examination. Written informed consent was obtained from each patient before the endoscopic examination.

Survival and control rates were measured from treatment of the corresponding hypopharyngeal or esophageal cancer. Each patient was followed until 31 December 2008 or death. The overall survival and local control rates were estimated by the Kaplan–Meier method. Statistical analysis was performed using GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA, USA).

RESULTS

Hypopharyngeal Cancer Treatment

The 5-year overall survival rate for hypopharyngeal cancer was 58% (Fig. 1). When sorted by cancer stage, the 5-year overall survival rates were 100% for stage I, 39% for stage II, 51% for stage III and 61% for stage IV. The first relapse sites were the primary tumors (T) in nine patients, cervical lymph nodes (N) in 9, T + N in 2, T and distant metastases (M) in 1, N + M in 1 and M in 2. In patients with an associated cancer, it was not possible to determine definitely whether the metastases were from the hypopharyngeal cancer or the associated cancer. For the first relapse,

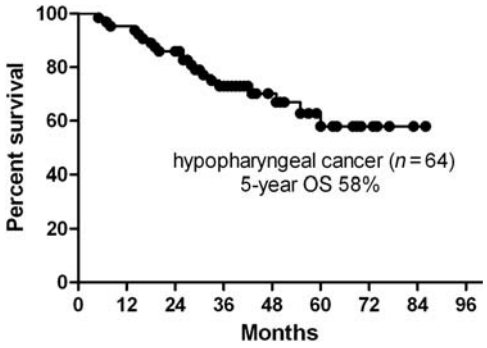

Figure 1. Overall survival (OS) rate for hypopharyngeal cancer ($n = 64$).

Table 2. Stage of esophageal cancer

Stage	Synchronous esophageal cancer	Metachronous esophageal cancer	Total, cancers/patients
0 (TisN0M0)	6	2	8[a]/7
I (T1N0M0)	10	5	15[b]/14
IIA(T2N0M0)	1	1	2/2
IIB (T2N1M0)	0	1	1/1
III (T3N1M0)	1	0	1/1
IVB (T2N0M1b)	0	1	1/1
Total	18	10	28/26

[a]One patient had stage 0 synchronous and stage 0 metachronous cancers.
[b]One patient had stage I synchronous and stage I metachronous cancers.

20 patients underwent a salvage operation for first relapses, which was successful in 8.

Incidence and Stage of Associated Esophageal Cancer

Following a chromoendoscopic screening, 26 patients (41%; 26/64) were diagnosed with esophageal cancer during treatment for the hypopharyngeal cancer (synchronous) and/or during follow-up (metachronous) (Table 2). Because two patients developed synchronous and metachronous cancers, there were 28 esophageal cancers (18 synchronous and 10 metachronous). The intervals between the treatment for hypopharyngeal cancer and the diagnosis of metachronous esophageal cancers were 6, 13, 16, 19, 22, 37, 46, 47, 57 and 67 months. The total number of esophageal cancerous lesions was 39, because eight patients had multiple lesions. Of these lesions, 2 were located in the cervical esophagus, 3 in the upper thorax, 25 in the middle thorax, 8 in the lower thorax and 1 was a mottled lesion. Each lesion was separated from the hypopharyngeal cancerous lesion and was defined as a second primary cancer. Histology confirmed that the esophageal cancer was squamous cell carcinoma in all but one patient who had carcinosarcoma.

The esophageal cancer stage is shown in Table 2. The most advanced stage was recorded for patients with multiple lesions. Stage I exceeded one half (54%; 15/28) followed by stage 0 (29%; 8/28). One of our authors histologically diagnosed all stage 0 esophageal cancers as high-grade intraepithelial neoplasia (HGIN) (Vienna classification category 4) and diagnosed most as carcinoma *in situ* (Vienna classification category 4.2) (Fig. 2) (26).

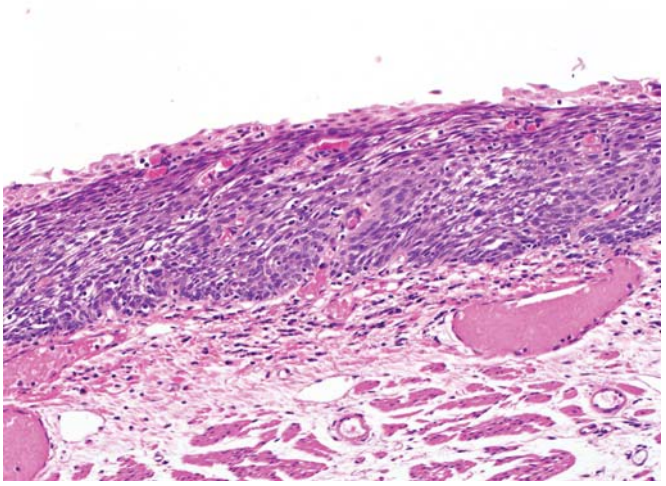

Figure 2. A microscopic picture of esophageal high-grade intraepithelial neoplasia (HGIN). Although neoplastic cells with atypical nuclei and prominent nucleoli are present throughout the epithelium, they do not invade the lamina propria.

Table 3. Treatment method for esophageal cancer

Stage	ER	Operation	CCRT	RT	Chemotherapy	Total
0	7	0	0	1	0	8
I	8 (4)	3	2	2	0	15
IIA	0	1	1	0	0	2
IIB	0	0	1	0	0	1
III	0	1	0	0	0	1
IVB	0	0	0	0	1	1
Total	15	5	4	3	1	28

ER, endoscopic resection; CCRT: concurrent chemo-radiotherapy; RT, radiation therapy; ( ), with additional CCRT.

Treatment and Outcome of Associated Esophageal Cancer

Treatment methods for esophageal cancer are presented in Table 3. Endoscopic resection (ER) is indicated at our hospital for mucosal lesions confined to the epithelium, lamina propria or submucosa without lymph node metastases. Fifteen of 23 patients with stage 0 or I esophageal cancer were treated with ER (endoscopic mucosal resection in nine patients and endoscopic submucosal dissection in six patients), and four of them received adjuvant CCRT for subclinical lymphadenopathy because they had a massive

submucosal cancer lesion. The surgical margin was negative of all patients after ER but one patient that received adjuvant CCRT. Total doses were 60 Gy for radical CCRT or radical radiation therapy alone and ranged from 38 to 50 Gy for adjuvant CCRT after ER. Chemotherapy regimens combined were two cycles of cisplatin and 5-fluorouracil, cisplatin, 5-fluorouracil and adriamycin or nedaplatin and 5-fluorouracil. Local control was achieved for all 23 with stage 0–I cancers regardless of treatment modality (Fig. 3). Among five patients with stage IIA–IVB cancers, local failure was observed in two patients with stage IIB (T2N1M0) and IVB (T2N0M1b).

Overall survival according to esophageal cancer stage, which was measured from treatment, is presented in Fig. 4. The follow-up time for survivors ranged from 2 to 81 months. The 5-year overall survival rates were 83% in stage 0, 47% in stage I and 0% in stage IIA–IVB. Six of 7 stage 0 patients were alive without diseases, but one died of pneumonia. Among 14 stage I patients, 9 were alive without diseases, 1 died of hypopharyngeal cancer and 4 patients died of distant metastases whose primary site could not be definitely determined. One stage IIA patient was alive without diseases, whereas the other died of hypopharyngeal cancer. All three stage IIB, III and IVB patients died of esophageal cancer within 3 years after treatment.

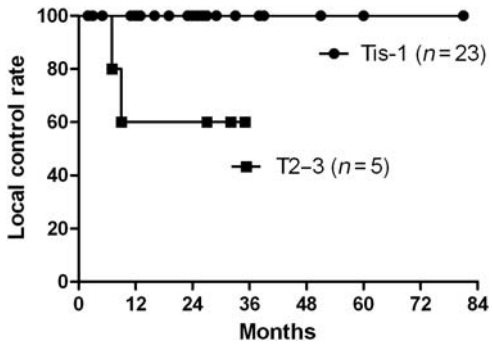

Figure 3. Local control rate for esophageal cancer according to the T classification ($n = 28$).

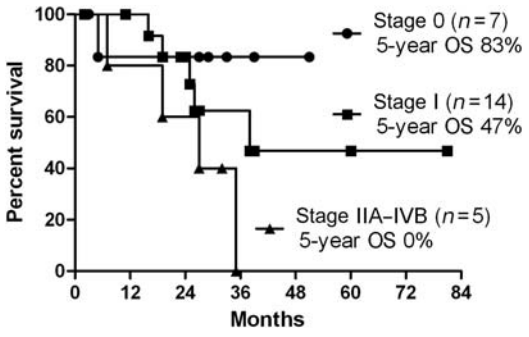

Figure 4. OS rate of esophageal cancer according to stage ($n = 26$).

DISCUSSION

In the present study, the incidence of a second primary esophageal cancer in patients with hypopharyngeal cancer was 41% (26/64). In previous studies, the reported incidence varied. Davidson et al. (23) reported that screening for esophageal cancer in 154 head and neck cancers resulted in no detection. Vandenbrouck et al. (7) and Keane et al. (8) reported a 4% incidence in their retrospective studies on hypopharyngeal cancer. Endoscopic screening reportedly detects associated esophageal cancer more frequently with an incidence of 5–32% and is useful for patients with head and neck cancer (9,10,18–22).

The incidence of associated esophageal cancer in the present study was higher than that observed in the reports mentioned above. One reason for the high incidence was that thorough endoscopic screening was performed. Another reason was that chromoendoscopic examinations, which efficiently detected early lesions, were routinely combined. Hashimoto et al. (20) performed chromoendoscopic esophageal screening in patients with primary head and neck cancers, detecting 28 cancerous lesions in 326 patients. Only 4 of these 28 lesions could have been diagnosed with conventional endoscopy. Shiozaki et al. (18) used chromoendoscopic screening in head and neck cancer patients and found 13 esophageal cancers in 178 patients. They stated that 9 of 13 lesions could not have been diagnosed by barium studies or conventional endoscopy because the lesions were completely flat. Thus, chromoendoscopy is a useful tool to diagnose early esophageal cancer and resulted in the detection of 8 Tis (stage 0) and 15 T1 (stage I) esophageal cancer in the present study.

In addition, the incidence of synchronous esophageal cancer was especially high (28%; 18/64). Wang et al. (21) also evaluated the efficacy of endoscopic screening for esophageal lesions at the diagnosis of hypopharyngeal cancer. They reported a similar incidence of synchronous esophageal cancers: 6 esophageal cancers in 27 hypopharyngeal cancer patients (22%). In addition to the high incidence, the majority of synchronous esophageal cancers were at the early curable stages in our study, suggesting that endoscopic screening is essential at hypopharyngeal cancer diagnosis. Our annual endoscopic screening detected sporadic secondary esophageal cancer from 6 to 67 months after treatment for hypopharyngeal cancer. We consider annual screening appropriate for metachronous esophageal cancer. However, from our analysis, it is unclear how long the screening should be continued.

We treated hypopharyngeal cancer with radiotherapy, whereas treatment for synchronous esophageal cancer has some challenges. If the esophageal cancer is also to be treated with radiation therapy, the radiation fields could be very large to deliver radical doses. If esophageal cancer is to be treated with surgery, the sequence of the two treatments is a problem. Surgery for esophageal cancer requires a long postoperative recovery time of weeks or even months. The radiation therapy for hypopharyngeal cancer also takes about

2 months. Therefore, the second treatment could take long to start.

ER has a clear advantage of not requiring an extended recovery period and enables radiotherapy for synchronous hypopharyngeal cancer to start early. Takeshita et al. (27) treated 56 patients of early esophageal cancer with ER. Of these, 53 patients were alive at the end of the follow-up period. This was the first report of a large series that demonstrated the efficacy of ER. Makuuchi et al. (28) removed 540 esophageal cancer lesions with ER that were localized within the mucosa. They reported that local recurrence occurred in only 11 lesions (2%). Thus, having a high curative rate and providing the benefit to maintain quality of life, ER for early esophageal cancer is a favorable alternative to surgery or radiation therapy in Japan.

Although, in the present study, many early stage 0 or I esophageal cancers were successfully resected with ER, intraepithelial neoplasia treatments of the esophagus are controversial. This issue has been caused by large discrepancies in the diagnosis of dysplasia versus carcinoma of the gastrointestinal tract between Western and Japanese pathologists. Western pathologists use the term dysplasia to indicate noninvasive neoplastic epithelial proliferation, and invasion into the lamina propria is mandatory to diagnose a carcinoma. In contrast, for Japanese pathologists, the diagnosis of carcinoma is based on atypism of cells or architectural change. To solve the problem, the Vienna meeting proposed five gastrointestinal neoplasia categories, the Vienna classification (26). In the Vienna classification, intraepithelial high-grade dysplasia and carcinoma *in situ* are integrated into HGIN, which have a substantial risk for invasion. Epidemiological follow-up studies by Dawsey et al. (29) demonstrated that the relative risk for subsequent development of invasive esophageal squamous cell carcinoma was 72.6 in patients with severe dysplasia, which was higher than in those with mild dysplasia (2.2) or moderate dysplasia (15.8). Consequently, whether the lesion was high-grade dysplasia or carcinoma *in situ*, the Vienna classification advocates local treatments for HGIN (30). ER, which was developed in Japan, was recently reported to be a standard treatment modality for early esophageal squamous cell carcinoma in Western countries also (31).

Schwartz et al. analyzed a large number of patients (851 patients) with head and neck cancer and found 54 second esophageal cancers whose 5-year survival rate was as low as 2.6% (2). Patients with head and neck cancer and secondary esophageal cancer had 5-year survival rates of 9–10% in a study by Tachimori et al. (3) and did not survive 3 years in a study by Leon et al. (4). Thus, prognosis of patients with associated esophageal cancer was extremely poor. To improve prognosis, Atabek et al. (5) introduced active screening for patients with head and neck cancer to detect simultaneous esophageal cancer; however, this screening had a low rate of detection and a median survival of 5.3 months after diagnosis of esophageal cancer for 41 multiple primary patients. The authors concluded that the screening yielded no substantial survival benefit. We supposed that their conclusions were derived from a lack of routine chromoendoscopic examination and a resulting failure to detect early esophageal cancer. In the present study, all three patients with stage IIB–IVB esophageal cancer did not survive 3 years.

We consider that chromoendoscopy benefits double cancer patients by efficiently detecting early esophageal cancer, although our results could not always be applied to Western countries where the incidence of esophageal squamous cell carcinoma is relatively low (32). In addition, combined ER can effectively cure esophageal cancer. In this study, 5-year overall survival rate for patients with associated esophageal cancer was considerably improved compared with previous reports (2–6).

In conclusion, There is a possibility that chromoendoscopic examination efficiently detects associated early esophageal cancer in hypopharyngeal cancer patients, and ER plays a substantial role for achieving a good prognosis and maintenance of quality of life.

Conflict of interest statement

None declared.

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